

# Case Study: Type 1 Diabetes With Subacute Presentation During Pregnancy

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## PRESENTATION

T.S. presented at age 17 with apparent gestational diabetes mellitus (GDM) in her first pregnancy. Her past medical history included allergic rhinitis and acne vulgaris; she had no history of polycystic ovarian syndrome, impaired glucose tolerance, or impaired fasting glucose. She also had no complaints of hirsutism, prior menstrual irregularity, or weight gain. Her family history was notable for diabetes in both parents. Her prepregnancy BMI was 26.2 kg/m<sup>2</sup>.

At diagnosis of pregnancy at ~ 5 weeks gestational age, a fingerstick glucose was 224 mg/dl; home testing at ~ 10 weeks revealed continued elevated glucose levels in the 200 mg/dl range, and the patient also had polyuria and polydipsia. She subsequently had a 50-g oral glucose tolerance test with a result of 262 mg/dl. She was diagnosed with GDM and started on nutritional therapy and glyburide once daily.

At the time of initial consultation with endocrinology, she was at 23 weeks gestational age. She had continued polyuria and polydipsia. Exam revealed a gravid young woman with stable vital signs. She had normal thyroid and cardiac exams and no acanthosis nigricans.

Because of her young age, relatively low BMI, and lack of stigmata of insulin resistance, labs were sent to look for evidence of autoimmune diabetes. Laboratory data included an A1C of 6.5%, C-peptide of 2.3 ng/ml (reference range

0.9–7.1 ng/ml), and GAD antibody of < 1.00 (reference range < 1.46).

Review of her glucose meter download showed poor control with persistent hyperglycemia and average blood glucose of 155 mg/dl. Because her diabetes was not adequately controlled with glyburide, it was discontinued at the first endocrinology visit, and she was started on an insulin regimen of glargine and aspart with carbohydrate counting for her mealtime doses.

The rest of the pregnancy was complicated by poor adherence, difficulty with carbohydrate counting, and continued hyperglycemia, with occasional hypoglycemia. Her regimen was adjusted several times. At the time of delivery at 39 and 3/7 weeks of pregnancy, however, she had not returned for follow-up in the prior 8 weeks, nor had she sent blood glucose data to the clinic. She delivered a healthy 10 lb, 3 oz infant. She had also developed pregnancy-induced hypertension.

At ~ 6 weeks postpartum, she presented to an internist to establish care. She had stopped insulin therapy but continued to have nocturia. At that visit, labs included a random glucose of 492 mg/dl, A1C of 11.7%, and C-peptide of 0.7 ng/ml. Insulin antibodies were not checked. She was diagnosed with type 1 diabetes and started back on intensive insulin therapy.

The patient returned for follow-up with endocrinology ~ 4 weeks later. On repeat labs, C-peptide was

0.4 ng/ml, islet cell IgG antibody was < 1:4, and GAD antibody was positive at 1.75. Insulin doses were increased to improve her glyce-mic control; however, adherence remained a problem. Although 2-week follow-up was scheduled, the patient did not keep this appointment and presented to the hospital with altered mentation in diabetic ketoacidosis within a month.

## QUESTIONS

1. What proportion of patients presenting with diabetes during gestation will subsequently be diagnosed with type 1 or type 2 diabetes?
2. What clinical features are suggestive of type 1 diabetes or latent autoimmune diabetes in adults (LADA)?
3. What antibodies should be tested when autoimmune diabetes is suspected?

## COMMENTARY

GDM, defined as carbohydrate intolerance that begins or is first recognized during pregnancy, affects ~ 7% of pregnancies annually, with a higher incidence in some ethnic groups.<sup>1</sup> Even normal pregnancy is a state of increased insulin resistance induced by weight gain and placental hormone secretion, including human placental lactogen and growth hormone variant. By the third trimester, insulin sensitivity is about 50% less.<sup>2</sup> In a normal pregnancy, insulin secretion increases by ~ 30% to compensate for this defect. Thus,

GDM results from a combination of increased resistance and lack of sufficient compensatory insulin increase, leading to relative insulin deficiency.

Some patients with GDM may still have relatively normal insulin resistance in the nonpregnant state. Other patients who are diagnosed with GDM may also have underlying impaired glucose tolerance that is exacerbated by pregnancy. More rarely, type 1 diabetes may be first detected in pregnancy, when the prodromal phase of the disease is present in the pregestational time period.<sup>3</sup> The physiological stressor of pregnancy may then unmask the disease.

Fewer than 1 in 10,000 women may become pregnant during the prodromal phase of type 1 diabetes.<sup>1</sup> More frequently, type 2 diabetes may be first detected in pregnancy when the pregnancy exacerbates hyperglycemia or as a result of patients receiving routine medical care while pregnant. Among patients with GDM in the United States, it has been estimated that 50% will develop overt diabetes within 10 years after delivery.<sup>2</sup> In Finland, where the 6-year risk for diabetes after GDM is estimated at 10%, 4.6% of patients developed type 1 diabetes after GDM, and 5.3% eventually developed type 2 diabetes.<sup>4</sup>

Among patients with a new diagnosis of diabetes, be it during gestation or not, several clinical features may suggest an underlying diagnosis of type 1 diabetes or LADA. LADA is considered by some to be a distinct disease state and by others to be on the continuum of type 1 diabetes, but a characteristic feature is antibody positivity; disease onset is often insidious. Features that may raise suspicion include age < 50 years; presentation with acute symptoms such as weight loss, polyuria, or polydipsia; personal history of autoimmune

disease; family history of autoimmune disease; and BMI < 25 kg/m<sup>2</sup>.

One study using these criteria found that, among patients with two or more of these features, 75% had LADA, whereas 24% had type 2 diabetes.<sup>5</sup> For patients meeting only one criterion, 98% did not have antibodies indicative of LADA. Despite a lower BMI being suggestive of an autoimmune process, most patients with LADA are overweight or obese. Similarly, a family history of type 2 diabetes did not predict against LADA.<sup>5</sup> However, testing for antibodies and clinical suspicion for an autoimmune process should be considered in patients with two or more of these clinical features.

Diabetes-associated antibodies include antibodies to GAD, islet cell antibodies, antibodies to the protein tyrosine-phosphatase-related protein 2 (IA2), and insulin antibodies.<sup>4,6</sup> These autoantibodies have been studied in relatives of patients with type 1 diabetes, and their presence, in the absence of apparent metabolic abnormalities, has a high predictive value for diabetes in those relatives. Patients can develop diabetes in the setting of one or more antibodies being positive, although some studies have correlated increased numbers of antibodies as well as higher titers of antibodies with increased risk for frank diabetes.<sup>5</sup> The insulin antibodies and IA2 are more likely to be positive in children with type 1 diabetes, whereas GAD antibodies are more frequently detected in adult patients. Among patients with diabetes who are not insulin-requiring at diagnosis, antibody positivity predicts requirement for insulin in 80% of cases.<sup>7</sup> Other autoimmune diseases are also increased in frequency in these patients. Although at this point there is no definite way to prevent diabetes in patients with positive

antibodies, animal and human studies are ongoing.

## CLINICAL PEARLS

GDM affects ~7% of pregnancies. When it is diagnosed, clinicians should keep in mind the possibility of a new diagnosis of type 1 or type 2 diabetes.

Clinical features can be used to assess risk of autoimmune diabetes in patients with a new diagnosis and to guide appropriate antibody testing.

Although a lower BMI may suggest LADA or type 1 diabetes, the majority of patients with LADA are overweight, so an elevated BMI should not exclude consideration of this diagnosis.

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