Published in final edited form as:

J Matern Fetal Neonatal Med. 2010 July ; 23(7): 622–626. doi:10.3109/14767050903258746.

Evidence for Distinct Preterm and Term Phenotypes of Preeclampsia

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Abstract

Objective—To determine if there are differences in maternal and fetal characteristics in pregnancies complicated by preterm versus term preeclampsia.

Methods—Using our electronic database we identified 143 women who met the ACOG criteria for preeclampsia between January 1995 and August 2003. We collected data on age, weight, height, smoking status, maternal serum biochemical markers and newborn data. We compared the group delivering preterm (<37 weeks) with those delivering at term (≥37 weeks). Analyses were based on ANOVA, Wilcoxon Rank Sum tests and chi-square tests. Statistical significance was determined based on alpha = .05. Data are expressed as mean ± s.d. unless otherwise indicated.

Results—Eighty women delivered preterm and 63 delivered at term. Women who delivered preterm with preeclampsia were younger (age 24.4 ± 4.9 years vs 27.7 ± 6.0 yrs, P<0.001), lighter (BMI 25.8 ± 5.6 vs 28.9 ± 7.3 kg/m², P=0.01) and were more likely to smoke cigarettes (28% vs 9%, P=0.008) than those delivering at term with preeclampsia. Maternal serum liver enzyme concentrations were significantly greater in the preterm group (peak AST 38 vs 30 U/L, P=0.006), (peak ALT 31 vs 23 U/L, P=0.001). Newborn birth weight percentile (gestational age specific) was significantly lower for preterm preeclampsia (25th ± 29 vs 47th ± 32 percentile, P<0.001). We found no significant differences in maternal platelet count nadir, peak uric acid concentration, or newborn gender between groups.

Conclusions—Differences exist in maternal and fetal characteristics between women who develop preterm preeclampsia and those who develop preeclampsia at term. These data support the hypothesis that multiple preeclamptic phenotypes exist.

Introduction

Preeclampsia is a polymorphic syndrome unique to pregnancy that affects 3–5% of all pregnancies. It is defined as hypertension accompanied by proteinuria. Traditionally, this definition has been used to classify one disease with varying degrees of severity. However, more recent data suggest that preeclampsia may be better segregated into two or more distinct phenotypes, with differing etiologies and manifestations (1,2). One mechanism of sub-classification is based on the gestational age at the time of clinical recognition of disease. Preterm preeclampsia occurring before 37 weeks commonly represents a more severe and complicated form of preeclampsia than preeclampsia occurring at term.

Recent evidence supports differences in preterm versus term preeclampsia independent of gestational age. For example, lower mean birthweight percentiles have been observed in

pregnancies complicated by pre-term preeclampsia in contrast to term preeclampsia where birthweights may be at or above the normal range for gestational age (3,4,5). The prevalence of gestational diabetes is also higher in preterm versus term preeclampsia (3). Furthermore, women with preeclampsia and a preterm delivery have a higher long term risk of mortality due to cardiovascular causes than women who delivered at term with preeclampsia (6,7,8). Pregnancies complicated by preeclampsia at 28 weeks or less are also more likely to end in a maternal death (9).

These observations raise the possibility that unique pathophysiologic mechanisms related to both the mother and the fetus contribute to the unique timing of disease onset. Furthermore, it suggests that preeclampsia occurring preterm is phenotypically different than preeclampsia occurring at term. Preeclampsia may be a common endpoint of, at least two, distinct pathophysiologic processes. Few studies have quantified phenotypes of women who develop term versus preterm preeclampsia nor have they looked at their specific disease progression. We hypothesized that there are distinct features of women who develop preeclampsia at term when compared to those who develop preterm preeclampsia. We also hypothesized that there would be gestational age independent differences in indices of newborn size comparing neonates from pregnancies complicated by term versus preterm preeclampsia.

Methods

We examined our electronic medical delivery record (ObNet; Fletcher Allen Health Care, Burlington, VT) and queried all singleton pregnancies in primiparous women delivering between January 1995 and August 2003 with the identifier preeclampsia. For each identified pregnancy, the medical record was retrieved and reviewed to confirm the diagnosis of preeclampsia as defined by the American College of Obstetrics and Gynecology (ACOG). These criteria included women at greater than 20 weeks gestation with a blood pressure of 140/90 mmHg documented on two separate occasions at least six hours apart and greater than or equal to 300 mg proteinuria in a 24 hour collection. We also collected data on maternal age, prepregnancy weight and height, smoking status, maternal serum biochemical markers and newborn data including gender, birth weight and gestational age both at delivery and at onset of the diagnosis of preeclampsia. We also included data regarding past medical history of chronic hypertension, chronic renal disease, thrombophilia, and/or diabetes mellitus.

