Original Article

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Quick Response Code:

Website: www.pogsjournal.org

DOI: 10.4103/pjog.pjog_42_23

Association of maternal clinical factors with neonatal respiratory morbidity in meconium-stained labor among term parturients: A retrospective cohort study

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Abstract:

OBJECTIVE: This study aimed to determine the maternal clinical factors associated with neonatal respiratory morbidity and other adverse neonatal outcomes in meconium-stained labor among term parturients.

METHODOLOGY: A retrospective cohort study was done on admitted obstetric patients with term gestation and had meconium-stained labor. Maternal clinical factors such as age, parity, gestational age, manner of delivery, duration of labor, presence of term prelabor rupture of membranes (PROM), character of meconium-stained liquor (MSL), and presence of comorbidities were identified and analyzed to determine their association with neonatal respiratory morbidity and other adverse neonatal outcomes.

RESULTS: In this study, there were 986 cases identified to have meconium-stained labor, and 168 developed neonatal respiratory morbidity. As to primary outcome, maternal clinical factors, such as age >35 years, multiparity, age of gestation >41 weeks, prolonged labor, presence of PROM, significant MSL upon admission, presence of change from nonsignificant to significant MSL, presence of intrauterine growth restriction, and hypertension, were all shown to be statistically significant.

CONCLUSION: The presence of maternal clinical factors in meconium-stained labor was observed to be a risk factor in developing neonatal respiratory morbidity and other adverse neonatal outcomes. Hence, identification of maternal risk factors and early detection of meconium-stained amniotic fluid are vital in administering timely intervention to labor and delivery to reduce neonatal complications.

Keywords:

Maternal risk factors, meconium-stained liquor, neonatal respiratory morbidity

Introduction

In any obstetrical unit, meconium-stained amniotic fluid (MSAF) during labor in term parturients is a common event. Its significance may vary from being a physiological sign of maturity of the fetus to a sign of fetal distress and response to hypoxic insult. Although preventable, this occurrence is associated with high incidence of neonatal morbidity, or worse, neonatal mortality.

Term pregnancies are complicated by MSAF in 10%–20% of cases. Although the etiology and pathophysiology of MSAF is poorly understood, *in utero* passage of meconium during labor occurs as a response of the fetus to having a temporarily reduced oxygen supply. Factors leading to placental

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Submitted: 16-Jun-2023
Revised: 28-Jun-2023
Accepted: 11-Jul-2023
Published: 13-Nov-2023

How to cite this article: Magno JA, Zamora BB. Association of maternal clinical factors with neonatal respiratory morbidity in meconium-stained labor among term parturients: A retrospective cohort study. Philipp J Obstet Gynecol 2023;47:165-77.

insufficiency, such as hypertensive disorders, anemia, or prolonged labor, contribute to MSAF. Several studies have shown that the incidence of meconium aspiration syndrome (MAS) is 5% of the neonates who were born through MSAF. More importantly, majority of these neonates require mechanical ventilation and develop other complications.[1,2]

Significance of the study

This research aims to identify and analyze associated maternal clinical factors with neonatal respiratory morbidity in meconium-stained labor. With this obtained knowledge, close labor monitoring and cautious decisions on the timing and mode of delivery will be observed to reduce perinatal morbidity and mortality.

Review of related literature

Meconium is described as a sterile, viscous, odorless, dark green material that is present in the fetal intestines as early as the 12th week of gestation. It is made up of gastrointestinal secretions and swallowed amniotic fluid containing vernix caseosa, lanugo, and other cellular debris. As the fetus matures, meconium is stored in the colon and is normally passed within the first 24–48 h after birth.[3-5] However, in certain situations, meconium is passed *in utero* or during labor-producing MSAF.

The exact mechanism of meconium passage *in utero* is still unknown. However, some studies have concluded that umbilical cord compression during labor initiates vagal stimulation causing fetal hypoxic stress. This results in increased peristalsis and relaxation of the fetal anal sphincter leading to passage of meconium into the amniotic fluid.[6,7]

Meconium-stained liquor (MSL) complicates approximately 10%–20% of term pregnancies. The Royal College of Obstetricians and Gynaecologists classified MSL into nonsignificant and significant MSL. Nonsignificant MSL is described as a yellow-to-light green-tinged fluid containing nonparticulate meconium amniotic fluid, whereas significant MSL is defined as an amniotic fluid that is a thick, dark green-to-black fluid containing lumps of meconium.[3]

The incidence of MSL is uncommon before the 37th week of gestation but increases with the duration of pregnancy. Several studies have identified maternal and obstetrical risk factors in MSAF. A cross-sectional study done by Addisu *et al*., in 2018, showed that among the 495 parturients, 88 of them presented with MSAF. It was found that maternal age of more than 30 years, presence of preeclampsia, duration of labor of more than 24 h, and obstructed labor were significantly associated with MSAF. This could be explained that as the uterus contracts, it creates a stressful environment for the fetus, which results in passage of meconium due to increased peristalsis of the fetal gastrointestinal tract and anal sphincter relaxation.[3,8]

Preeclampsia is the most commonly reported form of hypertension that complicates a pregnancy. It is primarily defined by the occurrence of new-onset hypertension, usually after 20 weeks of gestation, and with associated proteinuria. The incidence of MSAF in patients with preeclampsia is possibly explained by placental insufficiency that leads to intrauterine fetal hypoxia or intestinal ischemia.[3]

In another cross-sectional study performed by Osava *et al*., in 2011, in a local hospital in Brazil, MSAF was identified in 11.9% of the births, wherein 68.2% were delivered via normal vaginal delivery and 38.8% were via cesarean section. The risk factors to MSAF development were primigravidity, gestational age of more than 41 weeks, and induced labor. However, the mother's age has shown no link to MSAF during delivery.[9]

Similar to the previous studies, Desai *et al*., in 2013, identified pregnancy-induced hypertension and gestational age of more than 40 weeks as risk factors among the 150 participants who developed MSAF. Moreover, the incidence of meconium passage was relatively higher in patients with identified intrauterine growth restriction (IUGR) and anemia.[10-12]

