Meconium aspiration syndrome: do we know?

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Meconium is a common finding in amniotic fluid and placental specimens, particularly in the term or post-term pregnancy. The most important consequence of meconium-stained amniotic fluid (MSAF) is meconium aspiration syndrome (MAS), and at least 5% of infants born through MSAF develop MAS. MAS continues to be a threat to many newborns throughout the world, with a case fatality rate of 5% (as much as 40%), in addition to short- and long-term pulmonary and neurodevelopmental sequelae. The exact pathophysiology of meconium passage into the amniotic fluid and consequences of meconium aspiration are unknown. There are three prevailing and possibly compatible theories for mechanisms of meconium release. Firstly, meconium passage is probably related with the maturation of the gastrointestinal tract, because meconium passage in the preterm third trimester fetus has been reported to be a rare event, as typically it occurs near or post-term. Secondly, an alternate hypothesis for in utero meconium passage is that pathologic processes, such as stress via hypoxia or infection, can trigger meconium passage. However, the predictive values of MSAF for fetal distress and acidosis at birth are poor and controversial. Thirdly, an alternative route for the presence of MSAF in the presence of fetal hypoxia is reduced clearance of defecated meconium due to impaired fetal swallowing or unidentified placental dysfunction in addition to or instead of an increase in its passage. The pathophysiology of MAS is multifactorial and extremely complex. Meconium causes mechanical obstruction and pulmonary air leak, induces surfactant inactivation, causes pulmonary inflammation, and induces apoptosis. Preventing prolonged pregnancy by labor induction might reduce the risk of MSAF. Labor induction with prostaglandins appears to be associated with the occurrence of MSAF. Amnioinfusion for suspected umbilical cord compression has no clear effect on the occurrence of MSAF. Intrapartum suctioning of the naso- and oropharynx before delivery of the shoulders as well as postnatal endotracheal suctioning of vigorous infants with MSAF are no longer recommended. Currently, endotracheal suction is recommended only in neonates born through MSAF who are not vigorous at birth. Indications for mechanical ventilation in infants with MAS are arbitrary. Surfactant administration may reduce the severity of MAS. Bronchoalveolar lavage with surfactant in infants with MAS is risky and it cannot be recommended for routine use. At present, there is insufficient evidence to propose routine steroid therapy in the management of MAS. Although prophylactic antibiotics in infants with MAS are not justified, most of these patients receive antibiotics during the first days of life, before the diagnosis of pneumonia can be completely ruled out. Children surviving severe MAS are in fact reported to have higher prevalence of asthmatic symptoms and bronchiolar hyperreactivity than children in the general population. It remains undetermined how often and at what intensity systemic inflammation occurs in association with MAS and what its significance is for the outcome of infants with severe MAS.

Key words: meconium passage, meconium aspiration, pathogenesis, prophylaxis, treatment.

μηκονειον (mekoneion) is the Greek word for poppy juice or opium. Both the sedative effects on the unborn infant observed by Aristotle and the physical resemblance with poppy juice explain why the sticky dark green material from the fetal intestinal tract is called meconium.

Meconium contains gastrointestinal secretions (bilirubin, bile acids, intestinal enzymes, pancreatic juice, mucus, etc.), blood, swallowed vernix caseosa, lanugo, and cellular debris variably composed of water (as much as 80%). The characteristic green coloration is attributable to bile pigments, which are not released in significant amount until midpregnancy[1].

Meconium is a common finding in amniotic fluid and placental specimens, particularly in the term or post-term pregnancy. Frequencies of meconium-stained amniotic fluid (MSAF) in 37, 40 and >42 weeks of gestation are 3%, 13% and 18%, respectively[2]. Although MSAF has been considered a sign of fetal maturity, some evidence suggests that it may also represent a response of the fetal gastrointestinal tract to pathologic conditions, such as acute or chronic hypoxia.

The most important consequence of MSAF is meconium aspiration syndrome (MAS), which occurs in 1% to 3% of pregnancies. About 5% (as much as 14%) of infants born through MSAF develop MAS[3,4].

The prevalence and mortality of MAS in children born through MSAF have decreased over the years, mainly due to improved healthcare and changing obstetric practices (e.g. a better diagnosis of abnormalities by electronic fetal monitoring, higher frequency of cesarean sections, increased use of prenatal ultrasound, significant decrease in post-term deliveries). Nevertheless, MAS continues to be a threat to many newborns throughout the world, with a case fatality rate of 5% (as much as 40%), in addition to short- and long-term pulmonary and neurodevelopmental sequelae[5].

