Pregnancy outcome of Japanese patients with glucokinase–maturity-onset diabetes of the young

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ABSTRACT

Aims/Introduction: Glucokinase–maturity-onset diabetes of the young (GCK-MODY; also known as MODY2) is a benign hyperglycemic condition, which generally does not require medical interventions. The only known exception is increased birthweight and related perinatal complications in unaffected offspring of affected women. As previous data were obtained mostly from white Europeans, the present study analyzed the pregnancy outcomes of Japanese women with GCK-MODY to better formulate the management plan for this population.

Materials and Methods: The study participants were 34 GCK-MODY families whose members were diagnosed at Osaka City General Hospital during 2010–2017. A total of 53 pregnancies (40 from 23 affected women, 13 from 11 unaffected women) were retrospectively analyzed by chart review.

Results: Birthweights of unaffected offspring born to affected women were significantly greater as compared with those of affected offspring (\(P = 0.003\)). The risk of >4,000 g birthweight (16%), however, was lower as compared with that previously reported for white Europeans, and none of the offspring had complications related to large birthweight. Insulin treatment of the affected women resulted in a significant reduction in the birthweights of unaffected offspring. Perinatal complications including small-for-gestational age birthweight were found only in affected offspring born to insulin-treated women.

Conclusions: In Japanese GCK-MODY families, unaffected offspring born to affected women were heavier than affected offspring. However, insulin treatment of affected women might not be advisable because of the lower risk of macrosomic birth injury, and an increased risk of perinatal complications in affected offspring.

INTRODUCTION

Glucokinase–maturity-onset diabetes of the young (GCK-MODY; also known as MODY2) is a form of dominantly inherited diabetes/hyperglycemia caused by heterozygous, inactivating mutations in the glucokinase (GCK) gene. Glucokinase serves as a glucose sensor in pancreatic β-cells. Affected individuals, therefore, have elevated thresholds of blood glucose for insulin secretion, usually presenting with mildly elevated fasting hyperglycemia (5.5–8.0 mmol/L) and limited glucose excursions (<4.6 mmol/L) after 75 g oral glucose tolerance test.
Micro- and macrovascular diabetic complications are exceedingly rare across different ethnicities\(^2\), and they normally do not need any pharmacological interventions\(^1\). The only exception appears to be the pregnancy of women with GCK-MODY\(^4\). When an affected woman carries an unaffected fetus, the pregnancy could result in neonatal macrosomia and associated complications\(^5\).

Several investigators have advocated different management strategies; some supported insulin treatment during pregnancy\(^7\), whereas others promoted close monitoring of pregnancy and interventions as early delivery or insulin treatment when required\(^6\). Of note, most of these observations and management plans are based on experiences in white Europeans, and there have been few reports of pregnancy in Asians with GCK-MODY. In the present study, we carried out a retrospective analysis of pregnancy outcomes of Japanese patients with genetically confirmed GCK-MODY.

**METHODS**

The study participants were individuals with genetically confirmed GCK-MODY diagnosed at Osaka City General Hospital, Osaka, Japan, between 2010 and 2017. The details of the mutational analyses were reported previously\(^3\). A total of 53 pregnancies from 34 families were analyzed in the current study. Of these, 40 pregnancies from 23 families involved affected mothers, while 13 pregnancies from 11 families involved affected fathers. For both, multiple pregnancies and premature birth before 28 weeks were excluded from the analysis. In addition, the following clinical information was collected by chart review: (i) gestational age at delivery; (ii) fetal birthweight; (iii) details of maternal antenatal treatment; and (iv) perinatal complications. The birthweight centiles were corrected for sex, gestational age and birth order of Japanese newborns according to the standard published by the Japanese Society of Pediatric Endocrinology and the Japanese Society for Human Auxology (http://www.auxology.jp/taikakubirthlongcross). The study protocol was approved by the institutional review board at Osaka City General Hospital (No. 1610072), and written informed consent was obtained from the study participants or their guardians.

For statistical analysis, quantitative variables were analyzed using the Kruskal–Wallis test or the Mann–Whitney U-test, and categorical variables were compared using the \( \chi^2 \)-test or Fisher’s exact test. All tests were carried out using SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA). For all statistical analyses, \( P < 0.05 \) was considered as significant.

**RESULTS**

Table 1 summarizes the clinical features of GCK-MODY pregnancies in the present study. There were no significant differences in the sex and the gestational age of offspring between groups. However, compared with the affected offspring of affected or unaffected (i.e., with affected fathers) women, both the birthweights and the birthweight centiles were significantly greater (\( P = 0.003 \)) in the unaffected offspring born to affected women (Table 1). In fact, four of the unaffected offspring (\( n = 12 \)) had birthweights greater than the 90th centiles for gestational age, whereas only one exceeded the 90th centiles in the affected offspring. Two of the unaffected neonates had macrosomia (birthweight >4,000 g); however, none of these had complications related to the larger birthweight. On average, unaffected offspring of affected women were 690 g heavier compared with affected offspring (Table 1; Figure 1).

Of the 40 pregnancies involving affected women, 13 were treated by insulin injections during pregnancy; nine in the affected offspring group and four in the unaffected group. As shown in Table 2, in the unaffected group, the offspring of insulin-treated women had significantly lower birthweight centiles than those of women treated with the diet alone intervention. The birthweight of affected offspring also tended to be lower in the insulin-treated group, although the difference did not reach statistical significance (Table 2; Figure 2).

