The outcome of newborns born through grade 3 meconium-stained amniotic fluid in a regional hospital in Durban, KwaZulu-Natal

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Background. Meconium-stained amniotic fluid (MSAF) may reflect normal fetal gut maturation or may indicate fetal compromise. Protocols on the management of newborns with grade 3 MSAF exposure who do not require immediate resuscitation at birth, are required.
Objectives. To determine the outcomes of newborns born through grade 3 MSAF.
Methods. A retrospective chart review was conducted at King Edward VIII Hospital (KEH) in Durban, KwaZulu-Natal (KZN), South Africa (SA) from 1 January to 31 December 2018. Data were collected from 238 newborns born through grade 3 MSAF to determine the incidence of neonatal sepsis, respiratory complications and neurological complications associated with grade 3 MSAF exposure. Descriptive statistics were used.
Result. Neonatal sepsis was suspected in 10.5% of the grade 3 MSAF-exposed newborns and confirmed in 1.7% of the cases. Respiratory distress occurred in 18.9% of newborns, with 9.2% requiring supplementary oxygen. Neurological complications occurred in 2.9% of grade 3 MSAF- exposed newborns and 2.2% of newborns complicated with seizures
Conclusion. There was a low rate of neonatal sepsis, respiratory distress, neurological complications and perinatal asphyxia in newborns exposed to grade 3 MSAF. Neonates who are stable at birth can be observed in the postnatal ward for a short period after birth before discharge.

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Newborns typically pass meconium within the first 24 - 48 hours of birth. However, staining of the amniotic fluid with meconium can occur *in utero* and may represent normal gastrointestinal maturation or may indicate intrauterine hypoxia.[1-3] Meconium-stained amniotic fluid (MSAF) is classified from grade 1 to 3, based on the degree of staining. An increasing grade may be associated with adverse maternal and fetal outcomes.[4,5] Meconium aspiration syndrome (MAS) occurs when meconium, passed *in utero*, is aspirated into the lungs by the fetus and causes severe respiratory distress.[6] MSAF is observed in 8 - 20% of pregnancies, and 2 - 9% of newborns born through MSAF may develop MAS.[2,7] The passage of meconium in amniotic fluid, in association with an abnormal cardiotocography (CTG), variations in the fetal heart rate (FHR) and a decrease in the fetal scalp blood pH, are indicators of fetal distress.[4] Thick MSAF alone is not associated with adverse fetal outcomes but cases with thick MSAF associated with non-reassuring fetal heart rate patterns, fetal acidosis, low Apgar score, aspiration of meconium and the need to intubate, have an increased risk of developing MAS.[2,6] Meconium passage is rare before 34 weeks' gestation, but its incidence increases with gestational age.[3] The incidence of MSAF ranges from 5% before 37 weeks of gestation, 25% at term to 25 - 52% in post-term gestation.[8]

National policies guide the management of newborns born through MSAF who require delivery-room resuscitation due to perinatal asphyxia or severe respiratory distress.[9,10] However, there is no standard management of newborns born through grade 3 MSAF who do not require immediate resuscitation post delivery. In Durban eThekwini District, some neonatal units admit all grade 3 MSAF-exposed newborns for a baseline septic screen (which includes full blood count (FBC), C-reactive protein (CRP), and blood culture), empiric antibiotic therapy and neuro-observation for 24 hours post delivery. Other neonatal units in the area do not routinely admit MSAF grade 3-exposed newborns for observation.

Between 80 - 86% of newborns born through MSAF do not exhibit respiratory distress symptoms immediately after delivery, and only routine care is indicated.[3,11] However, newborns born through MSAF are 100 times more likely to develop respiratory distress than newborns born through clear amniotic fluid.[1,12] Complications such as birth asphyxia, MAS, hypoxic ischaemic encephalopathy (HIE), septicaemia and death may occur. Therefore, close monitoring is recommended for early intervention, potentially reducing neonatal adverse effects.[13]

In this study, MSAF was diagnosed on inspection of amniotic fluid by a midwife or a medical doctor, following spontaneous or artificial rupture of membranes. Grade 3 MSAF was classified as opaque and deep green amniotic fluid.[4] This study aimed to determine the outcomes of newborns born through grade 3 MSAF who are vigorous at birth and to determine if a routine septic screen, empirical antibiotic cover, neuro-observations or neonatal admission is required.

