Metformin Use in an Obese Diabetic Patient from Weeks 1 to 21 of Pregnancy.

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A 43-year-old diabetic woman was admitted in the 15th week of her first pregnancy. When HbA1c levels were 8.2%, we began diet therapy and continuous subcutaneous insulin infusion (CSII) therapy. The HbA1c levels subsequently ranged from 6.2 to 6.7%. She was delivered without complications of a healthy male infant (3120g) in the 38th week. Metformin was then administered. Six months later she was diagnosed as being in the 21st week of pregnancy. We changed from metformin to CSII therapy immediately. The HbA1c levels had ranged from 6.0 to 6.4% before the CSII therapy and from 5.8 to 6.3% after the CSII therapy during the entire second pregnancy. A macrosomia delivery (4070g) occurred in the 37th week. Although glycemic control was better during the 2nd pregnancy than the 1st pregnancy, metformin use until the 21st week may have induced macrosomia. (Kitakanto Med J 2005 ; 55 : 37~39)

Key Words : metformin, continuous subcutaneous insulin injection, macrosomia

Introduction

Good glycemic control during pregnancy in women with Type 1 diabetes mellitus is important in minimizing the risk of fetal malformation and macrosomia. Although some studies have suggested that glycemic control in the immediate pre-conception period and 1st trimester has a greater influence on birth weight than glycemic control during the 2nd or 3rd trimesters,^{1,2} others consider glycemic control during the last trimester of pregnancy to also be important.^{3,4}

Metformin, a biguanide, is normally used to treat Type 2 diabetes mellitus. It lowers insulin resistance by direct stimulation of peripheral glucose uptake.⁵ The drug is used for the treatment of polycystic ovary syndrome as it reduces the plasma luteinizing hormone and ovarian androgen levels, and hyperinsulinism.⁶

We have reported on macrosomia delivery in a Type 2 diabetic patient using metformin until the twenty-first week of pregnancy.

Case report

A 43-year-old woman was admitted for hyperglycemia (238mg/dl) in the 15th week of her first pregnancy. Her weight was 60kg at age 20. Her maximal weight was 85kg at age 35. Urine glucose was present at age 37. Her older sister and mother had diabetes mellitus. There was no previous history of any disease other than diabetes mellitus. She did not smoke or drink alcohol. Her physical examination showed the following findings: height 160cm, weight 76kg (body mass index: 29.7kg/m²), blood pressure 115/71mmHg, pulse rate 80/min, temperature 36.8°C. Funduscopic examination revealed no diabetic retinopathy. There was no abnormality in her neck, chest or abdomen and there was no lymphadenopathy. There were symmetrically normal tendon reflexes and sensation.

Urinalysis, hematology, liver function, renal function and electrolyte levels were normal. Total cholesterol; 178mg/dl, high density lipoprotein (HDL) - cholesterol; 36mg/dl, triglyceride; 158mg/dl, fasting blood glucose; 149mg/dl, HbA1c; 8.2%, fasting immunoreactive insulin; 15μU/ml (HOMA-R⁷5.52) and urine C-peptide reactivity 158μg/day.

We had started diet therapy (before the 20th week

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Fig.1 Clinical course

of pregnancy: 1520kcal/day, after 21st week of pregnancy: 1680kcal/day), and continuous subcutaneous insulin infusion (CSII) (used by SP-3HQ, Nipro, Osaka, Japan) therapy. The CSII involved basal 0.4 u/hr and an additional (30 minutes prior to breakfast: 6u, lunch: 6u, dinner: 6u). After that the HbA1c levels ranged from 6.2 to 6.7% (Fig.1). She was delivered without complications of a healthy male infant (3120g) in the 38th weeks' pregnancy. Although she had been on a diet therapy after birth, the HbA1c levels had elevated from 5.6 to 8.3%. Therefore we administered metformin hydrochloride (Sumitomo Co.Ltd., Osaka) 500mg, twice a day. The HbA1c levels subsequently improved (Fig.1). Six months later, she was diagnosed as being in the 21st week of pregnancy. At this time, her weight was 69kg (body mass index: 27.0kg/m²), blood pressure 101/62mmHg, total cholesterol; 198mg/dl, HDL-cholesterol; 49mg/dl, triglyceride; 143mg/dl, fasting blood glucose; 94mg/dl, HbA1c; 6.0% and fasting immunoreactive insulin; 8μU/ml (HOMA-R 1.86). We had changed metformin hydrochloride to CSII therapy involving basal 0.4 u/hr and an additional (30 minutes prior to breakfast: 5u, lunch: 5u, dinner: 5u). The HbA1c levels had ranged from 6.0 to 6.4% before the CSII therapy and from 5.8 to 6.3% after the CSII therapy during the entire pregnancy. No hypoglycemia was noted. A macrosomia delivery (4070g) occurred at the 37th pregnancy.

Discussion

From the immediate pre-conception period to the 1st trimester, the HbA1c levels were 8.2% in the 1st pregnancy and the levels had ranged from 6.2 to 6.4% in the 2nd pregnancy. During the 2nd or 3rd trimesters, the HbA1c levels had ranged from 6.2 to 6.7% in the 1st pregnancy and from 5.8 to 6.3% in the 2nd

pregnancy. Although the HbA1c levels were poorer from the immediate pre-conception period to the 3rd trimester in the 1st pregnancy than in the 2nd pregnancy, she was delivered of a normal infant in the 1st pregnancy while a macrosomia delivery occurred in the 2nd pregnancy. Since siblings are not genetically identical, macrosomia in the 2nd pregnancy may not have been due to the blood glucose control effect, in particular, from the immediate pre-conception period to the 1st trimester. She had taken metformin until the 21st week of pregnancy during her 2nd pregnancy. The HOMA-R levels reflecting increased peripheral insulin resistance were lower at the 21st week of the 2nd pregnancy than at the 15th week of the 1st pregnancy due to weight reduction after diabetes mellitus treatment using insulin-lowering therapies such as metformin.⁵ Although metformin has no adverse effects on mouse embryos or human fetal and neonatal development,⁸ it is predicted by a placental transport model to rapidly cross to the fetus because of its low molecular weight.⁹ Metformin therapy throughout pregnancy in women with polycystic ovary syndrome reduces the otherwise high rate of first trimester spontaneous abortion seen among women not receiving metformin and does not appear to be teratogenic.¹⁰ However, treatment with metformin during pregnancy is associated with increased prevalence of pre-eclampsia and a high perinatal mortality.¹¹ The mean birth weight in the metformin user (3350g) is slightly higher than in glibenclamide user (3245g) or insulin users (3231g).¹² The other report shows macrosomia from 16 to 17% in metformin users and 17 to 26% in diet therapy alone.¹³ Therefore, the cause of macrosomia in the 2nd pregnancy may have been due to metformin administration until the 21st week of pregnancy. Because metformin primarily targets peripheral insulin resistance with no effect on insulin secre-

tion,⁵ we use it to treat obese diabetes mellitus with insulin resistance. However, it must be carefully used in young obese sexually active diabetic women.

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