OBSTETRICS

Discontinuation of antihypertensive drug use during the first trimester of pregnancy and the risk of preeclampsia and eclampsia among women with chronic hypertension

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OBJECTIVE: The goal of this study was to investigate the association between the discontinuation of antihypertensive medication use during the first trimester of pregnancy and the risk of preeclampsia and eclampsia.

STUDY DESIGN: We conducted a nested case-control approach within a cohort that was reconstructed from the linkage of 3 databases. To be included in the study, women had to match the following criteria: (1) between 15-45 years old on the first day of gestation, (2) covered by Québec's Drug Insurance Plan for at least 12 months before and during pregnancy, (3) exposed to an antihypertensive drug on the first day of gestation, and (4) have had a delivery. Multivariate conditional logistic regression models were used to estimate the risk.

RESULTS: Adjusting for confounders, the odds ratio was 0.66; 95% confidence interval, 0.27-1.56.

CONCLUSION: Our finding does not support the presence of a statistically significant association between antihypertensive discontinuation during the first trimester of pregnancy and the risk of preeclampsia and eclampsia.

Key words: antihypertensive drug discontinuation, chronic hypertension, eclampsia, preeclampsia, pregnancy

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Hypertension is 1 of the most frequently reported medical disorders of pregnancy and occurs in up to 10% of pregnancies;[1] the prevalence increases with maternal age.[2] Preeclampsia/eclampsia (PE/E) is thought to be a consequence of abnormalities in the maternal vessels supplying the placenta, leading to poor placental perfusion and the release of factors causing widespread endothelial dysfunction with multiorgan system clinical features.[3] It is estimated that 25% of women with preexisting hypertension will have PE/E develop during gestation.[4] Worldwide, 10-15% of the half million maternal deaths that occur every year are associated with hypertensive disorders of pregnancy, mainly PE/E.[5] In Canada, PE/E was 1 of the leading causes of maternal death in 1997-2000, accounting for 21% of direct maternal deaths.[6]

Antihypertensives are routinely used to reduce the risk of progression to severe hypertension and PE/E, thereby improving maternal and neonatal outcomes. However, some still argue that there is no immediate need to lower blood pressure at the beginning of a pregnancy because of the maternal physiologic decrease in blood pressure that causes one-third of pregnant women with prepregnancy chronic hypertension to become normotensive in the first half of their pregnancy.[7]

The impact of antihypertensive drugs to prevent progression to PE/E is unclear and remains an area of controversy in the absence of well-designed clinical trials.[8,9] Hence, given the high prevalence of hypertension, widespread use of antihypertensives and their possible teratogenicity during pregnancy and knowledge of the association between antihypertensive discontinuation during the first trimester of pregnancy and the risk of PE/E are important public health issues. Therefore, the goal of this study was to investigate the independent association between the discontinuation of antihypertensive drug use during the first trimester of pregnancy and the risk of PE/E.

Materials and Methods

Study setting

This study was conducted within the Québec Pregnancy Registry. This registry was built with the linkage of 3 administrative databases: Régie de l'Assurance Maladie du Québec (RAMQ), MedEcho, and le fichier des événements démographiques du Québec (birth and death registries) of the Institut de la statistique du Québec (ISQ). These data-

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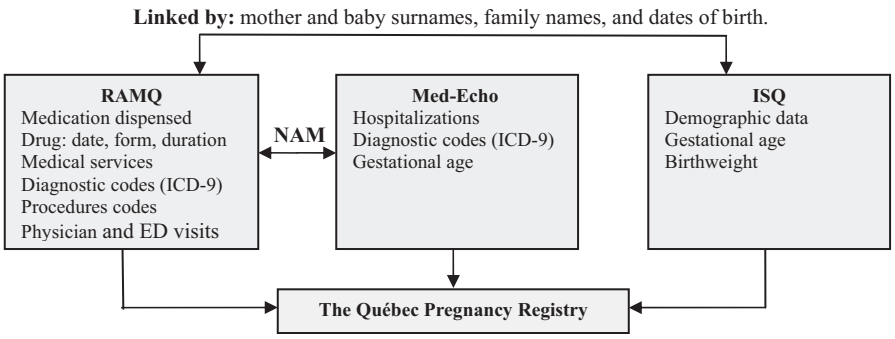
FIGURE
The Québec Pregnancy Registry



Linkage between the administrative databases used in the study.

