

# Insulin autoantibody-related hypoglycemic coma in a pregnant woman with type I diabetes mellitus

## Abstract

Autoimmune hypoglycemia is a rare disease entity especially in pregnant women with type 1 diabetes mellitus (T1DM). A 34-year-old woman with T1DM treated with basal insulin detemir once daily and bolus insulin as part before each meal was pregnant at the 24<sup>th</sup> week of gestation. She was found to have gestational hypertension. Because of limited choices of anti-hypertensive medications during pregnancy, the patient was placed on hydralazine. However, two weeks later, she began to experience several episodes of hypoglycemia-related sudden loss of consciousness. In one witnessed episode, hypoglycemia with elevated insulin but undetectable C-peptide was noted. Under the suspicion of insulin autoantibody-related hypoglycemic coma, free form insulin autoantibody was checked and a positive result was reported using immunoradiometric assay. We then applied a multidisciplinary approach to treat the patient. First, hydralazine was discontinued. Second, hydroxychloroquine was administered as an immunosuppressant to suppress autoantibody production. Third, insulin regimen was modified and changed to using insulin glargine as the basal and insulin lispro as the prandial injectable. Fourth, acarbose was given to help control post-prandial glycemic excursion. No more major hypoglycemic event occurred after the treatment. She delivered a live mature female baby smoothly at week 37. She was then started on pulse steroid therapy with 500mg of methylprednisolone once weekly for four weeks, followed by 250mg once weekly for four weeks, and the insulin antibody levels declined to normal.

Volume 6 Issue 2 - 2017

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**Received:** January 26, 2017 | **Published:** February 09, 2017

## Learning points

- i. Autoimmune hypoglycemia is a rare occurrence in pregnancy but should be kept in mind if patient experiences unusual and/or major hypoglycemic events especially after using potentially offensive medications including hydralazine.
- ii. Except for discontinuing the offensive medication, choosing an immunosuppressant such as hydroxychloroquine that is safe and effective in pregnancy might help suppress autoantibody production in pregnant women with autoimmune hypoglycemia.
- iii. Adopting a safe and effective insulin regimen and adjustment strategy to treat patients with concomitant diabetes mellitus and autoimmune hypoglycemia is important.
- iv. Acarbose, an alpha-glucosidase inhibitor, category B in pregnancy, can be used safely and effectively in pregnant diabetes with marked glycemic excursion.
- v. Pulse steroid therapy is effective in reversing autoimmune hypoglycemia syndrome

## Background

Autoimmune hypoglycemia poses diagnostic and therapeutic challenges in pregnant diabetic women. Since insulin autoantibody assays are not widely available, simultaneous blood samplings to check the plasma glucose, serum insulin and C-peptide help provide clues for the diagnosis. Low blood glucose combined with extraordinarily high insulin and low C-peptide levels prompted the physician to consider the diagnosis of autoimmune hypoglycemia, and further order a specific test to confirm the diagnosis using special assay.

Regarding the treatments, discontinuation of offensive medications, such as sulfhydryl group-containing drugs and hydralazine that will cause autoimmune hypoglycemia is mandatory. Optimal selection of immune-suppressants and insulin regimens is important to reduce the antibody titers and provide patients the most safe and effective treatments. Finally, alpha-glucosidase inhibitor, an oral anti-hyperglycemic agent which exhibits good efficacy in reducing the risk of post-prandial, reactive hypoglycemia, and can be used safely in pregnant women with remarkable glycemic excursion alternating from hyperglycemia to hypoglycemia.

## Case presentation

This 35-year-old, gravida-2 para-1 woman with type 1 diabetes mellitus (T1DM) was pregnant at a gestational age of 24weeks+2days on January 19, 2015. Her body height was 150cm, and weight was 62.5kg, the calculated body mass index (BMI) was 27.8kg/m<sup>2</sup>. She received regular prenatal examination at obstetric clinics. The pregnancy course was uneventful throughout the gestation; neither major anomaly of the fetus nor medical complications of the mother was found in the serial follow-ups, except for the mother's poorly controlled diabetes mellitus.

