

Placental Pathology and Clinical Outcomes in a Cohort of Infants Admitted to a Neonatal Intensive Care Unit

Luc Beaudet, MD, PhD,¹ Stella Karuri, PhD,² Jacqueline Lau, MD, PhD,³ Fergall Magee, MB BCh, BAO, MHSc,⁴ Shoo K. Lee, MB, BS, PhD,^{2,4,5} Peter von Dadelszen, MB ChB, DPhil^{1,2}

¹Department of Obstetrics and Gynaecology, University of British Columbia, Vancouver BC

²Centre for Healthcare Innovation and Improvement, Child and Family Research Institute, University of British Columbia, Vancouver BC

³School of Medicine, Queen's University, Kingston ON

⁴Department of Pathology and Laboratory Medicine and Department of Pediatrics, University of British Columbia, Vancouver BC

⁵Department of Paediatrics, University of Alberta, Edmonton AB

Abstract

Background: Placental pathology predicts persistent neurological impairment, even in normally grown infants. However, few studies have linked placental pathology with neonatal outcomes in a large population.

Methods: We matched the clinical outcomes of a cohort of neonates admitted to a neonatal intensive care unit (NICU) with placental pathology, where available, and examined (by multivariable logistic regression) the relationship between placental pathologies and these outcomes. The outcomes included neonatal death, necrotizing enterocolitis, and intraventricular hemorrhage \geq grade 3. A forward selection model (10% significance level for entry) was used after adjusting for confounding factors.

Results: A detailed gross and microscopic pathological report was available for 1296 eligible infants (64%). Specific placental features were associated with specific neonatal outcomes. The Canadian Neonatal Network has previously determined that specific changes in the pattern of neonatal care can alter the incidence and severity of these outcomes. In the placentas from pregnancies delivering small for gestational age infants who were subsequently admitted to NICU, two different patterns of placental pathologies were found, one ischemic and the other inflammatory.

Conclusion: Frozen section examination of placentas may facilitate more timely delivery of tailored neonatal therapy.

Résumé

Contexte : La présence d'une pathologie placentaire permet de prédire les troubles neurologiques persistants, même chez les nouveau-nés ayant connu une croissance normale. Cependant, peu d'études ont lié la pathologie placentaire à des issues néonatales au sein d'une population de grande envergure.

Key Words: Placental pathology, subclassification, neonatal intensive care unit, neonatal outcomes, outcome prediction

Competing Interests: None declared.

Received on September 8, 2006

Accepted on November 9, 2006

Méthodes : Nous avons apparié les issues cliniques d'une cohorte de nouveau-nés présentant une pathologie placentaire et admis dans une unité néonatale de soins intensifs (UNSI), le cas échéant, et avons analysé (par régression logistique multivariable) la relation entre les pathologies placentaires et ces issues. Parmi les issues, on comptait le décès néonatal, l'entérocolite nécrosante et l'hémorragie intraventriculaire \geq grade 3. Une régression multiple ascendante (niveau de signification de 10 % pour l'admission) a été utilisée, une fois les facteurs confusionnels neutralisés.

Résultats : Un rapport pathologique macroscopique et microscopique détaillé était disponible chez 1 296 des nouveau-nés admissibles (64 %). Des caractéristiques placentaires particulières ont été associées à des issues néonatales particulières. Le Réseau néonatal canadien avait déjà déterminé que l'apport de changements particuliers au modèle de soins néonataux pouvait modifier l'incidence et la gravité de ces issues. Dans les placentas des grossesses qui ont donné lieu à la naissance d'enfants présentant une hypotrophie fœtale qui ont par la suite été admis dans une UNSI, deux modes différents de pathologies placentaires ont été constatés : ischémique et inflammatoire.

Conclusion : L'examen en coupe à congélation des placentas pourrait faciliter l'offre plus opportune de soins néonataux adaptés.

J Obstet Gynaecol Can 2007;29(4):315-323

INTRODUCTION

An assessment of placental pathology is useful for couples in resolving issues arising from pregnancy complications, including perinatal loss.¹ It is also useful to clinicians for determining the underlying mechanisms leading to pregnancy complications and for guiding future investigations and interventions relating to pre-pregnancy counselling and pregnancy care.^{1,2} Placental pathology can correlate with adverse neonatal and, particularly, neurodevelopmental outcomes, even in the normally grown infant.^{3,4} Despite this, very few studies have examined the relationship between placental pathology and neonatal

Table 1. Comparison of infants with and without placental pathology

Characteristic	Examination	No examination
Total infants	1296	716
Inborn	1114 (86%)*	76%*
Mean GA in weeks (SD)	33.2 (0.4)*	37.3 (0.2)*
Mean birth weight in Kg (SD)	2.1 (0.1)*	3.0 (0.1)*
Antenatal corticosteroids	607 (46.8%)*	6.7%*
Maternal hypertension	201 (15.5%)*	8.6%*
Caesarean delivery	599 (46.2%)*	30.4%*
Male	574 (44.3%)*	38.5%*
Multiple birth	162 (12.5%)	11.7%

GA: gestational age; SD: Standard deviation.

