

## Cushing's syndrome in pregnancy: Effect of associated diabetes on fetal and neonatal complications

JEROME H. CHECK, M.D.

JOSÉ F. CARO, M.D.

BENJAMIN KENDALL, M.D.

LEON A. PERIS, M.D.

BURTON L. WELLENBACH, M.D.

*Department of Obstetrics and Gynecology, Division of Gynecologic Endocrinology, and Department of Medicine, Division of Endocrinology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania*

THE COMBINATION of Cushing's syndrome and pregnancy is rare. Grimes, Fayez, and Miller<sup>1</sup> reported case No. 22 in 1973 and reviewed the previous 21 cases. They concluded that the prognosis for pregnancy during well-established hyperadrenocorticism is poor and were recommending unilateral surgical extirpation for adrenal adenomas and bilateral adrenalectomy for Cushing's disease.

In 21 pregnancies in patients with untreated Cushing's syndrome five had premature births and four had stillbirths. In two of the pregnancies complicated by stillbirths glucose tolerance tests were abnormal, whereas no mention of glucose levels was made in the other two cases. Of the five premature births, two had abnormal glucose tolerances, one had normal 2 hour postprandial sugar, and no mention of glucose studies was made in the other two cases. Since stillbirths and prematurity are two complications of diabetes in pregnancy it is possible that the high fetal risk in Cushing's syndrome is related to the high incidence of associated abnormal glucose levels rather than to the glucocorticoids directly. This would be supported by the absence of any significant increase of these complications in pregnant women treated with glucocorticoids.<sup>2</sup>

We present a case of a woman with Cushing's disease whose first pregnancy ended in a stillbirth and her second in a normal viable birth. The patient was diabetic; her sugars were uncontrolled in the first pregnancy and were meticulously controlled during the second one in the last trimester.

The patient was 23 years of age and was referred because of uncontrolled diabetes during her sixth month of gestation. She gave a history of having a stillbirth at 30 weeks' gestation 2 years previously when her blood sugars were similarly out of control.

Physical examination revealed a rounded, moonlike, plethoric face. She had significant trunkal obesity with thin extremities secondary to muscle atrophy. Body hair was increased in a male pattern, especially the chin, with a male type

of escutcheon. Wide red striae were present on the abdomen. The remainder of the examination was normal. Pelvic examination revealed a 6 month size uterus.

The 8 A.M. serum cortisol was 33.4  $\mu\text{g}/100\text{ ml}$ ; at 4 P.M., 30.5; at 9 P.M., 24. 17-Ketosteroids were 11 mg/gram of urinary creatinine; the 17-hydroxycorticosteroids were 9.7 mg/gram of urinary creatinine (normal, less than 6.5). Urinary free cortisol was 1,556  $\mu\text{g}/\text{gram}$  of urinary creatinine (normal, under 90). The patient failed to suppress with the standard 2 mg dexamethasone suppression test but not with 8 mg. This helped establish the diagnosis of Cushing's disease (bilateral adrenal hyperplasia).

The patient was admitted when 6½ months pregnant for close observation of her blood glucose levels. Her fasting glucose levels were kept below 95 and 2 hour postprandial levels below 160.

The patient went into spontaneous labor on May 24, 1976, and was delivered of a term male neonate. Four months postpartum she was treated with pituitary irradiation. Within 6 months following therapy she went into total remission.

The stillbirth of the first pregnancy may certainly have resulted from the uncontrolled diabetes rather than the probable Cushing's disease (glucocorticoids were not measured but she had the clinical appearance of hypercortisolism). She had a successful term second delivery when the diabetes was meticulously controlled.

In the stillbirths and premature births review by Grimes, Fayez, and Miller<sup>1</sup> at least four of nine had elevated glucose levels. This, coupled with the fact that patients treated with steroids during pregnancy do not seem to have these same complications,<sup>2</sup> has to make one suspicious that it is the abnormal glucose metabolism rather than the hypercortisolism responsible for the increased fetal risks.

The nonpregnant patient with bilateral adrenal hyperplasia (Cushing's disease) would more likely be treated with pituitary irradiation or transphenoidal hypophysectomy, rather than bilateral adrenalectomy, since the latter will result in permanent adrenal insufficiency and may allow the development of a rapidly expanding basophilic pituitary adenoma (Nelson's syndrome).

We certainly do not have sufficient evidence to make a definite conclusion that the fetal and neonatal complications of Cushing's syndrome are related to associated diabetes. However, in view of the risk to the mother with bilateral adrenalectomy in Cushing's disease, we do not feel that there is sufficient evidence to warrant bilateral surgical adrenal extirpation for the purpose of increasing fetal salvage when meticulous control of the plasma glucose may be all that is necessary to prevent fetal complications.

### REFERENCES

1. Grimes, E. M., Fayez, J. A., and Miller, G. L.: Cushing's syndrome and pregnancy, *Obstet. Gynecol.* **42**:550, 1973.
2. Bongiovanni, A. M., and McPadden, A. J.: Steroids during pregnancy and possible fetal consequences, *Fertil. Steril* **11**:181, 1960.

Reprint requests: Jerome H. Check, M.D., 1015 Chestnut St., Suite 1020, Philadelphia, Pennsylvania 19107.