

# Case Study: Latent Autoimmune Diabetes in Adults and Pregnancy: Foretelling the Future

Julia P. Dunn, MD; Jennifer M. Perkins, MD; and Shubhada M. Jagasia, MD

## PRESENTATION

W.S. is a 25-year-old woman referred for newly diagnosed gestational diabetes mellitus (GDM) after having a 1-hour plasma glucose (PG) of 150 mg/dl during a 50-g glucose challenge test at 28 weeks' gestation. She denied any history of polyuria, polydipsia, polyphagia, or visual disturbances. During this pregnancy, she had gained only 5 lb by 31 weeks and denied any complications. Before the pregnancy, her baseline weight was 205 lb, and her BMI 33 kg/m<sup>2</sup>. Overall, she was feeling well and tolerating her pregnancy well.

Her medical history was significant for a single pregnancy 4 years ago that was not complicated by GDM. She delivered a healthy, full-term girl weighing 7 lb, 4 oz, by an uncomplicated spontaneous vaginal delivery (SVD). She denied any subsequent history of impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). She denied a family history of type 2 diabetes. However, her 4-year-old daughter had been diagnosed with type 1 diabetes. She denied any tobacco or alcohol use.

After being diagnosed with GDM, she received appropriate dietary counseling and was instructed in home blood glucose monitoring. Secondary to persistent fasting hyperglycemia, she was started on human insulin NPH, 5 units subcutaneously daily at bedtime. She continued to monitor fasting and 2-hour postprandial blood glucose values. Her GDM was followed closely, and her NPH insulin was titrated to 14 units at bedtime.

Because of ongoing postprandial hyperglycemia, insulin lispro was added for prandial coverage, in a dose of 1 unit/20 g of carbohydrate consumed. Her blood glucose control improved on intensive insulin therapy. Her hemoglobin A<sub>1c</sub> (A1C) was excellent at 5.5%. At term, she delivered a healthy boy of 8 lb, 8 oz, by uncomplicated SVD.

The patient was scheduled for a postpartum follow-up, including a 75-g oral glucose tolerance test (OGTT). She denied any symptoms of hyperglycemia, and sporadic blood glucose monitoring had revealed normal readings. She had lost a total of 17 lb since delivery and was close to her baseline weight at 207 lb. Her 75-g OGTT revealed a fasting blood glucose value of 117 mg/dl (normal 70–100 mg/dl) and a 2-hour value of 179 mg/dl (normal < 140 mg/dl). Her A1C was 5.8% (normal 4.0–6.5%).

Since her test was consistent with IGT and she was still nursing, it was planned that she return to clinic in 8 weeks for a repeat OGTT and continue to monitor her blood glucose at home. Four weeks later, she called with symptoms of polyuria, polydipsia, and blurry vision. Her blood glucose values had been between 200 and 350 mg/dl for 3 days.

W.S. was seen immediately in clinic. Insulin therapy was initiated with basal insulin glargine, 15 units at bedtime, and insulin lispro for bolus insulin coverage at meals. Because of the family history of type 1 diabetes in her daughter and acute exacerbation of hyperglycemia, an autoantibody test was ordered to evaluate her for type 1 diabetes.

Results showed that the glutamic acid decarboxylase (GAD65) antibody was 34.2 U/ml (normal < 1.5 U/ml), the islet cell IgG autoantibody (ICA) was 80 JDF units (normal < 4.1), and the nonfasting C-peptide level was 794 pg/l (stimulated state 497–3,145 pg/l).

Because of the presence of pancreatic antibodies, she was diagnosed with latent autoimmune diabetes in adults (LADA). Intensive insulin therapy was started with insulin lispro for prandial coverage and insulin glargine for basal coverage. Within the next 6 months, she was started on an insulin pump and had excellent glycemic control. One year after her diagnosis, she became pregnant with her third child. She had an uncomplicated pregnancy, and her diabetes was well controlled during pregnancy on insulin pump therapy.

## QUESTIONS

1. What is LADA?
2. How is LADA diagnosed?
3. Why is it important to recognize and diagnose LADA?
4. How does LADA treatment vary from treatment of type 1 or type 2 diabetes?

