MECONIUM STAINED AMNIOTIC FLUID AND ITS EFFECT ON THE EARLY MATERNAL AND NEONATAL OUTCOMES

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements of the degree of Master of Medicine in the branch of Obstetrics and Gynaecology, 2019

DECLARATION

I, Relebogile Sekele, hereby declare that this research is my own work. I am submitting this research report for the degree Master of Medicine in the branch of Obstetrics and Gynaecology at the University of the Witwatersrand, Johannesburg. This research report has not been submitted before for any degree or examination at this or any other university.

This MMed research report is submitted in the format of a submissible research article entitled "Meconium Stained Amniotic Fluid and its effects on the early maternal and neonatal outcomes". The article will be submitted to the British Journal of Obstetrics and Gynaecology. The article conforms to the author guidelines for this journal.

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To my friend Dr Setswakae Khoele, my mother Martha Sekele and my two amazing children, a huge thank you for your unconditional love and support.

I would not have achieved any of this without your constant support.

ABSTRACT

Background

The presence of meconium during delivery is a common finding and may be associated with significant neonatal and maternal outcomes.

Objectives

To determine the incidence of meconium stained amniotic fluid (MSAF) at Chris Hani Baragwanath Academic Hospital. To describe the characteristics of women with MSAF and to determine the maternal and fetal outcomes.

Methodology

A secondary data analysis of the women and neonates exposed to MSAF born between July 2014 and December 2016. We used data that was collected for the V98_28OBTP study, which aimed to establish a sero-correlate of protection, based on maternal and newborn levels of Group B streptococcus anti-capsular antibody and the risk to developing serotype-specific invasive Group B streptococcus disease in the newborn.

Only singleton deliveries of birthweight ≥1000g and cephalic presentation were included in this study. Exclusion criteria included presence of congenital abnormalities and stillbirths. A comparison was made in women whose neonates had a normal outcome vs. those with severe fetal outcomes.

Results

Among the 37,725 deliveries, 4218 (11.18%) had meconium stained amniotic fluid (MSAF). Delivery was by caesarean section in 2628 (62.30%) women and 2343 (89.16%) of these were emergency caesarean sections. Of the 1590 vaginal deliveries, 71 (4.47%) were assisted deliveries. Chorioamnionitis was noted in 20(0.47%) women.

Most of the women were black (98.15%), with a mean age of 27.35 and a mean body mass index (BMI) of 29.98. There were 3835(90.92%) term deliveries, with the mean birthweight of 3151g (SD±503.81). The median Apgar score at 5 minutes was 10 (IQR 7-10, range 0-10). There were 232(5.50%) neonates that required resuscitation after delivery. There were 380(9.03%) neonates that were born preterm. The median gestational age of those born preterm was 35 weeks (IQR 29-36; range 25-36).

In the comparison of neonates with good outcomes vs. those with severe neonatal outcomes, neonates of the women with offensive amniotic fluid were more likely to have severe neonatal outcomes (P=0.00).

Conclusion

The incidence of meconium stained amniotic fluid (MSAF) is 11.18%. The incidence of preterm deliveries is 9.03%. The presence of MSAF is associated with a high caesarean rate of 62.30%. The presence of offensive amniotic fluid is associated with severe neonatal outcomes. Women with MSAF should therefore be referred to a centre where caesarean sections and intensive neonatal care are provided.

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ABBREVIATIONS

ACOG	American College of Obstetricians and Gynaecologists
BMI	Body Mass Index
CFM	Continuous fetal monitoring
CHBAH	Chris Hani Baragwanath Academic Hospital
CPAP	Continuous positive airway pressure
CTG	Cardiotocography
ICU	Intensive care unit
NICU	Neonatal intensive care unit
MAS	Meconium aspiration syndrome
MSAF	Meconium stained amniotic fluid
MSL	Meconium stained liquor
MOU	Midwife obstetrics unit
NICE	National Institute for Health and Care Excellence
RCT	Randomized controlled trial
RPR	Rapid plasma reagin

DEFINITIONS

Meconium: Meconium is the intestinal content of the foetus.

The meconium staining of the amniotic fluid can be classified as Grade I, II, and III. Grade I meconium stained amniotic fluid is translucent, light yellow-green in colour, grade II MSAF is opalescent with deep green and light yellow in colour. Grade III is opaque and deep green in colour(1, 2)(1, 2). Meconium can also be classified as thin or thick based on its consistency.

Chorioamnionitis: Chorioamnionitis is defined as inflammation of the amniochorionic (fetal) membranes of the placenta, typically in response to microbial invasion.

CHAPTER 1: PROTOCOL AND EXTENDED LITERATURE REVIEW

1.1 Introduction

The passage of meconium in utero is common among term and post-term infants in whom it is a marker of the infant at risk for adverse outcomes.[3] The incidence of meconium stained amniotic fluid is 11-18%.[4-7] The presence of MSAF has been associated with higher rates of stillbirths, low APGAR scores, hypoxic ischaemic encephalopathy and overall poor perinatal outcomes.[4, 5]

1.2 Literature review

1.2.1 Definition of meconium

Meconium is the intestinal content of the foetus and is composed of water (as much as 80%), mucopolysaccharides, bilirubin, intestinal enzymes, hair and squamous cells. The characteristic green colour is attributable to bile pigments.[6] Other constituents include cholesterol and it's precursors, proteins, lipids, bile acids and salts, pancreatic enzymes, interleukin-8, phospholipase A2 and vernix caseosa (white substance coating the skin of neonate).[7]

1.2.2 Physiology of passage of meconium

The passage of meconium in the new born is a developmentally programmed event normally occurring within the first 12 to 48 hours after birth.[8] In-utero passage of meconium is rare before 34 weeks of gestation and the incidence steadily increases beyond 37 weeks of gestation.[9]

