The Effects of Preeclampsia on Perinatal Risks and Infant Temperaments Among Mothers With Antenatal Depression

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Importance: Preeclampsia and depression are two of the most prevalent disorders known to affect pregnant women and unborn infants. However, few studies have prospectively examined the adverse influence of in-utero exposures to the two disorders on the optimal development in their offspring, including mortality, adverse birth outcomes, and infant temperament styles. **Objectives:** (1) To examine whether exposures to preeclampsia and antenatal depression were associated with developmental indices of offspring at birth and temperament at 3 months; and (2) To evaluate how preeclampsia and antenatal depression were associated with offspring temperamental style. **Design:** Prospective cohort study with regular assessment of mother's blood pressure at each prenatal visit, offspring were followed till three months. **Setting:** Two prenatal clinics, New York City, USA. **Participants:** A cohort of 233 pregnant women were followed throughout pregnancy. Of those, 141 provided ratings of infant temperament at three months. **Exposures:** Diagnostic outcome of maternal depression by clinical interviewers blind to preeclampsia

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status were ascertained using the Structured Clinical Interview for DSM-IV Axis I Disorders. The development of preeclampsia, defined by the onset of hypertension ($> 140/90$ mm HG) after 20 weeks' gestation, accompanied by 300 mg of protein, monitored via electronic medical records. Main Outcome Measures: Birth outcomes were assessed via standardized ratings at delivery. Infant temperament was reported by the mother at six months, using the 91-item IBQ-R (Infant Behavioral Questionnaire-Revised). Results: Preeclampsia was associated with an over 5-fold increased risk for fetal/infant mortality, a 3- to 7-fold increased risk for poorer birth outcomes, and flatter affect and distress in infants. Furthermore, infants born to preeclamptic mothers with co-occurring depression displayed lower levels of smiling/laughter, high-intensity pleasure seeking behavior, perceptual sensitivity, and approach behavior. Conclusion: Preeclampsia was associated with a few difficult temperament styles in the first three months after birth. Moreover, its negative impact was amplified by mother's antenatal depression. Our findings regarding additive risk for negative infant outcomes in babies exposed to preeclampsia and antenatal depression suggest that the development of early detection programs to identify and monitor women who are at heightened risk for these conditions can potentially have a positive influence on long-term infant neurobehavioral development.

Keywords: preeclampsia, antenatal depression, birth outcomes, infant temperaments, epigenetics, high-risk pregnancy

Introduction

Preeclampsia, a hypertensive disorder unique to human pregnancy, affects 5%-10% of all pregnancies (McCalla, Nacharaju, Muneyyirci-Delale, Glasgow, & Feldman, 1998; Williams, Miller, Qiu, Cripe, Gelaye, & Enquobahrie, 2010). It is defined by the onset of hypertension (140/90 mm HG) after 20 weeks gestation in the index pregnancy, accompanied by 300 mg of protein in a 24 hour urine specimen, or persistent $> 30\text{mg/dL}$ (1+) protein on a dipstick (Williams et al., 2010; Podymow & August, 2007). In the United States among 2,748,302 births in 2008, there were 104,850 cases of preeclampsia (Osterman, Martin, Mathews, & Hamilton, 2011). While the etiology of preeclampsia is currently elusive, it remains a leading cause of mortality and morbidity among mothers and their babies (Podymow & August, 2007; Chang et al., 2003; Saadat, Nejad, Habibi, & Sheikhvatan, 2007).

Severe preeclampsia may cause symptoms such as hypertension, proteinuria, eclampsia, cerebral edema, cerebral hemorrhage, long-term neuro-cognitive dysfunction, blindness, liver swelling, and other liver damage leading to elevated serum transaminase, oliguria, thrombocytopenia, pulmonary edema necrotizing pancreatitis, all of which could be fatal to mothers and their unborn child in-utero, as well as causing various degrees of child morbidity after birth (Williams et al., 2010; Swank, Nageotte, & Hatfield, 2012). The main impact of preeclampsia to the fetus is under-nutrition, resulting from utero-placental vascular insufficiency hypoxia, which restricts nutrient supplies and oxygen flow from the placenta to the fetus (Kajantie, Thornburg, Eriksson, Osmond, & Barker, 2010). This leads to various perinatal and neonatal problems, including IUGR (intra-uterine growth restriction, defined as birth weight below the 10th percentile) (Saadat et al., 2007; Kajantie et al., 2010; Liu, Cheng, & Chang, 2008; Rasmussen & Irgens, 2003; Powe et al., 2011; Odegard, Vatten, Nilsen, Salvesen, & Austgulen, 2000; Jelin, Cheng, Shaffer, Kaimal, Little, & Caughey, 2010; Habli, Levine, Qian, & Sibai, 2007) emergency C-section (Saadat et al., 2007), preterm delivery (Rasmussen & Irgens, 2003; Liggins & Howie, 1972; Bramham, Briley, Seed, Poston, Shennan, & Chappell, 2011), reduced birth weight (Saadat et al.,

