Incidence of and Risk Factors for Neonatal Respiratory Depression and Encephalopathy in Rural Sarlahi, Nepal

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KEY WORDS

neonatal encephalopathy, neonatal respiratory depression, birth asphyxia, Nepal, developing country, neurodevelopment, intrapartum

ABBREVIATIONS

NRD—neonatal respiratory depression

NE—neonatal encephalopathy

IPR—intrapartum-related

RR—relative risk

CI—confidence interval

This trial has been registered at www.clinicaltrials.gov (identifier NCT00109616).

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WHAT'S KNOWN ON THIS SUBJECT: Intrapartum-related (IPR) hypoxic events ("birth asphyxia") result in an estimated 2 million fetal/neonatal deaths and 1 million impaired survivors each year, primarily in low- and middle-income countries. Limited data on the incidence, risk factors, and morbidity associated with IPR events are available from these settings.

WHAT THIS STUDY ADDS: In Sarlahi, 20% of newborns experienced respiratory depression at birth; the incidence of neonatal encephalopathy was 28 to 33 cases per 1000 live births. The case fatality rate for IPR neonatal encephalopathy was 46%. Long-term implications for survivors are poorly understood.

abstract

FREE

OBJECTIVES: To characterize the incidence of, risk factors for, and neonatal morbidity and mortality associated with respiratory depression at birth and neonatal encephalopathy (NE) among term infants in a developing country.

METHODS: Data were collected prospectively in 2002–2006 during a community-based trial that enrolled 23 662 newborns in rural Nepal and evaluated the impact of umbilical-cord and skin cleansing on neonatal morbidity and mortality rates. Respiratory depression at birth and NE were defined on the basis of symptoms from maternal reports and study-worker observations during home visits.

RESULTS: Respiratory depression at birth was reported for 19.7% of live births, and 79% of cases involved term infants without congenital anomalies. Among newborns with probable intrapartum-related respiratory depression ($N = 3465$), 112 (3%) died before their first home visit (presumed severe NE), and 178 (5%) eventually developed symptoms of NE. Overall, 629 term infants developed NE (28.1 cases per 1000 live births); 2% of cases were associated with congenital anomalies, 25% with infections, and 28% with a potential intrapartum event. The incidence of intrapartum-related NE was 13.0 cases per 1000 live births; the neonatal case fatality rate was 46%. Infants with NE more frequently experienced birth complications and were male, of multiple gestation, or born to nulliparous mothers.

CONCLUSIONS: In Sarlahi, the incidence of neonatal respiratory depression and NE, associated neonatal case fatality, and morbidity prevalence are high. Action is required to increase coverage of skilled obstetric/neonatal care in this setting and to evaluate long-term impairments. *Pediatrics* 2011;128:e915–e924

Intrapartum-related (IPR) hypoxic injury, or “birth asphyxia,” results in 2 million neonatal deaths and stillbirths¹ and an estimated 1 million disabled survivors² each year. Estimates of the burden of IPR morbidity and long-term impairment are imprecise. Data are scarce from low-income regions, particularly community settings, where the majority of births are unattended and morbidity and impairment are not commonly measured. The inconsistency in definitions related to birth asphyxia^{1,3} also contributes to the data gap. Infants with neonatal respiratory depression (NRD) require resuscitation; however, this clinical condition may reflect multiple causes, including intrapartum hypoxia, prematurity, congenital anomalies, infections, maternal analgesia, and neurologic disorders. Furthermore, NRD, which often is characterized by low Apgar scores, poorly predicts long-term outcomes or impairment.^{4,5} Intrapartum hypoxia that is sufficient to result in long-term disability progresses through neonatal encephalopathy (NE), which is defined as a “disturbance of neurological function in the earliest days of life in the term infant manifested by difficulty initiating and maintaining respiration, depression of tone or reflexes, abnormal level of consciousness and often by seizures.”⁶ Moderate or severe NE is predictive of long-term impairment^{7,8}; therefore, NE has emerged as an epidemiological marker of the burden of morbidity related to intrapartum hypoxic events.^{1,9}

Because the burden of neonatal death and morbidity related to birth asphyxia is concentrated in developing countries with weak health care systems,¹ it is critical to quantify both the need for neonatal resuscitation and the burden of IPR impairment in such settings. This article aims to describe the incidence rates of NRD and NE, associated case fatality rates, neonatal

morbidity rates, and risk factors for a rural, community-based, birth cohort in Sarlahi, Nepal.