*Significant difference (*t* test or χ^2 ; *P* < 0.05, as appropriate)

outcomes in a large population. Also, the placental pathology report often arrives weeks or months after the delivery, at which time it is of little use in guiding early neonatal care.

The Canadian Neonatal Network has identified practice variations that improve neonatal outcomes, and has found that these practices vary between neonatal intensive care units (NICUs) across Canada.⁵⁻¹²

It is currently unknown whether or not specific patterns of placental pathology may predict specific neonatal complications that are amenable to risk modification through changes in early neonatal intensive care unit (NICU) care. If such patterns are identified, then it may be justifiable to request a frozen section assessment of placental pathology to guide the early management of infants admitted to NICU in the same way that frozen sections are used to guide intraoperative management in surgical cases.¹³⁻¹⁹

We undertook this study to validate the examination of the placenta by identifying any significant factors that could lead to specific interventions to improve neonatal outcomes. In a cohort of infants admitted to the NICU of our tertiary care hospital, we examined clinical outcome and size for gestational age and related these to placental pathological features.

METHODS

This was a retrospective cohort study that included all neonates admitted to the NICU at British Columbia's Children's Hospital from January 1996 to October 1997 for whom a placental pathology report was available. We matched clinical outcome measures with placental pathological features extracted from pathology reports. A single reviewer who was blinded to the maternal and neonatal outcomes (J.L.) reviewed these data, using a standardized form and standardized definitions, as previously described.²⁰ The

pathologists who performed the placental examinations, however, were not blinded to clinical history. We obtained approval from our university and hospital ethics boards for this study.

Placental Pathology

Abstracted information included specific placental and birth characteristics and neonatal outcomes. Recorded variables from gross placental examination included umbilical cord length, insertion, vessel number, and placental weight, from which the fetoplacental index (birth weight/placental weight²¹) was computed. Pathological features were divided into seven types: (1) ischemic changes such as hemorrhagic endovasculitis (HEV), perivillous fibrin deposition, villous ischemia and hemorrhage, and chorangiomas; (2) villous infarction and decidual necrosis; (3) chronic villitis; (4) abnormal villus maturity (delayed, advanced, variable, and dysmaturity); (5) placental abruption; (6) meconium staining; and (7) others, such as villous edema, intervillous thrombosis, amnion nodosum, and congested villi, after Beebe et al.²² The pathologies were noted as present or absent, and no attempt was made to quantify the extent of the lesions. Pathological definitions were based on the guidelines published by the College of American Pathologists.²³ The data specifically examining chorioamnionitis and neonatal outcomes have been published previously.²⁰

Neonatal Outcomes

Clinical data included birth weight for gestational age, gender, inborn/outborn status, mode of delivery, prenatal care, maternal hypertension, antenatal corticosteroid administration, antibiotic use, multiple births, and 5-minute Apgar score < 7. Neonatal outcomes included mortality, bronchopulmonary dysplasia (BPD), respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH),

Table 2. Pregnancy and delivery characteristics

	Total n = 1296	AGA n = 1050	SGA < 3rd percentile n = 71	<i>P</i> (χ^2 vs. AGA)	SGA < 10th percentile n = 246	<i>P</i> (χ^2 vs. AGA)
Multiple births	319	254 (24%)	18 (25%)	0.88	65 (26%)	0.46
Male sex	576	469 (45%)	37 (52%)	0.18	107 (43%)	0.74
Caesarean births	597	447 (43%)	57 (80%)	< 0.0001	150 (61%)	< 0.0001
Outborn	183	162 (16%)	6 (8.5%)	< 0.0001	21 (8.0%)	< 0.0001
Antenatal corticosteroids	546	462 (49%)*	35 (51%) †	0.79	84 (38%) ‡	0.004
Maternal hypertension	184	119 (11%)	26 (37%)	< 0.0001	65 (26%)	< 0.0001
Mean GA at birth in weeks (SD)		33.2 (4.3)	33.7 (4.0)	0.34	34.6 (3.9)	0.26

AGA: Appropriately grown for gestational age (≥ 10 th percentile); GA: gestational age; SD: standard deviation;
SGA: small for gestational age (as defined).

