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Adrenal Disease and Pregnancy

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1. Introduction

During pregnancy, maternal-endocrine regulation, as well as all their physiology, undergoes profound adaptive changes in the framework of a functional organization structured in three interrelated compartments: the mother, placenta and fetus. Many of these changes are initially induced by estradiol and progesterone produced by the corpus luteum, combined with chorionic gonadotropin. As the pregnancy progresses, steroid and peptide hormones produced by the fetoplacental unit, took over. As a result of these adaptive phenomena is achieved adequate nutritional support of the fetus, uterine quiescence is maintained during childbirth, and breastfeeding is finally possible (Schindler, 2005).

2. Cushing's syndrome

During normal pregnancy, serum cortisol increase gradually from the second quarter, keeping the circadian rhythm. Part of the increase in serum cortisol is due to increased estrógens and secundarily to increased cortisol binding protein (CBG), although serum free cortisol, urine and saliva can be elevated up to 2-3 times. The plasma concentration of ACTH is usually normal, although during pregnancy can be reduced or increased. There is a gradual increase in late pregnancy and during delivery (Lindsay & Nieman, 2005). The placenta during gestation can produce CRH which is released into the maternal circulation, although this may have implications in the regulation of ACTH and cortisol secretion are not well known.

Cushing's syndrome is uncommon during pregnancy, because hypercortisolism produces anovulation and infertility by altering androgenos and gonadotropin.

The frequency of ACTH-independent cases is increased in pregnant as compared to non pregnant individuals. Of the approximately 136 reported cases, approximately 60% had ACTH independent Cushing's Syndrome: 44% adenoma y 11% carcinoma and the remainder a mix of primary pigmented nodular adrenal disease, ACTH independent hyperplasia and ectopic ACTH secretion. Five pregnant women with the ectopic ACTH syndrome have been reported (Guilhaume et al., 1992).

The fetus is partially protected from the hypercortisolemia because placental 11-betahydroxysteroid dehydrogenase converts 85% of maternal cortisol to biologically inactive cortisone. However, untreated Cushing's syndrome has been associated with spontaneous abortion (25%), premature delivery (50%) and rarely, neonatal adrenal insufficiency (Aron et al., 1990).

Maternal complications also can occur. These include hypertension in nearly 70%, gestational diabetes in 25%, myopathy, opportunistic infections, fractures, preeclampsia and rarely heart failure. Two maternal deaths have been reported (Vilar et al., 2007).

2.1 Diagnosis

The presence of Cushing's Syndrome during pregnancy may be masked since some of the symptoms and signs of this disorder (weight gain, hypertension, striae) can also occur in normal pregnant women. Biochemical changes during normal pregnancy can interfere with the diagnosis:

The normal pregnancy rises in ACTH and cortisol levels. The hypercortisolism of pregnancy continues to exhibit a normal circadian rhythm, though with a higher nighttime nadir; loss of diurnal rhythm is characteristic of all forms of Cushing syndrome. Salivary cortisol measurements may assist in determining this lack of diurnal response, but normal midnight levels have not been standardized for pregnancy. Urinary free cortisol levels greater than 3 times the upper limit of normal may be interpreted as indicating Cushing's syndrome in the second and third trimester. There are limited or no data using antibody based assays or mass spectrometry. Normal pregnancy is also associated with inadequate suppression of ACTH and cortisol during the overnight dexamethasone suppression test (Carr et al., 1981). ACTH levels may not reliably distinguish between pituitary and adrenal etiologies, as the levels may be normal or high in all form of Cushing syndrome, likely from placental ACTH production. When plasma ACTH levels are suppressed, preferably as measured using a two-site immunometric assay, no further biochemical testing is needed.

The high dose dexamethasone suppression test will cause >80% suppression of serum cortisol in normal pregnancy. Patient with adrenal Cushing may be identified with this test as they don't suppress, but the test may misclassify those with Cushing disease, as three of seven cases failed to suppress in small series (Lindsay et al., 2005).

2.2 Differential diagnosis

Because of the persistent elevations of ACTH in pregnancy, an ACTH suppressed is not always found in independent causes of Cushing syndrome. Thus, while its measurement may be useful, lack of suppressed value does not exclude an ACTH independent cause.

There are limited data on the response to dexamethasone, 8 mg, of women with adrenal causes of Cushing's syndrome and pituitary adenomas. In general, those with an adrenal etiology do not suppress, while those with Cushing disease do suppress serum cortisol. (Barasch et al., 1988).

Because adrenal form of Cushing's syndrome are common in pregnancy, it is reasonable to perform an adrenal ultrasound to look for a mass, as well as an ACTH level and dexamethasone suppression test as an initial evaluation.

