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Correlation of Preterm Infant Illness Severity with Placental Histology

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Abstract

Introduction—A major goal of neonatal medicine is to identify neonates at highest risk for morbidity and mortality. Previously, we developed PhysiScore (Saria *et al.*, 2010), a novel tool for preterm morbidity risk prediction. We now further define links between overall individual morbidity risk, specific neonatal morbidities, and placental pathologies.

Methods—102 placentas, including 38 from multiple gestations, were available from the previously defined PhysiScore cohort (gestational age ≤ 34 weeks and birth weight ≤ 2000 grams). Placentas were analyzed for gross and histologic variables including maternal malperfusion, amniotic fluid infection sequence, chronic inflammation, and fetal vascular obstruction. Risk as determined by PhysiScore and recorded neonatal morbidities were tested for statistical association with placental findings.

Results—In pair-wise correlations, respiratory distress syndrome, bronchopulmonary dysplasia, acute hemodynamic instability, post-hemorrhagic hydrocephalus, culture positive sepsis, and necrotizing enterocolitis each significantly correlated with at least one placenta histology variable. Amniotic fluid infection sequence ($p = 0.039$), specifically the fetal inflammatory response ($p = 0.017$), correlated with higher PhysiScores (greater morbidity) but was not independent of

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gestational age and birth weight. In multivariate analyses correlating variables with all nine morbidities, gestational age ($p < 0.001$), placental size $<10^{th}$ percentile, ($p = 0.031$) full thickness perivillous fibrin deposition ($p = 0.001$), and amniotic fluid infection sequence (umbilical arteritis, $p = 0.031$; ≥2 chorionic plate vessels with vasculitis, $p = 0.0125$), each were significant associations.

Discussion—Amniotic fluid infection sequence plays a significant role in neonatal morbidity. Less neonatal morbidity was observed in older and heavier infants and those with small placental size and full thickness perivillous fibrin deposition. The combined assessment of placental gross and histologic findings together with physiologic risk evaluation may allow more precise prediction of neonatal morbidity risk soon after delivery.

Keywords

preterm infant; morbidity; placenta; fetal inflammatory response; histology

INTRODUCTION

The clinical outcome of prematurity varies widely in terms of infant morbidity, and predicting an individual neonate's morbidity risk will allow tailored interventions. Many different prediction methods have been developed to try to determine the risk of severe morbidity or mortality in neonates. Recently, PhysiScore was published as a robust tool for integrating physiologic data within the first 3 hours of life in order to predict morbidity in the premature infant (Saria *et al.* [1]). Specifically, PhysiScore uses the mean, base, and residual variability of the heart rate and respiratory rate, mean oxygen saturation and cumulative hypoxia time, gestational age, and birth weight to calculate a probability score between 0 and 1, with higher scores indicating a higher risk of severe morbidity due to cardiopulmonary and infectious complications. Increased gestational age and birth weight have long been known to decrease the risk of death and illnesses including respiratory distress syndrome (RDS), high grade intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and sepsis [2; 3]. However, PhysiScore is the first method to also take into account physiologic data derived from routine monitoring.

Placental evidence of antenatal conditions also likely correlates with morbidity, but studies are few, and many fail to incorporate newer entities in placental pathology. Of the published studies, there is conflicting evidence of placental histology correlating with neonatal morbidities. For instance, one study correlates chorioamnionitis with many morbidities including bronchopulmonary dysplasia (BPD) [4], whereas other studies refute a significant relationship between chorioamnionitis and BPD [5; 6]. Placental histologic features of maternal malperfusion, including distal villous hypoplasia, and chronic inflammation, including chronic chorionitis, are not often cited or examined as risk factors for neonatal disease.

In this study, we report a detailed retrospective review of placental histology from the PhysiScore cohort of preterm NICU neonates. Using 18 placental gross and histologic variables to represent the more severe or novel placental findings, we performed a comprehensive analysis to identify links between neonatal physiology, risk of morbidities

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associated with preterm birth, and specific pathologies, testing the hypothesis that placental pathological features correlate with postnatal physiology predictive of risk in preterm infants.

METHODS

Preterm Cohort

The preterm cohort employed the same infants as those in the PhysiScore study [1]. In brief, infants admitted to the NICU at Lucile Packard Children's Hospital between March 2008 and March 2009 were eligible for enrollment. With approval of Stanford's Panel on Human Subjects, a total of 138 neonates were enrolled, meeting the criteria of gestational age ≤34 weeks, birth weight ≤2000 grams, available cardiorespiratory monitor data within the first three hours of birth, and without major malformations. Electronic medical records, imaging studies, and laboratory values were noted. Gender, 5 minute Apgar score, and multiple gestations were recorded. Documented morbidities included RDS, pneumothorax, BPD, acute hemodynamic instability (characterized by hypotension requiring 3 or more days of pressor support or adrenal insufficiency requiring hydrocortisone), retinopathy of prematurity (ROP), IVH, post-hemorrhagic hydrocephalus (PHH), culture positive sepsis, and NEC. Criteria for identifying BPD, ROP, IVH, and NEC are as previously described [7–10]. The highest unilateral stage or grade for ROP and IVH respectively, were noted. For analyses, only moderate and severe BPD, high stage (≥2) ROP, and high grade (≥3) IVH were included. Of these nine morbidities, 7 were considered severe: bronchopulmonary dysplasia, acute hemodynamic instability, retinopathy of maturity, intraventricular hemorrhage, post-hemorrhagic hydrocephalus, culture positive sepsis, and necrotizing enterocolitis. PhysiScores were recorded as previously calculated [1].