*Data available for only 941 cases
†Data available for only 69 cases
‡Data available for only 219 cases

necrotizing enterocolitis (NEC), nosocomial infections (NI), retinopathy of prematurity (ROP), patent ductus arteriosus (PDA), and chronic lung disease (CLD).

Indices of neonatal outcome were defined according to the Canadian Neonatal Network Data Abstractor Manual.⁷ Gestational age (GA) was defined as the best obstetric estimate based on early prenatal ultrasound, obstetric examination, and obstetric history; if the postnatal pediatric estimate of gestation differed from the obstetric estimate by more than two weeks, the pediatric estimate was used instead. Infants were classified by their birth weights as appropriate for gestational age (AGA) at ≥ 10 th percentile, small for gestational age (SGA) at < 10 th percentile, and SGA at < 3 rd percentile based on the British Columbia provincial growth charts established by Whitfield.²⁴ Intraventricular hemorrhage was defined according to the criteria of Papile et al.,²⁵ from head ultrasound performed before 14 days of life. Necrotizing enterocolitis was defined according to the criteria of Bell et al.²⁶ (stage 2 or higher) and was classified as medical (clinical symptoms and signs plus evidence of pneumatosis on abdominal radiographs) or surgical (histologic evidence on surgical specimen of intestine). Retinopathy of prematurity was defined according to the International Classification for Retinopathy of Prematurity²⁷ and the Reese Classification of cicatricial disease.²⁸ Nosocomial infection was confirmed using blood and cerebrospinal fluid culture results according to criteria established by Freeman et al.²⁹ Patent ductus arteriosus was confirmed by clinical diagnosis plus treatment with indomethacin or surgical ligation or both. Respiratory

distress syndrome was defined as the presence of respiratory symptoms, such as grunting and chest retraction, typical chest x-ray findings or treatment with surfactant, and the need for mechanical ventilation for more than 24 hours. Chronic lung disease was defined as oxygen dependency at 36 weeks' corrected gestational age for an infant who was born at ≤ 32 weeks' gestation.³⁰

Statistical Analysis

Descriptive statistics were used to examine the data; proportional differences were analyzed using Pearson chi-square and Fisher exact tests, with $P = 0.01$ chosen as the level of significance to account for multiple comparisons. We used Student *t* test to compare placental weights and the fetoplacental index between groups. We used multivariable logistic regression analysis to examine the relationship between placental pathologies and the various neonatal outcome measures (i.e., death, NEC, BPD, NI, CLD, RDS, PDA and grades 3 and 4 IVH). Cross-tabulation was used to identify significant associations between placental factors and infant outcomes. We included the significant factors in a forward selection ($P < 0.1$ for entry) after adjusting for confounding factors such as gender, GA at birth, SGA status, antenatal administration of corticosteroids, multiple births, size for GA, the presence of maternal hypertension, and congenital anomalies. A receiver operating curve (ROC) was computed for each model, and the area under the curve with confidence intervals was reported. Computations were performed with

Table 3. Pathological features in SGA versus AGA placentas

Pathological feature	Total number (%)	AGA n (%)	SGA < 3rd percentile (n (%))	<i>P</i> (χ^2 vs. AGA)	SGA < 10th percentile (n (%))	<i>P</i> (χ^2 vs. AGA)
Ischemic changes						
Hemorrhagic endovasculitis	14 (1)	8 (0.8)	1 (1.4)	0.548	6 (2.4)	0.035
Perivillous fibrin deposition	147 (11)	86 (8.2)	22 (2.8)	0.001	53 (21.5)	0.001
Villous ischemia	70 (5)	41 (3.9)	14 (19.7)	0.001	29 (11.8)	0.001
Villous edema	149 (11)	132 (12.6)	6 (8.5)	0.269	17 (6.9)	0.006
Hemorrhage	89 (7)	66 (6.3)	3 (4.2)	0.264	23 (9.3)	0.066
Placental infarction						
Villous infarcts	153 (12)	93 (8.9)	23 (32.4)	0.001	60 (24.4)	0.001
Decidual necrosis	146 (11)	118 (11.2)	9 (12.7)	0.409	28 (11.4)	0.530
Villitis	132 (10)	87 (8.3)	15 (21.1)	0.004	45 (18.3)	0.001
Maturity						
Delayed	96 (7)	66 (6.3)	7 (9.9)	0.27	30 (12.2)	0.002
Advanced	193 (15)	144 (13.7)	15 (21.1)	0.094	49 (19.9)	0.012
Dysmaturity						
Variable	53 (4)	34 (3.2)	7 (9.9)	0.023	19 (7.7)	0.003
Abruption	69 (5)	60 (5.7)	5 (7.0)	0.327	9 (3.7)	0.120
Meconium	118 (9)	88 (8.3)	10 (14.1)	0.13	30 (12.2)	0.06
Other						
Intervillous thrombosis	132 (10)	99 (9.4)	8 (11.3)	0.441	33 (13.4)	0.048
Chorangiosis	33 (3)	28 (2.7)	0 (0)	0.151	5 (2.0)	0.374
Cord edema	11 (1)	9 (0.9)	1 (1.4)	0.464	2 (0.8)	0.647
Congested villi	121 (9)	98 (9.3)	2 (2.8)	0.029	23 (9.3)	0.544
Fibrinosis	27 (3)	19 (1.8)	4 (5.6)	0.056	8 (3.3)	0.126
Amnion nodosum	8 (1)	5 (0.5)	0 (0)	0.636	3 (1.2)	0.183