Furthermore, perinatal complications were found in four newborns: neonatal jaundice in two, small-for-gestational age in one and patent ductus arteriosus in one. All these complications were found in affected offspring born to insulin-treated

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**Table 1 | Pregnancy outcome of offspring born to affected or unaffected mothers**

|                     | Affected mother | Unaffected offspring | Affected father |
|---------------------|-----------------|----------------------|-----------------|
| Sex (male/female)   | 13/15           | 9/3                  | 8/5             |
| Gestational age (weeks) | 38.4 ± 2.3 | 39.3 ± 1.0           | 39.2 ± 0.9      |
| Birthweight (g)     | 2713 ± 551      | 3403 ± 559           | 2838 ± 306      |
| Birthweight centiles| 406 ± 30.5      | 749 ± 26.7           | 37.2 ± 25.8     |
| Macrosomia > 4,000 g | 0 (0%)         | 2 (16%)              | 0(0%)           |
| Insulin treatment during pregnancy | 9 (32.1%) | 4 (33.3%) |               |

For gestational age, birthweight and birthweight centiles, the mean ± standard deviations are shown.*Pearson’s \( \chi^2 \)-test. **Kruskal–Wallis test. ***Kruskal–Wallis test with post-tests. \( P = 0.002 \) group 1 versus group 2, \( P = 0.031 \) group 2 versus group 3. ****Kruskal–Wallis test with post-tests. \( P = 0.005 \) group 1 versus group 2, \( P = 0.009 \) group 2 versus group 3. Fathers were affected in the unaffected mothers group.
In fact, one was born at 37 weeks of gestation with a birthweight of 1,542 g (−3.21 standard deviations).

DISCUSSION

Previously, it was reported in the UK that among white Europeans (82 offspring of 42 women with GCK-MODY), unaffected offspring of affected women were, on average, 700 g heavier (mean birthweight 3.9 kg) than affected offspring (mean birthweight 3.2 kg), probably because of the elevated glucose levels in utero. In a different study of Irish women (41 offspring of 12 women with GCK-MODY), unaffected offspring of affected women were significantly heavier (mean birthweight 3.2 kg) than affected offspring (mean birthweight 3.2 kg). In the present series of Japanese women with GCK-MODY, similar to the results of the UK study, unaffected offspring born to women with GCK-MODY were 690 g heavier than affected offspring. However, the mean birthweight of affected offspring was lower (3.4 kg) in the Japanese cohort when compared with those in the UK or Ireland. Two of the unaffected offspring in the present series had a birthweight >4,000 g, which is known to result in increased birth complications both in white European and Japanese people. The risk of macrosomia (16%) was relatively lower than that in previously reported incidences, 31.2% for Ireland and 39% for the UK, and none of the unaffected offspring had complications attributable to macrosomia in the present series.

Currently, the reported average birthweight of Japanese neonates is 3,050 g for males and 2,960 g for females, as opposed to 3,436 g for males and 3,316 g for females in the UK. The birthweight difference in the current study is likely to reflect this racial difference in birthweight.

Out of the 40 pregnancies among GCK-MODY women, 13 were managed by insulin injections to the affected women without prior knowledge of GCK-MODY. Previously, difficulties have been reported in lowering the blood glucose of individuals with GCK-MODY by insulin injections, which was attributed to the elevated threshold of the counter-regulatory reactions. In the present series, however, insulin treatment resulted in a significant reduction in the birthweight of unaffected offspring (3,025 g vs 3,593 g; Table 2). The birthweight of affected offspring was also lower in the insulin-treated group (2,532 g vs 2,800 g). The reason for this difference in the efficacy of insulin treatment is currently unknown. This could be due to the difference in the dosage or the timing of insulin treatment. Unfortunately, the details of insulin treatment of each woman were not available in the present study.

Although effective in reducing the birthweight, for the following reasons, we do not advocate insulin treatment for the
management of pregnancies of Japanese women with GCK-MODY. First, in Japanese women, the risks of macrosomia, and hence the risks of perinatal complications, are lower than previously reported for white European women. Second, on the reverse side of the effectiveness of insulin treatment, the risks of small-for-gestational age birthweight will be elevated when treating pregnancies without knowing the genetic status of the offspring; that is, when treating pregnancies with affected offspring. In fact, one of the affected offspring of insulin-treated women was born with overt small-for-gestational age birthweight, and all perinatal complications were observed in the affected offspring born to insulin-treated women. Finally, insulin treatment of GCK-MODY women will, theoretically, place these women in adenosine triphosphate deficiency, which could also be a cause of complications, especially in the affected offspring. Therefore, serial ultrasound observations during pregnancy and earlier induction of delivery when the fetuses exceed a specific weight limit will be the most practical management. After 36 weeks of gestation, perinatal complications are rare, even if delivery is induced earlier than the expected date of delivery.

Importantly, in most cases, GCK-MODY is not diagnosed in these pregnant women. The population incidence of GCK-MODY was previously estimated at 1.1 in 1,000. The population incidence in Japan is expected to be similar, because common mutations causing a founder effect are absent across different ethnicities. Therefore, in Japan, with an annual number of births of 946,060 as of 2017, approximately 1,040 GCK-MODY pregnancies should be occurring each year, and probably only a very small fraction of these are correctly diagnosed. Typically, these women have glycated hemoglobin levels of 5.6–7.4% in Japan; therefore, if the responsible diabetologists follow the standard procedure of gestational management, unnecessary or sometimes harmful insulin treatment could be instituted. Screening protocols have been proposed for certain ethnic groups, and similar protocols need to be developed for Japanese patients as well.

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DISCLOSURE
The authors declare no conflict of interest.

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