Development of postpartum Graves' disease and type 1 diabetes after delivery in a patient with gestational diabetes

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ABSTRACT

Pregnancy and the postpartum period are associated with changes of the immune system. These changes might eventually result in autoimmune diseases, such as Graves' disease and type 1 diabetes mellitus, in the postpartum period. We describe a case of a patient with gestational diabetes who developed both Graves' disease and type 1 diabetes mellitus in the postpartum period. The pathology of gestational diabetes (GDM) is close to that of type 2 diabetes mellitus. However, the present case emphasizes the importance of screening and monitoring high-risk GDM patients for all available autoimmune antibodies throughout pregnancy and the postpartum period, as GDM has a risk of developing into type 1 diabetes and multiple autoimmune diseases. In addition, only Graves' disease was transient, whereas type 1 diabetes mellitus remained permanent in the present case. Thus, the present case shows etiological differences between these two autoimmune diseases. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00089.x, 2011)

KEY WORDS: Gestational diabetes mellitus, Postpartum thyroiditis, Type 1 diabetes mellitus

INTRODUCTION

Pregnancy induces physiological alternations including insulin resistance and immunosuppression[1]. Gestational diabetes mellitus (GDM), which is close to type 2 diabetes mellitus, develops in 2–6% of pregnancies[2]. In addition, a risk of developing autoimmune diseases, such as type 1 diabetes mellitus and autoimmune thyroid disease, increases in the postpartum period. Classic type 1A diabetes is classified as autoimmune diabetes, characterized by autoantibodies such as glutamic acid dehydrogenase (GAD). Postpartum Graves' disease is known to occur and account for 10% of postpartum autoimmune thyroid disease (PPATS)[3]. In the present case report, we report a case of a patient with gestational diabetes that is complicated with Graves' disease and type 1 diabetes mellitus after delivery. Insulin dependency remained almost a year after delivery, despite normalization of thyroid function.

CASE REPORT

The present case was a 28-year-old woman with a family history of type 2 diabetes. She presented with glucosuria in the 12th week of pregnancy. Fasting plasma glucose level was 7.8 mmol/L (140 mg/dL) in the 32nd week of pregnancy. She was then diagnosed with GDM and treated by diet modification. The baby (3780 g bodyweight) was delivered by cesarean section in the 40th week of pregnancy. A month after delivery, the patient's postpartum evaluation of GDM was carried out. Her height was 163 cm, bodyweight was 54.0 kg and body mass index was 22.9. She had no history of smoking or alcohol consumption. Physical examination showed that her thyroid gland was swelling at a degree of III and a diffuse goiter was detected by ultrasound sonography. Laboratory tests showed 9.9 mmol/L (178 mg/dL) fasting plasma glucose level, and 8.0% hemoglobin A_{1c} (HbA_{1c}). Thyroid-stimulating hormone (TSH) level was 1.05 μU/mL, thyroid microsomal antigen (MCHA) was positive (1:1600). Liver and renal function were normal. It has been concluded that the patient had developed diabetes after delivery and had been treated by dietary modification. Three months after delivery, the patient presented with palpitations and finger tremor. On laboratory examination, the free T4 level was 7.77 ng/dL and the free T3 level was 26.3 pg/mL. TSH level was lower than 0.05 μU/mL and TSH receptor antibody (TRAb) was positive (30.4%). She was diagnosed with postpartum thyroid dysfunction (Graves' disease) and given propylthiouracil. After 6 months from delivery, the patient showed poor glycemic control, and high levels of urine and serum ketones. The patient's plasma glucose level was elevated to 24.6 mmol/L (443 mg/dL), HbA_{1c} level was 12.1% and serum C-peptide level was 0.47 ng/dL. Anti-GAD antibody was 144 U/mL and insulin autoantibody

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was 6.1%. Based on these results, the patient was diagnosed with type 1 diabetes and insulin therapy was initiated. After 11 months from delivery, TRAb became negative and thyroid dysfunction showed remission. However, GAD remained positive and the patient is currently receiving insulin therapy.

The patient gave her written informed consent for publication of the present case report in *Journal of Diabetes Investigation*.