METHODS

The Nepal Newborn Washing Study was conducted in 2002–2006; details of the methods and procedures were reported previously.^{10,11} The original design included 2 nested, cluster-randomized, community-based trials evaluating the impact of newborn skin and umbilical-cord cleansing with chlorhexidine on neonatal morbidity and mortality rates. Nepal is a low-income country with a gross national income per capita of \$400 in 2008.¹² Sarlahi District, in south-central Nepal, is a rural agrarian community with poor transportation and road infrastructure; three-fourths of inhabitants live below the Nepalese poverty line.^{13,14} Less than 10% of births occur in a hospital that has the capacity for basic emergency obstetric care, and <20% of home births are attended by a skilled birth attendant.

Households were visited as soon as possible after birth, to determine the vital status of the mother and newborn and to deliver the skin washing intervention (median time: 6 hours). The first visit by a study coordinator was conducted shortly after birth (median time: 12 hours), to interview mothers about labor and delivery and the condition and care of the newborn and to apply the assigned cord care intervention. Additional home visits were conducted on days 2, 3, 4, 6, 8, 10, 12, 14, 21, and 28. During each visit, study workers conducted a basic newborn examination, including assessment of temperature, respiratory rate, and skin/umbilical-cord infection, and the mother was queried about symptoms of neonatal morbidity. The study worker facilitated referral and treatment at the local health post for all sick mothers and newborns.

This study was a secondary analysis of data collected during the chlorhexidine cleansing trials. Computer algorithms were generated to classify newborns with NRD and NE, on the basis of symptoms reported by mothers and observed by study workers. NRD was defined as a newborn failing to cry at the time of birth, experiencing delayed onset of breathing (>1 minute), or requiring assistance to initiate breathing (ranging from drying, stimulation, and milking of the umbilical cord to mouth-to-mouth breaths). Probable IPR NRD was defined as NRD among term infants without congenital malformations. Cases were not excluded from classification as IPR if the criteria for infection were met, because clinical observations for infection were made after childbirth, during the first home visit, and we desired to characterize the potential interaction between neonatal infections and intrapartum hypoxia in the development of NE.^{15–17} We further ascertained the subset of cases of probable IPR NRD that progressed to NE. NE was defined on the basis of neurologic abnormalities observed in the first 7 days of life (seizures or 2 of the following: lethargy, poor suck, or respiratory depression, defined as a respiratory rate of <40 breaths per minute, as measured by the study worker).¹⁸ Although there were limited data to ascertain NE grade, the observation of seizures was used to differentiate moderate or severe from mild NE.^{6,19,20} Prematurity was defined as a gestational age of <37 weeks according to the date of the last menstrual period (late preterm: 34 to <37 weeks; early preterm: <34 weeks). A congenital anomaly was classified as any major external malformation observed by the study worker; minor normal malformations such as caput succedaneum, molding, or internal tibial torsion were excluded. Neonatal infection was defined on the basis of (1) a temperature of

TABLE 1 Maternal Reports of Symptoms of NRD in Sarlahi Birth Cohort (*N* = 23 662)

Symptom	<i>n</i> (%)
Time to start breathing ^a	
After 1 min	3548 (16.1)
After 5 min	1313 (5.9)
Did not cry after birth ^b	2257 (10.2)
Received help to start breathing ^c	2303 (10.5)
Did not move limbs after birth ^d	1588 (7.3)
Blue, gray, or pale color ^e	702 (3.3)

^a Missing 1584 values.^b Missing 1522 values.^c Missing 1638 values.^d Missing 1848 values.^e Missing 2195 values.