The exact pathophysiology of meconium passage into the amniotic fluid and consequences of meconium aspiration are unknown[2]. The following questions remain (a) Why do some neonates born through MSAF develop MAS and (many) others do not, and (b) What causes the variable clinical expression of MAS?

Clinical Findings

Clinically, MAS is usually defined as a respiratory dysfunction in an infant who is born with MSAF (i.e. visual observation of greenish fluid discoloration) and shows symptoms that cannot be otherwise explained. Unfortunately, there is no definitive test that confirms the clinical impression of meconium in amniotic fluid or on histopathological specimen.

The majority of infants with thin meconium staining of the amniotic fluid at birth are apparently healthy; infants born through thicker MSAF often develop respiratory difficulties; and finally, a subset of thick meconium-stained, depressed infants with MAS have the most severe clinical course and often fatal outcome.

However, since there is a wide variation between the degrees of meconium staining and subsequent respiratory symptoms in the affected infants, additional factors (e.g. meconium- associated pulmonary inflammation, pulmonary infection, and persistent pulmonary hypertension) are evidently also responsible for respiratory manifestations of MAS. Aspiration time of meconium (before birth or during the birth process) may be another determining factor for the clinical findings. Many of the severe cases of MAS are proposed to be initiated by fetal distress and intrauterine aspiration of meconium, but this connection remains controversial[6].

Typical radiographic findings described in infants with MAS are over-expansion of the lungs with widespread coarse infiltrates. However, the severity of the X-ray pattern does not always correlate with the clinical picture. Some patients with severe disease may have minimal X-ray findings, while others have marked X-ray findings without clinical disease. The lack of correlation between clinical severity and radiographic pattern suggests that the disease is less dependent on the amount of meconium obstruction and parenchymal damage than on other aspects of MAS, such as the presence and severity of pulmonary hypertension[6].

In-Utero Meconium Release

There are three prevailing and possibly compatible theories for the mechanisms of meconium release.

(1) Normal maturation of the gastrointestinal tract results in meconium passage: Peristalsis of the fetal intestines is present as early as 8 weeks gestation. Intestinal enzymes including the disaccharidases and alkaline phosphatase have been recovered from amniotic fluid specimens in the mid-trimester (14-22 weeks), suggesting that there is free passage of the intestinal contents into the amniotic cavity. The anal sphincter develops at about 20-22 weeks.

Although the intestinal contents may be released into the amniotic cavity as early as the mid-trimester, they are whitish in color at this point[7]. Therefore, the presence of a greenish discoloration in mid-trimester amniotic fluid should not be considered evidence of meconium passage. Intra-amniotic hemorrhage antedating amniocentesis may cause greenish discoloration of amniotic fluid.

Meconium passage in the preterm third trimester fetus has been reported to be a rare event, as typically it occurs near or post-term. MSAF is a very common finding in term pregnancies and the incidence may be as high as 30% in post-term pregnancies. Fetal motilin secretion is probably not related to the meconium passage[2].

(2) Fetal distress: An alternate hypothesis for in utero meconium passage is that pathologic processes, such as stress via hypoxia or infection, can trigger meconium passage. Meconium passage is associated with reduced amniotic fluid index (< 5 cm), reduced middle cerebral artery pulsatility index, maternal fever, opiate and cocaine use, and multiple nuchal cord loops in postdate pregnancies[8].

Therefore, the presence of MSAF is commonly taken as an indication of possible fetal distress. However, the predictive values of MSAF for fetal distress and acidosis at birth are poor and controversial[9]. In addition, the preterm infant exposed to stress prenatally, as demonstrated by abnormal Doppler indices of the uterine, umbilical and middle cerebral artery, has poor postnatal intestinal motility, which can lead to delayed meconium passage[10].

Associations between meconium passage and microbiologic evidence of intra-amniotic infection, histologic evidence of acute inflammation, and clinical evidence of higher rates of chorioamnionitis and endometritis have been reported[11]. The problem is whether intrauterine infection causes meconium passage, or presence of meconium facilitates ascending infection.