We excluded those with HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome (n = 32), incomplete or irretrievable charts (n = 6), and those whose charts could not confirm the ACOG criteria for pre-eclampsia (n = 136). This resulted in 143 women with a confirmed diagnosis of pre-eclampsia. The majority of those excluded did not have a 24 hour urine collection.

We stratified the gestational ages into two groups: preterm (<37 weeks) and term (≥37 weeks) based on the timing of onset of preeclampsia. Analyses were based on analysis of variance, Wilcoxon Rank Sum tests and chi-square tests. Statistical significance was determined based on alpha = 0.05. Data are expressed as mean ± SD unless otherwise indicated.

We compared maternal and fetal variables based on timing of onset of preeclampsia. We also looked at the distribution of gestational age and birth weight percentile based on the Vermont Hybrid Growth Curve (10) in both preterm and term pre-eclamptics.

Results

Eighty women delivered preterm (56%) and 63 delivered at term (44%). Table 1 compares the characteristics of patients with preterm versus term preeclampsia. The average age for women who delivered preterm with preeclampsia compared to those who delivered at term was 24.4

± 4.9 vs. 27.7 ± 6.0 yrs ($P < 0.001$). Women with preeclampsia who delivered preterm had a lower prepregnancy BMI than those at term (preterm 25.8 ± 5.6 , term 28.9 ± 7.3 kg/m², $P = 0.01$). Those delivering preterm were also more likely to smoke cigarettes (preterm 28%, term 9%, $P = 0.008$) than those delivering at term with preeclampsia. The background incidence of maternal smoking in our population during this time frame was approximately 20%.

The sample size was not large enough to detect any significant difference between groups (if any) of the percent of women with chronic hypertension, pre-gestational and gestational diabetes mellitus, thrombophilia, or chronic renal disease.

Maternal serum liver enzyme concentrations were significantly greater in the preterm preeclampsia group. The median peak AST for the preterm preeclamptics was 38 units/L (interquartile range (IQR) 27 – 63) and the median peak AST for term preeclamptics was 30 (IQR 23–37), $P = 0.006$. This was also true for maternal serum ALT (median peak ALT: preterm 31 (IQR 23 – 44), term 23 (IQR 19–37) U/L, $P = 0.001$) (Table 2). We found no significant differences in maternal platelet count nadir or peak uric acid concentration.

Newborn birth weight percentile was significantly lower in women who developed preterm preeclampsia compared to those who developed preeclampsia at term (preterm 25th ± 29 , term, 47th ± 32 percentile, $P < 0.001$) (Figure 1). In particular, preterm delivery appears to be associated with reduced fetal growth while term delivery appears to be associated with both small and large newborn size. There was no difference in newborn gender between groups (data not shown).

Conclusion

A growing body of evidence suggests that the development of early and late preeclampsia are two distinct pathophysiological processes with distinct maternal phenotypes predisposing to the development of each. Multiple hypotheses regarding the etiology of preeclampsia exist including abnormal trophoblast invasion of uterine blood vessels, immunological intolerance between fetoplacental and maternal tissues, maladaptation to cardiovascular and inflammatory changes of pregnancy, genetic predispositions and dietary deficiencies (11,12,13). The different maternal and fetal characteristics unique to preterm preeclampsia support a more prominent role for both an underlying uteroplacental insufficiency, and a potentially important contribution of maternal prepregnancy physiology as reflected by the increased risk for long term disease outside of pregnancy in those who develop preterm preeclampsia.

Distinct maternal hemodynamic states have been shown between women who develop preeclampsia prior to 34 weeks and those who develop preeclampsia after 34 weeks (14). Early preeclampsia appears to be characterized by a state of high total vascular resistance and low cardiac output, while low total vascular resistance and high cardiac output mark term and near-term preeclampsia. These different maternal cardiovascular adaptations to the development of preeclampsia supports different etiologies of early versus late preeclampsia and the hypothesis of distinct maternal phenotypes in term versus preterm preeclampsia. Additionally, women who develop early onset preeclampsia have been shown to have more abnormal uterine artery doppler velocimetry, increased incidences of gestational diabetes mellitus (3), intrauterine growth restriction (3,4,5), chronic hypertension (15), recurrence of preeclampsia (16), and maternal cardiovascular morbidity and mortality (6,7,17).

