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THE MANAGEMENT OF MECONIUM ASPIRATION SYNDROME*

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SUMMARY: Roberton NRC. (Rosie Maternity Hospital, Cambridge, United Kingdom). The management of meconium aspiration syndrome. Turk J Pediatr 33: 65-78, 1991.

Meconium aspiration is one of the important causes of mortality and morbidity in the neonatal period. Recently, advances for preventing meconium aspiration syndrome by the use of fetal monitoring, mechanical ventilation and supportive treatment have decreased the incidences of morbidity and mortality in this syndrome. In this paper, the management of this syndrome is reviewed and recent advances noted. *Key words: meconium aspiration syndrome, newborn.*

The incidence of meconium aspiration syndrome varies, perhaps as an indication of the standards of intrapartum care. In Europe, the incidence is between 1:1000 - 1:2000 whereas in North America and the Middle East rates of 2-6:1000 have been reported, with a mortality ranging from 5-30% (Table I).

It is a common cause of neonatal mortality and morbidity in otherwise normal term babies and frequently co-exists with hypoxic-ischemic encephalopathy (HIE) babies who have suffered severe birth asphyxia.

TABLE I: Incidence of Meconium Aspiration Syndrome (MAS)

Years	Incidence/1000 Births	Mortality	Country	Reference
1970-74	2.4	28%	U.S.A.	Carson et al[1]
1976-77	0.9	0%	Sweden	Hjalmarson[2]
1976-84	3.0	7.2%	Lebanon	Mounla[3]
1983-84	0.5	0%	U.K.	Field et al[4]
1984-88	3.4	?	Saudi Arabia	Roberton[5]
1985-89	1.8	4.5%	U.K.	Roberton[6]
1973-87	6.5	4.2%	U.S.A.	Wiswell et al[7]

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Etiology

Three things have to happen for a baby to develop meconium aspiration syndrome (MAS): he has to pass meconium, he then has to inhale it, and finally the inhaled material has to damage the lungs.

About 15-20% of babies are born in the presence of meconium stained liquor[8], and MAS is primarily a disease of term and post-term pregnancies[9,10] and only occurs in a very small percentage of preterm pregnancies unless there is concomitant infection with listeria[11]. It is of course, a very poor marker of fetal asphyxia, and is not a feature of small-for-dates pregnancies[12].

Once passed, the meconium can be inhaled either prenatally or postnatally. Meconium inhalation can occur pre-delivery since it is found in the lungs of stillborn babies[13], and in the lungs of babies who die in the early neonatal period, but could not have inhaled meconium intrapartum[14-16]. Hooper, et al[17] have recently shown that prolonged fetal hypoxia can stimulate fetal breathing to the extent that amniotic fluid is inhaled.

Postnatally, meconium inhalation can occur if the baby breathes or gasps with his mouth, pharynx or larynx full of meconium stained liquor. It is, of course, crucial to realize that meconium can be inhaled whether or not the baby is asphyxiated. A normal baby with his mouth and pharynx full of meconium stained liquor may inhale it, and become critically ill even if he did not suffer any problems pre-delivery.

Once inhaled, meconium has at least four deleterious effects on a neonatal lung (Fig. 1).

1. It creates a ball valve mechanism in the airways, whereby air can be sucked past the plug but cannot be exhaled.

2. It acts as a chemical irritant: 24-48 hours after inhalation there is an exudative and inflammatory pneumonitis with alveolar collapse and cellular necrosis.

3. The organic nature of the inhaled material, although initially sterile, may pre-dispose the baby to pulmonary infection, particularly with *E.coli*[18].

4. It displaces surfactant off the alveolar surface[19].

These four factors combine to cause severe airway and alveolar disease, but from studies in animals it may be that severe disease will only occur if there is co-existing asphyxial lung damage[20].

