

DOI: 10.38173/RST.2022.23.1.14:123-129

| | |
|-----------------|--|
| Title: | <i>SLOW ONSET TYPE 1 DIABETES ASSOCIATED WITH PREGNANCY: A CASE REPORT</i> |
| Authors: | Ana-Maria CAŞLATOI Elena Georgiana BERNEA Denisa Isabella TĂNASIE Dragoş Eugen GEORGESCU Cristian GUJA Doina-Andrada MIHAI Constantin IONESCU-TÎRGOVIŞTE |

Section: MEDICINE

Issue: 1(23)/2022

| | |
|-----------------------------------|--|
| Received: 11 December 2021 | Revised: 28 January 2022 |
| Accepted: 15 February 2022 | Available Online: 15 March 2022 |

Paper available online [HERE](#)

SLOW ONSET TYPE 1 DIABETES ASSOCIATED WITH PREGNANCY: A CASE REPORT

Ana-Maria CAȘLATOI¹
Elena Georgiana BERNEA²
Denisa Isabella TĂNASIE³
Dragoș Eugen GEORGESCU⁴
Cristian GUJA⁵
Doina-Andrada MIHAI⁶
Constantin IONESCU-TÎRGOVIȘTE⁷

ABSTRACT:

GESTATIONAL DIABETES MELLITUS (GDM) IS DEFINED AS ANY GLUCOSE INTOLERANCE WITH FIRST RECOGNITION DURING PREGNANCY AND IT CAN BE REVELATORY OF UNDERLYING BETA-CELL DYSFUNCTION, WHICH CONFERS AN INCREASED RISK FOR LATER DEVELOPMENT OF DIABETES, BOTH TYPE 1 DIABETES (T1DM) AND TYPE 2 DIABETES (T2DM), THE LAST BEING THE MOST COMMON. A SUBGROUP OF PATIENTS WITH GDM, ESPECIALLY THOSE WITH AUTOANTIBODY POSITIVITY DURING AND AFTER PREGNANCY, MAY EVOLVE, OFTEN SEVERAL YEARS AFTER PREGNANCY, INTO CASES OF LATENT AUTOIMMUNE DIABETES OF ADULTHOOD (LADA), THE "SLOWLY PROGRESSIVE AUTOIMMUNE DIABETES". WE REPORT THE CASE OF A 29-YEAR-OLD CAUCASIAN WOMAN, WHO FIRST PRESENTED TO OUR HOSPITAL IN OCTOBER 2014 FOR A POSTPARTUM FOLLOW-UP OF A GDM, WHICH WAS DIAGNOSED SHORTLY BEFORE DELIVERY AT 36TH WEEK OF GESTATION, DUE TO FETAL DISTRESS. SHE RECEIVED METFORMIN ASSOCIATED WITH BASAL INSULIN THERAPY. SUBSEQUENTLY SHE CONVERTED TO BASAL BOLUS INSULIN THERAPY. RECENTLY, THE PATIENT PRESENTED WITH POOR METABOLIC CONTROL (11.5% HBA1C) AND HAS DEVELOPED DIABETIC PAPILOPATHY. THE SPECIFIC PHENOTYPIC FEATURES AND THE MANAGEMENT OF LATENT AUTOIMMUNE DIABETES IN ADULTS ARE CHALLENGING AND FURTHER RESEARCH SHOULD BE PERFORMED.

KEY WORDS: GESTATIONAL DIABETES MELITUS, LATENT AUTOIMMUNE DIABETES OF ADULTHOOD, DIABETIC PAPILOPATHY, INSULIN THERAPY

¹ „N. Paulescu” National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest

² University of Medicine and Pharmacy “Carol Davila”, Bucharest

³ National Institute of Endocrinology C.I.Parhon

⁴ University of Medicine and Pharmacy “Carol Davila”, Bucharest, „Dr I Cantacuzino” Hospital Bucharest