2007; Edwards, Benediktsson, Lindsay, & Seckl, 1993; Benediktsson, Lindsay, Noble, Seckl, & Edwards, 1993), more frequent and prolonged NICU (neonatal intensive care unit) stay (Saadat et al., 2007; Habli et al., 2007; Masoura et al., 2012), and increased acute respiratory distress syndromes after birth (Habli et al., 2007; Kalder, Ulrich, Hitschold, & Berle, 1995). In some cases, fetal damage is so severe that it results in fetal/child mortality such as fetal demise, still-birth, and neonatal death (Jones, Bell, & Maroof, 1999). However, a longer term health and developmental consequences of exposure to preeclampsia to the surviving child is relatively unexplored.

Pregnancy is considered a stressful life-events, as women have to adapt to biological and emotional changes, to a new environment characterized by financial and social pressures, restrictions on time for pre-natal care, and to a new role as a primary caretaker of the infant. Moreover, depression during pregnancy is highly prevalent, with prior studies reporting its range from 14% to 23% (Gaynes et al., 2005). Pregnancy can be a highly stressful experience (Marcus, Flynn, Blow, & Barry, 2003). When women suffer from pregnancy-induced medical problems, such as preeclampsia, the level of stress may be aggravated. Both preeclampsia and antenatal depression are known to be linked to perinatal problems, such as miscarriages (Sugiura-Ogasawara, Furukawa, Nakano, Hori, Aoki, & Kitamura, 2002), preterm delivery (Straub, Adams, Kim, & Silver, 2012), and fetal growth effects including LBW (low birth weight) and IUGR (Chung, Lau, Yip, Chiu, & Lee, 2001). While growing efforts have been made to find associations between perinatal problems, including IUGR (Bos, Einspieler, & Prechtl, 2001; Tolsa et al., 2004), preterm birth (Moster, Lie, & Markestad, 2008; Marlow, Wolke, Bracewell, & Samara, 2005; Allin et al., 2001), and LBW (Sung, Vohr, & Oh, 1993; Mikkola et al., 2005; Hack, Schluchter, Cartar, Rahman, Cuttler, & Borawski, 2003), and child neurobehavioral development (Davis, Glynn, Schetter, Hobel, Chiciz-Demet, & Sandman, 2007; Field, Diego, & Hernandez-Reif, 2006; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003; Marcus et al., 2011) in recent years, the extent of adverse developmental and neurobehavioral outcomes of surviving infants owing to specific maternal problems during pregnancy, such as preeclampsia and antenatal depression, has been investigated less frequently.

Among those, Many, Fattal, Leitner, Kupferminc, Harel, and Jaffa (2003), for example, reported that IQ at age three years was significantly lower among IUGR children with maternal preeclampsia, compared to those without (85.5 vs. 96.9, $p = 0.03$). Similarly, Cheng, Chou, Tsou, Fang, and Tsao (2004) documented that pre-term infants of preeclamptic mothers, compared to those of non-preeclamptic mothers, had a compromised neuro-developmental index, as measured by the Bayley Scales of Infant Development. Children born to mothers with preeclampsia had a lower MDI (Mental Developmental Index) than children born to mothers without preeclampsia at two years of age ($p = 0.04$); there was no significant difference between the two groups in the PDI (Physical Developmental Index) ($p = 0.56$). Furthermore, they reported that preeclampsia was associated with an over 10-fold increased risk ($p = 0.007$) of mildly delayed MDI, after controlling for demographic and biomedical confounders.