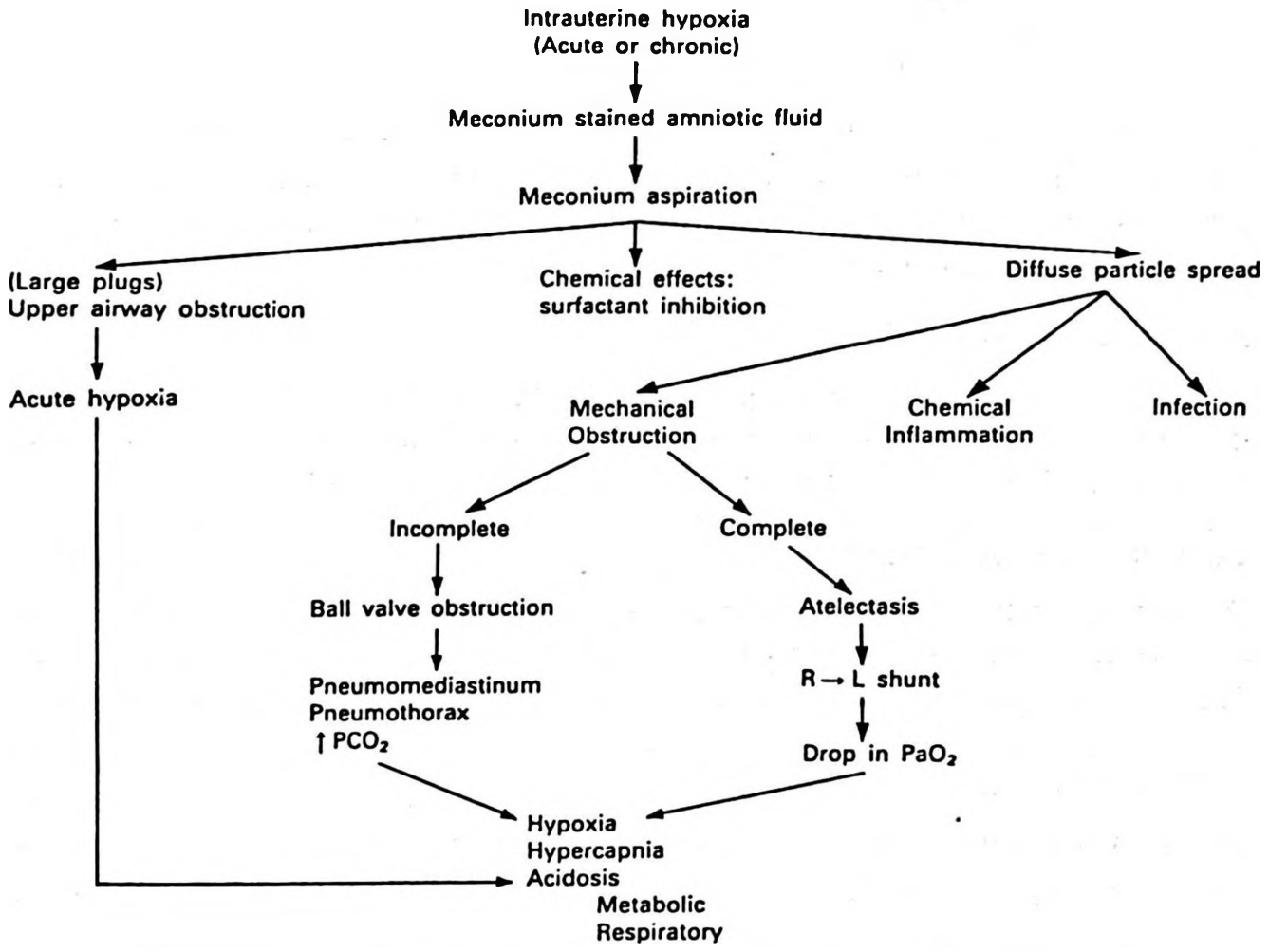

Fig. 1: Schema for the pathophysiology of meconium aspiration pneumonia[48].

SIGNS AND SYMPTOMS

General Appearance

The baby is usually mature or post-mature. The skin, nails and umbilical cord are often stained greenish yellow. The baby is not usually febrile, unless he becomes secondarily infected. Peripheral edema is not a feature, and if present, it suggests either central nervous system (CNS) damage, renal failure, or iatrogenic fluid overload.

Respiratory

The respiratory rate may exceed 120/min with intercostal and subcostal recession, the use of accessory muscles, and flaring of the nostrils. The meconium in the airways causes widespread sticky crepitations, and occasional ronchi, and an overdistended chest with an increased anteroposterior diameter.

Cardiovascular

In uncomplicated MAS the heart rate tends to be rather low, at around 110-125/min, and the blood pressure is maintained within the normal range. Hypotension suggests that there has been asphyxial myocardial damage. If pulmonary hypertension develops, S_2 may remain single, and there may be the murmur of tricuspid incompetence.

