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EFFECT OF STEROIDS ON OXYGEN DEPENDENCY IN NEONATES WITH MECONIUM ASPIRATION SYNDROME

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Abstract:
OBJECTIVE: *The objective of the study was to determine effectiveness of corticosteroid therapy in neonates with meconium aspiration syndrome in comparison with control.*
DESIGN: *Randomized controlled trial.*
SETTING: *The study was conducted in Pediatrics department of Allied/DHQ Hospital Faisalabad.*
DURATION OF STUDY: *Six months after the approval of synopsis.*
RESULTS: *Out of 92 cases (46 in each group) 46.67% (n=19) in Group-A and 56.67% (n=22) in Group-B were between 1-3 hours of life, 36.67% (n=16) in Group-A and 30% (n=14) in Group-B were between 4-6 hours while only 16.67% (n=11) in Group-A and 13.33% (n=10) in Group-B were between 6-8 hours of life, mean and sd was calculated as 3.78±2.26 in Group-A and 4.12±2.77 years in Group-B, 63.33% (n=29) in Group-A and 56.67% (n=26) in Group-B were male while 36.67% (n=17) in Group-A and 43.33% (n=20) in Group-B were females, oxygen therapy was significantly reduced in children administered corticosteroid therapy.*
CONCLUSION: *Corticosteroid therapy in neonates with meconium aspiration syndrome is effective in terms of oxygen therapy while comparing with symptomatic treatment only*
KEY WORDS: *Meconium Aspiration Syndrome, Neonates, Corticosteroid Therapy, Oxygen Therapy.*

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INTRODUCTION:

Meconium is the infant's earliest stool. It can be found in the gastrointestinal tracts of fetuses as early as 14-16 weeks of gestation [1]. Meconium aspiration syndrome (MAS) is when the newborn has respiratory distress and the only explanation for the distress is that the infant has swallowed meconium-stained amniotic fluid (MSAF). Meconium-stained amniotic fluid occurs when the fetus defecates prior to delivery and it occurs in approximately 10-15% of term (37 weeks of gestation) or post term pregnancies. MAS occurs in only 1-4% of newborns that are born with meconium-stained fluid [2-4].

Meconium aspiration syndrome (MAS) is a major cause of respiratory failure in the term and post-term neonates. Pathophysiology of MAS is complex and not yet completely understood. In the acute phase, aspirated meconium causes mechanical obstruction of the airways. When reaches the alveoli, meconium evokes surfactant dysfunction, inflammation, vasoconstriction, and airway hyperactivity [5]. Resulting leak of proteinaceous fluid and cells including neutrophils into the alveolar spaces further deteriorates the acute lung injury. Hypoxia and higher levels of thromboxane A2, leukotrienes, prostaglandins, and endothelin-1 may result in pulmonary vasoconstriction, while Broncho active substances such as leukotrienes and platelet-activating factor may be responsible for airway hyperreactivity. Oxidative damage to lung tissue is further aggravated by ventilation with high oxygen concentrations nitrogen species, and other biologically active substances. In the presence of these findings, administration of anti-inflammatory drugs, e.g., corticosteroids (CS) may diminish the inflammatory response, edema, vaso- and bronchoconstriction, and thereby improve the lung functions in MAS. In the previous studies, significant reduction was noted in need for oxygen therapy. Moreover, treatment with intravenous dexamethasone has improved the gas exchange and has reduced pulmonary vascular resistance, lung edema, and number of lung neutrophils. Nebulized budesonide has improved lung function in chlorine gas-injured piglets [5-9]. Pilot studies have shown that duration of oxygen therapy (in hours) was significantly reduced (10±1.5, 4±1.2 hrs) in those who were given corticosteroids and in those who were not given respectively. Since the information on the advantages of Corticosteroids administration in MAS is scant rationale of our study is to evaluate the effects of corticosteroids on the clinical course and outcome of neonates with MAS especially with reference to duration of oxygen therapy in hours.

REVIEW OF LITERATURE

HISTORICAL BACKGROUND

AF is a fluid balance of the fetus and placenta**.** It is a solution in which undissolved material is suspected. This material is a mixture of cellular and unorganized insoluble matter which gives the AF a fluid appearance. Meconium staining of AF during labour has long been implicated as a factor influencing fetal well being during the intrapartum and postpartum period. Its appearance during labour was even known to the women of Hippocratic period, who took it as a bad sign for the outcome of fetus. Also German midwives considered long before the appearance of MSAF as a sign of fetal death. John Sim (1817), The English Obstetrician and others contemporary workers thought that the presence of meconium in AF during labour was sign of fetal death in utero. Schwartz [10,11]. was the first to show (in 1858) that the appearance of meconium during labour mean impending fetal death. He in a masterly treatise described the clinical situations under which meconium was passed. He suggested that some change in fetal physiology was responsible and stated. "The presence of meconium is always proof of the suppression or reduction of respiratory placental communication and is a reliable sign of death of the fetus or of an endangering of life in the act of birth." Tarnier (1869) opined that, in breech presentation, passage of meconium carries no significance as it is expressed by mechanical expression of abdomen. He called it unfavorable when present in cephalic presentation. He thought that it was almost always due to cord compression.

FORMATION AND COMPOSITION OF MECONIUM

The name meconium is derived from the name meconium-arion, meaning "opium-like", and has been linked with Aristotle's belief that it induced sleep in the fetus. It first appears within the fetal gastrointestinal tract at 70e85 days' gestation as a viscous substance made up primarily of water (70e80%). Other constituents include intestinal epithelial cells, squamous cells, lanugo, amniotic fluid, bile acids and salts (giving the characteristic green colour), phospholipase A2, interleukin-8, mucus glycoproteins, lipids and proteases.

The main theories accounting for the passage of meconium before birth are based on those of fetal maturation and fetal stress. Fetal maturation: although meconium appears very early in the gastrointestinal tract, MSAF rarely occurs before 34 weeks' gestation and appears increasingly with advancing gestational age with its incidence

increasing to 30e40% over 42 weeks. Motilin, an intestinal polypeptide which stimulates contraction of intestinal muscle, is found in higher concentrations in post-term than pre-term fetal gastrointestinal tracts. Furthermore, intestinal parasympathetic innervation and myelination also increase in later gestations implying that the increasing incidence may reflect the maturation of peristalsis in the fetal intestine. Therefore, at increasing gestations, particularly post-term, MSAF may be a physiological event, simply reflecting the maturation of fetal intestinal function.

FETAL STRESS

MSAF has also been attributed to a fetal response to intrauterine stress and hypoxia, with the passage of meconium occurring more frequently when umbilical vein oxygen saturations are below 30%. Furthermore, the degree of MSAF is related to the degree of hypoxia with "thick" stained MSAF being associated with lower oxygen concentrations than "light" stained MSAF. One theory to explain this is that of intestinal ischemia, which is thought to result in relaxation of the fetal anal sphincter and increased gastrointestinal peristalsis, thereby, leading to the passage of meconium. It has been theorized, therefore, that during hypoxia, the fetal circulation shunts blood away from the bowel and directs it to the brain and heart, thereby contributing to intestinal ischemia and subsequently MSAF. Conversely, in animal studies, term rabbits failed to pass meconium during a hypoxic insult, calling into question, whether this mechanism is a major cause for meconium passage in a hypoxic human fetus. Vagally mediated gastrointestinal peristalsis in response to head or cord compression (the same reflex which initiates variable decelerations) may also be associated with meconium passage in the absence of fetal distress.