Placentas

Of the 138 neonates in the preterm cohort, 102 infants had placentas submitted for macroscopic and microscopic examination that were available for re-review. Histologic sections included sections of umbilical cord, membrane rolls, and at least 2 full-thickness placenta sections. Blinded to clinical data, the placenta reports and slides were reviewed by a perinatal pathologist for a comprehensive set of 73 gross and microscopic features. Of these features, 18 major findings were chosen for further analysis, as we hypothesized that more severe placental pathology would correlate with significant neonatal morbidity. In addition, we included some more recently described entities such as chronic chorionitis [11] to determine if there were any associations with the neonatal clinical findings. The gross variables included a marginal (within 1 cm of the margin) or velamentous umbilical cord insertion, and trimmed placental weight, from which weights ≤10^{th} percentile and ≥90^{th} percentile were determined using the reference values for singleton and twin placental weights [12]. Placenta weight:birth weight ratios were calculated. For twins with fused placentas (no triplets had three fused placentas), the placenta weights were divided by two. Two fetal and two maternal variables were classified as features of amniotic fluid infection sequence: fetal inflammatory responses (umbilical arteritis and ≥2 chorionic plate vessel with vasculitis) and maternal inflammatory responses (acute subchorionitis with abscess formation, and subacute or necrotizing acute chorioamnionitis) [13]. Of note, all of the cases

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found to have ≥2 chorionic plate vessel with vasculitis also demonstrated umbilical arteritis. Maternal malperfusion was delineated by four features: placental size ≤10th percentile, distal villous hypoplasia, severe maternal decidual vasculopathy (fibrinoid necrosis and/or acute atheromatous changes) and ≥2 infarcts [14]. Full thickness perivillous fibrin was noted when at least one slide demonstrated an exaggeration of Langhan's stria encasing both stem villi and regional distal villi from the chorionic plate to basal fibrin [15]. Two features of chronic inflammation (chronic chorionitis and basal chronic villitis, and parenchymal chronic villitis), were chosen as features of an aberrant maternal immune response. Chronic chorionitis, a more recently described entity, was diagnosed based upon the presence of band-like infiltrates of mononuclear cells associated with membranous cytotrophoblast cell dropout, and/or lymphohistiocytic inflammation of the basal chorionic plate obvious on low power. Basal chronic villitis is chronic villitis limited to the area adjacent to or at the decidual basalis, and is commonly associated with lymphoplasmacytic deciduitis [11; 16]. The cases of parenchymal chronic villitis were all villitis of unknown etiology, representing more than 10 villi per focus on more than one slide (high-grade villitis) [16]; some of these cases were also associated with fetal vasculopathy. No viral cytopathic effects or plasma cells were present in these cases of chronic villitis to suggest an infectious etiology. The two variables of large vessel thrombi and villous damage from fetal ischemia (avascular villi or villous stromal-vascular karyorrhexis) were grouped under the heading of fetal vascular obstruction [17]. In addition to a placental size ≥90th percentile, the morphologic variable of villous edema was subgrouped under a large, edematous placenta. Diffuse chorionic hemosiderosis was an additional variable, as defined by Redline and Wilson-Costello [18]. Lastly, nucleated red blood cells enumerated a >10/10 high power fields was recorded as an indicator of fetal hypoxia [19].

Statistics

The baseline and disease characteristics of the study cohort were summarized with mean and standard deviation for continuous variables and actual counts for binary variables. The two-sided Wilcox rank test was used to test the difference in gestational age between infants with and without each morbidity of interest. The Fisher's exact test was used to test the association between binary histology measures and comorbidities. The odds ratio and the corresponding 95% confidence intervals were obtained. The proportional odds regression model was used to test associations between histology characteristics and PhysiScore, with or without the adjustment of gestational age and birth weight, where PhysiScore was treated as an ordinal response. The association of interest was summarized by odds ratio of having a high PhysiScore versus low PhysiScore and the associated 95% confidence interval. Similarly, associations between histology characteristics and the number of morbidities were examined. The statistical analysis was performed using R 3.1.3 (The R Foundation for Statistical Computing).

RESULTS

Correlation of Neonatal Outcomes with Placental Histology

Table 1 details the characteristics and morbidities of the 102 preterm infants in this study. Thirty-eight infants (37.2%) were the products of multiple gestations. As listed, the most

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common morbidity was RDS (77%). In total, 9.8% of infants had moderate or severe BPD, 8.8% had high stage (stage II or III) ROP in at least one eye, and 20.6% high grade (grade 3 or 4) IVH detected on radiography. Sepsis was suspected in many infants, but only proven by culture in 5.9%. No severe morbidities were identified in 18.6% infants.

Placentas from the 102 infants were subjected to gross and histological review. Figure 1 displays some of the identified histologic features. Table 2 lists the percent of each infant morbidity showing each histologic feature, using pair-wise associations with two-tailed T-tests; this table also lists the mean gestational age, PhysiScore, and placenta weight:birth weight ratio for each morbidity.

Increased gestational age was significantly protective ($p \leq 0.01$) of all morbidities except for IVH; similarly PhysiScores were significantly increased ($p \leq 0.05$) in all morbidities except for IVH. Placenta weight:birth weight ratios were significantly increased in all morbidities compared to unaffected infants, except for those with RDS, IVH, and culture positive sepsis. Placental size less than 10^{th} percentile and increased full-thickness perivillous fibrin were significantly protective against RDS. Of note, out of 46 cases with placental features of maternal malperfusion, only 20 (43%) had clinical maternal pre-eclampsia (data not shown).

