OBSTETRICS

Placental pathology suggesting that preeclampsia is more than one disease

David B. Nelson, MD; Mandolin S. Ziadie, MD; Donald D. McIntire, PhD; Beverly B. Rogers, MD; Kenneth J. Leveno, MD

OBJECTIVE: Our purpose was to evaluate the placental pathology in women with preeclampsia occurring at varying gestational ages.

STUDY DESIGN: This was a secondary analysis of a prospective observational study of placentas from prespecified complicated pregnancies routinely submitted for standardized examination. For this study, a database of placental diagnoses from liveborn singleton gestations without major malformations was linked to a computerized obstetric database. The rates of standardized placental findings including vascular (atherosis, infarction) and nonvascular (hyperplasia) changes were evaluated according to gestational age at diagnosis of preeclampsia.

RESULTS: Between Jan. 1, 2001, and Sept. 30, 2007, a total of 7122 women with pregnancies complicated by preeclampsia were delivered at our hospital. Of these, 1210 (17%) had placental examinations. Within this cohort, 209, 355, and 646 women were diagnosed with preeclampsia at gestations of $24^{0/67}$ to $33^{6/7}$, $34^{0/7}$ to $36^{6/7}$, and $37^{0/7}$ weeks or longer, respectively. Placental findings revealed hypoplasia was significantly associated with preeclampsia early in the third trimester, and histological evidence of placental vascular lesions was significantly increased at gestations of $24^{0/67}$ to $33^{6/7}$ weeks (53%) compared with 34% and 26% at $34^{0/7}$ to $36^{6/7}$ and 37 weeks or longer, respectively ($P < .001$).

CONCLUSION: The placentas of women with preeclampsia onset before 34 weeks' gestation were significantly different from those with preeclampsia at term. The former group demonstrated placental findings predominantly consistent with insufficiency because of vascular abnormalities. Such differing placental findings support the hypothesis that preeclampsia is a different disease, depending on the gestational age at diagnosis.

Key words: placental pathology, preeclampsia

Cite this article as: Nelson DB, Ziadie MS, McIntire DD, et al. Placental pathology suggesting that preeclampsia is more than one disease. Am J Obstet Gynecol 2014;210:66.e1-7.

Preeclampsia-eclampsia, once designated toxemia of pregnancy, has been referenced within the ancient Egyptian, Chinese, Indian, and Greek medical literature as a concern to the accoucheur.[1] Historical observations and etiopathogenic theories have evolved with advancements in the obstetric care of women.[2] Remarkably, some of these historical findings remain relevant to this day, such as Mauriceau's 17th-century observation of the disease affecting predominantly primigravidas.[2,3]

Occurring in 5-8% of pregnancies, the disorder has led to the development of significant advancements in contemporary obstetric care to include the National High Blood Pressure Education Program Working Group, identification of numerous risk factors, and classification schema of mild and severe to better define the disease.[4-11] Efforts to further define the disease include characterization of early and late onset based on the gestational age at diagnosis as much of the neonatal outcomes are predicated on the precise knowledge of the age of the fetus.[2,4,12-15] Moreover, some investigators have considered the early and late diseases represent more than one pathophysiologic process.[16]

Investigation of placentas in pregnancies complicated by preeclampsia can be traced to the work of Williams in 1915[17] and further developed by Page[18] and others[19] with studies of placental perfusion in the 1930s. The discovery of a specific placental pathological lesion, termed acute atherosis, by Zeek and Assali[20] in 1950 prompted Robertson et al[21] to further investigate the vessels of the placental bed in hypertensive pregnancies. Building on these earlier studies of the placenta, investigators have now begun reporting placental lesions associated with varying severity of preeclampsia.[22,23]

Other investigators have found that histopathological lesions differ, depending on when in gestation the diagnosis of preeclampsia is established.[24,25] Our aim was to examine placental histopathological findings at varying gestational ages in an effort to determine whether preeclampsia is more than one disease, depending on when in pregnancy the disease is manifest.

Materials and Methods

Beginning in January 2001, the Departments of Pathology and Obstetrics and Gynecology at the University of Texas Southwestern Medical Center at Dallas and Parkland Hospital developed a protocol to

From the Departments of Obstetrics and Gynecology (Drs Nelson, McIntire, and Leveno) and Pathology (Drs Ziadie and Rogers), University of Texas Southwestern Medical Center at Dallas, Dallas, TX.

Received May 6, 2013; revised July 29, 2013; accepted Sept. 9, 2013.

The authors report no conflict of interest

Presented at the 33rd annual meeting of the Society for Maternal-Fetal Medicine, San Francisco, CA, Feb. 11-16, 2013.

Reprints: David B. Nelson, MD, Maternal-Fetal Medicine Division, Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75390-9032. DavidB.Nelson@UTSouthwestern.edu.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2013.09.010

routinely submit placentas for standardized histologic examination. Parkland Hospital is a county-supported institution serving the medically indigent women of Dallas County, Texas. The obstetric service is staffed by faculty, house officers, fellows, and certified midwives under the aegis of the Department of Obstetrics and Gynecology at the University of Texas Southwestern Medical Center.

