Invited Commentary

Invited Commentary: Identifying Women with Hypertension during Pregnancy—Is High Specificity Sufficient?

William M. Callaghan

From the Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA.

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Hypertensive complications of pregnancy contribute to the burden of maternal morbidity and subsequently have an impact on neonatal morbidity and mortality. Although codes from the International Classification of Diseases should delineate the specific subtypes of pregnancy-related hypertension, how diagnoses are applied and how these codes are used in clinical settings are largely unknown. This commentary discusses the implications of using administrative codes to identify women with preeclampsia syndromes, especially when used to define outcomes or exposures for etiologic research.

Hypertension; pregnancy; sensitivity and specificity; women


Hypertensive disorders are a leading cause of maternal mortality worldwide (1, 2). Moreover, although difficult to quantify, hypertensive complications of pregnancy contribute to the burden of maternal morbidity and subsequently have an impact on neonatal morbidity and mortality; in the United States, hypertension with first onset during pregnancy complicates 6–8 percent of pregnancies (3). The nomenclature of hypertension during pregnancy—gestational hypertension, transient hypertension of pregnancy, preeclampsia, severe preeclampsia—suggests the syndromic nature of this group of disorders. Women who are assigned one of the pregnancy-related diagnoses are defined by their clinical presentation rather than by markers of pathophysiologic change. As aptly stated by Dekker and Sibai (4), even an accurate diagnosis reflects meeting the “definition” of the assigned disorder without necessarily having a link to a pathologic consequence for the mother or neonate.

Gestational hypertension is defined as new onset of elevated blood pressure (≥140/≥90 mmHg) after the 20th week of pregnancy in a woman with no history of hypertension prior to pregnancy. Gestational hypertension is severe if there is sustained elevation of blood pressure (≥160/≥110). Most women with hypertension in pregnancy have gestational hypertension; this clinical presentation represents a group of women who have previously undiagnosed chronic hypertension, evolving preeclampsia, or transient hypertension of pregnancy. Transient hypertension of pregnancy is diagnosed postpartum in a woman with gestational hypertension without proteinuria who is normotensive by 12 weeks after delivery. Preeclampsia is defined as gestational hypertension with proteinuria. Severe preeclampsia occurs when there is severe gestational hypertension with proteinuria, when there is gestational hypertension with severe proteinuria, or when there is preeclampsia in the presence of multiorgan deterioration (3, 5–7). In theory, a specific code from the International Classification of Diseases (ICD) should delineate each of these entities. How diagnoses are applied and how these codes are used in clinical settings, however, are largely unknown. A survey of 33 of 34 obstetric departments in Denmark showed wide variability in diagnostic criteria and ICD reporting practices for preeclampsia (8). Geller et al. (9) reported an overall

Correspondence to Dr. William M. Callaghan, Division of Reproductive Health, Centers for Disease Control and Prevention, 4770 Buford Highway, Mailstop K-23, Atlanta, GA 30341 (e-mail: wcallaghan@cdc.gov).
positive predictive value of 54 percent when ICD, Ninth Revision, codes were used to identify women with preeclampsia. Although the positive predictive value for eclampsia (preeclampsia with seizures) was low (42 percent) in their study, if ICD, Ninth Revision, identified cases of eclampsia were included with ICD, Ninth Revision, identified cases of severe preeclampsia, the positive predictive value was 87 percent.

Even when the code is accurately applied to the diagnosis, what pathophysiologic entity is denoted and what is its consequence? Adverse perinatal outcomes may be greater for women with severe gestational hypertension than for women with mild preeclampsia (10). Data from the National Institute of Child Health and Human Development’s Calcium for Preeclampsia Prevention trial showed minimal impact of mild gestational hypertension or mild preeclampsia arising late in pregnancy; the mean birth weight in this group exceeded the mean birth weight of infants born to women with no hypertension (11). On the other hand, maternal and perinatal morbidity and mortality are considerable when women develop preeclampsia early in gestation; it is not clear whether these entities represent the same pathogenic mechanisms (12).

The etiologies of gestational hypertension and preeclampsia are unknown; preeclampsia has been a disease of theories. Contemporary etiologic research has focused on abnormal placentation with failure of the normal remodeling of maternal spiral arteries, maladaptive maternal-fetal immunologic response, oxidative stress, dietary deficiencies, and genetic abnormalities (6, 7, 13, 14). Recent work has focused on an imbalance in anti- and proangiogenic factors (15–17). As might be expected for a syndrome with such dynamic and nuanced nomenclature, multiple etiologic hypotheses, and a lack of biomarkers for its pathophysiology, no reliable predictors have been discovered, and prevention trials have not been fruitful (4, 13, 18–20).

