THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (September–October 2018) 68(5):360–365
https://doi.org/10.1007/s13224-017-1043-y

ORIGINAL ARTICLE

# New Evidence to Support Antibiotic Prophylaxis in Meconium-Stained Amniotic Fluid in Low-Risk Women in Labor a Prospective Cohort Study

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Received: 4 June 2017 / Accepted: 19 August 2017 / Published online: 1 September 2017


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## Abstract

*Purpose of study* To assess the maternal and perinatal complications associated with meconium-stained amniotic fluid (MSAF) in low-risk women in labor.

*Methods* This prospective cohort study was conducted at CMC Hospital, Vellore, India. Two hundred low-risk women who had artificial or spontaneous rupture of membranes after admission with MSAF were included in the study. Two hundred similar women with clear liquor were taken as controls. The primary outcomes considered were the incidence of chorioamnionitis and endomyometritis in the mothers. The secondary outcomes included postpartum hemorrhage and retained placenta in the mothers and respiratory distress, meconium aspiration, sepsis, and NICU admission in the newborn. Statistical analysis was done using Fischer exact test. Odds ratio, 95% confidence interval, and $P$ value were estimated.

*Results* Compared to controls, those with MSAF had significantly higher rates of chorioamnionitis (2 vs. 8%, $P = 0.006$) and endomyometritis (3 vs. 9.5% $P = 0.007$). Among the secondary end points, only neonatal respiratory distress (8.5 vs. 1.5%; $P = 0.001$) and meconium aspiration (4 vs. 0%; $P = 0.007$) were found to be significantly increased in the meconium group.

*Conclusion* Statistically significant increased incidence of chorioamnionitis and endomyometritis in women with

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MSAF in labor established in our study strongly supports the use of prophylactic antibiotics in these women to prevent immediate and long-term consequences.

**Keywords** Meconium-stained liquor · Chorioamnionitis · Endomyometritis · Respiratory distress syndrome · Meconium aspiration syndrome · Neonatal sepsis

## Introduction

Meconium-stained amniotic fluid (MSAF) is a common phenomenon encountered during labor (7–22%) [1]. Earlier it was considered to be one of the manifestations of intrauterine fetal hypoxia. The proposed theory now is that presence of meconium in amniotic fluid is a normal phenomenon for a term fetus, and it reflects adequate gut maturity and motility, unless associated with non-reassuring fetal heart patterns.

Many retrospective studies done during 1990–2003 have shown significant increase in chorioamnionitis and endomyometritis in women who had MSAF, but there are no recent studies done under current obstetric management guidelines. Histopathological studies have also established an increased association of MSAF in women with histologically proven chorioamnionitis. Considering neonates, in addition to inherent risks of MSAF including RDS, MAS, and neonatal sepsis, chorioamnionitis is also a well-known predisposing factor for cerebral palsy in term infants. Cochrane reviews on antibiotic prophylaxis in labor for women with MSAF, published in 2010 and 2014, showed a significant reduction in the incidence of chorioamnionitis and endomyometritis with the use of antibiotic prophylaxis in labor. All these studies called for more focused attention on the infective morbidity associated with MSAF.

More than a decade has gone by since the last publication on this subject, and there has been a paucity of prospective clinical trials on this important problem. Maternal mortality rates have declined dramatically worldwide due to the multipronged strategies taken to deal with it; the same cannot be said about maternal morbidity. In keeping with the motto of every obstetrician—'healthy mother and healthy baby'—efforts need to be taken to address the problem of maternal morbidity with its attendant physical, emotional, and financial burden. Any steps that reduce maternal morbidity would be welcomed by both obstetricians and patients alike. With this in mind, we embarked on this study, the objective being to determine whether MSAF contributed significantly to maternal morbidity. The study would be of greater relevance in the Indian/'resource-poor' settings where not only do majority of births continue to occur but also where compromise of aseptic precautions is more likely to occur owing to the twin problems of high delivery rates and lack of adequate personnel.

