CUSHING'S DISEASE IN PREGNANCY

by

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Summary

A case of Cushing's disease in 28 Y female during pregnancy is reported. Diagnostic studies suggested bilateral adrenal hyperplasia. She had total right and subtotal left adrenalectomy at 28 weeks of gestation. She spontaneously delivered a premature normal female baby (1.5 Kg) at gestation of 35 weeks.

Introduction

Pregnancy following successful treatment of Cushing's syndrome is not uncommon but successful pregnancy in patients with active disease is rare (Cope and Raker, 1955). Till recently only 23 such cases were reported. Of them 5 had term or near term delivery, while others had abortion prematurity or still birth. We report a patient of pregnancy with Cushing's disease due to bilateral adrenal hyperplasia who underwent bilateral adrenalectomy in pregnancy and delivered at 35 gestation weeks.

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CASE REPORT

P.K. 28 years 4th gravida was seen with history of fullness of face, recurrent boils and purple striae on abdomen, axillae and buttocks for 18 months and 10 months amenorrhoea. She also had oliguria, oedema feet, frontal headache, acne, mild facial hirsutism, orthopnoea, palpitation and generalised obesity for about 18 months.

She had menarche at age of 13. Menses were irregular for the initial 2 years but were regular thereafter until her first successful pregnancy, 9 years ago. Her 2nd and 3rd pregnancies resulted in normal deliveries, the last one being 2½ years ago. She then had oligo-menorrhoea for 1½ years, followed by 10 months amenorrhoea.

Physical Examination

Physical examination revealed a obese female, weight 66 kg against height of 156 cms. She had typical features of Cushing's disease including the characteristic facies (Fig. 1). supraclavicular and cervical fat pads (buffalo hump) facial acne, hirsutism, extensive purple striae over abdomen, axillae, medial aspects of thighs and gluteal regions, pelvic girdle myopathy, acchymoses and occasional petechiae. She had multiple boils. Temperature 37°C, pulse 98/min regular, resp. 22/min, BP 160/110 mm Hg and mild pedal edema, visual fields and occular fundii were normal. Examination of heart, lungs and abdomen did not reveal any abnormality. The height of the uterus was 26 weeks and normal fetal heart sounds were audible in ROA position.

Investigations

Hb 12.8 gms/dl, PCV 39.3%, WBC-7, 100/cmm with P-70%, L-26%, M-1% and E-3%. Serum electrolytes, Na 140 meq/L, K-4.1 meq/L, HCO3-18 meq/L, Blood sugar fasting; 92 mg/dl, and 2 hrs. postprandial-136 mg/dl. Blood urea, serum creatinine, serum proteins, Ca, PO4, alkaline phosphatase and SGOT, SGPT were within the respective range (normal). ECG and chest roentgenogram were normal. The size of the pituitary fossa was normal. Pus swab from boils grew Staph pyogenes, sensitive to erythromycine and pseudomonas aeruginosa, sensitive to gentamycine and polymyxin. Her basal cortisol at 8 AM was 1324.8 nmol/L and at 4 PM was 1076.4 nmol/L. Following overnight 1 mg dexamethasone serum cortisol remained at 1366.2 nmol/L. With 2 mg and 8 mg dexamethasone suppression, the serum cortisol values were 1260 nmol/L and 320 nmol/L respectively. Following 1 mg synechane IM, serum cortisol was increased to 2898 nmol/L at 4 hrs. and 4140 nmol/L at 7 hrs. from the prestimulatory levels of 1320 nmol/L. Twenty-four hour urinary excretion of 17 KS was 20.2 mg and 17 KGS 25.6 mg and they were partially suppressed with dexamethasone.

