Effect of gestational diabetes on endothelium-dependent vasodilation of human myometrial and omental arteries

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Gestational diabetes (GD) is an increasingly prevalent complication of pregnancy. GD alters foetal growth patterns and increases the likelihood of metabolic disorders developing later in life, for both mother and offspring. Related conditions including high blood pressure and obesity are also more prevalent following GD (ADA, 2012). Microvascular dysfunction contributes to the deleterious health effects of diabetes, and relatively few studies have examined the effects of diabetes on human microvasculature. The current study investigated endothelial function of myometrial and omental arteries isolated from women with gestational diabetes (GD).

Arterioles were obtained from caesarean-section non-diabetic and GD women at term (internal diameter approx. 200 μm); GD was defined as by fasting blood glucose ≥ 5.5 mmol/L and a glucose tolerance test (GTT) yielding glucose ≥ 8.0 mmol/L after 2 hours. Protein expression in arterial segments was assessed using immunohistochemistry (IHC). Endothelial function and other functional responses were measured through pressure myography; arteries were maintained at 60 mmHg, pre-constricted with vasopressin (3 or 10 nM). Protocols were approved by UNSW and Health District Human Ethics Committees.

In myometrial arteries, IHC showed punctate labelling of the endothelium with anti-NOS antibody and strong, diffuse labelling of the endothelium with antibody to the intermediate-conductance Ca^{2+}-activated K^+-channel (IK_{Ca}). GD decreased expression of both eNOS and IK_{Ca} in the vessels. The maximum endothelium-dependent vasodilation induced by bradykinin (Control 86.8 ± 2.6%, n = 8; GD 69.7 ± 5.6%, n = 12, $P<0.05$). GD reduced the potency of bradykinin in omental arteries, but not the maximum response (Control pEC_{50} 8.61 ± 0.10, n = 9; GD 8.04 ± 0.12, n = 5, $P<0.05$). GD did not alter endothelium-independent vasodilation (sodium nitroprusside) in either vessel. In myometrial arteries from non-diabetic women, nitric oxide (NO) pathway inhibition with L-NAME (100 μM) and ODQ (10 μM) inhibited bradykinin-induced vasodilation, as did inhibitors of both IK_{Ca} and the small-conductance K_{Ca} (SK_{Ca}), TRAM-34 (1 μM) and apamin (0.1 μM) respectively. In contrast NO- and IK_{Ca}-inhibition had no effect on bradykinin-induced responses in GD, while vasodilation induced by the IK_{Ca} activator, SKA-31, was also decreased in GD.

In omental arteries, IHC showed weak labelling of the endothelium with anti-NOS antibody and diffuse, punctate labelling of the endothelium with antibody to IK_{Ca}. GD had no apparent effect on expression of both eNOS expression, but decreased IK_{Ca} expression in the vessels. GD decreased the potency of bradykinin without reducing the maximum response (pEC_{50} normal 8.67 ± 0.07, n = 10; GD 8.02 ± 0.12, n = 3; $P<0.05$). In contrast to myometrial vessels, inhibition of the NO pathway did not significantly alter bradykinin-induced relaxation of omental vessels from normo-glycemic women. Subsequent inhibition of I- and SK_{Ca} using TRAM-34 and apamin respectively, did cause further rightward-shift of the bradykinin concentration-response curve. In omental arteries from women with GD, inhibition of NO-mediated vasodilation using L-NAME/ODQ enhanced the vasodilator potency of bradykinin (pEC_{50} 8.30 ± 0.06, n =3), while TRAM-34 and apamin continued to inhibit responses.

These studies suggest that GD inhibits endothelium-dependent vasodilation of myometrial arteries through inhibition of nitric oxide production and IK_{Ca} activity, while effects in omental arteries seemed limited to NO-mediated vasodilation only.

American Diabetes Association (2012). Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* **35:** S64–S71.