⁵ „N. Paulescu” National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest

University of Medicine and Pharmacy “Carol Davila”, Bucharest

⁶ „N. Paulescu” National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest

University of Medicine and Pharmacy “Carol Davila”, Bucharest

⁷ „N. Paulescu” National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest

University of Medicine and Pharmacy “Carol Davila”, Bucharest

INTRODUCTION

For a long time, gestational diabetes mellitus (GDM) was defined as any glucose intolerance with first recognition during pregnancy, due to the physiological insulin resistance associated with pregnancy⁸. Since the last becomes significant during the third trimester, current guidelines⁹ recommend testing for GDM between weeks 24-28 of gestation. Numerous international studies estimate that diabetes Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM) and GDM occurs annually in approximately in 1–14% of all pregnancies¹⁰. GDM is associated with short- and long-term maternal and fetal risks, such as preeclampsia, spontaneous abortion, major fetal malformations, macrosomia, increased perinatal mortality and delivery by cesarean section¹¹.

Frequently, GDM is revelatory of underlying beta-cell dysfunction, which confers an increased risk for later development of diabetes, type 2 diabetes being the most common type, but also type 1 diabetes¹². A 23-year-long cohort study that examined the progression to type 1 and type 2 diabetes after GDM, revealed that in 5.7% cases GDM evolved into type 1 diabetes, which was developed during the first 7 years after GDM pregnancy. In addition, by the end of the follow-up period, approximately 50% of cases evolved into type 2 diabetes¹³. GDM thereby may facilitate the identification of women at risk of developing diabetes later in life¹⁴.

A subset of patients with GDM presents autoantibody positivity during and after pregnancy and in some patients beta cell autoantibodies can appear for the first time after delivery¹⁵. Studies¹⁶ revealed that these patients have a high risk of developing diabetes after pregnancy, usually but not exclusively type 1 diabetes¹⁷. Alternatively, some cases may evolve, often some years after their pregnancy, into cases of slow onset autoimmune diabetes, also known clinically as latent autoimmune diabetes of adulthood (LADA)¹⁸. The distinction between adult-onset type 1 diabetes and LADA is sometimes difficult and several studies or

⁸ Luz Yolanda Toro Suarez, “International Textbook of Diabetes Mellitus, 4th edition,” pp. 1–27, 2015; American Diabetes Association “STANDARDS OF MEDICAL CARE IN DIABETES — 2021 American Diabetes Association Medical Care in Diabetes 2021,” *Diabetes Care* vol. 44, Suppl. 1 January, 2021

⁹ American Diabetes Association “STANDARDS OF MEDICAL CARE IN DIABETES — 2021 American Diabetes Association Medical Care in Diabetes 2021,” *Diabetes Care* vol. 44, Suppl. 1 January, 2021

¹⁰ Luz Yolanda Toro Suarez, “International Textbook of Diabetes Mellitus, 4th edition,” pp. 1–27, 2015

¹¹ American Diabetes Association “STANDARDS OF MEDICAL CARE IN DIABETES — 2021 American Diabetes Association Medical Care in Diabetes 2021,” *Diabetes Care* vol. 44, Suppl. 1 January, 2021; E. C. Johns, F. C. Denison, J. E. Norman, and R. M. Reynolds, “Gestational Diabetes Mellitus: Mechanisms, Treatment, and Complications,” *Trends in Endocrinology and Metabolism*. 2018

¹² American Diabetes Association “STANDARDS OF MEDICAL CARE IN DIABETES — 2021 American Diabetes Association Medical Care in Diabetes 2021,” *Diabetes Care* vol. 44, Suppl. 1 January, 2021

¹³ A. Lapolla, M. G. Dalfrà, and D. Fedele, “Diabetes related autoimmunity in gestational diabetes mellitus: Is it important?,” *Nutr. Metab. Cardiovasc. Dis.*, vol. 19, no. 9, pp. 674–682, 2009

¹⁴ M. Incani, M. G. Baroni, and E. Cossu, “Testing for type 1 diabetes autoantibodies in gestational diabetes mellitus (GDM): Is it clinically useful?,” *BMC Endocr. Disord.*, vol. 19, no. 1, pp. 1–6, 2019

¹⁵ A. Lapolla, M. G. Dalfrà, and D. Fedele, “Diabetes related autoimmunity in gestational diabetes mellitus: Is it important?,” *Nutr. Metab. Cardiovasc. Dis.*, vol. 19, no. 9, pp. 674–682, 2009