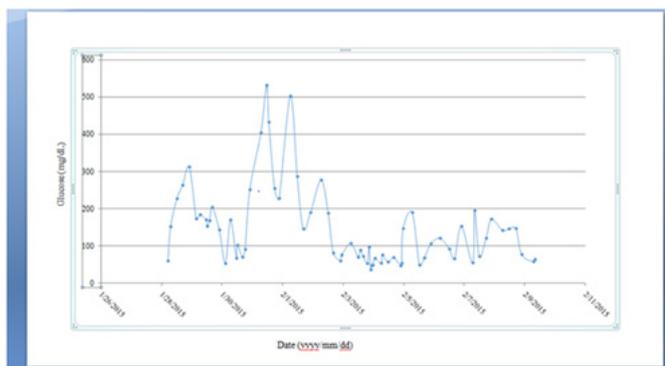
The patient was diagnosed as T1DM at 28y/o. Since then, she has been receiving insulin injections at least four times daily to help control blood glucose within ideal ranges. After giving birth to the first child at 31y/o, she had poor adherence to insulin therapy, and the HbA1c was usually above 10%, yet she experienced occasional hypoglycemia. During this pregnancy, she still had off and on hypoglycemic episodes which manifested as dizziness and general weakness. Gestational hypertension was noted, but she denied

headache, blurred vision or pedal edema. Labetalol 200 mg bid and nifedipine 5mg tid were prescribed, and nifedipine was later switched to long-acting nifedipine (Adalat® OROS) at a dose of 30mg bid. She had been admitted to obstetric ward from December 26, 2014 to January 6, 2015 for insulin dosage adjustment to help control blood glucose levels, and the last HbA1C was 7.5% on December 26, 2014. During admission, the hypertension remained uncontrolled despite the use of maximum allowed doses of labetalol and nifedipine, thus hydralazine was started at a dose of 10 mg bid on December 26, 2014, and later titrated up to 50 mg bid before discharge.

After discharge, the self-monitoring blood glucose (SMBG) levels were about 100-200mg/dL, and the home systolic blood pressure was about 130mmHg. However, she had experienced at least two episodes of loss of consciousness in one week (January 12-19, 2015) which she attributed to the occurrence of hypoglycemia. On January 19, because of sudden loss of consciousness, she was taken to another medical facility, where low blood glucose of around 20-30mg/dl was detected. After intravenous glucose infusion, the patient regained consciousness. Upon request, she was transferred to our hospital for further care.

Several episodes of hypoglycemia unawareness were detected after she was admitted to our hospital, with no obvious dizziness, cold sweating, blurred vision or any other discomfort. We carefully adjusted the insulin regimen to determine the most appropriate dose for the patient. However, a witnessed abrupt loss of consciousness developed at around 8:00PM, 3hours after dinner, on January 26, 2015, when the blood glucose was 24mg/dL measured with a glucometer. Her level of consciousness improved after intravenous injection of 20ml of 50% glucose water. She complained of decreased fetal movements after the hypoglycemic event. Obstetric doctor conducted a bedside sonography for the patient, which showed normal fetal movements.

The blood glucose levels still fluctuated significantly (up to >500 and down to <20mg/dl) and were difficult to control after the event (Figure 1). We checked free form insulin autoantibody (IAA) by using immunoradiometric assay (free anti-insulin-antibody radio immuno assay kit, Cisbio Bioassays) on January 29, 2015, which was positive (20.9%, normal <5.5%). Both the glutamic acid decarboxylase (GAD) and islet (IA-2) auto antibodies were negative (0.22 and 0.35 U/ml, normal <1U/ml respectively). We simultaneously carried out the following laboratory tests, the venous plasma glucose was 50mg/dl, the serum C-peptide was <0.1ng/ml (0.9-7.1), and the insulin was 45.7µIU/mL (5-20) using Immulite® 2000 (Siemens Healthcare Diagnostics); the test results were compatible with the diagnosis of insulin antibody-related autoimmune hypoglycemia.



