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Meconium stained fluid: approach to the mother and the baby

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Meconium aspiration syndrome (MAS) is a common problem that most pediatricians will encounter in the delivery room and normal newborn nursery. Approximately 13% of all live births are complicated by meconium-stained amniotic fluid (MSAF). Fortunately, only 5% of neonates born through MSAF develop MAS [1,2]. An estimated 25,000 to 30,000 cases and 1000 deaths related to MAS occur annually in the United States. Yoder et al [3] documented a decline in the incidence of MAS from 5.8% to 1.5% during the period 1990 to 1997, which they attributed to a 33% reduction in the incidence of births at more than 41 weeks' gestation. MAS is defined as respiratory distress in an infant born through MSAF whose symptoms cannot be otherwise explained [2]. Cleary and Wiswell [2] have proposed severity criteria to define MAS: (1) mild MAS is disease that requires less than 40% oxygen for less than 48 hours, (2) moderate MAS is disease that requires more than 40% oxygen for more than 48 hours with no air leak, and (3) severe MAS is disease that requires assisted ventilation for more than 48 hours and is often associated with persistent pulmonary hypertension.

Pathogenesis

Causes of meconium-stained amniotic fluid

Under normal circumstances, the passage of meconium from the fetus into the amnion is prevented by the lack of intestinal peristalsis, which is caused by several factors, including low motilin levels, tonic contraction of the anal sphinc-

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Box 1. Risk factors for meconium-stained amniotic fluid

- Maternal hypertension
- Maternal diabetes mellitus
- Maternal heavy cigarette smoking
- Maternal chronic respiratory or cardiovascular disease
- Postterm pregnancy
- Pre-eclampsia/eclampsia
- Oligohydramnios
- Intrauterine growth retardation
- Poor biophysical profile
- Abnormal fetal heart rate patterns

Adapted from Hachey WE. Meconium aspiration. In: Gomella TL. Neonatology. 4th edition. New York: Lange Medical Books; 1999. p. 507.

ter, and a terminal cap of viscous meconium. MSAF may be a natural phenomenon that neither indicates nor causes fetal distress but simply reflects a postterm fetus with a mature gastrointestinal tract in which motilin levels have risen. Vagal stimulation produced by cord or head compression also may be associated with the passage of meconium in the absence of fetal distress. In contrast, meconium passage may occur secondary to an in utero stress, with resultant fetal hypoxia and acidosis producing relaxation of the anal sphincter. Term and postterm neonates are more likely to pass meconium in response to such a stress than preterm neonates. Perinatal conditions associated with an increased risk of MSAF are listed in Box 1. Passage of meconium into the amniotic fluid may increase the risk of intra-amniotic infection [4,5].

Causes of meconium aspiration syndrome

It is unclear why some infants born through MSAF develop an aspiration syndrome whereas others do not. Aspiration of meconium may occur in utero or after delivery with the first few breaths. Chronic fetal hypoxia and acidosis may lead to fetal gasping and the subsequent in utero aspiration of meconium. Mounting evidence suggests that a chronic in utero insult may be responsible for most cases of severe MAS as opposed to an acute peripartum event [6,7]. In contrast to these severe cases, the vigorous infant who aspirates meconium-stained fluid from the nasopharynx at birth usually develops mild to moderate disease.

Further support for this view is provided by the recent randomized trial of the delivery room management of the vigorous meconium-stained infant conducted by Wiswell et al [8]. Two thousand ninety-four neonates were studied at

12 participating centers. Infants were randomized to receive intubation and tracheal suctioning in the delivery room or were managed expectantly and treated only if they developed symptoms of respiratory distress. One hundred forty-nine (7.1%) enrolled infants subsequently developed respiratory distress, 62 of whom (3%) were diagnosed with MAS and 87 of whom (4.2%) were diagnosed with other respiratory disorders (including transient tachypnea, delayed transition from fetal circulation, sepsis, and persistent pulmonary hypertension of the newborn). There was no difference in the rate of MAS in infants who were intubated (3.2%) and infants who were not intubated (2.7%). There was no difference between the groups in subanalyses that adjusted for the thickness of the meconium in the amniotic fluid.

