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Maternal Hemoglobin Concentration and its Association with Birth Weight in Newborns of Mothers with Preeclampsia

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Abstract

OBJECTIVE—Maternal hemoglobin concentration is inversely related to newborn size presumably through plasma volume constriction. We sought to determine whether birth weight would show an inverse relationship to hemoglobin concentration in a group of infants whose mothers had preeclampsia, where plasma volume constriction is common.

METHODS—Electronic and paper chart review identified 142 nulliparous women with preeclampsia (excluding HELLP syndrome). Birth weight percentile was determined based on cross-sectional hybrid growth curves. Maximal third trimester maternal hemoglobin concentrations were obtained and standardized to z-scores based on gestational age matched normative data. Birth weight percentile was examined as a function of hemoglobin z-score using appropriate statistics.

RESULTS—Average gestational age at delivery was 35.9±1.9 weeks. Mean birth weight percentile for infants of preeclamptic mothers was 34±32. Mean hemoglobin z-score for mothers with preeclampsia was 0.3±1.5, significantly higher than a control population ($p = 0.04$). Maternal hemoglobin z-score was inversely associated with birth weight percentile ($r = -0.18$, $P = 0.03$).

CONCLUSION—Maternal hemoglobin concentrations are significantly elevated prior to delivery in women with preeclampsia. There is a statistically significant inverse correlation of maternal hemoglobin concentration to birth weight percentile.

Keywords

hemoglobin; birth weight; intrauterine growth restriction; preeclampsia

Introduction

During the past three decades, the relationship between maternal hemoglobin level and fetal outcome has been examined at length. Maternal anemia has long been considered a risk factor for poor pregnancy outcome [1–3]. In addition, elevated hemoglobin levels have also emerged as being predictive of intrauterine growth restriction (IUGR) [1,3–8]. An inverse association between elevated second or third-trimester hemoglobin levels and fetal weight has been established in a general cohort of women in multiple studies [1,3–8]. This relationship has held

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when women are analyzed for gravidity, the presence or absence of iron supplementation, as well as smoking habits [3,9–10].

Maternal hemoconcentration is often attributed to decreased plasma volume expansion, also an identified risk factor for poor perinatal outcome [6,9,11,12–14]. Preeclampsia is also associated with a plasma volume constriction, with evidence of reduced plasma volumes both during pregnancy and the postpartum period [15–18]. To date, the relationship between maternal hemoglobin concentration and fetal birth weight has not been analyzed in a subset of women with preeclampsia. We sought to determine whether the previously described inverse relationship between maternal hemoglobin concentration and **birth weight** would hold in a group of infants whose mothers had preeclampsia, where plasma volume constriction is common to the underlying disease state.

Methods

After obtaining Institutional Review Board approval, a retrospective electronic and medical record review was conducted (ObNet; Fletcher Allen Health Care, Burlington, VT). Nulliparous women with no underlying medical conditions delivering at our institution between January 1, 1995 and August 1, 2003, with the diagnosis of preeclampsia were eligible for inclusion. Preeclampsia was defined per American College of Obstetricians and Gynecologists (ACOG) guidelines: by blood pressures of $\geq 140 / 90$ mmHg, obtained on 2 separate occasions at least 6 hours apart, and the presence of proteinuria of ≥ 300 mg within a 24 hour collection. Exclusion criteria included patients with HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome ($n=32$), or incomplete charts ($n=2$). We also excluded subjects with pregestational diabetes to avoid confounding the interpretation of the relationship of hemoglobin and newborn size.

Patient information recorded included demographics, use of iron supplementation, pregnancy complications such as development of gestational diabetes, gestational age at delivery, birth weight, and third-trimester maternal hemoglobin concentrations. Birth weight percentile was determined using locally derived cross-sectional hybrid growth curves validated against intrauterine fetal growth patterns [19–21]. These curves combine cross-sectionally acquired preterm (<35 weeks gestation) ultrasound estimates of fetal weight with near-term and term birth weight to generate accurate modeling of longitudinal intrauterine growth.