**Figure 1** The patient's glycemic excursion improved after identification and treatment of autoimmune hypoglycemia.

## Treatment

We discontinued hydralazine, the potential offending agent resulting in autoimmune hypoglycemia<sup>1,2</sup> and encouraged modest salt reduction for controlling her hypertension.<sup>3</sup> Because of the significance of dietary and behavioral interventions in management of insulin antibody-induced hypoglycemia,<sup>4</sup> a dietitian was consulted for education about carbohydrate counting and encourage the choice of food with low-glycemic index. We prescribed hydroxychloroquine, a safe immunosuppressant during pregnancy<sup>5</sup> at a dose of 200mg bid. We also prescribed acarbose, an alpha-glucosidase inhibitor that was safe during pregnancy<sup>6</sup> and effective in treating autoimmune reactive hypoglycemia,<sup>7</sup> at a dose of 50mg tid with meal. We switched the long-acting basal insulin from insulin detemir to insulin glargine according to a recent real-world observation study that support switching from detemir to glargine for better glycemic control.<sup>8</sup> We also switched the short-acting bolus insulin from insulin as part to insulin lispro, which was reported to be suitable for the treatment of diabetic patients with substantially increased insulin antibody levels.<sup>9</sup> We adjusted the dosage of insulin glargine to 12U bid and insulin lispro to 9U, 8U, 7U tid with a sliding scale according to the SMBG data. Laboratory tests on February 5, 2015 showed that the fasting glucose was 187mg/dL, the concomitant C-peptide was 0.2ng/ml, and the insulin was 11.8µIU/ml. After the adjustment of medications, her blood glucose levels became more stable (Figure 1).

## Outcome and follow-up

The patient was discharged on February 9, 2015, and was followed up at both the obstetric and diabetology clinics. No major anomaly of the fetus was found in the subsequent follow-ups. However, on the morning of April 23, 2015, at week 37 plus four days of pregnancy, the patient suddenly fainted at our hospital and was sent directly to the obstetric department, where hypoglycemia with blood glucose of 30mg/dl was detected. Therefore, she was admitted for emergent Cesarean section. A live mature female baby was delivered via Cesarean section, the Apgar score was 9 to 9, and the birth weight was 2356gm, and there was no hyper- or hypoglycemia after delivery. The patient's postpartum course was uneventful. The insulin antibodies declined gradually from 20.9% (January 30, 2015), 16.9% (March 7, 2015), to 11.6% (July 8, 2015), and the patient's HbA1c levels were 6.3%, 5.6%, and 7.5%, respectively. Because of persistent intermittent hypoglycemia, she was then started on pulse steroid therapy with 500 mg of methylprednisolone once weekly for four weeks, followed by 250mg once weekly for four weeks, and the insulin antibody levels gradually declined to 4.75% on August 10, 2016 (normal <5.5%).

## Discussion

Insulin autoimmune syndrome is a relatively rare condition that is easily under diagnosed in clinical settings. Autoimmune hypoglycemia poses diagnostic and therapeutic challenges especially in pregnant diabetic women. Since insulin autoantibody assays are not widely available, simultaneous blood sampling to check the plasma glucose, serum insulin and C-peptide might provide some clues to the diagnosis. Low blood glucose levels combined with high insulin and low C-peptide prompted the physician to consider the diagnosis of autoimmune hypoglycemia, and order a specific test to confirm the diagnosis using special assay. It has been reported that in the insulin analyzer used in our hospital, Immulite® 2000 (Siemens Healthcare Diagnostics), all insulin analogues including insulins lispro, aspart, glargine, detemir, probably except for glulisine, showed significant

interference and caused detectable insulin levels in type 1 patients receiving the insulin analogue treatments.<sup>10</sup>

We report a pregnant woman with type 1 diabetes mellitus, who presented with an abrupt loss of consciousness due to autoimmune insulin antibody-related hypoglycemic coma that was successfully treated using a multidisciplinary approach. The patient was diagnosed as T1DM at 28 years old. It has been reported that GAD autoantibodies were present in 82% patients with T1DM at disease onset, and the next most frequently identified anti-islet autoantibodies were IA-2 auto antibodies (58%) followed by autoantibodies targeted to insulin, or insulin autoantibody (IAA) (55%). Both GAD and IA-2 autoantibodies were negative in our patient. On the other hand, IAA was positive in this patient during admission, which might contribute to the insulin autoimmune hypoglycemia.