Course and Management

After treating the infection and hypertension with adequate antibiotics and thiazide and methyle Dopa she was operated at 28 weeks of gestation. Total right and left subtotal (9/10) adrenalectomy was done through a transabdominal approach. The left adrenal weighed 7 gm and the right 7.5 gms. Histology: bilateral adrenal hyperplasia (Fig. 2 inset). The cortical width exceeded 3 mm. The zona fasciculata cells were typically enlarged, forming club shaped cords. Nodules projecting into the medulla and microscopic nodules in zona fasciculata were seen. Ultrastructurally, EM showed distinct differences in left and right adrenal which histologically under light microscope showed no differences. The cortical cells of left adrenal showed abundant (Fig. II, S) electron dense vacuolated granules of 1200-1500 um. The right adrenal was devoid of such granules. The left adrenal cells also showed an inactive lamellae of the REF (Fig. II, R) and fewer lipid droplets. Supplemental hydrocortisone was given during the preoperative and post-operative periods in doses adequate to prevent adrenal crisis (Williams 1981). The post-operative course was uncomplicated except that of recurrent upper abdominal pain, which responded to analgesics. Prednisolone was subsequently reduced to 10 mgs AM, 5 mg PM. She went into spontaneous premature labour 6 weeks following adrenal surgery. After an uneventful labour of 10 hours during which she received a total of 300 mgs hydrocortisone I.V., a normal female child weighing 1500 gms, APGAR 4/10 was delivered. In the immediate postpartum period, she received 100 mg hydrocortisone every 8 hours I.V. and the dose was tapered thereafter. The baby was looked after in premature nursery for about a month. At discharge she weighed 2.8 kg. She did not have any congenital malformations. At the time of discharge she was receiving Prednisone 5 mg AM, 2.5 mg PM. There was no peripartum haemorrhage and the postpartum period was uneventful.

Since her delivery the patient had been well. Her blood pressure remained normal and weight 120 lbs. The clinical markers of Cushing's disease have gradually regressed.

Discussion

Early in the development of Cushing's disease, amenorrhoea is noted in 30% and, an additional 20% have oligomennorrhoea (Cope and Raker, 1955; Saffer, 1961). However, as the disease progresses, the incidence of amennorrhoea increase. In only a minerity, normal menses continue throughout the course of the illness (Safer, 1961). The amonnorrhoea in Cushing's disease is probably related to secondory alterations in ovarian structure and function (Iannaccene, 1959). Cope and Raker, 1955) reported atrophy of the ovaries in 10 patients with Cushing's syndrome. Iannaccene *et al* (1959) examined the ovaries of 6 patients with Cushing's syndrome at 30-37 years of age and found reduction in all phases of follicular activity and the number of primordial follicles (Iannaccene, 1959). These gonadal abnormalities are most likely due to increased levels of circulating adrenocritical steroids which depress the

basal as well as stimulated gonadotropin secretion (White *et al*, 1959).

The prognosis of pregnancy during well established hyperadrenocarticism is generally poor. Of the 21 cases reviewed by Grimes *et al* there was a total of 26 deliveries (Grimes *et al*, 1973). The approximate incidence of abortion, prematurity, still birth and viable or term deliveries are 19%, 23%, 15%, 42% respectively. Untreated cases with adrenocortical adenoma had very poor prognosis.

Because of the documented changes in glucocorticoid and mineralo corticoid metabolism during pregnancy, the diagnosis of Cushing's disease during pregnancy is somewhat difficult. Circulating cortisol rises progressively during pregnancy with peak levels during the third trimester (Pama and Cruz Krohn, 1966; Schteingart, 1967). The cortisol levels in normal pregnancy are sometimes as high as in some cases of Cushing's disease. However, the symptoms and signs of the disease are rarely seen and levels return to normal following delivery. Both 2 and 8 mg dexamethasone suppression have been used in the diagnosis of Cushing's disease. In this case, 8 mg dexamothasone suppression led to the diagnosis. The documentation with florid Cushing's disease warranted the adrenal exploration. There appears to be a consensus that early diagnosis of Cushing's disease in pregnancy is extremely important. Once the diagnosis is confirmed, appropriate treatment should be instituted (Brawney *et al*, 1960).

Our patient became pregnant after the disease had been manifest for more than a year. The disease was of moderate severity. The explanation for the patient's fertility is not apparent. Maternal hypertension is considered to be the chief threat for fetal loss (Grimes *et al*, 1973. In our patient hypertension was controlled by use of thiazides and methyl Dopa. Adrenal cortical steroids have produced congenital anomalies in experimental animals like cleft palate in offspring (44%) (Bongiovanni, 1960). In the humans only 2 instances have been recorded (Bongiovanni, 1960; Yackel *et al*, 1966). The actual management of labour is no different from a case of Addison's disease and stress and we followed a similar regime (Willioms, 1981).

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