Abdominal Examination

The liver and spleen are often palpable due to downward displacement of the diaphragm caused by air trapping. In a severely affected infant, bowel sounds may be absent, and no further meconium will be passed.

Central Nervous System

Depending on the severity of the co-existing neurological insult, the baby may behave normally, or may show any of the neurological features of HIE. Convulsions may occur, and he may be jittery for a period of three-four days.

DIFFERENTIAL DIAGNOSIS

This should rarely be a problem. A term baby who is dyspneic and has meconium stained liquor in his trachea and larynx at delivery has MAS until proved otherwise.

PATHOPHYSIOLOGY

The respiratory failure and hypoxemia in babies with MAS are due to stiff lungs, marked ventilation-perfusion imbalance and pulmonary hypertension precipitating extra-pulmonary right-left shunts.

Bancalari et al[21] (Table II) showed that babies with MAS have a reduced compliance and tidal volume, and an increased airways resistance, but the tachypnea increased the minute volume to twice normal. In the early stages of the disease, when the airways are plugged by meconium, as in the animal model[22],

TABLE II: Respiratory Function in Meconium Aspiration Syndrome (MAS) (Bancalari et al[21])

Investigation	Values in (Mean 1SD)	Normal
Tidal volume (ml)	16.3 (6.7)	24
Minute ventilation (ml/min)	1647 (611)	800
Compliance (ml/cmH_2O)	1.82 (0.76)	4-6
Inspiratory resistance (cmH_2O/L/sec)	100 (67)	15-30

there is a marked ventilation perfusion abnormality which lessens as the lungs recover[23,24]. Later in the disease, shunting increases as the chemical pneumonitis becomes a dominant factor[22]. In those who develop pulmonary hypertension, the pulmonary artery pressure will be higher than the systemic[25] with right-left shunting at the ductus arteriosus[26] and/or the foramen ovale.

INVESTIGATIONS

Blood and biochemistry

The hemoglobin should be checked daily, and coagulation disturbances sought in those who were severely asphyxiated, show a bleeding diathesis or are ventilated. The electrolytes, urea and albumin should be measured daily and abnormalities corrected.

Blood gases

Hypoxia is common, but in cases with mild-moderate disease who are mature, with an efficient respiratory pump, ventilation is not a problem and the $PaCO_2$ may even be low, normal or only slightly raised. A $PaCO_2 > 60$ mm/Hg is unusual, and is seen only in patients with severe lung disease.

Changes in pH initially reflect the metabolic acidemia of intrapartum asphyxia, but if they persist, hypotension and septicemia should be sought.

Electrocardiography and echocardiography

If there has been severe intrapartum asphyxia, there may be electrocardiographic changes suggesting sub-endocardial ischemia and echocardiography will show a reduced cardiac contractility.

Chest X-ray

Many different x-ray patterns may be seen in neonates with MAS. A common early change is widespread patchy infiltration with small pleural effusions in 20-30% of cases. Over-expansion is also common in the early stages, and is best seen on the lateral chest X-ray.

In severe cases, by 72 hours of age, with or without ventilation, the chest x-ray shows diffuse and homogeneous opacification of both lung fields, presumably due to a pneumonitis and interstitial edema secondary to the irritant effects of the inhaled meconium. These changes gradually resolve over the next week, but in severe cases, the X-ray may still be abnormal at 14 days and merge into the changes of bronchopulmonary dysplasia. Air leaks, in particular pneumothorax and pneumomediastinum, are very common in MAS.

Microbiology

All babies suffering from MAS should have full set of swabs taken together with the blood culture as soon after admission to the Neonatal Intensive Care Unit (NICU) as possible. This is the only way to establish the co-existence of sepsis, and since antibiotics will be used in virtually all cases, this provides the essential base-line information upon which further antibiotic therapy can be planned.

TREATMENT

On the basis of the etiology and pathophysiology of MAS outlined above, treatment can be divided into two components. Firstly the impact of meconium in the amniotic fluid must be minimized by meticulous airway toilet in the labor ward; secondly if meconium is inhaled, the baby must be kept alive until the normal lung mechanisms for removing inhaled foreign material have cleared meconium from the airways and alveoli.