Since hypertensive disorders and maternal depression are the two most common chronic conditions that women of reproductive age (15-44 years) experience, examining the negative effect of exposure to preeclampsia, as a specific distal, attributable risk for perinatal problems in offspring, while considering conjoined roles of antenatal depression on suboptimal developmental and neurobehavioral outcomes in offspring could help us understand the short- and long-term consequences of exposures to common clinical conditions mothers experience during pregnancy.

Methods

Participants

A total of 300 pregnant women were contacted at the prenatal OB/GYN (obstetrics and gynecological) clinic at Mount Sinai Medical Center between September 2010 and June 2012. The clinic draws patients from East Harlem and the South Bronx in New York City, where the majority of residents are low-income ethnic minorities.

Exclusion criteria for participation included HIV (Human Immunodeficiency Virus) infection, maternal psychosis, maternal age less than 15 years, life-threatening medical complications related to the mother, and congenital or chromosomal abnormalities in the fetus. Demographic information, including maternal age, ethnicity, education level, welfare status, marital status, and previous obstetric histories, were obtained through self-administered questionnaires during the second trimester and structured clinical interviews during the third trimester. Data on gestational age at birth, delivery method, infant gender, birth weight, body length, and Apgar scores were recorded at birth.

Of the 300 contacted, 47 did not meet inclusion criteria and an additional seven later chose an elective termination of their pregnancy. The remaining 246 participants were followed from the 2nd trimester of pregnancy to delivery. Of those, 13 participants withdrew from the study during their pregnancy, mainly due to time constraint or changing hospitals, resulting in 233 participants in the study. Additionally, 14 pregnancies ended with fetal and neonatal death, including one abortion due to a medical condition, nine miscarriages, and five stillbirths, resulting in 218 participants. When offspring reached six months old, mothers were re-contacted to assess infant temperament; 141 of those contacted responded (65%).

All patients were consented as per protocol approved by the institutional review boards at Queens College, City University of New York and Icahn School of Medicine at Mount Sinai. The study also obtained a certificate of confidentiality from the National Institute of Health (MH-10-138) to protect the integrity of the data and the privacy of the participants.

Measures

Demographics and obstetric history and problems. Demographics, obstetric history including prior loss of pregnancy, parity, adverse pregnancy outcomes, and history of psychosocial-financial problems, including welfare status, were obtained through self-report questionnaires during the initial prenatal assessment (1st to 2nd trimester). Presence of common but potent risk behaviors, such as smoking and drinking, were monitored at each perinatal appointment.

(1) Preeclampsia: Clinical status of preeclampsia was ascertained from participants' electronic medical records throughout pregnancy. Based on the current practice at the clinic from which the participants were drawn, two conditions were required for the diagnosis: (1) elevated blood pressure at either 140 systolic or 90 diastolic on a minimum of two separate occasions, at least 6 hours apart; and (2) presence of proteinuria as indicated by at least 300 mg/24 hours and/or 1+ on urine dipstick. The diagnosis was confirmed by the blood pressure reading at the time of the diagnosis and proteinuria from the lab report. There was no discrepancy except for one case, where the consensus was made to give a positive endorsement for preeclampsia status after the chart review;

(2) Antenatal depression: Clinical status of maternal depression during pregnancy was ascertained using the SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders) (First, Spitzer, Gibbins, & Williams,

2002) by trained research clinical interviewers who were blind to maternal preeclampsia status. The clinical interview covered a period between the first prenatal visit and the third trimester. DSM-IV diagnosis of major depressive disorder, dysthymia, adjustment disorder with depressed mood, or depressive disorder not otherwise specified were coded as positive for depression. Both definite and probable cases were included;

(3) Infant perinatal problems: Gestational age at birth, birth weight, 5-minute APGAR scores, and delivery method were recorded at the time of birth by the delivery nurse. Preterm birth (gestational age at birth < 37 weeks), LBW (weight < 2,500g), and low 5 minute APGAR scores (global score < 7) were then calculated. Fetal, perinatal, and neonatal deaths were recorded from the electronic medical chart;