Meconium stained amniotic fluid is less common in the preterm pregnancy. A study in Scotland showed an incidence of 4.3% of pregnancies below 33 weeks gestation.[10] A study in the US found an incidence of meconium staining of 16% in preterm deliveries, diagnosed on microscopy. They looked at neonates with a birthweight of <1350g. The neonates exposed to meconium in the study were younger, associated with

chorioamnionitis, lower APGAR scores and poor outcomes including bronchopulmonary dysplasia, grade 3 or 4 intraventricular haemorrhage and need of endotracheal intubation or cardiopulmonary resuscitation at delivery.[3]

Under normal circumstances, the passage of meconium from the foetus into the amniotic fluid is prevented by the lack of intestinal peristalsis, which is caused by several factors, including low motilin levels, tonic contraction of the anal sphincter, and a terminal cap of viscous meconium. Meconium stained amniotic fluid may be a natural phenomenon that neither indicates nor causes foetal distress but simply reflects a post term foetus with a mature gastrointestinal tract in which motilin levels have risen. Vagal stimulation produced by cord or head compression also may be associated with the passage of meconium in the absence of foetal distress.[11]

1.2.3 Risk factors for in-utero passage of meconium

The presence of MSAF is associated with several maternal and fetal factors. The presence of MSAF has been a feature of more advanced gestational age. Studies have shown that the incidence of MSL is 3-6.7% [3, 9] in preterm pregnancies and 5-20% in term pregnancies. A study in 15 maternity units in West London with 499 096 singleton livebirths weighing at least 500g at 24 or more completed weeks of gestation showed that there is a statistically significant association with the presence of MSAF with every week increase in gestational age.[5]

The presence of MSL in women who are induced has been shown to be associated with the type of agent used. In the study done in Egypt, it was noted that complications including passage of meconium occurred more with women who received misoprostol compared to those who received dinoprostone for induction of labour for postdates.[12] The use of herbal medicines with oxytocic properties has also been associated with passage of meconium in utero.[13] A systematic review published in 2016 compared three studies that looked at the outcomes of labour induced with castor oil. Ingestion of castor oil was found to be associated with increased incidence of MSL.[14] Gray et al[15] found the presence of nicotine in meconium of women who reported to have smoked in the last trimester of pregnancy. The neonates with the presence of nicotine in their meconium

were noted to have lower gestational age, smaller birth weights and head circumferences.

Primiparity[16, 17], prolonged rupture of membranes in preterm deliveries[10], unbooked patients[17], prolonged labour[18] have all consistently been associated with passage of meconium prior to delivery.

1.2.4 Diagnosis of meconium staining

The diagnosis of meconium stained liqour can be made on clinical inspection or can be based on histological or microscopic examination. Zaidie[19] describes meconium staining as "Green brown discoloration of the cord, fetal surface and membranes: differentiate between deposition of slimy green meconium across placental surface that is washed off with a gentle rinse (normal fetus that passes meconium shortly after delivery) and true meconium staining (exposure to meconium for several hours). Membranes may be oedematous or slimy." The microscopic or histological diagnosis is described as follows "Vacuolation of the amniotic epithelium, oedema of the soft tissue plane between the amnion and chorion and pigment laden macrophages within the amnion and chorion."

The meconium staining of the amniotic fluid can be classified as Grade I, II, and III. Grade I meconium stained amniotic fluid is translucent, light yellow-green in colour, grade II MSAF is opalescent with deep green and light yellow in colour. Grade III is opaque and deep green in colour.[1, 2]Meconium can also be classified as thin or thick based on its consistency.[20]

1.2.5 Effects of in-utero passage of meconium on the mother and foetus

There are several risks in the mother that are present when MSAF is diagnosed.

Studies consistently found that women exposed to intrauterine MSAF have higher likelihood of chorioamnionitis and endometritis.[21] A retrospective analysis of 43 200 term deliveries from 1992 to 2002 found that the deliveries with MSAF had higher rates of chorioamnionitis and endometritis.[22]

Clinical chorioamnionitis is diagnosed by the presence of maternal fever (temperature > 3 7. 8°C) accompanied by two more of the following criteria: 1) maternal tachycardia (heart rate >100 beats/min); 2) uterine tenderness; 3) foul-smelling amniotic fluid; 4) fetal tachycardia (heart rate >160 beats/min); and 5) maternal leukocytosis (leukocyte count >15,000 cells/mm3).[23]

Multiple studies have consistently made an association between MSAF and high rate of operative deliveries (caesarean sections, assisted deliveries and episiotomies) when compared with clear amniotic fluid.[1, 7, 21]

A Cochrane review on the use of antibiotics for prevention of maternal and neonatal infections found that antibiotics may reduce the occurrence of chorioamnionitis but there was no evidence that antibiotics could reduce postpartum endometritis, neonatal sepsis and NICU admission.[7]

The most important outcome of the fetus exposed to MSAF is meconium aspiration syndrome which is a designation for the respiratory distress occurring in newborn infants born to pregnancies complicated by MSAF.[24] In a South African study published in 1998, the incidence of meconium aspiration was found to be 4-11/1000.[25] It is a leading cause of morbidity and mortality in term infants. The pathophysiology of MAS is complex and incompletely understood but only occurs in the presence of MSAF. Factors associated with MAS include fetal distress and hypoxia but it is important to note that over three quarters of infants with MSAF are vigorous at birth. Meconium aspiration syndrome is associated with airway obstruction which explains the typical radiologic findings of atelectasis (complete obstruction) and over-expansion (partial obstruction) and pulmonary hypertension. These findings can also be confirmed by clinical signs and echocardiographic findings. Meconium may produce direct toxicity on type II pneumocytes, displace surfactant from the alveolar surface, and decrease surfactant protein A and B concentrations.[24]