## Materials and Methods

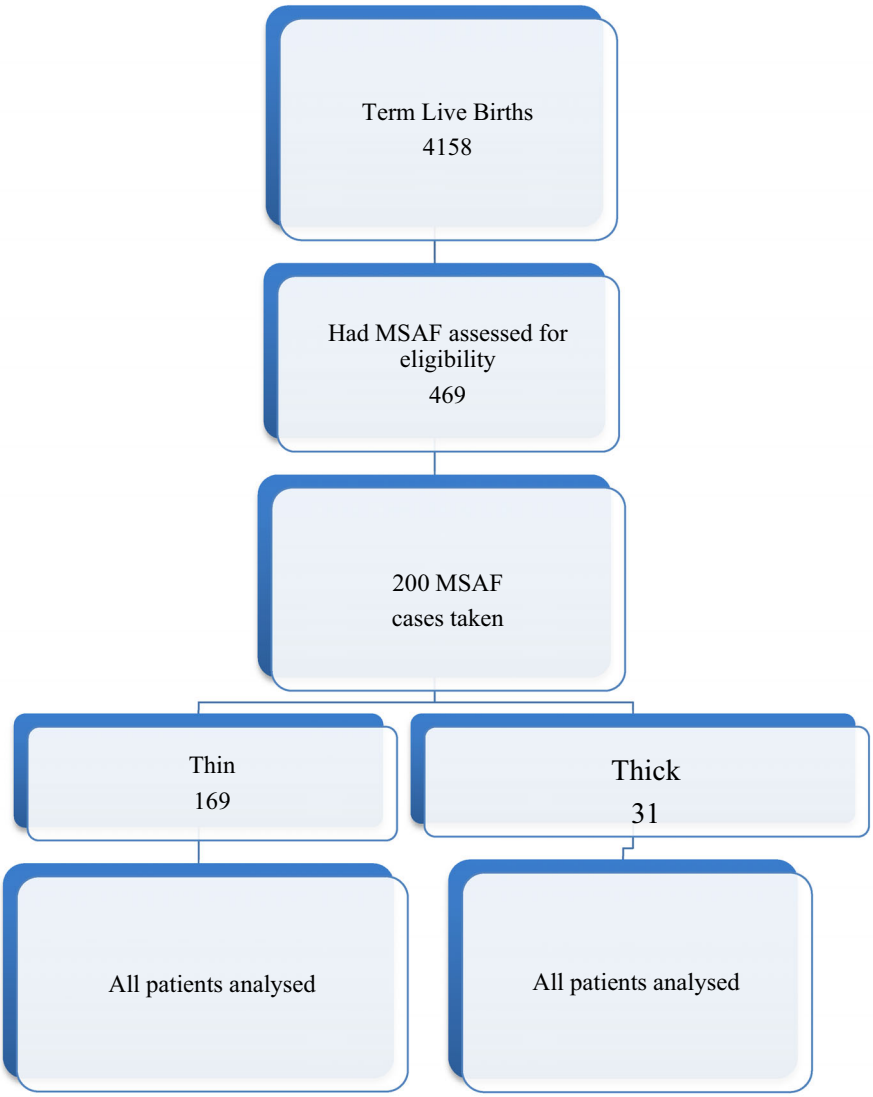
Patient recruitment was carried out in the labor and delivery unit of a tertiary referral center in South India, from May 2014 till September 2014. This prospective cohort study was approved by the institutional review board, and informed consent was obtained prior to inclusion in the study. Primigravidae with uncomplicated pregnancies and gestational age >37 weeks, with singleton fetus in cephalic presentation, who had MSAF identified after artificial or spontaneous rupture of membranes after admission to hospital were eligible to be included in the study. The exclusion criteria included rupture of membranes or fever prior to admission, malpresentations, preterm labor, multiple gestation, and HIV-positive women.

Sample size calculation was based on a retrospective study done by Shelley Chapman and Patrick Duff in 1994. Accordingly a sample size of 200 (200—women with MSAF; controls—200 with clear liquor) in each group was determined on the basis of an ability to have an 80% likelihood of demonstrating a clinically meaningful co-relation between MSAF and intrauterine infection with an alpha error of 0.05.