Maximal third trimester pre-delivery maternal hemoglobin concentrations were obtained. As normal and average hemoglobin values change markedly during gestation, these values were standardized to z-scores based on gestational age-matched normative data [5]. The hemoglobin z score is calculated based on each patient's gestational age according the following formula: (measured hemoglobin – reference hemoglobin for gestational age) / standard deviation of reference hemoglobin distribution [5]. Reference values for hemoglobin per week gestational age were obtained from Milman et al indices of hemoglobin values during normal pregnancy with iron supplementation [22]. These reference values were chosen to standardize and normalize our data, as the vast majority of our population was on prenatal vitamins containing iron. Birth weight percentile was examined as a function of hemoglobin z-score using regression analysis. Birth weight percentiles were used to control for the strong influence of gestational age on birth weight. Data are expressed as mean $\pm$ standard deviation. Data were analyzed by Pearson correlation coefficient and Student's *t*-test where appropriate. P values less than 0.05 were considered significant.

Results

142 primigravid women with singleton pregnancies meeting ACOG criteria for preeclampsia were identified. One woman was omitted due to an incomplete medical record. The group had a maternal age of 25.8 ± 5.4 years and a pre-pregnancy body mass index of 27.2 ± 6.4 kg/m². Sixty-eight percent of patients were Caucasian and 18% were tobacco users. All women were on iron sulfate supplementation as they were taking prenatal vitamins. The incidence of gestational diabetes as well as the development of renal disease in the group was 5.7%. The average gestational age at delivery was 35.9 ± 1.9 weeks, with 80 patients (56%) delivering prior to 37 completed weeks gestational age. The mean birth weight percentile for infants was $34 \pm 32\%$, with a mean birth weight of $2,507 \pm 925$ grams.

The highest hemoglobin value recorded after admission to the hospital and prior to delivery was used in our analysis. The majority of these hemoglobin values were collected within 48 hours prior to delivery, and over 95% of them were collected within one week of delivery. The mean hemoglobin z-score for the mothers with preeclampsia was 0.3 ± 1.5 . This was significantly higher than a control population with z-score of zero ($p = 0.04$). As seen in Figure 1, maternal hemoglobin z-score was inversely associated with birth weight percentile ($r = -0.18$, $p = 0.03$), suggesting maternal hemoglobin concentration accounted for approximately 3% of infant birth weight percentile variance. Subset analyses were performed for deliveries between 26 – 36 weeks gestational age as well as for deliveries between 37 – 42 weeks gestational age. Trends were similar within both preterm and term subsets as were noted for the overall group where an inverse correlation between higher z-score and birth weight percentile was noted, though there was insufficient power to detect a statistically significance association. We did observe a significant inverse relationship between hemoglobin z-score and gestational age ($r = -0.38$, $p < 0.001$), suggesting that hemoconcentration was more common in our preterm preeclamptic women.

Discussion

Normal pregnancy is associated with a 45 – 50% increase in plasma volume between 6 and 24 weeks of gestation [1,23]. There is an accompanied linear increase in red cell mass of approximately 25 – 30%, leading to a physiologic anemia of pregnancy. This is reflected in reduced hemoglobin levels, which generally fall through 20 week's gestational age, and remain relatively constant between 20 – 30 weeks gestation before rising slightly near term [1,11, 24]. Studies tracking plasma volume, red cell mass and hemoglobin levels indicate the fall of hemoglobin in the first 12 weeks of pregnancy is due to plasma volume expansion, while plasma volume and red cell mass are significantly correlated to hemoglobin concentration during the remainder of pregnancy [12].

In general, elevated hemoglobin levels are defined as being greater than two standard deviations from normal reference. However, studies have varied in defining “high” hemoglobin cutoffs, ranging between 13.3 – 17 g/dl [3,24]. Utilizing a z-score for statistical analysis allows for continuous assessment of hemoglobin levels and a robust evaluation of its association with abnormal pregnancy outcome.