Mechanisms of injury

Meconium seems to be toxic to the lungs in many ways, and it may be difficult to determine which mechanisms predominate at a given point in time. Mechanisms of injury in MAS are as follows: (1) mechanical obstruction of airways, (2) chemical pneumonitis, (3) vasoconstriction of pulmonary vessels, and (4) inactivation of surfactant.

Mechanical obstruction

Meconium is thick and viscous and may cause complete or partial airway obstruction. With the onset of respiration, meconium migrates from central to peripheral airways. Particles of meconium inhaled into the small distal airways cause further obstruction and atelectasis, which lead to areas of unventilated lung with resultant mismatch of ventilation and perfusion with resultant hypoxemia. Partial obstruction produces a ''ball-valve'' effect in which inhaled air is allowed to enter the alveoli but is unable to escape. This causes air trapping in the alveoli with further V/Q mismatch and may lead to hyperexpansion and air leak syndromes. The risk of pneumothorax is estimated to range from 15% to 33% [2].

Pneumonitis

Meconium seems to have a direct toxic effect mediated by inflammation. Within hours, neutrophils and macrophages are found in the alveoli, larger airways, and lung parenchyma. The release of cytokines, such as tumor necrosis factor-α, interleukin-1β, and interleukin-8, may directly injure lung parenchyma or lead to vascular leakage, which causes a toxic pneumonitis with hemorrhagic pulmonary edema. Meconium contains many substances, such as bile acids, that, when present in the amniotic fluid, are known to cause direct injury of the cord vessels and amniotic membranes. They also have a direct vasoconstrictive effect on the placental and umbilical cord vessels.

Pulmonary vasoconstriction

Severe MAS may be complicated by persistent pulmonary hypertension. This pulmonary vasoconstriction seems to be partially the result of the underlying in utero stressor. The release of vasoactive mediators, such as eicosanoids, endothelin-1, and Prostaglanden E2 (PGE2), as a result of injury from meconium seems to play a role in the development of persistent pulmonary hypertension [9].

Surfactant inactivation

In the early 1990s, researchers recognized that meconium inactivates surfactant. Meconium displaces surfactant from the alveolar surface and inhibits its surface tension-lowering ability [10]. Studies demonstrated a direct inhibitory effect of meconium on the function of surfactant in vitro [11] and in in vivo animal models [12,13]. Lung lavage fluid in infants with MAS has shown evidence of known surfactant inhibitors [14]. A full-term baby born with a sufficient quantity of surfactant may develop surfactant deficiency by inactivation that leads to increased surface tension with atelectasis, decreased lung compliance, decreased lung volumes, and resultant poor oxygenation [15].

Diagnosis

MAS must be considered in any infant born through MSAF who develops symptoms of respiratory distress. The classic roentgenographic findings in MAS are described as diffuse, asymmetric patchy infiltrates, but because of the diverse mechanisms that cause disease, various radiographic findings may be present (Fig. 1). Frequently, overaeration is present, which may lead to air leak syndromes, such as pneumothorax, pneumomediastinum, or pulmonary interstitial emphysema (Fig. 2). A series of 80 cases showed an association between the degree of radiographic abnormalities and the severity of MAS, with consolidation or atelectasis most predictive of poor outcome [16]. Other studies, however, have not confirmed this relationship [17–18]. In patients with the classic radiographic findings of MAS, radiographic clearing is slow over a period of days or weeks [19]. A two-dimensional echocardiogram to evaluate for pulmonary hypertension may be useful early in an infant's course.

Management

Obstetric considerations during labor

The obstetric focus is on the possible need for intervention designed to decrease the risk of MAS. MSAF should be considered a possible warning sign of fetal distress. Many authors recommend that in the case of MSAF, obstetricians should monitor carefully the fetal heart rate tracing and have a low threshold for performing additional testing, such as fetal scalp pH [20].

