Adrenocortical failure in diabetic pregnancy

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Summary
A Caucasian class F diabetic developed features suggestive of adrenocortical insufficiency during the second half of pregnancy. Serial biochemical and hormonal studies confirmed a diagnosis of progressive primary adrenal failure. Replacement therapy was introduced at 31 weeks' gestation and the pregnancy ended successfully 6 weeks later. Addison's disease is another autoimmune disorder that may occur in association with diabetic pregnancy.

Introduction
The pregnant, juvenile onset, diabetic with long-standing disease may have complications secondary to diabetic microangiopathy or even associated diseases, such as Graves' disease or hypothyroidism (Soler and Nicholson, 1979). Insulin-dependent diabetics who are HLA B8 and Dw3 positive have an increased incidence of autoimmune disorders of the thyroid and adrenal glands (Christy, Deckert and Nerup, 1977). Moreover, premature ovarian failure affects about 25% of women with Addison's disease (Irvine and Barnes, 1975), decreasing the likelihood of pregnancy amongst this group of patients. The following case report documents adrenocortical failure of autoimmune aetiology complicating the course of diabetic pregnancy.

Case report
A 28-year-old female had had insulin-dependent diabetes since 4 years of age. In the past she had been admitted to the hospital at least 5 times in ketoacidosis, the last episode having occurred 4 years ago. She was known to have background diabetic retinopathy and nephropathy and was advised against having children. However, she presented when already 11 weeks pregnant. She was feeling well and had no complaints apart from occasional morning sickness. Her weight was 63.5 kg and her BP was 152/90 mmHg. Her serum electrolytes were normal (Table 1). She had proteinuria (800 mg/24 hr) and normal thyroid function tests with a free thyroxine index of 2.3 (normal 1.2–4.2) and a TSH of 5.0 μi.u./ml (normal <10 μi.u./ml).

Early in pregnancy this patient was receiving 46 U of insulin as a combination of regular insulin and isophane insulin injected twice daily, and her diabetic control was fair, as shown by a glycosylated haemoglobin (HbA1) of 11% (normal 5.5–8.5%). The total daily insulin dose increased progressively

<table>
<thead>
<tr>
<th>Gestation (weeks)</th>
<th>Weight (kg)</th>
<th>Daily insulin dose (units)</th>
<th>BP (mmHg)</th>
<th>Na (mmol/l)</th>
<th>K (mmol/l)</th>
<th>Urea (mmol/l)</th>
<th>Cr Cl (ml/s)</th>
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</thead>
<tbody>
<tr>
<td>11</td>
<td>63.5</td>
<td>46</td>
<td>152/90</td>
<td>137</td>
<td>4.5</td>
<td>3.5</td>
<td>1.22</td>
</tr>
<tr>
<td>24</td>
<td>68.1</td>
<td>75</td>
<td>150/70</td>
<td>135</td>
<td>5.1</td>
<td>3.2</td>
<td>1.69</td>
</tr>
<tr>
<td>27</td>
<td>70.3</td>
<td>100</td>
<td>150/80</td>
<td>136</td>
<td>5.4</td>
<td>3.2</td>
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<td>29</td>
<td>71.0</td>
<td>114</td>
<td>118/68</td>
<td>132</td>
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<td>3.9</td>
<td>1.67</td>
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<tr>
<td>31</td>
<td>72.0</td>
<td>114</td>
<td>130/70</td>
<td>134</td>
<td>5.3</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>33*</td>
<td>73.6</td>
<td>124</td>
<td>140/90</td>
<td>140</td>
<td>4.6</td>
<td>3.2</td>
<td>1.69</td>
</tr>
<tr>
<td>35*</td>
<td>72.6</td>
<td>124</td>
<td>130/80</td>
<td>139</td>
<td>4.6</td>
<td>3.2</td>
<td>1.69</td>
</tr>
<tr>
<td>36*</td>
<td>72.6</td>
<td>124</td>
<td>140/82</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>one week postpartum*</td>
<td>56</td>
<td></td>
<td>120/70</td>
<td>141</td>
<td>4.7</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>

*The asterisks indicate that at these times the patient was receiving therapy for adrenal failure.
†, supine; B, standing.

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to 75 u. at 24 weeks and up to 114 u. at 29 weeks' gestation. From 24 weeks onwards, the patient reported feeling increasingly tired and nauseated in spite of good control of diabetes, with HbA1 levels consistently below 7.5%. Her face also became pigmented. There was a mild fall in the BP and the serum electrolytes were clearly abnormal by 29 weeks' gestation (Table 1). Basal measurements of serum cortisol and aldosterone and of plasma renin and adrenocorticotrophic hormone (ACTH) were carried out in the morning, in the supine position, after an overnight rest period and the results are shown in Table 2. On 2 separate occasions 30 min following adrenal stimulation with i.v. synthetic ACTH (Cortrosyn, 0.25 mg), there was a negligible increment in serum cortisol and serum aldosterone (Table 2). The diagnosis of adrenocortical failure was made conclusively once the hormone measurements were available. Treatment with cortisone acetate and fludrocortisone (0.05 mg daily) was started at 31 weeks' gestation. The dose of cortisone was increased gradually to 40 mg daily and was accompanied by a 10-u. increment in the total daily insulin dosage.