The risk of RDS was significantly increased in the presence of amniotic fluid infection sequence, specifically fetal inflammatory response, especially multifocal chorionic plate vasculitis. Placental weight greater than 90th percentile also correlated with an increased risk of RDS. The risk of high grade BPD was significantly elevated in placentas with a marginal or velamentous cord insertion and diffuse chorionic hemosiderosis; BPD also trended with large vessel thrombi. Acute hemodynamic instability was significantly correlated with villous edema. High grade ROP trended with large vessel thrombi and marginal or velamentous cord insertion, and was significantly associated with the absence of features of maternal malperfusion. Chronic inflammation in general, and chronic chorionitis and basal chronic villitis specifically, significantly increased the risk of PHH. An increased risk of culture-positive sepsis was evident in infants whose placentas demonstrated amniotic fluid infection sequence, specifically a fetal inflammatory response and a maternal inflammatory response of subacute or necrotizing acute chorioamnionitis. In addition, culture-positive sepsis correlated with chronic inflammation, specifically chronic chorionitis and basal chronic villitis. Lastly, NEC was increased in those infants with placentas demonstrating fetal vascular obstruction, specifically large vessel thrombi.

Comparing the multiple gestation infants (n=38) to the singleton infants (n=74) showed few statistically significant differences. The multiple gestations infants were born at increased gestational age (31.1 weeks versus 29.7 weeks, $p = 0.01$), and had mothers with increased maternal age (35.1 years versus 31.2 years, $p = 0.002$). The only morbidity with any statistically significant difference between these infants was retinopathy of prematurity, which was decreased in the multiple gestations ($p = 0.025$), likely due to increased gestational age. The multiple gestation infants also had fewer features of amniotic fluid infection: umbilical arteritis (7.9% vs 27.0%, $p = 0.022$), ≥2 chorionic plate vessel with vasculitis (2.7% vs 24.2%, $p = 0.004$), and subacute or necrotizing acute chorioamnionitis (5.3% vs 20.3%, $p = 0.045$). Multiple infarcts were very uncommon in twins (0.0% vs

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15.6%, p = 0.012). Interestingly, there was no statistically significant difference in rate of marginal or velamentous cord insertion (29.7% vs 15.8%, p = 0.129), a finding often identified in multiple gestation pregnancies [20].

Correlation with PhysiScore with placental histology

PhysiScores had been previously calculated [1] and ranged from 0.0170 to 1.000, with a median of 0.0576, and average of 0.236; the higher the PhysiScore, the higher the risk of severe morbidity. To determine if the calculated PhysiScores correlated with the placental gross or histologic features, a proportional odds regression model was used to test for associations, with and without adjustment for gestational age and birth weight (Table 3). Amniotic fluid infection sequence was associated with higher unadjusted PhysiScores, indicating loss of physiological variability and increased risk of morbidity. Full thickness perivillous fibrin deposition was associated with lower unadjusted PhysiScores. Maternal malperfusion, chronic inflammation, fetal vascular obstruction, and large and/or edematous placenta, were not statistically associated with PhysiScore. When amniotic fluid infection sequence components were assessed, only the fetal inflammatory response was associated with unadjusted PhysiScore. However, when PhysiScore was adjusted for both gestational age and birth weight, these fetal inflammatory responses and full thickness perivillous fibrin deposition associations were lost.

Correlation of Neonatal Outcomes with PhysiScore

In performing proportional odds regression model analyses of PhysiScore, gestational age, birth weight, and placental variables against the group of all nine morbidities and against the group of the 7 severe morbidities, older gestational age and higher birth weight decreased the risk of morbidities (Table 4). Small placental size and full thickness perivillous fibrin deposition also each decreased the risk of morbidities (when all nine morbidities were grouped together). The fetal inflammatory responses of umbilical arteritis and multifocal chorionic plate vasculitis each increased the risk of morbidities (when analyzed against all 9 morbidities and the 7 severe morbidities). Diffuse chorionic hemosiderosis trended with increased morbidities when compared to both groups of morbidities.

DISCUSSION

In this study, we correlated placental gross and histologic features in a preterm cohort with our previously calculated risk predictor, PhysiScore. Higher PhysiScores, adjusted for birth characteristics, primarily reflect short-term decreased variability in heart rate and respiratory rate [1]. PhysiScore helps to predict with high accuracy short and longer-term morbidities, including infection and cardiopulmonary problems. We find that this decreased physiological variability (autonomic dysfunction) presented by PhysiScore is strongly associated with placental evidence of amniotic fluid infection sequence (p = 0.017), and more specifically, the fetal inflammatory response (p = 0.039). PhysiScore reflects acute perinatal autonomic instability and therefore, correlation with acute placental pathology such as amniotic fluid infection sequence suggests that the autonomic instability is associated with that pathology. Other than full thickness perivillous fibrin deposition, PhysiScore did not have any statistically significant associations with other placental histology, suggesting

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that chronic pathologic conditions such as FTV and maternal malperfusion might not be as readily detected by PhysiScore. Fetal inflammatory response, as exemplified by plasma interleukin-6 (IL-6) levels, has been linked to higher rates of severe neonatal morbidity in prior literature reports. Gomez *et al.* [21] identified that fetuses with plasma IL-6 greater than 11 pg/mL had significantly higher rates of overall severe neonatal morbidity, as well as RDS and proven or suspected sepsis. Further studies have reported the significant relationship between umbilical arteritis/severe fetal inflammatory response and severe neonatal morbidity [22; 23]. Our findings are in agreement with the prior reports that the fetal inflammatory response is highly correlated with neonatal morbidity.