$\geq 100.4^{\circ}\text{C}$ or $\leq 95.9^{\circ}\text{C}$, (2) significant periumbilical erythema and pus, or (3) either chest indrawing or a respiratory rate of >70 breaths per minute, in addition to a temperature of $\geq 100.4^{\circ}\text{C}$. For calculation of the risks of NRD and NE, the control group for the NRD comparison included infants without NRD (ie, breathing infants who did not require resuscitative measures) and the control group for the NE comparison included infants who did not meet case criteria for NE in the first week of life. For all infants who died during the study, a verbal autopsy was conducted by trained supervisory workers in Nepali, by using local terminology. The verbal autopsy was based on the World Health Organization standard verbal autopsy form with minor modifications.^{21,22}

Simple descriptive statistics were used to characterize cases of NRD and NE. Because of the prospective cohort design, the relative risk (RR) of case status was calculated by using logarithmic binomial regression, with adjustment of the SEs for mothers contributing >1 child to the cohort. Stata 9.0 (Stata Corp, College Station, TX) was used to conduct all analyses. The main study was approved by the Nepal Health Research Council (Kathmandu, Nepal) and the Johns Hopkins University Bloomberg School of Public Health Committee on Human Research (Baltimore, MD).

FIGURE 1

Causes of NRD. All infants shaded in blue were classified as having probable IPR NRD (*n* = 3465).

RESULTS

During the study period, there were 23 662 live births. The vast majority (91%) occurred at home, and $<20\%$ of home births were attended by a skilled attendant. None of the births was observed directly by study workers; however, 80% of newborns were visited within 48 hours of life, and 95% were visited at least once in the first week. The overall neonatal mortality rate was 32 deaths per 1000 live births.

Neonatal Respiratory Depression

Approximately 16.1% and 5.9% of all infants did not start breathing within 1 and 5 minutes of life, respectively (Table 1). Failure to cry immediately after birth was reported for 10.2% of infants, and 7.3% did not move their limbs. Blue, gray, or pale color at birth were reported for 3.3%.

A total of 4364 infants (19.7% [95% confidence interval [CI]: 19.1%–20.2%]) were born with NRD, of whom 805 (18.4%) were preterm and 118 (2.7%) had a major congenital malformation

(24 with comorbidity) (Fig 1). Therefore, 3465 term infants without congenital anomalies (15.6% of live births [95% CI: 15.1%–16.1% of live births]) had NRD potentially related to intrapartum events. Of the 2786 infants with NRD who were visited on the first day of life, 536 (19.2%) had symptoms of a possible neonatal infection, of whom 112 (20.9%) were preterm. Those infants were not excluded from the IPR cohort, however, because the symptoms were not observed until after birth. If those cases of NRD were attributed to infection, then the number of cases of IPR NRD would decrease to 3054 (13.7% of live births [95% CI: 13.3%–14.2% of live births]).

Table 2 shows risk factors for NRD stratified according to gestational age categories, compared with breathing infants. Significant risk factors for term and preterm NRD included male gender, birth to a nulliparous mother, and maternal pregnancy or labor complications, such as preeclampsia/eclampsia (swelling of the face, hands, or

