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Is preeclampsia associated with fetal malformation? A review and report of original research

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Abstract

Objective—To examine fetal malformations in mother–infant pairs with and without pregnancy-related hypertension.

Methods—This was an observational, population-based study of women delivering a singleton at our hospital. Specific fetal malformations identified in women with gestational hypertension or preeclampsia were compared to those without pregnancy-related hypertension. Women with chronic hypertension, superimposed preeclampsia on chronic hypertension and pregestational diabetes were excluded.

Results—Between March 2002 and December 2012, a total of 151 997 women delivered, and 10 492 (7%) had preeclampsia, 4282 (3%) had gestational hypertension and 137 223 (90%) were referent normotensive controls. Women with preeclampsia were significantly more likely to deliver infants with malformations when compared to normotensive controls (2.5% versus 1.6%, $p < 0.001$), whereas women with gestational hypertension were not (1.9% versus 1.6%, $p = 0.16$). The overall risk for fetal malformation associated with preeclampsia remained significant following logistic regression for age, race, parity and maternal body-habitus (adjusted OR 1.5; 95% CI: 1.3–1.7). Only single-organ system malformations – microcephaly and hypospadias – remained associated with preeclampsia ($p < 0.001$), and fetal growth restriction was a co-factor for both.

Conclusions—Preeclampsia was associated with increased rates of fetal malformations when compared to normotensive women – specifically microcephaly and hypospadias. These associations appear predominantly as a consequence of impaired fetal growth.

Keywords

Fetal malformation; gestational hypertension; preeclampsia

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Declaration of Interest

The authors report no conflict of interest.

Introduction

Preeclampsia is a disease specific to pregnancy that results in pathophysiologic changes that can affect nearly every organ system, and at its worst, can result in multi-organ deterioration in the mother [1–3]. This disorder is thought to be a result of vasospasm, endothelial dysfunction and ischemia, resulting in derangements manifest in the mother as edema, visual disturbances, headache and epigastric pain in the severe forms of the disease [3,4]. As related to the infant, preeclampsia is also associated with fetal growth restriction and preterm birth, which corresponds to an increase in neonatal morbidity and mortality [3,5].

Despite our current understanding of the maternal and infant consequences of preeclampsia, little information is available to describe if there are fetal effects as related to congenital malformation. The possibility of a relationship between congenital abnormalities and pregnancies complicated by preeclampsia is often discounted because the onset of preeclampsia is during the second part of pregnancy, while the critical period for most congenital abnormalities is the early weeks of gestation [6]. Indeed, there is no mention of preeclampsia as a factor for or against fetal malformation in the Task Force [5]. Review of Chesley's Hypertensive Disorders in Pregnancy textbook [1] as well as other contemporary texts [3,7,8] failed to mention an association of preeclampsia and fetal malformation. The aim of this study was to examine the epidemiology of malformations in mother–infant pairs with and without pregnancy-related hypertension at our institution and to review the literature on this topic.

Methods

Parkland Hospital is a tax-supported institution serving Dallas County. The obstetric service is staffed by house officers, certified nurse midwives, nurse practitioners' and faculty of the Department of Obstetrics and Gynecology at the University of Texas Southwestern Medical Center. Our service maintains a computerized database of selected obstetric and neonatal outcomes for all women delivering at Parkland. An obstetrical data sheet is completed at each delivery, and nurses assess the data for consistency and completeness before the data are stored electronically. Evaluation for congenital anomalies is routinely performed by attending neonatologists in the Department of Pediatrics at the University of Texas Southwestern Medical Center, and this information was abstracted into the obstetric database by trained obstetric research nurses. This database includes information about all structural and chromosomal abnormalities. Information about stillbirths, defined as those with birthweight 500 g or more, is also recorded. Pregnancy outcomes were obtained from the prospectively maintained obstetric database as described above, and discharge medical records were reviewed to verify the specific type of malformation. Data were entered into a secure password-protected file server, de-identified and accessible only by the departmental epidemiologist (D. D. M.). This analysis was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas.