Interestingly, when using multivariate analyses to correct for both gestational age and birth weight, the significant association between PhysiScore and fetal inflammatory response was lost. This finding suggests that increased fetal inflammatory response correlates with younger gestational age and lower birth weight, and that the overall increased morbidity associated with fetal inflammatory response is actually due to earlier premature birth. Previously, chorionic vasculitis was found to correlate with infants of younger gestational age at birth (22–27 weeks) versus older but still premature infants (28–33 weeks at birth) [24].

In the pair-wise associations part of this study, we identified increased gestational age to be significantly protective of almost all morbidities. This finding is consistent with multiple prior reports [2; 3; 21], including Robertson *et al.* [2] who reported that the incidence of RDS, NEC, and sepsis decreased with increasing gestational age and birth weight.

The placenta weight:birth weight ratios were statistically significantly elevated in pneumothorax, BPD, acute hemodynamic instability, ROP, PHH, and NEC compared to the unaffected infants. This elevation is not surprising since, recently, Shehata *et al.* [25] linked high placenta weight:birth weight (PW/BW) ratios to an increased risk of short-term adverse perinatal outcomes, including neonatal intensive care unit admissions. Interestingly, the current study did not find an association between IVH, gestational age, or placenta weight:birth weight ratio. Since there is a well-documented association between increasing gestational age and a decreasing risk of IVH [2; 26], the lack of gestational age and IVH association is likely due to the small number of IVH cases (n=5) in the current study.

Our study did identify a significant correlation between chronic chorionitis, a more recently described entity, and basal chronic villitis with PHH. Interestingly, when we performed individual correlations between chronic chorionitis alone and each of the neonatal morbidities, we not only identified chronic chorionitis to be statistically significantly correlated with PHH, but to also trend with an increased risk of IVH ($p = 0.072$, data not shown). As PHH follows IVH, this finding suggests a true correlation between chronic chorionitis and these two entities. Histologic features of chronic inflammation in the placenta are thought to represent maternal anti-fetal cellular rejection [27]. Studies have shown elevated concentrations of the chemokines CXCL9, CXCL10, CXCL11, and CXCL13 in the plasma of fetuses born preterm with placentas demonstrating chronic inflammation [28; 29]. While preterm IVH has been previously linked to acute inflammation (acute chorioamnionitis) in the placenta with increased inflammatory factors including IL-6,

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IL-1β, and TNF-α in the neonate, it has not been associated so far with chronic inflammation in the placenta [30]. While based on a very limited sample set, this new association is worthy of further investigation.

RDS had multiple associations and was the only disease to be correlated with placental weight. In RDS, a placenta less than tenth percentile in weight was protective, and a placenta greater than 90th percentile in weight increased the risk. Prior reports have correlated acute antenatal hypoxia and RDS with placentomegaly [31]. In addition, villous edema has been associated with umbilical cord arterial blood pH values, low Apgar scores, resuscitation at birth, assisted ventilation, increased hyaline membrane disease, and neonatal mortality [32]. Villous edema can be nearly impossible to distinguish from delayed maturation in the premature placenta. Both conditions may be associated with a heavy placenta.

We confirmed a significant role for prolonged amniotic fluid infection in RDS and neonatal sepsis. In this study, the fetal inflammatory response, specifically multiple chorionic plate vessels with vasculitis, was correlated with an increased risk of RDS, and trended with an increased risk of culture positive sepsis. In addition to overall severe neonatal morbidity, Gomez *et al.* [21] also looked at specific morbidities, including RDS and proven or suspected sepsis, both of which were also correlated with increased fetal plasma IL-6. The current study also identified a trend between maternal inflammatory response increasing RDS and culture positive sepsis, as well as a significant correlation between culture-positive sepsis and subacute or necrotizing acute chorioamnionitis. The relationship between neonatal sepsis and chorioamnionitis has previously been established [4; 33].

Interestingly, no other significant relationships existed between each other neonatal morbidity and features of amniotic fluid infection sequence; however, fetal inflammatory response, in general, and specifically umbilical arteritis, trended with acute hemodynamic instability, ROP, and NEC. Prior reports have linked fetal inflammatory response to sepsis [21; 22; 34], BPD [22; 35], IVH [22; 24; 36–38], and ROP [38]. In addition, the maternal inflammatory response, specifically chorioamnionitis, has been correlated with BPD, IVH, and ROP [4; 33; 39; 40]. The lack of any of these associations in this study could be due to the smaller number of cases (n=102). This study also only performed correlations between findings considered higher grade in the placenta as well as some novel entities.

BPD was significantly correlated with diffuse chorionic hemosiderosis. Diffuse chorionic hemosiderosis, defined as hemosiderin-laden macrophages in the membranes and chorionic plate, is a chronic lesion associated with marginal placental abruption, recurrent maternal bleeding in earlier trimesters, and oligohydramnios [18]. This placental finding has been reported to be increased in infants with persistent pulmonary hypertension of the newborn, pulmonary hypoplasia, and chronic lung disease [41; 42]. Lung injury in these cases may be due to the effects of oligohydramnios on the developing lung as well as possible toxic effects of hemoglobin breakdown in the aspirated amniotic fluid.