Methods

Study design and setting

This was a retrospective observational chart review of newborns born through grade 3 MSAF who presented to the King Edward VIII Hospital (KEH) neonatal unit, a regional hospital in Durban, South Africa (SA), between 1 January and 31 December 2018.

Ethics approval

Permission to collect and analyse clinical data was obtained from the Human Research Ethics Committee of the University of KZN (ref. no. BE118/19), management from KEH and the KZN Department of Health (KZN-DoH).

Inclusion criteria

Newborns born through grade 3 MSAF at gestational age ≥35 weeks with complete medical records who presented to the KEH neonatal unit.

Exclusion criteria

Newborns born through grade 3 MSAF at <35 weeks of gestation and who required delivery-room resuscitation or had an Apgar score <7 at 5 minutes.

Data collection

Data from the hospital's digital medical records database were captured on a study datasheet. Demographic characteristics, mode of delivery, Apgar scores, sepsis screening (FBC, CRP and blood culture), respiratory complications (respiratory distress, development of MAS, use of supplementary oxygen or use of ventilatory support) and neurological complications (seizures, poor feeding, or tone disturbances) were retrieved. Confidentiality and anonymity were assured by not using patient names and storing data on a password-protected computer.

Data analysis

Data analysis was conducted using R Statistical Computing Software (Version 3.66) and presented as descriptive statistics.

Results

There was a total of 7 005 live births with 3 349 admissions to the KEH neonatal unit. Grade 3 MSAF accounted for 303 admissions and the incidence of grade 3 MSAF was 4.3% of live births.

Study participants characteristics

A total of 238 patients satisfied the inclusion criteria. There were 123 (51.7%) female and 115 (48.3%) male newborns. The mean (standard deviation (SD)) gestational age was 39 (1.5) weeks, while 27.7% were at 40 weeks' gestation and 16% late-term deliveries (41 - 42 weeks' gestation). The mean birthweight was 3 110 (484) g, while 10.9% were small for gestational age and 3.4% were large for gestational age. In 2018, the total number of newborns exposed to HIV *in utero* was 1 095. The overall incidence of HIV exposure in the KEH neonatal unit was 32.7%. Among the grade 3 MSAF-exposed newborns, 107 (45%) were exposed to HIV *in utero* and 129 (54.2%) were unexposed to HIV. The maternal HIV status was unknown in two (0.8%) cases. Using the binomial proportion test for comparing two proportions, the incidence of HIV exposure in general neonatal admissions and the incidence of HIV exposure in grade 3 MSAF was significantly different. The test statistic of the two proportions is equal to 3.87, which is greater than the z-statistic at the 5% significance or critical level (z=1.96). In the HIV-exposed group, 83 (77.57%) neonates had low-risk HIV exposure (maternal viral load <1 000 copies), 5 (4.67%) had high-risk exposure (maternal viral load >1 000 copies) and in 19 (17.76%) cases the maternal viral load was unknown (Table 1).

Mode of delivery and Apgar score

There were 129 (54.2%) caesarean section deliveries and 109 (45.8%) normal vaginal deliveries (NVD). The indications for caesarean section were fetal distress or suspected fetal compromise (42.6%), grade 3 MSAF exposure (20.2%), previous caesarean section in labour (20.9%), delayed second stage of labour (7.7%), cephalopelvic disproportion (2.3%), breech presentation (1.6%), imminent eclampsia (0.8%), extrauterine pregnancy (0.8%) and big baby (0.8%). For three (2.3%) deliveries, the indication was not documented. The median Apgar score at 1 minute was 8 (range 4 - 9) and the median Apgar at 5 minutes was 9 (range 7 - 10).