(4) Infant temperament: IBQ-R (The Infant Behavior Questionnaire-Revised) Short Form (Rothbart & Gartstein, 2003), a 91-item questionnaire, was used to assess infants' behavior and temperament in 14 different domains. These 14 domains included: activity level, distress to limitations, fear, duration of orienting, smiling and laughter, high pleasure seeking, low pleasure seeking, soothability, falling reactivity (rate of recovery from distress), cuddliness, perceptual sensitivity, sadness, approach and vocal reactivity. "Activity level" refers to the baby's gross motor activity, including movement of arms and legs, squirming and locomotor activity. "Distress to limitations" is defined as the baby's fussing, crying or showing distress while either in a confined space, engaged in caretaking activities, or the inability to perform a desired action. "Fear" describes the baby's startle or distress to sudden changes in stimulation such as new objects or people. "Duration of orientating" measures the baby's attention to and/or interaction with a single object for extended periods of time. "Smiling and laughter" is defined as smiling or laughter from the child in general caretaking and play. "High and low pleasure seeking" items refer to the amount of pleasure or enjoyment related to stimulus characteristics (high and low intensity, rate, complexity, novelty and incongruity). "Soothability" refers to the baby's ability to stop fussing, crying, or evidencing distress when soothing techniques are used by the caretaker. "Falling reactivity" (i.e., rate of recovery from distress) is defined as the rate of recovery from peak level of distress, excitement, or general arousal, and ease of falling asleep. The "cuddliness" scale refers to the baby's enjoyment of and molding to the body of a caregiver when held. "Perceptual sensitivity" is the degree to which slight, low intensity stimuli from the external environment are detected. "Sadness" refers to general low mood, lowered mood and activity related to personal suffering, physical state, or object loss, or an inability to perform a desired action. "Approach" describes rapid approach to, excitement about and positive anticipation of pleasurable activities. Lastly, "vocal reactivity" is the amount of vocalization exhibited by the baby in daily activities. The mothers were asked to report the relative frequency of specified infant reactions in the past week using a seven item Likert scale, with an option to indicate if she had not seen the baby in that situation and therefore unable to rate (Gartstein & Rothbart, 2003).

Potential confounders. Maternal educational attainment, marital status, age, parity, and sex of the baby were deemed a priority as potential demographic confounders. A history of maternal smoking during the 1st and 2nd trimesters of the current pregnancy was included in the model as an additional confounder because of the well-known negative effects on both birth outcomes (Anblagan et al., 2013; Cnattingius, 2004; Pollack, Lantz, & Frohna, 2000) and infant temperament (Martin, Dombrowski, Mullis, Wisenbaker, & Huttunen, 2006; Pickett, Wood, Adamson, D'Souza, & Wakschlag, 2008; Roza et al., 2009; Stene-Larsen, Borge, & Vollrath, 2009). These confounders were included in models for statistical adjustment. Moreover, when analyzing temperament, the maternal depressive symptom as measured by Edinburgh Postnatal Depression Scale (Murray & Carothers, 1990) at six month postpartum (at the time of the infant temperament assessment) was included as

an additional confounder. We refer to the model without confounders as the unadjusted model and with confounders as the adjusted model.

Statistical method. Preliminary analyses of group differences in rates of perinatal problems were compared by the X^2 test. This was followed by logistic regression with a prior determined set of potential confounders. We conducted multi-variable analyses using GLM (a general linear model) to examine the main effect of preeclampsia and antenatal depression on infant temperament, because the temperament measure consists of 14 sub-scales which are inherently correlated. The same GLM was followed by the model with an additional interaction term between preeclampsia and antenatal depression, in order to evaluate whether having two separate unrelated common problems during pregnancy aggravate the effect of each factor alone on infant temperament. All GLM analyses were performed first without potential confounders (i.e., unadjusted model) and then with potential confounders (i.e., adjusted model). When infant temperament style was evaluated, mother's postnatal depressive scale at the time of the infant assessment was included in the GLM as an additional confounder.

Results

Demographic Characteristics

Table 1 shows that there was no difference in demographic characteristics and depressive diagnosis during pregnancy between mothers who developed ($N = 43$) and who did not develop preeclampsia ($N = 190$) during pregnancy.