During the study period, the criteria for defining hypertensive disorders during pregnancy were 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 [4,9]. These include the following for the diagnosis of preeclampsia: (1) blood pressure of 140/90 mm Hg or greater after 20 weeks' gestation in a woman not known to be chronically hypertensive plus one 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/ μ L, (5) aspartate transaminase elevated two times above upper limit of normal range, (6) persistent headache or scotomata or (7) persistent midepigastriac or right-upper quadrant pain. Gestational hypertension was defined as systolic blood pressure 140 or diastolic blood pressure 90 mm Hg for the first time during pregnancy with the following: (1) no proteinuria and (2) blood pressure returning to normal before 12 weeks postpartum.

This study now reported was limited to women with gestational hypertension or preeclampsia who were compared to those women without pregnancy-related hypertension. This analysis did not include women with chronic hypertension or women with preeclampsia superimposed on chronic hypertension. Each pregnancy was analyzed based on the specific fetal malformation identified. Women with pregestational diabetes were excluded from this analysis. Only women with singletons were included.

Briefly, each anomaly was diagnosed by using the International Classification of Diseases, ninth edition as previously described in another study from our institution [10]. Of over 100 categories of malformations analyzed, the most common ones were the following: anencephaly, meningocele-meningomyelocele, hydrocephaly, microcephaly, cardiac malformations, tracheoesophageal fistula, esophageal atresia, omphalocele, gastroschisis, rectal atresia-stenosis, malformed genitalia, renal agenesis, cleft lip, cleft palate, syndactyly, adactyly, club foot, hypospadias and diaphragmatic hernia. The remainder of infants with other malformations were grouped as follows: central nervous system abnormalities, circulatory or respiratory anomalies, gastrointestinal anomalies, urogenital anomalies, musculoskeletal anomalies and integumental anomalies. Infants with abnormal karyotypes were classified as Down syndrome (trisomy 21), trisomy 18, trisomy 13 or other chromosomal abnormalities. Infants with multiple anomalies were classified according to their principal organ system involvement and counted only once in the calculation of prevalence; however, analysis for multiple anomalies included multiple conditions for up to three separate coded organ system malformations. The principal organ system allocation for infants with multiple anomalies was based on a judgment of the clinical significance of the malformations. For example, in the case of an infant with both a neural tube defect and hypoplastic left heart, the infant's principal organ system malformation was categorized as cardiac because hypoplastic left heart was the most life-threatening anomaly. Infant growth restriction was defined as birthweight less than the 10th percentile for gestational age [11]. Sporadic malformations were defined as those with occurrence rates less than 1 per 10 000 deliveries.

Initial evaluation for each anomaly as categorized above was conducted using a univariable analysis. Univariate analysis of infants' malformation according to pregnancy-related hypertension was performed with use of chi-square statistics. Following identification of those women with gestational hypertension or preeclampsia, a multivariable analysis was

completed adjusting for maternal age, race, parity and body habitus. The estimates and significance levels were adjusted for the mother's age, race, parity and body habitus by the Cochran–Mantel–Haenszel method. Bonferroni corrections were used in cases of multiple testing. Specific fetal malformations that were identified to be associated with pregnancy-related hypertension were then analyzed on an individual basis. Analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC), and p values less than 0.05 were judged significant.

Results

Between 14 March 2002 and 31 December 2012, a total of 151 997 women delivered at our hospital and met inclusion criteria for this analysis. Of them, 10 492 (7%) were diagnosed with preeclampsia, 4282 (3%) were identified to have gestational hypertension and 137 223 (90%) women were defined as referent normotensive controls. Selected demographic characteristics are listed in Table 1. Women with hypertensive disorders related to pregnancy were older, more often black, less parous and had larger body habitus (Table 1). Selected perinatal outcomes in relation to diagnosis of hypertensive disorders of pregnancy to include preeclampsia and gestational hypertension when compared to normotensive women are listed in Table 2. Gestational age at delivery, neonatal intensive care, infant growth restriction and stillbirth were all significantly increased in women with preeclampsia when compared to normotensive women, whereas neonatal death was not increased (Table 2). When comparing pregnancies with gestational hypertension to normotensive women, infant growth restriction was also noted to be increased in women with gestational hypertension (Table 2). Although an increase in stillbirth was noted in the normotensive women compared to women with gestational hypertension, no differences were noted for neonatal intensive care or neonatal death (Table 2).