Screening for neonatal sepsis and empirical antibiotic use

There were four (1.7%) patients with confirmed neonatal sepsis based on a positive admission blood culture and 25 (10.5%) patients with suspected neonatal sepsis based on abnormal septic markers, including CRP, white cell counts or platelet counts (Fig. 1). A blood culture was taken on admission in 193 patients. Of those, 177 (91.7%) patients had no growth on the blood culture, 25 (6.2%,) patients had suspected contamination in their specimen and four (2%) patients grew either a drug-sensitive *Staphylococcus aureus*, *Pseudomonas oryzihabitans*, *Enterococcus faecalis* or *Achromobacter denitrificans,* respectively, on the blood culture. The median white cell count in this study was 15.6 × 10^9/L (Q1:12.6 - Q3:19.5). In the confirmed cases of neonatal sepsis, the white cell count range was 6.10 × 10^9/L - 22.1 × 10^9/L. In the suspected cases of neonatal sepsis, the white cell count range was 5.10 × 10^9/L - 64.7 × 10^9/L. The median platelet count in the study was 259 × 10^9/L (Q1:212 – Q3:301). In the confirmed cases of neonatal sepsis, one patient had mild thrombocytopenia (platelet count of 132 × 10^9/L). Among the suspected cases of neonatal sepsis, four patients had moderate thrombocytopaenia (platelet count of 90, 94, 96 and 97 × 10^9/L, respectively).

A total of eight (3.4%) patients in the sepsis group also had respiratory symptoms. One patient with confirmed neonatal sepsis had mild respiratory distress and received supplementary oxygen for less than 12 hrs. The other seven patients had suspected sepsis, five had mild respiratory distress and two had moderate respiratory distress. Both patients with moderate respiratory distress required supplementary oxygen for 12 - 24 hrs and one patient with mild respiratory distress required supplementary oxygen for less than 12 hrs. All eight patients received empiric antibiotics.

Empiric antibiotic therapy was administered to 176 (73.9%) patients upon admission to the KEH neonatal unit. Ampicillin served as first-line therapy for 172 patients. Penicillin G was used for one patient with suspected syphilis exposure *in utero*, while tazobactum + piperacillin was administered to another patient who grew an organism sensitive to tazobactum + piperacillin on the blood culture. A single dose of ceftriaxone was used for one patient with suspected conjunctivitis, while amoxicillin + clavulanic acid was administered to one patient as a continuation of therapy commenced at Inkosi Albert Luthuli Central Hospital (central and tertiary care referral hospital). The antibiotic therapy spanned 1 day for 16 (9.1%) patients, 2 days for 81 (46%) patients, 3 days for 40 (22.7%) patients, 5 days for 30 (17%) patients and ≥6 days for 8 (4.5%) patients.

Respiratory complications and management

Respiratory distress occurred in 45 (18.9%) patients. Of those, 40 had mild respiratory distress, four had moderate respiratory distress and one had severe respiratory distress (Fig. 2). Supplementary oxygen was administered to 9.2% of the patients. The duration of oxygen therapy was less than 12 hrs for 13 (59.1%) patients, 12 - 24 hrs for six (27.3%) patients, 72 - 96 hrs for two (9.1%) patients and 10 days for one (4.5%) patient. One patient needed non-invasive ventilation for 3 days, while another patient needed invasive positive pressure ventilation for 2 days. MAS was suspected in 13 (5.5%) patients. Of those, 11 were determined to be mild MAS, one moderate MAS and one severe MAS that required invasive mechanical ventilation. Among the suspected MAS cases, oxygen therapy was administered in 10 (76.9%) patients, dexamethasone was used in 11 (84.6%) patients and empirical antibiotics were administered in all 13 patients, as part of the management of MAS. No surfactant therapy was used in any of the patients in the study.

Neurological complications and management

Neurological complications including seizures, tone disturbances and abnormal primitive reflexes occurred in seven (2.9%) patients. Seizures occurred in five (2.2%) patients at 60 min, 90 min, 3 hrs, 30 hrs and 120 hrs after delivery, respectively. Neonatal seizures were aborted in three cases with intravenous lorazepam, two cases self-aborted and all cases received an intravenous phenytoin loading dose. Single maintenance therapy was phenobarbitone in three patients, phenytoin in one patient and one patient required an intravenous benzodiazepine infusion for 4 days and dual oral maintenance therapy (phenobarbitone and sodium valproate).