Labor ward care

It cannot be emphasized too strongly that the most important part of the treatment of MAS is meticulous removal of meconium from the baby's airway as soon after delivery as possible. Since babies can be born through meconium stained liquor, but not be asphyxiated, and there is no way of identifying which type of meconium staining (thick vs thin: early vs late) is most sinister, this means that someone skilled in laryngoscopy must attend all deliveries at which there is meconium staining of the liquor, even though this may mean attending up to 20 percent of all deliveries.

Airways suctioning

Although meconium can be inhaled prenatally, most cases of MAS are due to inhalation of meconium when the baby gasps during the last few moments of the second stage of labor, or with the initial few breaths or gasps after his head is delivered. Therefore, as soon as the baby's head is crowned and the mouth and nose visible, both should be efficiently and gently sucked out. Carson et al[1] showed that this would prevent many, but not all babies, from developing MAS, and that in addition, subsequent meticulous airway toilet was necessary. As soon as the pediatrician receives the baby, therefore, he should laryngoscope him, and carefully clear the upper airway of any meconium stained material present. This requires skill and experience in a vigorous howling term neonate. If no meconium is seen down the trachea distal to the vocal cords, there is no need to pass the suction catheter through the cords to suck the baby out[27]. If, however, meconium is seen in the trachea, direct endotracheal suction is indicated[28] and can be repeated several times, since some meconium will stay in the trachea and major bronchial divisions for several minutes after the onset of respiration[29].

Intubation and positive pressure ventilation

The presence of meconium in the airway is the one situation that takes precedence over immediate ventilation in the apneic neonate. Irrespective of the heart rate (even if it is zero) the upper airway must be cleared before the baby is intubated and resuscitated in the usual way. If the baby needs to be intubated for resuscitation, suck out the endotracheal tube before giving Intermittent Positive Pressure Ventilation (IPPV) or use the endotracheal tube as the suction tube[30] and then replace it. After giving the minimum IPPV necessary to cause a satisfactory increase in the heart rate, and an improvement in the baby's color, the endotracheal tube should be sucked out again to ensure that there is no residual meconium.

Bronchial lavage

Instilling water or saline into the lower respiratory tract is damaging, and repeated bronchial lavages can do harm. However if a baby, despite adequate endotracheal suctioning, is thought to have inhaled large amounts of meconium, instill 0.5-1.0 ml of saline down the endotracheal tube, hand ventilate the baby 4-5 times and suck out the tube. If no meconium is obtained, there is no need to persist. Only one or two lavages should be attempted.

Postnatal gastric aspiration

If the baby has inhaled meconium at delivery, it is likely that he has also swallowed some as well. His stomach should, therefore, be emptied as soon after delivery as possible.

Subsequent labor ward care

For the baby who, despite being covered in meconium, has no evidence of intratracheal meconium and who is pink and vigorous with no respiratory distress by 10 minutes of age, it can be assumed that he has not inhaled meconium. Such a baby does not need to be transferred to the neonatal unit, and should be given to his mother for routine postnatal care. Babies should only be transferred to the neonatal unit if they show signs of respiratory disease.

Care in the neonatal unit

If the baby is admitted to the Neonatal Unit (NNU) with respiratory difficulty, it is essential to obtain baseline investigations within the first 30-60 minutes. These must include a set of arterial blood gases, a measurement of blood pressure and a chest X-ray. If these procedures are not carried out in term babies, who may show surprisingly few clinical features of serious cardiorespiratory or acid-base abnormalities, profound acidemia, myocardial damage or serious hypoxia may all be missed.

Oxygen therapy

Despite the damaging effects of meconium in their airways, the relative efficiency of the respiratory system in mature babies enables them normally to control their $PaCO_2$ unless the disease is very severe or respiration is depressed by drugs or asphyxia. Since mature babies are not susceptible to retinopathy of prematurity, hyperoxemia is not a threat, and the prime concern is, therefore, preventing hypoxemia.

Most babies with MAS can, therefore, be managed by the introduction of an adequate concentration of warmed humidified oxygen into a headbox. This can be at a concentration of 80-90% if indicated, and may need to be sustained at this concentration for up to two weeks for those with severe disease. Unlike preterm babies with Respiratory Distress Syndrome (RDS), there is no need to intervene and give Continuous Positive Airway Pressure (CPAP) in the first 36-48 hours, just because the oxygen requirement exceeds 10-60%, or the $PaCO_2$ rises to 45-48.8 mm/Hg or greater.