The presence of MAS is associated with persistent pulmonary hypertension. In a study of 100 neonates with MAS 19 had PPHN as diagnosed using pulse oximetry, ABG, chest X-ray, ECG and 2D colour echocardiography.[26]

There are other risks in the neonate when there is exposure to MSAF. The presence of meconium is also associated with high rate of birth asphyxia and stillbirth rates, and hypoxic encephalophatic ischaemia [2, 3]; admission to neonatal ICU [6-9] and neonatal sepsis. Among 8129 infants in a study conducted in Soweto, South Africa and published in 2012, 289 had early-onset sepsis and 34 had late-onset sepsis; and MSAF was identified to be one of the factors associated with early-onset sepsis. [27] In the same study, MSAF was also associated with late onset sepsis. It is not clear in the study whether the infections were a result of the MSAF, or if the infection was already in the uterus and predisposed to the presence of MSAF and neonatal infections.

1.2.6 Management of a patient with MSAF:

The management is aimed at the identification of fetal distress and reducing aspiration of MSAF by the neonates. The management of neonates born with MSAF has changed over the years, from routine ET intubation and tracheal suctioning for all neonates born through MSAF to ET intubation and tracheal suctioning if non-vigorous/depressed infants. The vigorous meconium-stained infant should not be separated from the mother and should be placed skin-to-skin with her where initial steps of newborn care can be provided. In 2017, the ACOG recommended that infants with MSAF should no longer routinely receive intrapartum suctioning, whether they are vigorous or not and that resuscitation should follow the same principles for those with clear fluid.[28]

The South African maternity care guidelines[29] and the NICE guidelines[30], categorises the management of meconium in labour according to whether it is grade I/ thin MSL or grade II and III/thick. For thin MSL, labour is managed as routine. For thick MSL, the labour needs to be managed in a hospital setting with continuous fetal monitoring. The paediatrician is alerted and should be prepared for neonatal resuscitation. The NICE guidelines further add that if the CTG shows features of fetal hypoxia, then a fetal blood sample is obtained and an emergency delivery is ordered if the pH is below 7.21. Fetal blood sampling is not performed in our setting.

1.2.7 The role of amnio-infusion in the management of meconium stained amniotic fluid

Since MAS is more prevalent in cases of thick meconium, clinicians have attempted to decrease its incidence by diluting meconium through amnio-infusion. Several RCTs have evaluated this technique. The most recent Cochrane review of women in labour with moderate or thick meconium staining of the amniotic fluid evaluated 14 trials and included 4435 women. For settings with adequate peripartum surveillance, there were no differences in the incidence of MAS, neither in perinatal nor maternal morbidity and mortality. However, when the three studies performed in settings with suboptimal perinatal management were evaluated as a subgroup, there were decreases in the incidence of MAS, in perinatal mortality, and in other short-term morbidities. The review concludes that it is not clear whether the benefits resulted from dilution of meconium or from relief of oligohydramnios. The studies were too small to evaluate the potential risks of maternal complications of the procedure.[25, 31, 32]

1.2.8 Problem statement & justification of the study

Meconium stained amniotic fluid is a common occurrence during delivery. It is an important predictor of adverse maternal outcomes (operative deliveries, chorioamnionitis, and endometritis) and neonatal outcomes (birth asphyxia, admission to NICU, stillbirths)

The South African maternity care guidelines recommends referral of all labours complicated by MSL grade two and three to a hospital. CHBAH is a tertiary hospital, but also serves as an immediate referral centre for two MOUs. There is a district hospital that gets direct referrals from four MOUs. However CHBAH serves as the immediate referral centre for all of the MOUs because of staffing problems at the district hospital

The incidence of MSL in unknown in our institution. This study was performed so that we can identify the incidence of MSL and to describe the maternal factors associated with passage of meconium in labour; and to describe the possible complications thereof.

This will help with resource allocation and to modify our current protocol.

1.3 Objectives of the study

The main objective of this study is to determine the foetal and maternal outcomes in a cohort of mother-infant pairs where MSAF was present between the months of July 2014 to July 2016.

The specific objectives are:

- To describe the incidence (per 1000 births) of meconium stained amniotic fluid in all deliveries of ≥1000g or at >28 weeks at CHBAH.
- To describe the maternal complications including (i) chorioamnionitis, (ii) rate of caesarean section.
- To describe the immediate maternal and neonatal factors that are associated with meconium stained amniotic fluid.

1.4 Study methods

1.4.1 Study setting:

CHBAH is the third largest hospital in the world. Approximately 20 000 deliveries take place in the maternity hospital annually. It is a tertiary hospital which is also a teaching hospital for the University of the Witwatersrand. It is situated in Soweto, Johannesburg, South Africa. The population of Soweto in 2017 was estimated to be 1.516 million (STAT SA, 2017). Total deliveries for the period of the study were 50 822 at CHBAH (Departmental statistics).

1.4.2 Study population:

This study was a secondary data analysis using data collected for V98_28OBTP study. The aim of the V98_28OBTP study was to establish a sero-correlate of protection, based on maternal and newborn levels of Group B streptococcus (GBS) anti-capsular antibody and

the risk of developing serotype-specific invasive Group B streptococcus disease in both the early neonatal period of 0-6 days age as well as late onset disease of 7-90 days age. They had aimed to recruit thirty- five thousand mother infant dyads between July 2014 and December 2016, but ended up with 37,725.

Pregnant women were recruited for enrolment of themselves and their newborns into the study either at the time of attending antenatal clinic, during the early stages of labour or immediately post-delivery. Antenatally women were enrolled at five midwife obstetric units (Diepkloof, Lillian Ngoyi, Mofolo, Michael Maponya and Chiawelo) and at Chris Hani Baragwanath Academic Hospital (CHBAH). In labour and after delivery women were recruited at CHBAH.