CRH stimulation test has been performed rarely in pregnant patients. Magnetic resonance (MRI) cannot be performed in the first trimester because of concerns about potential adverse fetal effects; during the remainder of gestation it is not commonly given with gadolinium contrast.

2.3 Treatment

Adrenal surgery has been performed at the 16 to 21 weeks of pregnancy without complicating the pregnancy (Buescher, 1996). It can be performed using a laparoscopic

approach. There is no clear evidence that early treatment is more beneficial than later treatment, this is likely because treatment is generally begun late. Early second trimester surgical treatment would be optimal. For women who do not want surgery or are diagnosed later, maternal hypercortisolism can be controlled with metyrapone. Metyrapone has side effects including hypertension and preeclampsia. (Blanco et al., 2006). Ketoconazole therapy is associated with intrauterine growth retardation, but no malformation or neonatal adrenal insufficiency (Berwaerts et al., 1999). Aminoglutethamide may cause fetal masculinization and mitotane is teratogenic; both should be avoided.

Transsphenoidal surgery and pituitary radiation have both been used without complicating the pregnancy (Casson et al., 1987).

Treating the Cushing's syndrome does not reduce the frequency of intrauterine growth restriction (about 30%) or premature birth (about 65%), but it does appear to prevent stillborn deliveries (about 10% with treatment) (Buescher, 1996).

3. Adrenal insufficiency

The adrenal insufficiency (AI) is rare, but early diagnosis is very important to improve maternal-fetal treatment. The primary AI or Addison's disease involves adrenal cortex atrophy with response insensitivity to ACTH and angiotensin 2, which causes a deficiency of glucocorticoids and aldosterone. The secondary and tertiary AI due to lack of ACTH or CRH are secondary to hypothalamic-pituitary diseases or chronic administration of exogenous corticosteroids. The secondary and tertiary AI are not associated with mineralocorticoid deficiency (Ambrosi et al., 2003).

The prevalence of primary adrenal insufficiency in pregnancy is unknown, with a series from Norway suggesting an incidence of 1 in 3000 births from 1976 to 1987. The most common etiology for primary adrenal insufficiency is autoimmune adrenalitis, which may be associated with autoimmune polyglandular syndrome. Primary adrenal insufficiency from infections, bilateral metastatic disease, hemorrhage or infarction is uncommon. Secondary adrenal insufficiency, from pituitary neoplasm or glucocorticoid suppression of the hypothalamic-pituitary-adrenal axis is more common (Stechova, 2004).

Gestation in patients with AI should be considered high-risk pregnancy (Lindsay & Nieman, 2005). Maternal mortality is rare today, after the introduction of hydrocortisone in 1950, as well as improved diagnosis and early treatment. When AI is not diagnosed during pregnancy, may not have negative effects to mother or fetus, indicating the transplacental passage of maternal fetal glucocorticoids. In these cases, disease appears in the postpartum. When the disease is previously known, it is necessary to adjust the dose of corticosteroids in order to avoid a default adrenal crisis defect or undesirable effects of excess treatment as hypertension and preeclampsia.

The prevalence of fetal mortality is unknown, although cases have been reported about intrauterine death, most undiagnosed in pregnant women. Intrauterine growth retardation and low birth weight are the most frequent effects in untreated mothers. The concomitance between AI and other autoimmune diseases (DM, lupus, anticardiolipin antibodies) increases maternal-fetal morbidity.

3.1 Diagnosis

Most cases are diagnosed before pregnancy.

Adrenal insufficiency is associated with laboratory findings of hyponatremia, hyperkalemia, hypoglycemia, eosinophilia and lymphocytosis. Hyperkalemia may be absent, because of the pregnancy increase in the rennin angiotensin system (Gradden et al., 2001). Early morning plasma cortisol levels of <3.0 mcg/dl confirms AI, while a cortisol >19 mcg/dl in the first or early second trimester excludes the diagnosis in a clinically stable patient. Plasma cortisol levels may fall in the normal "nonpregnant" range due to increase in CBG concentrations in the second and third trimesters, but will not be appropriately elevated for the stage of pregnancy. Appropriate pregnancy-specific cutoffs for diagnosis with the standard cosyntropin test using 250 mcg dose have not been established. Plasma cortisol levels were 60% to 80% above nonpregnant responses in normal pregnant women tested in the second and third trimesters in one series (Nolten et al., 1978).

