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Placenta, Secret Witness of Infant Morbidities: The Relationship Between Placental Histology and Outcome of the Premature Infant

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ABSTRACT

Objective: The microscopic and macroscopic features of the placenta can contribute to the clinical understanding of premature delivery. The aim of our study was to figure out the relationship between the histopathological findings of the placentas of premature deliveries and its effects on neonatal morbidity and mortality.

Material and Method: The placentas of 284 singleton preterm infants with <35 weeks of gestation were examined. Three groups were created as the normal, chorioamnionitis and vasculopathy groups according to the histopathological findings in the placentas of the subjects.

Results: The mean gestational age of the infants in the study group was 30.5 ± 3.2 weeks, and the mean birth weight was 1588 ± 581 g. The pathology was normal in ninety-six (33.8%), vasculopathy in 153 (53.9%) and chorioamnionitis in 35 (12.3%). The gestation age of the infants was lower in the chorioamnionitis group. Moreover, retinopathy of prematurity, early onset neonatal sepsis, and duration of respiratory support were found to be higher in the chorioamnionitis group. In the vasculopathy group, preeclampsia and small for gestational age were found to be significantly higher.

Conclusion: Histopathological findings of the placentas from preterm deliveries provided important data in determining the etiology of preterm delivery and outcomes of infants. Infants delivered by mothers with chorioamnionitis were particularly found to be more preterm, and these preterm infants would have a longer hospital stay, higher respiratory support requirement, and more serious morbidities.

Key Words: Chorioamnionitis, Neonatal morbidity, Placental pathology, Prematurity, Vasculopathy

INTRODUCTION

Prematurity is an important cause of serious morbidity and mortality after delivery (1). During pregnancy, the placenta has essential roles in fetal nutrition, gas exchange and removal of residual products of catabolism. The placenta has a strategic position at the fetal-maternal interface reflecting the problems of both the mother and the fetus (2). The placenta also serves as a barrier to protect the fetus against toxins and infective organisms (3). Any damage to the placenta, such a critical organ for fetal life, affects the development of a normal fetus and may lead to an adverse perinatal outcome (2). Recently, data about placental lesions have contributed to a better idea of how the placenta functions. In addition, current findings indicate that placental function abnormalities can cause severe morbidity and mortality of mothers and fetuses (4). Increasing evidence has also indicated that placental dysfunction during the antenatal period is an important risk factor for preterm birth and/or poor neurodevelopment outcomes in the later life of live-born infants (5,6). However, little is known about the benefit of placental findings for neonatal care among pediatricians (3). Many of the abnormalities in the placenta have long been known to affect fetal outcomes. Therefore, our study was aimed to ascertain the relationship between placental histology and outcomes of premature neonates.

MATERIALS and METHODS

The present study was prospectively conducted in the neonatal intensive care unit (NICU) of the Children Hospital of Ankara University Faculty of Medicine between November 2012 and February 2015, The Local Ethical Committee and the Institutional Review Board (IRB) of Ankara University School of Medicine approved the study (IRB No. 05-2014-15). Informed consent was obtained from the mothers enrolled in the study. This study was performed only in accordance with the ethical standards

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provided by the responsible committee of the institution and in accordance with the Declaration of Helsinki.

Study Population

Placentas of singleton pregnancies resulting in preterm hospitalized babies less than 35 weeks of gestational age were included. Multiple pregnancies, infants who were born ≥ 35 weeks of gestation, infants with major congenital anomaly and infants whose parents refused informed consent were excluded from the study. Pregnancy-related issues and neonatal outcomes such as neonatal morbidities and mortality were retrieved from the medical records.

Data Collection (demographic characteristics and clinical outcomes)

Birth weight (BW), gestational age (GA), small for gestational age (SGA), antenatal steroid exposure, preeclampsia, gestational diabetes mellitus (GDM), gender, type of delivery, premature rupture of membranes (PPROM), preterm labor (PTL), early onset neonatal sepsis (EOS), positive blood cultures (culture proven), requirement of delivery room resuscitation, five minute Apgar score <7, duration of mechanical ventilation (MV), noninvasive ventilation (NIV) and oxygen supplementation, duration of neonatal intensive care unit (NICU) stay and day of starting full enteral feeding were recorded. Additionally, clinical outcomes including respiratory distress syndrome (RDS) (8), intraventricular hemorrhage (IVH) (grade ≥3), hemodynamically significant patent ductus arteriosus (hsPDA)(9), moderate or severe bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) requiring laser treatment, and necrotizing enterocolitis (NEC) (grade ≥2), mortality were recorded.