Inclusion criteria for maternal participants in the main/parent study (V98_28OBTP) were pregnant women attending antenatal care at one of the participating antenatal-clinics and/or delivering at CHBAH, aged ≥18 years, ability to understand and comply with planned study procedures and provide a written informed consent. Stillbirths' deliveries were not included in the study.

This study was a secondary data analysis using base line data collected between July 2014 and December 2016. The inclusion criteria for the present study were the presence of meconium noted in labour or delivery, singleton deliveries, birthweight of ≥1000g or ≥28 weeks, vertex presentation and absence of foetal abnormalities. Of the 35 000 women from the original study, there were 4218 women that met the criteria for this study.

1.4.3 Study Design

This was a cross sectional study.

1.5 Data Management

1.5.1 Data collection

The data for the primary study, V98_28OBTP, were collected onto paper documents from the maternity files, antenatal cards and neonatal files, and then entered into an electronic database using SQL. There was double entry from paper to data base.

1.5.2 Data analysis

Data was extracted from the database in an Excel format and analysed using Stata 14 (4905 StataCorp, Lakeway College Station, Texas 77845 USA). Categorical variables were described using frequencies with percentages and continuous variables were described using, means and standard deviations, and/or medians with IQR ranges where appropriate. A new variable "severe neonatal outcome" was created. This variable included neonates born with an APGAR <7 at 5 minutes, neonates requiring resuscitation. Resuscitation included the need for supplemental oxygen, continuous positive airway pressure, bag mask ventilation, endotracheal intubation, chest compressions, epinephrine, bicarbonate, and suctioning of the airway.

The women were compared between those with severe neonatal outcomes and those without. Severe neonatal outcomes were defined as I continuous positive airway pressure, bag mask ventilation, endotracheal intubation, chest compressions, epinephrine, bicarbonate, and suctioning of the airway. The outcomes were compared using a chi^2 to compare categorical variables and a t-test or Kruskal-Wallis was used to compare continuous variables.

1.6 Limitations

The limitations encountered were that the grade of meconium was not routinely assessed and recorded by all health care workers. Inter-observer differences in recording may impact quality of data for this variable. Calculation of gestational age was not done uniformly. The data for the main study were not collected to address the research question and therefore some of the variables were not recorded i.e. whether there was induction of labour and the type of induction agent used, type of rupture of membranes. The current study did not look at neonates with meconium aspiration. The type of hypertension and diabetes mellitus was not described. The data on stillbirths was not recorded because it was an exclusion criterion of the main study.

The strengths of the study included the large sample size and the data are representative of the community because we get referrals from all the hospitals across Soweto.

1.7 Ethics

Permission was granted by Professor Shabir Madhi, the principal investigator and Dr Clare Cutland, the clinical lead investigator of the V98_28OBTP study, to use the data. Ethics approval for the original study

Ethical approval was obtained from the Human Research Ethics committee of the University of the Witwatersrand (Wits HREC) in October 2017 (Wits HREC reference: M171033).

1.8 Funding

The original study was funded Novartis, and subsequently by GlaxoSmithKline (GSK). No funding was required for the study.

1.10 Timing

	AUG-2017	SEPT 2017	OCT 2017	NOV 2017	DEC 2017	JAN 2018	FEB 2018	MAR 2018	APRIL 2018
PROTOCOL SUBMISSION	X								
ETHICS SUBMISSION									
ETHICS APROVAL									
POSTGRADUATE COMMITTEE									
PERMISSION FROM CEO									
DATA CAPTURING									
DATA PROCESSING AND ANALYSIS									
WRITE UP									
SUBMISSION OF MMED									

CHAPTER 2: SUBMISSIBLE ARTICLE

TITLE: MECONIUM STAINED AMNIOTIC FLUID AND ITS EARLY MATERNAL AND NEONATAL OUTCOMES.

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Conflict of interest: Nil

Keywords: meconium, amniotic fluid, Soweto, South Africa

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ABSTRACT

Background

The presence of meconium during delivery is a common finding and may be associated with significant neonatal and maternal outcomes.

Objectives

To determine the incidence of meconium stained amniotic fluid at Chris Hani Baragwanath Academic Hospital (CHBAH). To describe the characteristics of women with meconium stained amniotic fluid and to determine the maternal and fetal outcomes.

Methodology

A secondary data analysis of the women and neonates exposed to MSAF born between July 2014 and December 2016. We used data that was collected for the V98_28OBTP study, which aimed to establish a sero-correlate of protection, based on maternal and newborn levels of Group B streptococcus anti-capsular antibody and the risk to developing serotype-specific invasive Group B streptococcus disease in the newborn.

Only singleton deliveries of birthweight 1000g≥ and cephalic presentation were included in this study. Exclusion criteria included presence of congenital abnormalities and stillbirths. A comparison was made in women whose neonates had a normal outcome vs. those with severe fetal outcomes.

Results

Among the 37,725 deliveries, 4218 (11.18%) had MSAF. Delivery was by caesarean section in 2628 (62.30%) women and 2343 (89.16%) of these were emergency caesarean sections. Of the 1590 vaginal deliveries, 71 (4.47%) were assisted deliveries. Chorioamnionitis was noted in 20(0.47%) women.

Most of the women were black (98.15%), with a mean age of 27.35 and a mean BMI of 29.98. there were 3835(90.92%) term deliveries, with the mean birthweight of 3151g (SD±503.81). The median Apgar score at 5 minutes was 10 (IQR 7-10, range 0-10). There were 232(5.50%) neonates that required resuscitation after delivery. There were 380(9.03%) neonates that were born preterm. The median gestational age of those born preterm was 35 weeks (IQR 29-36; range 25-36).