Fetal vascular obstruction has been associated with poor outcomes including neonatal death, major thrombotic events, and fetal cardiac abnormalities [43–47]. In addition, some studies have identified a relationship between NEC and fetal thrombotic vasculopathy or fetal

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vascular obstructive lesions [4; 48]. In our study, fetal large vessel thrombi were significantly associated with an increased risk of NEC and trended with an increased risk of ROP and BPD. In addition, marginal or velamentous cord insertion significantly correlated with BPD and trended with ROP. This abnormal cord insertion has been associated with disrupted cord blood flow, stasis, thrombosis within the fetal vasculature, and avascular villi [49; 50]. The data presented here support the hypothesis that large vessel thrombi within the placenta may be associated with systemic vasculopathy. Thrombi or microthrombi in the placenta are continuous with the circulation of the neonate, resulting in a disruption of oxygen distribution and hypoxia. Interestingly, these three morbidities associated with fetal vascular obstruction – ROP, NEC, and BPD – were classified as "oxygen radical disease of neonatology" by Saugstad [51; 52] and their pathogenesis appears to involve oxidative stress.

Proportional odds regression model analyses of gestational age and placental variables against all nine morbidities identified gestational age, small placenta size, and full thickness perivillous fibrin as independently associated with a decreased risk of morbidities. These three findings may all have their basis in accelerated placental maturation. Full thickness perivillous fibrin is uncommon in the premature placenta, and is an exaggeration of Langhan's stria (accumulation of fibrin surrounding large stem villi), a normal finding of placental maturation. It is important to distinguish this finding from massive perivillous fibrin deposition, which we did not diagnose in any of the cases from this cohort. In this study, full thickness perivillous fibrin correlated strongly with increased gestational age. We suggest that in these cases, the association of small for gestational age placentas and full thickness perivillous fibrin with fewer morbidities may reflect accelerated maturation of the placenta, likely as a result of maternal stressors such as uteroplacental malperfusion. Conversely, the fetal inflammatory response features of umbilical arteritis and multifocal chorionic plate vasculitis were associated with an increased risk of the morbidities. Similar decreased risks (gestational age, birth weight) and increased risks (placental histology of fetal inflammatory response) were noted when comparing gestational age and placental variables against the 7 severe morbidities. This data complements the finding that features of amniotic fluid infection correlates with PhysiScore.

Our study did have limitations. Most importantly, we had a small number of cases (n=102), and many of the morbidities only affected a small group of this cohort, greatly decreasing statistical power. Given that we studied nine neonatal morbidities and 18 placental variables, there was a risk for false associations; however, as discussed above, many of our findings are substantiated by other studies. Our identified associations should be confirmed in independent studies with higher numbers of cases. Another limitation of this study was that we did not do any corrections for placentas demonstrating overlapping pathologic findings (for example, placentas demonstrating both amniotic fluid infection and fetal vascular obstruction). However, review of our results does not suggest that any histology group carried another histology group to any statistically significant associations. Another disadvantage of this study was potential selection bias of placentas available for review. Of the 138 infants originally used in the PhysiScore paper [1], only 102 (74%) had placentas submitted to pathology for gross and histologic examination. An additional disadvantage of this study was the inclusion of such a high fraction of twins and triplets; in total 38 of 102

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infants were the results of multiple gestations. However, there were few statistically significant differences between these multiple gestations infants and singleton infants.

In this study, both small placental size and full thickness perivillous fibrin correlated with decreased number of morbidities, using multivariate analyses and were protective of the single morbidity RDS, using pair-wise analyses. Both of these features are associated with accelerated maturation of the placenta, suggesting that the infant who has adapted to *in utero* stressors resulting in accelerated placental maturation at the expense of further placental growth, may be more "fit" for prematurity than one born because of amniotic fluid infection. This hypothesis would need further study to substantiate. However, features of amniotic fluid infection sequence did correlate with increased number of morbidities using multivariate analysis and pair-wise analysis.

Use of a combination of information available shortly after birth – rapid placental exam and early physiological risk assessment - may allow more precise prediction of individual risk well beyond general predictions based on gestational age and birth weight. Placental exam adds information reflecting both the acute and chronic *in utero* environment while PhysiScore reflects the neonate's immediate physiological state in the first hours of life, physiology presumably shaped by this *in utero* environment. Moreover, some morbidities, such as PHH, may be better predicted by pathological assessment rather than physiology. Such risk prediction of morbidity allows individually targeted treatment and improved parental counseling. As the tools for personalized risk prediction grow, preventions and therapies can be better targeted to specific risks that individual preterm neonates face.

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Abbreviations

BPD	bronchopulmonary dysplasia
IVH	intraventricular hemorrhage
NEC	necrotizing enterocolitis
PHH	post-hemorrhagic hydrocephalus
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity

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Highlights

- Placentas from premature infants show a spectrum of pathologies.
- Increased gestational age is protective of neonatal morbidities.
- Amniotic fluid infection sequence is associated with higher morbidity by PhysiScore.
- Small placental size is associated with a low number of morbidities.
- Full thickness perivillous fibrin is associated with a low number of morbidities.