Perinatal asphyxia was suspected in four (1.7%) patients, all of whom experienced seizures within the first 30 hrs of life. Poor feeding and tone disturbances occurred in three of the four patients before seizures. All four patients had mild metabolic acidosis and elevated cardiac enzymes (troponin, creatinine kinase and creatinine kinase-MB) on admission. However, all 5-minute Apgar scores were ≥7. In one of the four patients, HIE monitoring showed a Thompson score of 13 on day 7 of life. One patient presented with abnormal primitive reflexes, hypertonia, and seizures 120 hrs after delivery. Post delivery, the patient was determined to have mild MAS and was treated with dexamethasone, received <24 hours of supplementary oxygen and was administered empiric antibiotics for 4 days. Before the onset of seizures on day 5 of life, the patient had a normal septic screen and respiratory symptoms had resolved. A brain computerised tomography (CT) confirmed that the neurological sequelae stemmed from a left middle cerebral artery territory infarct.

Six of the seven patients with neurological complications experienced respiratory distress at birth. Five of them had mild respiratory distress, while one had moderate respiratory distress

Table 1. Participant characteristics stratified according to the outcome of neonatal sepsis

Outcome of sepsis	Confirmed, *n* (%) (*N*=4)	No, *n* (%) (*N*=209)	Suspected, *n* (%) (*N*=25)	Overall, *n* (%) (*N*=238)
Sex				
Female	2 (50)	111 (53.1)	10 (40)	123 (51.7)
Male	2 (50)	98 (46.9)	15 (60)	115 (48.3)
Race				
Black	4 (100)	205 (98.1)	25 (100)	234 (98.3)
Coloured	0	3 (1.4)	0	3 (1.3)
Indian	0	1 (0.5)	0	1 (0.4)
RVD exposure				
Exposed	0	100 (47.8)	7 (28)	107 (45.0)
Enexposed	4 (100)	108 (51.7)	17 (68)	129 (54.2)
Unknown	0	1 (0.5)	1 (4)	2 (0.8)
Maternal VL		(*n*=100)	(*n*=7)	(*n*=107)
<50	0	69 (69)	6 (85.7)	75 (70.1)
51 - 1 000	0	8 (8)	0	8 (7.5)
>1 000	0	5 (5)	0	5 (4.7)
Unknown	0	18 (18)	1 (14.3)	19 (17.8)

RVD = retroviral disease; VL = viral load.

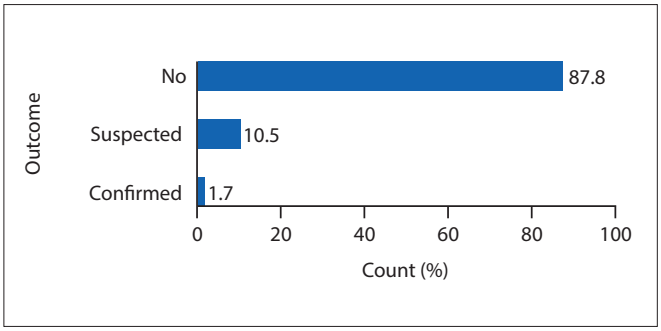

Fig. 1. Neonatal sepsis in newborns born through grade 3 meconium-stained amniotic fluid, n=*238.*

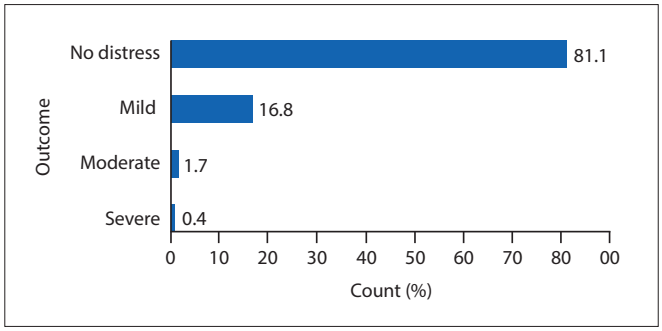

Fig. 2. Respiratory distress in newborns born through grade 3 meconium-stained amniotic fluid, n=*238.*

secondary to suspected MAS, necessitating non-invasive ventilation for 3 days. One patient was asymptomatic at birth but developed mild respiratory distress, poor feeding and seizures 30 hours after delivery. Meningitis was suspected in two patients due to pleocytosis in CSF, resulting in tone disturbances and abnormal primitive reflexes. However, both patients were seizure-free. No patients with confirmed sepsis had neurological complications. There were no deaths in the study.