Meconium passage, which may be secondary to smooth muscle contraction in the fetal gastrointestinal tract, has also been linked to the use of misoprostol when inducing labour. The exact mechanism for meconium passage in the human fetus is still not completely understood and may be a combination of all the above. It should be emphasized, however, that despite being complicated by the presence of MSAF, many pregnancies do not have any adverse outcome, and indeed fetal distress occurs frequently in the absence of the passage of meconium, therefore, more research is required for us to fully understand the relationship between MSAF and fetal distress.

GRADING OF MECONIUM

For many years' attempts have been made to correlate increased meconium thickness with a worse perinatal outcome, but due to the subjectivity of assessing meconium thickness, it makes it very difficult to compare studies with any scientific rigour. Indeed, it has been shown that inter- and intra-observer agreement on visual grading of MSAF thickness is poor illustrates a common grading system of meconium). However, there does appear to be a significant linear association between meconium thickness and abnormal fetal heart rate patterns during labour, low Apgar scores and risk for caesarean section delivery. There also appears to be a higher risk of neonatal intensive care admission in pregnancies with thick meconium as compared to those with clear amniotic fluid, suggesting that thick meconium, not thin, is associated with an increased risk for perinatal complications during labour and delivery. A system of measuring quantitative meconium concentrations using a "meconiumcrit" (percentage by volume of the solid component of meconium) was proposed in the 1990s, but this has not been adopted clinically, as a study investigating the value of measuring meconiumcrit showed no significant correlation with umbilical artery pH or Apgar score and no clinical benefit. However, it should be noted that two cases of meconium aspiration syndrome occurred within this study, both of which were from the "thick" meconium group. Although there is limited good quality evidence suggesting that the use of a system to grade meconium has any significant impact on neonatal outcome, most obstetricians would consider thick meconium a more ominous sign than thin and the National Institute of Clinical Excellence (NICE) recommends a standardized scoring system for the degree of meconium staining and its association with neonatal outcome. Further to this, accurately estimating the degree of meconium thickness is of importance as it helps determine the intensity of monitoring required following birth.

COMPONENTS AND CHARACTERISTICS OF MECONIUM

Meconium is the intestinal content of the fetus and is variably composed of water (as much as 80%), mucopolysaccharides, bilirubin, intestinal enzymes, hair and squamous cells [12]. The characteristic green coloration is attributable to bile pigments, which are not released in significant amount until mid-pregnancy. Indeed, clear amniotic fluid has been retrieved by amniocentesis soon after 3-D ultrasonographic documentation of fetal defecation in utero [13]. The composition (and coloration) of

meconium may not only change with advancing gestation, perhaps due to alterations in gut motility, but also depend upon the process underlying its passage (physiologic vs pathologic). Some have suggested that newborns exposed to birth asphyxia have a greater amount of bilirubin in meconium compared to those without [14]. The physical properties of meconium at term have been characterized by high adhesiveness with poor transportability by airflow, even when diluted [14].

Typically, the diagnosis of meconium rests on visual observation of greenish fluid discoloration. Unfortunately, there is no definitive test that confirms the clinical impression of meconium in amniotic fluid or on histopathological specimen (ie, immuno histo-chemistry). Efforts have been made to identify the material chemically by establishment of characteristic spectrophotometric absorbance peaks (which are typically in the 405–415 nm range), but the variable composition of meconium and the similarity with other blood breakdown products make this technique imperfect for evaluating amniotic fluid samples [15]. In terms of histopathology, most assessments of placental meconium are made by gross appearance of greenish discoloration or H & E staining, which can be variable in its origins and differentially interpreted [16,17].

GESTATIONAL AGE INFLUENCES ON MECONIUM PASSAGE

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.[13] Therefore, the presence of a greenish discoloration in mid-trimester amniotic fluid should not be considered evidence of meconium passage. Indeed, cases of mid-trimester "meconium" –brown or green tinged amniotic fluid – reflect discoloration for other reasons, most commonly hemolysis of intra-amniotic bleeds, and do not represent intestinal passage. The presence of green or brown pigment in second trimester amniotic fluid is not an uncommon event, occurring in approximately 2% of amniotic fluid retrieved by genetic amniocenteses [18,19]. Spectrophotometric studies suggest that discoloration in such fluid is more likely due to hemolysis resulting from intra-amniotic hemorrhage antedating amniocentesis [20,21]. Regardless of the etiology, green or brown fluid is associated with a higher rate of spontaneous abortion or fetal death than clear fluid [21,22].

Meconium passage in the preterm third trimester fetus has been reported to be a rare event, as typically it occurs near or post term [23]. Reports of early meconium passage (ie, 26 weeks) are difficult to interpret because of the difficulty of identifying meconium with confidence. Alternative explanations for the finding of greenish stained membranes or fluid would include the presence of decomposed blood as a result of abruption. Staining for hemosiderin may help make the distinction [23].

On an experimental level, preterm fetal motilin levels are noted to be lower in the preterm than in term infants, suggesting that defecation in the preterm infant may not be secondary to physiologic peristalsis [24] though this finding has been disputed [25]. Interestingly, regardless of in utero intestinal behavior, 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, that can lead to delayed meconium passage [26]. Meconium-stained amniotic fluid is a very common finding in term pregnancies (Table 1) and the incidence may be as high as 30% in post-term pregnancies [27]. In one study of over 13,000 placentas, some degree of gross meconium staining was seen in about 20% of cases, the vast majority of which were term gestations [16].

MECHANISMS OF MECONIUM RELEASE

The mechanism of meconium passage in the term and post-term fetus is hotly debated and probably there are variable and complex factors leading to the event. There are two prevailing and possibly compatible theories. One is that normal maturation of the gastrointestinal tract results in meconium passage. The alternate hypothesis is that pathologic processes, such as stress via hypoxia or infection, can trigger meconium passage. The issue is complicated by the observation that, independently from the factors leading to meconium passage, presence of meconium may subsequently cause complications, such as meconium-associated vascular necrosis of umbilical and placental chorionic vessels, [28] inhibition of neutrophil oxidative burst and phagocytosis [29] facilitating growth of pathogens within the amniotic fluid and subsequent intrauterine infection, [30] and vasoconstrictive activity on the placental vasculature [31].

MECONIUM AS A RESULT OF GASTROINTESTINAL MATURATION

Clinical observations suggest that normal maturation of the gastrointestinal system may be implicated in a sizable proportion of cases of in utero meconium passage. Traditionally it was thought that passage of meconium in the amniotic fluid was related to release

of fetal motilin, a 22-amino-acid polypeptide which promotes peristalsis. Indeed, cord blood motilin levels are higher in term infants passing meconium in utero compared with those who do not [32]. The low level of cord blood motilin in the extremely preterm (ie, midtrimester) fetus thus was interpreted as to militate against the hypothesis of in utero defecation in the mid-trimester [32]. The issue has been recently challenged by 3-D documentation of fetal defecation throughout the second and early third trimester in physiologic pregnancies, suggesting that motilin may not be a hormone indispensable for fetal defecation.

Using animal experimentation, researchers have sought to demonstrate that meconium passage may reflect normal physiology in some cases. In one study, a non-hydro soluble contrast medium was introduced via nasogastric tube to fetal goat and its passage over time to the gastrointestinal tract and into the amniotic cavity was monitored. Contemporaneously, venous blood gases were measured, which were normal throughout [33]. The authors concluded that the fetus defecates routinely into the amniotic cavity even in the absence of distress. A similar study using technetium 99 injections into fetal rabbit muscle also demonstrated its excretion into the gastrointestinal tract and amniotic cavity, allowing to reach a similar conclusion [34]. Caution is advised in the interpretation of the findings from these animal studies: even if not undergoing hypoxic stress, the fetuses in the experiments had undergone anesthesia and invasive handling compared to non-instrumented fetuses, and it is hard to know what effect the experimental design itself may have had on meconium passage.

