OBSERVATIONS

Sulfonylurea Use During Entire Pregnancy in Diabetes Because of *KCNJ11* Mutation: A Report of Two Cases

Mutations of the *KCNJ11* gene are a common cause of permanent neonatal diabetes (PNDM) (1,2) and sometimes result in other diabetic phenotypes (2). Sulfonylureas (SUs) are effective and safe in most diabetic *KCNJ11* mutation carriers (3). However, their application risk is sometimes uncertain. We have previously described glibenclamide use in a pregnant woman with *KCNJ11*-related PNDM (4); for the first time, we report two cases treated with SU throughout the entire pregnancy.

The first case was a Hungarian woman with the E229 K *KCNJ11* mutation resulting in relapsing neonatal diabetes. The patient experienced remission between the ages of 3 and 10 years, at which point insulin was restarted. At the age of 13, after genetic testing, the patient was switched to gliclazide 60 mg/day. The woman became pregnant at the age of 16 years. When she was referred to the clinic in the 11th week of pregnancy, HbA_{1c} was 8.2%. Because diabetes was brittle during the insulin treatment on which she had been earlier, it was decided to continue gliclazide; the Bioethical Committee was informed. She was normoglycemic (HbA_{1c} 5.8, 5.2, and 5.2%) on a stable SU dose. Cesarean delivery was performed in the 38th week. The Apgar score of the baby girl (birth weight 3,010 g) was 10 at the first minute; the neonatal period was uneventful. Genetic testing from the umbilical cord blood showed the E229 K mutation. So far, the baby, currently 18 months old, has not been diagnosed with diabetes and is developing normally.

The second case, a previously reported R201H *KCNJ11* mutation carrier with multiple diabetes complications from Poland (4,5) became pregnant again at the age of 39 years when she was on glibenclamide 45 mg/day. Informed about the risks, she ruled out switching to insulin and decided to continue SU. HbA_{1c} at the 5th month of pregnancy was 5.8%. The amniocentesis in the 16th week showed the fetal DNA without chromosomal abnormalities or the R201H mutation. The woman delivered prematurely in the 33rd week via Cesarean section; the indication was the mother's status: edema, proteinuria, and renal function impairment. The latter was probably responsible for the need for glibenclamide dose reduction (10 mg/day). The Apgar score of the newborn (birth weight 2,720 g, >90 percentile) was 7 at the first minute. The baby girl presented with decreased muscle tension and cyanosis. She was also diagnosed with hypoglycemia requiring intravenous glucose, hyperbilirubinemia (treated with phototherapy), and respiratory acidosis. The latter was initially treated with continuous positive airway pressure and then, for 2 days, noninvasive mechanical ventilation. The recovery was uneventful. No birth defects were recorded. The child's development at the 18th month was normal.

In summary, we provide evidence that SUs constitute an alternative to insulin in pregnant women with Kir6.2-related diabetes, particularly in those refusing standard treatment or not adherent to this approach. The use of SUs did not result in developmental abnormalities. As in the first pregnancy (4), transient complications occurred in the baby of the mother with the R201H mutation receiving glibenclamide. Nevertheless, one should be careful with attributing them to the specific drug because they are common in prematurity.

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References

1. Gloyn AL, Pearson ER, Antcliff JF, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 2004;350:1838–1849
2. Gloyn AL, Reimann F, Girard C, et al. Relapsing diabetes can result from moderately activating mutations in KCNJ11. Hum Mol Genet 2005;14:925–934
3. Klupa T, Edghill EL, Nazim J, et al. The identification of a R201H mutation in KCNJ11, which encodes Kir6.2, and successful transfer to sustained-release sulphonylurea therapy in a subject with neonatal diabetes: evidence for heterogeneity of beta cell function among carriers of the R201H mutation. Diabetologia 2005;48:1029–1031
4. Klupa T, Kozek E, Nowak N, et al. The first case report of sulfonylurea use in a woman with permanent neonatal diabetes mellitus due to KCNJ11 mutation during a high-risk pregnancy. J Clin Endocrinol Metab 2010;95:3599–3604
5. Klupa T, Skupien J, Mirkiewicz-Sieradzka B, et al. Diabetic retinopathy in permanent neonatal diabetes due to Kir6.2 gene mutations: the results of a minimum 2-year follow-up after the transfer from insulin to sulphonylurea. Diabet Med 2009;26:663–664