Cushing’s Syndrome in Pregnancy

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Abstract

Pregnancy is uncommon in patients with Cushing’s syndrome (CS), with fewer than 150 cases reported till date, as high serum levels of androgens and cortisol impair gonadotropin axis. There is a significant difference between the frequency of etiologies of CS in pregnant and in non-pregnant women. During pregnancy, the incidence of adrenal disorders (particularly adenomas) and CD is 60 and 33% respectively, in contrast to non-pregnant patients, where the incidence is 15% for adrenal adenoma and 70% for CD. This preponderance is probably related to the exclusive cortisol production from adrenal adenomas as compared to CD, which exhibits a mixed secretion of cortisol and androgens. CS is associated with significant maternal morbidity and mortality in approximately 70% of cases. The most common complications in pregnancy are hypertension and diabetes or impaired glucose tolerance. The clinical features of pregnant and non-pregnant women with CS are identical exhibiting weight gain, hypertension, bruising, and hirsutism. Unfortunately, CS is often not detected until 12-26 weeks of gestation, partially because changes in physical appearance are ascribed to pregnancy rather than CS. A combination of urinary free cortisol (UFC) assessment and measurement of midnight salivary cortisol is recommended for screening of CS in pregnancy. In patients with confirmed CS, a low plasma ACTH level should prompt imaging of the adrenals. Surgery is the treatment of choice for CS in pregnancy, except perhaps late in the third trimester, with medical treatment being a second choice.

INTRODUCTION

Pregnancy is uncommon in patients with Cushing’s syndrome (CS), with fewer than 150 cases reported till date, as high serum levels of androgens and cortisol impair gonadotropin axis [1,2]. However, because CS results in increased fetal and maternal complications, its early diagnosis and treatment are essential.

Hypothalamic Pituitary axis (HPA) during pregnancy

Gestation dramatically affects the maternal HPA axis. Increasing placental secretion of oestrogen stimulates the production of corticosteroid binding globulin (CBG) by the liver, thus stimulating cortisol production (serum, salivary and urinary) and thus increasing circulating levels of bound cortisol [3]. Total and free plasma cortisol concentrations rise in parallel across gestation, with plasma cortisol reported to be 2- to 3-fold higher in comparison with the non-pregnant controls. The increase in plasma cortisol occurs as early as the 11th week of gestation [4], reaching a peak between the first and second trimesters, and a plateau in the third trimester [5]. The hepatic production of CBG remains elevated until at least the 12th postpartum day [3]. The circadian rhythm of cortisol is preserved but may be partly blunted [3,6].

CRH and adrenocorticotropin (ACTH) plasma levels increase exponentially in the first trimester of gestation as a result of their placental production. The corticotropin-releasing hormone (CRH) is one of the most important modulators of the HPA axis; it is not only produced in the hypothalamus but also in theca cells, stromal cells and in the cells of the ovarian corpora lutea [3]. In addition, the epithelial cells of the endometrium encompass CRH and have been shown to have specific CRH receptors [7,8].

Pregnancy with Cushing’s syndrome (CS)

CS is rarely associated with pregnancy, probably because hypogonadotropic hypogonadism secondary to cortisol and androgens excess prevents normal follicular development and ovulation [2,3].

The first description of CS occurring in pregnancy was reported by Hunt and Mc Conahey in 1953 [9]. The mean gestational age at diagnosis is approximately 18 weeks [3].

There is a significant difference between the frequency of etiologies of CS in pregnant and in non-pregnant women. During pregnancy, the incidence of adrenal disorders (particularly adenomas) and CD is 60 and 33% respectively, in contrast to non-pregnant patients, where the incidence is 15% for adrenal adenoma and 70% for CD [3]. This preponderance is probably related to the exclusive cortisol production from adrenal adenomas as compared to CD, which exhibits a mixed secretion of cortisol and androgens [10].

Muralak et al, in 1998 [11] reported that benign adrenal adenoma was the commonest cause of CS in pregnant women, in contrast to non-pregnant women where pituitary-dependent...
hyperplasia is the most common cause of CS. This may be attributed to the fact that patients with an adrenal adenoma are most likely to be purely Cortisol-producing, thus their ovulatory function remains unaffected.

Lindsay et al. [3], upon reviewing pregnancies in 122 women with CS, described the following etiologies: CD (n =40); adrenal adenoma (n =56); adrenal carcinoma (n =12); ectopic ACTH secretion (EAS) (n =4); Carney’s complex (n =1); and ACTH-independent hyperplasia (n =4), possibly resulting from aberrant receptor stimulation.