AGA: Appropriately grown for gestational age (≥ 10 th percentile); SGA: small for gestational age (as defined).

SPSS v14.0 (Chicago, IL) and SAS v8.1 (Cary, NC) statistical.

RESULTS

A placental pathology report was available for 1296 (64%) of 2012 infants admitted to the NICU during the study period. Infants whose placenta was examined had a higher percentage of inborn status, lower mean GA and birth weight, and higher rates of antenatal corticosteroid administration, maternal hypertension, birth by Caesarean section (CS), and male gender (Table 1). Of those for whom placental pathology was available, 19% were SGA < 10th percentile and 5.5% were SGA < 3rd percentile (Table 2). The SGA and AGA groups differed significantly in the proportion delivered by CS, outborn status, presence of maternal

hypertension on antenatal history, and the administration of corticosteroids antenatally (only the SGA < 10th percentile group differed with respect to corticosteroid administration). Mean GA at birth, proportion of males, and proportion of multiple births was not different between the AGA and the two SGA groups.

There was no statistically significant difference in the average placental weight and fetoplacental index between the AGA and SGA groups. However, a number of pathological features were found significantly more often in SGA infants (Table 3). The following pathological features were associated with the presence of maternal hypertension: advanced maturity ($P < 0.001$), dysmaturity ($P < 0.001$), villous infarcts ($P < 0.001$), and villous ischemia ($P < 0.001$).

Table 4. Factors independently contributing to various neonatal outcomes

Factor	Outcome OR (95% CI)							
	Death	NEC	BPD	NI	CLD	RDS	PDA	IVH
Gender*	NS	2.36 (1.08–5.16)	1.77 (1.16–2.69)	NS	NS	NS	NS	NS
22–28 weeks' GA†	9.55 (4.47–20.43)	16.18 (2.49–105.36)	NS	23.88 (10.45–54.59)	4.07 (2.68–6.16)	52.86 (30.67–91.11)	94.27 (32.47–273.68)	4.61 (1.38–15.37)
29–32 weeks' GA†	NS	NS	NS	5.31 (2.25–12.54)	1.57 (1.09–2.28)	7.48 (5.54–12.34)	6.29 (2.09–18.91)	NS
33–36 weeks' GA†	NS	NS	NS	NS	0.73 (0.55–0.97)	1.82 (1.15–2.87)	NS	NS
Antenatal corticosteroids	0.39 (0.22–0.69)	NS	NS	NS	1.34 (1.02–1.75)	1.42 (1.03–1.96)	NS	0.38 (0.18–0.82)
Multiple births	0.37 (0.18–0.76)	NS	0.55 (0.34–0.87)	NS	NS	NS	NS	NS
Maternal HTN	NS	NS	NS	NS	NS	NS	0.45 (0.25–0.80)	NS
SGA < 10th percentile	NS	4.77 (1.41–16.16)	3.4 (1.64–7.16)	3.06 (1.62–5.81)	NS	NS	NS	NS
Congenital anomalies	2.20 (1.21–4.01)	3.32 (1.30–8.52)	4.57 (2.53–8.28)	1.98 (1.15–3.41)	1.61 (1.17–2.22)	1.60 (1.08–2.38)	NS	NS
Villus edema	1.96 (1.14–3.37)	NS	NS	NS	1.46 (1.04–2.05)	NS	NS	2.18 (1.09–4.38)
Amnion nodosum	21.50 (4.85–95.33)	NS	NS	NS	NS	NS	NS	NS
Decidual inflammation	1.97 (1.10–3.50)	NS	NS	NS	NS	NS	NS	NS
Maternal and (or) fetal inflammation	NS	3.80 (1.67–8.67)	NS	NS	NS	NS	NS	2.23 (1.10–4.53)
Congested villi	NS	5.26 (2.14–12.93)	NS	NS	NS	NS	NS	NS
Delayed maturity	2.22 (1.12–4.39)	NS	NS	NS	NS	NS	NS	NS
Dysmaturity	NS	NS	NS	3.36 (1.72–6.57)	NS	NS	NS	NS
Meconium staining	NS	NS	NS	NS	NS	NS	0.18 (0.05–0.68)	NS
ROC area (95% confidence intervals)	0.80 (0.74–0.86)	0.84 (0.75–0.93)	0.82 (0.78–0.86)	0.87 (0.79–0.86)	0.69 (0.67–0.72)	0.84 (0.81–0.86)	0.90 (0.87–0.92)	0.64 (0.56–0.71)