In many mild cases, oxygen therapy at 40% or less for 24-48 hours is all that is required, and in all cases once the PaO_2 begins to rise, the Fi(fraction of) O_2 can be reduced. Many neonates with mild MAS have a normal PaO_2 in room air by 48 hours of age.

Acid base homeostasis

Carbon dioxide retention is only a problem in severe cases. However, a $PaCO_2$ of 56.3-60 mm/Hg is acceptable, so long as the pH is sustained above 7.25 and other factors in the baby such as his blood pressure, peripheral blood flow, urinary output and clinical condition are acceptable. If the $PaCO_2$ rises above 60 mm/Hg, particularly in the presence of a $PaO_2 < 45$ mm/Hg early in the disease, it is usually an indication for intubation and ventilation.

The first blood gas analysis taken after birth may show a marked metabolic acidemia. So long as the baby is otherwise stable, with a normal PaO_2 and $PaCO_2$ and in particular is passing urine, base deficits of –10 to –15 mmol/L can be left to correct themselves spontaneously and the baby should not be given sodium bicarbonate or THAM. However, once the base deficit has fallen to below –15 mmol/L or the pH below 7.10, it is prudent to correct the acidemia.

If the baby with MAS also has HIE, more rigid control of the blood gases may be called for; hypoxia, hypercapnia and acidemia are all undesirable if there is co-existing brain damage. The conservative management of the blood gases outlined above in babies with uncomplicated MAS may therefore have to be abandoned and the baby intubated and ventilated to teep the $PaCO_2 < 41.3$ mm/Hg.

Continuous positive airway pressure (CPAP)

Although CPAP at pressures of 4-7 cm H_2O increases the PaO_2 in babies with MAS[31], we rarely use it. It is not justified to intubate a baby just to give CPAP. Term neonates do not usually tolerate nasal CPAP and, furthermore, CPAP is likely to increase the risk of pneumothorax in a disease characterized by air trapping.

Intermittent positive pressure ventilation (IPPV)

In the absence of HIE, babies with MAS should only be intubated and ventilated if they collapse and become apneic with, for example, a pneumothorax, or if severe blood gas abnormalities occur: in general this means a $PaCO_2 > 60$-63.8 mm/Hg or a $PaO_2 < 41.3$ mm/Hg in 90% oxygen. Once intubated, these babies virtually always fight the ventilator, and pancuronium should be given.

To prevent air trapping as long an expiratory time as possible should be used, and it is rarely necessary to give more than 2-3 cm of positive end expiratory pressure (PEEP). Rates > 60-80/min should not be used, since particularly in paralyzed babies, this is likely to be associated with an increase in inadvertent PEEP. Initial ventilator settings should, therefore, be:

Rate 60-80/min
Inspiratory time 0.3 sec (i.e., ratio therefore approximately 1:2)
Peak inspiratory pressure 25 cmH_2O
End expiratory pressure 3 cmH_2O
Oxygen concentration 80%

The ventilator settings can then be adjusted in the light of the blood gas analyses.

When these large babies start to improve on IPPV, weaning can usually be rapid. Once they are in 50-60% oxygen and on pressures < 22/3 cmH_2O, they will usually be off pancuronium and will be breathing well on their own. The rate can then be reduced quickly, and they can be extubated without a period of CPAP.

Pulmonary vasodilators

Babies with MAS do benefit from these drugs[32,33]. In general, we would reserve them from those already on the ventilator, but as an alternative to intubating them and giving IPPV, it is sometimes worth trying the effect of a single i.v. push of tolazoline in a spontaneously breathing baby who just has severe hypoxemia if his blood pressure is stable, and he has a normal pH and $PaCO_2$. Whether ventilated or not, if there is an acceptable response in PaO_2 after a bolus of 2 mg/kg/i.v. of tolazoline, this can be followed by an i.v. infusion of 2 mg/kg/hr.

Physiotherapy

Intuitively this should be good for patients whose airways are plugged with nasty extraneous material. In practice, in the common mild-moderate cases who are not

ventilated and require 60% O_2, the prognosis is excellent whatever therapy is given, and I see little point in disturbing the baby to give chest physiotherapy. In the severely affected neonate who is intubated and paralyzed, 6-8 hourly percusion and endotracheal tube suction should be carried out. If this results in the production of significant amounts of greenish material, the benefits are clear cut, but if it makes the neonate irritable, restless and hypoxic, and little or no meconium is obtained, it is contraindicated.

