Impact of Twin Gestation and Fetal Sex on Maternal Risk of Diabetes During and After Pregnancy

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Pancreatic β-cell dysfunction is the central pathophysiological defect underlying both gestational diabetes mellitus (GDM) and the subsequent postpartum progression to type 2 diabetes mellitus (T2DM) (1). It has recently emerged that, in singleton pregnancies, carrying a boy is associated with poorer maternal β-cell function and hence an increased risk of GDM (1,2). Moreover, women who develop GDM while carrying a girl have a higher risk of postpartum progression to T2DM than those who develop GDM with a boy (3,4), possibly reflecting comparatively poorer β-cell function in the former (as they developed GDM in the absence of the adverse impact of the male fetus). It thus emerges that the sex of the fetus is associated with maternal risk of diabetes during and after a singleton pregnancy. In this context, we sought to evaluate the impact of twin gestation and the sex of both fetuses on maternal risk of diabetes during and after pregnancy.

Using population-based administrative databases, we identified all women in Ontario, Canada, with a live-birth first pregnancy between April 2000 and March 2012. There were 775,707 women with singleton pregnancies and 13,521 women with twins (31.7% female/female, 36.0% female/male, and 32.3% male/male). The crude rate of GDM per 100 pregnancies was 5.63 in twin gestation and 3.79 with singletons. After adjustment for age, income, and region of residence, the incidence of GDM was higher in twin versus singleton pregnancies (adjusted odds ratio [OR] 1.30 [95% CI 1.21–1.40], $P < 0.001$). In twin gestation, the crude rate of GDM per 100 pregnancies was 5.56 if both fetuses were female, 6.08 if one was male and one was female, and 5.20 if both were male. Upon adjustment for covariates, however, neither male/male (adjusted OR 0.92 [95% CI 0.76–1.11]) nor male/female (adjusted OR 1.02 [95% CI 0.86–1.22]) carried greater risk of GDM than female/female. Among women who developed GDM ($n = 30,123$) followed over median 6 years after delivery, the incidence of postpartum progression to diabetes was 3.86 per 100 patient-years in those with a singleton pregnancy and 2.96 per 100 patient-years in those who had twins (Fig. 1*A*). After adjustment for age, income, and region of residence, the risk of progression to diabetes was lower in women who had GDM with twins than in those who had GDM with singletons (adjusted hazard ratio 0.76 [95% CI 0.65–0.90], $P = 0.001$). However, among women who developed GDM with twins, the risk of subsequently progressing to diabetes did not differ between those with male/male, male/female, and female/female twins (Fig. 1*B*).

In summary, this population-based study shows that twin gestation carries an increased risk of GDM but that affected women have a lower risk of postpartum progression to T2DM than women who develop GDM with a singleton pregnancy. The sex of the twins does not appear to affect maternal risk of diabetes either during or after pregnancy. Instead, other factors (such as antepartum insulin resistance [5]) potentially may be driving the higher risk of GDM in twin pregnancy that is coupled with a lesser risk of subsequent postpartum diabetes. Overall, these data suggest that the impact of the twin gestation itself on maternal glucose metabolism supersedes that of fetal sex.

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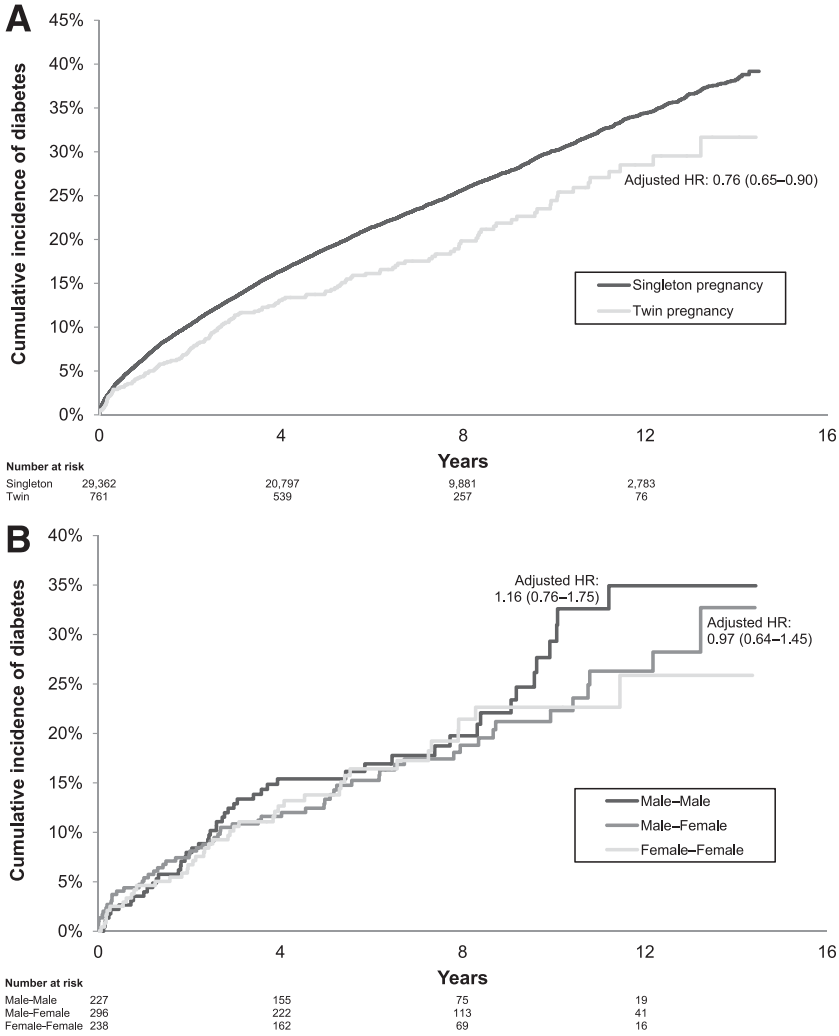

Figure 1—*A*: Cumulative incidence of diabetes in the years after delivery in women who had GDM with a twin pregnancy vs. women who had GDM in a singleton pregnancy (reference group). *B*: Cumulative incidence of diabetes in the years after delivery in women who had GDM with a twin pregnancy, stratified according to the sex of the twins: male/male, male/female, and female/female (reference group).

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References

1. Retnakaran R, Kramer CK, Ye C, et al. Fetal sex and maternal risk of gestational diabetes mellitus: the impact of having a boy. Diabetes Care 2015;38:844–851

2. Jaskolka D, Retnakaran R, Zinman B, Kramer CK. Sex of the baby and risk of gestational diabetes mellitus in the mother: a systematic review and meta-analysis. Diabetologia 2015;58:2469–2475

3. Retnakaran R, Shah BR. Fetal sex and the natural history of maternal risk of diabetes during and after pregnancy. J Clin Endocrinol Metab 2015;100:2574–2580

4. Retnakaran R, Shah BR. Sex of the baby and future maternal risk of type 2 diabetes in women who had gestational diabetes. Diabet Med. 15 October 2015 [Epub ahead of print]. DOI: 10.1111/dme.12989

5. Callesen NF, Ringholm L, Stage E, Damm P, Mathiesen ER. Insulin requirements in type 1 diabetic pregnancy: do twin pregnant women require twice as much insulin as singleton pregnant women? Diabetes Care 2012;35:1246–1248