DOI: 10.1111/dme.12659

Case Report

Successful pregnancy outcomes in a patient with type A insulin resistance syndrome

B. Enkhtuvshin[1], S. Nagashima[1], N. Saito[1], T. Wakabayashi[1], A. Ando[1], M. Takahashi[1], K. Sakai[1], D. Yamamuro[1], S. Nagasaka[1], H. Tamemoto[2] and S. Ishibashi[1]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine and [2]Division of Medical Biochemistry, Department of Biochemistry, School of Medicine, Jichi Medical University, Shimotsuke, Tochigi, Japan

Accepted 1 December 2014

Abstract

Background The management of severe insulin resistance during pregnancy is challenging because of the increased risk of perinatal complications for both mother and fetus. We describe two consecutive pregnancies in a patient with severe insulin resistance caused by a mutation in the β subunit of the insulin receptor.

Case report A non-obese Japanese woman was diagnosed as having diabetes mellitus during her first pregnancy at age 31 years. She presented at 6 weeks' gestation with a fasting plasma glucose concentration of 15.1 mmol/l and an HbA_{1c} level of 95 mmol/mol (10.8%). Fasting insulin concentration was high at 68.8 μU/ml, suggesting severe insulin resistance. Anti-insulin and insulin-receptor antibodies were both negative. Genetic analysis revealed an in-frame heterozygous deletion mutation (ΔLeu^{999}) in the insulin receptor gene. Despite large daily doses (up to 480 units per day) of insulin aspart and isophane, the patient's postprandial plasma glucose level exceeded 11.1 mmol/l. In the patient's second pregnancy, the addition of metformin at a dose of 2250 mg per day achieved tighter glycaemic control, with lower doses of insulin lispro and isophane (up to 174 units/day). Both newborns, who were found to carry the same mutation, were small for gestational age and developed transient hypoglycaemia after birth.

Conclusion Adding metformin to the conventional insulin regimen effectively achieved tight glycaemic control with a lower dose of insulin. The mutation of the insulin receptor gene might underlie the intrauterine growth retardation of the newborns. To our knowledge, this is the first report of successful management of diabetes mellitus in a pregnant woman with type A insulin resistance syndrome.

Diabet. Med. 32, e16–e19 (2015)

Introduction

The prevalence of pregnancy complicated by diabetes and/or gestational diabetes mellitus has been increasing [1]. Hyperglycaemia during pregnancy substantially increases the risk, for both mother and fetus, of developing various complications [2], which can be prevented by vigorous glycaemic control with insulin and/or metformin [3–8].

In the present paper, we report the successful outcomes of two pregnancies complicated by diabetes in a Japanese woman with severe insulin resistance, which was caused by a heterozygous mutation in the insulin receptor (INSR) gene: type A insulin resistance syndrome [9]. To date, only two cases of pregnant women with type A insulin resistance syndrome have been reported, and neither of these women developed diabetes [10,11].

Correspondence to: Shun Ishibashi. E-mail: ishibash@jichi.ac.jp

Case report

A 31-year-old woman presented at 6 weeks of gestation in her first pregnancy. Physical examination revealed acanthosis nigricans in the neck and axillary areas but no signs of hyperandrogenism. The patient's BMI was 24.4 kg/m^2 and her blood pressure was 121/80 mmHg and remained stable thereafter. Fasting plasma glucose concentration was elevated (15.1 mmol/l). A 75-g oral glucose tolerance test showed marked fasting and post-load hyperglycaemia (fasting glucose: 11.9 mmol/l; 2-h glucose: 21.7 mmol/l). Fasting serum insulin (68.8μU/ml) and HbA_{1c} levels (95 mmol/mol; 10.8%) were also high (reference range: < 16 μU/ml and 4.6–6.2%, respectively). Fasting serum C-peptide concentration