In a prospective case–control study conducted by Sundaram and Murugesan in 2016 in a tertiary hospital for a period of 6 months, the incidence of MSAF was 9.45%. Contrary to the previous studies, maternal age and anemia were not significantly associated with MSAF in this particular study. Moreover, maternal risk factors significantly associated with MSAF were term prelabor rupture of membranes (PROM) and postdatism.[13]

The mode of delivery in MSAF cases has contradicting results in several studies. Operative deliveries were performed for obstetric indications, such as obstructed labor and nonreassuring fetal heart rate pattern. However, it showed that in the presence of MSAF, the risk of cesarean delivery is significantly higher and is associated with neonatal morbidity due to fetal distress.[14,15]

Meconium in amniotic fluid has been a soft marker for fetal distress. If not identified, it may lead to neonatal respiratory morbidity which was defined as the presence of either respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), MAS, or the need for ventilatory support. A number of mechanisms have been suggested to have caused these adverse effects, such as chemical pneumonitis, airway obstruction, pulmonary vessel vasoconstriction, and surfactant inactivation. Moreover, the possibility of neonatal sepsis is high due

to the repressed bacteriostatic property of amniotic fluid and MSAF may serve as a growth factor for bacteria.[9,15]

The main cause of admission at the neonatal intensive care unit (NICU) associated with MSAF is birth asphyxia. In a study conducted by Rajput and Jain in 2013, neonates born in the significant MSL group had an incidence of 58.3%. They developed worse complications, such as development of MAS, need for ventilator support, and a mean stay of 4 days at the NICU. The mortality rate in this group was 9%.[10]

In 2016, similar results were observed in a 1-year cross-sectional study performed by Rajput *et al*. Among the 1685 neonates admitted at the NICU, 200 were born with MSAF. The incidence of significant and nonsignificant MSL was 35% and 65%, respectively. Neonatal morbidities were observed in this group. These included MAS, hypoxic-ischemic encephalopathy (HIE), and RDS, with the incidence of 27.5%, 11.5%, and 5%, respectively. Moreover, MSAF resulted in a relatively high incidence of mortality at 17.5%.[16]

In a case–control study conducted by Desai *et al*. in 2017, neonatal morbidity and mortality were noted to be significantly increased in the MSAF group compared to the control group with clear amniotic fluid. Neonates in the cases group required NICU admission for more than 24 h and developed other neonatal morbidities such as sepsis, HIE, and MAS.[6] These findings were consistent with that of other studies, such as the one conducted by Hiersch in 2015, wherein he concluded that approximately 10% of low-risk pregnancies at term developed MSAF and had neonatal morbidities.[15]

The association of a wide variety of bacterial, fungal, viral, and protozoan infections with pregnancy outcome has been studied throughout the years. Sexually transmitted infections, such as chlamydia and genital mycoplasmas, are associated with neonatal pneumonia which could lead to respiratory distress of the newborn, neonatal sepsis, or the need for ventilatory support. Moreover, Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19, and newer pathogens such as *Zika*), Rubella, *Cytomegalovirus* and Herpes simplex virus, or collectively known as TORCH infection, as well as most sexually transmitted infections have been observed to commonly cause congenital defects, neurological impairment, and even fetal anemia.[17,18] These adverse outcomes are associated with neonatal morbidity and poorer neonatal outcomes.

Operational definition of terms

MSL refers to the passage of meconium by a fetus *in utero* during the antenatal period or labor.[3]

Significant MSL is defined as an amniotic fluid that is a thick, dark green-to-black fluid containing lumps of meconium.[3]

Nonsignificant MSL is described as a yellow-to-light green-tinged fluid containing nonparticulate meconium amniotic fluid.[3]

Preeclampsia is defined by the occurrence of new-onset hypertension, usually after 20 weeks of gestation, and with associated proteinuria.[19]

IUGR is defined as an ultrasonographic estimated fetal weight or an abdominal circumference below the 10th percentile for gestational age.[20]

Maternal anemia in pregnancy is defined as hemoglobin of <11 g/dL (approximately equivalent to a hematocrit of <33) during the first trimester, hemoglobin of <10.5 g/dL in the second trimester, and/or hemoglobin of <10.5–11 g/dL (approximately hematocrit of <33) in the third trimester.[21]

Neonatal sepsis is a clinical syndrome in an infant 28 days of life or younger, manifested by systemic signs of infection and isolation of a bacterial pathogen from the bloodstream.[22]

RDS is caused by abnormal respiratory function, which is manifested by tachypnea, nasal flaring, intercostal or subcostal retractions, audible grunting, and cyanosis, during the transition from fetal to neonatal life.[22]

TTN is a parenchymal lung disorder characterized by pulmonary edema resulting from delayed resorption and clearance of fetal alveolar fluid that causes respiratory distress in the newborn.[22]

MAS is defined as respiratory distress in newborn infants born through MSAF.[22]

Persistent pulmonary hypertension of the newborn (PPHN) occurs when pulmonary vascular resistance remains abnormally elevated after birth, resulting in right-to-left shunting of blood through fetal circulatory pathways which leads to severe hypoxemia.[22]

Research question

What are the maternal clinical factors associated with neonatal respiratory morbidity in meconium-stained labor among term parturients admitted at a tertiary hospital?

Objectives

General objective

To determine the maternal clinical factors associated with neonatal respiratory morbidity in meconium-stained

labor among term parturients admitted at a tertiary hospital.

Specific objectives

1. To describe the clinico-demographic profile of the parturients as to:
   a. Maternal age
   b. Parity
   c. Presence of hypertensive complication/s in pregnancy
   d. Presence of IUGR
   e. Presence of maternal anemia
   f. Age of gestation (AOG)
   g. Manner of delivery
   h. Presence of PROM
   i. Character of MSL on admission
   j. Duration of labor
   k. Presence of change from nonsignificant MSL (yellow-to-light-green-tinged fluid containing nonparticulate meconium) to significant MSL (thick, dark green-to-black fluid containing lumps of meconium) from admission to delivery.
2. To determine the incidence of neonatal respiratory morbidity (primary outcome) and other adverse neonatal outcomes (secondary outcomes) in meconium-stained labor among term parturients
3. To determine the association of maternal clinical factors with neonatal respiratory morbidities including:
   a. RDS
   b. TTN
   c. MAS
   d. Need for ventilatory support.
4. To determine the association of maternal clinical factors with the following adverse neonatal outcomes, namely:
   a. NICU stay more than 4 days
   b. Sepsis
   c. Persistent pulmonary hypertension (PPHN)
   d. HIE
   e. Neonatal death.

Methods

Research design

This is a retrospective cohort study design that will determine the association of significant maternal clinical factors associated with neonatal respiratory morbidity (primary outcome) in meconium-stained labor among term parturients admitted at a tertiary hospital from January 2015 to December 2020.

Research population

Women with a term pregnancy in labor admitted at a tertiary hospital with the following criteria:

Inclusion criteria

- Term pregnancy (>37-week AOG)
- Singleton pregnancy
- Cephalic presentation
- Presence of MSL at any point from admission to delivery
- No contraindications to trial of labor
- No fetal congenital anomaly.

Exclusion criteria

- History of maternal drug addiction/abuse
- Maternal infection or chorioamnionitis.

Maternal clinical factors

a. Maternal age
b. Parity
c. AOG
d. Manner of delivery
e. Presence of PROM
f. Presence of hypertensive complication/s in pregnancy
g. Presence of IUGR
h. Presence of maternal anemia
i. Character of MSL on admission
j. Duration of labor
k. Presence of change from nonsignificant MSL (yellow-to-light-green-tinged fluid containing nonparticulate meconium) to significant MSL (thick, dark green-to-black fluid containing lumps of meconium) from admission to delivery.

Clinical outcome

Primary

Neonatal respiratory morbidity-presence of any one of the following: RDS, TTN, MAS, or the need for ventilatory support.

Secondary

a. NICU stay of more than 4 days
b. Sepsis
c. Persistent pulmonary hypertension
d. HIE
e. Neonatal death.

Data collection

The department daily census was reviewed from time period of January 2015 to December 2020 to identify the patients who delivered at term with meconium-stained amniotic fluid. Once these specific patients were identified, chart review of both the mother and neonate was done. Data collected were placed in an Excel file, which was password protected with a corresponding ID number in the researcher's personal laptop, in accordance with the Data Privacy Act.

The patient's demographic profile was collected from the patient's datasheet. The parity, established AOG, the presence or absence of hypertensive disorders of pregnancy, and personal and social history were

reviewed from the history taken upon admission. The presence or absence of IUGR and maternal anemia was obtained from the laboratory results attached to the chart. The presence or absence of PROM, character of MSL upon admission, and change from nonsignificant MSL to significant MSL and length of labor were extracted from the physician's notes and partogram. The manner of delivery was obtained from the operative technique in the chart. The neonatal outcomes were reviewed from the newborn's book of life and individual charts. In case of missing or questionable information in the medical chart, the resident-in-charge was interviewed.

Sample size and sampling

The sample size was calculated based on the comparison of the incidence of neonatal respiratory morbidity among term parturients with MSAF with and without maternal risk factors. Assuming that the incidence of neonatal respiratory morbidity patients without maternal risk factors was 55.56% (Akhila *et al.*,[1] 2018) and among those with maternal risk factors, the incidence was hypothesized to be 25% higher at 66.7%, with an alpha error of 5%, power 80%, and a one-tailed alternative hypothesis. The sample size calculated was 235 per group or a total of 470 for two groups. Controlling for 11 more variables in the analysis with an additional 10% for each variable, the final sample size was 940.

Statistical analysis plan

Determination of maternal risk factors associated with neonatal respiratory morbidity was analyzed using univariate and multivariate statistics. Chi-square test was used in the univariate analysis. Odds ratio (OR) and 95% confidence interval (CI) were also calculated. Multiple logistic regression was then utilized in the multivariate analysis. The level of significance was set at an alpha of 0.05.

Table 1: Clinico-demographic characteristics of women who presented with meconium-stained liquor (*n*=986)

Maternal characteristics	*n* (%)
Maternal age (years)	
<35	775 (78.6)
>35	211 (21.4)
Parity	
Nulliparity	557 (56.5)
Multiparity	429 (43.5)
Age of gestation	
37w0d–40w6d	739 (74.9)
>41w0d	247 (25.1)
Manner of delivery	
Abdominal	682 (69.2)
Vaginal	304 (30.8)
Duration of labor (h)	
<24	826 (83.8)
>24	160 (16.2)
PROM	
Present	505 (51.2)
Absent	481 (48.8)
Character of MSL upon admission	
Significant	488 (49.5)
Not significant	498 (50.5)
Presence of change from NS to significant MSL	
Present	169 (17.1)
Absent	817 (82.9)
Presence of IUGR	
Present	58 (5.9)
Absent	928 (94.1)
Hypertension	
Present	196 (19.9)
Absent	790 (80.1)
Maternal anemia	
Present	34 (3.4)
Absent	952 (96.6)

PROM: Prelabor rupture of membranes, MSL: Meconium-stained liquor, IUGR: Intrauterine growth restriction, NS: Not significant

Results

Maternal clinico-demographic profile

The tertiary hospital had a total of 50,664 term live births from January 2015 to December 2020. In this study, 986 cases were identified to have had meconium-stained labor and the maternal clinico-demographic data are summarized in Table 1.

Of these, 775 (78.6%) of the mothers were in the age group of <35 years, and more than half (56.5%), 557, were nulliparous. Majority (74.9%) of the gestational age at delivery was at 37–40 weeks and 6 days. 247 (25.1%) mothers had postterm pregnancy. With the manner of delivery, 682 (69.2%) were delivered abdominally via cesarean section, and 304 (30.8%) were delivered vaginally. There was higher incidence (83.8%) of MSAF among mothers who underwent labor for <24 h than those who had longer labor duration. The presence of term PROM was present in 505 cases (51.2%). Upon admission to the laboring unit, 488 (49.5%) cases were observed to have significant MSL, and 498 (50.5%) cases had nonsignificant MSL. There was presence of change from nonsignificant to significant MSL in 169 (17.1%) of cases.

Concerning maternal medical conditions, hypertensive disorders of pregnancy were present among 196 (19.9%) parturients. There was presence of IUGR in 58 (5.9%) cases. Moreover, a total of 34 (3.4%) mothers were reported to have had anemia during the pregnancy.

Clinical neonatal outcomes

Among the 986 identified cases in this study, 168 (17.01%) had neonatal respiratory morbidity, as shown in Table 2. After delivery, 84 (8.5%) babies presented with TTN,

Table 2: Clinical neonatal outcomes in meconium-stained labor among term parturients (*n*=986)

Neonatal outcomes	*n* (%)
Respiratory morbidity	168 (17.01)
Respiratory distress syndrome	30 (3.0)
Transient tachypnea of the newborn	84 (8.5)
Meconium aspiration syndrome	45 (4.6)
Need for ventilatory support	78 (7.9)
NICU stay of >4 days	250 (25.4)
Neonatal sepsis	147 (14.9)
Persistent pulmonary hypertension of the newborn	14 (1.4)
Hypoxic-ischemic encephalopathy	11 (1.1)
Neonatal death	16 (1.6)

NICU: Neonatal intensive care unit

whereas 78 (7.9%) babies needed ventilatory support. MAS was diagnosed in 45 (4.6%) cases and RDS in 30 (3.0%) cases.

Furthermore, other adverse neonatal outcomes are presented in Table 2. The most common of which was NICU stay of more than 4 days, observed in 250 (25.4%) cases. This was followed by neonatal sepsis identified in 147 (14.9%) cases, PPHN in 14 (1.4%) cases, and HIE in 11 (1.1%) cases. There were 16 (1.6%) neonatal deaths among the meconium-stained labor cases.

Neonatal respiratory morbidity (primary outcome)

The collected data were analyzed using univariate and multivariate statistics with the results, as summarized in Table 3. Multiple logistic regression analysis revealed that parturients who were more than 35 years of age have twice the odds of developing neonatal respiratory morbidity compared to those of <35 years of age (OR = 1.68, 95% CI: 1.03–2.74, $P < 0.036$). Multiparity had a significant association with neonatal respiratory morbidity, having OR: 2.04, 95% CI: 1.30–3.19, $P < 0.002$. It was also shown that pregnancies with gestational age of more than or equal to 41 weeks had three times increased risk of having neonatal respiratory morbidity at birth when compared to those delivered at 37–40-week and 6-day AOG (OR = 2.52, 95% CI: 1.63–3.89, $P < 0.001$).

Labor prolonged for 24 h or more increased the risk of having neonatal respiratory morbidity at birth by about five times as compared to labor which was shorter in duration (OR = 4.59, 95% CI: 2.81–7.51, $P < 0.001$). Similarly, those presenting with PROM and with significant MSL upon admission increased the risk of neonatal respiratory morbidity by about three times (95% CI: 2.75–4.29, $P < 0.001$) and 2.4 times (95% CI: 1.47–3.91, $P < 0.000$), respectively, compared to having intact bag of waters and nonsignificant MSL.

The presence of IUGR and hypertension had a significant association with neonatal respiratory morbidity having six times (OR = 6.24, 95% CI: 3.17–12.29, $P < 0.000$) and two times (OR = 2.09, 95% CI: 1.29–3.37, $P < 0.003$), respectively, compared to having no comorbid.

On the other hand, manner of delivery and presence of anemia were the only maternal clinical factors not associated with the primary outcome with the following OR, respectively, OR = 1.28, 95% CI: 0.76–2.14, at $P < 0.355$, and OR = 1.63, 95% CI: 0.68–3.89, at $P < 0.279$.

Neonatal intensive care unit stay of more than 4 days (secondary outcome)

Table 4 illustrates the association of maternal clinical factors with NICU stay of more than 4 days. Neonates who delivered to mothers whose age was more than 35 years and were multiparous at the time of delivery were about two times (OR = 1.87, 95% CI: 1.15–3.02, $P < 0.011$) and two times (OR = 2.12, 95% CI: 1.37–3.27, $P < 0.001$), respectively, more likely to have a NICU stay of more than 4 days. Postterm pregnancy increases the risk of NICU stay twice compared to pregnancies at early and full term (OR = 2.00, 95% CI: 1.31–3.05, $P < 0.001$).

Prolonged labor showed a significantly increased risk of NICU stay compared to shorter labor by about three times (OR = 3.12, 95% CI: 1.86–5.23, $P < 0.001$). Similarly, those presenting with significant MSL upon admission were statistically significant to NICU stay by about six times (OR = 5.59, 95% CI: 3.31–9.43, $P < 0.001$). The presence of change from NS to significant MSL was found to have a 12-fold increase in the risk of NICU stay, compared to those who had no change in the consistency of liquor during labor (OR = 11.87, 95% CI: 6.52–21.63, $P < 0.001$).

The presence of IUGR, hypertension, and maternal anemia has shown a statistically significant increased risk of NICU stay by 47 times (OR = 47.05, 95% CI: 18.39–120.40, $P < 0.001$), two times (OR = 1.78, 95% CI: 1.10–2.86, $P < 0.018$), and four times (OR = 3.35, 95% CI: 1.27–8.84, $P < 0.014$), respectively, compared to those parturients not presenting with the previously mentioned comorbidities.

Manner of delivery was shown to be the only maternal clinical factor that was not significantly associated with the secondary outcome with OR = 1.55, 95% CI: 0.95–2.55, at $P < 0.082$.

Neonatal sepsis (secondary outcome)

As summarized in Table 5, several maternal clinical factors were found to have an increased risk of developing neonatal sepsis. Maternal age of more than 35 years, multiparity, and more than 41-week AOG were statistically significant with the following OR, respectively, OR = 2.17, 95% CI: 1.32–3.56 at $P < 0.002$;

Table 3: Maternal clinical predictors of neonatal respiratory morbidity (primary outcome)

Maternal factors	Respiratory morbidity, *n* (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*
Maternal age (years)				
<35	112 (14.5)	-	-	<0.036
≥35	56 (26.5)	2.14 (1.48–3.08)	1.68 (1.03–2.74)	
Parity				
Nulliparity	74 (13.3)	-	-	<0.002
Multiparity	94 (21.9)	1.04 (0.30–2.19)	2.04 (1.30–3.19)	
Age of gestation				
37w0d–40w6d	99 (13.4)	-	-	<0.001
>41w0d	69 (27.9)	2.51 (1.77–3.55)	2.52 (1.63–3.89)	
Manner of delivery				
Abdominal	137 (20.1)	2.21 (1.46–3.36)	1.28 (0.76–2.14)	<0.355
Vaginal	31 (10.2)	-	-	
Duration of labor (h)				
<24	84 (10.2)	-	-	<0.001
>24	84 (52.5)	9.76 (6.65–14.3)	4.59 (2.81–7.51)	
PROM				
Present	125 (24.8)	3.35 (2.31–4.86)	2.74 (1.75–4.29)	<0.001
Absent	43 (8.9)	-	-	
Character of MSL upon admission				
Significant	108 (22.1)	2.08 (1.47–2.93)	2.40 (1.47–3.91)	<0.000
Not significant	60 (12.0)	-	-	
Presence of change from NS to significant MSL				
Present	74 (43.8)	5.99 (4.13–8.69)	3.74 (2.15–6.48)	<0.000
Absent	94 (11.5)	-	-	
Presence of IUGR				
Present	31 (53.4)	6.63 (3.84–11.45)	6.24 (3.17–12.29)	<0.000
Absent	137 (14.8)	-	-	
Hypertension				
Present	56 (28.6)	2.42 (1.68–3.50)	2.09 (1.29–3.37)	<0.003
Absent	112 (14.2)	-	-	
Maternal anemia				
Present	15 (44.1)	4.12 (2.05–8.29)	1.62 (0.68–3.89)	<0.279
Absent	153 (16.1)	-	-	

PROM: Prelabor rupture of membranes, MSL: Meconium-stained liquor, IUGR: Intrauterine growth restriction, OR: Odds ratio, CI: Confidence interval, NS: Not significant

OR = 1.70, 95% CI: 1.07–2.70, at $P < 0.025$; and OR = 1.63, 95% CI: 1.03–2.58, at $P < 0.039$.

Mothers who have undergone labor for more than 24 h were shown to have an increased risk of neonatal sepsis by about six times (95% CI: 3.62–9.89, $P < 0.001$). The presence of term PROM was also shown to have an increased risk for neonatal sepsis by five times compared to those with intact bag of water (OR = 4.55, 95% CI: 2.74–7.56, $P < 0.001$). The presence of significant MSL upon admission and change in MSL character from nonsignificant to significant both have a significant association with neonatal sepsis with OR = 2.66, 95% CI: 1.59–4.45 and OR = 3.10, 95% CI: 1.73–5.54, respectively, at $P < 0.001$. On the other hand, manner of delivery was not statistically significant for developing neonatal sepsis with OR = 1.11, 95% CI: 0.65–1.87, at $P < 0.712$.

Among the comorbidities, only hypertension was the only maternal clinical risk factor associated with secondary outcome with OR: 1.75, 95% CI: 1.06–2.91, $P < 0.030$. The presence of IUGR and maternal anemia did not show a statistically significant association with neonatal sepsis with the following values, respectively, OR = 1.68, 95% CI: 0.79–3.60, $P < 0.181$, and OR = 0.89, 95% CI: 0.34–2.29, $P < 0.802$.

Persistent pulmonary hypertension (secondary outcome)

PPHN was seen among 14 cases with meconium-stained labor. Multiparity, AOG more than 41 weeks, longer duration of labor, and presence of hypertension were the only maternal clinical factors associated with developing persistent pulmonary hypertension in the neonate with the following OR, respectively, OR = 4.27, 95% CI: 1.06–17.21 at $P < 0.041$, OR = 3.71, 95% CI: 1.09–12.67 at $P < 0.037$, OR = 8.90, 95% CI: 1.92–41.19 at $P < 0.005$, and OR = 7.16, 95% CI: 2.03–25.24 at $P < 0.002$. On the other hand, maternal age, manner of delivery, presence of PROM, character of MSL upon admission, presence of change from NS to significant

Table 4: Maternal clinical predictors of neonatal intensive care unit stay >4 days

Maternal factors	NICU stay, *n* (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*
Maternal age (years)				
<35	171 (22.1)	-	-	<0.011
≥35	79 (37.4)	2.11 (1.53–2.93)	1.87 (1.15–3.02)	
Parity				
Nulliparity	119 (21.4)	-	-	<0.001
Multiparity	131 (30.5)	1.62 (1.21–2.16)	2.12 (1.37–3.27)	
Age of gestation				
37w0d–40w6d	155 (21.0)	-	-	<0.001
>41w0d	95 (38.5)	2.36 (1.72–3.22)	2.00 (1.31–3.05)	
Manner of delivery				
Abdominal	208 (30.5)	2.74 (1.90–3.94)	1.55 (0.95–2.55)	<0.082
Vaginal	42 (13.8)	-	-	
Duration of labor (h)				
<24	146 (17.7)	-	-	<0.001
>24	104 (65.0)	8.65 (5.97–12.53)	3.12 (1.86–5.23)	
PROM				
Present	183 (36.2)	3.51 (2.56–4.81)	3.69 (2.38–5.72)	<0.001
Absent	67 (13.9)	-	-	
Character of MSL upon admission				
Significant	172 (35.2)	2.93 (2.16–3.98)	5.59 (3.31–9.43)	<0.001
Not significant	78 (15.7)	-	-	
Presence of change from NS to significant MSL				
Present	106 (62.7)	7.86 (5.49–11.27)	11.87 (6.52–21.63)	<0.001
Absent	144 (17.6)	-	-	
Presence of IUGR				
Present	51 (87.9)	26.69 (11.93–59.72)	47.05 (18.39–120.40)	<0.001
Absent	199 (21.4)	-	-	
Hypertension				
Present	79 (40.3)	2.44 (1.75–3.41)	1.78 (1.10–2.86)	<0.018
Absent	171 (21.6)	-	-	
Maternal anemia				
Present	23 (67.6)	6.68 (3.21–13.91)	3.36 (1.27–8.84)	<0.014
Absent	227 (23.8)	-	-	

PROM: Prelabor rupture of membranes, MSL: Meconium-stained liquor, IUGR: Intrauterine growth restriction, OR: Odds ratio, CI: Confidence interval, NICU: Neonatal intensive care unit, NS: Not significant

MSL, presence of IUGR, and maternal anemia did not show a statistically significant association with PPHN, as shown in Table 6.

Hypoxic-ischemic encephalopathy (secondary outcome)

There were 11 cases of HIE who were recorded in this study, as summarized in Table 7. No maternal clinical risk factor was found to be significantly associated with an increased risk of developing HIE in the neonate. However, it was found that both multiparity and abdominal delivery were protective to developing HIE in the newborn wherein the risk is decreased by 13% (OR = 0.87, 95% CI: 0.22–3.49, $P < 0.847$) and 62% (OR = 0.38, 95% CI: 0.92–1.58, $P < 0.183$), respectively, though these were not statistically significant in the multivariate analysis.

Neonatal death (secondary outcome)

In this study, there were a total of 16 neonatal deaths seen. Multiparity and AOG more than 41 weeks have increased risk for neonatal death, with computed values OR = 5.56, 95% CI: 1.65–18.69, $P < 0.006$ and OR = 5.14, 95% CI: 1.56–16.92, $P < 0.007$), respectively. Another maternal clinical factor that was shown to have about 18 times increased risk for neonatal death is the presence of significant MSL upon admission compared to having nonsignificant MSL (OR = 17.66, 95% CI: 1.98–157.61, $P < 0.010$). Furthermore, having hypertension was shown to be statistically significant with OR 3.47, 95% CI: 1.05–11.46, at $P = 0.041$. Maternal age, duration of labor, presence of PROM, change from NS to significant MSL, and maternal anemia did not show any significant association with neonatal death [Table 8].

Discussion

In utero passage of meconium may happen as a normal physiologic event. However, there have been theories proposed that it may signal fetal compromise as a result of hypoxia. Increased bowel peristalsis due to

Table 5: Maternal clinical predictors of neonatal sepsis

Maternal factors	Neonatal sepsis, *n* (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*
Maternal age (years)				
<35	93 (12.0)	-	-	<0.002
≥35	54 (25.6)	2.52 (1.73–3.68)	2.17 (1.32–3.56)	
Parity				
Nulliparity	63 (11.5)	-	-	<0.025
Multiparity	83 (19.3)	1.85 (1.30–2.63)	1.70 (1.07–2.70)	
Age of gestation				
37w0d–40w6d	94 (12.7)	-	-	<0.039
>41w0d	53 (21.5)	1.88 (1.29–2.72)	1.63 (1.03–2.58)	
Manner of delivery				
Abdominal	117 (17.2)	1.89 (1.24–2.90)	1.11 (0.65–1.87)	<0.712
Vaginal	30 (9.9)	-	-	
Duration of labor (h)				
<24	66 (8.0)	-	-	<0.001
>24	81 (50.6)	11.81 (7.92–17.60)	5.99 (3.62–9.89)	
PROM				
Present	122 (24.2)	5.81 (3.70–9.12)	4.55 (2.74–7.56)	<0.001
Absent	25 (5.2)	-	-	
Character of MSL upon admission				
Significant	96 (19.7)	2.15 (1.49–3.09)	2.66 (1.59–4.45)	<0.001
Not significant	51 (10.2)	-	-	
Presence of change from NS to significant MSL				
Present	65 (38.5)	5.60 (3.81–8.23)	3.10 (1.73–5.54)	<0.001
Absent	82 (10.0)	-	-	
Presence of IUGR				
Present	17 (29.3)	2.55 (1.40–4.62)	1.68 (0.79–3.60)	<0.181
Absent	130 (14.0)	-	-	
Hypertension				
Present	43 (21.9)	1.85 (1.25–2.76)	1.75 (1.06–2.91)	<0.030
Absent	104 (13.2)	-	-	
Maternal anemia				
Present	10 (29.4)	2.48 (1.16–5.30)	0.89 (0.34–2.29)	<0.802
Absent	137 (14.4)	-	-	

PROM: Prelabor rupture of membranes, MSL: Meconium-stained liquor, IUGR: Intrauterine growth restriction, OR: Odds ratio, CI: Confidence interval, NS: Not significant

vagal stimulation from umbilical cord compression, which commonly happens during labor, may result in meconium in the amniotic fluid. It is an uncommon event to occur in a preterm fetus; however, as it approaches term gestation, the occurrence of MSAF increases.[6,7,23]

In this retrospective study, several maternal clinical factors were assessed to determine their association with neonatal respiratory morbidity and other adverse neonatal outcomes in meconium-stained labor. The overall incidence of MSAF among term live births at the tertiary hospital in this 6-year period is 1.9%. This finding is comparable to other studies where the rate of MSAF varies from 1% to 18%.[7,23] This is the first study at the tertiary hospital that looked into the association of maternal clinical factors with the development of poor neonatal outcome in the presence of MSAF.

Meconium-stained labor was observed with higher incidence among mothers with <35 years of age, nulliparity, at early and full term, abdominal delivery, shorter labor duration, and presence of term PROM. In hypertensive mothers, 196 (19.9%) had MSAF. Fifty-eight (5.9%) cases presented with IUGR and 34 (3.4%) had maternal anemia. Comprising approximately half (488, 49.5%) of the sample population exhibited thick MSL upon admission [Table 1].

Neonatal respiratory morbidity was seen among 17% of the sample population [Table 2]. This was represented by the presence of any one of the following: RDS, TTN, MAS, and the need for ventilatory support. As depicted in the data gathered, the primary outcome was found to be significantly associated with the identified maternal clinical factors in this study, excluding abdominal delivery and presence of maternal anemia. In a cross-sectional study done by Addisu *et al*. in 2018, it was found that maternal age of more than 30 years, presence of hypertension, IUGR, gestational age, and prolonged labor were all significantly associated with

Table 6: Maternal clinical predictors of persistent pulmonary hypertension

Maternal factors	PPHN, *n* (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*
Maternal age (years)				
<35	8 (1.0)	-	-	<0.424
≥35	6 (2.8)	2.81 (0.96–8.18)	1.69 (0.47–6.10)	
Parity				
Nulliparity	4 (0.7)	-	-	<0.041
Multiparity	10 (2.3)	3.30 (1.03–10.59)	4.27 (1.06–17.21)	
Age of gestation				
37w0d–40w6d	6 (0.8)	-	-	<0.037
>41w0d	8 (3.2)	4.08 (1.41–11.90)	3.71 (1.09–12.67)	
Manner of delivery				
Abdominal	12 (1.8)	2.70 (0.60–12.16)	1.92 (0.36–10.20)	<0.443
Vaginal	2 (0.7)	-	-	
Duration of labor (h)				
<24	4 (0.5)	-	-	<0.005
>24	10 (6.3)	13.70 (4.24–44.25)	8.90 (1.92–41.19)	
PROM				
Present	8 (1.6)	1.274 (0.44–3.70)	0.75 (0.21–2.59)	<0.651
Absent	6 (1.2)	-	-	
Character of MSL upon admission				
Significant	7 (1.4)	1.021 (0.36–2.93)	1.20 (0.31–4.69)	<0.795
Not significant	7 (1.4)	-	-	
Presence of change from NS to significant MSL				
Present	9 (5.3)	9.14 (3.02–27.62)	2.11 (0.45–9.76)	<0.341
Absent	5 (0.6)	-	-	
Presence of IUGR				
Present	-	-	-	<0.997
Absent	14 (1.5)	-	-	
Hypertension				
Present	7 (3.6)	4.14 (1.44–11.95)	7.16 (2.03–25.24)	<0.002
Absent	7 (0.9)	-	-	
Maternal anemia				
Present	2 (5.9)	4.9 (1.05–22.79)	2.59 (0.44–15.42)	<0.295
Absent	12 (1.3)	-	-	

PPHN: Persistent pulmonary hypertension of the newborn, PROM: Prelabor rupture of membranes, MSL: Meconium-stained liquor, IUGR: Intrauterine growth restriction, OR: Odds ratio, CI: Confidence interval, NS: Not significant

MSAF.[3] Similarly, several studies have identified pregnancy-induced hypertension, gestational age, and IUGR as risk factors in MSAF development.[10-12,24] These could be explained by uteroplacental insufficiency that leads to fetal hypoxia and passage of meconium. Consequently, inhalation of MSAF causes respiratory morbidity in the neonate by airway obstruction, chemical pneumonitis, surfactant dysfunction or inactivation, and pulmonary hypertension and, if presents as severe, may lead to neonatal death.

The tertiary hospital primarily caters to complicated pregnancies, and most of these are cases referred from other hospitals and lying-in clinics. While abdominal deliveries are performed for obstetric indications, the presence of MSAF may signal an impending fetal asphyxia; hence, obstetricians tend to be more aggressive in their management considering the timing to when vaginal delivery can occur before metabolic acidosis in the fetus sets in. Consistent with other published studies, there was a higher incidence of abdominal delivery in the setting of MSAF compared to vaginal delivery.[14,15,25] In a prospective case–control study done by Desai *et al*. in 2017, it was found that MSAF was associated with having lower SpO_2 values and portray a nonreassuring fetal heart rate pattern on intrapartum monitoring.[6]

Jain *et al*. conducted a study on perinatal outcome of MSL in preterm, term, and postterm pregnancies conducted in 2017. Increased incidence of MSAF was observed among cases with increasing maternal age and gestational age. However, on further analysis, there was no significant effect found on both variables. Despite the results, it was concluded in the study that MSAF has an increased association with poor neonatal outcomes such as lower Apgar score, NICU admission, MAS, and death.[26] These were consistent with the findings of this study wherein there is an increased risk of developing poor neonatal outcomes with MSAF together with the presence of the maternal clinical factors.

Table 7: Maternal clinical predictors of neonatal hypoxic-ischemic encephalopathy

Maternal factors	HIE, *n* (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*
Maternal age (years)				
<35	7 (0.9)	-	-	<0.341
≥35	4 (1.9)	2.12 (0.62–7.31)	2.01 (0.48–8.45)	
Parity				
Nulliparity	6 (1.1)	-	-	<0.847
Multiparity	5 (1.2)	1.08 (0.33–3.57)	0.87 (0.22–3.49)	
Age of gestation				
37w0d–40w6d	7 (0.9)	-	-	<0.666
>41w0d	4 (1.6)	1.72 (0.50–5.93)	1.34 (0.36–4.99)	
Manner of delivery				
Abdominal	7 (1.0)	0.78 (0.23–2.68)	0.38 (0.92–1.58)	<0.183
Vaginal	4 (1.3)	-	-	
Duration of labor (h)				
<24	4 (0.5)	-	-	<0.072
>24	7 (4.4)	9.4 (2.72–32.51)	4.12 (0.88–19.26)	
PROM				
Present	9 (1.8)	4.35 (0.93–20.22)	3.00 (0.60–14.87)	<0.179
Absent	2 (0.4)	-	-	
Character of MSL upon admission				
Significant	7 (1.4)	1.80 (0.52–6.18)	2.59 (0.58–11.48)	<0.211
Not significant	4 (0.8)	-	-	
Presence of change from NS to significant MSL				
Present	6 (3.6)	5.98 (1.80–19.82)	2.96 (0.57–15.28)	<0.195
Absent	5 (0.6)	-	-	
Presence of IUGR				
Present	-	-	-	<0.997
Absent	11 (1.2)	-	-	
Hypertension				
Present	2 (1.0)	0.90 (0.19–4.17)	0.83 (0.17–4.08)	<0.813
Absent	9 (1.1)	-	-	
Maternal anemia				
Present	2 (5.9)	6.55 (1.36–31.55)	3.66 (0.65–20.60)	<0.142
Absent	9 (0.9)	-	-	

HIE: Hypoxic-ischemic encephalopathy, PROM: Prelabor rupture of membranes, MSL: Meconium-stained liquor, IUGR: Intrauterine growth restriction, OR: Odds ratio, CI: Confidence interval, NS: Not significant

Histologic evidence have shown direct effects of meconium exposure *in utero* on the fetal, umbilical cord, and placental tissues. Meconium *in utero* causes inflammation in the lung tissues causing neonatal pneumonia, as well as focal inflammation and, if severe, ulceration in the umbilical cord.[11,14] Consequently, decreased glycogen stores in the placenta and umbilical cord were found and may have resulted from the vasoconstrictive effect of the meconium on the vessels.[27,28] These findings were found to be significantly associated with neonatal morbidity from fetal distress.[23,26] Comparable to the results of these studies, MSAF was significantly associated with developing adverse neonatal outcomes after delivery.

There were 16 identified neonatal deaths in cases of meconium-stained labor. The incidence of neonatal death was particularly low in this study and may be attributed to the increased incidence of abdominal delivery with the presence of MSAF. This was found to be statistically significant with AOG more than 41 weeks and with the presence of significant MSL upon admission. With the presence of these factors, the fetus is at higher risk because of diminished amniotic fluid and cord compression during labor leading to uteroplacental insufficiency.[1,6,23] Moreover, the presence of hypertension contributing to increased risk for intrauterine fetal hypoxia was seen to be significantly associated with neonatal death.

Conclusion

The presence of maternal clinical factors was found to be significantly associated with poor neonatal outcomes in meconium-stained labor in this particular study. Among the maternal clinical factors, maternal age of <35 years, nulliparas, early- and full-term gestation, abdominal deliveries, labor of <24-h duration, and presence of term PROM had increased incidence of MSL. There were several cases of MSL in the presence of maternal hypertension, anemia, and IUGR that were reported.

Table 8: Maternal clinical predictors of neonatal death

Maternal factors	Neonatal death, *n* (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*
Maternal age (years)				
<35	12 (1.9)	-	-	<0.782
≥35	4 (1.5)	1.23 (0.39–3.85)	0.83 (0.22–3.08)	
Parity				
Nulliparity	5 (0.9)	-	-	<0.006
Multiparity	11 (2.6)	2.91 (1.00–8.43)	5.56 (1.65–18.69)	
Age of gestation				
37w0d–40w6d	5 (0.7)	-	-	<0.007
>41w0d	11 (4.5)	6.84 (2.35–19.89)	5.14 (1.56–16.92)	
Manner of delivery				
Abdominal	16 (2.3)	-	-	<0.993
Vaginal	-	-	-	
Duration of labor (h)				
<24	9 (1.1)	-	-	<0.133
>24	7 (4.4)	4.15 (1.52–11.32)	2.76 (0.74–10.37)	
PROM				
Present	10 (2.0)	1.60 (0.58–4.44)	0.88 (0.29–2.73)	<0.830
Absent	6 (1.2)	-	-	
Character of MSL upon admission				
Significant	15 (3.1)	15.76 (2.07–11.98)	17.66 (1.98–157.61)	<0.010
Not significant	1 (0.2)	-	-	
Presence of change from NS to significant MSL				
Present	6 (3.6)	2.97 (1.07–8.29)	2.79 (0.67–11.57)	<0.158
Absent	10 (1.2)	-	-	
Presence of IUGR				
Present	-	-	-	<0.997
Absent	16 (1.7)	-	-	
Hypertension				
Present	6 (3.1)	2.46 (0.88–6.86)	3.47 (1.05–11.46)	<0.041
Absent	10 (1.3)	-	-	
Maternal anemia				
Present	1 (2.9)	1.89 (0.24–14.76)	0.62 (0.61–6.26)	<0.682
Absent	15 (1.6)	-	-	

PROM: Prelabor rupture of membranes, MSL: Meconium-stained liquor, IUGR: Intrauterine growth restriction, OR: Odds ratio, CI: Confidence interval, NS: Not significant

As to the primary outcome, among the identified maternal clinical factors, all, except manner of delivery and presence of anemia, were statistically significant in developing neonatal respiratory morbidity.

With NICU stay of more than 4 days, manner of delivery was shown to be the only maternal clinical factor that was not significantly associated with the secondary outcome. The rest of the maternal clinical factors were observed to have increased risk for NICU stay. Neonatal sepsis was found to be significantly associated with maternal age of >35 years, multiparity, longer duration of labor, presence of PROM, significant MSL, change of MSL from NS to significant, and hypertension. Moreover, only four maternal clinical factors, namely multiparity, ≥41-week AOG, prolonged duration of labor, and change in the character of MSL, were found to have increased risk of developing PPHN in the newborn. On the other hand, all maternal clinical factors were not statistically significant for developing HIE in the newborn. Although, multiparity and abdominal delivery were shown to be protective risk factors.

While the incidence of neonatal mortality as a consequence of MSL was low in this study, the presence of maternal clinical factors, such as multiparity, AOG >41 weeks, presence of significant MSL, and hypertension, has a significantly increased risk for neonatal death. Thus, identification of maternal risk factors and early detection of MSAF are vital in administering timely intervention to labor and delivery to reduce neonatal morbidity and mortality.

Recommendations

The results of the study may be applied to devise a risk-scoring system which may be prospectively validated. Such scoring system will be able to facilitate the formulation of clinical pathways to prevent adverse neonatal outcomes. Clinical evaluation will be able to emphasize the identification of more high-risk patients,

closer intrapartum monitoring, and facilitating delivery in an equipped tertiary center with appropriate neonatal care.

Authorship contributions

Jelli Ann Magno - Involved in the conceptualization, methodology, data curation, writing of the original draft, review and editing.

Brenda Bernadette Zamora - involved in conceptualization, methodology, review and editing of the draft.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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