Fetal growth and well-being were monitored closely in the third trimester and delivery was carried out at 37 weeks' gestation, when the lecithin/sphingomyelin (L/S) ratio was 6:0 and phosphatidylglycerol was detected in the amniotic fluid. Delivery by elective Caesarean section was uncomplicated. On the day of delivery the patient received hydrocortisone i.v. (100 mg/8 hr), isophane insulin injection 24 u. subcutaneously and an i.v. infusion of dextrose (10 g/hr). At birth, the female infant weighed 1.98 kg and the Apgar scores were 7 and 9, at one and 5 min respectively. The infant did not experience any neonatal problems.

In the postpartum period this patient's insulin requirements were 56 u. daily and she continued treatment with cortisol acetate (25 mg/daily) and fludrocortisone (0.1 mg daily). Six weeks after delivery, cortisol and fludrocortisone were stopped for 48 hr before repeating the measurements of plasma ACTH and renin and an adrenal stimulation test with synthetic ACTH (Table 2). The results of these tests confirmed that the patient still had adrenal failure. Adrenocortical antibodies and islet cell antibodies were also detected in the serum (Scripps Institute, La Jolla, California).

**Discussion**

The adrenocortical insufficiency recorded in this patient during pregnancy persisted after delivery and was due to autoimmune disease. The sense of well-being, the lack of severe hypoglycaemic episodes and the normal serum electrolytes suggested that adrenal function was well maintained during the first half of pregnancy. Addison's disease can be missed during pregnancy because the classical features of this condition include nausea, vomiting and pigmentation which are also common accompaniments of pregnancy. However, adrenocortical insufficiency is suspected, appropriate hormonal studies will lead to the correct diagnosis. If Addison's disease is left undiagnosed the pregnant woman's life is put in jeopardy, especially at the time of delivery, and fetal well-being is also impaired. Although adrenal antibodies cross from the maternal to the fetal circulation they do not appear to affect fetal adrenocortical function (Gamlen et al., 1977).

Partial or complete anterior pituitary infarction is a recognized complication of diabetic pregnancy, usually affecting women with microvascular disease (Dorfman, Dillaplain and Gambrell, 1979). In the present patient, the absence of suggestive symptoms of pituitary infarction and the high plasma ACTH level ruled out a diagnosis of hypo-adrenalism secondary to pituitary disease. Hyporeninaemic hypo-aldosteronism may occur in diabetics with renal disease (Cristlieb, 1976) but, in the present case, hypo-aldosteronism led to a secondary rise in the renin concentration, to a level above that usually recorded in the third trimester of pregnancy (Becker et al., 1978). Both ACTH and renin concentrations were still elevated after delivery, as would be expected in primary adrenal failure.

In normal women, the cortisol secretion rate may double during late pregnancy (Cope and Black,

<table>
<thead>
<tr>
<th>Table 2. Hormone studies during pregnancy and postpartum</th>
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<tbody>
<tr>
<td>Pregnancy (weeks)</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>29</td>
</tr>
<tr>
<td>31</td>
</tr>
<tr>
<td>Postpartum</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>Normal</td>
</tr>
</tbody>
</table>

*Increment following synthetic ACTH. **In non-pregnant women. ***In third trimester pregnant women.
1959). However, in individually reported cases with Addison’s disease during pregnancy the dose of cortisone has varied between 25 and 50 mg daily and only a small dose of fludrocortisone has been necessary (Cope, 1972). The need for the latter drug decreases further towards term because of mineralocorticoid production by the placenta (Barnes, 1974).

The increased insulin requirements of diabetic pregnancy are commonly attributed to high circulating concentrations of human placental lactogen and other hormones including oestrogen, progesterone and cortisol. In spite of this patient’s adrenocortical insufficiency, her insulin requirements increased normally and the introduction of replacement therapy led to only a small increase in the daily insulin requirement. These findings suggest that increased free cortisol plays only a minor role in the changed insulin requirements of diabetic women during pregnancy.

The low infant birth weight recorded in this case, following strict control of diabetes, corresponds with the weight expected among infants of women with Addison’s disease. On the other hand, from a review of 3 cases, Osler and Pedersen (1962) concluded that diabetic women with Addison’s disease had large infants secondary to poorly controlled diabetes.

The association between insulin-dependent diabetes and Addison’s disease is well established (Irvine and Barnes, 1975) and the 2 diseases may occasionally occur together during pregnancy. The presence of islet cell antibodies after 24 years of diabetes in the present patient fits in with an autoimmune polyendocrinopathy (Irvine, McCallum and Gray, 1977). Although it is rare for adrenocortical failure to present during the course of diabetic pregnancy, this diagnosis should be considered in the diabetic with suggestive symptoms or with a family history of autoimmune disease.

References


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