DISCUSSION

GDM is defined as glucose intolerance with onset or first recognition during pregnancy[2]. The physiological changes during pregnancy include increase in insulin resistance, manifesting GDM[1]. The initiating factor is likely to be increased peripheral insulin resistance of normal pregnancy, but in an attempt to overcome the increased insulin resistance, relative pancreatic insufficiency develops. Thus, the pathology of GDM is similar to type 2 diabetes[2]. It is known that women with GDM have a considerable risk of developing type 2 diabetes later in life[2].

Pregnancy induces alterations in the immune system. This is because the fetus continuously needs protection against the mother's immunological system[1]. After delivery, the immune response is accelerated by a rebound phenomenon. This response is known to have a risk of causing autoimmune disease including type 1 diabetes and autoimmune thyroid disease to the mother[1,3]. Type 1 diabetes is thought to arise from an autoimmune attack against the pancreatic β-cells, which leads to failure to regulate blood glucose levels. Usually, antibodies against islets, insulin and GAD are found to be positive in patients[4].

PPATS is a thyroid dysfunction occurring within the first year after delivery[5,6]. It has been reported that 11–17% of women experience thyroid dysfunction after delivery. Graves' disease after delivery is a PPATS[7,8]. Approximately 5% of these women develop postpartum Graves' disease[9]. The presence of antimicrosomal antibodies, a family history of autoimmune disease and insulin dependent diabetes are known to increase its risk[4]. High-risk mothers for postpartum thyroid dysfunction are well screened by MCHA and antithyroid therapy might be a good choice for first-line therapy, as postpartum Graves' hyperthyroidism is often transient[7,8]. Activation of the disease occurs within 4 months postpartum [7,8]. There was also a report showing the development of both type 1 diabetes and Graves' disease after delivery[10]. The association of GAD with thyroid antibodies might be explained by the fact that GAD is not exclusively present in the brain and pancreas, but can also be found in the thyroid gland[11]. It has been reported that in patients with type 1 diabetes and Graves' disease, HLA-DRB1*0405-DQB1*0401 haplotype was detected[12,13] and T-helper 1 lymphocytes in peripheral blood were reduced[14]. In addition, hyperthyroidism might aggravate glucose intolerance by multiple mechanisms[15].

In the case of our patient, although the pathological mechanism of GDM is considered to be analogous to that of type 2 diabetes, GDM developed into type 1 diabetes with the presence of islet antibodies. In the past, it has been reported that GDM has a risk of developing into type 1 diabetes as well[16]. Järvelä *et al.*[17] reported that 4.6% of GDM developed into type 1 diabetes, whereas 5.3% developed into type 2 diabetes. They also identified that young age (<30 years), the need for insulin treatment during pregnancy, and positivity for islet cell antibodies (ICA) and GAD conferred a high risk of progression to type 1 diabetes[17]. Füchtenbusch *et al.*[18] suggested that β-cell autoantibodies determined at delivery in GDM were highly predictive for the development of type 1 diabetes in the postpartum period. They reported that single antibody screening with GAD yielded the highest sensitivity of 63%. However, by screening with all three markers (GAD, ICA and antibodies to the protein tyrosine phosphatase-related protein 2 molecule; IA2A), sensitivity can be increased up to 82%. They also pointed out that women with one or more pregnancies before the index pregnancy had a higher risk for developing type 1 diabetes after delivery compared with women who were in their first pregnancy[18].

Usually, the examination of GAD antibodies is used for the screening of type 1 diabetes in Japan. The aforementioned findings emphasized the importance of screening and monitoring high-risk GDM patients, not just after delivery, but during pregnancy and at delivery. In addition, the importance of checking all available autoimmune antibodies in diagnosing type 1 diabetes in GDM patients.

Interestingly in our case, TRAb became negative and thyroid dysfunction showed remission, whereas still GAD remained positive. The patient is currently receiving insulin therapy. Postpartum Graves' disease is usually transient. Although it is likely that in the case of our patient both Graves' disease and type 1 diabetes had a common cause, only Graves' disease was transient whereas type 1 diabetes remained permanent. Thus, the present case might show etiological differences between these two autoimmune diseases. Management of diabetes might be needed throughout pregnancy and the postpartum period.

