The impact of chronic hypertension on adverse maternal smoking during pregnancy and risk of type 1 diabetes: whole-of-population study

Background Chronic hypertension affects up to 5% of all pregnancies, and this is expected to rise due to increasing prevalence of maternal obesity. This study aimed to systematically review observational studies to investigate the risk of adverse perinatal outcomes among pregnant women with chronic hypertension compared with normotensive women.

Methods Medline/PubMed, EMBASE, and Web of Science were searched (from first publication until 10th January 2019) to identify peer-reviewed articles without restriction on language or study period. We included observational studies based on the following criteria: 1) participants were pregnant women; 2) exposure was chronic hypertension; 3) comparison was normotensive women; 4) outcomes included measures of at least one of the following: superimposed pre-eclampsia, small for gestational age, stillbirth, preterm birth, caesarean section, neonatal intensive care unit admission, low birth weight, post-partum hemorrhage maternal death and neonatal death. This review is registered in PROSPERO (CRD42019120088).

Two investigators independently reviewed the eligibility criteria, extracted the data and assessed the quality of included studies using the Newcastle-Ottawa tool. A meta-analysis was performed using RevMan 5.3 for each exposure-outcome association, when data allowed. Random effect models were applied for pooling crude and adjusted odds ratios (ORs) respectively. Heterogeneity among studies was assessed using a Cochrane Q statistic and the Higgins I² test. Sensitivity analysis was performed by study design, study location, decade of publication, and according to study quality. Publication bias was assessed using Begg’s funnel plot and Egger’s test. The effect of using antihypertensive medications on the risk of adverse maternal and perinatal outcomes will also be analysed as part of this review.

Results Of the 9739 articles identified, 69 studies met the inclusion criteria. Thirteen studies reported adjusted estimates for small for gestational age (including 7,070,558 participants); adjusted pooled OR=1.97 (95% CI, 1.46, 2.67) among women with chronic hypertension compared to normotensive. Similarly, eleven studies reported adjusted estimates for still-birth (including 15,231,939 participants), with a pooled adjusted OR=2.36 (95% CI, 2.18, 2.53). Four studies reported adjusted estimates for neonatal death, the adjusted pooled OR=2.29 (95% CI, 2.03, 2.60). The analyses of other outcomes are ongoing.

Conclusion There are strong associations between chronic hypertension and adverse perinatal outcomes, including small for gestational age, stillbirth and neonatal death. Most studies in this review did not take severity of hypertension into account when comparing the outcomes. This review summarises current knowledge on the association between chronic hypertension and adverse perinatal outcomes and may be used to optimise antenatal care and pregnancy outcomes.
detect bias due to unmeasured confounding; and 3) to combine estimates from population-based and case-control studies in meta-analyses.

Methods This whole-of-population study of children born from 1999–2013 (n=286,058, aged <15 years) used de-identified linked administrative datasets from the South Australian Early Childhood Data Project. T1D was diagnosed for 557 children during hospitalization (ICD-10-AM codes, E10, E101-E109) from 2001–2014. Maternal smoking data was sourced from the South Australian Perinatal Statistics Collection, where information at birth is collected by midwives/neonatal nurses using a validated tool. Hospitalization for any injury occurring at school was used as a negative-control outcome. Adjusted Cox proportional hazard ratios (HR) were calculated in the main analysis and the negative-control outcome. Random-effects meta-analysis was used to summarize effects of prenatal smoking on childhood T1D.

Results Compared with non-smokers, smoking throughout pregnancy was associated with 23% lower childhood T1D risk (HR 0.77; 95% CI 0.60–1.00), with similar effects for smoking in first-half (HR 0.78; 95% CI 0.60–1.01) and second-half (HR 0.75; 95% CI 0.57–0.98) of pregnancy. The negative-control outcome analysis (HR 0.95; 95% CI 0.86–1.05) suggested the effect of prenatal smoking on T1D was not due to unmeasured confounding. These results were consistent with meta-analytic estimates of prenatal smoking and childhood T1D risk from population-based (HR 0.70; 95% CI 0.60–0.81) and case-control studies (OR 0.71; 95% CI 0.55–0.86).

Conclusion Maternal smoking in pregnancy was associated with lower risk of childhood T1D. The negative-control outcome analysis suggests this effect is unlikely to be due to unmeasured confounding. Our meta-analytic estimates also showed lower risk of T1D for children exposed to maternal smoking during pregnancy. Smoking causes irreversible harm to the fetus, however understanding the mechanism of protective effects (e.g. nicotine exposure, gene expression) might lead to new insights about T1D.