Placental submission was coordinated with obstetric and fetal conditions requiring attendance at delivery of specialized pediatric resuscitation teams as previously outlined by our colleagues.[26] Briefly, placentas were submitted for the following high-risk delivery conditions: (1) fetuses less than 36 weeks' gestation; (2) estimated fetal weight less than 2000 g; (3) emergency forceps; (4) thick meconium; (5) nonreassuring fetal heart rate status; (6) insulin-dependent diabetes; (7) presence of life-threatening fetal anomalies; (8) fetal hydrops; (9) chorioamnionitis; (10) infant depression at birth requiring bag-mask ventiliation for longer than 15 seconds; and (11) any other situation that the obstetrician determined to warrant the resuscitation team. Gestational age was assigned as previously described on the basis of the last menstrual period and the results of obstetric ultrasonography performed during the gestation.[26,27]

The current study was an analysis of the prospectively maintained electronic database of placentas submitted for standardized histological examination. These placental findings were linked to an obstetric database to analyze the rates of standardized placental findings according to gestational age and diagnosis of preeclampsia. Obstetric and neonatal outcomes for women who deliver at Parkland are entered into a computerized database. Nurses present at delivery complete data sheets that are checked by research nurses for accuracy before electronic storage. Data on infant outcomes are abstracted from discharge records. Periodically, the stored data are audited by reviewing trends using control chart methods as well as reevaluation of randomly selected records.

For this study, the analysis was limited to the placentas received from live-born singletons without major anomalies between Jan. 1, 2001, and Sept. 30, 2007. At our institution, severe preeclampsia is not expectantly managed,[4] and thus, the gestational age at delivery was used for the gestational age at the time of diagnosis of preeclampsia. This study protocol was approved by the institutional review board of the University of Texas Southwestern Medical Center.

Clinical definitions

At Parkland Hospital, the criteria for defining hypertensive disorders during pregnancy are those described in the Report of National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (Working Group) and practice bulletin number 33 of the American College of Obstetricians and Gynecologists.[5,6] These include the following: (1) blood pressure of 140/90 mm Hg or greater after 20 weeks' gestation in a woman not known to be chronically hypertensive and 1 or more of the following: (2) proteinuria of 2+ or greater as measured by dipstick in a catheterized urine specimen, (3) serum creatinine more than 1.0 mg/dL, (4) platelets less than 100,000/μL, (5) aspartate transaminase elevated 2 times above upper limit of normal range, (6) persistent headache or scotomata, or (7) persistent midepigastic or right-upper quadrant pain.

At our institution, gestational diabetes was defined as diabetes diagnosed during pregnancy, regardless of the gestational age at diagnosis.[28] This included both women with gestational diabetes treated with diet and those with gestational diabetes treated with insulin. The diagnosis of gestational diabetes was made using a 1-hour, 50-g screening test and a 100-g 3-hour tolerance test. If 2 or more plasma levels using the National Diabetes Data Group criteria, and accepted by the American Congress of Obstetricians and Gynecologists, were abnormal, then the diagnosis of gestational diabetes was made.[29] Prolonged rupture of membranes was defined as rupture at 18 hours or longer.

Placental evaluation

Placental evaluation was conducted by members of the Department of Pathology using a standardized examination. The umbilical cord, membranes, and placental disk were inspected for any gross abnormalities. The placenta was weighed after removing the umbilical cord, fetal membranes, and nonadherent blood clots. Placentas weighing below the 10th percentile for estimated gestational age were considered to be small for gestational age or hypoplastic.[30,31] Placentas weighing above the 90th percentile for estimated gestational age were considered to be large for gestational age or hyperplastic. The placental disk was then serially sectioned at 1-2 cm intervals, and the tissue was examined for intraparenchymal lesions.

Representative sections of the umbilical cord, membranes, placental parenchyma, and any abnormalities seen on gross examination were submitted for standard histological examination. Each case had a minimum of 4 blocks examined (one with 2 sections of cord, one with 2 membrane rolls, and 2 or more of the placental disc). The sampling was the same for all cases, irrespective of gestational age as per our standard grossing protocol.

For this study, vascular lesions included atherosis and infarction, whereas nonvascular lesions included hyperplasia. Additional pathological diagnoses included the following:

1. Inflammatory lesions
   a. Umbilical vasculitis: neutrophils (with or without eosinophils) in the walls of the umbilical vessels. When inflammation extended into the Wharton jelly, the modifier, with funisisits, was added. A severe modifier was added when neutrophils were confluent within the wall and associated with attenuation or degeneration of the vascular smooth muscle cells.
   b. Chorionic plate vasculitis: neutrophilic inflammation of the chorionic plate vessels, histologically identical to umbilical vasculitis with the similar severe modifier.
   c. Acute chorioamnionitis: neutrophils in the chorion of the membrane roll with or without extension into the chorioamniotic