In the comparison of neonates with good outcomes vs. those with severe neonatal outcomes, neonates of the women with offensive amniotic fluid were more likely to have severe neonatal outcomes (P=0.00).

Conclusion

The incidence of MSAF is 11.18%. The incidence of preterm deliveries is 9.03%. The presence of MSAF is associated with a high caesarean rate of 62.30%. The presence of offensive amniotic fluid is associated with severe neonatal outcomes. Women with MSL should therefore be referred to a centre where caesarean sections and intensive neonatal care are provided.

Introduction

Giving birth is probably one of the most fulfilling moment in a woman's life, and it is perceived as an achievement by many. In the practice of obstetrics, our main aim is to have a healthy baby and a healthy mother. The passage of meconium is a physiological process but may be a marker of fetal hypoxaemia.[1] The presence of meconium stained amniotic fluid (MSAF) has been associated with higher rates of stillbirths, low Apgar scores, hypoxic ischaemic encephalopathy and overall poor perinatal outcomes.[4, 5] The reported incidence of MSL is 11-18%.[4-7] The incidence of meconium aspiration was reported to be between 4-11/1000 in a study done among 11 South African institutions in 1998.[33]

A South African report published in 2002 using routinely collected PPIP (Perinatal Problem Identification Problem) data reported that the most frequent causes of death from birth asphyxia were labour-related asphyxia (65.8%), cord prolapse (11.2%), cord around the neck (7.2%), meconium aspiration (7.0%) and difficult breech delivery (4.7%).[34]

Women with MSAF are more likely to develop maternal complications including chorioamnionitis, endometritis, and higher rate of caesarean section.[1, 7, 8, 21]

The maternity care guidelines in SA state that women with Grade II/III MSAF should be referred to a hospital because of the risk of foetal distress and caesarean section.[29] Women with meconium stained amniotic fluid require continuous foetal monitoring. They should also deliver at a facility where there are paediatric services and facilities for emergency caesarean sections.

CHBAH is a tertiary hospital affiliated with the University of the Witwatersrand and is located in Soweto, Johannesburg, South Africa. It has direct referrals from 4 Midwife Obstetric Units and a district hospital in Soweto.

The V98_28OBTP study was conducted in the period between July 2014 and December 2016. This therefore provided the opportunity to use the data to describe what the incidence of MSAF is at CHBAH and to characterise and assess the perinatal and maternal outcomes of deliveries complicated by the presence of MSAF.

Methods

Study setting:

CHBAH is the third largest hospital in the world. It is a tertiary hospital which is also a teaching hospital for the University of the Witwatersrand, situated in Soweto, Johannesburg, South Africa. The population of Soweto in 2017 is estimated to be 1.516 million (STAT SA, 2017). The total deliveries for that period was 50 822.

Study population:

This study was a secondary data analysis using data collected for V98_28OBTP study. The aim of this study was to establish a sero-correlate of protection, based on maternal and newborn levels of Group B streptococcus (GBS) anti-capsular antibody and the risk of developing serotype-specific invasive Group B streptococcus disease in the 90 days of life (Early Onset Disease & Late onset disease).

They had aimed to recruit thirty- five thousand mother infant dyads between July 2014 and December 2016, but ended up with 37,725.

Recruitment was during the antenatal, during the early stages of labour or immediately post-delivery. Antenatally women were enrolled at five midwife obstetric unit and CHBAH. In labour and after delivery women were enrolled at CHBAH. Stillbirths' deliveries were not included in the study.

Inclusion criteria for maternal participants in the main/parent study (V98_28OBTP) were pregnant women attending antenatal care at one of the participating antenatal-clinics and/or delivering at CHBAH, subjects aged ≥18 years, ability to understand and comply with planned study procedures and provide a written informed consent.

The inclusion criteria for the present study were the presence of meconium noted in labour or delivery, singleton deliveries, birthweight of ≥1000g or ≥28 weeks, vertex presentation and absence of foetal abnormalities. Of the 35 000 women from the original study, 4218 met the criteria for our study.

Data Management:

Data collection:

The data for the primary study, V98_28OBTP, were collected onto paper documents from maternity files, antenatal cards and neonatal files, and then entered into an electronic RedCAP database. The following variables were extracted from the Data base; maternal demographics, obstetric history, past medical history, history of the current pregnancy, gestational age at delivery and complications. MSL was recorded as present or absent. When meconium was present, it was either described as MSL I, II, III or thick/thin. It was never described as particulate or non-particulate.

Data analysis:

Data was extracted from the database in an Excel format and analysed using Stata 14 (4905 StataCorp, Lakeway College Station, Texas 77845 USA). Categorical variables were described using frequencies with percentages and continuous variables were described using, means and standard deviations, and medians with IQR ranges. A new variable "severe neonatal outcome" was created. All neonates who were born with an APGAR <7 at 5 minutes or who were resuscitated were included. Resuscitation included any baby who was given supplemental oxygen, CPAP, bag mask ventilation, endotracheal intubation, chest compressions, epinephrine, and had suctioning of the airway.

There was a comparison between the two neonatal outcomes. The chi2 to compare categorical variables and a t-test or Kruskal-Wallis was used to compare continuous variables.

Ethics

Permission was granted by Professor Shabir Madhi, the principal investigator and Dr Clare Cutland, the clinical lead investigator of the V98_28OBTP study, to use the data.

The V98_28OBTP study was reviewed and approved by the Human Research Ethics committee (HREC) of the University of the Witwatersrand in June 2014 (M 140203).

Ethical approval for this study was obtained from the HREC in October 2017 (M171033).

Funding

The original study was funded Novartis, and subsequently by GlaxoSmithKline (GSK). No funding was required for this study.