¹⁶ Flavius-Cristian Mărcău, Sorin Purec, George Niculescu, „Study on the refusal of vaccination against Covid-19 in Romania” în *Vaccines* 2022, 10, 261. <https://doi.org/10.3390/vaccines10020261>

¹⁷ A. Kumar, A. De Leiva, and R. Corcoy, “Autoimmunity in Gestational Diabetes Mellitus,” *Front. Diabetes*, vol. 28, pp. 234–242, 2019

¹⁸ A. Kumar, A. De Leiva, and R. Corcoy, “Autoimmunity in Gestational Diabetes Mellitus,” *Front. Diabetes*, vol. 28, pp. 234–242, 2019

reviews concerning type 1 diabetes revealed during pregnancy have claimed that it compares to LADA¹⁹.

CASE HISTORY

A 29-year-old Caucasian woman, smoker, with no other significant past medical history, first presented to our hospital in October 2014 for a postpartum follow-up of a gestational diabetes mellitus,

Family history. Negative for both type 1 or type 2 diabetes, but positive for Hashimoto's disease, gastric cancer and ischemic cardiomyopathy.

Maternal history. Menarche at 13 years old, primigravida, primipara with a pregnancy BMI of 26.36 kg/m² (W = 78 kg, H = 1.72 m). The weight gain during pregnancy was of 4 kg. The patient presented a neglected mild polyuro-polydipsic syndrome, which started during the second trimester of pregnancy, associated with a slight weight loss. Due to fetal distress, a C-section was performed in the 36th week of gestation and the baby was delivered (birth weight 3160 g) with a mild form of perinatal hypoxia and a neonatal jaundice. The workup during the admission showed a high glucose level (over 200 mg/dl), but no treatment was initiated in the obstetrics clinic and the patient was discharged with a referral to a diabetologist.

Postpartum. The patient displayed a poor glycemic profile with fasting plasma glucose levels of 170-350 mg/dl during the two months between her delivery and her hospitalisation in our hospital. During her first hospitalisation in our clinic in December 2014, the average fasting plasma glucose levels were approx. 150 mg/dl, the Glutamic Acid Decarboxylase (GAD) antibodies were positive, the C peptide had a below normal value and the glycated haemoglobin (HbA1c) was 9.0%. Her BMI was 24.8 kg/m² (W = 74 kg, H = 1.72 m). Taking all the above into consideration, including her favourable blood glucose profile evolution with a low carbohydrate diet, latent autoimmune diabetes of adulthood (LADA) was diagnosed. Patient was recommended Metformin therapy with low doses (500 mg BID), associated with basal insulin therapy (detemir 10 IU). After 15 months, due to deteriorating glucose control, in March 2016 it has been decided to start the basal-bolus insulin therapy consisting of rapid-acting insulin analogue -aspart (8U-8U-8U) and detemir (28U).

The patient presented again in January 2021 with poor glycemic control (HbA1c was 11.5% in December 2020). Consequently patient increased by herself insulin doses which led to frequent hypoglycemia (2 hypoglycemic episodes per week), presumably causing diabetic papillopathy (diagnosed also in December 2020). We attribute her chronic metabolic imbalance to lack of carbohydrate counting and self-monitoring of blood glucose and possibly intermittent non-compliance to insulin therapy. There was no other significant personal medical history. At the clinical examination, there was nothing particular, excepting abdominal lipodystrophy.

During the hospitalization, a new dietary plan was instituted and the insulin therapy regimen was changed to fast acting insulin aspart (Fiasp) 4U-5U-5U and long-acting insulin analogue - degludec (Tresiba) (20U). The patient was discharged with significantly improved blood glucose profiles.

¹⁹ H. Wucher, J. Lepercq, and J. Timsit, "Onset of autoimmune type 1 diabetes during pregnancy: Prevalence and outcomes," *Best Pract. Res. Clin. Endocrinol. Metab.*, vol. 24, no. 4, pp. 617–624, 2010

DISCUSSION

Whereas in young people autoimmune diabetes is defined by a quickly evolving disease presenting with overt diabetes symptoms and insulin requirement from diagnosis, the slowly progressive beta-cell destruction form usually appears in adults (>30 years) and is described as latent autoimmune diabetes in adults (LADA)²⁰. In spite of this, some international experts suggest a different nomenclature for this clinical condition: “slowly progressive insulin dependent diabetes”²¹. The ADA 2021 Clinical Practice Recommendations state that, despite the fact there is a debate if slowly progressive autoimmune diabetes should be named LADA or type 1 diabetes, the use of the LADA term is acceptable in clinical practice²².

