Meconium aspiration syndrome in term neonates with normal acid-base status at delivery: Is it different?

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OBJECTIVE: Our aim was to compare the clinical characteristics of meconium aspiration syndrome in cases with pH ≥7.20 and in those with pH <7.20.

STUDY DESIGN: Medical records of diagnostic codes from the *International Classification of Diseases, Ninth Revision,* were used to identify neonates with severe meconium aspiration syndrome who had been delivered at our institution from 1994 through 1998. Severe meconium aspiration syndrome was defined as a mechanical ventilator requirement of >48 hours. Clinical data including neonatal outcomes of cases of meconium aspiration syndrome associated with umbilical pH ≥7.20 at delivery were compared with data on outcomes of cases with pH <7.20.

RESULTS: During this 4-year study period, 4985 singleton term neonates were delivered through meconium-stained amniotic fluid. Forty-eight cases met all study criteria, and pH values at delivery were as follows: pH ≥7.20, n = 29, and pH <7.20, n = 19. There were no differences between groups in the incidence of clinical chorioamnionitis, in the presence of meconium below the vocal cords, or in birth weight. Neonates with meconium aspiration syndrome and umbilical pH ≥7.20 at delivery developed seizures as often as those with pH <7.20 (20.1% vs 21.1%; $P = 1.0$).

CONCLUSION: Normal acid-base status at delivery is present in many cases of severe meconium aspiration syndrome, which suggests that either a preexisting injury or a nonhypoxic mechanism is often involved.
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Key words: Meconium-stained amniotic fluid, meconium aspiration syndrome, umbilical cord pH, acid-base status

Meconium aspiration syndrome occurs in approximately 5% to 25% of neonates delivered through meconium-stained amniotic fluid; severe disease requiring mechanical ventilation develops in as many as 30% of cases.[1] Its clinical spectrum ranges from transient symptoms to severe and persistent pulmonary hypertension. Review of the obstetrics literature reveals a strong relationship between intrapartum fetal hypoxemia-ischemia and the development of meconium aspiration syndrome. Rossi et al[2] noted that fetal heart rate abnormalities, cesarean delivery for fetal indications, and fetal acidemia occurred more often with meconium aspiration syndrome. Ramin et al[3] reported an inverse relationship between umbilical pH at delivery and the risk of meconium aspiration syndrome in neonates delivered through meconium-stained amniotic fluid. However, in this same study 55% of all cases of meconium aspiration syndrome occurred with an umbilical pH ≥7.20 at delivery. In fact, severe meconium aspiration syndrome may occur without acidemia at delivery. Sunoo et al[4] described 4 cases of severe meconium aspiration syndrome after elective cesarean delivery without any abnormal fetal heart rate pattern or evidence of fetal compromise.

Although the association of "fetal distress" and meconium aspiration syndrome has been extensively explored, few studies have examined in detail those cases of meconium aspiration syndrome without hypoxia-ischemia at delivery. The purpose of this study was to compare the clinical characteristics of meconium aspiration syndrome cases with normal-acid base status and the clinical characteristics of those with acidemia.

Methods

Neonates with meconium aspiration syndrome delivered at Hutzel Hospital between January 1, 1994, and December 31, 1998, were identified from medical records by the code "meconium aspiration syndrome" (code 770.1, *International Classification of Diseases, Ninth Revision*). Severe meconium aspiration syndrome was defined as the need for mechanical ventilation longer than 48 hours

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Table I. Demographic and antenatal characteristics of neonates with meconium aspiration syndrome and pH ≥7.2 versus pH <7.2

Variable	*pH ≥7.2 (n = 29)*	*pH <7.2 (n = 19)*	*Statistical significance*
Maternal age (y, mean ± SD)	25.1 ± 5.8	25.0 ± 7.8	NS
African American ethnicity (No., %)	26 (90%)	19 (100%)	NS
Parity (median and range)	1 (0-5)	0 (0-3)	NS
Gestational age (wk, median and range)	40 (37-44)	40 (37-42)	NS
Clinical chorioamnionitis (No., %)	3 (10.3%)	2 (10.5%)	NS
Cesarean delivery (No., %)	12 (41.4%)	16 (84.2%)	$P = .006$
Fetal indications (No.)*	5 (41.3%)	13 (81%)	$P = .001$
Labor arrest (No.)*	3 (25%)	2 (12.5%)	NS
Other (No.)*	4 (33.3%)	1 (6.5%)	NS

NS, Not significant.
*Expressed as percentage of cesarean deliveries.