Primary outcomes looked at were the incidence of chorioamnionitis and endomyometritis. The secondary end points included incidence of postpartum hemorrhage and retained placenta (which are known sequelae of chorioamnionitis), neonatal sepsis, respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), neonatal intensive care unit (NICU) admission and Apgar score <6 at 1 min. Chorioamnionitis was diagnosed when there was maternal fever ≥100.4 °F with at least 2 of the following—maternal tachycardia (>100/min), fetal tachycardia (>160/min), uterine tenderness, foul smelling amniotic fluid, or maternal leucocytosis (>15,000 cells/$mm^3$). Endomyometritis was defined as postpartum fever ≥100.4 °F, excluding the first 24 h, on 2 or more occasions associated with uterine tenderness and foul smelling lochia or postpartum fever without any other localizing signs. Third-stage complications such as postpartum hemorrhage (PPH) (>500 ml blood loss) and retained placenta requiring manual removal were recorded. Neonatal sepsis was identified if the baby required treatment with antibiotics for ≥5 days. NICU admissions for complications of MSAF like respiratory distress and meconium aspiration syndrome were also noted.

Baseline demographic data and information regarding amnioinfusion, number of per vaginal examinations,

**Fig. 1** Consort figure




duration of rupture of membranes, and mode of delivery which may act as confounding factors for infectious morbidity were also collected. After delivery, mothers and babies were followed up in the ward/NICU till discharge.

The two groups were compared using Fischer exact probability test. Odds ratio and 95% confidence interval were calculated using univariate linear regression analysis. $P$ value <0.05 was considered as significant.

## Results

Of the 4158 live births during the study period, 469 women who had MSAF were screened for eligibility to be included in the study. Two hundred women who met the inclusion criteria were taken into the study. Among them, 169 had thin MSAF and 31 had thick MSAF (Fig. 1). Two hundred matching controls were also recruited during the same period. All the 400 patients were taken for analysis. Both the groups were similar with respect to maternal age, BMI, gestational age, and birth weight of the babies (Table 1).

**Table 1** Demography—baseline characteristics

| Variables | Clear ($N = 200$) Mean ± SD | MSAF ($N = 200$) Mean ± SD |
|---|---|---|
| Mean age in years | 25.08 ± 3.61 | 25.55 ± 3.77 |
| Mean BMI | 25.09 ± 4.6 | 24.5 ± 3.9 |
| Mean gest. age (months) | 39.54 ± 0.92 | 39.48 ± 0.89 |
| Mean birth weight (kg) | 3.16 ± 0.34 | 3.11 ± 0.35 |

The groups were also compared for maternal and fetal factors which might prove to be etiologically significant in the occurrence of MSAF, including maternal age >35 years ($P = 1.0$), BMI > 30 ($P = 0.07$), gestational age >41 weeks ($P = 0.2$) and birth weight >4 kg ($P = 0.2$). But no significant correlation was found.

**Table 2** Analysis of primary outcomes

| Outcomes | Clear | MSAF | Odds ratio | 95% confidence interval | *P* value |
|---|---|---|---|---|---|
| Chorioamnionitis | 4 (2%) | 16 (8%) | 4.2 | 1.39–12.98 | 0.006 |
| Endomyometritis | 6 (3%) | 19 (9.5%) | 3.39 | 1.32–8.68 | 0.007 |

**Table 3** Secondary outcomes

| Variables | Clear | MSAF | *P* value |
|---|---|---|---|
| Maternal outcomes | | | |
| PPH | 16 (8%) | 21 (10.5%) | 0.388 |
| Retained placenta | 0 | 1 (0.5%) | 1.000 |
| Neonatal outcomes | | | |
| Sepsis | NIL | NIL | NA |
| MAS | NIL | 8 (4%) | 0.007 |
| RDS | 3 (1.5%) | 17 (8.5%) | 0.001 |
| NICUadm | NIL | 14 (7%) | <0.001 |
| Apgar <6 at 1 min | 3 (1.5%) | 4 (2%) | 0.72 |

**Table 4** Analysis of confounding factors for chorioamnionitis

| Variable | Clear | MSAF | *P* value |
|---|---|---|---|
| Duration of ROM (min) | 442.5 | 357.34 | 0.004 |
| ARM | 175 (87.5%) | 151 (75.5%) | 0.002 |
| No: of PV >3 | 28 (14%) | 17 (8.5%) | 0.082 |
| Amnioinfusion given | 8 (4.0%) | 17 (8.5%) | 0.063 |
| Mode of delivery | | | |
| Operative delivery (LSCS + instrumental) | 72 (36%) | 104 (52%) | 0.003 |

The incidence of chorioamnionitis was 8% in the study group and 2% among the controls ($P = 0.006$; 95% CI 1.39–12.98; OR 4.2). Endomyometritis occurred in 9.5% in the study group compared to 3% in the control group ($P = 0.007$; 95% CI 1.32–8.68; OR 3.3). Both the primary end points were found to be significantly higher in the study subjects (Table 2). The secondary end points assessed did not show any significant difference between the groups, but there was a trend toward increased incidence of both PPH (10.5 vs. 8% $P = 0.38$) and retained placenta (0.5 vs. 0%; $P = 1.0$) in the MSAF group (Table 3).

Analysis of neonatal outcomes showed that the incidence of RDS (8.5 vs. 1.5%; $P = 0.001$), MAS (4 vs. 0% $P = 0.007$), and NICU admission (7 vs. 0% $P = < 0.001$) was significantly higher in the MSAF group. None of the babies developed sepsis. Apgar <6 at 1 min was not significantly different between the groups. (2 vs. 1.5% $P = 0.72$) (Table 3).

Subanalysis of patients who had thick and thin MSAF showed increased incidence of chorioamnionitis (12.9 vs. 7.1% $P = 0.2$), endomyometritis (25.8 vs. 6.5% $P = 0.003$), RDS (16.1 vs. 7.1% $P = 0.15$), and MAS (12.9 vs. 2.4% $P = 0.02$) in the former group, but statistically significant difference was seen only in the incidence of endomyometritis and MAS.

The confounding factors for intrauterine infection include artificial rupture of membranes, prolonged rupture of membranes, multiple pelvic examinations, amnioinfusion, and the mode of delivery. The first three factors were more in controls, owing to induction of labor and prolonged labor, the latter being permissible and therefore allowed in the low-risk group. Though amnioinfusion done for variable decelerations was more in the MSAF group, the difference did not reach statistical significance ($P = 0.06$) (Table 4). There were more LSCS and instrumental deliveries in the study group (52 vs. 36%, $P = 0.003$) probably reflecting the lower threshold for expediting delivery in the presence of MSAF. This is likely to have had a confounding effect on the incidence of endomyometritis reported in this study but not on the

incidence of chorioamnionitis diagnosed in labor prior to delivery.

## Discussion

Meconium is found in the fetal gut from 10 weeks, but passage into amniotic fluid is rare before 37 weeks. The incidence of MSAF increases with gestational age and reaches approximately 30% at 40 weeks and 50% at 42 weeks [1]. It is rarely seen in preterm labor. During our study period, the incidence of MSAF was found to be 11.2% in women with term gestation. The reduction in incidence could be attributed to the widespread use of antenatal ultrasound enabling early detection and management of oligohydramnios thus reducing the instances of cord compression and fetal hypoxia. All studies on women with term gestation and MSAF done previously have limitations owing to their retrospective nature and small sample size. Our study has the advantage of being both a prospective study and having a good sample size (200 women with MSAF and 200 with clear liquor).

The theories proposed for pathological MSAF at term gestation are many. These include increased gut motility resulting from the following causes: increased motilin and arginine vasopressin released during fetal hypoxia; vagal stimulation as a result of cord compression; fetal enteritis following intrauterine infections by Listeria, Ureaplasma, Rotavirus, and elevated levels of bile acids in the mother due to obstetric cholestasis [1]. In the past, meconium-stained liquor was viewed as a warning sign of perinatal asphyxia. But in current obstetric practice, it is considered as a normal variation unless associated with non-reassuring fetal heart rate patterns. This has translated into decreased rates of LSCS done explicitly for MSAF in many centers. In our institution the LSCS rates for MSAF has decreased from 5.6 to 0.6% in the past 6 years (2009–2014—unpublished data). But recently Monen et al. [2] have found evidence to support the association of asphyxia and peripartum infections with MSAF.

Several biochemical studies have found that the antibacterial defense mechanism of amniotic fluid may be breached by the presence of meconium. Meconum inhibits neutrophil oxidative burst, alters zinc–phosphorus ratios, and thus becomes a good culture medium for the growth of *E. coli*, Listeria Monocytogenes, and *S. aureus*. Studies have also shown increased rates of positive amniotic fluid cultures in women with MSAF, with the predominant organism being Listeria. In addition, bacterial endotoxin in maternal circulation was also found to be significantly more in women with MSAF. Romero et al. [3] opined that in term labor the ingestion of infected amniotic fluid would initiate fetal enteritis followed by increased meconium passage. The findings of these biochemical and microbiological studies formed the basis of our scientific query—Is maternal infective morbidity increased with MSAF?

It is well known that MSAF is an ominous sign in preterm pregnancies being an indicator of intrauterine infection especially with Listeria [4]. But literature search could not find any recent studies done on maternal morbidity associated with MSAF. Our study was designed with the aim to bring to light any maternal morbidity, associated with MSAF under the present clinical management protocols. Both the primary outcomes looked at-chorioamnionitis and endomyometritis, were found to be significantly high in the study group as compared to the control group (8 vs. 2% $P = 0.006$; 9.5 vs. 3% $P = 0.007$ respectively).

The secondary outcomes—PPH and retained placenta, which are complications associated with chorioamnionitis, did not show any significant difference between the groups probably because all the patients diagnosed with chorioamnionitis were started on broad spectrum antibiotics as per our institutional protocol. Assessment of parameters of neonatal morbidity revealed that there were no instances of either neonatal sepsis or perinatal asphyxia. On the other hand RDS, MAS, and NICU admissions were found to be significantly higher in the study group as compared to the control group. This is similar to findings reported in earlier studies [5–10].

According to current guidelines, only patients with clinical chorioamnionitis are started on broad spectrum antibiotics. But it is well established that subclinical chorioamnionitis is significantly more, the clinical cases representing only the tip of the iceberg (10 vs. 2%) [11]. As mentioned above, it has also been proven by histopathological studies that there is a significantly higher incidence of MSAF in these women.

In conclusion, even though passage of meconium into amniotic fluid may not be detrimental for perinatal health under present obstetric protocols, it may augment the growth of pathogens which cause maternal infective morbidity. Our study identifies a highly significant incidence of chorioamnionitis and endomyometritis in these women which could in turn result in grave complications like subinvolution, uterine wound necrosis and secondary PPH. Intrapartum infective morbidity can have long-term effects on the health of these women including pelvic inflammatory disease, infertility and abnormal uterine bleeding. Our study brings out compelling evidence which supports the need of antibiotic prophylaxis in these women. Our views have been strongly supported by Cochrane Reviews published in 2010 and 2014 in women with MSAF in labor which showed significant reduction in both chorioamnionitis and endomyometritis with antibiotic prophylaxis [12, 13]. But it is out of the scope of this study to suggest

the best antibiotic regimen in this scenario. This study identifies the need for more randomized controlled trials comparing different antibiotic protocols for women with MSAF.

**Acknowledgements** Ms. Grace Rebecca for statistical analysis.

**Compliance with Ethical Standards**

**Conflict of interest** All authors declare that they have no conflict of interest.

**Ethical Standards** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki, as revised in 2008 (5).

**Informed Consent** Informed consent was obtained from all patients for being included in the study.

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