Synopsis

During pregnancy, beta cells normally increase their insulin secretion to compensate for a decrease in insulin sensitivity. Therefore, a potential etiology for gestational diabetes mellitus (GDM) is a limitation in beta cell reserves. Available evidence with regard to beta cell function in pregnancy is based on studies conducted in Caucasian and Hispanic women. In the current study, we performed a retrospective cohort study to investigate beta cell function in Japanese pregnant women. Firstly, we assessed insulin sensitivity and insulin secretion in a total of 580 Japanese women who underwent a diagnostic 2-h, 75-g oral glucose tolerance test (OGTT) because of a positive two-step screen (i.e. universal early testing in women with high-risk characteristics and a standard one hour, 50g oral glucose challenge test between 24 and 27 weeks of gestation for all women not previously found to have glucose intolerance) between 2004 and 2009 at our institution. Beta cell function was evaluated by the oral glucose tolerance test (OGTT)-derived measures for beta cell function (Oral Disposition Index: DIo), using the product of insulin sensitivity and insulin secretion (i.e. $IS_{OGTT} \times AUC_{ins/glu}$). In women with GDM (n = 82), the DIo was significantly lower than that in those without GDM, irrespective of maternal obesity, indicating beta cell dysfunction in GDM. Additionally, the DIo in women with GDM was significantly correlated with levels of fasting and mean daily capillary glucose and HbAlc before initiating insulin therapy ($R = -0.46$, -0.41, and -0.36, respectively). Furthermore, there was a significant negative correlation between the DIo and total insulin dosage to achieve glycemic goal ($R = -0.42$). These results indicate that the level of beta cell dysfunction in GDM was associated with the severity of glucose intolerance.

Secondly, we investigated the relation between antepartum DIo and postpartum glucose tolerance status in women with GDM. Of 53 women with GDM who were followed by postpartum OGTT, 18 (diabetes 3, borderline 15) showed glucose intolerance defined by the Japan Diabetes Society criteria three to six months postpartum. Compared with normal glucose tolerance, women with glucose intolerance postpartum demonstrated significantly lower levels of antepartum DIo. On receiver operating characteristic analysis, antepartum DIo $\leqq$ 1.44 was a useful predictor for glucose intolerance postpartum (sensitivity, 61%; specificity, 80%). Our results suggest that the DIo could help to identify those at highest risk of postpartum glucose intolerance.

In 2010, the new consensus criteria for diagnosing and classifying diabetes in pregnancy was proposed, based on the association of maternal hyperglycemia with perinatal outcomes. To date, however, beta cell function in GDM defined by the new consensus criteria has not been reported. Of women who underwent the diagnostic OGTT (n = 711) between 2004 and 2010 at our institution, 213 were reclassified into GDM using the new criteria. Levels of the DIo in GDM by the new criteria were significantly lower than those in non-GDM. Especially, the DIo was highest in the normal OGTT group, followed by single, two, and three abnormal OGTT values, respectively. These findings revealed that beta cell dysfunction became remarkable with the increased number of abnormal OGTT values.

Recent genome-wide association studies revealed convincing evidence for the contribution of genes to the pathogenesis of type 2 diabetes. Especially, single nucleotide polymorphisms (SNPs) are regarded as the major determinants of the individual predisposition to T2DM. Similar to T2DM, genetic variants could contribute to the pathogenesis of GDM. With this background, we conducted preliminary SNP analysis followed by case-control association study in Japanese pregnant women. Of the 13 examined T2DM risk variants, five risk alleles were more frequent among women with GDM.

In conclusion, beta cell dysfunction was evident in Japanese women with GDM. The OGTT-derived measures for beta cell function (i.e. Oral Disposition Index) was useful for the prediction of postpartum glucose intolerance, as well as the evaluation of the severity of glycemic disorders. In our preliminary analysis, several genetic variants are likely to be associated with the development of GDM. To characterize the pathogenesis of GDM in Japanese women, further studies on the risk variants related to GDM are needed.