Passage of meconium is more prevalent in pregnancies complicated by gestational cholestasis. In these cases, passage of meconium is not associated with evidence of placental dysfunction, as manifested by rates of fetal growth restriction or oligohydramnios. A significant and independent correlation has also been reported between maternal serum bile acid levels and MSAF[12]. Studies in animal models have shown that high maternal serum bile acid levels stimulate fetal colonic motility, causing passage of meconium[13].

Independently from the factors leading to meconium passage, presence of meconium may cause complications, such as meconium-associated vascular necrosis of umbilical and placental chorionic vessels[14], inhibition of neutrophil oxidative burst and phagocytosis[15] facilitating growth of pathogens within the amniotic fluid and subsequent intrauterine infection[16], and vasoconstrictive activity on the placental vasculature[17]. These findings suggest that if passage of meconium before labor may be a physiologic phenomenon related to the maturation of the gastroenteric nervous system, passage of fresh meconium during labor is more likely due to pathologic processes.

(3) Reduced clearance of defecated meconium: An alternative route for the presence of MSAF in the presence of fetal hypoxia is reduced clearance of defecated meconium. Impaired fetal swallowing in acute hypoxia[18] may cause abnormality in the clearance of meconium that is physiologically passed, and causes meconium accumulation in the amniotic fluid[19-21]. In addition to the gastrointestinal clearance, high incidence of meconium in the amniotic membranes of placentas from healthy term deliveries with clear amniotic fluid at delivery suggests a role for the placenta in meconium clearance[22]. It may be that the pathological clinical situations associated with MSAF (i.e. fetal hypoxia) are related to the failure of defecated meconium clearance due to impaired fetal swallowing or unidentified placental dysfunction in addition to or instead of an increase in its passage. The impaired

clearance hypothesis may be supported with the findings of Ramon y Cajal, who observed fetal defecation in a 35-week gestation using four-dimensional (4-D) ultrasonography[23]. At the uncomplicated delivery of a healthy neonate several weeks later, clear amniotic fluid was documented. Indeed, clear amniotic fluid has been retrieved by amniocentesis soon after 3-D ultrasonographic documentation of fetal defecation in utero[3]

Pathophysiology

The pathophysiology of MAS is multifactorial and extremely complex[24].

(1) Mechanical obstruction: Thick but not thin meconium staining of the amniotic fluid is associated with poor perinatal outcome[25,26]. Aspirated meconium may partially or completely obstruct smaller airways. Partial obstruction (ball valve phenomenon) will lead to air trapping and hyperinflation of certain lung fields, and pneumothorax may occur. Complete obstruction of the smaller airways by meconium causes the air to be absorbed and atelectasis ensues.

In addition to larger airway obstruction, meconium causes direct toxic damage of lung tissue, surfactant inactivation and meconium-associated pulmonary inflammation ("chemical pneumonitis"). Furthermore, immediate changes in pulmonary vasoreactivity lead to a rise in pulmonary vasomotor tone and subsequently to persistent pulmonary hypertension and prolonged (severe) hypoxemia[27].

(2) Meconium-induced surfactant inactivation: Another mechanism contributing to meconium-induced neonatal respiratory distress is surfactant inactivation. Meconium interferes with surfactant in several ways: inactivation of its function depending on the concentration (functional deficiency), direct toxicity on type II pneumonocytes, displacement of surfactant from the alveolar surface, and decrease in surfactant protein A and B levels. However, treatment with surfactant did not significantly affect mortality in infants with respiratory disorders like MAS[28].

(3) Meconium-associated pulmonary inflammation: Meconium may trigger lung inflammatory cells to express proinflammatory cytokines (e.g. interleukin (IL)-1β, IL-6, IL-8 and tumor necrosis factor (TNF)-α). Meconium is an extrinsic source of many proinflammatory cyto- and chemokines [e.g. IL-1β, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (INF)-γ and TNF-α] as well[27,29,30]. These mediators may contribute in vivo to local pulmonary inflammation with influx of leukocytes, T-lymphocytes, monocytes, and macrophages, leading to parenchymal injury and remodelling of lung tissue. Meconium is also a potent activator of complement, a key mediator of inflammation, and may thus contribute to the MAS-related inflammation and lung injury[31]. Therefore, the term "meconium-associated pulmonary inflammation" is probably more accurate than "chemical pneumonitis".

Phospholipase A2 (PLA_2) is a potent proinflammatory enzyme, triggering proinflammatory cells to produce cytokines and possibly leading to surfactant dysfunction and cellular destruction with tissue necrosis and, presumably, apoptosis. Meconium itself is a source of this enzyme. Possibly, bile acids present in meconium raise PLA_2 activity even more[32]. Therefore, aspiration of meconium might also have systemic inflammatory and injurious effects through phospholipase activation[33].