Pregnancies were then analyzed based upon the type of hypertensive disorder and rates of infant malformation (Table 3). Fetal malformations were identified in 260 (2.5%) of women with preeclampsia, 81 (1.9%) of women with gestational hypertension and 2218 (1.6%) of normotensive women. As listed in Table 3, women with preeclampsia were significantly more likely to deliver infants with malformations when compared to normotensive controls ($p < 0.001$), whereas women with gestational hypertension were not ($p = 0.16$). The overall risk for fetal malformation in women with preeclampsia remained significant following logistic regression adjusting for age, race, parity and maternal body habitus (adjusted OR 1.5; 95% CI: 1.3–1.7). The categories of fetal malformations characterized according to organ system or chromosomal abnormalities are also listed in Table 3. Only single organ system malformations were significantly associated with preeclampsia. As listed in Table 3, microcephaly was the most common single malformation ($N = 39$); the rate was 0.4% versus 0.1% in normotensive controls ($p < 0.001$). Hypospadias occurred in 36 pregnancies complicated by preeclampsia for a rate of 0.3% compared to 0.2% in normotensive controls, $p < 0.001$ (Table 3). The remaining single organ system malformations ($N = 104$ cases) comprised 52 categories with individual rates so low as to be considered sporadic. A total of 36 (92%) of the 39 births with microcephaly had isolated microcephaly (Table 3). The remaining three infants included associated findings of ventriculomegaly, holoprosencephaly and a complex cardiac abnormality. Fetal growth restriction was a co-

factor for microcephaly as well as hypospadias in women with preeclampsia (Table 3). Specifically, when expecting 10% of the 10th percentile related to fetal growth, there was an eightfold increase in growth restriction among infants with microcephaly compared to controls. Similarly, there was a fivefold increase in growth restriction among infants with hypospadias.

Discussion

In this study of 151 997 singleton pregnancies, preeclampsia was associated with an increased rate of malformations compared to normotensive women. Gestational hypertension, on the other hand, was not associated with malformation. Further analysis of malformations in women with preeclampsia showed that both isolated microcephaly as well as hypospadias was associated with preeclampsia, whereas chromosomal and multi-organ system malformations were not increased. Moreover, isolated microcephaly and hypospadias were linked to fetal growth restriction in women with preeclampsia. Our results suggest several findings: (1) fetal malformations related to preeclampsia are limited to isolated microcephaly and hypospadias; and (2) both microcephaly and hypospadias are associated with impaired fetal growth in women with preeclampsia. Taken all together, the fetal malformations associated with preeclampsia – that is, microcephaly and hypospadias appear to be acquired malformations, presumably due to the placental insufficiency characteristic of preeclampsia, whereas intrinsic genetic malformations are not increased. This presumably reflects the onset of preeclampsia in the second half of pregnancy and beyond the period of organogenesis.

For this analysis, the rate of preeclampsia was 7%, which appears consistent with prior reports of preeclampsia such as the National Institute of child Health and Human Development Maternal Fetal Medicine Network for Clinic Trials (MFMU Network) trial of low-dose aspirin to prevent preeclampsia in which 6.3% of women receiving placebo therapy developed preeclampsia [12]. The rate of gestational hypertension in our analysis, however, was 3%. Is this rate of gestational hypertension lower than expected? In our review of the literature, it is difficult to determine the exact, or expected, frequency of gestational (i.e. transient) hypertension as frequencies vary significantly by report. Rates of gestational hypertension appear to range between 6% and 17% in healthy nulliparous women and between 2% and 4% in multiparous women [13–16]. There may be several reasons to explain these differential frequency estimates. First, there appear to be disparities in many of the definitions used when classifying the various types of hypertension in pregnancy [17]. Second, some of the prior reports of frequency have used discharge diagnosis (International Classification of Diseases [ICD9] coding) as a mechanism to identify rates of preeclampsia – a methodology fraught with inaccuracies [18]. Third, some prior analyses used only nulliparous women which may inflate frequencies given risk differences in hypertensive disorders when compared to multiparous women [12]. Fourth, many of the women studied were those electing to participate in preeclampsia prevention, which may also include a group of women that would subsequently have greater risk in developing hypertension in pregnancy [12]. Taken altogether, the frequency of gestational hypertension appears to be variable as the diagnosis depends heavily on ethnic and racial components of the populations studied in addition to variations in the definition (i.e. criteria)