Preeclampsia was identified according to the following criteria including hypertension (blood pressure of mothers ≥130/90 mmHg) along with proteinuria (1+ or 2+ protein on a dipstick recognized by using two different urine samples that were checked with 6-hour intervals or proteinuria >0.3 grams after a 24-hour urine collection) (10). Gestational diabetes mellitus, called pregnancy-induced diabetes, was diagnosed by an abnormal glucose tolerance test (11). Spontaneous rupture of membranes without onset of labor < 37 weeks of gestation was determined as preterm premature rupture of membranes (12).

Small for gestational age was determined as a birth weight below the 10th percentile for GA according to Lubchencho curves (13). Bronchopulmonary dysplasia was identified as continuing oxygen supplementation in the post conceptual 36 weeks of age (14). Intraventricular hemorrhage was diagnosed by transfrontal ultrasonography in the first week of life (15). Modified Bell's criteria were used for the diagnosis of NEC (16). Retinopathy of prematurity was diagnosed by skilled ophthalmologists according to the international classification of retinopathy of prematurity revisited (17). Early onset sepsis was distinguished as culture proven or clinical sepsis (18).

Preparation of Placental Tissues

The obtained placenta tissue samples were kept in formalin for at least 24 hours. Then, at least four specimens were taken from each placenta including two from the maternal and two from the fetal side, and additional samples were obtained from regions detected by macroscopic examination at the same time. Moreover, tissue samples from four different parts of the umbilical cord and placental membranes were allocated. These obtained tissue samples were subjected to alcohol and then paraffin embedded. Paraffin blocks were cut in to 3-4 μm sections using a microtome (Leica SM 2000, Germany). Slides were stained with hematoxylin and eosin and evaluated under a light microscope for histopathological findings. All histopathological analyses described were performed by an investigator with no prior knowledge of the groups. All sections were examined on slides at x100 magnification.

Histopathological Evaluation

Placentas were divided into three groups and assigned as normal placenta, vasculopathy (VP) and chorioamnionitis (CA) groups. The current Amsterdam Placental Workshop Group Consensus Statement which provides eleven different categories was used to evaluate and classify the pathological findings of the placentas (19). Vasculopathy was defined based on certain findings such as placental vascular processes (maternal stromal-vascular lesions and fetal stromal-vascular lesions). Chorioamnionitis was defined as placental inflammatory-immune processes (infectious inflammatory lesions and immune/idiopathic inflammatory lesions) (19). Normal histopathological findings were identified as the normal placental group (Figure 1A-C). Histopathological examinations of the placentas were performed at the Pathology Department of Ankara University. All slides were examined by the same pathologist in a blinded fashion.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 15 for Windows (SPSS Inc., St. Louis, MO) were used to compare variables, and a p value < 0.05 was considered significant. The t-test and/or Mann-Whitney U-test were implemented to compare non-parametric continuous variables between groups. Categorical variables were analyzed by using

chi-square or Fisher's exact tests. Continuous variables were stated as mean ± standard deviation (SD), and/or median (minimum-maximum). Categorical variables were expressed as percentage and distribution of frequency.

RESULTS

During the study period, 298 singleton preterm infants, who were born < 35 weeks of gestation, were evaluated among 1034 hospitalized newborns. The placentas of 4 patients with major congenital malformation and 10 patients who refused to participate in the study were excluded. The pathology was normal in 96 (33.8%), VP in 153 (53.9%) and CA in 35 (12.3%) (Figure 2).

The mean GA of the infants in the study group was 30.5 ± 3.2 weeks, and mean BW was 1588 ± 581 g. Demographic variables and clinical outcomes are shown in Table I and II. The mean GA (28.5±3.2 weeks) and delivery by cesarean section (51.4%) were found to be significantly lower in the CA group compared with the other two groups of normal pathology and VP groups. Additionally, in the CA group, PPROM, EOS and PTL were determined to be significantly higher than the other two groups (normal and VP groups) ($p<0.05$). In the CA group, ROP requiring laser treatment, duration of NIV and oxygen requirement, NICU stay were shown to be significantly higher ($p=0.010$, $p=0.002$, $p=0.015$, $p=0.005$) than in the normal and VP groups (Table I and II).