Fetal pancreatic enzymes that are present in meconium might play a direct role in the pathogenesis of MAS through digestion of pulmonary tissues[34].

(4) Meconium-induced apoptosis: In some cases, meconium causes lung airway epithelial cell injury and death through apoptosis[35]. Several pulmonary cell types in newborn rabbits express angiotensin II-receptors (type 1) abundantly after instillation of human meconium, which was associated with increases in cell death[36]. Possibly, the pulmonary renin-angiotensin system (RAS) contributes to the pathophysiology of MAS, and receptor blockade or ACE inhibition may be useful as new treatment strategies for preventing angiotensin II-induced apoptosis in lung cells[37].

Prophylaxis of Meconium Aspiration

Airways suctioning of the neonate may reduce, but does not eliminate, the occurrence of meconium aspiration. Strategies have therefore been sought to reduce fetal meconium aspiration before birth[38-42].

Preventing post-term deliveries: The physiological propensity of the fetus to pass meconium, and thus the incidence of MSAF, increases with increasing gestational age. Preventing prolonged pregnancy by labor induction might reduce the risk of MSAF.

Labor induction methods: The process of labor induction might increase the risk of meconium passage by causing fetal hypoxia or by other mechanisms. Labor induction with prostaglandins, particularly misoprostol, appears to be associated with the occurrence of MSAF. These uterine smooth muscle stimulants might cross from mother to the fetus and cause meconium passage by direct stimulation of the bowel. Amniotomy during labor might increase the risk of MSAF by causing increased uterine contractions, increased direct pressure on the baby's head, or increased umbilical cord compression due to reduced amniotic fluid volume[38].

Amnioinfusion: Amnioinfusion with saline or Ringer's lactate has been described as a method of preventing or relieving umbilical cord compression during labor, or of diluting meconium in the amniotic fluid to try to reduce the risk of meconium aspiration. However, amnioinfusion for suspected umbilical cord compression has no clear effect on the occurrence of MSAF. Amnioinfusion for MSAF also has no clear effect on the risk of MAS, except in centers with limited peripartum surveillance where the effects may be indirect[9].

Intrapartum oro- and nasopharyngeal suction: Meconium below the vocal cords has long been considered to be associated with an increased risk of MAS. During the 70s, oro- and nasopharyngeal suctioning before the delivery of the shoulders and immediate postnatal intubation and tracheal suctioning were practices considered as valuable measures to prevent MAS in infants born through MSAF. During the 80s and 90s, a more selective approach for intubation was taken. However, large randomized controlled trials (RCTs) after 2000 showed that suctioning of the naso- and oropharynx before delivery of the shoulders in newborns with MSAF decreases neither the incidence nor the severity of MAS[43-45]. Intrapartum suction of infants with MSAF is no longer recommended[46-49].

Despite the described evidence and recommendations, some authors still recommend intrapartum suction if there is MSAF, especially for infants born in communities with limited resources, on the feeling that "the procedure is simple and does not carry significant adverse effects". However, suctioning of the hypopharynx is not a risk-free procedure. Potential complications such as delay in the delivery of the infant and in the onset of resuscitation efforts, damage to the mouth and hypopharynx, and cardiac arrhythmias secondary to vagal stimulation may result from this practice.

Laryngeal intubation and suction: Intubation and suction of all (vigorous and non-vigorous) infants with MSAF was a standard practice after birth. The guidelines for cardiopulmonary resuscitation from the American Academy of Pediatrics (AAP) in 1992 recommended intubation and suction of babies born through MSAF for those at high risk for MAS (mainly thick and particulate consistency). Reports later showed that tracheal suction did not decrease the incidence of MAS and that some complications were related to intubation of vigorous infants in the delivery room.

Intrapartum suctioning as well as postnatal endotracheal suctioning of vigorous infants with MSAF is no longer recommended. Currently, endotracheal suction is recommended only in neonates born through MSAF who are not vigorous at birth[46]. It should be noted that suctioning of the airway at birth to remove meconium before starting positive-pressure ventilation in non-vigorous infants with MSAF, as presently recommended by the AAP and International Liaison Committee on *Resuscitation* (ILCOR), has not been evaluated through clinical trials.