Steroids

Randomized prospective controlled trials in animals and humans have shown no benefit from these drugs[34,35]; they should not be used.

Antibiotics

In the first few hours it it impossible to be certain whether a baby has just MAS, or MAS complicated by intrapartum infection with, for example, the Group B streptococcus. The presence of organic material in the lung may predispose to pneumonia[18]. Therefore, after taking a full set of cultures, but not doing a lumbar puncture, we put all neonates diagnosed as MAS on broad spectrum antibiotics using penicillin and gentamicin in most cases, though, in preterm babies who may be at risk for listeria, ampicillin would be substituted for penicillin. We would continue the drugs until the baby was in the convalescent stage of his illness and requiring < 30-40% oxygen.

Blood volume and blood pressure

Anemia is not usually a problem in babies with MAS either immediately after delivery or as a result of blood sampling, but if the hemoglobin falls below 13 g/dl, the baby should be transfused[36]. Blood pressure control is essential in all neonates with MAS, aiming to keep the pressure above 50-55/30 mmHg. Hypotension is usually only a problem in those babies who have suffered intrapartum asphyxia with co-existing myocardial injury or after administration of tolazoline. If hypotension does occur, an infusion of albumin or blood (15 ml/kg) should be given. If this is not effective, dopamine should be given starting at 5 μg/kg/min intravenously.

Fluid and electrolyte balance

In uncomplicated MAS this is rarely a problem. Intravenous fluids should be started at 60 ml/kg/day on the first day and increased thereafter as indicated. If the MAS was accompanied by severe birth asphyxia, a much stricter fluid regime giving only 40-45 ml/kg/24 hours is indicated. The initial fluid given should be 10% Dextrose, with electrolytes added after 24-48 hours. Hypoglycemia is always a possibility, and babies with MAS should have their blood glucose checked twice or thrice a day for the first 48 hours.

Nutrition

In the first day or two of the disease enteral feeding is not justified. Mild-moderate cases of MAS have a short duration so that some enteral feeding can usually be started by 2-3 days of age in most babies. For those still on IPPV at this stage, and for the small number of non-ventilated cases who by 5-6 days are not suitable for enteral feeding, intravenous nutrition can be started.

MONITORING

There is a temptation to undermonitor the large full-term baby with MAS, because, despite marked tachypnea and a dreadful chest X-ray he often looks surprisingly pink and vigorous. This temptation should be resisted, not only because of the importance of early detection of blood gas abnormalities, electrolyte disturbance or hypotension before secondary effects develop, but because the baby with MAS has a major risk of sudden deterioration with a tension pneumothorax.

Heart rate and respiration (apnea) must be monitored continuously, and if continuous blood pressure recording is not available, it should be checked by one of the oscillometric devices on admission and 2-4 hourly thereafter.

Since hyperoxemia is not a threat to mature babies, in mild cases requiring 30-40% oxygen by headbox adequate control can be obtained by measuring blood gases on samples drawn 2-3 times a day by direct arterial puncture. Umbilical catheterization is indicated for ease of sampling in infants requiring high FiO_2, IPPV, and in those with neurological problems, in whom frequent blood gas measurements are necessary. Transcutaneous PO_2 and PCO_2 monitors are less accurate in term babies with their thick skin[37]. Pulse oximetry, however, is a very effective way of monitoring oxygenation.

COMPLICATIONS

Pneumothorax, air leaks

These are the most feared and common complications, occurring in 15-20% of unventilated babies[38,39], and in 30-50% of those who require IPPV[40,21]. Pulmonary interstitial emphysema is rare, but pneumomediastinum, pneumopericardium and pneumoperitoneum can all occur.

Pneumothoraces may be both bilateral and under tension, and commonly cause acute deterioration in the baby's condition. It is essential, therefore, that babies with severe MAS are only cared for in units that have the wherewithall to respond instantaneously and effectively when a tension pneumothorax occurs.

Pulmonary hypertension (persistent fetal circulation)

The North American experience would suggest that this is a common complication of MAS and on histological and clinical grounds it would appear to be particularly common in fatal cases[41]. The incidence of this complication does seem to vary[42,43], but this may be merely a matter of definition. In my experience it is rare, and usually responds promptly to tolazoline and conventional ventilation.