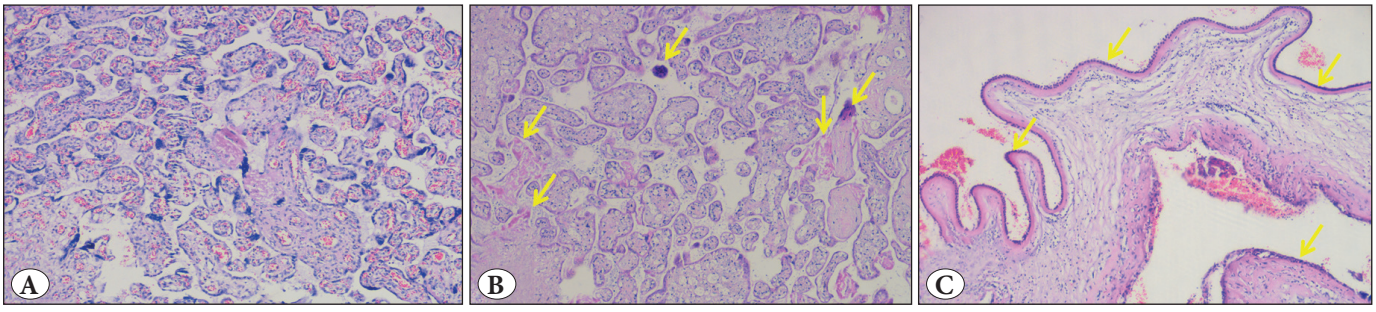

Figure 1: A) Normal placenta: indicating normal placental tissues (H&E; x100). **B)** Vasculopathy: indicating neutrophils as a vital reaction to the retroplacental hemorrhage, syncytial knots and intervillous fibrin deposition (H&E; x100). **C)** Chorioamnionitis: indicating neutrophils in the subchorial intervillous space (H&E; x100).

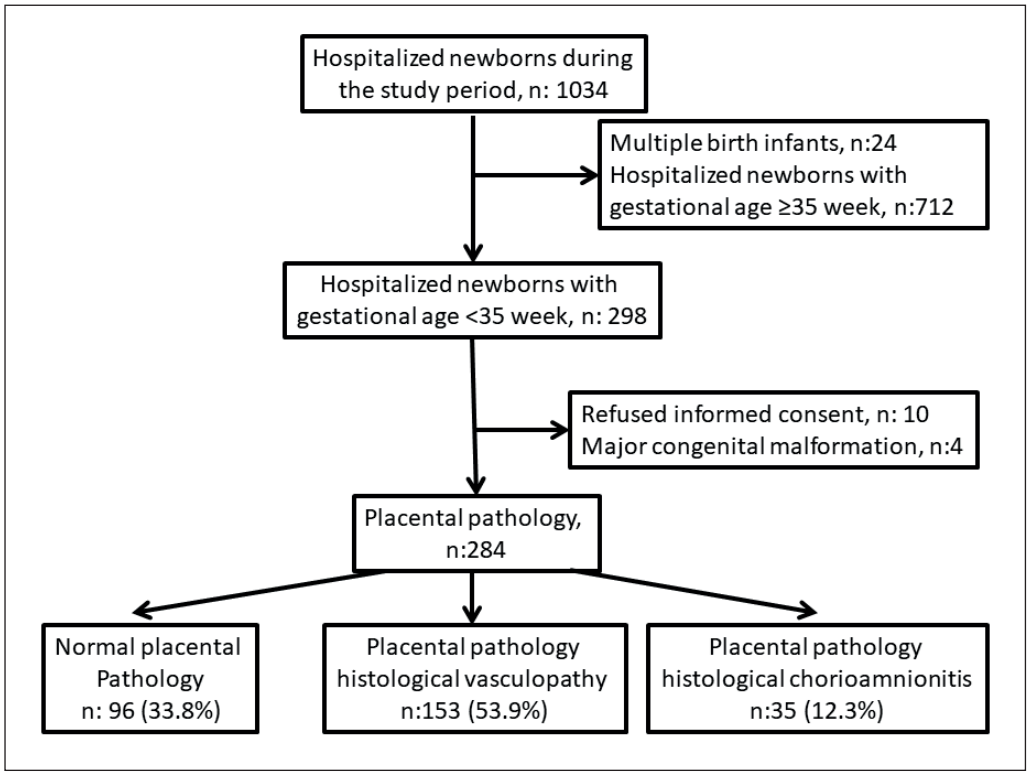

Figure 2: Flow diagram of assessing and including eligible participants in the trial.