In some cases, the normal process of colonic filling may lead to activation of the colonic cholinergic system and subsequent meconium passage independent of systemic factors like hypoxia or infection. Sheep studies have suggested that cholinergic-induced passage of gastrointestinal contents to the distal colon results in local expulsive mechanisms and in utero defecation [35]. The colonic cholinergic system may not be fully functional until postnatally in some cases, suggesting a maturational effect. Despite the epidemiological and experimental evidence to support a relationship between meconium passage and gastrointestinal maturation, the finding of meconium at third trimester amniocentesis does not guarantee fetal lung maturity. It should be remembered that meconium passage influences some lung maturity studies, such as lecithin–sphingomyelin ratio [36].

MECONIUM PASSAGE AS A CONSEQUENCE OF FETAL HYPOXIA

The relationship between meconium passage in utero, as evidenced by meconium-stained amniotic fluid, and fetal acidosis at birth is controversial. Some authors [36] have reported no association between meconium passage in utero and either mean umbilical artery pH or frequency of acidosis, whereas others [37] have found a relationship between meconium-stained amniotic fluid and lower fetal blood gas values. In part the discrepancy among reports can be explained by the low frequency of indicators of fetal hypoxemia associated with meconium passage. In a series of over 19,000 pregnancies at term (37 weeks or beyond) those with meconium-stained amniotic fluid had a non-reassuring FHR in less than 14% of cases, 5-minute Apgar score below 7 in less than 3.2% of cases, and umbilical artery pH<7.10 in less than 3.6% of cases, [38] suggesting that hypoxia is not a common cause of meconium passage. Nonetheless, we have recently shown that the new appearance of meconium during labor or thickening of meconium during labor have a greater than 2-fold increased risk of umbilical artery pH<7.10 and 5-minute Apgar score<7 compared with presence of clear fluid or persistently thin meconium during labor [38]. 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. In this context, the reported association between induction of labor with misoprostol and meconium passage is probably mediated by the significantly higher rates of uterine hyper stimulation with misoprostol [39].

Animal studies have demonstrated that meconium passage related to hypoxia is mediated by the sympathetic nervous system. Sympathectomised sheep subjected to repeated episodes of acute hypoxia failed to produce meconium, whereas controls also exposed to severe hypotension and metabolic acidosis had heavily stained amniotic fluid [40]. An alternative route for the presence of meconium-stained amniotic fluid in the presence of fetal hypoxia is reduced clearance of defecated meconium. Ovine studies have demonstrated impaired fetal swallowing in the setting of acute hypoxia [41] and it may be that stress impedes clearance of meconium that is physiologically passed, and it may be via this route that meconium accumulates in the amniotic fluid. Finally, Anhanya et al. have hypothesized that stress-induced glucocorticoid mediated changes in corticotrophin-releasing factor (CRF) receptor

subtypes expression may alter colonic motility, a finding supported by their experiments in which intragastric betamethasone injection elicited meconium passage in utero, a finding not seen in saline-injected animals [42].

MECONIUM PASSAGE AS A RESULT OF INTRAUTERINE INFECTION

Hematogenous spread of maternal Listeria monocytogeneses infection to the uterus has long been known to be causally associated with fetal meconium passage, as well as preterm delivery and high risk of perinatal death [43]. More recently, an association between meconium passage and microbiologic evidence of intra-amniotic infection, [44] histologic evidence of acute inflammation, [45] and clinical evidence of higher rates of chorioamnionitis and end metritis [46] have been reported. The crux of the issue is whether intrauterine infection causes meconium passage, or presence of meconium facilitates ascending infection. A study utilizing intrapartum antibiotic prophylaxis in the presence of meconium documented a significant reduction in incidence of clinical chorioamnionitis (from23.3% to 6.7%) [47]. These findings can be cautiously interpreted (in light of biologic plausibility) as to suggest that nearly two-thirds of cases of infection in the presence of meconium may be secondary rather than primary in origin. Alternatively, subclinical intra-amniotic infection may lead to meconium passage and antibiotics may only prevent the onset of maternal clinical manifestations (indeed prophylaxis did not decrease the rate of neonatal sepsis).

MECONIUM PASSAGE IN GESTATIONAL CHOLESTASIS

Passage of meconium is more prevalent in pregnancies complicated by gestational cholestasis. In one of the largest series on the topic, meconium passage before 37 weeks occurred in 18% of cases, a rate significantly higher than that of the general obstetric population at less than 37 weeks during the study period (3%; OR=7.3, 95% CI 3.3, 16.0) [48]. Moreover, at an average gestational age at delivery of 37.5+/−1.6 weeks, the rate of meconium-stained fluid was 12%, a rate usually reported in deliveries at or after 40 weeks. Finally, gestational cholestasis managed expectantly is associated with a stillbirth rate of 16.8% and such stillbirths are associated with meconium-stained fluid in 86% of cases, [49] a rate significantly higher than that commonly reported in large series of stillbirths. An understanding of the pathophysiology of meconium passage in the context of gestational cholestasis would also help to appropriately monitor at risk fetuses. Passage of meconium with obstetric cholestasis is not associated with evidence of placental dysfunction, as manifested by rates of fetal growth restriction or oligohydramnios [49]. Instead, the rate of asphyxia is higher in cholestatic gestations than in the general pregnant population, [50] and it is independently correlated with the maternal serum bile acid level [50]. A significant and independent correlation has also been reported between maternal serum bile acid levels and probability of meconium-stained fluid. The frequency of meconium passage was 22% with maximum bile acid levels of<40μmol/L, and 44% when the levels were 40 or greater. Studies in animal models have shown that high maternal serum bile acid levels stimulate fetal colonic motility, causing passage of meconium. Less clear is the role of bile acids in fetal death. A recent histologic study of 49 placentas from patients with gestational cholestasis found no correlations between histopathology placental lesions and clinical or laboratory markers of gestational cholestasis; moreover, no pathognomonic lesions were detected in such placentas. Experimental evidence has shown a dose-dependent vasoco constrictive effect of bile acids on placental chorionic veins. Recently, Serrano et al. reported abnormal microscopic placental findings in a rat model of cholestasis, including enhanced apoptosis and reduced trophoblastic tissue.[51] More studies are needed to establish whether fetal death is related to vasoconstriction of placental vessels and it is mediated by the maternal bile acid level.

MECONIUM IN THE PRE-TERM FETUS

The incidence of MSAF in the pre-term fetus is approximately 5% but is associated with a poorer neonatal outcome when compared to similar gestations with clear amniotic fluid, suggesting that meconium-stained amniotic fluid is a gestational age independent risk factor. At term, only a relatively small amount of stress is required to result in the passage of meconium, however, in the pre-term fetus, the greater colonic distance over which the meconium has to travel, implies a greater severity and/or duration of stress, and may explain the increased perinatal morbidity and mortality seen in this group, particularly the increased incidence of cerebral palsy and intraventricular hemorrhage.

MSAF in the pre-term fetus, especially in the mid-trimester, may also be associated with acute ascending infections, and it has been speculated that intra-amniotic infections may cause fetal gastroenteritis and diarrhea. Women in pre-term labour with meconium-stained liquor have a higher

incidence of clinical chorioamnionitis when compared to those with clear liquor.

Amniocenteses conducted on women presenting with pre-term labour with intact membranes have shown a significantly increased rate of positive amniotic fluid microbial cultures when meconium liquor is present and these women are more likely to deliver pre-term, suggesting that meconium passage is a risk factor for microbial invasion, chorioamnionitis and pre-term delivery. Hematogenous Listeria infection has also been associated with pre-term MSAF. However, the incidence of this has been found to be quite low and the presence of meconium is not a useful indicator of listeriosis infection.

