REVIEW ARTICLE

Microbiological Profile and Inflammatory Markers in Meconium Aspiration Syndrome: Review

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Abstract

Meconium aspiration syndrome (MAS) is characterized by respiratory distress in newborns exposed to meconium-stained amniotic fluid (MSAF) with no alternative explanations. Earlier, it was stated that the womb is a sterile environment and microbial colonization in neonates begins at birth. Recent studies showing the presence of microorganisms in the MSAF *in utero* suggest that the meconium in the fetus does contain microorganisms. These microorganisms present in MSAF and meconium may cause intrauterine infection, chorioamnionitis in mothers, neonatal sepsis, and pneumonitis in neonates. In addition, this review discusses the fetal inflammatory response to MAS. The combined involvement of obstetricians, neonatologists, and pediatricians in prevention and treatment further reduces MAS cases. Understanding the microorganisms and drug-resistant patterns in neonates with MSAF aids in diagnosing and prescribing antibiotics, which is vital in antibiotic stewardship for managing neonates with MAS.

Key words: Inflammation, meconium aspiration syndrome, meconium-stained amniotic fluid, microorganisms

INTRODUCTION

Meconium aspiration syndrome (MAS) is the most common problem experienced by neonatologists, pediatricians, and obstetricians. MAS is distinguished by respiratory distress in newborns exposed to meconium-stained amniotic fluid (MSAF) with no other alternative explanation.[1] Globally, MSAF occurs in <5% of preterm, 7–22% of term deliveries, and 23–52% of births at more than 42 weeks. About 2–9% of cases of MSAF suffer from MAS.[2] The prevalence of MSAF was 17.8% in lower-income countries, while it was 11.9% in upper-middle-income countries, such as Brazil.[3,4] In high-income countries, the incidence of MAS has declined from 0.1% to 0.4%.[5] Non-reassuring or abnormal cardiotocography, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score >7 at 1st and 5th min, and thick meconium act as important fetomaternal risk factors.[6]

The meconium in infants differs from adult stool in consistency and microbial load.[7] Meconium is a black-green, viscous material that is present during gestation in the bowel of the developing fetus.[8] The composition of meconium majorly contains water and other components such as amniotic fluid (AF), lanugo, bile acids, salts, mucus, desquamated cells, and other inflammatory modulators.[2] The greenish colorization of the meconium is due to the presence of bile pigments. The meconium is produced by the 10th–16th gestational week in the fetal gastrointestinal tract (GIT).[9] As gestational week increases, the fetal gut matures, and the meconium will proceed toward the distal end of the colon and rectum.[10]

Based on severity criteria by Cleary and Wiswell, MAS is defined as: (i) Mild MAS (i.e., <40% oxygen requirement

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for <48 h), (ii) moderate MAS (i.e., >40% oxygen requirement for >48 h without air leak, and (iii) severe MAS (i.e., assisted ventilation need for >48 h and frequently associated with persistent pulmonary hypertension).[11] The release of meconium will reduce the antibacterial activity of AF, which will further help in enhancing the growth of microorganisms.[12] The microorganisms present in the MSAF may cause intrauterine infection (IUI) in mothers and neonatal sepsis or pneumonitis in neonates. The bacteria and bacterial products will induce the release of pro-inflammatory markers.[13] Meconium has high levels of chemokines and proinflammatory cytokines. The inflammation will contribute to fetal distress in MAS. The process of inflammatory response in MAS is similar to the inflammation noted in pneumonia caused by microbes.[14]

The role of micro-organisms in the MAS is discussed little. In this review, we discuss the presence of micro-organisms in MSAF and meconium and their role in MAS. In addition, we discuss the fetal inflammatory response to the MAS. The review's objective is to gain knowledge about microbial analysis in MAS and discuss inflammatory markers in the fetal response to MAS.

PATHOPHYSIOLOGY

Meconium in the term and post-term fetus

The MSAF development may be due to the physiological maturation of the intestinal tract of the fetus, and this is the commonest mechanism of meconium passage *in utero*.[15] In addition to this, fetal hypoxia will also cause the passage of meconium. In fetal hypoxia, the fetal pituitary releases arginine vasopressin, which stimulates the smooth muscles of the colon and relaxes the anal sphincter, allowing meconium to pass *in utero*.[16] Further, the stimulation of the vagal nerve increases the peristalsis and relaxation of the anal sphincter, causing the intrauterine passage of meconium.[12,16] Figure 1 provides a clear explanation of the mechanisms of meconium passage *in utero*. According to Klingner and Kruse, in the mature fetus, the myelination of nerve fibers increases motilin concentration. Motilin is a peptide, a hormone responsible for stimulating the intestinal muscle's contraction and defecation, causing meconium passage in AF. Motilin levels are higher in term and post-term compared to preterm neonates.[9,17]