The patient also had hypertension under hydralazine treatment for about 2 weeks prior to the severe hypoglycemic episodes. Hydralazine was notorious culprit to cause autoimmune diseases including lupus erythematosus<sup>11</sup> however, hydralazine-related autoimmune hypoglycemia was rarely reported before.<sup>2</sup> In a previous case report, a 74-year-old man who had taken hydralazine for more than 3 years suffered from reactive hypoglycemic coma after several episodes of symptomatic hypoglycemia.<sup>1</sup> We discontinued hydralazine immediately after the diagnosis of insulin antibody-related hypoglycemia was made, and began to place the patient on hydroxychloroquine, an immune-modulator that was safe and effective in improving pregnancy outcome,<sup>5</sup> to help suppress the antibody titers. Hydroxychloroquine, although classified as a category C drug in pregnancy, was a safe choice and would not lead to fetal anomaly in previous reports.<sup>12</sup>

We also added acarbose to help prolong the carbohydrate absorption after a meal. Acarbose is a safe oral hypoglycemic agent during pregnancy.<sup>6</sup> It is an inhibitor of alpha glucosidase that executed effect on intestinal disaccharides, altering the intestinal absorption of carbohydrates through inhibition of their conversion into monosaccharides, and thus decrease the bioavailability of carbohydrates in the body.<sup>13</sup> Besides its anti-hyperglycemic effects, acarbose is effective in treating reactive hypoglycemia, whether the cause is autoimmune<sup>7</sup> or non-autoimmune.<sup>14</sup>

We changed the bolus insulin from insulin as part to insulin lispro. In previous case reports, changing the short-acting insulin from human insulin to insulin lispro help prevent the occurrence of insulin autoimmune hypoglycemia.<sup>9,15</sup> There is no data regarding insulin aspart and occurrence of autoimmune hypoglycemia. On the contrary, another short-acting insulin glulisine has been reported to cause autoimmune hypoglycemia<sup>16</sup> besides, the safety profile of insulin glulisine in pregnancy is still unknown.<sup>17</sup> Finally, insulin glargine has a longer duration of action as compared with insulin detemir, so we switched the basal insulin to insulin glargine to help maintain a more stable baseline glycemic status.<sup>8</sup>

After application of the above multidisciplinary strategies, the patient's blood glucose levels stabilized, no more post-prandial hypoglycemic coma developed after medication adjustment. However, just before delivery of the baby, she had hypoglycemic coma again and was sent directly to the obstetric department, when she was already pregnant at 37 weeks and was ready to undergo Cesarean section. Fortunately, her baby was delivered smoothly, and no obvious congenital anomaly was detected after birth. Besides,

there was no neonatal hypo- or hyperglycemia. Because of persistent elevation of high insulin antibody levels, pulse steroid treatment was administered, with insulin antibodies gradually declining to normal.

In this case report, we would like to stress the importance of clinical awareness of autoimmune hypoglycemia during pregnancy in patients with type 1 diabetes mellitus, and probable with gestational or type 2 diabetes mellitus, especially when sulfhydryl group-containing drugs or hydralazine were used, and suggest optimal treatment options in this unusual but critical situation.

## Funding statement

This study was supported by “Liver Disease Prevention & Treatment Research Foundation, Taiwan” to J.-Y. L. The author expresses gratitude to Chiu Hospital for their kindness in assisting with anti-insulin antibody assays.

## Acknowledgements

None.

## Conflict of interest

The author declares no conflict of interest.

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