COMPLICATIONS OF MECONIUM-STAINED AMNIOTIC FLUID

MSAF in the presence of fetal heart rate abnormalities is a strong indicator of fetal distress; however, it is also associated with complications in the newborn. Meconium directly alters the amniotic fluid, reducing its antibacterial activity, thereby; increasing the risk of perinatal bacterial infection, however, the most severe complication of MSAF is meconium aspiration syndrome.

MECONIUM ASPIRATION SYNDROME

Various components of meconium, in particular, bile salts and enzymes can cause complications if aspirated into the lungs of an infant prior to, during or immediately after birth, thereby, resulting in the Meconium Aspiration Syndrome. This occurs in approximately 5% of infants born with MSAF and has a mortality rate in the region of 3 to 5%. Meconium aspiration syndrome describes a wide spectrum of respiratory disease, ranging from mild respiratory distress to severe disease and death despite mechanical ventilation. Prior to the late 1970s it was thought that aspiration of amniotic fluid and meconium only occurred during the first few breaths after delivery, however, meconium has been found distally as far as the alveoli in stillborn infants. Further to this, studies with radio-opaque contrast and Cr51 labelled erythrocytes injected into amniotic fluid have demonstrated that amniotic fluid enters the fetal lungs in the non-asphyxiated human fetus, suggesting that meconium aspiration occurs in utero. Animal studies have also shown that intrauterine gasping, resulting in greater aspiration of meconium, occurs in fetuses exposed to hypoxia, implying that fetal distress is a risk factor for development of meconium aspiration syndrome. Currently, there is no way to distinguish those who develop meconium aspiration from intrauterine gasping and those who develop it by inhalation at birth.

Perhaps the most significant risk factor for meconium aspiration syndrome is post-term delivery, due to the high prevalence of MSAF in this population and the increased incidence of oligohydramnios in these pregnancies. Oligohydramnios predisposes to cord compression which may help explain the higher frequency of meconium passage at this gestation, but more importantly, meconium passage in the presence of oligohydramnios results in a thicker meconium-stained amniotic fluid which can result in amore serious meconium aspiration syndrome and poorer neonatal outcome.

DEFINITION

The most popularly used definition of MAS is respiratory distress occurring soon after birth in an infant born from a meconium stained milieu with compatible radiological findings which cannot be otherwise explained.

EPIDEMIOLOGY

In the United States, a retrospective multi-center study of 162,075 term infants born between 1997 and 2007 reported 1.8 percent of infants had an admission diagnosis of meconium aspiration syndrome (MAS) [52]. MAS occurs in about 2 to 10 percent of infants born through meconium-stained amniotic fluid (MSAF). This was illustrated in a study from a single tertiary center of 20,047 live births between 1994 and 1998 that reported MSAF occurring in 9.2 percent and MAS in 0.1 percent of all live births [53]. This 10-fold difference in the incidence of MAS may be due to differences between the two studies in the rigor that MAS was diagnosed and measures used to prevent MAS. The incidence of MSAF varies with gestational age with a nadir at about 31 weeks. This was best illustrated by a large English multicenter study of about 500,000 singleton births that reported rates of MSAF in preterm, term, and post term infants of 5.1, 16.5, and 27.1 percent, respectively [54]. However, in the subgroup of premature infants, rates were higher for those born ≤30 weeks compared with those with a gestational age between 31 and 36 weeks. After 31 weeks, the incidence of MSAF increases with gestational age. After excluding preterm infants, the rates of MSAF were higher in black (22.6 percent) and South Asian infants (16.8 percent) compared with those who were white (15.7 percent). Logistic regression analysis showed independent predictors for MSAF included advanced

gestation, black or South Asian ethnicity, and vaginal breech delivery.

The risk of MAS and MSAF is greatest in post mature infants and small for gestational age [55]. Changes in obstetric care, especially a reduction in postmature births, appear to be associated with a decrease in the incidence of MAS. This was illustrated in the following studies:

- In a prospective study of 1365 infants ≥37 weeks' gestational age born through MSAF at a single center from 1990 to 1998, MAS decreased nearly fourfold (5.8 to 1.5 percent in 1990 to 1992 and 1997 to 1998, respectively) [56]. This was associated with a significant reduction in births ≥41 weeks' gestation (42 to 28 percent), as well as increased use of amnioinfusion, diagnosis of nonreasoning fetal heart rate patterns, and cesarean delivery.
- A significant decrease in the incidence of severe MAS (requiring intubation and mechanical ventilation) was also noted over an eight-year period in Australia and New Zealand from 1995 to 2002 [57]. The lowest incidence was 0.35 per 1000 live births in 2002. The lower incidence was attributed to improving obstetrical management with fewer deliveries beyond 41 weeks' gestation and fewer infants with five-minute Apgar scores of less than 7. These two changes accounted for approximately 62 percent of the reduction in severe MAS cases.

MECONIUM-INDUCED LUNG INJURY AND DEVELOPMENT OF THE MECONIUM ASPIRATION SYNDROME

The pathophysiology of meconium aspiration is a complex series of events, superimposed on the normal switch that occurs when (intrauterine) fluid-filled lungs are changed into an air-filled organ, required for adequate gas exchange. Perinatal aspiration of meconium may interfere with this normal transitional process, causing airway obstruction, direct toxic damage of lung tissue, surfactant inactivation, meconium associated pulmonary inflammation ('chemical pneumonitis') and decreased arterial oxygen tension [58,59]. Furthermore, immediate changes in pulmonary vasoreactivity lead to a rise in pulmonary vasomotor tone and subsequently to persistent pulmonary hypertension and prolonged (severe) hypoxemia [58,59].

MECHANICAL EFFECTS

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. Tyler et al. showed in adult rabbit lungs that small airway obstruction by meconium is followed by a transitional period leading to (partial) alveolar collapse and cellular necrosis within 48 h. Due to (partial) alveolar obstruction (with relatively good perfusion) a ventilation–perfusion mismatch develops, resulting in a fall in PaO2. Complete obstruction of the smaller airways by meconium, causes the air to be absorbed and atelectasis ensues. Furthermore, a direct damaging effect on alveolar cells has been reported by Zagariya et al., who demonstrated several morphological changes following meconium exposure in rabbit lungs. The major features were detachment of airway epithelium from stroma and shedding of epithelial cells into the airway, indicating a direct deleterious effect of meconium on lung alveolar cells [59]. The lung areas which do not or only partially participate in ventilation (because of obstruction and/or destruction) will become hypoxic and subsequently, an inflammatory response may follow. In addition, a rise in FRC leads to an increase in pulmonary vascular resistance. Together with a patent ductus arteriosus and foramen ovale (due to postnatal cardiovascular changes), elevations of pulmonary artery pressure cause right-to left shunting across the duct or foramen, resulting in a further deterioration of the PaO2 and an increase in hypoxemia. Chronic hypoxia will lead to an increase in pulmonary vascular smooth muscle tone and persistent pulmonary hypertension causing respiratory and circulatory failure [60].