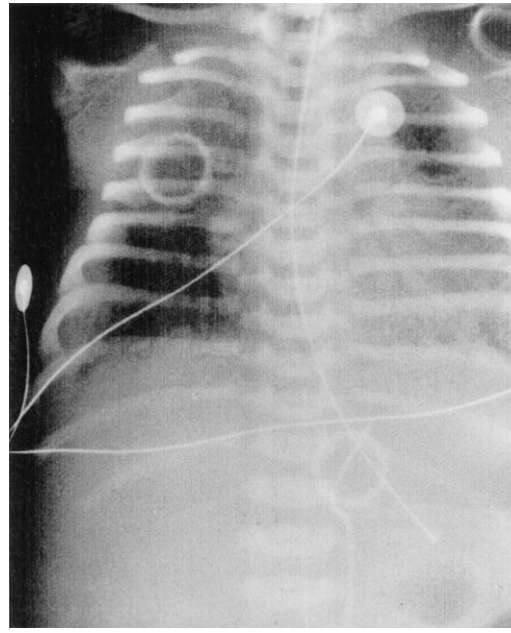

Fig. 1. Chest radiograph of a full-term infant with MAS.

A newer modality for monitoring the fetus is fetal pulse oximetry. Fetal pulse oximetry was approved for use by the Food and Drug Administration in May 2000 and is finding increased acceptance among obstetricians [21]. In the case of nonreassuring fetal heart rate patterns, studies have shown a high correlation between fetal oxygen saturation below 30% and a scalp pH value of 7.2 [22].

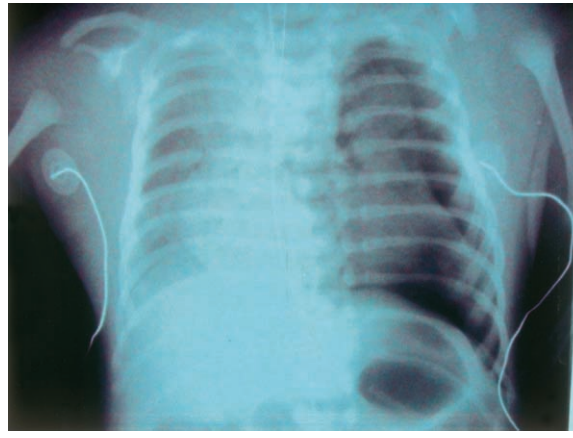

Fig. 2. Pneumothorax is a dreaded complication of meconium aspiration that may occur is as many as 33% of cases.

There are some limitations, however. Not only must the membranes be ruptured but also the probe cannot be placed until the cervix is dilated at least 2 to 3 cm. With current technology, an adequate signal can be obtained only approximately 70% of the time [23]. As technology improves and experience widens, fetal pulse oximetry seems to have great potential to improve abilities to monitor the at-risk fetus, including fetuses exposed to MSAF.

Amnioinfusion

Amnioinfusion is the primary intervention aimed at reducing the incidence of MAS. During this procedure, a sterile isotonic solution is infused into the amniotic cavity via catheter. By adding volume into the cavity, the meconium is diluted. The decreased risk of cord compression may decrease hypoxia and decrease fetal gasping [24]. Good evidence exists that amnioinfusion is effective at reducing the consistency of the meconium [25]. The procedure also seems to be relatively safe [26]. What is less clear is whether amnioinfusion is effective at preventing MAS, a difficult issue to study because of its low incidence. In one prospective, randomized study of pregnancies complicated by thick meconium and oligohydramnios, amnioinfusion significantly reduced the rates of fetal distress, meconium aspiration, and MAS [27]. A recent meta-analysis found a 76% reduction in MAS with amnioinfusion [24]. Prophylactic amnioinfusion for MSAF when the fetus otherwise seems well has not been shown to decrease morbidity. When moderate to thick meconium is accompanied by evidence of fetal compromise, such as variable fetal heart rate decelerations, however, therapeutic amnioinfusion should be considered as a potential method to decrease the risk of MAS [1].