What's new

- This is the first report of successful pregnancy outcomes in a heterozygous carrier of insulin receptor mutation.
- Adding metformin to conventional insulin regimen enabled the insulin dose to be reduced by > 50% and achieved tight glycaemic control in a severely insulin-resistant state that developed during pregnancy.
- Combined therapy can be used as a practical tool for the management of severe insulin resistance such as type A insulin resistance syndrome complicated with pregnancy.

was 2.1 ng/ml and the molar ratio of insulin to C-peptide was low (0.68). Urinary C-peptide excretion was high at 318.3 μg/day (18.3–124.4 μg/day). Other hormone levels were within their reference ranges except for moderate hyperandrogenaemia: testosterone (0.74 ng/ml; reference range 0.11–0.47 ng/ml). The patient's serum biochemical profile, including lipid profile, was unremarkable. A computed tomography scan, performed while the patient was not pregnant, showed no tumorous or polycystic changes in the ovaries. Antibodies against insulin and insulin receptor were undetectable.

The patient and family members gave informed consent to the following genetic studies being undertaken. The 22 coding exons and flanking introns of the INSR gene were checked for potential mutation. We identified a deletion of three bp (CTT) in one allele of the INSR, which resulted in the loss of leucine (ΔLeu^{999}) in exon 17 (Fig. 1). The same heterozygous mutation was detected in the patient's father, who also showed severe insulin resistance (casual insulin 259 μU/ml, casual plasma glucose 13.9 mmol/l). The patient's mother, who had no mutation of the INSR gene, had type 2 diabetes mellitus without hyperinsulinaemia (casual insulin 16.5 μU/ml, random plasma glucose 7.8 mmol/l).

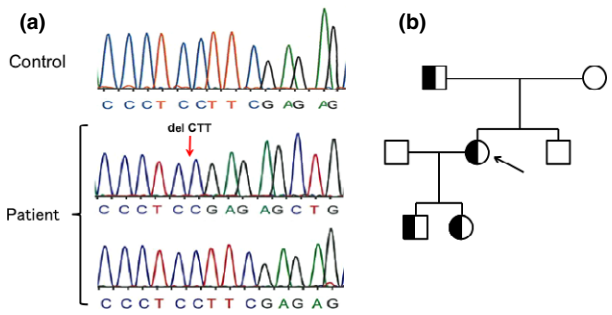

FIGURE 1 Nucleotide sequences of the region around Leu^{999} in the insulin receptor (INSR) gene in a control subject and the patient. (a) Nucleotide sequences of the plasmids to which the fragments amplified by PCR from the genomic DNA were subcloned. The red arrow indicates the heterozygous deletion of nucleotides at 2995_2997 in exon 17(c.2995_2997delCTT) in the mutant allele of the patient (middle), according to the traditional nomenclature numbering the initial nucleotide coding the first amino acid of αchain as + 1. According to nomenclature numbering the translation start site as + 1, the same mutation can be defined as c.3076_3078delCTT, which causes ΔLeu^{1026}, because 27 amino acids signal peptide is included. The wild-type allele was also found (bottom), indicating that the patient was a heterozygote for the mutation. (b) A family pedigree representing carriers of the heterozygous $\triangle Leu^{999}$ mutation. We did not genotype the patient's brother. The arrow denotes the proband; black denotes the mutant allele.

The patient was commenced on insulin therapy consisting of 18 units/day of insulin aspart, a rapid-acting human insulin analogue, and 4 units/day of human insulin isophane, along with caloric restriction (1600 kcal/day; Fig. 2). The doses were progressively increased and when they reached 380 units/day (insulin aspart 300 units/day and insulin isophane 80 units/day) at 17 weeks' gestation, the patient's blood glucose concentration was slightly decreased (average fasting and casual levels for the week were 78 and 11.4 mmol/l, respectively). HbA_{1c} concentration was lowered to 64 mmol/mol (8%). During the third trimester, the patient's blood glucose began to increase and the insulin dose was gradually increased, reaching 480 units/day at 35 weeks' gestation. The patient gained only 1.6 kg of weight during the pregnancy. At 37 weeks' gestation, she vaginally delivered a boy with a weight of 2224 g (< 10th percentile), who turned out to be heterozygous for the ΔLeu^{999} mutation of the INSR gene. Apgar scores at 1, 5 and 10 min were normal. The baby had no abnormality and showed only transient tachypnoea. His blood glucose was 5.8 mmol/l just after birth, gradually fell to 1.1 mmol/l by 3 h later, despite treatment with intravenous dextrose, and rose to 4.6 mmol/l after 10 h.