In the VP group, SGA, preeclampsia, and female sex were found to be significantly higher (p=0.037, p<0.001, p=0.009, p=0.022) when compared with the normal pathology and CA groups (Table I). The birth weight was found to be higher in the normal group (p <0.001) and day of starting full enteral feeding were lower than in the other groups (p=0.011) (Table I and II).

The outcomes were the same among all groups in terms of antenatal steroid administration, GDM, positive bacterial culture, requirement of delivery room resuscitation, five minute Apgar score <7, the duration of MV, RDS, IVH (grade ≥3), hsPDA, BPD, NEC (grade ≥2), and mortality (p>0.05) (Table I and II).

Table I: Demographic variables and clinical outcomes.

Variables	Normal n=96 (33.8%)	Vasculopathy n=153 (53.9%)	Chorioamnionitis n=35 (12.3%)	P
GA, mean±SD (week)	32.5±2.4	31.3±2.5	**28.5±3.2**	**<0.001***
BW, mean±SD (g)	**1961±582**	1504±562	1320±593	**<0.001***
SGA, n (%)	5 (5.2)	**33 (21.6)**	2 (5.7)	**0.037***
Antenatal steroid, n (%)	44 (45.8)	69 (45.1)	19 (54.2)	0.541
Preeclampsia, -n (%)	4 (4.2)	**53 (34.6)**	2 (5.7)	**<0.001***
GDM, n (%)	7 (7.3)	8 (5.2)	1 (2.8)	0.131
Female sex, n (%)	24 (25)	**75 (49)**	11 (31.4)	**0.022** *
Born by cesarean, n (%)	71 (73.9)	140 (91.5)	**18 (51.4)**	**0.016***
PPROM, n (%)	9 (9.3)	7 (4.5)	**14 (40)**	**<0.001***
PTL, n (%)	47 (49)	72 (47)	**31 (88.5)**	**<0.001***
EOS, n (%)	8 (8.3)	15 (9.8)	**29 (82.8)**	**<0.001***
Positive bacterial cultures, n (%)	2 (2.1)	11 (7.2)	4 (11.4)	0.631
Delivery room resuscitation, n (%)	11 (11.4)	35 (22.8)	9 (25.7)	0.214
Five minute Apgar score <7, n %	7 (7.2)	16 (10.4)	6 (17)	0.174
MV duration, days, mean±SD	1.2±2.7	1.3±3.54	2.9±9.8	0.098
NIV duration, days, mean±SD	2.4±4.2	2.5±4.9	**5.2±7.3**	**0.002***
Oxygen requirement, days, mean±SD	6.1±12.3	9.3±14	**22.1±28.8**	**0.015***
NICU stay, days, mean±SD	12.4±14	21.7±22.2	**30.5±29.5**	**0.005***

* Values of P<0.05 were considered significant.

GA: Gestational age, **BW:** Birth weight, **SGA**: Small for gestational age, **GDM:** Gestational diabetes, **PPROM**: Premature rupture of membranes, **PTL**: Preterm labor, **EOS**: Early onset neonatal sepsis, **MV**: Mechanical ventilation, **NIV**: Non invasive ventilation, **NICU**: Neonatal intensive care unit.

Table II: Clinical outcomes.

Variables	Normal n=96 (33.8%)	Vasculopathy n=153 (53.9%)	Chorioamnionitis n=35 (12.3%)	P
Day of full enteral feeding, days, mean±SD	**5.3±5.7**	9.1±9.4	11.4±10.2	**0.011***
RDS, n (%)	26 (27.1)	49 (32)	18 (51.4)	0.082
IVH (grade ≥3), n (%)	4 (4.1)	15 (9.8)	8 (22.8)	0.184
hsPDA, n (%)	9 (9.4)	14 (9.1)	7 (20)	0.243
Moderate or severe BPD, n (%)	5 (5.2)	13 (8.5)	7 (20)	0.118
ROP requiring laser treatment, n (%)	1 (1)	3 (1.9)	**6 (17.1)**	**0.010***
NEC (grade ≥2), n (%)	4 (4.1)	16 (10.4)	7 (20)	0.189
Mortality, n (%)	7 (7.2)	14 (9.1)	7 (20)	0.105

* Values of P<0.05 were considered significant.