Abnormally high maternal hemoglobin concentrations in normotensive women have long been associated with decreased fetal birth weight and intrauterine growth restriction [1,3–8,24–26]. Although elevated second trimester hemoglobin levels confer the highest risk of delivering an infant weighing less than the 10%, even elevated first trimester hemoglobin values are associated with increased rates of IUGR [5]. Fetal outcome has also been examined in women with cyanotic congenital disease, a known risk factor for IUGR [27]. Presbitero et al found hemoglobin levels ≤ 16 g/dl displayed a strong correlation to chance of live birth compared to

hemoglobin levels ≥ 17 g/dl again associating hemoconcentration with poor pregnancy outcome [28].

There is also a well-documented association between hemoconcentration and hypertensive diseases of pregnancy [3,9,14–16]. Murphy et al documented elevated intake hemoglobin values even as early as 13 weeks gestational age to be associated with the subsequent development of a hypertensive disorder of pregnancy [3]. Our findings were also consistent with prior observations that maternal hemoglobin values are significantly elevated prior to delivery in women with preeclampsia.

Low pre-pregnancy plasma volume has been associated with preeclampsia, and the ability to produce a large increase in plasma volume has been recognized as one of the hallmarks of a successful pregnancy since the 1970s [29–30]. Koller et al hypothesized that since the reduction of plasma volume during preeclampsia and eclampsia is roughly in proportion to severity of disease, and this reduction might be the common denominator for hemoconcentration and growth restriction [6–7].

There are multiple possible explanations for elevated hemoglobin levels correlating with fetal growth restriction. Most authors attribute the etiology of hemoconcentration to decreased plasma volume expansion [1,4–5]. Low plasma volumes is also an identified risk factor for poor perinatal outcome, presumably though reduced uterine perfusion [31]. Consistent with this theory of pathophysiology, Naeye et al found a correlation between frequency of large placental infarcts and increasing maternal hemoglobin values [32]. Another potential etiology of hemoconcentration is hematopoietic overproduction. There has long been an association of IUGR with maternal smoking, **cyanotic congenital heart disease** and living at high altitudes, all of which are associated with hemoconcentration [27,33–35].

This study used reference parameters for hemoglobin values throughout the third trimester, compiled from a group of 99 women taking iron supplementation throughout pregnancy [20]. These values were used as our patients are uniformly prescribed prenatal vitamins containing ferrous sulfate. A review of 20 randomized controlled trials show no detectable effect on fetal outcome, including changes in preterm delivery rates or IUGR with iron supplementation [11].

Our study is the first to analyze the relationship between third-trimester hemoglobin levels and fetal birth weight in a cohort of preeclamptic women. The previously noted inverse relationship present in normotensive women was found to hold for preeclamptic women, with a statistically significant inverse correlation of maternal hemoglobin level to birth weight percentile. Interestingly, there was a strong correlation between hemoglobin z-score and gestational age, indicating preterm preeclamptic women are more likely to demonstrate hemoconcentration as compared to term women with preeclampsia.

One possible confounding factor to the results of this study is the inclusion of patients that developed gestational diabetes in addition to preeclampsia. However, only 5.7% of the patients included in the analyses developed this complication of pregnancy.

Previous studies in normotensive women have suggested that differences in plasma volume may account for up to 40% of the variance in newborn size [12,36]. In our study, maternal hemoglobin concentration accounted for only approximately 3% of birth-weight variance. As the direct relationship between maternal plasma volume and newborn size is generally stronger than observed in our preeclamptic cohort, it is plausible that hemoconcentration in preeclamptic women may result from an underlying mechanism distinct from plasma volume reduction, including augmented red blood cell production or increased peripheral red blood cell availability.

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Figure 1. Maternal hemoglobin z-scores are inversely associated with fetal birth weight percentile ($r = -0.18$, $p=0.03$).