Table II. Delivery characteristics between meconium aspiration syndrome in neonates with pH ≥7.2 versus pH <7.2

Variable	*pH ≥7.2 (n = 29)*	*pH <7.2 (n = 19)*	*Statistical significance*
Birth weight (g, mean ± SD)	3264.7 ± 452.8	3388. 8 ± 511.9	NS
Meconium below cord (No., %)	20 (71%)	10 (56%)	NS
Apgar score (median and range)			
At 1 min	7 (1-9)	4 (1-8)	$P = .008$
At 5 min	8 (6-9)	7 (5-9)	$P = .005$
Umbilical artery pH (mean ± SD)	7.28 ± 0.05	7.09 ± 0.07	$P < .001$
Umbilical artery carbon dioxide tension (mean ± SD)	46.3 ± 8.2	70.4 ± 13.9	$P < .001$
Umbilical artery base excess (mean ± SD)	–6.1 ± 3.4	–10.7 ± 3.2	$P < .001$

NS, Not significant.

in a neonate delivered through meconium-stained amniotic fluid for which no other cause of lung disease was identified. Maternal and neonatal charts were reviewed for confirmation of the diagnosis and pertinent clinical data. Exclusion criteria were gestational age <37 weeks, multiple gestations, or the presence of fetal structural anomalies.

Cases of meconium aspiration syndrome were divided into 2 groups on the the basis of the umbilical artery pH at delivery: group 1, pH ≥7.20, and group 2, pH <7.20. Demographic characteristics, clinical data (antenatal and intrapartum factors), and neonatal outcomes were compared between groups.

During the study period it was standard practice at our institution to use electronic fetal monitoring and transcervical amnioinfusion in all patients with meconium-stained amniotic fluid. Standard care also included oropharnygeal suctioning by the delivering personnel and intratracheal suctioning by the pediatric resuscitation team, who were present for all deliveries complicated by meconium-stained amniotic fluid. After delivery a segment of the umbilical cord was double-clamped and arterial blood was collected with a heparinized syringe that was immediately placed on ice and transported for acid-base analysis. Analysis was performed with a commercial blood gas evaluation system (model 278, CIBA-Corning Diagnostics Corporation, Medfield, Mass).

Statistical analysis was performed with the SPSS statistical package (SPSS Inc, Chicago, Ill). Categoric variables were compared with the Fisher exact test or by χ^2 analysis, and continuous variables were evaluated with the Student *t* test or Mann-Whitney test where appropriate. A *P* value < .05 was considered significant.

Results

During the 4-year study period, 22,588 live singleton infants were born at term. Of these, 4985 (22.1%) were delivered through meconium-stained amniotic fluid and severe meconium aspiration syndrome developed in 50 (0.2% of the total; 1.0% of cases with meconium-stained amniotic fluid). Forty-eight cases had umbilical blood gas results and met all study criteria, 29 with pH ≥7.20 (group 1) and 19 with pH <7.20 (group 2).

There were no differences in demographic or antenatal characteristics between groups (Table I). There were also no differences in the rate of prenatal care, maternal medical complications, or maternal substance abuse between groups. The incidence of thick meconium-stained amniotic fluid (compared with "moderate" or "thin") did not differ between those with pH ≥7.20 and those with pH <7.20 (91.7% [22/29] vs 93.8% [15/19]; $P > .05$). However, group 2 neonates were more likely to have been born by cesarean delivery ($P = .006$) and to have had cesarean delivery because of fetal indications ($P = .001$).

Both 1-minute and 5-minute Apgar scores and umbilical artery pH, carbon dioxide tension, and base excess values were significantly different between groups (Table II). Group 2 neonates were no more likely to have meco-

Table III. Neonatal outcomes of meconium aspiration syndrome in neonates with pH ≥7.2 versus pH <7.2

Variable	*pH ≥7.2 (n = 29)*	*pH <7.2 (n = 19)*	*Statistical significance*
Neonatal intensive care (d, median and range)	5 (2-17)	5 (2-14)	NS
Ventilator use (d, median and range)	3 (2-12)	3 (2-11)	NS
Seizures (No., %)	6 (20.7%)	4 (21.1%)	NS

NS, Not significant.

nium below the vocal cords (71% vs 56%; $P = .4$). No neonate in either group died. There were also no cases of intraventricular hemorrhage or necrotizing enterocolitis. All measures of neonatal outcome, such as the need for phototherapy, neonatal sepsis, and duration of oxygen therapy, were similar between groups. There were also no differences in the duration of neonatal intensive care, in the need for ventilator therapy, or in the development of seizures (Table III).