RDS: Respiratory distress syndrome, **IVH**: Intraventricular hemorrhage, **hsPDA**: Hemodynamically significant patent ductus arteriosus, **BPD**: Bronchopulmonary dysplasia; **ROP**: Retinopathy of prematurity, **NEC**: Necrotizing enterocolitis

DISCUSSION

In the literature, several studies have separated the placenta as either CA or VP for histopathological examination, and the results have been discussed after the main groups were divided into subgroups. It is known that there are many factors affecting placental pathology. The main aim of this study was to evaluate the effects of placental pathologies on preterm infants. As far as we know, our study included both low gestational ages and all placental histopathologies for the first time. Therefore, we did not divide the patients into more subgroups, and the results obtained by comparing these groups were discussed.

The placental histopathology, including term and preterm deliveries have declared that the placental VP rate ranges between 3.5% and 6.4% (20,21). The vasculopathy rate in pregnancy induced hypertension are observed to rise to as high as 82% (1). Particularly, VP was found to be higher in pregnant women with preeclampsia, and according to our findings, the present VP rate was consistent with the recent literature data. This result emphasized the fact that placental VP is associated more closely with prematurity and SGA. These findings were obviously parallel to recent literature data (22,23). In recent studies, the relationship between preeclampsia / SGA and fetal and maternal face placental pathology due to vascular mal-perfusion has been shown based on the new placental classification (23-25). That is, infants with small gestational age can be seen in any of the subgroup of histopathological VP. This may be a sign that placental perfusion is impaired for any reason. The available evidence supports that there is no relationship between placental pathology and gender (26,27). Kim et al. found that the male gender ratio was high in the CA group (28). According to our results, the female gender ratio in the VP group was higher. However, we did not have the markers related to VP. It may be speculated that gender could affect placental pathology.

Placental VP, which causes utero-placental deficiency, may lead to fetal circulatory adaptive changes to hypoxia. Necrotizing enterocolitis may develop after hypoxic-ischemic injury of the bowel (12). It has been found in the literature that there is a relationship between NEC and fetal vascular obstructive lesions (fetal thrombotic vasculopathy, congested villi, coagulation-related lesions), with a ORs ranging from 2.6 to 9.1 (3). These results support the idea that placental lesions such as VP emerging at low GA in utero have a slight effect on the NEC. Such contradictory data suggest that pathophysiological mechanisms outside of those related to histologic VP lesions may also be responsible for adverse effects on the infant's health. It is known that placental VP causes fetal hypoxemia and may lead to PTL through cytokines (29). Although no relationship has been found between CA and PPROM and PTL in term infants, we found a fine association between CA and PPROM and PTL in preterm infants (6,26,27). Premature rupture of membranes is observed in 2-3.5% of term, but in up to 30-40% of preterm deliveries (30,31). PPROM increases the incidence of CA by up to 48% (32). In our study, the PPROM incidence was determined to be 9.3% in the normal placenta group; however, it was 40% in the CA group. As expected, we found that the EOS incidence was higher (10-fold) in the CA group compared to the normal placental group.

During pregnancy, the incidence of histopathological CA varies from 11.5 to 57.3% (27). However, it has been determined that the incidence of CA is 60-80%, 40-50%, and 5-30% in deliveries according to GA, involving <28 weeks, between 29 and 34 weeks, and > 34 weeks, respectively (33). In one study, the CA rate was particularly considerable in deliveries less than 30 weeks with a rate of 83.3%. However, mothers without CA have given birth on the 31st gestational week on average. In contrast, in the CA group, the delivery week has been observed to decrease to 27 weeks (18). In our study, the CA rate was found to be lower (12.3%) than in current data. This result suggests that VP may be a more prominent placental lesion than CA as the gestational week decreases.