In the total sample of 233, the average (*SD*) age of the mothers was 27.5 (5.7) years and parity 2.7 (2.8). Approximately 48.1% mothers are Black, 34.8% are Latina, 5.1% are White, 8.1% are Asian, and 3.9% identified their ethnicity as "other". Many of the participants were of low socioeconomic backgrounds and education levels, with 31.4% not completing high school, 87.1% receiving public assistance, and 3.9% homeless. Approximately 70% of the participants reported that they were single and 20% were clinically depressed during pregnancy. Of the babies' gender, 54% are male and 46% are female.

Risk of Perinatal Problems at Birth by Maternal Preeclampsia Among Neonates

As Table 2 shows, preeclampsia during pregnancy was associated with a 2- to 3-fold increased risk of perinatal problems, including perinatal/fetal demise ($OR = 3.57, p = 0.02$), pre-term birth ($OR = 2.69, p = 0.02$), LBW ($OR = 3.71, p = 0.002$), and low APGAR scores ($OR = 3.86, p = 0.02$) among women with preeclampsia relative to women without. When the effect of confounders was controlled for, all the associations remained not only significant but the estimated increased risks were elevated substantially, including an over five-fold increased risk for perinatal/fetal demise ($p = 0.01$), LBW ($p = 0.001$), and APGAR scores ($p = 0.01$), as well as a 3-fold increased risk for pre-term birth ($p = 0.01$).

The Profiles of Infant Temperament at Six Months Old by Preeclampsia and Antenatal Depression

Table 3 shows the main effects of preeclampsia and antenatal depression on infants' temperament analyzed simultaneously in the same GLM. In the unadjusted model, infants of mothers with preeclampsia compared to infants of mothers without it had greater levels of low-pleasure seeking (6.04 vs. 5.57, $p = 0.04$) and vocal reactivity (5.90, vs. 5.48, vs., $p = 0.05$). Infants of mothers with antenatal depression compared to infants of mothers without it had lower high pleasure seeking (5.34 vs. 6.18, $p = 0.05$), less soothability (4.93 vs. 5.65, $p = 0.002$), lower falling reactivity (i.e., recovery from the distress) (4.56 vs. 5.33, $p = 0.001$), and greater

sadness (4.09 vs. 3.13, $p = 0.001$).

The effects of confounders were then controlled for in the adjusted model. Between infants of mothers with and without preeclampsia, the difference for low-pleasure seeking ($p = 0.02$) remained significant but vocal reactivity was only marginally significant ($p = 0.09$). Similarly, between infants of mothers with and without antenatal depression, high pleasure seeking ($p = 0.01$), soothability ($p = 0.02$), falling reactivity ($p = 0.001$), and sadness ($p = 0.004$) remained significant.

Infant Temperament at Six Months Old as a Function of Interaction Between Maternal Preeclampsia and Depression

Table 4 shows the different profiles of infant temperament by both preeclampsia and maternal depression. Of the 14 sub-scales of infant temperaments, there were four significant and marginally significant interaction effects, including duration ($p = 0.05$), high-pleasure seeking ($p = 0.003$), perceptual sensitivity ($p = 0.009$), and approach ($p = 0.006$). Specifically, among depressed mothers, infants of mothers with preeclampsia, as compared to infants of mothers without preeclampsia, exhibited a lower level of smiling/laughter, high-intensity pleasure seeking behavior, perceptual sensitivity, and approach. Figure 1 presents the adjusted means for the 14 sub-scales of infants' temperament by maternal preeclampsia and depression for a visual inspection of interactions.

Discussion

The current study examined whether preeclampsia and antenatal depression, both independently and in combination, had negative effects on offspring's temperament at six months of age. Our data are consistent with, and expand upon the results of prior studies, providing the following four main findings. First, preeclampsia was associated with poorer birth outcomes, including a 3- to 5-fold increased risk for LBW, preterm birth, low APGAR scores, and fetal/neonatal death. Second, while preeclampsia was not associated with temperamental profiles, antenatal depression was associated with reduced pleasure seeking behavior, poorer recovery from distress, and greater sadness. Lastly, having exposure to both preeclampsia and antenatal depression accelerated the observed withdrawn temperament in infants, including reduced pleasure seeking behaviors, approach, and perceptual sensitivity.