Results

There were 4218 women with meconium stained amniotic fluid (MSAF) amongst the 37,725 (11.18%) women that were enrolled. The mean age was 27.35 (SD± 6.20). Most of the women were Black (4134(98.15%)), 69(1.64%) were Coloured, 8(0.19%) were Asian and 1(0.02%) was Caucasian. The gestational age at delivery was determined by hierarchical assessment, with early sonar 1343(32.14%) being the most accurate, then last menstrual period 2148(51.41%), then fundal height 685(16.40%) at first visit, then other 2(0.05%). The figure below describes the method of gestational age calculation. There were 383(9.08%) preterm deliveries. The median gestational age for preterm deliveries was 35 weeks (IQR 29-36; range 25-36).

There were 1028(24.37%) women who were primiparous and 3190(75.36%) who were multiparous. A history of a previous stillbirth was reported in 138(3.27%) of the women. There were 91(2.16%) women who had had an abortion and 475(11.26%) had a previous miscarriage.

The mean mid upper arm circumference (MUAC), the height, the weight and the body mass index (BMI) was 29.33cm (SD±4.35), 1.59m (SD±0.07), 74.44 kg (SD± 17.44) and 29.98 kg/m^2(SD±6.75) respectively. The mean haemoglobin (HB) was 11.62 mg/dl (SD±1.71), with a range of 5.00-18.30 mg/dl. The HIV status was positive in 1270(30.11%) of the women, negative in 2929(69.44%) and unknown in 19(0.45%). Rapid plasma reagin (RPR) testing was positive in 40(0.95%), negative in 3910(93.14%) and unknown in 248(5.91%).

A history of smoking in the current pregnancy was recorded in 3392 of the women. There were 122(3.60%) women who smoked. History of alcohol intake in the current pregnancy was recorded in 3370. There were 210(6.23%) women who had used alcohol.

Hypertension in the current pregnancy was recorded in 2704 of the women. Women with hypertension were 508(18.79%). Diabetes mellitus (DM) was recorded in 2655 of the women. Women with DM were 38(1.43%). The type of hypertension or diabetes was not described.

Pregnancies complicated with antepartum haemorrhage (APH) were noted in 2655 women and 89(3.35%) had APH. A complication of postpartum haemorrhage (PPH) was recorded in 2681 of the women. Women with PPH were 503(18.76%).

Tachycardia was present in 343(8.13%) of the women, offensive liqour in 73(1.73%), vaginal discharge in 47(1.11%), urinary tract infection in 28(0.66%), chorioamnionitis in 20(0.47%), pyrexia in 6(0.14%) and uterine tenderness in 2(0.05%).

Fetal distress was diagnosed in 3361(79.68%) using CTG's. The mode of delivery was a caesarean sections in 2628(62.30%) women and a NVD in 1590(37.70%). Of those who had a caesarean section, caesarean section was performed as an emergency in 343(89.16%) and as an elective delivery in 285(10.84%).

Of those who had vaginal deliveries, 71(4.47%) had assisted deliveries; an episiotomy was performed in 333(20.94%) and lacerations occurred in 367(23.08%).

Neonatal outcomes

Term deliveries were 3835(90.92%) and preterm deliveries 383(9.08%). There were 2113(50.11%) males and 2104(49.89%) female neonates. The mean birthweight was 3151g (SD±503.81) and median birthweight was 3170g (IQR 2300-3930, range: 1650-4270). The median Apgar score at 1 minute was 9 (IQR 4-9; range 0-10). The median Apgar score at 5 min was 10 (IQR 7-10; range 0-10).

Neonatal resuscitation was performed in 232(5.5%) of the neonates. Of these supplemental oxygen 86 (2.04%), suctioning of the airway 80(1.90%), bag mask ventilation 18(0.43%), continuous positive airway pressure 8(0.19%), endotracheal intubation 5(0.12%), chest compressions 3(0.07%), use of epinephrine 2(0.05%) and use of Narcan 2(0.05%). There were no neonates who were given bicarbonate. Some of the babies would have required more than one intervention.

Comparison

Severe neonatal outcomes in this study refers to the neonates that required an intervention shortly after birth. The interventions include use of supplemental oxygen, continuous positive airway pressure, bag mask ventilation, endotracheal intubation, chest compressions, epinephrine, and suctioning of the airway, and had an APGAR less than 7 at 5 minutes.

There was no difference in outcomes between neonates born through caesarean section and those born through vaginal delivery (P=0.84).

The table 1 below describes the maternal demographics between those with severe neonatal outcomes and those without. Parity, maternal nutritional status, use of alcohol or smoking during pregnancy did not have any effect on the outcome of neonates exposed to meconium stained amniotic fluid.

Table 1: A comparison of the maternal characteristics between those with severe neonatal outcomes and those without.

Variable	Severe neonatal outcomes n=232	Without severe neonatal outcomes n=3986	P value
Maternal age	26.72 (SD 5.92)	27.83 (SD6.21)	0.13*
Previous pregnancy (n=4197) Present	145(62.77%)	2482(62.58%)	0.95#
History of past stillbirth (n=3495) Present	10(5.75%)	128(3.85%)	0.21#
History of past early pregnancy loss n=3504 Present	27(15.52%)	448(13.45%)	0.44#
Haemoglobin (g/dL) Mean	11.78 SD 1.76	11.61 SD 1.71	0.92$
HIV status (n=4199) Positive	61(26.52%)	1209(30.46%)	0.206#
Syphilis n=3950 Positive	3(1.40%)	37(0.99%)	0.56#
MUAC Median	29 IQR 23-38	29 IQR 23-37	0.27*
BMI Median	30.76 IQR 20.69-48.07	29.00 IQR 20.70-42.59	0.02*
Smoking yes	4(2.04%)	118(3.69%)	0.23#
Alcohol intake yes	11(5.56%)	199(6.27%)	0.69#

#-chi2 *-t test

muac=mid upper arm circumference

As can be seen in table 2, the neonates of the women with offensive amniotic fluid were more likely to have severe neonatal outcomes (P=0.00). The presence hypertension and obstetric haemorrhage have no effect on the neonatal outcomes.