BPD: bronchopulmonary dysplasia; CLD: chronic lung disease; GA: gestational age; HTN: hypertension; IVH: intraventricular hemorrhage (≥ grade 3); NEC: necrotising enterocolitis; NI: nosocomial infection; NS: Not significant; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome; ROC: receiver operator curve; SGA: small for gestational age.

*Reference gender: female

†Reference GA group: 37–42 weeks

Modelling

In general, the models constructed had good predictive value, with an area under the curve (ROC) of 0.80 or more for most outcomes except IVH grades 3 or 4 and CLD (Table 4). Those factors that contributed independently to each of the adverse neonatal outcomes are shown in Table 4.

DISCUSSION

It is generally accepted that intrauterine events have an important effect on neonatal mortality and the development of long-term morbidity.^{4,31} Therefore, placental examination may represent a means of investigating the intrauterine past to explain the present condition of the neonate. Timely examination of the placenta may even help in guiding therapies or surveillance of infants deemed at increased risk for mortality or significant morbidity.³² The results of this study provide new evidence for the relationship between intrauterine events, reduced fetal growth velocity, and postnatal consequences. Specific patterns of placental pathological findings may be predictive of specific adverse neonatal outcomes.

Placental Pathology and SGA

Our data support a role for placental abnormalities in the development of intrauterine growth restriction (IUGR),^{22,33–37} and suggest the convergence of at least two pathologic developmental pathways leading to IUGR, presumably through placental insufficiency. One of these pathways probably involves placental ischemia and placental infarction, leading to decreased placental perfusion. Changes associated with decreased placental perfusion such as ischemic changes and those related to maternal thromboembolic events have been reported before in association with growth restriction.^{35,36} Many of these changes are also associated with maternal hypertension, and it is likely that hypertensive disorders of pregnancy are associated with this pathway to IUGR.³⁶ Changes of this nature are seen most frequently in fetuses with IUGR who show abnormalities in umbilical artery Doppler measurements.³⁸ Whether villous maturation abnormalities are the result of a decrease in placental perfusion or somehow share in its etiology is not clear, but these abnormalities may be partially explained by the presence of maternal hypertension.

An alternative path to placental insufficiency and IUGR may involve chronic villous inflammation. In general, 5% of cases of villitis can be attributed to intrauterine infection, whereas the great majority are classified as villitis of unknown etiology (VUE).²³ In our population, this pathology was seen most frequently in the placenta of SGA infants, but this feature was not related to the presence of maternal hypertension, suggesting that this represents an independent path to growth restriction. It may therefore be

possible to subclassify and group placental pathologies associated with SGA infants, as shown in Table 5.

Neonatal Outcome and Placental Pathology

SGA was predictive of increased odds of NEC, BPD, and susceptibility to NI. However, our data further support the concept that specific placental pathologies may be markers for adverse neonatal outcomes, independent of growth restriction. Very few studies have attempted to relate placental pathologies to discrete neonatal outcomes.^{39–44}

A recurrent theme in our predictive models is the significant effect of extreme prematurity on neonatal outcomes. This is not surprising, because this factor continues to be one of the stronger predictors of neonatal and long-term mortality and morbidity.⁴⁵ Our finding of an almost 20-fold increase in the odds of dying when amnion nodosum is present is more strongly predictive than extreme prematurity in our population. Amnion nodosum tends to be associated with oligohydramnios arising from various causes²³; oligohydramnios itself can be a presenting feature of placental insufficiency. Whether oligohydramnios was a presenting feature in those infants whose placenta exhibited amnion nodosum is not known for our population. The significant correlation of villous edema with neonatal complications such as death, CLD, and IVH concurs with the findings of Redline et al.,⁴⁴ who found that grade 3 villous edema was associated with long-term neurological impairment in low birth weight neonates (OR 5.7; 95% CI, 1.5–21.0). Villous edema, which has been linked to placental ischemia on the fetal side,⁴⁶ is probably associated with impaired placental function, as emphasized by its correlation with SGA in our population. Finally, placental maturity disorders were associated with both the presence of maternal hypertension and increased odds of neonatal death and of contracting nosocomial infections.

Chorangiosis, which has been associated with hypoxic insults to the placenta and adverse neonatal outcome by others,^{47,48} was not associated with SGA or adverse outcome in our population. However, this pathology was associated with the presence of maternal hypertension. A relationship with adverse neonatal outcome may have been identified if we had attempted to quantify the extent of the lesions.

Limitations of the Study

Because of the retrospective nature of this study, we could not control many of the variables that may have influenced intrauterine development and neonatal outcomes. There were significant differences between the infants whose placenta was sent for pathological examination and those whose placenta was not sent. The former were more likely to have been born in our tertiary referral centre, where

Table 5. Proposed system of subclassification of placental pathologies associated with SGA

Subclassification	Placental findings
Vascular or ischemic pathology	Congested villi Villous hemorrhage (intravillous) Villous infarction (gross & microscopic) Intervillous thrombus Decidual vasculopathy Decidual hemorrhage Abruptio Fetal surface vessel/umbilical vessel thrombosis
Inflammatory pathology	Villitis (principally villitis of unknown etiology)
Villous maturation disorder	Delayed Advanced Dysmaturity Variable Chorioangiomas
Other isolated abnormalities	Isolated membrane abnormality Amnion nodosum Meconium deposition Isolated cord edema Isolated villous edema

expertise in placental pathology is readily available and where, therefore, greater access to the service may translate into closer adherence to published guidelines for pathological examination of placentas.²³ In addition, it appeared that pathological examination of the placenta was more likely to have been performed after the diagnosis of an abnormal pregnancy, as suggested by higher proportions of prematurity, low birth weight, antenatal administration of corticosteroids, maternal hypertension, and Caesarean section in the pregnancies in which the placenta was examined. Therefore, unexpected postpartum complications may have been encountered more often in those infants whose placenta was not examined. However, it is difficult to explain why the placenta was examined in a larger proportion of deliveries resulting in male infants than in females. SGA infants also showed some difference in basic characteristics when compared with their normally grown counterparts. The larger proportion of these infants born in our tertiary centre may reflect the ability to detect IUGR antenatally. Mothers with pregnancies showing IUGR were more likely to be transferred to a tertiary care centre prior to delivery. For the same reason, these infants were also probably more

likely to have received antenatal corticosteroids; we controlled for corticosteroid administration in our predictive modelling of neonatal outcome.

The pathologists who reviewed the placentas were not blinded to clinical histories, and this may have influenced their analyses. In light of our observation that pathologists do not use a standard approach to the reporting of placental findings, we would prefer a standardized approach to reporting that would include comments, in order, on the umbilical cord, fetal membranes, fetal surface vessels, maternal decidual vessels, villous histology, and “other.” Extracting this information would potentially result in a diagnostic conclusion for every report.

No attempt was made on the part of the pathologists to grade the severity of the various pathological features. The strength of association between various pathologies and SGA and neonatal outcomes may have been increased with the addition of quantifiers of severity, as suggested by Ghidini et al.⁴⁹ Our present approach does not routinely comment numerically on villous size, vessel number, or

relative composition of stroma, nor does it comment on the vascular branching pattern.

CONCLUSION

Specific placental pathologies independently predict specific adverse neonatal outcomes. The incidence and severity of these outcomes are susceptible to variations in neonatal intensive care practice. In view of this, examination of frozen sections of the placenta by a skilled on-call anatomic pathologist may help to tailor neonatal therapy for an infant admitted to NICU. This possibility warrants further investigation in an appropriately powered and designed prospective study.

ACKNOWLEDGEMENTS

This work was supported by funding from the Canadian Institutes for Health Research, the Child and Family Research Institute, and the Michael Smith Foundation for Health Research.

REFERENCES

- Baldwin VJ. Morphologic pathology of fetomaternal interaction. *Contrib Gynecol Obstet* 1982;9:1–16.
- Magee JF. Investigation of stillbirth. *Pediatr Dev Pathol* 2001;4:1–22.
- Redline RW, O’Riordan MA. Placental lesions associated with cerebral palsy and neurologic impairment following term birth. *Arch Pathol Lab Med* 2000;124:1785–91.
- Redline RW. Severe fetal placental vascular lesions in term infants with neurologic impairment. *Am J Obstet Gynecol* 2005;192:452–7.
- Chien LY, Macnab Y, Aziz K, Andrews W, McMillan DD, Lee SK. Variations in central venous catheter-related infection risks among Canadian neonatal intensive care units. *Pediatr Infect Dis J* 2002;21:505–11.
- Chien LY, Ohlsson A, Seshia MM, Boulton J, Sankaran K, Lee SK. Variations in antenatal corticosteroid therapy: a persistent problem despite 30 years of evidence. *Obstet Gynecol* 2002;99:401–8.
- Lee SK, McMillan DD, Ohlsson A, Pendray M, Synnes A, Whyte R, et al. Variations in practice and outcomes in the Canadian NICU network: 1996–1997. *Pediatrics* 2000;106:1070–79.
- Shah PS, Shah V, Qiu Z, Ohlsson A, Lee SK. Improved outcomes of outborn preterm infants if admitted to perinatal centers versus freestanding pediatric hospitals. *J Pediatr* 2005;146:626–31.
- Skarsgard ED, Blair GK, Lee SK. Toward evidence-based best practices in neonatal surgical care-I: The Canadian NICU Network. *J Pediatr Surg* 2003;38:672–7.
- Skarsgard ED, Macnab YC, Qiu Z, Little R, Lee SK. SNAP-II predicts mortality among infants with congenital diaphragmatic hernia. *J Perinatol* 2005;25:315–9.
- Synnes AR, Chien LY, Peliowski A, Baboolal R, Lee SK. Variations in intraventricular hemorrhage incidence rates among Canadian neonatal intensive care units. *J Pediatr* 2001;138:525–31.
- Synnes AR, Macnab YC, Qiu Z, Ohlsson A, Gustafson P, Dean CB, et al. Neonatal intensive care unit characteristics affect the incidence of severe intraventricular hemorrhage. *Med Care* 2006;44:754–9.
- Gershenson DM. Clinical management potential tumours of low malignancy. *Best Pract Res Clin Obstet Gynaecol* 2002;16:513–27.
- Gipponi M, Di SC, Peressini A, Solari N, Gliori S, Nicolo G, et al. Sentinel lymph node biopsy in patients with Stage I/II melanoma: clinical experience and literature review. *J Surg Oncol* 2004;85:133–40.
- Ichihara T, Nomoto S, Takeda S, Nagura H, Sakamoto J, Kondo K, et al. Clinical usefulness of the immunostaining of the tumor markers in pancreatic cancer. *Hepatogastroenterology* 2001;48:939–43.
- Lloyd G, Lund VJ, Howard D, Savy L. Optimum imaging for sinonasal malignancy. *J Laryngol Otol* 2000;114:557–62.
- Trifiro G, Viale G, Gentilini O, Travaini LL, Paganelli G. Sentinel node detection in pre-operative axillary staging. *Eur J Nucl Med Mol Imaging* 2004;31 Suppl 1:S46–S55.
- van Diest PJ, Peterse HL, Borgstein PJ, Hoekstra O, Meijer CJ. Pathological investigation of sentinel lymph nodes. *Eur J Nucl Med* 1999;26 Suppl:S43–S49.
- Yachnis AT. Intraoperative consultation for nervous system lesions. *Semin Diagn Pathol* 2002;19:192–206.
- Lau J, Magee F, Qiu Z, Hoube J, von Dadelszen P, Lee SK. Chorioamnionitis with a fetal inflammatory response is associated with higher neonatal mortality, morbidity, and resource use than chorioamnionitis displaying a maternal inflammatory response only. *Am J Obstet Gynecol* 2005;193(Pt 1):708–13.
- Salafia CM, Pezzullo JC, Minior VK, Divon MY. Placental pathology of absent and reversed end-diastolic flow in growth-restricted fetuses. *Obstet Gynecol* 1997;90:830–6.
- Beebe LA, Cowan LD, Altshuler G. The epidemiology of placental features: associations with gestational age and neonatal outcome. *Obstet Gynecol* 1996;87(Pt 1):771–8.
- Langston C, Kaplan C, Macpherson T, Mancini E, Peevy K, Clark B, et al. Practice guideline for examination of the placenta: developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. *Arch Pathol Lab Med* 1997;121:449–76.
- Whitfield M. British Columbia Provincial Growth Chart. Vancouver, BC: British Columbia’s Children’s Hospital;1992.
- Papile LA, Munsick-Bruno G, Schaefer A. Relationship of cerebral intraventricular hemorrhage and early childhood neurologic handicaps. *J Pediatr* 1983;103:273–7.
- Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg* 1978;187:1–7.
- An international classification of retinopathy of prematurity. *Pediatrics* 1984;74:127–33.
- Reese AB, Ling MJ, Owens WC. A classification of retrolental fibroplasias. *Am J Ophthalmol* 1953;33:1333.
- Freeman J, Epstein MF, Smith NE, Platt R, Sidebottom DG, Goldmann DA. Extra hospital stay and antibiotic usage with nosocomial coagulase-negative staphylococcal bacteremia in two neonatal intensive care unit populations. *Am J Dis Child* 1990;144:324–9.
- Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. *Pediatrics* 1988;82:527–32.
- MacLennan A. A template for defining a causal relationship between acute intrapartum events and cerebral palsy: international consensus statement. International Cerebral Palsy Task Force. *Aust N Z J Obstet Gynaecol* 2000;40:13–21.
- Mendilcioglu I, Kilicarslan B, Gurkan ZC, Karaveli S, Uner M, Trak B. Placental biopsy by frozen section: does it have a role in evaluation of fetal well-being? *Aust N Z J Obstet Gynaecol* 2003;43:433–7.
- Rayburn W, Sander C, Compton A. Histologic examination of the placenta in the growth-retarded fetus. *Am J Perinatol* 1989;6:58–61.

34. Redline RW, Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. *Hum Pathol* 1995;26:80–5.
35. Salafia CM, Pezzullo JC, Lopez-Zeno JA, Simmens S, Minior VK, Vintzileos AM. Placental pathologic features of preterm preeclampsia. *Am J Obstet Gynecol* 1995;173:1097–105.
36. Salafia CM, Minior VK, Pezzullo JC, Popek EJ, Rosenkrantz TS, Vintzileos AM. Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features. *Am J Obstet Gynecol* 1995;173:1049–57.
37. Viscardi RM, Sun CC. Placental lesion multiplicity: risk factor for IUGR and neonatal cranial ultrasound abnormalities. *Early Hum Dev* 2001;62:1–10.
38. Madazli R, Somunkiran A, Calay Z, Ilvan S, Aksu MF. Histomorphology of the placenta and the placental bed of growth restricted fetuses and correlation with the Doppler velocimetry of the uterine and umbilical arteries. *Placenta* 2003;24:510–6.
39. De Felice C, Toti P, Laurini RN, Stumpo M, Picciolini E, Todros T, et al. Early neonatal brain injury in histologic chorioamnionitis. *J Pediatr* 2001;138:101–4.
40. Lee J, Croen LA, Backstrand KH, Yoshida CK, Henning LH, Lindan C, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. *JAMA* 2005;293:723–9.
41. Mehta R, Nanjundaswamy S, Shen-Schwarz S, Petrova A. Neonatal morbidity and placental pathology. *Indian J Pediatr* 2006;73:25–8.
42. Ogunyemi D, Murillo M, Jackson U, Hunter N, Alperson B. The relationship between placental histopathology findings and perinatal outcome in preterm infants. *J Matern Fetal Neonatal Med* 2003;13:102–9.
43. Ohyama M, Itani Y, Yamanaka M, Goto A, Kato K, Ijiri R, et al. Maternal, neonatal, and placental features associated with diffuse chorioamnionic hemosiderosis, with special reference to neonatal morbidity and mortality. *Pediatrics* 2004;113:800–5.
44. Redline RW, Wilson-Costello D, Borawski E, Fanaroff AA, Hack M. The relationship between placental and other perinatal risk factors for neurologic impairment in very low birth weight children. *Pediatr Res* 2000;47:721–6.
45. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med* 2005;352:9–19.
46. Naeye RL. Functionally important disorders of the placenta, umbilical cord, and fetal membranes. *Hum Pathol* 1987;18:680–91.
47. Altshuler G, Hyde S. Clinicopathologic considerations of fusobacteria chorioamnionitis. *Acta Obstet Gynecol Scand* 1988;67:513–7.
48. Schwartz DA. Chorangiomas and its precursors: underdiagnosed placental indicators of chronic fetal hypoxia. *Obstet Gynecol Surv* 2001;56:523–5.
49. Ghidini A, Salafia CM, Pezzullo JC. Placental vascular lesions and likelihood of diagnosis of preeclampsia. *Obstet Gynecol* 1997;90(Pt 1):542–5.