TABLE 2 Risk Factors, Neonatal Death, and Morbidity Among Infants With NRD

Characteristic	Infants With NRD ^a			Infants Breathing at Birth (<i>n</i> = 17821)
	≥37 wk (<i>n</i> = 3465)	34–36 wk (<i>n</i> = 664)	<34 wk (<i>n</i> = 117)	
Male				
<i>n</i> (%)	1922 (55)	362 (55)	61 (52)	8999 (51)
RR (95% CI)	1.18 (1.11–1.26)	1.17 (1.01–1.36)	1.06 (0.73–1.55)	Reference
Madeshi ethnicity (reference: Pahadi) ^b				
<i>n</i> (%)	2251 (66)	557 (86)	96 (83)	12642 (72)
RR (95% CI)	0.80 (0.75–0.85)	2.37 (1.89–2.96)	1.85 (1.14–3.01)	Reference
Maternal nulliparity ^c				
<i>n</i> (%)	1249 (36)	256 (39)	45 (38)	3898 (22)
RR (95% CI)	1.77 (1.66–1.88)	2.17 (1.86–2.52)	2.22 (1.50–3.28)	Reference
Multiple pregnancy				
<i>n</i> (%)	62 (2)	15 (2)	17 (15)	241 (1)
RR (95% CI)	1.26 (0.99–1.60)	1.64 (0.90–3.01)	11.65 (6.12–22.17)	Reference
Pregnancy/labor complications				
Maternal fever during delivery ^d				
<i>n</i> (%)	125 (4)	45 (7)	20 (17)	572 (3)
RR (95% CI)	1.11 (0.94–1.30)	2.11 (1.57–2.82)	6.10 (3.64–10.21)	Reference
Maternal swelling of face and hands ^e				
<i>n</i> (%)	770 (22)	143 (21)	20 (17)	3012 (17)
RR (95% CI)	1.32 (1.23–1.42)	1.33 (1.11–1.60)	1.02 (0.61–1.73)	Reference
Vaginal bleeding during delivery ^f				
<i>n</i> (%)	161 (5)	25 (4)	16 (14)	634 (4)
RR (95% CI)	1.25 (1.09–1.45)	0.98 (0.66–1.45)	4.25 (2.51–7.20)	Reference
Prolonged labor ^g				
<i>n</i> (%)	1211 (35)	188 (29)	36 (31)	4584 (26)
RR (95% CI)	1.44 (1.35–1.53)	1.14 (0.96–1.35)	1.28 (0.85–1.92)	Reference
Prolonged rupture of membranes ^h				
<i>n</i> (%)	347 (10)	53 (8)	17 (15)	1087 (6)
RR (95% CI)	1.55 (1.41–1.71)	1.19 (0.90–1.57)	2.36 (1.37–4.06)	Reference
Maternal fever measured at first postpartum visit ⁱ				
<i>n</i> (%)	73 (2)	19 (3)	5 (4)	262 (2)
RR (95% CI)	1.34 (1.10–1.65)	1.91 (1.23–2.96)	2.98 (1.06–8.41)	
Neonatal death in first 28 d				
<i>n</i> (%)	182 (5)	64 (10)	68 (58)	350 (2)
RR (95% CI)	2.16 (1.91–2.45)	4.66 (3.67–5.91)	58.17 (40.32–83.92)	Reference
Newborn morbidity symptoms in first week of life ^j				
Poor feeding				
<i>n</i> (%)	407 (13)	82 (13)	26 (26)	1219 (7)
RR (95% CI)	1.65 (1.51–1.81)	1.94 (1.54–2.43)	7.26 (4.43–11.88)	Reference
Seizure				
<i>n</i> (%)	152 (5)	28 (5)	6 (7)	427 (2)
RR (95% CI)	1.67 (1.44–1.92)	1.79 (1.24–2.58)	2.92 (1.28–6.67)	Reference
Difficulty maintaining respiration				
<i>n</i> (%)	129 (4)	27 (4)	4 (4)	316 (2)
RR (95% CI)	1.83 (1.59–2.14)	2.30 (1.60–3.37)	2.47 (0.91–6.70)	Reference
Lethargy or unconsciousness				
<i>n</i> (%)	7 (0.2)	1 (0.2)	2 (3)	28 (0.2)
RR (95% CI)	1.26 (0.65–2.45)	1.01 (0.15–6.92)	18.81 (4.92–71.86)	Reference
Newborn morbidity symptoms later in first month of life				
Poor feeding				
<i>n</i> (%)	589 (17)	117 (18)	29 (38)	2267 (13)
RR (95% CI)	1.36 (1.25–1.47)	1.52 (1.25–1.85)	4.08 (2.55–6.55)	Reference
Seizure				
<i>n</i> (%)	214 (6)	39 (6)	5 (8)	795 (4)
RR (95% CI)	1.34 (1.19–1.52)	1.36 (0.98–1.88)	1.18 (0.48–2.92)	Reference
Difficulty maintaining respiration				
<i>n</i> (%)	214 (6)	39 (6)	5 (5)	871 (5)
RR (95% CI)	1.34 (1.18–1.51)	1.34 (0.97–1.86)	1.17 (0.48–2.89)	Reference
Lethargy or unconsciousness				
<i>n</i> (%)	12 (0.4)	3 (0.5)	2 (3)	61 (0.3)
RR (95% CI)	1.04 (0.62–1.74)	1.38 (0.46–4.17)	8.66 (2.21–33.89)	Reference