Table 2: Comparison of the maternal complications between those with severe neonatal outcomes and those without.

Variable	Severe neonatal outcomes n=232	Without severe neonatal outcomes n=3986k	P value
Offensive liqour Recorded in n=3888 Present	10(5.10%)	63(1.71%)	0.00#
Hypertension n=2704 Present	31(21.38%)	477(18.64%)	0.41#
Diabetes n=2655 Present	4(2.82%)	34(1.35%)	0.15#
APH n=2655 Present	7(4.96%)	82(3.26%)	0.27#
PPH n=2681 Present	30(21.13%)	473(18.63%)	0.46#

#-chi2 *-t test

Neonates born preterm are more likely to have severe neonatal outcomes. Table 3 shows the difference in gestational age at delivery between those with severe neonatal outcomes and those without.

Table 3: Comparison of gestation at delivery between those with severe neonatal outcomes and those without

Variable	Severe neonatal outcomes n=232	Without severe neonatal outcomes n=3986	P value
Term	198(85.34%)	3628(91.29%)	0.00[#]
Preterm	34(14.66%)	346(8.71%)	
Preterm gestation			
Median	34 IQR 26-36	35 IQR 29-36	0.06[*]

#- chi2 *- t test

The birthweight affects whether the neonate will have severe outcomes or not. The tables 4 show that smaller babies have severe outcomes compared to the larger ones (P=0.00).

Table 4: Birthweight categories: comparing those with severe neonatal outcomes and those without

Birth weight categories	Severe neonatal outcomes n=232	Without severe neonatal outcomes n=3986	P value
<1000g	1(0.43%)	3(0.08%)	0.00[#]
1000-1499	5(2.16%)	18(0.45%)	
1500-2499	38(16.38%)	297(7.45%)	
2500-3499	146(62.93%)	2719(68.21%)	
>3500	42(18.10%)	949(23.81%)	

#-chi2

Discussion

The incidence of MSAF is 11.18% in this study. This incidence is comparable to what is quoted in middle and high income countries. A Brazilian study done in 2005 found an incidence of 11.9%[35], an Indian study found an incidence of 12%[36] in 2013. Oyelese et al found an incidence of 12% in the US in 2004.[37]

All these studies consistently demonstrated the relationship between advancing gestational age and passage of meconium in utero.[8] This is consistent with the hypothesis that fetal maturation is a major etiologic factor in meconium passage.

Our study looked at the presence of meconium in deliveries of foetuses of ≥ 1000g. The proportion of preterm deliveries was 9.08%. A study done in the UK to estimate the rates of meconium-stained amniotic fluid over 12 years found the incidence of MSAF in term pregnancies to be 16.3% and the incidence of MSAF in preterm deliveries (24 weeks to 36 completed weeks) to be 5.1%. The predictor of MSL in the study was racial groups.[5]Mazor et al found an incidence of 5.7% in preterm deliveries with MSAF.[38]

The difference in the reported presence of MSL may be due to the way in which the presence of MSL is diagnosed, with other studies using other methods e.g. microscopic examination to identify the presence of meconium and in those cases, the incidence was found to be higher. According to Henry et al, the incidence of MSAF in preterm deliveries could actually be higher than what is currently reported. They found an incidence of 16% when microscopy was used to make diagnosis of meconium staining.[3]

Mean age of the women in the study is 27.35 ±6.20 years. This is comparable to what was found by Dohbit et al[39]; in their study, they did not find an age difference between women with clear amniotic fluid and those with MSAF.

Most of the women were Black (98.15%). This is because of the setting where the study was conducted. This is not a representation of the SA population, but is a representative of the hospital. Balchin et al[5] found in their study that belonging to either black or South Asian racial group independently predicted meconium stained amniotic fluid. Their findings

suggested that there is earlier fetal maturity of the blacks and South Asians compared with whites.

We found a caesarean section rate of 62.30% which is higher than the caesarean section rate of 40% in 2016 at CHBAH (departmental statistics) and what was found by the parent study (41.7%) it is comparable to what is documented in the literature. The high caesarean section rate for fetal distress may be because this is diagnosed with a CTG and to the lack of fetal scalp pH testing. The practice is that women with MSL will all have continuous electronic fetal heart rate monitoring. Becker et al quoted "a lower caesarean section of 17.4% rate in women with MSL because of the use of fetal scalp pH monitoring in their setting" (Germany). [40] Kumar et al did a study in India and found that umbilical cord blood pH is the best indicator of fetal hypoxemia and should be performed in all high risk births. The decision to perform caesarean sections based on the presence of MSL and abnormal fetal heart rate pattern results in high rate of caesarean sections.[41]

Our study compared outcomes among women with MSAF based on neonatal outcomes. Women with higher BMI were associated with severe neonatal outcomes (P=0.02). High BMI is known to be associated with poor perinatal outcomes. [42]

The number of women with chorioamnionitis was 20 (0.47%). This figure is lower than what is quoted in the literature for women with MSAF. [21, 22] This may be because of the way the data was collected. The researchers only recorded the presence of chorioamnionitis if it was specifically specified in the maternal file. Data on maternal tachycardia, offensive liqour, vaginal discharge, pyrexia, uterine tenderness and fetal distress were collected separately from chorioamnionitis. It is possible that the rate of chorioamnionitis was higher. There were 73 (1.73%) with offensive amniotic fluid and the neonates exposed to offensive amniotic fluid were noted to have more severe outcomes. Other studies have shown that MSAF is a risk factor for chorioamnionitis.[43]

Smoking has been shown as a risk factor for the presence of MSL in the other studies.[15] In our study, we could not make an association between the presence of history of smoking

and passage of MSL during delivery; and there was no difference in neonatal outcomes between the group of women with a history of smoking and those without.