Comment

Although current paradigms promote hypoxia-ischemia as a major causative factor in the development of meconium aspiration syndrome,[5] evidence of fetal compromise at delivery is absent in many cases. Of the 48 cases of severe meconium aspiration syndrome evaluated in this study, 29 (60%) had an umbilical artery pH ≥7.20 at delivery, which is similar to that found by Nathan et al.[6] The incidence of severe meconium aspiration syndrome in our population (1% of meconium-stained amniotic fluid) is slightly higher than that reported by Hernandez et al[7] (0.5% of meconium-stained amniotic fluid) but lower than that of Rossi et al[2] (2.9% of meconium-stained amniotic fluid). Meconium was absent below the vocal cords in 29% (pH ≥7.2) and 44% (pH <7.20) of cases ($P = .4$). In all cases optimal obstetric interventions (amnioinfusion and oropharnygeal suctioning) and pediatric interventions (intratracheal suctioning) were reportedly performed. These findings are consistent with other reports of treatment failure and with the concept that chronic prenatal processes may be involved in severe cases, rather than meconium aspiration syndrome's being solely the sequela of either aspiration or mechanical obstruction, or both.[8, 9] Other than the rate of cesarean delivery and the need for operative delivery for fetal indications, there were no significant differences in antenatal or intrapartum characteristics between pH groups. In fact, neonatal outcomes, including the development of seizures, were similar.

What are the implications of our findings? One explanation is that a hypoxic-ischemic insult, either prolonged or severe, occurred and then resolved before the intrapartum period. This may explain the 17% (5/29) cesarean delivery rate for fetal indications of meconium aspiration syndrome associated with pH ≥7.20 at delivery. Because of such an insult, these fetuses may have a decreased tolerance for the intrapartum process and may decompensate at lesser degrees of stress.[10] Our study was retrospective, so we were unable to rule out the potential bias of a lower physician threshold for abdominal delivery in the presence of meconium-stained amniotic fluid.

An alternative explanation is that other mechanisms, not related to fetal oxygenation or acid-base status, were involved. Meconium has both vasoactive and inflammatory properties that may cause pulmonary or vascular effects.[11, 12] Both in vivo and clinical studies have documented the ability of meconium and bile acids, a key component of meconium, to cause vasospasm and vascular damage.[13, 14] Cytokine-mediated inflammatory injury is another potential mechanism.[15] Neonates with meconium-staining at delivery have higher interleukin 6 levels,[16] and meconium has been shown to alter white blood cell chemotaxis by means of interleukin 8.[17] Although there is an association between infection and meconium staining,[18, 19] there are few data on the role of infection in meconium aspiration syndrome. Finally, the association of fetal vasculopathy and meconium aspiration syndrome suggests that vascular injury caused by thrombophilic disorders is another potential mechanism that requires further investigation.[20-22]

Although fetal acidemia in term pregnancies may be defined as an umbilical artery pH <7.15, [23] we chose to use a value of <7.20 to allow comparison of our results with prior studies that used this threshold. However, the use of a pH threshold of 7.15 would not have significantly altered our results. We included cases of meconium aspiration syndrome requiring ventilator therapy longer than 48 hours to ensure that truly pathologic cases were studied. Both anecdotal experience and a review of the literature on meconium aspiration syndrome make this distinction relevant. There is no uniform definition of meconium aspiration syndrome; various criteria, from radiographic signs to the presence of meconium below the vocal cords, are often key components of the diagnosis. Furthermore, with a wide disease spectrum, comparison between neonates with very mild symptoms, such as a transient need for oxygen, and those requiring ventilator therapy may account for some of the lack of clarity in the literature.

As previously stated by Naeye,[24] there is a strong need for a more comprehensive and detailed analysis of meconium aspiration syndrome. The cause and potential chronicity of factors leading to meconium aspiration syndrome may be better understood with a combination of

placental examination and measurements of biochemical markers of fetal hypoxemia (acute and chronic), fetal inflammatory responses, and maternal-fetal coagulation.

There are possible medicolegal implications to our findings. Intrapartum mismanagement is often alleged in meconium aspiration syndrome.[25] Normal acid-base status at delivery, even in cases with associated neurologic injury, suggests that either a preexisting injury or a nonhypoxic mechanism, rather than an intrapartum event, is involved in many cases of meconium aspiration syndrome.

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Discussion

Dr R.J. Carpenter, Jr, Houston, Texas. The presentation by Blackwell and colleagues asks a basic question: What are the outcomes of meconium aspiration syndrome in those infants who do and those infants who do not have normal acid-base status? Their conclusion of no difference in the outcomes raises important issues for the practicing obstetrician: documentation of the labor course, interpretation of placental pathologic changes, and evaluation of obstetric management.

