OBSTETRICS

Chronic hypertension in pregnancy and the risk of congenital malformations: a cohort study

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OBJECTIVE: Chronic hypertension is a common medical condition in pregnancy. The purpose of the study was to examine the association between maternal chronic hypertension and the risk of congenital malformations in the offspring.

STUDY DESIGN: We defined a cohort of 878,126 completed pregnancies linked to infant medical records using the Medicaid Analytic Extract. The risk of congenital malformations was compared between normotensive controls and those with treated and untreated chronic hypertension. Confounding was addressed using propensity score matching.

RESULTS: After matching, compared with normotensive controls, pregnancies complicated by treated chronic hypertension were at increased risk of congenital malformations (odds ratio [OR], 1.3; 95% confidence interval [CI], 1.2—1.5), as were pregnancies with untreated chronic hypertension (OR 1.2; 95% CI, 1.1—1.3). In our analysis of organ-specific malformations, both treated and untreated chronic hypertension was associated with a significant increase in the risk of cardiac malformations (OR, 1.6; 95% CI, 1.4—1.9 and OR, 1.5; 95% CI, 1.3—1.7, respectively). These associations persisted across a range of sensitivity analyses.

CONCLUSION: There is a similar increase in the risk of congenital malformations (particularly cardiac malformations) associated with treated and untreated chronic hypertension that is independent of measured confounders. Studies evaluating the teratogenic potential of antihypertensive medications must control for confounding by indication. Fetuses and neonates of mothers with chronic hypertension should be carefully evaluated for potential malformations, particularly cardiac defects.

Key words: birth defect, drug, epidemiology, hypertension, pregnancy

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Chronic hypertension is a common medical condition in pregnancy, and its prevalence is rising because a larger number of parturients are obese and of advanced maternal age.[1,2] As a consequence, exposure to antihypertensive medications during pregnancy, including in the first trimester when organogenesis occurs, is common and increasing.[3-5]

Certain classes of antihypertensive medications taken during the first trimester including beta blockers, diuretics, and angiotensin-converting enzyme inhibitors have been associated with an increased risk of specific congenital malformations.[6-11] However, several recent studies have suggested that it may be the underlying chronic hypertension that confers risk and not exposure to these medications per se, because of the following: (1) an elevation in risk of malformations was observed across antihypertensive classes and/or (2) the association with

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certain medications was no longer present when medication users were compared with a control group that included untreated hypertensive patients.[6,8,12]

Little is known about the role of chronic hypertension alone in conferring a risk of congenital malformations, and there has been a call from experts for further study in this area.[13] Specifically, there are few data on whether chronic hypertension confers a risk of malformations independent of other confounding factors (eg, diabetes, maternal age, antihypertensive agents) and which specific malformations, if any, are associated with hypertension. Such information may be useful to clinicians in counseling patients and in guiding screening for malformations.

It may also be important in informing the design of future studies of the teratogenic potential of antihypertensive medications. We therefore sought to examine the effect of chronic hypertension on the risk of congenital malformations in a large cohort of pregnancies in Medicaid beneficiaries.

Materials and Methods

Cohort

The cohort was derived from the Medicaid Analytic eXtract (MAX), which contains information on Medicaid beneficiaries; Medicaid is the joint state and federal health insurance program for low-income individuals in the United States.

MAX is a health care utilization database that records Medicaid enrollment and utilization claims, including those for inpatient admissions and outpatient visits as well as outpatient pharmacy dispensing claims. Using the MAX data from 2000 to 2007, a cohort was created for the study of drug utilization and safety in pregnancy, as previously described in detail.[14]

The use of this database for research was approved by the Partners' Institutional Review Board (Boston, MA). Women with a claim indicating delivery were linked to infants within states using the Medicaid case number (which is generally shared by families) and the infant's date of birth. The woman's last menstrual period (LMP) was assigned using a validated algorithm based on diagnostic codes in the maternal and infant records.[15]

We restricted the cohort to women who were eligible for Medicaid continuously from 3 months prior to the estimated LMP month through 1 month postpartum. To ensure complete ascertainment of relevant claims, we restricted our analysis to women with 28 days or more of enrollment each month and without restricted benefits, private insurance, or certain state-specific managed care programs (that underreport claims to MAX).

To allow for an accurate capture of congenital malformations, we also required that the linked infants met the same Medicaid eligibility criteria as the mothers for at least 3 months following the birth (unless they died, in which case a shorter eligibility period was allowed). The source cohort included 891,699 completed pregnancies with linked infants.

We excluded women who were exposed to known teratogenic medications including lithium, antineoplastic agents, retinoids, or thalidomide from the estimated LMP through the date of delivery based on claims for dispensed medications or who had an infant with an inpatient or outpatient diagnosis code indicating the presence of a chromosomal abnormality.

We also excluded women who were exposed to antihypertensive medications during the first trimester but who lacked diagnosis codes indicating chronic hypertension because of a significant risk of misclassifying the presence or absence of hypertension in these patients (because the women may have received the medications for other indications, for example, beta blockers for migraine prophylaxis, or have hypertension that was not properly coded). The final analytic cohort included 878,126 pregnancies (Figure 1).

Exposure

The following 3 groups of women were considered in the analysis: (1) women without chronic hypertension who did not receive antihypertensive medications in the first trimester, (2) women with chronic hypertension who were treated with an antihypertensive medication during the first trimester, and (3) women with chronic hypertension who were not treated with an antihypertensive medication during the first trimester.

Chronic hypertension was defined by codes recorded on 2 or more distinct dates indicating chronic or preexisting hypertension recorded in the maternal inpatient or outpatient record at any time from 3 months prior to the LMP through delivery. The codes were derived from the *International Classification of Disease-Clinical Modification*, ninth edition, and included codes 642.0x, 642.1x, 642.2x, 642.7x, and 401.xx through 405.xx. These codes are specific to chronic hypertension and are distinct from codes that indicate other hypertensive disorders of pregnancy including gestational hypertension and preeclampsia.

Antihypertensive exposure during the first trimester was defined by a filled prescription whose days' supply overlapped the period from the LMP to 90 days after the LMP. In defining this exposure, we used prescriptions filled from 3 months prior to the LMP until 90 days after the LMP. Duration of exposure was estimated based on the number of days' supply. We accumulated days' supply for consecutive prescriptions of the same medication if the medication was refilled prior to the day that the prior prescription was expected to run out. The list of antihypertensive medications considered in the analysis can be found in the Appendix (Supplementary Table 1).

Outcomes

The primary outcome was defined as the presence of a major congenital malformation in the offspring. Major congenital malformations were defined based on having codes on 2 or more separate days in the infant inpatient or outpatient records during the first 3 months of life indicating an organ-specific class of malformations including central nervous system malformations; eye, ear, neck, and face malformations; cardiac malformations; respiratory malformations; cleft palate or lip; gastrointestinal