Considerations in the delivery room

Intrapartum suctioning

Intrapartum suctioning has been considered standard procedure for more than 25 years based on the seminal work of Carson et al [28]. The goal is to clear as much meconium as possible from the airway before the infant is able to take a breath. This is accomplished by suctioning the mouth, pharynx, and nose with either a large-bore suction catheter (12F–14F) or a bulb syringe as soon as the head is delivered [29]. Ideally this suctioning occurs before the shoulders are delivered in a cephalic presentation or immediately after the head is delivered with a breech presentation [30]. Wiswell et al [8] confirmed the effectiveness of intrapartum suctioning in their trial that evaluated delivery room management of the vigorous infant. The study found a difference in the rate of MAS in infants who did not receive intrapartum oropharyngeal suction before delivery of the shoulders compared with infants who did receive suctioning (8.5% versus 2.7%; OR 3.35, CI: 1.55, 7.27).

Pediatric intervention

Intrapartum suctioning is not effective in removing meconium aspirated by the fetus into the lungs prior to delivery. Several studies have shown intrauterine meconium aspirated to the level of the alveolar spaces [31]. Although there is no way to prevent MAS in these unfortunate circumstances, it may be possible to suction meconium directly from the trachea in nonvigorous infants before the initiation of respiration. Whenever possible, a skilled resuscitation team should be present at all deliveries that involve MSAF to ensure a smooth transfer of care from the delivering team to the resuscitation team to continue efforts at preventing MAS.

Assuming the fetus is not in immediate distress and delivery is not imminent, the first step for the pediatrician is to perform a thorough review of the maternal chart. There are multiple risk factors for meconium passage (Box 1). Postterm pregnancy is the greatest risk factor. It affects close to 40% of deliveries [32]. Risk factors for infection also must be noted, because MSAF may be a risk factor for microbial invasion of the amniotic cavity [4].

The appropriate pediatric intervention in infants born through meconium-stained fluid depends on whether the infant is "vigorous." Current neonatal resuscitation guidelines define an infant as vigorous if he or she has (1) strong respiratory efforts, (2) good muscle tone, and (3) a heart rate more than 100 beats/min [33]. When this is the case, there is generally no need for tracheal suctioning, and the pediatrician may proceed with routine management (Fig. 3). The basis for this approach, which represents a change from prior guidelines, was validated by Wiswell et al [8] in a trial that involved 2094 infants 37 or more weeks Estimated Gestational Age (EGA) who were born through any consistency of MSAF and vigorous at birth. Infants were randomized to receive either routine intubation or suctioning or expectant management. There was no difference in the incidence of MAS (intubation = 3.2%; expectant = 2.7%) or other respiratory disorders (intubation = 3.8%; expectant = 4.5%). 3.8% (42/1098) of the intubated infants had transient complications from the intubation, such as bradycardia, hoarseness or stridor, or laryngospasm. These findings are supported further by a meta-analysis published in the Cochrane database [34].

When an infant is depressed (ie, poor respiratory effort, limp, heart rate <100 beats/min, the goal is to clear the airway as quickly as possible to minimize the amount of meconium aspirated. The infant may be given free-flow oxygen and placed under a radiant heater, but drying and stimulating should be delayed. At this point, direct laryngoscopy should be performed with suctioning of the mouth and hypopharynx (with a 12F or 14F suction catheter) under direct visualization, followed by intubation and then applying suction (approximately 100 mm Hg) directly to the endotracheal tube as it is slowly withdrawn. The process is repeated until either "little additional meconium is recovered, or until the baby's heart rate indicates that resuscitation must proceed without delay" [33]. Should positive pressure ventilation be required before complete airway clearance, a suction catheter inserted through the tracheal tube may be used to