ICD-9, International Classification of Diseases, Ninth Revision; NAM, numero d'assurance maladie (unique personal identification number).

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bases contain information on all pregnancies that occurred in Québec between Jan. 1, 1997-Dec. 31, 2003. The RAMQ database contains information on dispensed medical services (diagnoses and procedures) received by all residents of Québec; all diagnoses are classified according to the *International Classification of Diseases, Ninth Revision* (ICD-9).[10] Although the RAMQ covers all of Québec's residents with respect to visits to the physician and the inherent fees, hospitalizations, and procedures, not all residents are covered by its Public Prescription Drug Insurance Plan. The RAMQ drug plan covers the 3 following groups of individuals: those who are 65 years and older, those who receive social assistance, and those workers and families (adherents) who have no access to a private drug insurance plan through their employers. These individuals account for approximately 43% of the overall Québec population and 30% of pregnant women.[11] The Med-Echo database is a provincial database that records acute care hospitalization data for all Québec residents and also records gestational age for deliveries. The ISQ provides demographic information on the mother, father, and infant, as well as birthweight and gestational age for live births and stillbirths. The RAMQ, Med-Echo, and ISQ databases have often been used in the past for epidemiologic research.[12-14] The Québec Pregnancy Registry has often been used to assess risks, as well as the benefits, of drug use during pregnancy.[15-17] Data recorded in the RAMQ medication database have been suitably evaluated and found to be comprehensive and valid.[18] The same is also true for the medical diagnoses recorded in the Med-Echo database,[19] as well as for the data recorded in the ISQ database.[20]

Study population

The linkage between the 3 databases was performed using the women's Health Insurance Number, which is a unique identifier for all Québec residents (in both the RAMQ and Med-Echo databases), and using the date of birth of both mother and child, given names, and surnames (RAMQ and ISQ) (Figure). This population-based pregnancy registry is composed of women with a diagnosis or procedure code related to a pregnancy. Within the Québec Pregnancy Registry, all pregnancies occurring in Québec between Jan. 1, 1998-Dec. 31, 2003 are included. The date of entry in the registry is the first day of gestation (1DG), defined as the first day of the last menstrual period. To be eligible for this study, women had to be: (1) between 15-45 years old on the 1DG, (2) covered by the RAMQ drug plan for at least 12 months before the 1DG and during the pregnancy, (3) on an antihypertensive drug on the 1DG, and (4) have had a delivery. If a woman had more than 1 pregnancy between 1998-2003, the first pregnancy that met the eligibility criteria was included for analysis. This study was approved by the ethics committee of Sainte-Justine's Hospital and the Commission d'accès à l'information du Québec, the agency that grants ethics clearance for the use of linked administrative data in Québec.

Study design

We conducted a nested case-control approach within the Québec Pregnancy Registry cohort.[21]

Case and control selection

Within our study population, case status was defined as having a diagnosis of PE/E (ICD-9: 642.4-642.7) during gestation. The index date was defined as the gestational age at the time of the first diagnosis of PE or E, whichever occurred first. Once the risk set was defined, 10 controls were randomly selected for each case and matched on the cases' gestational age at index date. The nested case-control approach has greater statistical efficiency than the prospective cohort approach and provides similar effect sizes;[21] it is also a better suited design when studying rare outcomes such as PE/E. Exclusion of controls that eventually become cases will lead to much greater biases and should be avoided. It has also been shown that an inconsistent estimate might be obtained if previous controls are excluded from consideration as future controls, although remaining eligible to be included as a future case. Controls were selected among pregnant women who had not had the study outcomes develop at index date but who were at risk of their developing. They were then matched to cases on gestational age at index date. To protect the validity of the study, controls could have served for more than 1 case and could have become a case later during pregnancy if they had PE or E develop.[21]

Exposure to antihypertensive drugs

The following antihypertensive drugs were considered: selective and nonselective β-blockers (American Hospital Formulary System [AHFS] codes: 24:08.08); alpha adrenergic blockers (AHFS codes: 24:08.04); α- and β-blockers (AHFS codes: 24:24.00); angiotensin-converting enzyme (ACE) inhibitors