used for the diagnosis. In the current study, the diagnosis of both preeclampsia and gestational hypertension has been prospectively measured using a manual of operations, and thus, we are reasonably confident that the rates reported are reflective of our patient population consisting predominantly of Hispanic and black women.

Although pregnancy-induced hypertensive disorders are common in pregnancy, there are virtually no reports in the literature as to whether this pregnancy complication is associated with fetal malformations. According to a search of PubMed between 1966 and the present (using search terms, “pregnancy” AND “preeclampsia” AND “malformation”), a total of 833 articles were identified. Of these, two reports dealt with whether or not preeclampsia was associated with microcephaly. McElrath et al. [19] analyzed 1445 infants born before 28 weeks’ gestation and found that 10% had microcephaly compared to the 2.2% expected incidence. They also observed that microcephaly occurred in the setting of fetal growth restriction – which suggested that placental insufficiency due to preeclampsia may be the mechanism by which isolated microcephaly occurs. In the second report by Banhidy et al. [6], case-control methodology was used to analyze structural birth defects potentially associated with preeclampsia in 585 hypertensive women compared to 1017 matched controls. Preeclampsia was not found in association with malformations unless there was preeclampsia superimposed on chronic hypertension – meaning early pregnancy hypertension plus development of preeclampsia later in pregnancy.

There were five other reports (published between 2008 and 2014) where investigators found an association between hypospadias and preeclampsia also in growth restricted fetuses [20–24]. The common theme as to the pathophysiology of hypospadias in infants delivered of women with preeclampsia was placental insufficiency. How placental insufficiency might interfere with closure of the urethra was unclear [20–24].

One limitation of the study is the possibility for inaccuracies in our dataset used for this analysis – either incorrect classification of preeclampsia or incomplete ascertainment of infant abnormalities. At our institution, data collection is initiated with encounter forms prepared by labor and delivery nurses attending the procedure. Once collected, these encounter forms are reviewed and interpreted by trained research nurses with a minimum of five years’ experience in our data collection operation. Data entry is performed by dedicated data entry operators using a customized data entry system with checks and audits performed as a routine part of our data collection. Infant anomaly data is also ensured for accuracy. Specifically, research nurses with expertise in review of newborn discharge charts review each infant using a manual of operations for defining abnormalities at discharge. Of course, there are inevitable abnormalities that could have been missed; however, given the review of data entry, we believe there were few such cases.

We feel a need to emphasize that our results do not establish a cause-and-effect relationship of preeclampsia and fetal malformation – only an *association* of two malformations with this common pregnancy disease. We are of the view that a specific definition of malformation is central to understanding our results. That is, a malformation can be an intrinsic abnormality “programmed” during cellular development in contrast to a “disruption” where genetically normal fetal tissue is modified as a result of a specific insult – which is placental

insufficiency in the case of preeclampsia. If correct, and our results seem to make the latter scenario plausible, then the fetal malformations associated with preeclampsia are a consequence of the maternal disease – an extrinsic pathophysiology versus an intrinsic defect in the fetal genetic potential.

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Table 1

Maternal demographic characteristics in relation to diagnosis of preeclampsia or gestational hypertension compared to normotensive controls.