Discussion

Meconium passage is a normal physiological event that is an indicator of fetal maturity and usually occurs within the first 24 - 48 hrs following birth. However, its occurrence *in utero* may represent normal gastrointestinal maturation or indicate acute or chronic intrauterine hypoxia.[1-3] Newborns born through grade 3 MSAF accounted for 4.3% of live births and 9% of admissions to the KEH neonatal unit. International reports found that MSAF occurs in 8 - 20% of all pregnancies.[2,7] The incidence of MSAF increases with gestational age. Some studies have demonstrated a 50% prevalence of MSAF after 40 weeks gestation, with 25% of those cases occurring after 41 weeks gestation.[3,8] This study demonstrated an increasing incidence of grade 3 MSAF with gestational age. Specifically, 49.7% of cases were between 37 – 40 weeks' gestation, while 43.7% of cases occurred after 40 weeks' gestation, with 16% of the cases occurring after 41 weeks' of gestation. Divon *et al.*[14] demonstrated a significantly higher percentage of pregnancies delivered after term in male v. female newborns. In this study, 51.7% of the newborns born through grade 3 MSAF were female and 48.3% were male, with a mean gestational age of 39 weeks for both.

HIV exposure was reviewed in this study as previous studies suggest that HIV exposure may be a risk factor associated with MSAF. Gupta *et al.*[15] showed an increased risk of MSAF and MAS in newborns born to HIV-positive mothers. In this study, 54.2% of the newborns born through grade 3 MSAF were unexposed to HIV *in utero*, while 45% were born to HIV-positive mothers and 0.8% had an unknown HIV exposure status at the time of admission. Among the HIV-exposed group of newborns, 75.7% were considered to have low-risk HIV exposure. Further research is required to determine whether HIV infection itself or antiretroviral exposure may be associated with MSAF.[15]

Caesarean section accounted for 54.2% of the deliveries. The literature demonstrates that MSAF is associated with higher caesarean section delivery and some studies reported that caesarean sections were performed twice as frequently in cases with MSAF.[16] Nesa *et al.*[17] reported that 40.2% of patients had caesarean section delivery in the MSAF group and only 18.6% had caesarean section delivery in the clear liquor group. Fetal distress or suspected fetal compromise was the leading indication for caesarean section in this study, accounting for 42.6% of the deliveries. MSAF on its own is not a good indicator of fetal distress. However, MSAF in association with abnormal CTG, variations in the FHR and fetal acidosis are good indicators of fetal distress.[4] The presence of MSAF alone does not warrant urgent delivery, but close fetal monitoring in labour is required to decrease perinatal morbidity and mortality.[3,18,19]

This study focused on grade 3 MSAF-exposed newborns who did not require delivery room resuscitation. The median Apgar score was 8 and 9 at 1 and 5 minutes, respectively. Less than one-fifth of the newborns born through grade 3 MSAF had respiratory distress. This is consistent with previous studies that reported no respiratory symptoms indicating distress immediately after delivery in 80 - 86% of MSAF-exposed newborns, necessitating only routine care.[2,6,14] Van Ierland *et al.*[20] reported that most (76%) newborns born through MSAF with a 5-minute Apgar score ≥9 had a low risk of developing respiratory distress. Our study found that 5.5% of the newborns born through grade 3 MSAF had suspected MAS. Similar figures were reported by Swarnam *et al.*,[2] indicating that 2 - 9% of pregnancies with MSAF developed MAS and Van Ierland *et al.*,[20] reporting that 4.8% of newborns born through MSAF developed MAS.