A case of pregnancy with Cushing’s syndrome was reported by our institute in 2015 wherein a 30 yr old multigravida at 27 wks of gestation got admitted in the department of obstetrics and gynaecology, Era’s Lucknow medical college and hospital Lucknow. Decision to terminate the pregnancy was taken keeping in mind the patient’s condition. Post delivery CECT abdominal scan revealed adrenal adenoma, adrenelectomy was done and histopathology confirmed benign adenoma [12].

In another case reported in 2011, Cushing’s syndrome secondary to adrenal adenoma in which the diagnosis was made in the 22nd week of pregnancy. Due to the advanced gestational status and mild symptoms of hypercortisolism, only symptomatic treatment was introduced. The patient was under continuous obstetric and endocrinological care. At 35 weeks of gestation, the pregnancy was terminated by emergency caesarean section because of premature detachment of the placenta. A male infant weighing 2,450 g was delivered; neither adrenal insufficiency in the child nor hypercortisolemia complications in the mother was observed [13].

Maternal and fetal morbidity and mortality

CS is associated with significant maternal morbidity and mortality in approximately 70% of cases. The most common complications in pregnancy are hypertension (68%) and diabetes or impaired glucose tolerance (25%) and amongst fetus prematurity (43%) is the most common complication [3].

SCREENING AND DIAGNOSIS

Clinical features

The clinical features of pregnant and non-pregnant women with CS are identical exhibiting weight gain, hypertension, bruising, and hirsutism. Unfortunately, CS is often not detected until 12-26 weeks of gestation, partially because changes in physical appearance are ascribed to pregnancy rather than CS [3]. On the other hand, some of the manifestations of CS may be attributed to complications of pregnancy (gestational diabetes, preeclampsia, etc.), thus contributing to delay in the diagnosis of CS [1-3].

Screening test

A combination of urinary free cortisol (UFC) assessment and measurement of midnight salivary cortisol is recommended for screening of CS in pregnancy.

Diagnosis

The main tools for the differential diagnosis are the determination of plasma ACTH levels, non-invasive dynamic tests (CRH or desmopressin stimulation tests and high-dose dexamethasone suppression test (HD-DST), bilateral inferior petrosal sinus sampling (BIPSS), and imaging studies [14]. The measurement of plasma ACTH is the first step to be performed in order to determine the etiology of CS [14]. Hypercortisolism, regardless of the cause, inhibits ACTH secretion by normal corticotrophs. In non-pregnant women with CS, ACTH levels are typically reduced (< 10 pg/mL) in patients with autonomous adrenal disorders and inappropriately normal or increased in those with tumoral ACTH production (Cushing’s disease or EAS) [14].

In summary, in patients with confirmed CS, a low plasma ACTH level should prompt imaging of the adrenals. However, in cases with borderline or elevated ACTH, a combination of the 8-mg DST and CRH (or desmopressin) stimulation testing is suggested to establish the presence of, and distinguish between, the ACTH-dependent forms. BIPSS (bilateral inferior petrosal sinus sampling) may be necessary in patients with discordant biochemical or imaging findings [3].

TREATMENT

Approximately 150 cases of pregnancy and endogenous CS have been reported in the literature. Of those, treatment was performed in a subset of patients, but many cases, especially when discovered late in pregnancy, were managed conservatively by controlling co morbidities, such as hypertension and diabetes mellitus. Similar to non-pregnant women, surgery is usually the first treatment option in pregnant CS patients [3,15,16]. Adrenalectomy for patients with adrenal tumors seems to be beneficial and the birth rate after surgery is approximately 87% [3].

Medical therapy, which was generally initiated during the second or third trimesters, is a second treatment option. Of these, treatment with steroidogenesis inhibitors, particularly with metyrapone, is the option used most often. There are no adverse effects on maternal hepatic function or fetal development in the small number of cases reported till date [3]. However, there is one report of fetal hypoadrenalism after metyrapone [17]. Moreover, this drug may exacerbate hypertension and favour progression to preeclampsia, which may limit its use [8]. Ketoconazole has been used successfully in three pregnancies without adverse events [18-20].

Cyproheptadine is not recommended due to lack of efficacy [21]. Aminoglutethimide and mitotane are contraindicated [3]; the former can induce fetal masculinisation [22] whereas the latter has teratogenic effects [23].

CONCLUSION

Surgery is the treatment of choice for CS in pregnancy, except perhaps late in the third trimester, with medical treatment being a second choice. There does not seem to be a rationale for supportive treatment alone [3].

REFERENCES


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