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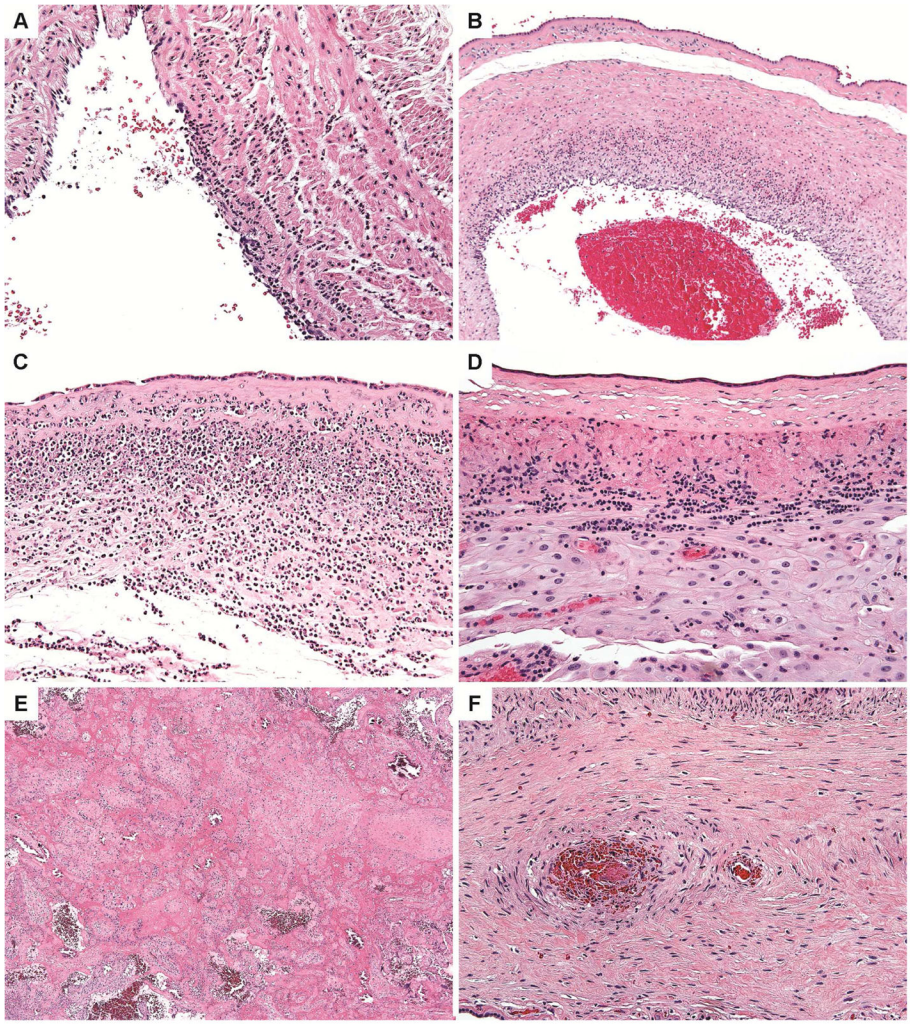

Figure 1. Placental Histology

Fetal inflammatory response features include umbilical arteritis (A) and chorionic plate vessels with vasculitis (B). A maternal inflammatory response includes necrotizing acute chorioamnionitis (C). Lymphocytic inflammation can be characterized by chronic chorionitis (D). Full thickness perivillous fibrin deposition was present in some placentas (E). A stem villous thrombus is identified (F).

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Table 1

Baseline and disease characteristics of the study cohort.

Infant Characteristics	**Number**
Subjects	102
Birth weight (average, g)	1405 ± 403
Gestational age (average, weeks)	30.2 ± 2.7
Gender, M:F	58:44
Apgar score at 5 min (average)	7.56 ± 1.82
Multiple gestation	
Total	38
Twins	32
Triplets	6
PhysiScore (average)	0.236 ± 0.315
Placenta weight (average)	309.7 ± 83.3
Placenta weight: birth weight ratio (average)	0.23 ± 0.08
Maternal Characteristics	Number
Maternal age (years)	32.6 ± 6.3
Gravida (average)	2.8 ± 1.8
Para (average)	0.9 ± 1.2
Pre-eclampsia, HELLP	24
Preterm premature rupture of membranes	36
Spontaneous preterm labor	56
Induction of labor	10
Clinical placental abruption	10
Cesarean section mode of delivery	76
Infant Morbidities	Number
Respiratory distress syndrome	79
Pneumothorax	8
Bronchopulmonary dysplasia, total	20
NOS[a]	2
Mild	8
Moderate	4
Severe	6
Acute hemodynamic instability[b]	16
Retinopathy of prematurity (ROP)[b], total	15
Stage I	6
Stage II	6
Stage III	3
Intraventricular hemorrhage (IVH)[c], total	21

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Infant Characteristics	Number
Grade 1	11
Grade 2	5
Grade 3	2
Grade 4	3
Post-hemorrhagic hydrocephalus	5
Culture-positive Sepsis	6
Necrotizing enterocolitis, total	6
Stage 1	2
Stage 2	2
Stage 3	2
No disease	19
Died	1

[a] Infants with oxygen requirement at 28 days for whom oxygen requirement was not known at 36 weeks after menstrual age; NOS, not otherwise specified

[b] Acute hemodynamic instability is characterized by hypotension requiring ≥3 days of pressor support or adrenal insufficiency requiring hydrocortisone.

[c] ROP is counted by the most severe stage in either eye during the hospitalization

[d] IVH is counted by the most severe grade in either cerebral hemisphere by Papile classification