Our data support two distinct maternal phenotypes segregated between those who develop preeclampsia before and after 37 weeks gestation. Those women developing preterm preeclampsia were younger, had a lower prepregnancy BMI, and were more likely to smoke cigarettes than those women who developed preeclampsia at term. In addition, maternal serum

liver enzyme concentrations were higher in preterm preeclampsia and infants were significantly smaller when corrected for gestational age.

Consistent with other studies, we showed significantly lower birth weights for those with preterm versus term preeclampsia when corrected for gestational age. In addition, we confirmed previous findings of a disproportionate number of large for gestational age infants in term preeclampsia. In our data, birthweight percentiles are underrepresented in the 40th – 70th percentile, followed by a rise in birth weight percentile representation above the 70th percentile in term preeclampsia. This suggests that even within the term subgroup, there are likely differing phenotypes and pathophysiological mechanisms underlying the development of disease (18,19).

Multiple studies have demonstrated an inverse relationship between tobacco use during pregnancy and the development of preeclampsia (20,21). Smoking during pregnancy has been associated with a 30–50% reduction in preeclampsia, in a dose dependent pattern (22,23). The etiology of this finding is unclear, but may be mediated by inhibition of cytokine production or reduced volume expansion of pregnancy in smoking mothers (24,25). Our data suggest that this observation may be restricted to the term phenotype as those patients who developed preterm preeclampsia were more likely to use tobacco. This would be consistent with the proposed difference in pathophysiological mechanisms between term and preterm preeclampsia.

Our study is limited by a relatively small sample size. Many women were excluded because they had not completed a 24 hour urine collection for proteinuria. These women may have been delivered on arrival due to disease severity and not had time to complete a 24 hour urine collection, therefore, more sick patients and more term patients may have been excluded. Also, we serve as a referral center for Vermont and Northern New York and therefore tend to treat a disproportionate number of preterm versus term preeclampsia.

In an attempt to improve our ability to identify maternal and fetal characteristics that describe a term or preterm preeclampsia phenotype, we additionally segregated the population at 34 weeks and based on birth weight percentile. However, these data, which are not shown, did not segregate maternal phenotypes with greater precision than the segregation of term and preterm delivery.

There is compelling evidence that preeclampsia should no longer be considered a single disease entity. Pathophysiologic mechanisms likely contribute differently to the development of preterm versus term preeclampsia. Distinct maternal phenotypes, which underlie abnormal pregnancy adaptation, and predict long term maternal cardiovascular risk, appear to exist which predispose individuals to preterm preeclampsia.

Acknowledgments

Supported in part by NIH RO-1 HL 71944 (IMB)

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Figure 1.
Birthweight distribution in newborns of preeclamptic mothers by gestational age at delivery

Table 1

Demographic Characteristics of Patients Developing Preeclampsia Before and After 37 Weeks

	Preterm (<37 weeks) N=80	Term (≥37 weeks) N=63	P
Age (years)	24.4 ±4.9	27.7 ±6.0 yrs	< 0.001
Tobacco use %(n)	28 (22/79)	9 (5/55)	0.008
BMI (kg/m ²)	25.8 ±5.6	28.9 ±7.3	0.01
CHTN %(n)	5 (4)	6.3 (4)	NS
Renal disease %(n)	6.3 (5)	0	NS
GDM %(n)	0	1.6 (1)	NS
Pre-gestational DM %(n)	3.8 (3)	1.6 (1)	NS
Thrombophilia %(n)	1.3 (1)	0	NS

Table 2

Maternal serum biochemical values of pre-term versus term preeclampsia

	Pre-term preeclampsia (n = 80)	Term Preeclampsia (n = 63)	P-value
Peak AST median U/L (IQR)	38 (27 – 63)	30 (23–37)	0.006
Peak ALT median U/L (IQR)	31 (23 – 44)	23 (19–37)	0.001
Lowest platelets median (IQR)	176,000	176,000	0.38
Peak uric acid median mg/dl (IQR)	6.8	6.4	0.29