At the same time, based on the literature, the following diagnostic criteria have been proposed: (1) the existence of GADA and/or Islet Cell Antibodies (ICA) at any time during the progress of the disease and (2) absence of ketosis at onset of DM and no need for insulin treatment to correct hyperglycemia in the first 3 months after diagnosis, although these are still under debate²³.

Studies on pregnancy and autoimmune latent diabetes in adults are restricted. From the data available in several reviews, autoimmune GDM has been reported in a small number of cases (about 10% of women with GDM become beta cell autoantibody positive)²⁴. This category of rare patients is likely to develop progression to overt classical type 1 diabetes or LADA after delivery²⁵. Due to the fact that pregnancy is a condition associated with insulin resistance, any subjacent glucose tolerance disorder may be unveiled and interpreted as just GDM, even though it could be a slowly developing autoimmune process even in the young women²⁶. Other studies showed that overt diabetes occurs generally from the first year after delivery²⁷.

Latent autoimmune diabetes is usually positive for a single islet autoantibody, usually GADA. Thus, the glutamic acid decarboxylase antibody (GADA) is the main autoantibody compared to other autoantibodies²⁸. Despite this autoantibody being accessible as a first line

²⁰ R. Buzzetti *et al.*, “Management of latent autoimmune diabetes in adults: A consensus statement from an international expert panel,” *Diabetes*, vol. 69, no. 10, pp. 2037–2047, 2020; P. Gill, J. Piris, and B. F. Warren, “Lesson of the month,” *Histopathology*, vol. 42, no. 1, pp. 88–90, 2003

²¹ L. Fadiga, J. Saraiva, D. Catarino, J. Frade, M. Melo, and I. Paiva, “Adult-onset autoimmune diabetes: comparative analysis of classical and latent presentation,” *Diabetol. Metab. Syndr.*, vol. 12, no. 1, pp. 1–9, 2020

²² American Diabetes Association “STANDARDS OF MEDICAL CARE IN DIABETES — 2021 American Diabetes Association Medical Care in Diabetes 2021,” *Diabetes Care* vol. 44, Suppl. 1 January, 2021

²³ H. Wucher, J. Lepercq, and J. Timsit, “Onset of autoimmune type 1 diabetes during pregnancy: Prevalence and outcomes,” *Best Pract. Res. Clin. Endocrinol. Metab.*, vol. 24, no. 4, pp. 617–624, 2010; L. Fadiga, J. Saraiva, D. Catarino, J. Frade, M. Melo, and I. Paiva, “Adult-onset autoimmune diabetes: comparative analysis of classical and latent presentation,” *Diabetol. Metab. Syndr.*, vol. 12, no. 1, pp. 1–9, 2020

²⁴ C. NILSSON, “Gestational Diabetes Mellitus Predicts,” *Diabetes Care*, vol. 30, no. 8, p. 19681970, 2007

²⁵ A. Lapolla, M. G. Dalfrà, and D. Fedele, “Diabetes related autoimmunity in gestational diabetes mellitus: Is it important?,” *Nutr. Metab. Cardiovasc. Dis.*, vol. 19, no. 9, pp. 674–682, 2009; H. Wucher, J. Lepercq, and J. Timsit, “Onset of autoimmune type 1 diabetes during pregnancy: Prevalence and outcomes,” *Best Pract. Res. Clin. Endocrinol. Metab.*, vol. 24, no. 4, pp. 617–624, 2010

²⁶ H. Wucher, J. Lepercq, and J. Timsit, “Onset of autoimmune type 1 diabetes during pregnancy: Prevalence and outcomes,” *Best Pract. Res. Clin. Endocrinol. Metab.*, vol. 24, no. 4, pp. 617–624, 2010; C. NILSSON, “Gestational Diabetes Mellitus Predicts,” *Diabetes Care*, vol. 30, no. 8, p. 19681970, 2007