McKenna et al (McKenna et al., 2000) examined the 1 mcg low dose cosyntropin test for diagnosis of secondary adrenal insufficiency in women at 24-34 weeks gestational age, and found high sensitivity of diagnosis using a cutoff of 30 mcg/dl. Accuracy of dosing is more difficult with this than with the standard cosyntropin test. The cosyntropin test is less sensitive to detect early secondary or tertiary forms of adrenal insufficiency. Cortisol and ACTH responses to CRH are blunted in pregnancy, making the CRH stimulation test unreliable for differentiating secondary and tertiary adrenal insufficiency in pregnancy. With primary AI, ACTH levels will be elevated and a level above 100 pg/ml is consistent with the diagnosis. However, ACTH will not be low with secondary forms because of the placental production of this hormone, which is nevertheless insufficient to maintain normal maternal adrenal function. ACTH values fluctuate widely, and a single value is insufficient for diagnosis. Adrenal antibodies may assist in confirming idiopathic adrenal insufficiency, as approximately 90% of patients will have 21 hydroxylase antibodies and 30% will have antibodies to 17-hydroxylase and side-chain cleavage enzymes. Aldosterone to renin ratios are low with elevated plasma rennin activity in patient with mineralocorticoid deficiency from adrenal atrophy (Symonds & Craven, 1978).

3.2 Treatment

Patients with AI should be managed during pregnancy and childbirth by a multidisciplinary team that includes endocrinologist, obstetrician and an expert neurosurgeon.

3.2.1 Glucocorticoids

The aim is to achieve a physiological replacement dose for optimal maternal and fetal monitoring.

The most important period is the first trimester, because the symptoms may go unnoticed by the emesis of pregnancy and childbirth stress. Hydrocortisone is the glucocorticoid of choice at doses of 12-15 mg/m² in 2 divided doses at breakfast and 1 / 3 at lunch. It is rare to increase the dose during pregnancy.

Women must be educated on the need for treatment with parenteral hydrocortisone in cases of nausea, vomiting or intercurrent systemic disease. Prednisone or prednisolone should be avoided because Hydrocortisone is more physiological.

3.2.2 Mineralocorticoids

They are only required in primary AI. The most widely used on the single dose is fluorocortisona 9 α (0.05 to 0.2 mg/day). The dose is stable during pregnancy, and it can be reduced in the third trimester if there are edemas or hypertension.

3.2.3 Adrenal crisis

It may appear at any time if the AI is not diagnosed, but it is more often during the delivery, when there is infection, preeclampsia or hemorrhage. Treatment should be started with hydrocortisone intravenous (bolus of 100 or 200mg and then 50-100 mg every 6-8 hours). In women with hypoglycemia, it is necessary to administer dextrose.

After stabilization, return to oral treatment. It is not necessary to administer Mineralocorticoids in the acute phase. During delivery, the dose of glucocorticoids should be doubled at onset of labor or to administer 50 mg of intravenous hydrocortisone. In case of caesarean, it is necessary to start treatment with hydrocortisone, 100 mg IV every 8 hours. The oral treatment must be restarted within 48 hours.

After delivery, all women must maintain treatment with corticosteroids and with doses of mineralocorticoids similar to the prepregnancy period.

It is not necessary to follow hypothalamic-pituitary axis in children of mothers with AI if they have been well treated during pregnancy. It can be necessary in mothers who have received supraphysiological doses.

The replacement therapy can continue during lactation. It is excreted 0.5% per liter of milk of the absorbed dose (Sidhu & Hawkins, 1981).

4. Primary hyperaldosteronism

Primary hyperaldosteronism rarely has been reported in pregnancy and is most often caused by an adrenal adenoma (Okawa et al., 2002). There are reports of glucocorticoid remediable hyperaldosteronism in pregnancy (Wyckoff et al., 2000). The elevated aldosterone levels found in patients are similar to those in normal pregnant women, but the plasma rennin activity is suppressed. Moderate to severe hypertension is seen in 85%, proteinuria in 52% and hypokalemia in 55%, and symptoms may include headache, malaise, and muscle cramps. Placental abruption and preterm delivery are risks. Progesterone has an antimineralocorticoid effect at the renal tubules, and the hypertension and hypokalemia may ameliorate during pregnancy (Matsumoto et al., 2000).