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Table 2

Premature Infant Morbidities Pair-Wise Correlated with Placental Histology

Placental Histology	Total	RDS[a]	Pneumothorax	BPD[b]	AHI[c]	ROP[d]	IVH[e]	PHH[f]	Culture+Sepsis	NEC[g]
Total Number (percent of total)	102	79 (77.5%)	8 (7.8%)	10 (9.8%)	16 (15.7%)	9 (8.8%)	5 (4.9%)	5 (4.9%)	6 (5.9%)	6 (5.9%)
Gestational age in weeks (mean)	30.2	29.5 *	27.0 *	26.4 *	26.4 *	25.6 *	29.2	26.7 *	25.3 *	26.0 *
PhysiScore (mean)	0.236	0.291 *	0.718 *	0.770 *	0.726 *	0.853 *	0.364	0.597 *	0.909 *	0.724 *
Placenta weight:birth weight ratio (mean)	0.23	0.24	0.31 *	0.33 *	0.32 *	0.33 *	0.24	0.31 *	0.29	0.37 *
Amniotic Fluid Infection Sequence	22/102 (21.6%)	26.6% *	37.5%	40.0%	37.5%	44.4% †	40.0%	40.0%	66.7% *	50.0%
Fetal inflammatory response	21/102 (20.6%)	25.3% *	37.5%	30.0%	37.5% †	44.4% †	40.0%	40.0%	50.0% *	50.0%
Umbilical Arteritis	20/101 (19.8%)	24.1% †	37.5%	30.0%	37.5% †	44.4% †	40.0%	40.0%	50.0% †	50.0% †
≥2 Chorionic plate vessels with vasculitis	16/99 (16.2%)	20.5% *	25.0%	20.0%	31.3%	33.3%	40.0%	40.0%	50.0% †	33.3%
Maternal inflammatory response	18/102 (17.6%)	21.5% †	25.0%	30.0%	25.0%	22.2%	20.0%	20.0%	50.0% †	33.3%
Acute subchorionitis with abscess formation	9/102 (8.8%)	10.1%	0.0%	0.0%	6.3%	0.0%	0.0%	0.0%	0.0%	0.0%
Subacute or necrotizing acute chorioamnionitis	15/102 (14.7%)	17.7%	25.0%	30.0%	18.8%	22.2%	20.0%	20.0%	50.0 *	33.3%
Maternal malperfusion	46/102 (45.1%)	41.8%	50.0%	40.0%	50.0%	11.1% *	20.0%	20.0%	16.7%	66.7%
Size ≤10th percentile	13/101 (12.9%)	7.7% *	0.0%	10.0%	6.3%	0.0%	20.0%	0.0%	16.7%	0.0%
Distal villous hypoplasia	34/102 (33.3%)	31.6	37.5%	30.0%	37.5%	11.1%	0.0%	0.0%	0.0%	50.0%
≥2 Infarcts	10/102 (9.8%)	7.6%	0.0%	10.0%	0.0%	11.1%	0.0%	0.0%	0.0%	0.0%
Maternal decidual vasculopathy, severe	11/83 (13.3%)	9.4%	20.0%	0.0%	8.3%	0.0%	0.0%	25.0%	0.0%	25.0%
Full thickness perivillous fibrin	10/102 (9.8%)	3.8% *	0.0%	0.0%	0.0%	33.3%	0.0%	0.0%	0.0%	0.0%
Chronic inflammation	34/102 (33.3%)	34.2%	12.5%	30.0%	25.0%	33.3%	60.0%	80.0% *	83.3% *	16.7%
Chronic chorionitis and basal chronic villitis	32/101 (31.7%)	33.3%	12.5%	30.0%	25.0%	33.3%	60.0%	80.0% *	83.3% *	16.7%
Parenchymal chronic villitis	9/102 (8.8%)	7.6%	12.5%	10.0%	12.5%	11.1%	20.0%	40.0% †	16.7%	16.7%
Fetal vascular obstruction	26/102 (25.5%)	25.3%	37.5%	50.0%	31.3%	44.4%	0.0%	20.0%	0.0%	50.0% *

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Placental Histology	Total	RDS[a]	Pneumothorax	BPD[b]	AHI[c]	ROP[d]	IVH[e]	PHH[f]	Culture+Sepsis	NEC[g]
Large vessel thrombi	11/101 (10.9%)	11.4%	25.0%	30.0% [t]	18.8%	33.3% [t]	0.0%	20.0%	0.0%	50.0% [*]
Villous damage from fetal ischemia	17/102 (16.7%)	16.5%	25.0%	30.0%	18.8%	22.2%	0.0%	0.0%	0.0%	33.3%
Marginal or velamentous cord insertion	21/100 (21.0%)	20.8%	0.0%	55.6% [*]	35.7%	50.0%	2.0%	20.0%	16.7%	25.0%
Large, edematous placenta	38/102 (37.3%)	44.3% [*]	37.5%	10.0% [t]	43.8%	33.3%	60.0%	40.0%	16.7%	50.0%
Size ≥90th percentile	24/101 (23.8%)	29.5% [*]	37.5%	10.0%	25.0%	33.3%	40.0%	40.0%	16.7%	33.3%
Villous edema	23/102 (22.5%)	26.6% [t]	25.0%	10.0%	43.8% [*]	33.3%	40.0%	40.0%	16.7%	50.0%
Diffuse chorionic hemosiderosis	3/101 (3.0%)	3.8%	12.5%	20.0% [*]	6.3%	11.1%	0.0%	0.0%	16.7%	16.7%
Nucleated red blood cells >10/10 high power fields	29/101 (28.7%)	28.2%	28.6%	50.0%	18.8%	33.3%	40.0%	20.0%	0.0%	50.0%

[*] considered statistically significant

[t] trending p-value (between 0.050 and 0.100)

[a] RDS: respiratory distress syndrome

[b] BPD: moderate and severe bronchopulmonary dysplasia

[c] AHI: acute hemodynamic instability characterized by hypotension requiring ≥3 days of pressor support or adrenal insufficiency requiring hydrocortisone