^a Excluding infants with major congenital malformations.^b Missing 389 values.^c Missing 3 values.^d Missing 1301 values; maternal self-report for 7 days before delivery.^e Missing 1295 values.^f Missing 1322 values.^g Missing 1373 values.^h Missing 1521 values.ⁱ Missing 1490 values. The first postpartum visit was conducted as soon as possible after delivery (median: 12 hours), and temperature was measured by a health care worker.^j A total of 95% of infants were visited at least once in the first week of life.

feet), vaginal bleeding, prolonged labor (nulliparous: >24 hours; multiparous: >12 hours), prolonged rupture of membranes (>24 hours), or measured postpartum maternal fever. Among preterm infants, multiple pregnancy and maternal self-report of fever before delivery were significant risk factors for NRD. Infants of Madeshi ethnicity (originating from the plains) were at greater risk than those of Pahadi ethnicity (originating from the hills), which likely is associated with maternal malnutrition and a higher prevalence of growth stunting. Infants with NRD were at increased risk of neonatal death, rates of which were substantially higher for both late and early preterm infants (Table 2). The primary chlorhexidine interventions resulted in lower neonatal mortality rates for the umbilical cleansing group¹⁰ and for the group of low birth weight infants who underwent whole-body washing¹¹; however chlorhexidine treatment did not modify significantly the mortality risk among infants with NRD. Neonatal morbidity symptoms (eg, poor feeding, seizures, or difficulty maintaining respiration), particularly in the first week of life, were more prevalent among infants with NRD, compared with breathing infants, and were even more prevalent among preterm infants with NRD (Table 2).

IPR NRD

Of the term infants with NRD associated with probable intrapartum injury ($N = 3465$), 182 (5.3%) died during the neonatal period (Fig 2). The majority of these early neonatal deaths occurred before the first home visit ($n = 112$). The median time of death was 12 hours; the vast majority of infants (75.3%) died within the first 48 hours of life, and almost all deaths (90.7%) occurred within the first 7 days. Figure 3 shows the frequency and timing of specific morbidity symptoms for in-

FIGURE 2

Timing of death for infants with IPR NRD ($n = 182$).

FIGURE 3

Morbidity symptoms among infants with IPR NRD ($n = 3465$).

fants with IPR NRD during the first month of life. Symptoms were concentrated in the first week. Approximately 17.5% of infants had poor feeding during any 1 follow-up home visit in the first month of life, whereas 6.3% had seizures, 6.3% had observed respiratory rates of <40 breaths per minute, and 0.4% had reported “unconsciousness.” NE (which required symptom

onset in the first week of life) was diagnosed for 178 infants (5.1%) with NRD of probable intrapartum cause.

Neonatal Encephalopathy

In the entire birth cohort, there were 629 term infants who met the case definition for NE, and 537 cases (85.4%) were graded as moderate or severe on the basis of reports of seizures on ≥ 1

FIGURE 4
Causes of NE.

day in the first week of life. The remaining 92 cases (14.6%) were graded as mild and met the criteria for NE on the basis of the combination of 2 symptoms (unconsciousness, poor suck, or respiratory depression).

Incidence and Case Fatality Rates for NE

The incidence of observed NE was 28.2 cases per 1000 live births (95% CI: 26.0–30.4 cases per 1000 live births). However, more than one-half of the deaths involving infants with IPR NRD occurred before the first home visit. With the assumption that neonatal deaths of unvisited newborns with IPR NRD ($n = 112$) represented cases of severe NE, the upper bound of NE incidence might be as high as 33.1 cases per 1000 live births (95% CI: 31.1–35.1 cases per 1000 live births) and the incidence of NE associated with intrapartum events 13.0 cases per 1000 live births (95% CI: 11.5–14.5 cases per 1000 live births). Almost one-half of infants with NE associated with IPR NRD died during the neonatal period (134 of 290 patients [neonatal case fatality

rate: 46.2%]). Chlorhexidine interventions did not modify significantly the mortality risk among infants with NE.

