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INVITED COMMENTARY

Pheochromocytoma complicating pregnancy

Lewis Landsberg

Department of Medicine, Northwestern University Medical School, Northwestern Memorial Hospital, Chicago, IL, USA

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Lewis Landsberg, Department of Medicine, Northwestern University Medical School, Northwestern Memorial Hospital, Wesley Pavilion 296, 250 E Superior Street, Chicago, IL 60611, USA

Pheochromocytoma occurring during pregnancy is potentially life-threatening for mother and fetus. Undiagnosed, the mortality for mother and offspring may approach 50% (1). Prepartum diagnosis and treatment markedly improves the prognosis for the mother but fetal morbidity and mortality are still high despite treatment. Delay in diagnosis by confusion with toxemia remains a problem even today. Pheochromocytoma usually can be diagnosed during pregnancy by the appropriate analysis of a 24-h urine sample for catecholamines and catecholamine metabolites, as was the case in the report by Dahia and colleagues in this issue of *European Journal of Endocrinology* (2). Once the diagnosis is established, treatment with adrenergic antagonists is clearly indicated. Spontaneous vaginal delivery in untreated patients is frequently disastrous for mother and infant. Provocation of a severe pressor crisis under these circumstances, with attendant placental ischemia and fetal hypoxia, are likely causes of the untoward outcome. Magnetic resonance imaging may be useful in localizing the tumor, as was the case here. In mid- or early pregnancy, surgical excision after a preoperative course of adrenergic blockade is usually recommended; in the third trimester, if the manifestations can be controlled with adrenergic blocking agents, and if the fetus is deemed to be of sufficient size, cesarean section can be performed with delivery of the infant followed by resection of the tumor, as in the present study by Dahia et al. (2). Although the safety of phenoxybenzamine during pregnancy is not firmly established, this agent would appear to be the drug of choice for inducing alpha-adrenergic blockade (3, 4). The long-acting, stable, non-competitive blockade induced by phenoxybenzamine is preferable for preoperative preparation as compared with shorter acting agents such as prazosin, which was used in the patient reported here. Limited use of phenoxybenzamine during pregnancy has not been associated with untoward effects. Propranolol is the beta-adrenergic blocking agent that has been used most during pregnancy; intrauterine growth retardation may be associated, but the risk is small compared with the clinical imperative required to block the high levels of circulating catecholamines in the mother. Antepartum diagnosis and treatment of pheochromocytoma substantially reduces or eliminates maternal mortality and improves fetal survival, but fetal wastage still remains at approximately 15% (3).

The present study by Dahia et al. (2) documents a considerable difference between catecholamine levels in the maternal circulation and cord blood, confirming previous reports of a markedly lower level of catecholamines in cord, as compared with maternal venous plasma (4, 5). As the authors point out, this suggests extensive metabolism of catecholamines by the placenta, which is known to have high levels of catechol-O-methyl-transferase and monoamine oxidase, the major catecholamine metabolizing enzymes. Studies in patients without pheochromocytoma, in which umbilical arterial and venous contribution to cord blood were analyzed separately, support the same conclusion; in normal controls, the umbilical arterial norepinephrine concentration is almost six times that of the umbilical vein (6). The implication of these observations is that catecholamines in cord blood originate largely from the fetus and that the umbilical artery, in particular, can be used to assess activation of noradrenergic activity within the fetus (6). Both hypoxia (7) and hyperinsulinemia in infants of diabetic mothers (6) are associated with increased cord norepinephrine levels, consistent with activation of noradrenergic activity within the fetus. The origin of this noradrenaline might be from the developing sympathetic nervous system or from extra-adrenal chromaffin cells, which are prominent in fetal and neonatal humans. The very low levels of epinephrine in this and other reports are consistent with the delayed development of the adrenal medulla, which in humans matures over the first few years of life.

Placental clearance of catecholamines implies, as well, that the fetal wastage associated with maternal pheochromocytoma is not the direct consequence of maternal catecholamines acting in the fetus.

Catecholamine-induced placental ischemia with attendant effects on fetal oxygenization and nutrition may be key elements in the adverse in utero effects on the fetus. Prompt and effective treatment with adrenergic blocking agents are, therefore, essential. Induction of stable adrenergic blockade, which may take as long as 2 weeks, should be followed by surgical removal of the tumor.

The present study by Dahia et al. (2) raises another area of potential interest. As blood from both the umbilical artery and the umbilical vein is easily accessible, physiological studies of hormonal influences both within the fetus and on subsequent development (8, 9) are entirely feasible and represent fertile areas of investigation. Nutritional factors in the mother, for example, may influence the fetal endocrine system, with potential long-range physiological and psychological effects on the offspring (8–10).

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