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REFERENCES

1. Clark D, Arck P, Chaouat G. Why did your mother reject you? Immunogenetic determinants of the response to environmental selective pressure expressed at the uterine level. *Am J Reprod Immunol* 1999; 41: 5–22.
2. Kaaja R, Greer I. Manifestations of chronic disease during pregnancy. *JAMA* 2005; 294: 2751–2757.
3. Lazarus J, Premawardhana L. Screening for thyroid disease in pregnancy. *J Clin Pathol* 2005; 58: 449–452.
4. Park J, Chong A, Cochran E, *et al.* Type 1 diabetes associated with acquired generalized lipodystrophy and insulin resistance: the effect of long-term leptin therapy. *J Clin Endocrinol Metab* 2008; 93: 26–31.
5. Muller A, Drexhage H, Berghout A. Postpartum thyroiditis and autoimmune thyroiditis in women of childbearing age:

recent insights and consequences for antenatal and postnatal care. *Endocr Rev* 2001; 22: 605–630.
6. Parkes A, Othman S, Hall R, *et al.* Role of complement in the pathogenesis of postpartum thyroiditis: relationship between complement activation and disease presentation and progression. *Eur J Endocrinol* 1995; 133: 210–215.
7. Amino N, Tada H, Hidaka Y. Postpartum autoimmune thyroid syndrome: a model of aggravation of autoimmune disease. *Thyroid* 1999; 9: 705–713.
8. Amino N, Tada H, Hidaka Y, *et al.* Therapeutic controversy: screening for postpartum thyroiditis. *J Clin Endocrinol Metab* 1999; 84: 1813–1821.
9. Kordonouri O, Hartmann R, Deiss D, *et al.* Natural course of autoimmune thyroiditis in type 1 diabetes: association with gender, age, diabetes duration, and puberty. *Arch Dis Child* 2005; 90: 411–414.
10. Sakaue S, Nagata M, Wakabayashi O, *et al.* A case of fulminant type 1 diabetes with elevated rheumatoid factor and the temporal presence of thyroid-stimulating hormone receptor antibody. *Diabetes Care* 2002; 25: 935–936.
11. Kawasaki E, Takino H, Yano M, *et al.* Autoantibodies to glutamic acid decarboxylase in patients with IDDM and autoimmune thyroid disease. *Diabetes* 1994; 43: 80–86.
12. Hashimoto K, Maruyama H, Nishiyama M, *et al.* Susceptibility alleles and haplotypes of human leukocyte antigen DRB1, DQA1, and DQB1 in autoimmune polyglandular syndrome type III in Japanese population. *Horm Res* 2005; 64: 253–260.
13. Eisenbarth G, Gottlieb P. Autoimmune polyendocrine syndromes. *N Engl J Med* 2004; 350: 2068–2079.
14. Aso Y, Matsuura H, Momobayashi A, *et al.* Profound reduction in T-helper (Th) 1 lymphocytes in peripheral blood from patients with concurrent type 1 diabetes and Graves' disease. *Endocr J* 2006; 53: 377–385.
15. Van den Driessche A, Eenkhoorn V, Van Gaal L, *et al.* Type 1 diabetes and autoimmune polyglandular syndrome: a clinical review. *Neth J Med* 2009; 67: 376–387.
16. Catalano P, Tyzbir E, Sims E. Incidence and significance of islet cell antibodies in women with previous gestational diabetes. *Diabetes Care* 1990; 13: 478–482.
17. Järvelä I, Juutinen J, Koskela P, *et al.* Gestational diabetes identifies women at risk for permanent type 1 and type 2 diabetes in fertile age: predictive role of autoantibodies. *Diabetes Care* 2006; 29: 607–612.
18. Füchtenbusch M, Ferber K, Standl E, *et al.* Prediction of type 1 diabetes postpartum in patients with gestational diabetes mellitus by combined islet cell autoantibody screening: a prospective multicenter study. *Diabetes* 1997; 46: 1459–1467.