CHEMICAL EFFECTS

Another mechanism contributing to meconium-induced neonatal respiratory distress is surfactant inactivation (functional deficiency). Surfactant reduces alveolar surface tension to facilitate lung expansion, preventing alveolar collapse after (the onset of) breathing. In 1987, Clark et al. postulated that, in dog lungs, free fatty acids present in meconium replaced surfactant phospholipids, possibly changing lung compliance in MAS [61]. Sun et al. likewise demonstrated in 1993 that meconium itself seems to interfere with the surface tension lowering capacity of surfactant [62]. It was suggested that surfactant inhibition leads to decreased lung–thorax compliance, increased paCO2, and histological evidence of atelectasis. This effect could be (partially) counter-acted by administration of large

doses of natural surfactant in animals with experimentally induced meconium aspiration syndrome, resulting in improved compliance and ventilation. In 2007, El Shahed et al. reported that surfactant administration in neonates with MAS leading to moderate or severe respiratory failure, will decrease the number of infants needed to treat with extracorporeal membrane oxygenation (ECMO). However, treatment with surfactant did not significantly affect mortality in infants with respiratory disorders like MAS [63]. Further research is needed to compare surfactant therapy and other currently used treatment strategies.

INFLAMMATORY RESPONSES

Aspirated meconium has long been associated with pneumonitis in neonates [64]. Many recent studies illustrate the involvement of inflammatory mediators and reactive oxygen species in the pathophysiology of MAS, eventually leading to local injury and interference with surfactant function. Given the current understanding of the pathophysiology, the term "meconium associated pulmonary inflammation" (MAPI) is probably more accurate than 'chemical pneumonitis'.

CYTOKINE AND CHEMOKINE ACTIVATION

Intrapulmonary meconium may trigger lung inflammatory cells to express inflammatory cytokines and oxygen radicals, resulting in lung airway epithelial cell injury and death through apoptosis. For instance, Zagariya et al. demonstrated that in saline-treated rabbit lungs, 94% of the cells were macrophages and 1% neutrophils, whereas in meconium-instilled rabbit lungs the proportion of neutrophils increased up to 7%, implying that meconium provokes a chemotactic reaction. In the rabbit lung cells meconium stimulated the production of proinflammatory cytokines, such as IL-1β, IL-6, IL-8 and TNFα. No differences were seen in the level of IL-10, a non-inflammatory cytokine, usually associated with decreased inflammation and inactivation of inflammatory cytokines [59]. Thus, changes in these cytokine levels may regulate the susceptibility for meconium-induced inflammatory responses and lung injury. Monoclonal human anti-IL- 8 inhibits human meconium-induced neutrophil chemotaxis in vitro in a dose-dependent way. Possibly, IL-8 from meconium itself, causes a neutrophil influx characteristic of pneumonitis in MAS. Meconium is an extrinsic source of other proinflammatory cyto- and chemokines, such as IL-1β, IL-6, GM-CSF, INF-γ and TNF-α, as well [58]. These mediators may contribute in vivo to local pulmonary inflammation with influx of leucocytes, T-lymphocytes, monocytes and macrophages, leading to parenchymal injury and remodeling of lung tissue.

COMPLEMENT ACTIVATION

Recently, it has been hypothesized that meconium is a potent activator of complement, a key mediator of inflammation, and may thus contribute to the inflammatory response in MAS. Lindenskov et al. showed in both in vitro and in vivo models of MAS that meconium locally activates the alternative pathway of complement. They found increased concentrations of the terminal sC5b-9 complex and subsequent cytokine release in newborn pigs and suggested that this local inflammatory reaction may be mirrored by a systemic inflammatory response as well [65]. The combined inhibition of complement and CD14 nearly completely abolishes meconium-induced formation of multiple inflammatory cytokines and chemokines and strongly reduces the formation of growth factors in human adult and umbilical cord blood. The same group suggested an important role for the lectin pathway of complement as well. In vitro, C1-INH, a serine protease inhibitor, inhibits the activation of the classical and lectin pathway of complement in meconium-induced inflammation in human umbilical cord blood. In summary, complement appears to play an important role in MAS-related inflammation and lung injury.

PHOSPHOLIPASE A2

Phospholipase A2 (PLA2) 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. PLA2 activity has been detected in human meconium and in meconium-contaminated lungs, indicating that meconium itself is a source of this enzyme. Possibly, bile acids present in meconium raise PLA2 activity even more, as was found in vitro in human neonates. Kääpä et al. suggested that aspiration of meconium might also have systemic inflammatory and injurious effects through phospholipase activation. They demonstrated the presence of elevated levels of human PLA2-concentrations in plasma during the first hours after intratracheal meconium administration in newborn piglets [66]. These findings suggest a significant role for PLA2 in the pathogenesis of functional and structural changes in neonatal lungs and MAS development.

MECONIUM-INDUCED APOPTOSIS

Apoptosis, programmed cell death, is an important mechanism in the clearance of injured cells and in tissue repair, however too much apoptosis may cause harm. Increased apoptosis may also play a role in acute lung injury, leading to damage and detachment of lung airway or alveolar cells [58]. Vidyasagar and Zagariya recently postulated that cytokine expression following meconium exposure leads to an angiotensin II-induced apoptosis in lung cells [67]. Others also reported a role for the pulmonary renin–angiotensin system (RAS) in the cellular response to MAS through angiotensin II-mediated cell death. Several pulmonary cell types in newborn rabbit's express angiotensin II-receptors (type 1) abundantly after instillation of human meconium. Increases in angiotensin II-receptors (type 1) were associated with dose-related increases in cell death. Possibly, pulmonary RAS contributes to the pathophysiology of MAS and receptor blockade or ACE inhibition may be useful as new treatment strategies for preventing the cellular responses to MAS.

WHY DO SOME NEONATES DEVELOP MAS, WHEREAS OTHERS DO NOT: RISK FACTORS FOR MAS DEVELOPMENT?

The incidence of MAS in children born through meconium-stained amniotic fluid has decreased over the years, mainly due to improved healthcare and changing obstetric practices [68]. However, around 5% of the meconium-stained infants still develop meconium aspiration syndrome [68]. In view of the current knowledge of MAS pathophysiology, the question remains why some neonates born through meconium-stained amniotic fluid develop MAS and (many) others do not. Many pre-disposing factors remain to be elucidated, even though much effort has been done to identify risk factors for MAS development. For example, the risk of MSAF is higher in black mothers compared to mothers from other ethnic groups [69]. Similarly, Sriram et al. concluded that the offspring of non-Hispanic black mothers was at a significantly greater risk for MSAF and MAS development than offspring of non-Hispanic white mothers [70]. Furthermore, advanced gestational age [69] and (often subsequently) high birth weight have been linked to MAS development [69]. Cheng et al. demonstrated a higher risk of MAS for neonates delivered at 40 (adjusted OR 1.55; 95%CI 1.43–1.69) and 41 (adjusted OR 2.12; 95%CI 1.91–2.35) weeks of gestation [71]. Zhang et al. reported that a birth weight greater than 4500 g and particularly greater than 5000 g, is associated with increased risks of perinatal and infant mortality and morbidity, including MAS [72]. Oligohydramnios, male gender or thick versus thin meconium has been suggested to increase the incidence of MAS [73]. However, these findings could not be reproduced in other studies [74].

Meconium below the vocal cords has long been considered to be associated with an increased risk of MAS [74]. However, current International Neonatal Resuscitation Guidelines do not recommend intrapartum or postnatal endotracheal suctioning of vigorous infants born through MSAF, based on the studies by Wiswell et al. and Vain et al [73,74]. They demonstrated that expectant management compared to intubation and suctioning of apparent vigorous meconium-stained newborns did not result in a decreased incidence of MAS. Subsequently, only for non-vigorous meconium-stained infants endotracheal suctioning is still recommended, despite lack of evidence. Foetal compromise (e.g. abnormal foetal heart rate tracings and/or low Apgar scores) and the association with MSAF and MAS have been extensively studied [73]. In a large Australian study Dargaville et al. showed a strong relation between a 5-minute Apgar score of less than 7 and MAS development, with an overall odds ratio of 52. Wiswell et al. found that 1-minute and 5-minute Apgar scores≤6 were independently related to respiratory disorders, like MAS (OR8.10; CI 5.18–12.64 and OR 17.70; CI 7.34–42.62, respectively) [73].