Although, preterm delivery rate was much lower in the normal placental group than in CA and VP. Normal vaginal delivery was found to be higher in the CA group due to PPROM and PTL. Based on this data, day of starting full enteral feeding and duration of NICU stay were found to be shorter. Moreover, laboratory findings of sepsis such as higher C-reactive protein, white blood cells and interleukin-6 were remarkably increased, and EOS rate was high in the CA group in the present study. However, neonatal sepsis may not always be associated with CA (4,27). Our results supported and were consistent with current evidences (28,34). Although the probable EOS rate may be high in the CA group, culture-proven EOS may not always be found.

Antenatal steroids have been reported to reduce some of the adverse effects of CA such as IVH and RDS in preterm infants and reduce mortality by suppressing inflammation (35). A study conducted by Perrone et al. has reported that the application of antenatal steroids does not change the frequency of CA in pregnant women (2). Additionally, CA increases the rate of RDS unrelated to antenatal steroid administration. In our study, antenatal steroid usage and

RDS were similar among the groups. Current evidence has shown the higher risk of RDS in infants with placental abruption, and it is already known that CA decreases the risk of RDS (36,37). In contrast, we did not find any relationship between CA and risk of RDS (26,38).

Inflammatory conditions in the placenta affect the lung development in utero and cause respiratory problems after birth such as RDS and BPD. Current evidence supports that CA reduces the incidence of RDS. CA can also promote BPD (3,39). However, in our study, RDS and BPD were found to be similar among the groups. A recent study has supported our results (40). Another study reported that funisitis increases the risk of BPD (41). However, in many studies, no association found between the presence of placental funisitis and BPD (28,40,42-44). The relationship between histopathological CA or subgroups and BPD is still unclear. That means that RDS and BPD not only result from CA but they might also arise from the adverse effects of preterm delivery. Many factors (multiple hits hypothesis) involving SGA, low gestational age, genetic predisposition, and postnatal insults (hsPDA, sepsis and mechanical ventilation therapy) have been suggested to be associated with BPD (40,45). Duration of respiratory support and NICU stay were longer in infants subjected to CA in our study. It may be due to prematurity and the nature of inflammation in the lungs in CA group. This hypothesis suggests that BPD emerges due to antenatal exposure to a proinflammatory condition that is followed by postnatal triggering insults (45). In the present study, our findings could not rule out this hypothesis.

Infectious and inflammatory events such as clinical CA may be a risk factor for NEC, IVH, and PDA (26,46,47). However, as supported with our results, CA might not always be related to severe morbidities like NEC, IVH, PDA and mortality (26,28,38,48). Retinopathy of prematurity is another adverse effect of preterm delivery that is particularly related to inflammatory lesions in the placenta (3). The severity of ROP was also determined to be positively associated with ascending intrauterine infections (45). Kim et al. demonstrated that ROP requiring laser treatment was found to be higher in infants exposed to CA (28). In contrast, some evidence has indicated that there may not be an association between inflammatory conditions and ROP (26). Therefore, these results might be related to more prematurity in the infants in the CA group.

We are aware of the study limitations. Our limitations can be stated as follows: 1) inflammatory cytokine levels were not measured in the cord blood, 2) the pH of umbilical arterial PH could not be measured immediately after delivery, 3) the study groups had a relatively limited size, 4) placental measurements of the subjects (placental weight, placental area, cord length, birth weight/placental weight ratio) could not be assessed, 5) the VP and CA criteria had a broad range. It is a reality that many different factors affect the placental pathology. However, this study aimed to evaluate the effect of major placental pathologies like VP and CA on preterm infants.

In conclusion, it is obvious that placental pathologies affect the outcomes of newborn infants from the intrauterine to the postnatal period. Particularly infants delivered by mothers with CA were found to be more preterm, and these preterm infants could have a long hospital stay, higher respiratory support requirement, and morbidities such as EOS and ROP requiring laser treatment. Additionally, VP leads to higher rate of SGA infants. In contrast to some studies on placental pathology, our results demonstrated a lower incidence of CA as well as a higher rate of VP. All in all, each infant is born with the risks of his or her own placenta and gestational age. The placenta is a secret witness for every infant. Physicians should be aware that the relationship between placental histology and the outcome of the premature infant is a reality. Further studies are warranted to evaluate the significance of placental pathologies prior to making any clinical decision.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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None

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