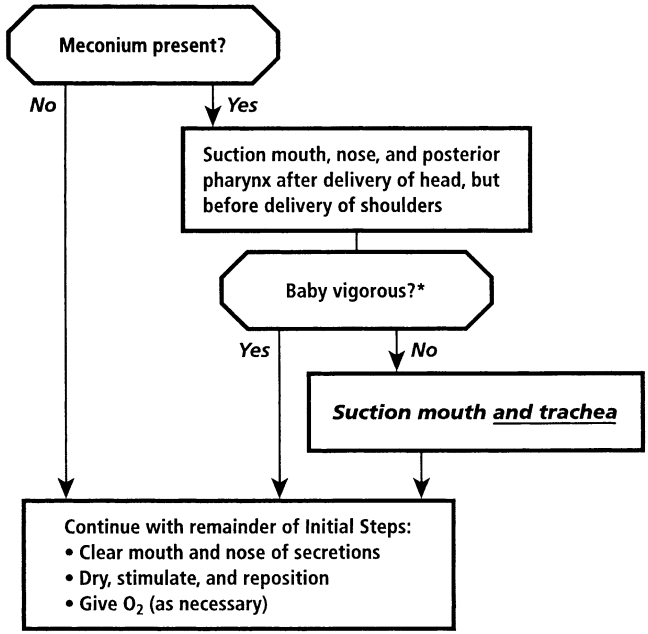

Fig. 3. Postpartum approach to the infant born through meconium stained amniotic fluid. "Vigorous" is defined as strong respiratory efforts, good muscle tone, and a heart rate more than 100 beats/min. (*From* American Academy of Pediatrics and American Heart Association. Neonatal resuscitation textbook. 4th edition. Chicago: American Academy of Pediatrics and American Heart Association; 2000. p. 2–7; with permission.)

continue meconium removal. At this point, gastric suctioning also should be delayed to avoid the aspiration of swallowed meconium.

Approach to the apparently well infant

Most infants born through MSAF require no interventions and may remain with their family in the delivery room. Because MAS does not always present immediately, however, it is important to monitor these infants closely for signs of respiratory distress. Initially, infants at risk for MAS may have signs of post-maturity, such as peeling skin, long fingernails, and yellow stained skin and umbilical cord. One should observe the infant for tachypnea and cyanosis and for grunting, nasal flaring, and accessory muscle use (retractions). The chest may appear barrel shaped as a result of overinflation secondary to a ball-valve effect as the meconium plugs the lower airways. Rales and rhonchi may be auscultated [35]. Most infants who develop symptoms do so in the first 24 hours of life.

Approach to the ill newborn

Infants at risk for MAS who show signs of respiratory distress must be transferred to the neonatal intensive care unit. Infants with MAS can deteriorate

rapidly and must be monitored closely. The full range of respiratory support measures—from oxygen to oscillators—must be rapidly available, as should other team members (ie, respiratory therapists) and diagnostic support (Arterial Blood Gas [ABG] analysis, imaging). Because sepsis is in the differential diagnosis, antibiotics are generally indicated in the management of infants with respiratory distress. Timely transfer to a center that is capable of performing extracorporeal membrane oxygenation (ECMO) may be life saving and may prevent later transfer to such a center.

Treatments in the neonatal intensive care unit environment

Once in the neonatal intensive care unit, conventional therapy for MAS is aimed at increasing oxygenation while minimizing the barotrauma that may lead to air leak syndromes. The infant with severe MAS can spiral into a vicious cycle of hypoxemia that leads to acidosis, which together cause pulmonary vein constriction. In its severest form, this condition may lead to persistent pulmonary hypertension. The resultant right-to-left shunting at the level of the ductus arteriosus, the atrial level, or both causes further cyanosis and hypoxemia, which perpetuate the cycle. It is imperative that the baby make a successful transition from intrauterine to extrauterine life, with a drop in pulmonary arterial resistance and an increase in pulmonary blood flow.

The amount of ventilatory support depends on the amount of respiratory distress. Some babies require only an oxygen hood, but in a recent multicenter study, approximately 40% of the babies required mechanical ventilation and an additional 10% required continuous positive airway pressure [8]. Hyperventilation with resultant alkalinization decreases pulmonary vascular resistance, but no trials have compared the outcome of MAS with hyperventilation versus a ''gentler'' ventilation strategy.