Bronchopulmonary dysplasia

Both in the literature[44,45] and in my experience this appears to be a rare complication of MAS, though it may occur in any baby who survives after long-term high pressure IPPV.

Outcome

With good labor ward care, most cases of MAS should be mild; only 10% of cases admitted to the Cambridge Neonatal Unit require IPPV. Even for these cases, survival should be the rule except for those who are virtually impossible to resuscitate in the labor ward, or those who have fetal co-existing HIE. Neurological sequelae in survivors are primarily limited to babies with HIE, but long-term damage to the lungs may occur even in those who are not ventilated[46,47].

REFERENCES

1. Carson BS, Losey RW, Bowes WA Jr, Simmons MA. Combined obstetric and pediatric approach to prevent meconium aspiration syndrome. *Am J Obstet Gynecol* 126:712, 1976.
2. Hjalmarson O. Epidemiology and classification of acute, neonatal respiratory disorders. A prospective study. *Acta Paediatr Scand* 70:773, 1981.
3. Mounla NA. Neonatal respiratory disorders. A prospective epidemiological study from a developing country. *Acta Paediatr Scand* 76:159, 1987.
4. Field DJ, Milner AD, Hopkin IE, Madeley RJ. Changing patterns in neonatal respiratory diseases. *Pediatr Pulmonol* 3:231, 1987.
5. Roberton NR. (unpublished data)
6. Roberton NR. (unpublished data)
7. Wiswell TE, Tuggle JM, Turner BS. Meconium aspiration syndrome: Have we made a difference ? *Pediatrics* 85:715, 1990.
8. Nelson KB, Ellenberg JH. Obstetric complications as risk factors for cerebral palsy or seizure disorders. *JAMA* 251:1843, 1984.
9. Meis PJ, Hall M, Marshall JR, Hobel CJ. Meconium passage: a new classification for risk assessment in labour. *Am J Obset Gynecol* 131:509, 1978.
10. Mathews TG, Warshaw JB. Relevance of the gestational age distribution of meconium passage in utero. *Pediatrics* 64:30, 1979.
11. Halliday HL, Hirata T. Perinatal listeriosis: a review of twelve patients. *Am J Obset Gynecol* 133:405, 1979.

12. Jones RA, Roberton NR. Problems of the small-for-dates baby. *Clin Obstet Gynaecol* 11:499, 1984.

13. Brown BL, Gleicher N. Intrauterine meconium aspiration. *Obstet Gynecol* 57:26, 1981.

14. Manning FA, Schreiber J, Turkel SB. Fatal meconium aspiration in utero: a case report. *Am J Obstet Gynecol* 132:111, 1978.

15. Byrne DL, Gau G. In utero meconium aspiration: an unpreventable cause of neonatal death. *Br Obstet Gynaecol* 94:813, 1987.

16. Sunoo C, Kosasa TS, Hale RW. Meconium aspiration syndrome without evidence of fetal distress in early labour before elective cesarean delivery. *Obstet Gynecol* 73:707, 1989.

17. Hooper SB, Harding R. Changes in lung liquid dynamics induced by prolonged fetal hypoxemia. *J Appl Physiol* 69:127, 1990.

18. Bryan CS. Enhancement of bacterial infection by meconium. *Johns Hopkins Med J* 121:9, 1967.

19. Clark DA, Nieman GF, Thompson JE, et al. Surfactant displacement by meconium free fatty acids: an alternative explanation for atelectasis in meconium aspiration syndrome. *J Pediatr* 110:765, 1987.

20. Jovanovic R, Nguyen HT. Experimental meconium aspiration in guinea pigs. *Obstet Gynecol* 73:652, 1989.

21. Bancalari E, Berlin JA. Meconium aspiration and other asphyxial disorders. *Clin Perinatal* 5:317, 1978.

22. Tyler DC, Murphy J, Cheney FW. Mechanical and chemical damage to lung tissue caused by meconium aspiration. *Pediatrics* 62:454, 1978.

23. Krauss AN, Soodalter JA, Auld PA. Adjustment of ventilation and perfusion in the full-term normal and distressed neonate as determined by urinary alveolar nitrogen gradients. *Pediatrics* 47:865, 1971.