The physiologic rise in aldosterone during pregnancy overlaps the levels seen in primary aldosteronism, making diagnosis difficult. Suppressed rennin in the setting of hyperaldosteronism, is diagnostic. Salt loading test may be used to diagnose hyperaldosteronism, but there are potential fetal risks and no normative data. If baseline and suppression testing are equivocal, or radiological scanning does not suggest unilateral disease, patients may be treated medically until delivery to allow more definitive investigations. Spironolactone, the usual nonpregnant therapy, is contraindicated in pregnancy as it crosses the placenta and is a potent antiandrogenic which can cause ambiguous genitalia in a male fetus. There is no published experience with the use during pregnancy of eplerenone, the new aldosterone receptor antagonist. Surgical therapy may be delayed until postpartum if hypertension can be controlled with agents safe in pregnancy, such as amiloride, methyldopa, labetalol, and calcium channel blockers. Potassium supplementation may be required, but as noted above, the hypokalemia may ameliorate in pregnancy because of the antikaliuretic effect of progesterone. Both hypertension and hypokalemia may exacerbate postpartum due to removal of the progesterone effect (Nursan et al., 2009).

5. Pheochromocytoma

Pheochromocytoma is a rare cause of hypertension during pregnancy, with clinical features similar to those in the general population (Keely, 1998). The prevalence is estimated at 1 in

54000 pregnancies (Botchan et al, 1995). As the uterus enlarges and an actively moving fetus compresses the neoplasm, maternal complications such as severe hypertension, hemorrhage into the neoplasm, hemodynamic collapse, myocardial infarction, cardiac arrhythmias, congestive heart failure, and cerebral hemorrhage may occur. Extra-adrenal tumours which occur in 10%, such as in the organ of Zuckerkandl at the aortic bifurcation, are particularly prone to hypertensive episodes with changes in position, uterine contractions, fetal movement, and Valsalva maneuvers. Unrecognized pheochromocytoma is associated with a maternal mortality rate of 50% at induction of anesthesia or during labor (Lau et al., 1996). There is a minimal placental transfer of catecholamines likely due to high placental concentrations of catechol-O-methyltransferase and monoamine oxidase. Adverse fetal effects such hypoxia are a result of catecholamine-induced uteroplacental vasoconstriction and placental insufficiency, and of maternal hypertension, hypotension, or vascular collapse (Saarikoski, 1974).

5.1 Diagnosis

Diagnosis of pheochromocytoma requires a high index of suspicion. Preconception screening of families known to have MEN 2 with RET proto-oncogene is essential. The diagnosis should be considered in pregnant women with severe or paroxysmal hypertension, particularly in the first half of pregnancy or in association with orthostatic hypotension or episodic symptoms of pallor, anxiety, headaches, palpitations, chest pain, or diaphoresis. Symptoms may occur or worsen during pregnancy because of the increased vascularity of the tumour and mechanical factors such as pressure from the expanding uterus or fetal movement (Harper et al, 1989). As in nonpregnant women, the diagnosis is usually based upon the results of 24-hour urinary fractionated metanephrines and catecholamines and plasma fractionated metanephrines. If possible, methyldopa and labetalol should be discontinued prior to the investigation as these agents may interfere with the quantification of the catecholamines. MRI is the imaging test of choice in the pregnant women. Stimulation test and ¹²³I-MIBG scintigraphy are not considered safe for pregnant women.

5.2 Treatment

Medical therapy should be initiated with alpha adrenergic blockade (usually phenoxybenzamine) (Stenström & Swolin, 1985).

It is started at a dose of 10 mg twice daily, with titration until the hypertension is controlled. Placental transfer of phenoxybenzamine occurs, but is generally safe (Santeiro et al., 1996). Beta blockade is reserved for treating maternal tachycardia or arrhythmias which persist after full alpha blockade and volume repletion.

Beta blockers may be associated with fetal bradycardia and with intrauterine growth retardation, when used early in pregnancy (Chatterjee & Parekh, 1985). All of these potential fetal risks are small compared to the risk of fetal wastage from unblocked high maternal levels of catecholamines. Hypertensive emergencies should be treated with phentolamine or nitroprusside, although the latter should be limited because of fetal cyanide toxicity.

The timing of surgical excision of the neoplasm is controversial. In the first half of pregnancy, surgical excision may proceed once adequate alpha-blockade is established, although there is a higher risk of miscarriage with first trimester surgery. In the early second trimester, abortion is less likely and the size of the uterus will not make excision difficult. If

the pheochromocytoma is not recognized until the second half of gestation, increasing uterine size makes surgical exploration difficult (Sarathi et al., 2010).

Successful laparoscopic excision of a pheochromocytoma in the second trimester of pregnancy has been described (Finkensted et al, 1999).

Other options include combined cesarean delivery and tumour resection or delivery followed by tumour resection at a later date. Delivery is generally delayed until the fetus reaches sufficient maturity to reduce postpartum morbidity, providing successful medical management exists. Although successful vaginal delivery has been reported, it has been associated with higher rates of maternal mortality than caesarean section (Schenker & Granat, 1982).