²⁷ M. Incani, M. G. Baroni, and E. Cossu, “Testing for type 1 diabetes autoantibodies in gestational diabetes mellitus (GDM): Is it clinically useful?,” *BMC Endocr. Disord.*, vol. 19, no. 1, pp. 1–6, 2019

²⁸ R. Buzzetti *et al.*, “Management of latent autoimmune diabetes in adults: A consensus statement from an international expert panel,” *Diabetes*, vol. 69, no. 10, pp. 2037–2047, 2020; Y. Xiang *et al.*, “Glutamic acid decarboxylase autoantibodies are dominant but insufficient to identify most Chinese with adult-onset non-

test to identify these patients, more recent research suggests that it is recommended to use markers of immune-mediated diabetes in GDM women and after delivery in two cases: when clinical traits intensely indicate a severely insulinopenic form of diabetes (young age, low body mass index, early insulin therapy, presence of ketones) and when the impaired glucose regulation continues after pregnancy²⁹.

A 2020 international expert panel reported that high GADA titers are linked to an increased risk of insulin requirement³⁰. Therefore, they can anticipate a better metabolic control in case of insulin treatment³¹. But it is still demanding to define a threshold regarding high and low GADA titers³². So far, other available data suggest that the development of islet immunity to overt type 1 diabetes is correlated with increasing HbA1c levels³³.

In 2014, the postpartum investigations on the current patient, who was 22 years old at that time, revealed anti-GAD positivity, C-peptide levels at the lower end of the normal range and a 9% HbA1c. Her family history was positive for Hashimoto's disease, but was negative for both type 1 and type 2 diabetes. Also, her pre-pregnancy BMI was normal and she had no other traits of insulin resistance. Considering the above aspects, a diagnosis of LADA was favored, but for a better metabolic control, the therapy consisted of Metformin and basal insulin for more than a year, until March 2016. It is not yet confirmed if insulin treatment should be initiated in the early stages of LADA or if this is the optimal treatment in any of the stages of the disease³⁴. However, studies concur that intervening with insulin is safe and effective for LADA patients³⁵.

CONCLUSION

The specific phenotypic features and the management of latent autoimmune diabetes in adults are still challenging in the clinical practice and further research should be performed. According to our case, women with GDM with no family history of diabetes or insulin resistance traits (lower blood pressure, normal pre-pregnancy BMI), C-peptide levels at the lower end of the normal range, a first degree relative with other autoimmune disorder (such as Hashimoto's thyroiditis) and age under 30 years, should be taken into account for a LADA diagnosis and screened for beta cell autoantibodies after delivery. Considering the limited evidence regarding the treatment approach, the optimum time of insulin therapy initiation in these patients needs to be better established.

insulin requiring autoimmune diabetes: LADA China study 5," *Acta Diabetol.*, vol. 52, no. 6, pp. 1121–1127, 2015

²⁹ M. Incani, M. G. Baroni, and E. Cossu, "Testing for type 1 diabetes autoantibodies in gestational diabetes mellitus (GDM): Is it clinically useful?," *BMC Endocr. Disord.*, vol. 19, no. 1, pp. 1–6, 2019

³⁰ R. Buzzetti *et al.*, "Management of latent autoimmune diabetes in adults: A consensus statement from an international expert panel," *Diabetes*, vol. 69, no. 10, pp. 2037–2047, 2020

³¹ A. O. Y. Luk *et al.*, "Diabetes-related complications and mortality in patients with young-onset latent autoimmune diabetes: A 14-year analysis of the prospective Hong Kong Diabetes register," *Diabetes Care*, vol. 42, no. 6, pp. 1042–1050, 2019

³² R. Buzzetti *et al.*, "Management of latent autoimmune diabetes in adults: A consensus statement from an international expert panel," *Diabetes*, vol. 69, no. 10, pp. 2037–2047, 2020

³³ L. C. Stene *et al.*, "Normal but increasing hemoglobin A1c levels predict progression from islet autoimmunity to overt type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY)," *Pediatr. Diabetes*, vol. 7, no. 5, pp. 247–253, 2006

³⁴ R. Buzzetti *et al.*, "Management of latent autoimmune diabetes in adults: A consensus statement from an international expert panel," *Diabetes*, vol. 69, no. 10, pp. 2037–2047, 2020

³⁵ R. Buzzetti *et al.*, "Management of latent autoimmune diabetes in adults: A consensus statement from an international expert panel," *Diabetes*, vol. 69, no. 10, pp. 2037–2047, 2020

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

ACKNOWLEDGEMENT

All authors had the same contribution.