Two years after delivery, because of poor HbA_{1c} control [98 mmol/mol (11.1%) with insulin aspart 120 U/day and insulin isophane 80 U/day], 1500 mg/day of metformin was added to the insulin treatment. Insulin and metformin doses were unchanged until the first trimester of the second pregnancy when the patient's HbA_{1c} concentration was decreased to 68 mmol/mol (8.4%).

Almost two and a half years after her first delivery, the patient was hospitalized for glycaemic control. The metformin dose was increased to 2250 mg/day and daily energy intake was decreased to 1200 kcal/day.

Soon after discharge the patient became pregnant again. Throughout the second pregnancy, metformin 2250 mg/day was administered along with insulin regimen and caloric restriction (1600 kcal/day). Insulin lispro was substituted for insulin aspart, with a starting dose of 36 and final dose of 150 units/day, and the insulin isophane dose was increased from 4 to 24 units/day. The patient's blood glucose was managed carefully with an average HbA_{1c} level achieved of 45 mmol/mol (6.3%). The patient gained only 1.3 kg of weight during the pregnancy. At 38 weeks' gestation, she delivered a girl with a weight of 2532 g (< 25th percentile) without any other abnormalities, who was also found to be heterozygous for the ΔLeu^{999} mutation of the INSR gene.

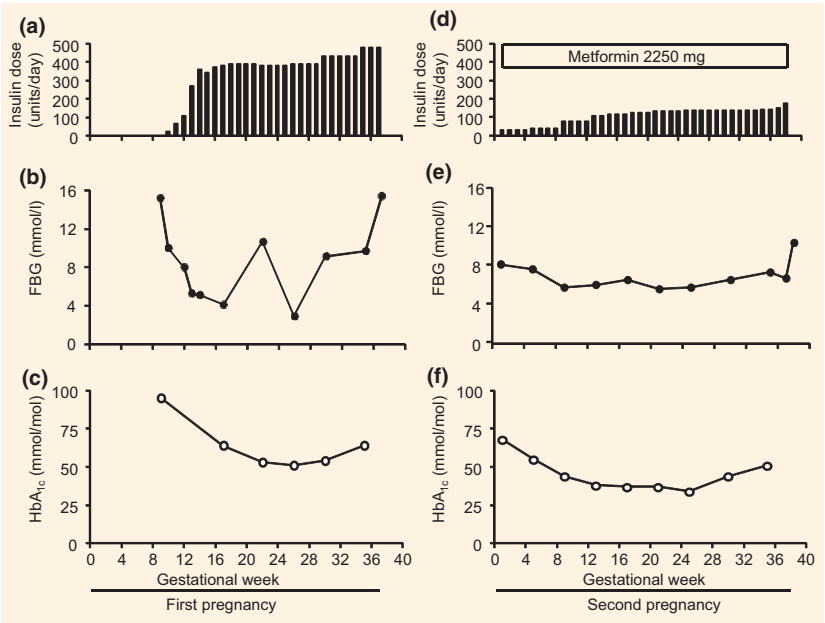

FIGURE 2 Fasting blood glucose and HbA_{1c} measurements in response to insulin and metformin treatment. (a–c) First pregnancy and (d–f) second pregnancy.

Apgar scores were normal. Just after delivery, the baby's blood glucose was 1.2 mmol/l but rose to 3.9 mmol/l within 3 h, after intravenous dextrose administration.