Meconium in the preterm fetus

Approximately 5% of preterm fetuses have MSAF, which is linked to a worsening of the newborn's prognosis when compared to clear AF with the same gestation. Because the meconium in a pre-term fetus must travel a longer distance through the colon, it suggests that a higher level of stress and/or longer duration is necessary for meconium transit. This could account for the higher rates of perinatal illness and mortality in this population.[10]

MAS

The pathophysiology of MAS involves air obstruction, inflammation, and surfactant dysfunction [Figure 2].

- Air obstruction: Based on the consistency and amount of the meconium, the resistance of the airflow and air trapping are caused in the airway of the neonates.[18] The ball-valve-like effect is seen in the smaller airways due to partial obstructions, where air is passed during inspiration but is trapped during expiration. These may lead to pulmonary air leak syndrome.[11,19]
- Inflammation: The presence of meconium in the airway of neonates causes an elevation in the count of alveolar neutrophils and chemotactic neutrophil activity up to 48 h after aspiration. They also cause complement activation and an increase in proinflammatory mediators.[18,19]
- Surfactant dysfunction: Bile salts and bilirubin found in meconium inactive the native surfactant, and the neonates with MAS are less able to synthesize surfactant. The fatty acids present in meconium cause surfactant inactivation by reducing the proteins A and B.[11,18]

FETOMATERNAL FACTORS ASSOCIATED WITH MSAF AND MAS

Several fetomaternal factors are associated directly or indirectly with the passage of meconium *in utero* and cause MSAF. The maternal factors, such as placental insufficiency, oligohydramnios, pregnancy-induced hypertension, post-term pregnancy, chorioamnionitis, duration of labor >15 h, and maternal drug abuse, cause MSAF.[20,21] As mentioned above in the pathophysiology, most of the maternal factors, such as pregnancy-induced hypertension and oligohydramnios, will cause hypoxia, which leads to the meconium passage. In the case of post-term pregnancy, the maturation of the GIT in the fetus causes the passage of meconium. In addition, the increase in colonic motility during labor with a long duration will pass meconium.[21]

The major and most discussed fetal risk factor of MAS is the thickness of meconium. The study conducted by Khazardoost *et al*. observed 63 out of 64 neonates having thick meconium, and they concluded that the thickness of the meconium plays a significant role as a risk factor for MAS.[22] In addition, the non-reassuring fetal heart rate pattern and APGAR score <6 at 1 and 5 min will also act as risk factors.

THE MICRO-ORGANISMS IN MAS

Understanding the microbiological profile in MAS helps in both early management and prevention of infection caused by meconium and also helps in the initiation of early empirical antibiotics in high-risk neonates. It plays major role in the mother with IUI or the cases with prolonged rupture of membrane and chorioamnionitis. The microbiology of