High-frequency ventilators minimize barotrauma through the use of subnormal tidal volumes at supraphysiologic rates, which allow use of high mean airway pressures without the concurrent use of high peak pressures. Theoretically, high-frequency ventilators should reduce air-leak syndromes in MAS, but animal and clinical models have yielded conflicting results. High-frequency ventilators may slow the progression of meconium down the tracheobronchial tree and allow more time for meconium removal [36]. No prospective, randomized, controlled trials have compared conventional ventilation versus high-frequency ventilation in MAS, but many clinicians who use high-frequency ventilators to hyperventilate and alkalinize infants find it useful in MAS.

Surfactant

Given the apparent surfactant resistance caused by surfactant inhibitors in infants with MAS, many researchers have investigated the role of exogenous surfactant administration in these babies [14]. Two randomized, controlled trials have evaluated the efficacy of exogenous surfactant therapy in MAS. The results have been promising, with a decrease in the number of infants requiring ECMO

[15,37] and a possible reduction in the risk of pneumothorax [15]. There was, however, no difference in mortality. There seems to be a differential resistance among types of surfactants to the surfactant inhibitors seen in MAS [38]. The search is ongoing for new synthetic surfactant preparations that are highly resistant to inactivation by meconium or other forms of toxic pneumonitis.

Surfactant lavage

In an attempt to remove noxious material from the lungs, minimize obstruction, and simultaneously offset the inactivation of surfactant by meconium, some investigators have examined lung lavage with dilute surfactant [39,40]. The benefits seem to be an increase in oxygenation and decrease in need for mechanical ventilation. The procedure, which generally requires sedation, often had to be halted because of hypotension or periods of hypoxemia. This is an exciting area of investigation, however, and additional trials are warranted.

Inhaled nitric oxide

Inhaled nitric oxide causes selective pulmonary vasodilation by acting directly on the vascular smooth muscle. It activates guanylate cyclase and increases cyclic GMP, then binds to hemoglobin and is inactivated. When nitric oxide is delivered as an inhaled drug, it causes selective pulmonary capillary vasodilation with minimal effects on other body systems. By dilating the blood vessels in well-ventilated areas of lung, inhaled nitric oxide decreases the ventilation perfusion ratio mismatch and improves oxygenation in infants with persistent pulmonary hypertension. Proper administration of inhaled nitric oxide requires adequate delivery to the alveoli. Pretreatment with surfactant seems to aid in delivery of inhaled nitric oxide to the alveoli, with a resultant increase in oxygenation [41]. In a large, randomized, multicenter trial, infants with MAS responded well to the combination of inhaled nitric oxide and High Frequency Oscillatory Ventilation (HFOV), likely because of improved lung inflation and better delivery of the drug [42]. Inhaled nitric oxide should be instituted only at centers with ECMO availability because ECMO may need to be started emergently should all other treatment modalities fail. Inhaled nitric oxide is approved by the Food and Drug Administration for the treatment of hypoxic respiratory failure in term and near-term infants.

Extracorporeal membrane oxygenation

Since the introduction of treatment of persistent pulmonary hypertension with inhaled nitric oxide, the need for ECMO has decreased. Approximately 40% of infants with MAS treated with inhaled nitric oxide fail to respond and require bypass, however [43]. Infants with MAS make up approximately 35% of the infant population who requires ECMO [44]. Compared with other population subsets that require ECMO, infants with MAS have a high survival rate (on the order of approximately 93%–100%) [45]. It is notable that many pediatricians underestimate this survival rate [46].

Summary

Like many aspects of the perinatal period, optimal care of an infant born through MSAF involves collaboration between obstetrician and pediatrician, each with separate but important roles. As always, effective communication and advanced preparation and anticipation of potential problems form the cornerstone of this partnership. Together the health of infants may be improved.

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