After the delivery, metformin was discontinued. HbA_{1c} levels were 95 mmol/mol (10.8%) with total insulin doses of 114 units/day. Despite the relatively poor glycaemic control before and after the two pregnancies, the only complication found at 1 year after the second delivery was simple diabetic retinopathy.

Discussion

As the patient was profoundly hyperglycaemic early in her pregnancy, she was diagnosed as having overt diabetes in pregnancy [12]. She was also severely insulin-resistant, prompting us to search for the causes of insulin resistance. She did not have polycystic ovary syndrome, one of the common causes of severe insulin resistance, and was diagnosed as having type A insulin resistance syndrome because heterozygous ΔLeu^{999}mutation was found in the INSR gene. The same mutation was originally reported in a hyperinsulinaemic patient, who did not have diabetes, in the same area of Japan, indicating that both patients shared the same ancestors, although we could not find any overlap in the pedigrees [13]. According to Awata *et al.* [13], tyrosine kinase activity of the INSR with ΔLeu^{999} mutation was significantly decreased compared with wild-type INSR.

In insulin-resistant patients with INSR mutations, hyperglycaemia is extremely difficult to treat. In the patient's first pregnancy, insulin aspart and insulin isophane were used, but glycaemic control was unfavourable. Insulin aspart has also been reported to control postprandial glucose in patients with gestational diabetes [6], although the dose (0.9 units/kg) in that study was substantially lower than the dose used in our patient (5.7–6.6 units/kg for gestational age ≥ 26 weeks). Our patient also needed supplementary insulin isophane (1.3–1.8 units/kg/day).

Before the patient's second pregnancy, metformin was added to the insulin regimen in an attempt to reduce insulin resistance and the total insulin dose. Metformin has been shown to be an effective and safe treatment option for gestational diabetes [3], although in almost half of the cases, supplementary insulin was needed to achieve the target level of glucose. In Japan, however, metformin use during pregnancy is recommended only if the benefit outweighs the risk. Because insulin lispro has more evidence on safety during pregnancy than insulin aspart [14], we used insulin lispro instead of insulin aspart. Combined therapy of metformin with insulin lispro and insulin isophane was able to reduce the total insulin dose to 174 units/day, which is less than half of the dose in the first pregnancy, supporting the hypothesis that metformin spares insulin by sensitizing insulin action through suppressing hepatic glucose output or increasing glucose uptake by peripheral tissues. The similar efficacy of additional use of metformin to insulin has been reported in patients with Type 2 diabetes mellitus [15,16], but not in pregnancy. The insulin dose and glycaemic control were similar during the lactation period when metformin was discontinued. It is also possible that more strict adherence to the caloric restriction caused better glycaemic control in the second pregnancy judging from the smaller weight gain.

It is noteworthy that both babies, who inherited the same mutation of the INSR gene from their mother, were small for gestational age. Although patients harbouring a bi-allelic defect of the INSR gene, such as that found in Donohue's syndrome and Rabson–Mendenhall syndrome, have intrauterine and postnatal growth deficiency, haploinsufficiency of INSR, type A insulin resistance syndrome, is not usually associated with intrauterine growth retardation [17]. It is possible that the ΔLeu^{999} mutation compromises insulin signalling more severely than most other mutations by a dominant negative effect, thereby conferring phenotypic similarity to patients with bi-allelic defects. It is also possible that the strict caloric restriction compromised the intrauterine growth of the babies.

In summary, we experienced successful outcome of pregnancies in a patient with type A insulin resistance syndrome caused by INSR with the ΔLeu^{999} mutation. Although a large dose of exogenous insulin was required, there were no abnormalities in the babies except for transient hypoglycaemia and low body weight. Adding metformin significantly reduced the required doses of insulin and achieved superior glycaemic control to insulin therapy alone. The combined therapy may be a practical tool for the management of severe insulin-resistant diabetes mellitus associated with pregnancy.

Funding sources

None.

Competing interests

None declared.

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