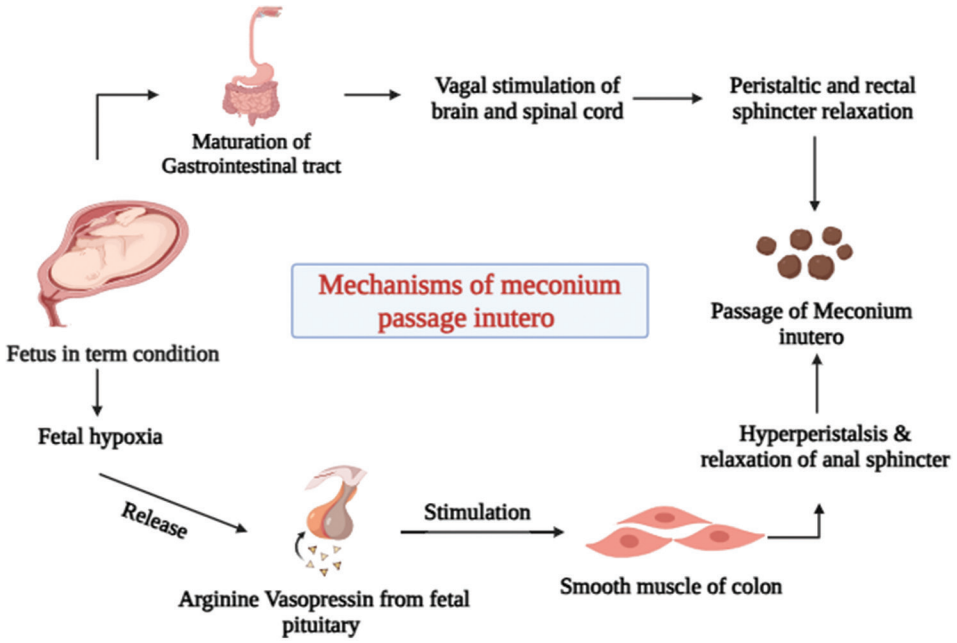

Figure 1: Mechanism of meconium passage *in utero* in term neonates (Created in Biorender.com) (Adapted from Dani, C.; Ciarcià, M.; Barone, V.; Di Tommaso, M.; Mecacci, F.; Pasquini, L.; Pratesi, S. Neonatal Outcomes of Term Infants Born with Meconium-Stained Amniotic Fluid. Children 2023, 10, 780

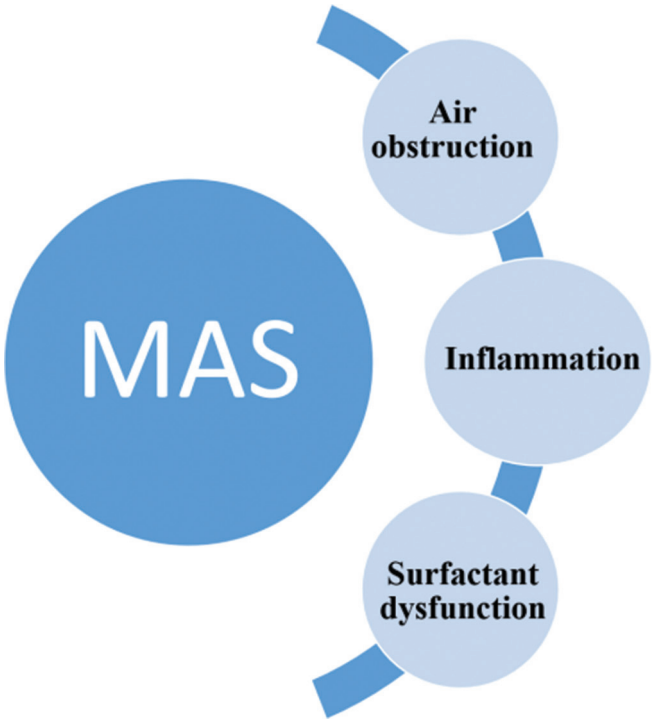

Figure 2: Pathophysiology of meconium aspiration syndrome

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the newborn intestine was initially described by Escherich (1886), who used culture methods to identify and recover bacteria. He stated that "Pure meconium contains no trace of microbial elements, but a rich microbial flora is present by the eighth day of life."[23] However, other studies showed that the meconium contains various microorganisms [Table 1]. Meconium microbiota is a component of gut colonization and has intrauterine origins. The micro-organisms in meconium increase the possibility that maternal germs could enter the fetal GIT by an internal route.[24] The meconium microbiome is associated with several maternal characteristics, such as antibiotic use during pregnancy, dietary habits, and other environmental factors. It is believed to function as a substitute for the fetal gut microbiota.[25]

In 1927, Burrage performed the culture of meconium using 100 samples, out of which 38% of the meconium had the presence of bacteria. In 1934, Hall *et al*., performed both microscopic and culture methods to detect the bacteria in meconium; only 6% of meconium showed positive by microscopic (Gram stain or methylene blue stain) and 38% showed culture positive, which had a similar result with the study conducted by Burrage. In addition to this, Synder (1936) performed a culture technique using enriched culture media, showing 36% of the bacteria in the meconium samples.[23] The presence of bacteria and the transmission of the gut microbiota *in utero* was explained by Jimenez E *et al*., in 2008 through culture and *in vivo* studies using the mouse model. The culture showed the predominant growth of the genus *Enterococcus* and *Staphylococcus*.[26] Kennedy *et al*., collected the fetal meconium sample before elective C-section delivery by a rectal swab of the neonates. The culture showed the growth of *Staphylococcus epidermidis,* which is a skin contaminant; therefore, this study concluded that gut colonization in infants will not occur before birth.[27] The recent study conducted by Turunen *et al*., in 2023 found the Phyla *Firmicutes*, *Proteobacteria,* and *Actinobacteria*, and the genera *Staphylococcus*, *Escherichia-Shigella*, and *Lactobacillus* in the meconium samples. The study supported that the first gut microbiota primarily forms during delivery.[25]