Causes of NE

A total of 178 infants with NE (28.3% [95% CI: 24.8%–31.8%]) had a history of probable IPR NRD. Twelve infants (1.9%) had serious congenital malformations associated with NE symptoms. Symptoms of possible neonatal infection preceded the development of NE symptoms for 156 infants (24.8%); 43 of those infants also had a history of probable IPR NRD (Fig 4).

Characteristics of NE Cases

Table 3 shows characteristics of infants with NE and presumed fatal cases of NE, compared with infants without NE. Infants with NE associated with IPR NRD were more frequently male, of Madhesi ethnicity, of a multiple gestation, and born to a mother who was nulliparous or experienced complications during labor, including symptoms of preeclampsia/eclampsia, prolonged labor, or prolonged rupture of membranes.

For infants with NE not associated with IPR NRD, factors that were significantly associated with case status included Pahadi ethnicity, maternal nulliparity, maternal symptoms of preeclampsia/eclampsia, prolonged labor, and prolonged rupture of membranes. A larger proportion of case subjects reported fever in the 7 days before delivery, although the difference was not statistically significant. The timing of neonatal morbidity symptoms for infants with NE is shown in Fig 5.

DISCUSSION

The term birth asphyxia is imprecise, nonspecific, and no longer recommended.^{1,23,24} In this community-based cohort with high rates of home delivery, 16% of live-born infants had IPR NRD. The incidence of NE was estimated to be between 28 and 33 cases per 1000 live births, and approximately one-third of cases were associated with a potential intrapartum hypoxic event. The case fatality rate for NE associated with IPR NRD was high; almost one-half of those infants died in the neonatal period.

NRD at birth may be attributable to multiple causes, ranging from intrapartum hypoxic insult to prematurity, maternal analgesia, neonatal sepsis, metabolic disease, or cardiac, pulmonary, or central nervous system malformations.²⁵ Our definition of NRD was broad and aimed to indicate the need for any neonatal resuscitation at birth (ranging from simple drying/stimulation to positive pressure ventilation), regardless of cause, in a setting in which infants typically receive no care. In Sarlahi, 19.7% of live births exhibited NRD, which indicates a substantial need for improved access to obstetric care and newborn resuscitation. Approximately 18% of NRD cases were attributed to prematurity, 3% to major congenital anomalies, and 12% to possible infection. Maternal analgesia is

TABLE 3 Characteristics of Infants With NE

Characteristic	IPR NE (<i>n</i> = 178)	Presumed Fatal IPR NE (<i>n</i> = 112)	NE Without IPR NRD (<i>n</i> = 451)	Non-NE Control (<i>n</i> = 22 268)
Male				
<i>n</i> (%)	109 (61)	62 (55)	236 (52)	11066 (51)
RR (95% CI)	1.50 (1.11–2.03)	1.18 (0.81–1.71)	1.04 (0.87–1.26)	Reference
Madeshi ethnicity (reference: Pahadi) ^a				
<i>n</i> (%)	103 (59)	81 (77)	206 (46)	15325 (72)
RR (95% CI)	0.57 (0.42–0.76)	1.31 (0.83–2.06)	0.34 (0.28–0.41)	Reference
Birth weight, mean $\pm$ SD, kg ^b	2.73 $\pm$ 0.46	NA ^c	2.70 $\pm$ 0.43	2.69 $\pm$ 0.46
Maternal nulliparity ^d				
<i>n</i> (%)	98 (55)	41 (37)	147 (33)	5274 (24)
RR (95% CI)	3.74 (2.79–5.02)	1.78 (1.22–2.61)	1.48 (1.22–1.80)	Reference
Multiple pregnancy				
<i>n</i> (%)	6 (3)	4 (3)	12 (3)	306 (1)
RR (95% CI)	2.40 (1.07–5.38)	2.56 (0.95–6.88)	1.87 (1.02–3.42)	Reference
Labor complications				
Maternal fever during delivery ^e				
<i>n</i> (%)	6 (3)	2 (2)	22 (5)	694 (3)
RR (95% CI)	1.01 (0.45–2.28)	0.53 (0.13–2.13)	1.51 (0.99–2.30)	Reference
Vaginal bleeding during delivery ^f				
<i>n</i> (%)	8 (5)	14 (3)	7 (6)	773 (4)
RR (95% CI)	1.22 (0.60–2.47)	1.71 (0.80–3.68)	0.86 (0.50–1.45)	Reference
Maternal swelling of face and hands ^g				
<i>n</i> (%)	43 (24)	107 (24)	43 (24)	3657 (18)
RR (95% CI)	1.49 (1.06–2.10)	1.63 (1.07–2.48)	1.49 (1.20–1.85)	Reference
Prolonged labor ^h				
<i>n</i> (%)	77 (44)	153 (35)	33 (29)	5622 (27)
RR (95% CI)	2.05 (1.53–2.76)	1.12 (0.75–1.68)	1.43 (1.18–1.73)	Reference
Prolonged rupture of membranes ⁱ				
<i>n</i> (%)	24 (14)	42 (10)	12 (11)	1385 (7)
RR (95% CI)	2.19 (1.43–3.37)	1.71 (0.94–3.11)	1.48 (1.08–2.04)	Reference
Maternal fever measured at first postpartum visit ^j				
<i>n</i> (%)	8 (4)	6 (1)	1 (1)	339 (1.7)
RR (95% CI)	2.77 (1.38–5.57)	0.55 (0.08–3.96)	0.84 (0.38–1.85)	Reference