Characteristic	Preeclampsia N = 10 492	Normotensive women N = 137 223	Gestational hypertension N = 4282	Overall <i>p</i> value
Age, years:				<0.001
15	205 (2)	1327 (1)	62 (1)	
16–26	5680 (54)	72772 (53)	2099 (49)	
27–31	2190 (21)	35348 (26)	1009 (24)	
32–34	1005 (10)	14218 (10)	457 (11)	
>35	1412 (13)	13558 (10)	655 (15)	
Race/ethnicity:				<0.001
Black	1801 (17)	13304 (10)	778 (18)	
White	460 (4)	4943 (4)	248 (6)	
Hispanic	8094 (77)	115323 (84)	3173 (74)	
Other	137 (1)	3653 (3)	83 (2)	
Parity:				<0.001
0	5275 (50)	39682 (29)	1953 (46)	
1	2102 (20)	43651 (32)	989 (23)	
2	1629 (16)	31526 (23)	758 (18)	
>3	1486 (14)	22364 (16)	582 (14)	
Body-mass index, kg/m ² :				<0.001
<18.5	9 (0)	87 (0)	0 (0)	
18.5–24.9	592 (6)	11696 (9)	122 (3)	
25.0–29.9	2478 (24)	44178 (32)	761 (18)	
>30	6517 (62)	69910 (51)	3085 (72)	
Missing	896 (9)	11352 (8)	314 (7)	

Data represented as *N* (%).

Table 2

Selected perinatal outcomes in relation to diagnosis of hypertensive disorders in pregnancy.

Outcome	Preeclampsia N = 10 492	p value *	Normotensive women N = 137 223	p value †	Gestational hypertension N = 4282
Gestational age at delivery, weeks:		<0.001		<0.001	
33 ^{6/7}	672 (6)		2067 (2)		21 (0)
34 ^{0/7} –36 ^{6/7}	1367 (13)		4597 (3)		142 (3)
37 ^{0/7} –41 ^{6/7}	8267 (79)		124 625 (91)		4043 (94)
>42 ^{0/7}	186 (2)		5934 (4)		76 (2)
Neonatal intensive care	763 (7.3)	<0.001	2825 (2.1)	0.13	74 (1.7)
Birthweight < 10th percentile‡	2501 (23.8)	<0.001	11 879 (8.7)	<0.001	525 (12.3)
Stillbirth	103 (1.0)	<0.001	624 (0.5)	0.01	8 (0.2)
Neonatal death	38 (0.4)	0.23	405 (0.3)	0.12	7 (0.2)

Data represented as N (%).

* p value for the comparison of preeclampsia with normotensive women.

† p value for the comparison of gestational hypertension with normotensive women.

‡ Birthweight percentiles for gestational age [11].

Table 3

Categories of fetal malformations in women with gestational hypertension or preeclampsia compared to normotensive women. Subsequent specific fetal malformations associated with preeclampsia compared to normotensive controls.

Malformation	Preeclampsia <i>N</i> = 10 492	Normotensive women <i>N</i> = 137 223	Gestational hypertension <i>N</i> = 4282
Malformed infant	260 (2.5)*	2,218 (1.6)	81 (1.9)
Organ system involvement:			
Single organ system	168 (1.6)*	1,305 (1)	50 (1.2)
Two organ system	39 (0.4)	365 (0.3)	11 (0.3)
>3 organ system	27 (0.3)	243 (0.2)	10 (0.2)
Any chromosomal	26 (0.3)	305 (0.2)	10 (0.2)
Specific single organ malformation			<i>p</i> value Odds ratio (95% CI)
Microcephaly:			
Total	39 (0.37)	130 (0.09)	<0.001 3.94 (2.75–5.63)
Isolated	36 (0.34)	92 (0.07)	<0.001 5.13 (3.49–7.55)
<10th percentile for gestational age [†]	28 (78)	55 (60)	0.055 2.36 (0.97–5.73)
Hypospadias:			
Total	36 (0.34)	205 (0.15)	<0.001 2.30 (1.61–3.28)
Isolated	19 (0.18)	118 (0.09)	0.002 2.11 (1.30–3.42)
<10th percentile for gestational age [‡]	10 (53)	18 (15)	<0.001 6.17 (2.20–17.31)

Data represented as *N* (%).

* $p < 0.05$ when compared with normotensive women; all other comparisons not significant.

[†] Percent of isolated microcephaly.

[‡] Percent of isolated hypospadias.

Specific malformation categories where $p > 0.05$ for preeclampsia compared to normotensive controls were excluded as were very rare malformation categories defined as occurrence rates less than 1 per 10 000 births.