Accurate prediction which infants born through MSAF will develop MAS and which ones will not, remains very difficult. Therefore, in many countries worldwide, meconium-stained infants are clinically observed during the first 24 h after birth. We found that infants uneventfully delivered through MSAF with a 5-minute Apgar score above 8 rarely develop MAS. We therefore suggest that 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.

MANAGEMENT

General Supportive Measures

Most babies born through meconium-stained liquor do not require any resuscitation at birth and remain well. Infants with MSAF who are born in good condition, are free of respiratory distress and have no other perinatal risk factors should receive routine postnatal care. Those who develop respiratory distress require further management, with admission to a neonatal unit.

There are little objective data on the optimal general management of babies developing MAS, but standard monitoring and treatment should generally include:

- close observation and monitoring of oxygen saturation, heart rate and respiratory rate.
- avoidance of excessive handling.
- use of intravenous fluids until the respiratory difficulty diminishes.
- monitoring of blood glucose as the infant may be at increased risk of hypoglycemia after a hypoxic-ischemic insult.
- use of oxygen therapy to maintain saturation in the upper 90s in order to minimize pulmonary hypertension.
- monitoring of pCO2 to detect worsening respiratory acidosis.

It is usual practice to give any newborn with respiratory symptoms antibiotics pending the results of blood cultures, even though in the majority of cases cultures are eventually negative. As meconium is sterile, there is no specific rationale for the use of antibiotics in the treatment of MAS, more a general concern that the meconium may not be the cause of the infant's symptoms or that infection triggered the stress response and passage of meconium. Studies have shown that in those without predisposing risk factors for infection, antibiotics do not appear to influence the outcome of MAS. Before abandoning antibiotic treatment, however, it should be borne in mind that, although sepsis is relatively infrequent, it is potentially devastating, so studies with large numbers of cases will be needed before it can be concluded reliably that antibiotics should not routinely be given. Current practice for the management of MAS can be divided into perinatal and postnatal management.

PERINATAL MANAGEMENT

Management of The 'Post Dates' Pregnancy:

There is a clear association between advancing gestation and the incidence of MAS, particularly beyond 40 weeks' gestation. This may partly explain the variations in incidence of MAS as management of 'post dates' delivery varies. MAS is reduced after induction of labour post dates in comparison with expectant management [75]. The relative risk of MAS after induction versus expectant management is 0.29 (95% CI 0.12–0.68) at 41 weeks and 0.66 (95% CI 0.24–1.81) at 42 weeks (not significant). However, the absolute risk is small and this in isolation is not considered an indication for induction of labour beyond term.

AMNIOINFUSION

The infusion of fluid transcervically during a labour complicated by meconium-stained liquor has been considered to be of possible benefit in reducing MAS, either by diluting thick meconium or by providing support to the umbilical cord and so reducing the risk of hypoxia–ischemia due to cord obstruction. In a systematic review of published studies, Xu et al. concluded that the practice may be of benefit in settings where close electronic intrapartum monitoring is not available, but does not prevent MAS in settings where close monitoring could be achieved [76]. These findings have been questioned, with discussion around the inclusion of trials in the analysis,10 but the practice of amnioinfusion has not been widely adopted.

PHARYNGEAL SUCTION BEFORE DELIVERY OF THE SHOULDERS:

Until recently it was common practice to recommend intrapartum suctioning of the fetal oropharynx at the maternal perineum, before delivery of the fetal shoulders, with the aim of removing meconium from the upper airway before the onset of breathing. A large multicenter randomized trial has shown that this is not effective in reducing the incidence of MAS, the need for mechanical ventilation or the risk of mortality. This practice is no longer recommended in neonatal resuscitation guidelines. Other practices aimed at promoting effective upper airway suction, such as chest splinting to prevent breathing before suction has been carried out, have not been studied properly and are not recommended.

POSTPARTUM MANAGEMENT

Tracheal Suction

There is still some uncertainty about the value of attempting to suction meconium directly from the trachea. The practice of suctioning the trachea immediately after birth was previously believed to reduce the incidence of MAS. However, another large multicenter trial has shown that in vigorous infants (defined as having a heart rate more than 100 beats/min, as well as presence of spontaneous respirations and reasonable tone), there is no benefit from routine suction of the trachea. It is still recommended that infants who are not vigorous at delivery undergo laryngoscopy and tracheal suction before the use of positive pressure ventilation, but the value of this practice has not been established with a definitive randomized study.

Nasal Continuous Positive Airway Pressure (nCPAP) is often used as an intermediate level of support in infants with impaired respiratory function. Although its use has been described in MAS, [77] it has not been studied systematically and shown to be of benefit. As MAS is associated with gas trapping and air leaks due to airway obstruction, some would consider nCPAP to be contraindicated. The use of nCPAP in MAS should be considered experimental until better evidence defines whether it has a role.

VENTILATION

Conventional – ventilating infants with MAS can be difficult and the indications for commencing ventilation are not established. As there can be different disease patterns, with some infants having very patchy disease and others a more homogenous problem, no single approach to ventilation is optimal. The most commonly described pattern is to use a low level of positive end expiratory pressure (PEEP) and a long expiratory time, to avoid worsening any gas trapping, though this approach may well need to be adapted depending on the response of the infant. Pulmonary flow graphics can be of use in tailoring the expiratory time to the mechanics of a particular infant's lungs to ensure that expiration is complete. Infants with MAS are often severely ill, with a requirement for a high FiO2 and airway pressures, and it is common for both sedation and paralysis to be used to optimize infant–ventilator interaction.

High frequency oscillatory ventilation (HFOV) – because the disease can be severe and high pressures are often required when conventional ventilation is used, HFOV is also a commonly used mode [77,78]. Again, the role of HFOV in MAS has not been defined through good quality trials, though in a sub-group of a larger trial, the use of HFOV lead to short-term improvements in gas exchange.

SURFACTANT

Replacement – meconium is a potent inhibitor of surfactant function.20 Clinical trials have not demonstrated a reduction in mortality with the use of surfactant replacement, but in a meta-analysis of two trials which enrolled 208 infants, the need for extracorporeal life support (ECLS) was significantly reduced (RR 0.64, 95% CI 0.46–0.91; NNT 6, 95% CI 3–25). The mortality of infants with MAS when treated with ECLS is now so low that it is unlikely that controlled trials of surfactant therapy in this condition could use mortality as an outcome. Most would now consider surfactant treatment to be an integral part of the treatment of MAS [79]. The response to a single dose of surfactant can be blunt and several doses can be required before the desired response is seen. It is not uncommon for treatment to be followed by a mild deterioration in condition for a few minutes, with reduced saturations and a mild increase in pCO2, but this is usually short lived.

Lavage – an alternative to surfactant replacement therapy is to use lavage with relatively large volumes of diluted surfactant to facilitate removal of meconium from the lungs, whilst maintaining sufficient surfactant function. This technique has shown promise in small preliminary studies but some infants do not tolerate it well. Experimental work is ongoing to establish the most effective treatment schedules and preparations. Larger clinical trials will be required to establish the place of this treatment. Given the evidence from controlled trials for the efficacy of 'conventional' surfactant therapy in MAS, lavage should probably not be compared to no surfactant treatment in future trials.