Gastric lavage to eliminate meconium from the stomach, chest physical therapy and bronchial lavage with saline to remove meconium from the airways have all been used without solid scientific support. All these techniques have potential risks and therefore cannot be recommended.

Accurate prediction of which infants born through MSAF will develop MAS and which ones will not remains very difficult. Since a strong relation between a 5-minute Apgar score of <7 and MAS development has been shown

in many countries worldwide, meconium-stained infants are clinically observed during the first 24 hours after birth. However, infants uneventfully delivered through MSAF with a 5-minute Apgar score >8 rarely develop MAS, and vigorous infants born through MSAF with a 5-minute Apgar score of 9 or 10 can be safely discharged from the hospital without 24-hour postnatal clinical observation[50].

Management of Infants with Meconium Aspiration

Respiratory support: Respiratory failure in infants with MAS is frequently treated initially with conventional or synchronized mechanical ventilation. The indications for mechanical ventilation in infants with MAS are arbitrary[51]. There are no RCTs to support a specific strategy for mechanical ventilation in infants with MAS. In some infants, meconium is repeatedly obtained when the endotracheal tube is suctioned during the first hours of life, which indicates some degree of obstruction. In these patients, a longer than usual inspiratory time (IT) is used (0.5 to 0.7 s) with respiratory rates of 30 or less. Extracorporeal membrane oxygenation (ECMO) should be used, when available, for infants with MAS who do not respond to the aforementioned therapies. High-frequency ventilation (HFV) is commonly used as rescue therapy for severe cases. Nitric oxide (NO) is added when severe pulmonary hypertension is demonstrated. ECMO is an option when other treatments have failed[42].

Although bolus administration of surfactant cannot be recommended for routine use in infants with MAS, its use in selected patients with predominantly parenchymal disease and severe respiratory failure appears indicated. The Cochrane Library concludes that surfactant administration may reduce the severity of MAS and decrease the number of infants with progressive respiratory failure requiring ECMO support[52].

Some case reports and small studies performing bronchoalveolar lavage with surfactant in infants with MAS have been published. The theory behind this technique is based on the potential removal of meconium and leaving a therapeutic amount of surfactant in the lungs at the end of the procedure. Lung lavage with dilute surfactant does not alter the duration of respiratory support, but may reduce mortality, especially in units not offering ECMO[53]. Surfactant lung lavage therapy also has no advantage over bolus surfactant treatment in infants with MAS complicated by persistent pulmonary hypertension[54]. However, the technique is risky and it cannot be recommended for routine use before large RCTs[55,56].

Antiinflammatory drugs: Based on studies suggesting that meconium generates an inflammatory response on lung tissue, steroids have been tried in infants with MAS[57,58]. At present, there is insufficient evidence to propose routine steroid therapy in the management of MAS.

Antibiotics: The presence of meconium increases the chances of positive cultures from amniotic fluid in preterm and term infants. However, studies evaluating the development of sepsis in infants with MSAF failed to demonstrate a relationship. Although prophylactic antibiotics in infants with MAS are not justified, most of these patients receive antibiotics during the first days of life, before the diagnosis of pneumonia can be completely ruled out[59,60].

Systemic Inflammation and Long-Term Sequelae

Whereas in the initial, acute phase of lung injury, the inflammatory response may be seen as a part of the local defense system, continuing excess production of inflammatory mediators may occasionally result in systemic inflammatory reaction and eventually lead to multiple organ dysfunction. Additional factors, like ventilatory treatment, may further propagate the inflammatory reaction and distant organ injury. Nevertheless, it remains undetermined how often and at what intensity systemic inflammation occurs in association with MAS and what its significance is for the outcome of infants with severe MAS.

Children surviving severe MAS are in fact reported to have higher prevalence of asthmatic symptoms and bronchiolar hyperreactivity than children in the general population. The exact cause and clinical significance of this finding has not yet been determined, but since inflammation may play a role and glucocorticoids may acutely reduce meconium-induced airway hyperreactivity[61], the possible long-lasting effects of anti-inflammatory agents,

administered during the neonatal period, should be evaluated.

Although intrauterine meconium is supposed to be able to impair fetal perfusion, and pulmonary meconium may induce systemic circulatory or inflammatory reactions, the mechanisms and clinical relevance of the meconium aspiration-associated long-lasting sequelae in the lungs and remote organs are still unclear and should be addressed in more detail.

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