6. Congenital Adrenal Hyperplasia (CAH)

It occurs in a family of monogenic inherited enzymatic defects of adrenal steroid biosynthesis, with manifestations secondary to an accumulation of precursors proximal to the enzymatic deficiency. The most common form of CAH is 21-hydroxylase deficiency, seen in more than 90% of the CAH cases in pregnancy (Forest, 2004).

Classic, severe 21-hydroxylase deficiency is associated with ambiguous genitalia, and inadequate vaginal introitus, and progressive postnatal virilization including precocious adrenarche, advanced somatic development, central precocious puberty, menstrual irregularity, a reduced fertility rate, and possible salt wasting (White & Speiser, 2000).

The spontaneous abortion rate is twice that in the normal population, and congenital anomalies are more frequent. Conception requires adequate glucocorticoid therapy, which then continues at stable rates during gestation, except at labor and delivery. Nonclassical 21-hydroxylase deficiency patients present with pubertal and postpubertal hirsutism and menstrual irregularity, and may have improved fertility with glucocorticoid therapy (Krone et al., 2001).

ACTH stimulation testing to measure 17-OH progesterone demonstrates overlap between heterozygotes for CAH and the normal population. Ideally CYP21 genotyping should be performed. Virilization is not seen in the female fetus with non classical 21-hydroxylase deficiency, but occurs in a fetus with classic 21-hydroxylase unless fetal adrenal androgen production is adequately suppressed.

Dexamethasone most readily crosses the placenta as it is not bound to CBG and is not metabolized at a dose of 20 mcg/kg maternal body weight per day to a maximum of 1.5 mg daily in 3 divided doses beginning at recognition of pregnancy before the 9th week of gestation, though lower doses are recommended by some (Coleman MA, Honour, 2004). Maternal plasma and/or urinary estriol levels reflect fetal adrenal synthesis and are monitored to assess efficacy. Maternal cortisol and DHEA-S levels will represent maternal adrenal suppression.

As only 25% of female fetuses are affected in a family with CAH, it is important to discontinue therapy as soon as possible in the male fetus and unaffected female fetus.

Chorionic villus sampling at 9-11 weeks gestation may be used for gender determination and direct ADN analysis for the 21-hydroxylase gene CYP21.

Side effects of dexamethasone therapy are potentially significant, including excessive weight gain, severe striae with scarring, edema, irritability, gestational diabetes mellitus, hypertension, and gastrointestinal intolerance. In affected pregnancies, dexamethasone may

be lowered to 0.75 to 1 mg/day in the second half of pregnancy to decrease maternal side effects while avoiding fetal virilisation (Pang et al, 1990).

7. Conclusion

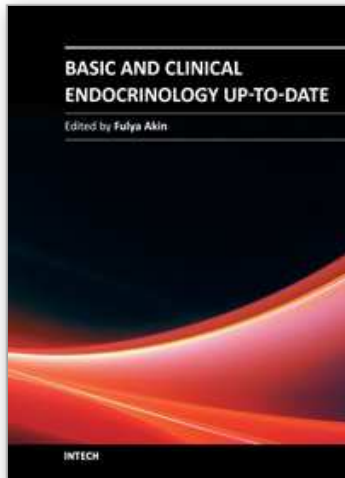
Pregnancy is a stage of life very important. It is important to recognize and to treat adrenal disease during pregnancy to avoid complications in the mother and fetus.

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Basic and Clinical Endocrinology Up-to-Date

Edited by Dr. Fulya Akin

ISBN 978-953-307-340-8

Hard cover, 350 pages

Publisher InTech

Published online 17, October, 2011

Published in print edition October, 2011

This book provides the most up-to-date information on the basic and clinical aspects of endocrinology. It offers both researchers and clinicians experts, gold-standard analysis of endocrine research and translation into the treatment of diseases such as insulinoma, endocrine disease in pregnancy and steroid induced osteoporosis. Investigates both the endocrine functions of the kidneys and how the kidney acts as a target for hormones from other organ systems. Presents a uniquely comprehensive look at all aspects of endocrine changes in pregnancy and cardiovascular effects of androgens.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Guadalupe Guijarro de Armas (2011). Adrenal Disease and Pregnancy, Basic and Clinical Endocrinology Up-to-Date, Dr. Fulya Akin (Ed.), ISBN: 978-953-307-340-8, InTech, Available from:

<http://www.intechopen.com/books/basic-and-clinical-endocrinology-up-to-date/adrenal-disease-and-pregnancy>

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