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Table 1: Microbiome in amniotic fluid, meconium-stained amniotic fluid, and meconium

Amniotic fluid	Meconium-stained amniotic fluid	Meconium
Escherichia coli	*Ureaplasma urealyticum*	Phyla: *Firmicutes*,
Ureaplasma species	*Listeria monocytogene*	*Proteobacteria*,
Staphylococcus epidermidis Staphylococcus sciuri	*Mycoplasma hominis*	*Actinobacteria*
Streptococcus intermedius, Streptococcus anginosus,	*Streptococcus viridians*	Genera: *Staphylococcus*,
Enterococcus faecalis	*Peptococcus asaccharolyticus,*	*Micrococcus*,
Klebsiella pneumoniae	*Bacteroides fragilis*	*Escherichia-Shigella*,
Coagulase-negative Staphylococci	Gram-negative rods	*Lactobacillus, Bacterium*
Streptococcus agalactiae, Lactobacillus species	Gram-positive cocci	*coli, Bacillus welchii*
Gram-negative rods		
Gram-positive cocci		

Adrissone AN *et al*., conducted the study using meconium and compared the results with the microbiota of AF from previously conducted studies. The comparison showed high similarities in the culture between meconium and AF. Thus, supporting the hypothesis that the fetal intestinal microbe is derived from the swallowed AF and might be involved in the premature birth of neonates.[28] Meconium presence in the AF enhances bacterial growth, as proved by Florman AL *et al*., in 1969. They used three bacterial isolates for the study, such as *Escherichia coli*, *Staphylococcus aureus,* and *Listeria monocytogenes*.[29] Later in 2003, Lembel *et al*., stated that meconium enhances the growth of perinatal bacterial pathogens. The study was conducted using the meconium of nine healthy neonates.[30] Chang *et al*. employed next-generation sequencing (NGS) in 2023 to find the microorganisms in the first pass meconium. The two most prevalent phyla, *Proteobacteria* and *Firmicutes*, made up 85.45% and 9.74% of the total. With an average of 17.35%, *Pseudomonas* sp. was the most prevalent species present in the meconium.[31] In addition to this work, Wang *et al*. identified the newborns' gut microbiota using NGS. *Proteobacteria* were the most abundant phylum found in the first pass meconium, with the presence of genus *Rhodococcus*, *Sphingobacterium*, *Acinetobacter*, *Methylobacterium*, and *Sphingomonas*.[32]

The study conducted by Romero *et al*., at Yale in 1991 and at Chile in 2013, showed the microorganisms in MSAF. The study carried out in 1991 involved 707 patients. Thirty out of 707 (4.2%) had MSAF. The positive microbial culture had greater significance in the MSAF group (33%) than in the clear AF group (11%). The bacteria found in the MSAF culture were mixed anaerobic bacteria, *Ureaplasma urealyticum, L. monocytogenes, Mycoplasma hominis, Streptococcus viridians, Peptococcus asaccharolyticus*, and *Bacteroides fragilis*.[33] In 2014, the study was conducted in the MSAF of the term labor. Similar to the previous study, the bacteria were frequently higher in the MSAF group (19.6%) than in clear AF (4.7%). The bacteria, such as Gram-negative rods, *U. urealyticum,* Gram-positive rods, and *M. hominis*, were found in the MSAF group.[34] In between, Mazor *et al*., in 1995, conducted a study involving the MSAF from preterm labor. The various species of bacteria were present, such as *U. urealyticum, M. hominis, S. viridians, E. coli, Proteus mirabilis, P. asaccharolyticus, Haemophilus influenzae, Campylobacter coli, Bacteroides asaccharolyticus, and B. fragilis.* In addition to these bacterial isolates, the fungal growth of *Candida albicans* was also seen in 3 MSAF.[35] Later in 2016, Lee *et al*., studied microbes in amniotic fluid (AF) and compared the results between MAS and non-MAS groups. The microorganisms isolated from the AF include *E. coli, Ureaplasma* species, *S. epidermidis, Staphylococcus sciuri, Streptococcus intermedius, Streptococcus anginosus, Enterococcus faecalis, Klebsiella pneumoniae,* coagulase-negative Staphylococci, *Streptococcus agalactiae*, *Lactobacillus* species, Gram-negative rods, and Gram-positive cocci. The positive AF culture was higher in the MAS group compared to the non-MAS.[36] The study conducted at Spain in 2015 by Gosalbes *et al*., stated that the resistance of β-lactam antibiotics and tetracycline was detected in meconium and early fecal samples of neonates and fecal samples of mothers. The result showed a high prevalence of β-lactam antibiotics and tetracycline in the samples. The *mecA* gene was elevated in both meconium and early fecal samples than in the fecal sample of the mother. The study concluded that the GIT of the mother may act as an antibiotic reservoir from birth.[37]