24. Corbet AJ, Burnard ED. Changes of venous admixture with inspired oxygen in hyaline membrane disease and foetal aspiration pneumonia. *Aust Pediatr J* 9:25, 1973.

25. Fox WW, Gewitz MH, Dinwiddie R, et al. Pulmonary hypertension in the perinatal aspiration syndrome. *Pediatrics* 59:205, 1977.

26. Levin DL, Heyman MA, Kitterman JA, et al. Persistent pulmonary hypertension of the newborn infant. *J Pediatr* 89:626, 1976.

27. Linder N, Aranda JV, Tsur M, et al. Need for endotracheal intubation and suction in meconium-stained neonates. *J Pediatr* 112:613, 1988.

28. Gage JE, Taeusch HW, Treves S, Caldicott W. Suctioning of upper airway meconium in newborn infants. *JAMA* 246:2590, 1981.

29. Pfenninger E, Dick W, Brecht-Krauss D, et al. Investigation of intrapartum clearance of the upper airway in the presence of meconium contaminated amniotic fluid using an animal model. *J Perinat Med* 12:57, 1984.

30. Gregory GA, Gooding CA, Phibbs RH, Tooley WH. Meconium aspiration in infants-a prospective study. *J Pediatr* 85:848, 1974.

31. Fox WW, Berman LS, Downes JJ, Peckham GJ. The therapeutic application of end-expiratory pressure in meconium aspiration syndrome. *Pediatrics* 56:214, 1975.

32. Goetzman BW, Sunshine P, Johnson JD, et al. Neonatal hypoxia and pulmonary vasospasm: response to tolazoline. *J Pediatr* 89:617, 1976.

33. Stevenson DK, Kasting DS, Darnall RA, et al. Refractory hypoxemia associated with neonatal pulmonary disease: the use and limitations of tolazoline. *J Pediatr* 95:595, 1979.

34. Frantz ID III, Wang NS, Thach BT. Experimental meconium aspiration: effects of glucocorticoid treatment *J Pediatr* 86:438, 1975.

35. Yeh TF, Srinivasan G, Harris V, Pildes RS. Hydrocortisone therapy in meconium aspiration syndrome: a controlled trial. *J Pediatr* 90:140, 1977.

36. Roberton NR. Top up transfusions in neonates. *Arch Dis Child* 62:984, 1987.

37. Hamilton PA, Whitehead MD, Reynolds EO. Underestimation of arterial oxygen tension by transcutaneous electrode with increasing age in infants. *Arch Dis Child* 60:1162, 1985.

38. Gooding CA, Gregory GA. Roentgenographic analysis of meconium aspiration of the newborn. *Radiology* 100:131, 1971.

39. Ting P, Brady JP. Tracheal suction in meconium aspiration. *Am J Obstet Gynecol* 122:767, 1975.

40. Madansky DL, Lawson EE, Chernick V, Taeusch HW Jr. Pneumothorax and other forms of pulmonary air leak in newborns. *Am Rev Respir Dis* 120:729, 1979.

41. Murphy JD, Vawter GF, Reid LM. Pulmonary vascular disease in fatal meconium aspiration. *J Pediatr* 104:758, 1984.

42. Segall ML, Goetzman BW, Schick JB. Thrombocytopenia and pulmonary hypertension in the perinatal aspiration syndromes. *J Pediatr* 96:727, 1980.

43. Valdes-Cruz LM, Dudell GG, Ferrara A. Utility of M-mode echocardiography for early identification of infants with persistent pulmonary hypertension of the newborn. *Pediatrics* 68:515, 1981.

44. Cohen RS, Stevenson DK, Malachowski N, et al. Late morbidity among survivors of respiratory failure treated with tolazoline. *J Pediatr* 97:644, 1980.

45. Mayes L, Perkett E, Stahlman MT. Severe bronchopulmonary dysplasia: a retrospective review. *Acta Paediatr Scand* 72:225, 1983.

46. Macfarlane PI, Heaf DP. Pulmonary function in children after neonatal meconium aspiration syndrome. *Arch Dis Child* 63:368, 1988.

47. Swaminathan S, Quinn J, Stabile MW, et al. Long-term pulmonary sequelae of meconium aspiration syndrome. *J Pediatr* 114:356, 1989.

48. Vidyasagar D, Yeh TF, Harris V, Pildes RS. Assisted ventilation in infants with meconium aspiration syndrome. *Pediatrics* 56:208, 1975.