The 1970s was a period of much improved obstetric knowledge and practice, including hypertension monitoring and glucose control during pregnancy. These practices helped prevent adverse obstetric (e.g., preeclampsia, hypertension, excessive weight gain, and Cesarean section) and neonatal mortality and morbidity (e.g., jaundice, nerve palsy, and respiratory distress syndrome). While these medical advances contributed to a reduction in infant mortality, they unfortunately were not designed to prevent long-term adverse effects on CNS dysregulation in the offspring (Nomura et al., 2012).

It remains unclear whether these negative developmental outcomes among infants were attributable to preeclampsia, perinatal problems, or a combination of the two. Therefore, the current study includes both infants with and without perinatal risks such as LBW and preterm birth. When the temperament profiles were examined, those perinatal problems were additionally controlled for in the model to examine the unique effects of preeclampsia. Although our sample size is relatively small and future studies are required to confirm our findings, we are able to document the effect of preeclampsia on suboptimal temperamental styles in early childhood.

Our findings show a direct link between different risks (i.e., preeclampsia and antenatal depression) and the different aspects of temperamental characteristics. Furthermore, we demonstrated that the effects of preeclampsia on adverse outcomes were amplified by the additional risk factor, i.e., antenatal depression, and further adversely influenced infant temperament. As temperamental dysregulation, or difficult temperament, in earlier stages of life are associated with various behavioral and emotional problems as child grow (Wasserman, Diblasio, Bond, Young, & Colletti, 1987), it would be beneficial to follow the infants into later childhood. As children grow older, it may become clearer which aspects of neurocognitive and behavioral functions are impaired by preeclampsia, depression or the interaction of the two. Better clarification of this relationship may allow us to develop tailored early interventions designed to shift the developmental trajectory of offspring in an optimal direction.

This study needs to be evaluated in light of its methodological strengths and weaknesses. Notable strengths include the population-based cohort, systematic prospective follow-up from early pregnancy until the birth of the baby, and assessment of the infant at 6 months old. Maternal blood pressures and presence of urine proteinuria ($+0.3\text{g/dL}$) were ascertained at every prenatal visit prospectively throughout pregnancy. Maternal antenatal depression was assessed using structured interviews administered by trained Ph.D. level interviewers blind to the mothers' preeclampsia and other biomedical risk status. Birth outcomes, including gestational age, BW, and APGAR scores were recorded by a nurse observer at the time of delivery, a method far superior to mothers' retrospective reports.

There are also several limitations. First, the sample was mainly drawn from a low-income population and was not designed to be representative of the broader US population, which potentially limits external validity. Second, while we included key confounders in our model, given that maternal preeclampsia occurs within a broad constellation of social and behavioral factors that may also influence infant developmental trajectory, our findings could have been subject to bias. Moreover, unmeasured confounding factors may have resulted in an overestimation of the effects of preeclampsia on adverse birth outcomes examined and infant temperament. Third, we had two different sample sizes to analyze birth outcomes ($N = 252$) and infant temperament ($N = 141$). However, there were no notable differences between the 252 mothers, including 15 mothers with perinatal fetal demise who were included in the first portion of the analysis, and 141 mothers with infant temperament information on maternal age (27.4 vs. 27.7, $p = 0.68$), parity (2.53 vs. 2.81, $p = 0.47$), marital status ($p = 0.14$), race ($p = 0.44$), and maternal education ($p = 0.48$), welfare status (89.6% vs. 87.4%, $p = 0.60$), and sex (i.e., female) of the infant (44.0% vs. 51.3%, $p = 0.30$) respectively.

Taken together, the current study represents an initial attempt to monitor the perinatal and early post-natal development course of the surviving infants born to mothers with preeclampsia, with or without depression. While it remains a challenge to reduce mortality among mothers and their infants due to preeclampsia, as is evident by the rate of intrauterine fetal demise in our participants with preeclampsia, it is also important to gain a better understanding of the neurobehavioral consequences of preeclampsia among surviving offspring. As early neurobehavioral intervention is often more effective during the time when the brain is still developing and plastic, early treatment and remediation could modify potentially mild mental and cognitive dysfunction among children born to mothers with preeclampsia. More specific and accurate delineation of underlying risk mechanisms in future birth cohort studies will clarify the extent to which the risk for preeclampsia can be modified through early cognitive remediation and intervention for improved neuro-cognitive functioning and possible behavioral regulation.

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