Nitric Oxide- Many infants with MAS have a degree of persistent pulmonary hypertension of the newborn (PPHN) and consequently have disproportionate difficulty with oxygenation in relation to their apparent degree of lung disease. Close attention to basic homeostasis, including maintenance of a generous systemic blood pressure, control of acidosis and avoidance of hypercarbia, should help to minimize this problem. Inhaled nitric oxide (iNO) has emerged as the treatment of choice for PPHN in term or near-term infants due to its efficacy in reducing the number of infants who go on to require ECLS and its relatively selective action on the pulmonary vasculature. As iNO is delivered as an inhaled gas, good alveolar recruitment is required to maximize its effectiveness and it may be more effective in combination with HFOV if the lung disease is severe. As a sub-group within larger studies of iNO in term and near-term infants with severe respiratory failure and or PPHN, infants with MAS represent a large proportion of the infants studied but they have not been studied in isolation or reported separately in sufficient numbers to enable definitive conclusions about the relative efficacy of iNO in MAS. A review did not show any reduction in mortality with the use of iNO, but did demonstrate a reduction in the need for ECLS, a technique discussed below. Avoidance of the need for this invasive and not universally available technique is viewed as a benefit of iNO therapy, so it has been widely adopted in the treatment of MAS-related PPHN.

CORTICOSTEROIDS

Corticosteroids are a class of chemicals that includes steroid hormones naturally produced in

the adrenal cortex of vertebrates and analogues of these hormones that are synthesized in laboratories. Corticosteroids are involved in a wide range of physiological processes, including stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.

BIOSYNTHESIS

The corticosteroids are synthesized from cholesterol within the adrenal cortex. Most steroidogenic reactions are catalyzed by enzymes of the cytochrome P450 family. They are located within the mitochondria and require adrenodoxin as a cofactor (except 21-hydroxylaseand 17α-hydroxylase). Aldosterone and corticosterone share the first part of their biosynthetic pathway. The last part is mediated either by the aldosterone synthase (for aldosterone) or by the 11β-hydroxylase (for corticosterone). These enzymes are nearly identical (they share 11β-hydroxylation and 18-hydroxylation functions), but aldosterone synthase is also able to perform an 18-oxidation. Moreover, aldosterone synthase is found within the zona glomerulosa at the outer edge of the adrenal cortex; 11β-hydroxylase is found in the zona fasciculate and zona glomerulosa.

CLASSIFICATION

By chemical structure

In general, corticosteroids are grouped into four classes, based on chemical structure. Allergic reactions to one member of a class typically indicate an intolerance of all members of the class. This is known as the "Coop man classification", after S. Coop man, who defined this classification in 1989 [80]. The highlighted steroids are often used in the screening of allergies to topical steroids.

Group A — Hydrocortisone Type

Hydrocortisone, hydrocortisone acetate, cortisone acetate, **tixocortol pivalate**, prednisolone, methylprednisolone, and prednisone (Short- to medium-acting glucocorticoids).

Group B — Acetonides (and related substances)

Triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, **budesonide**, desonide, fluocinonide, fluocinolone acetonide, and halcinonide.

Group C — Betamethasone Type

Betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, and fluocortolone.

Group D — Esters

Group D_1 — Halogenated (Less Labile)

Hydrocortisone-17-Valerate, aclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate,fluocortolone caproate, fluocortolone pivalate, and fluprednidene acetate.

Group D_2 — Labile Prodrug Esters

Hydrocortisone-17-butyrate, 17-aceponate, 17-buteprate, and Prednicarbate.

CORTICOSTEROIDS FOR MECONIUM ASPIRATION SYNDROME

Meconium produces a chemical pneumonitis as a major part of MAS. Despite this, a Cochrane review of two small studies of corticosteroids in MAS showed no benefit from steroid therapy. Infants treated with steroids remained oxygen dependent for longer. A further two small studies have since contradicted this finding [81]. Infants treated with steroids showed a reduction in the duration of oxygen dependence and improved X-ray appearances. Further studies are required and, with the concerns that have arisen from the use of steroids to treat bronchopulmonary dysplasia about the possible effects of high dose steroids on infant growth and development, speculative treatment should best be avoided in the interim. Given the complexity and expense of some of the other treatment modalities, it would be helpful to determine more reliably whether steroids have any role, particularly in settings where resources are more limited.

In 2003, Cochrane meta-analysis of two trials [81-82] including 85 infants with MAS showed that there was

no difference in mortality but a small increase in the duration of oxygen treatment in steroid-treated group [83]. Since then, two more trials reported that steroid therapy in MAS was associated with a decrease in the duration of oxygen therapy and hospital stay [84-85]. The choice of steroid and duration of therapy was different between the studies. Steroids may be beneficial in severe MAS with apparent lung edema, pulmonary vasoconstriction, and inflammation. At present, there is no conclusive evidence to propose routine steroid therapy in the management of MAS. Further research is needed regarding the dosing, timing, and ways of administration of steroids considering their individual properties and possible acute and long-term side effects [86].

ROLE OF 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 that relationship [87]. Three randomized control studies reported that routine antibiotic prophylaxis is not recommended in the management of MAS for those without perinatal risk factors [88-90]. Antibiotic therapy did not affect the clinical course and outcome related to infection in MAS without perinatal risk factors for infection and without ventilator use. The role of antibiotics in the management of MAS may need to be reevaluated in well-designed trials. Unless there is definite risk for infection, prophylactic use of antibiotics in MAS did not reduce infection. If antibiotics are started for suspected infection due to perinatal risk factors, consider discontinuing antibiotics once the blood culture results are negative.

NITRIC OXIDE

Severe MAS is often associated with PPHN, resulting in severe hypoxemia. Randomized clinical trials have demonstrated that iNO therapy decreases the need for ECMO in addition to mortality in full-term and near-term neonates with hypoxic respiratory failure and PPHN. For hypoxic respiratory failure due to MAS, infants responded well to combined iNO and HFV as compared to either treatment alone. The response to combined treatment with HFV and iNO reflects both decreased intrapulmonary shunt and augmented nitric oxide delivery to its site of action.

EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO has been used as a final rescue therapy in infants with severe and refractory hypoxemia associated with MAS. Use of ECMO has been decreased significantly in developed countries with the availability of iNO and HFV. Infants with MAS make up approximately 35% of the infant population who require ECMO. The survival rate has approached 95% of infants with MAS who underwent ECMO [91]. In the ECMO registry, the highest survival rates (>90%) were seen in the patients with MAS who qualified for ECMO

ADJUNCTIVE THERAPIES

All infants with MAS should be monitored using noninvasive monitors (pulse oximeter, transcutaneous O_2/CO_2 methods) and blood gas sampling should preferably be done with an indwelling arterial line. Sedation and analgesia are used frequently in infants with MAS and PPHN to alleviate pain and discomfort that may lead to hypoxia and right-to-left shunting. Opioids, particularly morphine or fentanyl, are frequently used to optimize gas exchange and also to avoid asynchrony, reflex catecholamine release, and aggravation of pulmonary vascular resistance.

Depolarizing muscle relaxants (pancuronium, vecuronium) were widely used in the past along with opioids to decrease agitation and subsequent hypoxic episodes in ventilated infants. The benefits of neuromuscular blockade include improved oxygenation, decreased oxygen consumption, and decreased accidental extubations. However, the use of neuromuscular blockade remains controversial and is reserved for the infant who cannot be treated with sedatives alone. Neuromuscular blockage can promote atelectasis of dependent lung regions and ventilation perfusion mismatch and may also be associated with increased risk of death [92]. Nearly 30–50% of infants with PPHN do not respond to iNO therapy. Infants who do not show initial response to iNO and those that deteriorate subsequently while on iNO therapy continue to have significant PPHN and need other alternative therapy [93]. Alternatives available include (a) phosphodiesterase-5 inhibitors like Sildenafil, Zaprinast, Milrinone, dipyridamole, (b) prostaglandins like Prostacyclin or PGE1, (c) tolazoline, Magnesium sulfate, (d) NO precursor L-Arginine, (e) free radical scavengers like Superoxide dismutase, (f) experimental agents like Bosentan (endothelin antagonist).