REFERENCES

1. **Luz Yolanda Toro Suarez**, "International Textbook of Diabetes Mellitus, 4th edition," pp. 1–27, 2015.
2. American Diabetes Association "STANDARDS OF MEDICAL CARE IN DIABETES — 2021 American Diabetes Association Medical Care in Diabetes 2021," *Diabetes Care* vol. 44, Suppl. 1 January, 2021.
3. **E. C. Johns, F. C. Denison, J. E. Norman, and R. M. Reynolds**, "Gestational Diabetes Mellitus: Mechanisms, Treatment, and Complications," *Trends in Endocrinology and Metabolism*. 2018.
4. **A. Lapolla, M. G. Dalfrà, and D. Fedele**, "Diabetes related autoimmunity in gestational diabetes mellitus: Is it important?," *Nutr. Metab. Cardiovasc. Dis.*, vol. 19, no. 9, pp. 674–682, 2009.
5. **M. Incani, M. G. Baroni, and E. Cossu**, "Testing for type 1 diabetes autoantibodies in gestational diabetes mellitus (GDM): Is it clinically useful?," *BMC Endocr. Disord.*, vol. 19, no. 1, pp. 1–6, 2019.
6. **A. Kumar, A. De Leiva, and R. Corcoy**, "Autoimmunity in Gestational Diabetes Mellitus," *Front. Diabetes*, vol. 28, pp. 234–242, 2019.
7. **H. Wucher, J. Lepereq, and J. Timsit**, "Onset of autoimmune type 1 diabetes during pregnancy: Prevalence and outcomes," *Best Pract. Res. Clin. Endocrinol. Metab.*, vol. 24, no. 4, pp. 617–624, 2010.
8. **R. Buzzetti et al.**, "Management of latent autoimmune diabetes in adults: A consensus statement from an international expert panel," *Diabetes*, vol. 69, no. 10, pp. 2037–2047, 2020.
9. **P. Gill, J. Piris, and B. F. Warren**, "Lesson of the month," *Histopathology*, vol. 42, no. 1, pp. 88–90, 2003.
10. **Flavius-Cristian Mărcău, Sorin Purec, George Niculescu**, „Study on the refusal of vaccination against Covid-19 in Romania” în *Vaccines* 2022, 10, 261.<https://doi.org/10.3390/vaccines10020261>.
11. **L. Fadiga, J. Saraiva, D. Catarino, J. Frade, M. Melo, and I. Paiva**, "Adult-onset autoimmune diabetes: comparative analysis of classical and latent presentation," *Diabetol. Metab. Syndr.*, vol. 12, no. 1, pp. 1–9, 2020.
12. **C. NILSSON**, "Gestational Diabetes Mellitus Predicts," *Diabetes Care*, vol. 30, no. 8, p. 19681970, 2007.
13. **Y. Xiang et al.**, "Glutamic acid decarboxylase autoantibodies are dominant but insufficient to identify most Chinese with adult-onset non-insulin requiring autoimmune diabetes: LADA China study 5," *Acta Diabetol.*, vol. 52, no. 6, pp. 1121–1127, 2015.
14. **A. O. Y. Luk et al.**, "Diabetes-related complications and mortality in patients with young-onset latent autoimmune diabetes: A 14-year analysis of the prospective Hong Kong Diabetes register," *Diabetes Care*, vol. 42, no. 6, pp. 1042–1050, 2019.
15. **L. C. Stene et al.**, "Normal but increasing hemoglobin A1c levels predict progression from islet autoimmunity to overt type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY)," *Pediatr. Diabetes*, vol. 7, no. 5, pp. 247–253, 2006.