In addition to questions about the etiologies of the hypertensive disorders of pregnancy, recent research has focused on the association between preeclampsia and subsequent health outcomes, particularly cardiovascular disease, in an effort to explore the hypothesis that the predisposing pathophysiology for preeclampsia and heart disease might be similar. Preeclampsia and atherosclerotic coronary disease have common risk factors, including chronic hypertension, obesity, insulin resistance, hypercholesterolemia, dyslipidemia, macroalbuminuria, antiphospholipid syndrome, and thrombophilias (21). Moreover, the association between these entities is stronger for women with severe, early onset preeclampsia or for women with preeclampsia that recurs in successive pregnancies (22–24). This line of research requires that preeclampsia be accurately identified as the exposure. Thus, whether preeclampsia is the outcome or the exposure of interest, there is a critical need to accurately identify this entity, prospectively and retrospectively, in large databases.

In this issue of the Journal, Klemmensen et al. (25) report the validity of ICD, Tenth Revision, codes for the family of pregnancy-related hypertensive disorders. Using the Danish National Patient Registry as the source for codes and medical record information from three hospitals as the “gold standard” for diagnosis, they report low sensitivities for all hypertensive disorders combined (49 percent) and for individual subtypes (10–69 percent). The specificities of codes from the ICD, Tenth Revision, were uniformly high (>99 percent) for all hypertensive disorders combined and for individual subtypes. Interview data specific to the data collection methods of the Danish National Birth Cohort did not substantially improve the findings, and information from interviews could not discriminate between mild and severe disease. On the basis of the high specificity of Danish National Patient Registry data for hypertensive disorders, Klemmensen et al. conclude that identifying cases by codes from the ICD, Tenth Revision, is satisfactory for etiologic studies where preeclampsia is the primary outcome or the primary exposure. Given the scope of contemporary research in this area, the challenges posed by the diagnosis of hypertensive disorders in pregnancy, and the uncertainty around their natural history, the data and conclusions from this study merit discussion.

Misclassification of exposure and outcome plagues epidemiologic research. Do the findings of Klemmensen et al. (25) provide reassurance for those who study the etiology of preeclampsia or the sequelae of exposure to preeclampsia? Investigations of the biology of hypertension in pregnancy have advanced to a place where it is necessary to understand the nuance of clinical presentation. It is increasingly important to know when in gestation the woman presents with her disease and the severity of disease at presentation and pregnancy termination. Even though discharge data are specific for meeting a definition of the disease, they cannot provide information that is sufficiently granular to accurately define a case of preeclampsia for those involved in this realm of research. Similarly, the burgeoning literature that reports associations between subsequent cardiovascular disease and severe, early onset, or recurrent hypertensive disorders calls for research methods that capture both timing and severity of pregnancy-associated hypertension.

Until or unless specific markers for the hypertensive disorders of pregnancy become available, research will necessarily depend upon the accurate characterization of disease presentation. At best, accurately coding a defined presentation will include sufficient disease heterogeneity that, for research purposes, can only be resolved by review of medical records to confirm the diagnosis and to obtain the important details of the clinical presentation. The data from this large study suggest something about the efficiency of conducting such a study. For example, if one needed detailed information to define and characterize cases of preeclampsia as either the exposure or the outcome in a large research setting, one could conceive of a large data set (thousands) composed of administrative codes as a screening test for the disease. In such a situation, review of all records to confirm a diagnosis and glean the details of the clinical presentation would impose an enormous burden. Given the very high specificity reported by Klemmensen et al. (25), the positive predictive value would be the pertinent test characteristic to focus on, since the burden of record review requires consideration of false positives. Klemmensen et al. report that one in four records identified as having any degree of preeclampsia did not have preeclampsia, and record.
review would result in reclassification as a noncase or as nonexposed. Because the reported sensitivity is only moderate, a number of records will be misclassified as noncases or nonexposed. However, in the setting of a rare outcome, such misclassification will have minimal impact on measures of association. Although the allocation of resources for research involving this degree of record review may still be substantial, it likely represents a reasonable balance between diagnostic accuracy and workload in that only women who “screen positive” would require review of records.

This study was done in a small European country with a uniform health-care system; it may be premature to extrapolate these results to other settings. For now, the data reported by Klemmensen et al. (25) provide one example of how readily available data might be used and the caveats associated with their use. However, simply improving the specificity of identifying women who meet a definition of questionable relevance will do little to advance our understanding of this truly vexing and enigmatic group of disorders.

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REFERENCES