## COMMENTARY

LADA is adult-onset diabetes with positive pancreatic autoantibodies and slowly progressive  $\beta$ -cell failure.<sup>1</sup> LADA does not present like type 1 diabetes with significant weight loss and ketoacidosis from rapidly progressive  $\beta$ -cell failure. Because of the slow progressive  $\beta$ -cell failure, LADA presents similarly to type 2 diabetes, with elevated blood glucose values and typical symptoms of hyper-

glycemia, such as polyuria, polydipsia, polyphagia, and visual blurring. The three keys to diagnosis of this disease are adult onset, positive antibodies, and lack of ketosis.

At diagnosis, C-peptide levels in LADA are at intermediate levels between type 1 and type 2 diabetes without positive antibodies (Figure 1). Within a few years, levels of  $\beta$ -cell failure are similar in type 1 diabetes and LADA.<sup>1</sup>

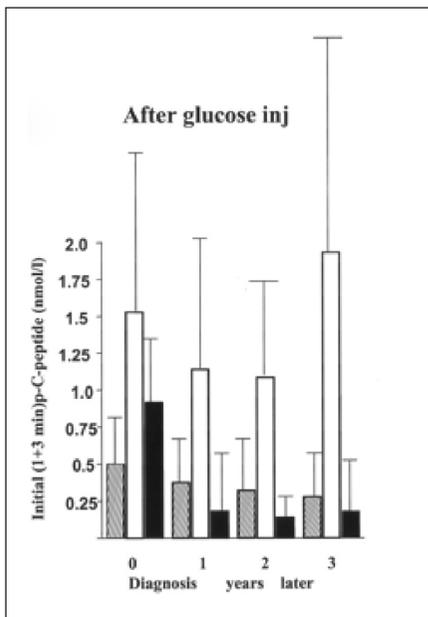


Figure 1. Intravenous glucose test at 1, 2, and 3 years after diagnosis in type 1 diabetes, type 2 diabetes (without antibodies), and LADA.

According to the U.K. Prospective Diabetes Study, ~ 10% of newly diagnosed type 2 diabetes cases have evidence of autoimmunity indicated by ICA and/or GAD65 antibody positivity. Autoimmunity is a strong predictor of insulin requirement within 6 years in all age-groups, and the predictive value increases with decreasing age, as seen in Figure 2.<sup>2</sup> Because of this earlier need for insulin therapy, it is important to identify patients with LADA. Insulin therapy can be started in a timely manner once this condition is diagnosed.

Multiple studies have tried to best distinguish LADA from type 2 diabetes.

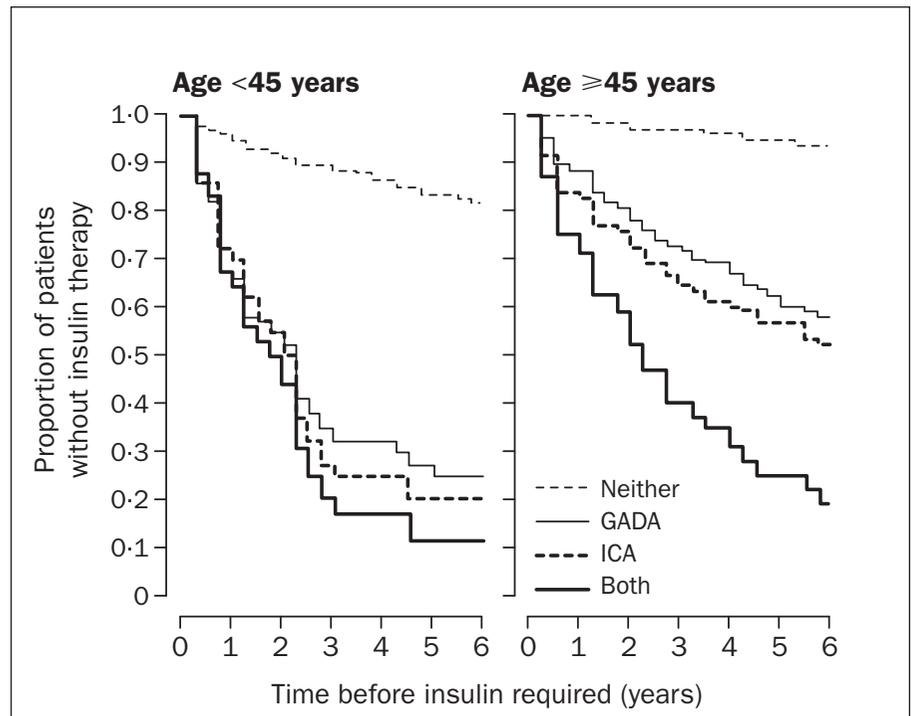


Figure 2. Kaplan-Meier plots of proportion of patients with and without ICA and GAD antibodies requiring insulin therapy during 6 years' follow-up.

A group from the University of Washington<sup>3</sup> conducted a study in patients with a diagnosis of type 2 diabetes for a mean of ~ 4 months and no history of ketosis. BMI, age, and acuity of presentation did not assist in distinguishing LADA from type 2 diabetes. They also tested multiple autoantibodies and found that the ICA and GAD65 antibodies had the highest prevalence in patients with positivity and recommended these two antibodies for screening.

Another study<sup>4</sup> developed a screening tool using the following five criteria:

1. Age of diabetes onset < 50 years
2. Acute symptoms of polyuria, polydipsia, and/or weight loss
3. Personal history of autoimmune disease
4. Family history of autoimmune disease
5. BMI < 25 kg/m<sup>2</sup>

This study found that 75% of patients with LADA had two or more criteria compared to only 24% of those with type 2 diabetes. Because the study was

conducted in a completely separate population in Melbourne, Australia, the BMI criteria may not apply to the American population, as seen in the University of Washington study discussed above.

Family history of type 2 diabetes has not been shown to distinguish between LADA and type 2 diabetes<sup>4</sup> and should not be used to exclude LADA.

Clinicians presented with patients with newly diagnosed type 2 diabetes without history of ketosis should consider both of these studies when trying to decide which patients should have pancreatic antibody testing. During the current obesity epidemic, BMI does not have the same predictive value as seen earlier. Nonetheless, low BMI still has utility, and we would recommend screening such patients. As with W.S., significant personal and family history of autoimmune diseases is clearly an indicator for screening. Younger age may be a more controversial indicator because the literature has been inconclusive. It is certainly appropriate to screen

younger patients because they are at an increased lifetime risk of complications from longer duration of disease, and traditional approaches to type 2 diabetes are frequently unsuccessful in patients with LADA.

Patients with LADA are more often unable to control their blood glucose through diet and lifestyle modifications than are type 2 diabetic patients without autoimmunity. Moreover, the failure rates for diet and lifestyle therapies are higher the younger the patient.<sup>2</sup> In patients with LADA, sulfonylurea therapy is associated with more rapid  $\beta$ -cell failure than insulin therapy,<sup>5,6</sup> but may still have a role. Metformin, especially as monotherapy, is considered an unsafe therapeutic option because of the risk of diabetic ketoacidosis.<sup>6,7</sup> Because there is eventual  $\beta$ -cell failure, early initiation of insulin therapy is recommended for patients with LADA.<sup>1</sup>

The optimum regimen has not been established.<sup>8</sup> A combination of insulin with insulin secretagogues could be considered early on. In obese patients who have avoided ketoacidosis, metformin with insulin could be used because this is effective in some patients with type 1 diabetes.<sup>6</sup> The key to therapy is to recall the underlying progress and the time course of  $\beta$ -cell failure and the risk this entails. As in type 1 and type 2 diabetes, microvascular and macrovascular complications occur in LADA.<sup>8</sup> Therefore, patients with LADA

require comprehensive preventive care and risk assessment, as do all patients with diabetes.

Although LADA is the most commonly used name for this disease in the literature, clinicians should be aware that it is also referred to in other ways, including slowly progressive type 1 diabetes, autoimmune diabetes in adults with slowly progressive  $\beta$ -cell failure, autoimmune diabetes not requiring insulin at diagnosis, autoimmune diabetes in adults,<sup>1</sup> and type 1.5 diabetes.<sup>3</sup>

### CLINICAL PEARLS

- LADA occurs in ~ 10% of adults who appear to present with type 2 diabetes.
- Screening requires clinical suspicion, and it is recommended to test for ICA and GAD65 antibodies. Clinical suspicion should be raised by a history of autoimmune disorders and lower BMI, but not excluded by elevated BMI or family history of type 2 diabetes.
- Within a few years,  $\beta$ -cell failure requires insulin therapy. Therefore, to preserve  $\beta$ -cell function, it is recommended that insulin therapy be started early.
- Patients with LADA require preventive screening and risk assessment for microvascular and macrovascular complications of diabetes.
- GDM patients need to undergo postpartum glucose tolerance testing

because of their high risk of developing IGT, IFG, and type 2 diabetes.

### REFERENCES

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