Prematurity is generally associated with poor neonatal outcomes [44], in this study we showed that preterm babies with MSL were more likely to have severe outcomes as compared with term neonates. The mean birthweight of all deliveries with MSL was 3151g (SD±503.81). Neonatal outcomes compared according to birthweight show that neonates with smaller weights have more severe outcomes. The median Apgar score at 5 min was 10 (IQR 7-10; range 0-10). Neonates with an Apgar score of less than 7 at 5 min was 127 (3.12%).

The patients with a stillbirth were not included in the origin data collection. Other studies have identified thick meconium as a significant risk factor for high stillbirth rates.[21]

The limitations encountered were that the grade of meconium was not routinely assessed and recorded by all health care workers. Inter-observer differences in recording may impact quality of data for this variable. Calculation of gestational age was not done uniformly. The data for the main study were not collected to address the research question and therefore some of the variables were not recorded i.e. whether there was induction of labour and the type of induction agent used, type of rupture of membranes. The current study did not look at neonates with meconium aspiration. The type of hypertension and diabetes was not described. The data on stillbirths was not recorded because it was an exclusion criterion of the main study.

The strengths of the study included the large sample size and the data are representative of the community because we get referrals from all the hospitals across Soweto.

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Conclusion

The incidence of MSAF is 11.18%. The incidence of preterm deliveries is 9.03%. The presence of MSAF is associated with a high caesarean rate of 62.30%. The presence of offensive amniotic fluid is associated with severe neonatal outcomes. Women with MSL should therefore be referred to a centre where caesarean sections and intensive neonatal care are provided.

CHAPTER 3: APPENDICES

3.1 DATA SHEET

MECONIUM STAINED AMNIOTIC FLUID AND ITS EFFCTS ON THE EARLY MATERNAL AND NEONATTAL OUTCOMES

Mother's date of birth (age): [__][__}/[__][__]/[__][__][__][__]

Race:

[_] Black [_] Coloured [_] Caucasian [_] Asian [_] Other

HIV Status:

[_] Negative [_] Positive [_] Unknown

CD4+ count: _____ Viral load: _____

Pregnancy history:

Has the subject been pregnant in the past?

[__] Yes [__] No

If yes,

Number of previous pregnancies [___][___] [__] Not recorded

Number of previous live births [___][___] [__] Not recorded

Number of previous intrauterine deaths/stillbirths [___][___] [___] Not recorded

Number of previous induced abortions (TOP) [___][___] [___] Not recorded

Number of previous spontaneous abortions [___][___] [___] Not recorded

Nutritional status:

Mid-upper arm circumference (MUAC): [__][__]cm

Height [__].[__][__]m [_] Not recorded

Weight [__][__][__]kg [_] Not recorded

Habits:

Smoking during pregnancy? [_] Yes [_] No [_] NR

Drink alcohol during pregnancy? [_] Yes [_] No [_] NR

Haemoglobin

Booking haemoglobin value? [__][__].[__] [_] NA

Syphilis

RPR result: [_] Negative [_] Positive [_] Unknown

If positive, did she receive any treatment (Bicillin)? [_] Yes [_] No [_] Unknown

Labour and delivery

Gestational age at delivery: [_] Term [_] Preterm

Gestational age determined by

[_] Fundal height

[_] Last menstrual period

[_] Ultrasound

[_] Other

Not recorded ☐ Yes ☐ No

Liqour:

Clear ☐ Yes ☐ No

Offensive ☐ Yes ☐ No

Meconium-stained ☐ Yes ☐ No

No recorded ☐ Yes ☐ No

Delivery related Complications:

Did the participant experience any complications during pregnancy, labour and delivery?
☐ Yes ☐ No

If yes, tick all that apply:

Pregnancy-Induced Hypertension (incl. PIH/Pre-eclampsia/Eclampsia/ HELLP)
☐ Yes ☐ No

Gestational Diabetes ☐ Yes ☐ No

Antepartum Haemorrhage ☐ Yes ☐ No

Postpartum Haemorrhage ☐ Yes ☐ No

Episiotomy ☐ Yes ☐ No

Perineal laceration/tear ☐ Yes ☐ No

Other: _____ ☐ Yes ☐ No

Assessment for Infection:

Clinical:

Maternal intrapartum temperature ≥38.0°C (oral)? • Yes • No

Maternal tachycardia (>100 bpm) recorded? • Yes • No

Chorioamnionitis noted in medical chart ☐ Yes ☐ No

Urinary tract infection ☐ Yes ☐ No

Uterine tenderness (unexpected) ☐ Yes ☐ No

Offensive/ purulent vaginal discharge • Yes • No

Other UGT abnormality_____ • Yes • No

Evidence of fetal distress ☐ Yes ☐ No

If yes, Specify (tick all that apply):

Meconium stained amniotic fluid (MSAF)? • Yes • No

Abnormal cardiotocograph? (CTG/NST) • Yes • No

Fetal distress unclassified • Yes • No

Other _____ • Yes • No

Has the participant received any antibiotics during the last 7 days?

[_] Yes [_] No

Did the participant receive any intrapartum antibiotics during this admission for delivery?

[_] Yes [_] No

Mode of delivery:

Vaginal delivery Yes No

If yes, complete

Normal cephalic Yes No

Forceps/ vacuum assisted Yes No

Caesarean section Yes No

If yes, complete

Emergency caesarean section Yes No

If yes, indication for caesarean section:……

Elective Caesarean Section Yes No

Gestational age Term (≥37 weeks) Preterm [___][___]weeks

If preterm, Ballard score [___][___] