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Prenatal events and the risk of subependymal/intraventricular haemorrhage in very low birthweight neonates

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Summary. The effects of prenatal factors on the risk of subependymal and/or intraventricular brain haemorrhage in very low birthweight (VLBW) neonates were studied. Data were collected on 201 consecutively born VLBW neonates without major congenital anomalies, who were born at a regional obstetric referral centre. Brain haemorrhage was identified by cranial ultrasound examinations. The reliability of these examinations (concordance among readers' interpretations) was assessed and found to be moderate (kappa = 0.47 for the finding of subependymal haemorrhage (SEH); kappa = 0.50 for the finding of intraventricular haemorrhage (IVH)). Prenatal factors were more strongly associated with IVH than with SEH. In univariable analyses, maternal pre-eclampsia, multiple gestation and maternal treatment with betamethasone were associated most strongly with a decreased risk of haemorrhage whereas labour and vaginal delivery were associated most strongly with an increased risk. These associations remained in a multivariable analysis which included prenatal events (maternal illnesses, fetal presentation and obstetrical interventions), as well as gestational age, birthweight, gender, treatment with assisted ventilation, and the occurrence of pneumothorax. Further aetiological study of the effects of prenatal factors could provide information useful in preventing SEH/IVH.

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Introduction

Brain haemorrhage occurs in about 25% of very low birthweight (VLBW) neonates.[1] Typically, the bleeding begins in the germinal matrix adjacent to the ependymal lining of the lateral ventricles (subependymal haemorrhage). If large, haemorrhages may extend into the ventricular system (intraventricular haemorrhage). Much of the aetiological research into this problem has emphasised the importance of postnatal events, in particular, severe respiratory distress syndrome (RDS) and its complications (e.g. pneumothorax).[1,2] Recently, the presumed importance of RDS in the pathogenesis of subependymal/intraventricular haemorrhage (SEH/IVH) has been questioned, since the amelioration of RDS by surfactant replacement has not consistently been accompanied by a reduced risk of SEH/IVH.[3]

Since most SEH/IVH occurs in the first 8 hours after delivery,[4,5] it seems likely that information useful in preventing SEH/IVH might be obtained from studying prenatal factors. Several investigators have reported that prenatal factors have little or no effect.[6–10] On the other hand, some studies have indicated that the risk of SEH/IVH is increased with the occurrence or duration of labour,[11–14] and other studies have found that vaginal delivery is associated with an increased risk.[11,15–19] Two groups of investigators have concluded that the risk of SEH/IVH is lowered by abdominal delivery only if the fetus presents breech.[9,20,21] In one study the risk was decreased among neonates born to pre-eclamptic mothers, a group frequently delivered abdominally without labour.[22]

Recently aetiological studies of SEH/IVH have used information from cranial ultrasonography to classify subjects with respect to the presence or absence of SEH/IVH. None of these studies has reported on the reliability of this method of classifying subjects. Our observations,[23] as well as those of Pinto *et al.*,[24] suggests that considerable inter-reader variability is characteristic of interpretations of cranial ultrasonography. This implies that considerable misclassification of subjects occurs when cranial ultrasonography is used to ascertain SEH/IVH. Misclassification of subjects may explain the failure of some studies to identify an effect of prenatal factors on the risk of SEH/IVH.

On the other hand, many studies[12–14,16,18] that identified an effect of vaginal delivery or labour on the risk of SEH/IVH have failed to consider generally recognised confounding factors, such as gestational age. For example, if extremely premature fetuses are less likely to be delivered abdominally, confounding could explain some of the observed association between vaginal delivery and the risk of SEH/IVH. Confounding might also result from associations among prenatal factors. For example, severe pre-eclampsia probably affects both the likelihood of maternal treatment with betamethasone, and the likelihood of abdominal delivery before labour. Thus, valid measurement of the effect of one prenatal factor may require simultaneous consideration of one or more other prenatal factors.

We report here an analysis of the effect of labour, vaginal delivery, and other prenatal events on the risks of SEH/IVH in a cohort of VLBW infants. We have attempted to avoid some of the limitations of prior investigations by: (1) studying the reliability of the interpretation of cranial ultrasonography in our institution (concordance among readers' interpretations); and (2) estimating the independent effects of prenatal factors by adjusting for the effects of confounders.

Methods

Subjects

Subjects were 201 consecutively born neonates who had birthweights between 650 and 1300 g and no major congenital anomalies, and who were born between 1 July 1984 and 30 June 1987, at Duke University Medical Center (DUMC). DUMC is a regional obstetric referral centre which serves primarily seven counties in central North Carolina with mixed urban and rural populations. Approximately two-thirds of VLBW infants born at DUMC are born to mothers residing in the perinatal care region served primarily by DUMC; the other third are born to mothers residing in other perinatal care regions. Referrals from other regions are accepted based on the availability of beds and not based on medical, social or demographic factors.

Ascertainment of subependymal/intraventricular haemorrhage

When estimating the effects of prenatal factors on the risk of SEH/IVH, subjects were classified as having SEH and/or IVH if the diagnosis was made at postmortem examination or if any ultrasound examination done in the first 2 weeks was interpreted as showing SEH or IVH. Fifteen subjects (7.5%) had data missing about the occurrence of ultrasound, and are described below. Five subjects died and underwent postmortem examination and, for these subjects, the presence of SEH and/or IVH was ascertained by reviewing the autopsy findings. For the other 181 subjects, the presence of SEH and/or IVH was ascertained by reviewing radiologists' descriptive summaries and interpretations of all ultrasound examinations performed in the first 2 weeks of life. If any of these examinations were interpreted as showing SEH and/or IVH, then the subject was classified as having the respective outcome.

The median age at which subjects' first sonograms were obtained was 4 days (5th–95th percentile: 2–7 days). Ninety per cent of all subjects with SEH and 80% of all subjects with IVH were identified either on postmortem examination or on their initial ultrasound. One hundred and two subjects (51%) had two cranial

ultrasounds in the first 2 weeks of life. The median age at which the second sonograms were obtained was 10 days (5th–95th percentile: 5–14 days). In seven subjects the initial sonogram was interpreted as normal and the second was interpreted as showing either SEH or IVH. In one subject the initial sonogram was interpreted as showing a SEH and the second sonogram was interpreted as showing an IVH.

Those infants who required assisted ventilation and those who had a pneumothorax were more likely to have undergone a second scan. Of the prenatal risk factors which we studied, only two, chorioamnionitis and multiple gestation, were associated with the likelihood of an infant having had two ultrasounds in the first 2 weeks. The former was associated with an increased, and the latter with a decreased likelihood of a second scan.

Reliability of interpretations of ultrasounds

To estimate the reliability of interpretations of the cranial ultrasounds used in this study, we used a sample of cranial ultrasounds performed on VLBW neonates at Duke University Medical Center between 1 July 1984 and 30 June 1988. For this sample we assessed the concordance between the initial interpretation, made by one of several radiologists, and a second interpretation made by a single radiologist. This sample comprised the first and second ultrasounds made on all infants whose first ultrasound was interpreted as showing IVH and a 25% random sample of infants whose first ultrasound was interpreted as not showing IVH.

Data about the initial interpretations of ultrasound examinations, which were made in the context of clinical care, were obtained from radiologists' narrative summaries included in each neonate's medical record. These summaries were reviewed by a neonatologist who decided whether the initial reader interpreted the sonogram as indicating the presence of SEH and/or IVH. Data about the second interpretations, which were made for the purpose of this study, were collected prospectively, while the sonograms were read by a single radiologist who had not seen the sonograms previously and who was unaware of the initial interpretations. As was the case for the initial readers, the second reader interpreted each infant's first ultrasound examination before viewing that infant's second examination. When the second reader read an infant's second ultrasound examination, she viewed that infant's first two ultrasounds, as would have been done during the initial interpretation of infants' second ultrasound examinations.

As suggested by Cohen,[25] kappa was used to describe the reliability of the interpretations. Kappa is an index of agreement which corrects for chance agreement. Kappa can assume a value between -1 and 1, with 1 indicating perfect agreement, and 0 indicating no more agreement than would be expected by chance alone. When kappa is estimated using a prevalence of positive readings

close to the prevalence of disease in the population used for aetiological studies, the estimate of kappa is, given certain assumptions, correlated highly with the following ratio: (observed odds ratio – 1)/(true odds ratio – 1).[26,27] Confidence limits for kappa were computed as described by Fleiss.[28] Inter-reader agreement was also described using the proportion of positive agreement (an index of agreement about the presence of SEH or IVH) and the proportion of negative agreement (an index of agreement about the absence of SEH or IVH).[28]

Data about risk factors

From each neonate's medical record, the following data were collected: birthweight, gestational age, gender, race, whether treatment with assisted ventilation was used for more than 48 hours, and whether a pneumothorax occurred. Estimates about gestational age were based on the date of last menstrual period, when this was known, unless this estimate disagreed by more than 2 weeks with the estimate based on a prenatal ultrasound or a paediatric examination,[29] in which case the latter estimate was used.

From the medical records of mothers and from delivery logbooks, the following data were collected: estimated date of confinement, route of delivery, fetal presentation, use of forceps, whether the mother was treated with tocolytic agents, betamethasone, magnesium sulphate or antibiotics, the time when labour began, when the membranes ruptured, and when delivery occurred, and whether chorioamnionitis, antepartum placental haemorrhage, multiple gestation or pre-eclampsia was diagnosed by an obstetrician. Chorioamnionitis was defined as the occurrence of either (1) a positive culture of fluid obtained by amniocentesis, or (2) rupture of membranes plus one or more of the following: maternal fever, mother's receipt of antibiotics antepartum, foul smelling amniotic fluid or uterine tenderness.

Data analysis

The effects of dichotomous factors on the risk of SEH and IVH were analysed by comparing the proportion with SEH/IVH among those subjects with the attribute, with the proportion among those without the attribute. Test-based 95% confidence limits (CL) were used to express the precision of risk ratios.[30] To adjust for confounders, we used stratified analysis, as described by Mantel and Haenszel,[30] as well as logistic regression models, with gestational age entered as a continuous variable. For logistic regression, the LOGISTIC program in SAS was used.[31] Linearity of the effect of gestational age on the log odds was assessed as described by Harrell and Lee.[32]

Results

Subjects without data about the occurrence of subependymal/intraventricular haemorrhage

As mentioned above, 15 subjects had no data about the occurrence of SEH/IVH: eight subjects (4%) died before sonography of the brain was performed and did not undergo postmortem examination, and seven neonates (3.5%) were discharged from our hospital without having undergone cranial ultrasonography. Labour and pneumothorax were associated with an increased likelihood of dying without having undergone ultrasonography. Since SEH/IVH was found in all five subjects who died and underwent postmortem examination, the bias resulting from missing data about the occurrence of SEH/IVH most likely resulted in an underestimation of the relative risk estimates for labour and pneumothorax.

Reliability of interpretations of ultrasonograms

Table 1 summarises the reliability of the interpretation of SEH and IVH. For both SEH and IVH, the reliability was in the range which Landis and Koch[33] have referred to as 'moderate'. The reliability of interpretations of first sonograms was nearly identical to that of second sonograms, so only the data for the former are presented. The observed proportion of agreement about the *presence* of SEH was higher than agreement about the presence of IVH; the observed proportion of agreement about the *absence* of SEH was lower than agreement about the absence of IVH.

Effects of prenatal and neonatal factors

Based on autopsy findings and the first readers' interpretations of ultrasound examinations, 72/186 (39%) of subjects had SEH and 34 (18%) had IVH. All cases of

Table 1. Inter-reader agreement for interpretation of first sonograms

					Agreement			
	+/+	−/−	+/−	−/+	Pos	Neg	Kappa (95% CL)	
SEH	43	45	9	23	0.73	0.74	0.47	(0.32, 0.63)
IVH	15	85	14	6	0.60	0.89	0.50	(0.31, 0.69)

Symbol to left of slash indicates reading by first reader; symbol to right of slash indicates reading by second reader: for example, −/+ indicates ultrasounds read as negative by the first reader and positive by the second reader.
SEH = subependymal haemorrhage; IVH = intraventricular haemorrhage; CL = confidence limits for kappa; Pos = proportion of specific agreement positive; Neg = proportion of specific agreement negative.

IVH also had SEH. With one exception, risk factors were associated more strongly with the occurrence of IVH than SEH. However, for all factors the direction of association was the same for SEH and IVH. For 23 subjects, IVH was diagnosed by postmortem examination or was diagnosed by an ultrasound examination about which both readers agreed. An analysis in which only these 23 subjects were classified as having IVH gave point estimates of relative risk very similar to those obtained when subjects were classified by the first reader's interpretation; thus, in the analyses summarised below, IVH was defined as IVH ascertained at autopsy or diagnosed by the first readers' interpretations of ultrasound examination(s) performed in the first 2 weeks of life.

Among the prenatal factors which we studied, labour and vaginal delivery were associated most strongly with an increased risk of SEH/IVH. Multiple gestation, pre-eclampsia, mother's receipt of tocolytic drugs and mother's receipt of betamethasone were associated most strongly with a decreased risk of SEH/IVH. Among the neonatal attributes and postnatal events considered, use of assisted ventilation and the occurrence of pneumothorax were associated most strongly with an increased risk of SEH/IVH. Increasing birthweight and gestational age were associated with a decreased risk of SEH/IVH. In general, when

Table 2. Prenatal events and the risk of IVH

Factor (prevalence)	Relative risk estimates and 95% confidence limits		
	Unadjusted	Adjusted for GA[a]	Multivariable adjusted[b]
Pre-eclampsia (0.27)	0.4 (0.1,0.9)	0.4 (0.1,1.2)	0.1 (0,4.1)
Chorioamnionitis (0.29)	1.3 (0.7,2.5)	1.2 (0.6,2.3)	1.5 (0.5,4.2)
Prepartum bleeding (0.19)	1.1 (0.5,2.3)	0.8 (0.3,1.7)	1.1 (0.4,3.4)
Multiple gestation (0.15)	0.4 (0.1,1.2)	0.7 (0.2,2.4)	0.6 (0.1,4.2)
Non-vertex (0.25)	0.9 (0.5,1.8)	1.0 (0.4,1.9)	1.4 (0.5,4.0)
Betamethasone (0.41)	0.5 (0.2,0.9)	0.5 (0.3,1.0)	0.4 (0.1,1.2)
Magnesium sulphate (0.19)	0.7 (0.3,1.7)	0.8 (0.3,2.0)	13.9 (0.5,414)[c]
Tocolytic drug (0.18)	0.6 (0.2,1.6)	0.5 (0.2,1.4)	0.6 (0.1,2.3)
Labour (0.61)	3.7 (1.6,8.2)	3.8 (1.6,9.2)	2.2 (0.5,9.4)
Vaginal delivery (0.40)	2.2 (1.2,4.0)	2.0 (1.1,3.8)	2.4 (0.7,8.6)
Forceps (0.15)	1.5 (0.7,3.2)	1.7 (0.6,4.5)	1.2 (0.3,4.1)

[a] Adjusted for gestational age by logistic regression; gestational age entered as continuous variable.

[b] Adjusted for gestational age, birthweight, gender, occurrence of pneumothorax, treatment with assisted ventilation, and all other prenatal factors.

[c] Only two mothers treated with magnesium sulphate did not have pre-eclampsia, and the infants of both of these mothers had IVH. Thus, the estimate for the effect of magnesium sulphate, adjusting for pre-eclampsia, is very high but is quite unreliable, being based on only two cases.

controlling for gestational age only and when controlling for multiple factors (prenatal events listed in Table 2, as well as birthweight, gestational age, gender, treatment with assisted ventilation and the occurrence of pneumothorax), most estimates of relative risk for prenatal factors were changed only slightly (Table 2). In a multivariable analysis which included all of the aforementioned factors except assisted ventilation and pneumothorax – both of which, plausibly, could be involved in a causal pathway between prenatal events and SEH/IVH – the estimate of relative risk for vaginal delivery was reduced to 1.3 (not shown).

As shown in Table 3, neonates delivered abdominally before the onset of labour were at lowest risk. Among infants whose mothers had labour, there did not appear to be a monotonic increase in risk with increasing length of labour, although neonates delivered after more than 10 hours of labour were at increased risk relative to those delivered after 10 or fewer hours of labour [RR = 2.2; 95% CL (0.7, 6.3)]. Excluding infants delivered without labour and adjusting for the duration of labour, vaginal delivery had little effect on the risk of IVH (RR = 1.3; 95% CL = 0.7, 2.7).

Discussion

Several findings in this study are relevant to future aetiological studies of SEH/IVH in VLBW neonates. First, when cranial ultrasound is used to diagnose SEH/IVH, errors may be common. If the likelihood of diagnostic errors is independent of prenatal events, misclassification will result in the attenuation of associations between prenatal events and the risk of SEH/IVH.[30,34] Attenuation of associations due to misclassification is particularly pertinent when studying factors with modest effects. The study by Pinto *et al.*[24] and, to a lesser degree, the

Table 3. Length of labour, route of delivery and risk of IVH: relative risks were computed with the subjects delivered without labour as the referent group

	Length of labour in hours			
	None	<4	4–10	>10
Vaginal delivery				
No. with IVH/at risk (%)		8/17 (47%)	7/41 (17%)	5/14 (36%)
Relative risk		6.8	2.5	5.1
(95% CL)		(2.8,16.6)	(0.9,7.1)	(1.8,14.7)
Abdominal delivery				
No. with IVH/at risk (%)	5/72 (7%)	1/5 (20%)	2/20 (10%)	6/15 (40%)
Relative risk		2.9	1.4	5.8
(95% CL)		(0.4,20.9)	(0.3,7.0)	(2.2,15.4)

study reported here, suggest that misclassification may occur more frequently when diagnosing SEH, as compared with IVH. Greater misclassification of subjects with respect to SEH could explain our observation that prenatal events had stronger effects on IVH. It seems likely that further study of the reliability of cranial ultrasound examinations will provide information useful for researchers studying SEH/IVH.

Despite our having only moderately reliable ultrasound interpretations, we observed that abdominal delivery without labour was associated with a marked decrease in the risk of SEH and IVH. In addition, infants of mothers with pre-eclampsia, who frequently are delivered abdominally before the onset of labour, were at greatly decreased risk. These associations remained after controlling for confounders including gestational age, gender, maternal illness and maternal medications. These findings are in agreement with recently reported results from a large prospective study by Leviton and his associates.[19,22]

A limitation of our study is the lack of information about the occurrence prenatally of SEH/IVH. It is possible that in some cases IVH may have preceded the onset of labour and, in fact, in some cases, IVH could have initiated labour. If so, at least some of the presumed effect of labour on the risk of IVH would in fact be an effect of prenatal IVH on the risk of preterm labour. Another limitation is that our ascertainment of the onset of labour (and thus the duration of labour) was sufficiently imprecise to attenuate any association between the duration of labour and the risk of SEH/IVH.

If, as we and others have observed, labour is associated with an increased risk of SEH/IVH, it is reasonable to question whether abdominal delivery could be used to reduce the incidence of SEH/IVH. The answer to this question would seem to depend, in part, on whether the duration (as opposed to the occurrence) of labour is associated causally with SEH/IVH. If the risk of SEH/IVH increases monotonically with the duration of labour, truncation of labour by abdominal delivery would be expected to result in a decreased risk of SEH/IVH. In three studies in which abdominal delivery was associated with a decreased risk of SEH/IVH, the duration of labour was shorter among subjects delivered abdominally.[12,17,19] Conversely, in the cohort we studied, the duration of labour was not shorter among subjects delivered abdominally and the length of labour was not associated with the risk of IVH. It should be emphasised that even if the duration of labour is associated monotonically with the risk of SEH/IVH, abdominal delivery of VLBW fetuses might not be beneficial, since labour might have salutary effects on lung compliance, thereby lowering the risk of ventilator-induced lung injury. In short, decisions about the clinical care of VLBW fetuses should involve consideration of all relevant clinical end points, and not just SEH/IVH.

In summary, our findings imply that errors in diagnosing SEH/IVH should be considered as a likely source of bias which possibly can account for the failure of some studies to detect an association between labour (and possibly vaginal

delivery) and the risk of SEH/IVH. Another implication of our study is that estimation of the effect of prenatal factors may often be confounded by labour. Finally, there is a need for further study not just of the occurrence of labour, but also of the *duration* of labour, since the clinical utility of truncating labour (by abdominal delivery) depends on there being a monotonic relationship between the length of labour and the risk of SEH/IVH.

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