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Meconium Aspiration Syndrome — More Than Intrapartum Meconium

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Meconium, the fecal material that accumulates in the fetal colon throughout gestation, is a term derived from the Greek *mekoni*, meaning poppy juice or opium. Beginning with Aristotle's observation of the association between meconium staining of the amniotic fluid and a sleepy fetal state[1] or neonatal depression, obstetricians have been concerned about fetal well-being in the presence of meconium-stained amniotic fluid.

The passage of meconium normally occurs within the first 24 to 48 hours after birth. However, the passage of fetal meconium, resulting in meconium-stained amniotic fluid, occurs in approximately 12 percent of all deliveries. The meconium aspiration syndrome, associated with aspiration or perhaps diffusion of meconium into the fetal airways, occurs in 5 percent of these infants. Of infants in whom the meconium aspiration syndrome develops, more than 4 percent die,[2] accounting for 2 percent of all perinatal deaths. The meconium aspiration syndrome is manifested by newborn respiratory compromise, with tachypnea, cyanosis, and reduced pulmonary compliance. Persistent pulmonary hypertension due to increased pulmonary vascular resistance may accompany the meconium aspiration syndrome; there is an increased prevalence of asthmatic symptoms and abnormal bronchial reactivity among survivors of the syndrome.[3,4]

When aspirated into fetal lungs, meconium particles mechanically obstruct the small airways. Meconium or the chemical pneumonitis it causes inhibits surfactant function, and inflammation of lung tissue contributes further to small-airway obstruction. Acute intrapulmonary meconium contamination induces a concentration-dependent pulmonary hypertensive response,[5] with 15 to 20 percent of infants with the meconium aspiration syndrome demonstrating persistent pulmonary hypertension.[6] However, evidence of a long-term process of muscularization of distal pulmonary arterioles in infants with the meconium aspiration syndrome who died suggests that factors other than meconium aspiration (e.g., chronic hypoxemia) may contribute to the pulmonary symptoms. Meconium may also stimulate the constriction and necrosis of umbilical vessels and the production of thrombi, although the clinical relevance of these effects is uncertain. The passage of meconium in utero occurs primarily in situations of advanced fetal maturity or fetal stress. Most infants who are delivered with meconium-stained amniotic fluid are 37 weeks of gestation or older; meconium rarely appears in amniotic fluid before 32 weeks of gestation. Fetal hypoxic stress may stimulate colonic activity, resulting in the passage of meconium, and also may stimulate fetal gasping movements that result in meconium aspiration.

Amnioinfusion, the injection of fluid into the

amniotic cavity, was originally devised as a therapeutic maneuver for umbilical-cord compression that results in variable decelerations in fetal heart rate during labor. Individual studies and meta-analyses[7] have shown significant reductions in the incidence of decelerations in fetal heart rate when therapeutic amnioinfusion is performed for the indication of variable decelerations. In turn, there also have been significant reductions in the rates of cesarean section for suspected fetal compromise and hospital lengths of stay.

Because compression of the umbilical cord occurs more frequently when there is a reduced volume of amniotic fluid, prophylactic amnioinfusion for such patients (i.e., those with oligohydramnios) was subsequently advocated to prevent decelerations in fetal heart rate and to improve outcome. Although prophylactic amnioinfusion for oligohydramnios has been shown to have efficacy when compared with no amnioinfusion, prophylactic amnioinfusion has no benefit over therapeutic amnioinfusion in cases of variable decelerations in fetal heart rate.[8] Because the passage of meconium in utero is often associated with oligohydramnios and has the associated risk of the meconium aspiration syndrome, prophylactic amnioinfusion has been advocated to increase the volume of amniotic fluid and to dilute or wash out the meconium. Several small studies have suggested a benefit associated with amnioinfusion in patients with meconium-stained amniotic fluid,[9] although other studies have not shown a clinical benefit.[10]

In this issue of the *Journal*, Fraser et al. report the results of an ambitious international, multicenter, randomized trial involving nearly 2000 women in labor (in 13 countries) with thick meconium staining of the amniotic fluid.[11] Prophylactic amnioinfusion resulted in no reduction in the rate of moderate or severe meconium aspiration syndrome (4.4 percent of infants of women in the amnioinfusion group vs. 3.1 percent of those in the control group), perinatal death (0.5 percent in both groups), or cesarean delivery (31.8 percent in the amnioinfusion group vs. 29.0 percent in the control group). Fraser et al. conclude that meconium staining of the amniotic fluid is not an indication for amnioinfusion for women in labor.

Given previous data suggesting a benefit to amnioinfusion in cases where there are variable decelerations in fetal heart rate, Fraser et al. also looked explicitly at the subgroup of women (19 percent of the total group) who presented with a minimum of three variable decelerations in fetal heart rate during the 30 minutes before randomization. No benefit was observed in this subgroup, but as the authors acknowledge, this analysis was underpowered. Fraser et al. note that fetal heart-rate abnormalities requiring clinical intervention developed in an additional 14 percent of patients in both the amnioinfusion and control groups, but the authors do not provide information on the effects of amnioinfusion in this subgroup.

There are several possible explanations for the failure of amnioinfusion to prevent the meconium aspiration syndrome. It is likely that most infants in whom this syndrome develops have meconium in the tracheobronchial tree before presentation in labor; amnioinfusion would not prevent meconium aspiration under these circumstances. Some infants with the diagnosis of the meconium aspiration syndrome have evidence of long-standing stress, including neonatal pulmonary hypertension and vascular hypertrophy. These findings reflect processes occurring over a period of days or longer, not simply the hours of labor,[12] and would not be affected by dilution of meconium in the amniotic fluid during labor. In addition, the risk of the meconium aspiration syndrome is particularly high in cases in which there is not only thick meconium but also hypoxia in utero, as reflected by low Apgar scores at five minutes. In the study by Fraser et al., less than 3 percent of all newborns had a five-minute Apgar score below 7. It is likely that the close observation of fetal heart patterns and interventions for suspected fetal compromise for patients in both study groups contributed to a low incidence of newborns with asphyxia.

Given the lack of benefit of amnioinfusion in the study by Fraser et al., what might the clinician do to prevent the meconium aspiration syndrome? Although routine intrapartum oropharyngeal and nasopharyngeal suctioning of term infants born through meconium-stained amniotic fluid is a mainstay of current therapy, it has recently been shown not to prevent the meconium aspiration syndrome.[13] Better understanding of how the maturation of the motility of the fetal colon accounts for the timing of the passage of meconium and its stimulation by fetal stress (thought to be mediated, in part, by means of the hypoxia-induced release of placental corticotropin-releasing factor[14]) ultimately may lead to future therapeutic interventions.

A reduction in the rate of post-term delivery was reported to be the most important factor underlying a decrease, by a factor of nearly four, in the incidence of the meconium aspiration syndrome from 1990 to 1998.[15] This probably can be explained by reductions in the number of infants passing meconium (in association with advanced maturity) and in the rate of intrauterine hypoxia (for which the risk is increased in post-term pregnancies). Although current standards of care involve the initiation of antepartum fetal monitoring and consideration of induction of labor by 42 weeks of gestation,[16] protocols for the earlier initiation of fetal monitoring (e.g., by 40 weeks) and the earlier induction of labor (e.g., by 41 weeks) may ultimately prove to be beneficial for the prevention of the meconium aspiration syndrome. In the meantime, the article by Fraser et al. provides strong evidence that amnioinfusion is not warranted to prevent this syndrome in women with thick meconium staining of the amniotic fluid.

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