INFLAMMATORY MARKERS IN MAS

Cytokines can be classified as pro-inflammatory and anti-inflammatory cytokines. The pro-inflammatory cytokines are immune regulatory cytokines that favor inflammation. The anti-inflammatory cytokines regulate the immune system by neutralizing the synthesis of pro-inflammatory cytokines and cell stimulation.[38] It is difficult to predict the development of MAS in neonates born with MSAF clinically and radiographically; the biomarkers play a major role in the prediction of MAS. MAS severity is significantly correlated with inflammatory markers, which indicate the degree of systemic and pulmonary inflammation caused on by meconium exposure. The biomarkers seen in cord blood are most commonly connected with the fetal inflammatory response. An immunological response in the fetus may be triggered by an IUI, which may cause inflammation or organ damage that could have long-term effects on the developing

neonate. Infants delivered to mothers with IUI are frequently treated empirically for neonatal sepsis.[39] The development of respiratory distress, and severe pulmonary dysfunction, as well as the progression from mild lung disease to severe lung injury, all are facilitated by the presence of cytokines in MAS. Cytokine profile variations can be helpful as diagnostic and prognostic markers for the severity of MAS. Overall, the inflammatory biomarkers help in detecting the severity of the infection and also help in all the stages of therapy, from the prognosis of the infection to the treatment of the infection.

The components of meconium are harmful to lung tissue and cause a strong inflammatory reaction that can lead to systemic inflammation and chemical pneumonitis. In alveoli and the airways, the occurrence of macrophages and neutrophils can be observed, followed by meconium aspiration.[40] Okazaki *et al,* conducted a study in Japan, measuring 17 types of cytokines and chemokines in sera of neonates with MAS. They found that the sera of MAS patients had significantly higher levels of the majority of inflammatory markers. The increase in Interleukin-10 (IL-10) might indicate the prevention of pulmonary inflammation.[14] A retrospective study by Ekmen *et al*., in Turkey explained the role of IL-6. IL-6 is considered a strong inflammatory mediator and prognostic factor. This can be used to predict the development of MAS in neonates.[41] Hsieh *et al*., conducted a study in 1997 where their team investigated the IL-1β and IL-6 in MSAF and fetal cord blood. The statistically significant results were seen in IL-6 among the MSAF and control groups ($P = 0.0036$). Significant value was not seen among IL-1β in MSAF and fetal cord blood, and IL-6 in fetal cord blood.[42] Yamada *et al.*, in 2000, conducted an assay for IL-8, tumor necrosis factor-alpha (TNF-α), and IL-1β using meconium suspension, AF, and turbid amniotic fluid. The concentration of TNF α and IL-1β in meconium suspension where high in AF and MSAF. The concentration of IL-8 in AF and MSAF was high compared to meconium suspension.[43] The animal study was conducted in 2000 to investigate the inflammatory response in 2-week-old white rabbit pups. The values of inflammatory markers were studied before and after the instillation of meconium into the lungs. The results showed an increase in IL-6, IL-8, and TNF-α and a decrease in IL-10 after the instillation of meconium compared to before the instillation of meconium.[44]

TREATMENT AND MANAGEMENT OF THE MAS

The management and pathophysiology of MAS have changed significantly in the past 40 years. To prevent MAS, it was previously advised that both vigorous and non-vigorous infants delivered through MSAF undergo routine intrapartum and postnatal endotracheal suctioning of meconium. Regular suctioning is no longer recommended due to recent research, suggesting it may not be beneficial.[19] Admission to the neonatal intensive care unit (NICU) is required for all newborns experiencing respiratory distress. These neonates require vigilant monitoring, supportive care, and respiratory support, as one of the essential pathophysiology is hypoxia. Respiratory support is the most significant treatment in MAS, aiming to achieve optimum oxygenation and ventilation. Oxygen therapy alone, either by hood or nasal continuous positive airway pressure (CPAP), is used to treat the mild form of MAS.