The authors correctly state that there is no uniform definition of meconium aspiration syndrome. However, despite meconium passage, when meconium is not noted at intubation, how do they justify stating that the ultimate outcome is meconium aspiration syndrome? The underlying pathologic change frequently consists of persistent pulmonary hypertension of the newborn. This condition may be found in the absence of meconium passage or meconium aspiration and is the process frequently causing the adverse neonatal outcome. Many of the authors' references clearly support the concept that babies who die early in the neonatal period (at <48 hours) have pulmonary artery changes that predate the onset of labor and delivery.

Despite the similarity of the groups, what was the reason for a 41% incidence of cesarean delivery in the nonacidotic group? What were the results of electronic fetal monitoring in their groups? Were there differences in the monitoring strips, and if so, how did they compare and contrast? After amnioinfusion, what changes, if any, occurred, and did they differ between group 1 and group 2?

Because amnioinfusion was used in all cases of meconium passage, what was the incidence of light versus thick meconium in the two populations? How did that compare with findings after neonatal intubation?

The intent of this research was to look at outcomes in two populations; however, the outcomes listed in Tables II and III include minimal information concerning the morbidity and mortality rates for the subjects. With the

potential difficulties of long-term follow-up in the entire population, what data do the authors have concerning neurologic outcomes in the first year of life? Was any attempt made to look at these issues? From my perspective, this comparison would substantially affect the "take home" message that there is or is not a difference in the outcomes for these two groups.

Last, not for the authors but for obstetric caregivers, several important points are addressed in the literature cited, as well as in other sources not cited. These points include the need for the caregiver to acquire cord gas measurements and to ensure the submission of the placenta in any case in which an adverse outcome is present. Because some of these babies are not acutely sick at birth, a means should be in place to allow for the recovery of placentas (with refrigeration for 24-48 hours) and perhaps for short-term storage of cord segments, which the Mississippi group has clearly shown can be analyzed in a post hoc manner to give reliable data of cord pH at delivery.

Dr Blackwell (Closing). I thank Dr Carpenter for his review of our work and comments. One of the important concepts that he emphasized is the issue of neurologic outcomes. The only neurologic outcome that we were able to use in this study was the development of neonatal seizures within the first 72 hours of life. In discussions with our neonatology colleagues and with those in the pediatric neurologic developmental clinics at our institution, I was surprised to learn that unless a neonate with meconium aspiration syndrome develops seizures or requires extracorporeal membrane oxygenation, it is not routine policy to follow these children longitudinally.

Despite an association between meconium staining and adverse neurologic outcomes in the literature, adequate studies of the long-term neurologic outcome of meconium aspiration are lacking. The patients in our study were delivered between 1994 and 1997, and the neonates are now 3 to 6 years old. We would very much like to find these children and evaluate how they are doing, but with our patient population it would be difficult to find a significant number after so many years.

Answering many of the scientific questions that were raised with our study would require a prospective observation study combining a comprehensive biologic evaluation with follow-up of clinical outcomes. Furthermore, this study would have to be large and to involve a high-risk population, because it took 4 years and approximately 20,000 deliveries to produce 50 cases of severe meconium aspiration syndrome.

Another issue raised by Dr Carpenter was our interest in "meconium aspiration syndrome" rather than "persistent pulmonary hypertension of the newborn." Pulmonary hypertension is one end product of the disease process of meconium aspiration syndrome, as premature birth is one end product of intrauterine infection. It is true that severe pulmonary hypertension occurs with clear amniotic fluid (at a much lower rate), although I hypothesize that the primary mechanisms involved are different. However, for a better understanding of the mechanisms of meconium-associated lung disease, all causes of pulmonary hypertension would need to be studied. The associations among neurologic injury, meconium staining, and meconium aspiration are another compelling reason for the focus of our study, rather than focusing on the end product of lung disease. Thus I am primarily interested in meconium aspiration, rather than pulmonary hypertension.

The final question is about the fetal heart rate patterns. Finding the appropriate intrapartum fetal heart rate tracings as far back as 1994, after they had been in a warehouse for several years, was difficult. I have found tracings for some cases, but the data collected were, I believe, insufficient to make statistical comparisons between the two groups. However, I can make some preliminary comments. In both groups, when cesarean delivery was contemplated for fetal indications, it was rarely for a pure fetal bradycardia; more often than not, it was for repetitive, "atypical" or severe variable decelerations or persistent late decelerations. I do believe that it would be interesting to study the fetal heart rate patterns for the entire cohort of patients with meconium aspiration and make comparisons on the basis of umbilical pH, the need for cesarean delivery for fetal indications, and the development of early-onset seizures.