INCLUSION CRITERIA

Newborns of any age and gender with a history of meconium stained amniotic fluid and clinical and radiological findings consistent with a diagnosis of meconium aspiration syndrome (areas of atelectasis

and consolidation along with regions of hyper expansion).

EXCLUSION CRITERIA

1. Meconium aspiration syndrome presented with complications like congenital pneumonia diagnosed on the basis of clinical examination and x-ray chest at the time of admission.
2. Meconium aspiration syndrome with associated conditions that may affect the outcome e.g.
   "MAS with stage III hypoxic ischemic encephalopathy diagnosed on the basis of history and clinical examination."
   "MAS with congenital heart diseases like ventricular septal defect and other cynotic heart diseases diagnosed on clinical examination and x-ray chest."
   "MAS with congenital malformation e.g turner syndrome, digeorge syndrome diagnosed clinically.
   "MAS with IDM (infant of diabetic mother)"

DATA COLLECTION

Approval of ethical committee was obtained. Risks and benefits of corticosteroids were discussed with the parents to take the informed consent. Neonates with above selection criteria were taken in the study. Meconium aspiration syndrome was confirmed by detailed history, clinical examination and chest X-ray. Children were divided into two groups using random number table. Group A neonates given i/v corticosteroids in a dose of 0.5mg/kg/24hrs in 3 divided doses and symptomatic treatment (oxygen inhalation via nasal canula, antibiotics, calcium, glucose and IV fluids). Group B neonates given symptomatic treatment only. Excluding the patients mentioned in exclusion criteria on the basis of history, examination and relevant investigations-controlled confounders. Proforma was filled on admission and follow up was carried out weekly for 4-week period by me. Duration of oxygen therapy (in hours) was noted in each group. Adherence was enforced by telephone contact to family.

DATA ANALYSIS

Data was analyzed using SPSS (Statistical Package for Social Sciences) version 10. Mean and standard deviation was calculated for quantitative variable like duration of oxygen therapy in hours. t-test was applied for comparison between two groups. P-value less then 0.05 was taken as statistically significant. Results were presented in tabulated and graphical forms.

RESULTS

A total of 92 patients (46 in each group) were enrolled to determine effectiveness of corticosteroid therapy in neonates with meconium aspiration syndrome in comparison with control. We recorded age distribution and it was presented in Table No. 1, where 46.67% (n=19) in Group-A and 56.67% (n=22) in Group-B were between 1-3 hours of life, 36.67% (n=16) in Group-A and 30% (n=14) in Group-B were between 4-6 hours while only 16.67% (n=11) in Group-A and 13.33% (n=10) in Group-B were between 6-8 hours of life, mean and sd was calculated as 3.78 ± 2.26 in Group-A and 4.12 ± 2.77 years in Group-B. Distribution of gender of the patients show 63.33% (n=29) in Group-A and 56.67% (n=26) in Group-B were male while 36.67% (n=17) in Group-A and 43.33% (n=20) in Group-B were females. (Table No. 2) Comparison of mean duration of oxygen therapy (in hours) reveals 24.58 ± 4.21 (hours) in Group-A and 51.38 ± 5.75 (hours) in Group-B which is significantly shorter in Group-A as P value was 0.001 i.e. <0.05. (Table No. 3)

TABLE No. 1
AGE DISTRIBUTION OF THE SUBJECTS
(n=92)

Age (in hours)	Group-A (n=46)		Group-B (n=46)	
	No. of patients	%	No. of patients	%
1-3	19	46.67	22	56.67
4-6	16	36.67	14	30
6-8	11	16.66	10	13.33
Total	46	100	46	100
Mean and sd	3.78±2.26		4.12±2.77	

TABLE No. 2
GENDER DISTRIBUTION OF THE SUBJECTS
(n=92)

Gender	Group-A (n=46)		Group-B (n=46)	
	No. of patients	%	No. of patients	%
Male	29	63.33	26	56.67
Female	17	36.67	20	43.33
Total	46	100	46	100

TABLE No. 3
COMPARISON OF MEAN DURATION OXYGEN THERAPY IN HOURS
(n=92)

Mean duration of oxygen therapy (in hours)	Group-A (n=46)	Group-B (n=46)
	24.58±4.21	51.38±5.75

P value=0.001

DISCUSSION:

Meconium aspiration syndrome (MAS) occurs in 2–22% of babies born through meconium-stained amniotic fluid and carries significant mortality and morbidity. It is diagnosed in a baby delivered through meconium-stained amniotic fluid who develops signs of respiratory distress in the presence of a supportive chest X-ray. Appropriate intrapartum care with early detection and management of fetal hypoxia is important in minimizing the risk from meconium

staining of amniotic fluid [94]. A chemical pneumonitis is believed to occur secondary to bile, bile acids and pancreatic secretions contained in meconium. It has therefore been hypothesized that corticosteroids may be of benefit in the management of this condition through their anti-inflammatory properties.

The findings of our study reveal a significant shorter duration of oxygen therapy by comparing both groups, mean duration of oxygen therapy (in hours) was 24.58±4.21 (hours) in Group-A and 51.38±5.75 (hours) in Group-B and P value was 0.001 i.e. <0.05. The results of our study are in agreement with pilot studies have shown that duration of oxygen therapy (in hours) was significantly reduced (21.8+3.94, 54.4+6.24 hrs in those who were given corticosteroids and in those who were not given respectively [5-9].

Another study double blinded randomized controlled trial and a prospective Interventional Study over one-year period in the neonatal unit of the Lady Hardinge Medical College and associated Kalawati Saran Children's hospital by Sandeep Tripathi and Arvind Saili [95] assessed infants in terms of duration of stay, oxygen dependence, X-ray clearances and also assessed for short term adverse effects and recorded that there was a statistically significant difference in the duration of stay, duration of oxygen dependence and radiological clearance. The use of steroids was not associated with an increased incidence of sepsis and concluded that steroids alter the course of Meconium Aspiration Syndrome and favorably affect the outcome.

On the other hand, Tripathi S [96] and Basu S [97] treated infants with steroids and remained oxygen dependent for longer, these findings are in contrast of the findings of our study, the reason for remaining on oxygen for longer may be due to any other complication i.e. respiratory distress syndrome. However, on the basis of the results of the current study with support of other published studies and considering the fact that steroids, by virtue of their anti-inflammatory properties, are potentially beneficial in MAS, where pulmonary inflammation ('pneumonitis') is a central component which justifies the hypothesis of the current study that "corticosteroids therapy is affective in meconium aspiration syndrome in terms of need for oxygen therapy of neonates as compared to controls".

CONCLUSION:

We concluded that corticosteroid therapy in neonates with meconium aspiration syndrome is effective while comparing with symptomatic treatment only

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EFFICACY OF COTICOSTEROIDS IN CLINICAL COURSE AND OUTCOME OF MECONIUM ASPIRATION SYNDROME IN TERTIARY CARE HOSPITAL IN FAISALABAD

PROFORMA

Case NO._____ Reg. NO._____ Date_____

Name: _____ Father's Name_____

Age/Sex_____ Tel. NO._____

Address_____

D.O.A._____ D.O.A._____

TREATMENT GIVEN

Group 1.Corticosteroids with antibiotics & fluids

Group 2.Only antibiotics with maintenance fluids

OUTCOME

1. Duration of oxygen therapy (in hours.)