Mechanical ventilation is required by around 40% of infants with MAS.[11,17] Moderate MAS requires increased fractional oxygen (FiO_2) concentrations and pressure supports. Non-invasive ventilation strategies such as CPAP or high-frequency nasal cannula ventilation may be beneficial in this category. Intubation and mechanical ventilation with increased pressure supports are needed if the neonate has a severe degree of MAS and is developing persistent pulmonary hypertension of the newborn. Indications of invasive ventilation include increasing FiO_2 requirements (>40%), persistent hypoxia (pO_2 <60 mm Hg), acidosis (pH <7.25), elevated pulmonary pressures and hemodynamic instability, levels up to a peak inspiratory pressure of 30 cm of H_2O Hg, and positive end-expiratory pressure of 7–8 cm of H_2O along with high inspiratory time and rate which are needed to maintain oxygen status and provide adequate lung expansion without causing barotrauma. The high-frequency oscillatory ventilation (HFOV) strategy is indicated in cases of persistent hypoxemia and an increase in oxygenation index. The HFV helps in enhancing oxygenation and minimizing barotrauma in neonates with MAS. About 15–33% of MAS cases have been found to have pulmonary air leaks. When paired with pulmonary surfactant, HFOV has a substantial therapeutic impact on MAS.[45]

It can also be advantageous to combine inhaled nitric oxide (iNO) with high-frequency ventilation. Increased responsiveness to iNO can be achieved by improving iNO supply to the pulmonary circulation and reducing intrapulmonary shunting during HFV.[46] The newly developed therapy has greatly reduced the number of newborns requiring ECMO. Infants with respiratory insufficiency have responded well to extracorporeal membrane oxygenation, with a 94% survival rate in neonates with MAS.[47]

The presence of micro-organisms in the neonates with MAS is often treated with antibiotics. The use of antibiotics to treat neonates is still in controversy. In 2007, Basu *et al*., conducted the study by dividing the neonates with MAS into two groups. Group A neonates were treated with Ampicillin and Amikacin, whereas group B was not given any antibiotics. The result of the study showed no significance in the use of antibiotics in neonates with MAS.[48] The systemic review conducted by Natarajan *et al*., also concluded the similar results as the study of Basu *et al*. For symptomatic newborns with MAS, the beneficial effects of antibiotic therapy are unclear but empiric use of ampicillin and gentamicin therapy is considered pending blood culture results given

the challenges in excluding invasive bacterial infection (e.g., early-onset sepsis). For well-appearing neonates born through MSAF and with no symptoms of early-onset sepsis, antibiotic therapy is not recommended.[49]

LIMITATIONS

The review focuses on bacteria and inflammatory markers in MAS, and other factors, such as other microbial factors and their products, were not involved. Other physiological parameters in the pathogenesis of MAS were not discussed in detail. The review does not include the further complications caused by MAS in neonates after delivery.

CONCLUSION

The evidence showing the presence of microorganisms in the MSAF *in utero* suggests that the meconium in the fetus does contain microorganisms. These micro-organisms present in MSAF and meconium may cause IUI, chorioamnionitis in mothers and neonatal sepsis, MAS, and pneumonitis in neonates.

The incidence of MAS was high in the post-term delivered neonates and neonates with thick meconium. Therefore, preferring the elective induction of labor for pregnancies ≥41 weeks will help in reducing the cases of MAS. The grade of the meconium should be noted immediately, and the neonates with thick meconium should be managed in the NICU. The treatment used in MAS, such as surfactant therapy and mechanical ventilation, should be well monitored.

The morbidity and mortality linked to MAS have significantly decreased as a result of improvements in clinical practice management. Still, the cases of MAS remain higher in low-income countries. The collaborative approach of obstetricians, neonatologists, and pediatricians helps further reduce MAS cases. Further investigation is needed to understand the pathogenesis of MAS and to detect the predisposing factors of MAS, which allows clinicians to anticipate MAS cases as soon as possible and treat the neonates. Understanding the micro-organisms and drug-resistant patterns in neonates with MSAF helps diagnostically prescribing antibiotics, which plays a key role in antibiotic stewardship for managing neonates with MAS.

AUTHORSHIP CONTRIBUTION STATEMENT

A. Veena Shetty: Writing – review and editing, validation, supervision, and conceptualization. P. Samruddhi: Writing – review and editing, data curation, and conceptualization. Seema Pavaman: Writing – review and editing, supervision, and data curation. Neetha Nandan: Writing – review and editing, supervision, and data curation.

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Author Queries???
AQ1: The author's name does not match with the ones in the reference list.