^a Missing 389 values.^b Missing 900 values.^c All infants died before the first visit; therefore, none was weighed.^d Missing 3 values.^e Missing 1301 values.^f Missing 1322 values.^g Missing 1295 values.^h Missing 1373 values.ⁱ Missing 1521 values.^j Missing 1490 values. The first postpartum visit was conducted as soon as possible after delivery (median: 12 hours), and temperature was measured by a health care worker.

not available for most deliveries in this setting, and the prevalence of metabolic and neuromuscular conditions is presumably low (although it has not been determined precisely). Therefore, in this community setting, the majority (~70%) of cases of term infants not breathing at birth likely resulted from IPR events. In rural Gadchiroli, India, the prevalence of “mild birth asphyxia,” defined as not breathing within 1 minute, was 14% of births (including preterm infants).²⁶ The prevalence of NRD is notably higher in these

community studies than in high-income hospital settings, where the prevalence of low Apgar scores ranges between 2% and 10%.^{27–29}

The incidence of NE in Sarlahi (~28 cases per 1000 live births) was >4 times the rate of NE reported from a maternity hospital in Kathmandu, Nepal (6 cases per 1000 live births).³⁰ Incidence rates have been reported from other hospital-based studies in low- and middle-income countries, ranging from 9.4 cases per 1000 live

births in Kuwait³¹ to 14 cases per 1000 live births in India³² and 22 to 26 cases per 1000 live births in Uganda and Nigeria.^{33,34} Hospital-based data are subject to selection biases that may result in overestimation or underestimation of population-based incidence rates. To our knowledge, this is the first population-based estimate of the incidence of NE from a community-based cohort in a developing country. With the assumption of a 30% disability rate among survivors of NE,^{16,17} the impair-

FIGURE 5
Morbidity symptoms among infants with NE ($n = 629$).

ment rate would be ~ 8 cases per 1000 live births.

Hypoxic-ischemic intrapartum events may contribute to 30% to 80% of cases of NE.^{30,35–37} In Perth, Australia, 30% of NE cases had evidence of intrapartum hypoxia, defined on the basis of abnormal fetal heart rates, meconium staining, and low Apgar scores.³⁵ In a hospital-based study in Kathmandu, Nepal, 60% of NE cases had evidence of intrapartum compromise with the use of similar criteria.^{30,36} Cowan et al³⁷ found diagnostic MRI findings of acute intrapartum insult in 80% of NE cases. In Sarlahi, NE was preceded by probable IPR NRD in 28% of cases. However, newborn clinical signs alone are insufficient to establish acute intrapartum hypoxia as a cause of NE, and it also is possible that NE cases related to acute intrapartum events did not meet symptom criteria for IPR NRD. Criteria to establish intrapartum causality recommended by the American College of Obstetrics and Gynecology and the American Academy of Pediatrics include metabolic acidosis, fetal brady-

cardia, multisystem involvement, brain imaging findings, and sentinel events before or during labor.^{5,24} Collection of such data and fetal monitoring are not feasible in the community setting; therefore, data limitations must be acknowledged when the validity of this estimate is considered. No similar data from a community-based, low-resource setting are available for comparison.