[d] ROP: high stage (≥2) retinopathy of maturity

[e] IVH: high grade (≥3) intraventricular hemorrhage

[f] PHH: post-hemorrhagic hydrocephalus

[g] NEC: necrotizing enterocolitis

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Table 3

Placental Histology Characteristics associated with PhysiScore

Placental Histology	Average GA (weeks)	Average BW (g)	Average PhysiScore	Association with PhysiScore unadjusted		Association with PhysiScore adjusted for GA and BW	
				OR[C]	p-value	OR	p-value
Amniotic Fluid Infection Sequence	28.4*	1271	0.42*	2.996	0.017**	1.330	0.554
Fetal inflammatory response	28.5*	1296	0.40*	2.598	0.039**	1.347	0.544
Maternal inflammatory response	28.4*	1259	0.40*	2.422	0.071	0.737	0.534
Maternal malperfusion	30.2	1322*	0.24	1.618	0.167	0.970	0.936
Full thickness perivillous fibrin	32.6*	1555	0.04*	0.330	0.049**	0.724	0.598
Chronic inflammation	29.6	1371	0.25	1.310	0.459	0.576	0.128
Fetal vascular obstruction	29.9	1292	0.29	1.619	0.220	1.138	0.751
Large vessel thrombi	28.7	1286	0.38	2.453	0.117	1.813	0.358
Villous damage from fetal ischemia	30.1	1281	0.27	1.370	0.489	1.026	0.955
Large and/or edematous placenta	29.6	1399	0.29	1.673	0.155	1.822	0.132
Diffuse chorionic hemosiderosis	27.2	1077	0.64*	6.639	0.085	1.271	0.686

GA: gestational age; BW: birth weight

[C]OR: odds ratio

*considered statistically significant in comparison to those without placental histology

**considered statistically significant

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Table 4

Associations with Total Number of Morbidities

Variable	All 9 morbidities[a]		7 severe morbidities[b]	
	OR[c] (CI[d])	p-value	OR[c] (CI[d])	p-value
PhysiScore	2.028 (1.656–2.484)	<0.001 *	1.912 (1.563–2.339)	<0.001 *
Gestational age	0.437 (0.351–0.545)	<0.001 *	0.441 (0.337–0.577)	<0.001 *
Birth weight	0.996 (0.995–0.998)	<0.001 *	0.995 (0.994–0.996)	<0.001 *
Amniotic Fluid Infection Sequence				
Fetal inflammatory response				
Umbilical Arteritis	3.075 (1.209–7.822)	0.018 *	2.942 (1.047–8.268)	0.041 *
≥2 Chorionic plate vessels with vasculitis	3.440 (1.272–9.307)	0.015 *	3.092 (1.036–9.225)	0.043 *
Maternal inflammatory response				
Acute subchorionitis with abscess formation	0.813 (0.251–2.630)	0.730	0.327 (0.039–2.726)	0.302
Subacute or necrotizing acute chorioamnionitis	2.620 (0.948–7.237)	0.063	2.572 (0.836–7.912)	0.100
Maternal malperfusion				
Size ≤10th percentile	0.270 (0.082–0.884)	0.031 *	0.770 (0.200–2.970)	0.705
Distal villous hypoplasia	0.776 (0.360–1.674)	0.518	0.811 (0.314–2.095)	0.665
≥2 Infarcts	0.445 (0.146–1.359)	0.155	0.369 (0.049–2.783)	0.334
Maternal decidual vasculopathy, severe	0.299 (0.085–1.051)	0.060	0.355 (0.042–2.988)	0.341
Full thickness perivillous fibrin	0.084 (0.020–0.351)	0.001 *	0.000 (0.000-inf)	0.992
Chronic inflammation				
Chronic chorionitis and basal chronic villitis	1.175 (0.537–2.573)	0.686	1.162 (0.444–3.043)	0.760
Parenchymal chronic villitis	1.042 (0.251–4.327)	0.954	1.843 (0.431–7.886)	0.410
Fetal vascular obstruction				
Large vessel thrombi	1.984 (0.561–7.022)	0.288	2.543 (0.670–9.642)	0.170
Villous damage from fetal ischemia	0.935 (0.348–2.512)	0.894	0.985 (0.292–3.321)	0.981

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Variable	All 9 morbidities[a]		7 severe morbidities[b]	
	OR[c] (CI[d])	p-value	OR[c] (CI[d])	p-value
Marginal or velamentous cord insertion	1.338 (0.530–3.382)	0.538	2.077 (0.729–5.914)	0.171
Large, edematous placenta				
Size ≥90th percentile	1.713 (0.748–3.923)	0.203	0.835 (0.276–2.524)	0.749
Villous edema	2.032 (0.863–4.784)	0.105	1.897 (0.704–5.110)	0.206
Diffuse chorionic hemosiderosis	8.783 (0.968–79.70)	0.053	7.681 (0.941–62.731)	0.057
Nucleated red blood cells >10/10 high power fields	0.986 (0.438–2.209)	0.967	0.995 (0.368–2.687)	0.992

[a] All 9 morbidities: respiratory distress syndrome, pneumothorax, moderate and severe bronchopulmonary dysplasia, acute hemodynamic instability, high stage (≥2) retinopathy of maturity, high grade (≥3) intraventricular hemorrhage, post-hemorrhagic hydrocephalus, culture positive sepsis, necrotizing enterocolitis

[b] 7 severe morbidities: Moderate and severe bronchopulmonary dysplasia, acute hemodynamic instability, high stage (≥2) retinopathy of maturity, high grade (≥3) intraventricular hemorrhage, post-hemorrhagic hydrocephalus, culture positive sepsis, and necrotizing enterocolitis

[c] OR: odds ratio

[d] CI: confidence interval

[*] considered statistically significant