The study demonstrated a low rate of confirmed neonatal sepsis, with only 1.7% of the cases having a positive blood culture on admission to the KEH neonatal unit. A further 10.5% of the cases had suspected neonatal sepsis based on abnormalities in the septic screen. Empirical antibiotics were administered to 73.9% of the patients admitted to the KEH neonatal unit with grade 3 MSAF exposure, and ampicillin was used in 97.7% of these patients. The duration of antibiotics was 2 - 3 days in most patients, with 46% of patients receiving antibiotics for 2 days and 22.7% of the patients receiving antibiotics for 3 days. Natarajan *et al.*[21] reported that the most common antibiotics used were penicillin and an aminoglycoside for an average of 3 - 7 days and reported no significant difference between those neonates who received and those who did not receive any systemic antibiotics. Kelly *et al.*[22] reported no significant difference in mortality or duration of hospital stay between groups administered antibiotics and the control group. Current evidence indicates that, compared to placebo, antibiotics administered to women with MSAF in labour may reduce chorioamnionitis. However, no evidence shows that antibiotics reduce postpartum endometritis, neonatal sepsis or NICU admissions.[23] The low incidence of confirmed sepsis in the study suggests that routine admission at birth and routine septic workup may not be required. However, 10.5% of patients had suspected sepsis based on abnormalities in their septic screen and empiric antibiotics may be considered.

In this study neurological complications occurred in 2.9% of newborns born through grade 3 MSAF. Perinatal asphyxia was suspected in 1.7% of grade 3 MSAF-exposed newborns who did not require delivery resuscitation but presented with mild metabolic acidosis, abnormal neurology and elevated cardiac enzymes. However, all 5-minute Apgar scores were ≥7, thus the criterion for perinatal asphyxia was not fulfilled.[24] Most (75%) of the suspected cases of perinatal asphyxia were complicated, with seizures within the first 3 hours of life, and one patient was asymptomatic at birth but presented with seizures, abnormal neurology, mild acidosis, and markedly elevated cardiac enzymes 30 hours after delivery. Cardiac enzymes may be used to detect myocardial compromise in newborns. Troponin appears 2 - 4 hours after perinatal asphyxia and remains detectable for up to 21 days.[25] In this study, seizures were seen in 2.2% of newborns born through grade 3 MSAF and were associated with either tone disturbances, poor feeding or abnormal primitive reflexes. Dhannaram *et al.*[12] observed seizures on 0.5% of the newborns born through MSAF, while Bhatia *et al.*[26] reported that seizures occurred in 3.35% of newborns born through MSAF.

In the study, 97.7% of newborns born through grade 3 MSAF who had respiratory distress developed symptoms at birth, while 85.7% developed neurological complications within the first 3 hours of life. Careful observation of newborns shortly after birth would identify most of the symptomatic newborns born through grade 3 MSAF before discharge. De Boer *et al.*[27] demonstrated that a 24-hour hospital observation period of newborns born through MSAF with a 5-minute Apgar score ≥9 did not provide additional benefits. Thus, based on the 5-minute Agar score, vigorous infants can be safely discharged. The objective of Van Ierland *et al.*[20] was to evaluate the 24-hour postnatal observations of infants born through MSAF. Prakash *et al.*[28] found that 98.07% of the newborns born through

MSAF developed respiratory distress within the first hour of life. A recommended observation period of 4 - 6 hours would further need to be tested using a randomised control study and include follow up of these newborns for at least 1 week after discharge to determine the best outcome.

There are several limitations to the current study. Data were collected from a single centre, over a relatively short period, with a limited sample size. Investigators conducted a thorough review of the charts. However, retrospective analysis limits the evaluation of certain variables, as there were large amounts of missing data due to incomplete medical records. Not all charts had data on maternal comorbidities, perinatal asphyxia risk factors, FHR, arterial cord blood pH, monitoring of suspected HIE or instrumental vaginal deliveries, for example. Due to the nature of the study, causality between variables could not be investigated.

Conclusion

This study found a low incidence of neonatal sepsis and neurological complications in newborns born through grade 3 MSAF who were vigorous at birth. Routine admission to a neonatal unit and septic workup is not recommended. Newborns born through grade 3 MSAF who are stable at birth can be observed in the postnatal ward for a short period after birth before discharge.

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