Maternal complications during labor and delivery were significantly associated with NE. Mothers who were nulliparous had a higher risk of NE associated with IPR NRD, and those with symptoms of preeclampsia, prolonged labor, or prolonged rupture of membranes demonstrated greater risk of NE, irrespective of association with IPR NRD. These risk factors for NE were corroborated in observational cohorts in Australia and Nepal.^{18,35,36}

Maternal fever and chorioamnionitis are influential in the pathophysiologic development of NRD and NE^{16,38,39} and play important roles in low-resource

settings, where infection risk is considerable. Maternal fever preceding delivery was a significant risk factor for NRD among preterm infants, and postpartum fever was significantly associated with NRD for all gestational ages and NE case statuses. Most deliveries were unattended; therefore, intrapartum temperatures were not measured. Prolonged rupture of membranes also was more frequent among NRD and NE cases, which suggests a potential role for infection in the pathogenesis of NE in these cases as well. In a previous analysis of data from this birth cohort, maternal fever had a synergistic effect with preterm birth on birth asphyxia mortality rates.¹⁵ Other prepartum factors that may contribute to the pathogenesis of NE but were not ascertained in this study include maternal thyroid disease, anemia, and alcohol consumption.^{18,35,36}

The high prevalence rates and early timing of morbidity symptoms for infants with NRD and NE emphasize the need for skilled birth attendance and early postnatal visits (<72 hours) in communities with high rates of home births. Thompson et al⁴⁰ similarly found that neurologic symptoms peaked among infants with NE on days 3 to 4. Furthermore, there is a dearth of information regarding longer-term morbidity and outcomes related to intrapartum events in low-income, community settings.¹ Ongoing community-based screening of young children (<2 years of age) for disabilities and impairments is possible by using an instrument validated for use by front-line workers.⁴¹ Longitudinal studies in high-income settings demonstrated cognitive impairment among school-aged and adolescent survivors of NE^{42,43}; such data from low- and middle-income countries are entirely lacking, and this is a critical research gap.

Throughout the world, 60 million

women give birth at home each year.¹² Urgent action is needed to increase the coverage and quality of obstetric/newborn care for these women and children, who bear the burden of IPR deaths and impairment. We have reviewed strategies to link mothers and newborns to health systems for skilled childbirth care, including demand- and supply-side strategies (eg, community mobilization, financing strategies, community referral/transport systems, and maternity waiting homes).⁴⁴ In 2005, the Nepalese government instituted the Safe Delivery Incentive Program to provide conditional cash transfers for women delivering in public facilities and incentives for skilled delivery providers. Initial program evaluation suggests increased utilization of skilled birth care; however, long-term outcomes and effects on neonatal mortality rates have yet to be evaluated.^{45,46}

There are several limitations to this analysis. Morbidity visits were conducted by study workers who were not medically trained, and only limited physical assessment (without a formal neurologic examination) was per-

formed. Symptoms used to define NE were based on maternal reports, which might be influenced by reporting or recall bias; however, this should have been minimized by the frequent immediate home visits after delivery. Finally, although there was excellent follow-up monitoring, a substantial proportion of infants with NRD died before the first study visit. We presumed that most of those infants would have developed NE before death. The births and deaths were not witnessed by a medical professional, however, and the cause of death cannot be confirmed; consequently, we reported estimates of NE with and without inclusion of those cases. Unfortunately, this is also the case for the majority of infants in low-income settings.

CONCLUSIONS

In Sarlahi, a rural, low-resource community in Nepal with poor access to obstetric care, the incidences of NRD and NE were high. The neonatal case fatality rate in this setting also was high, however, and the postneonatal survival and estimated disability rates thus were relatively low, because of

the early death of severely compromised infants. Urgent action is needed to increase coverage of skilled obstetric/neonatal care in this setting. Further research on the long-term impairments of survivors of NRD and NE from low-income and community-based settings also is needed to determine accurately the global burden of disease resulting from IPR events and the potential impact of interventions to reduce IPR mortality and morbidity.

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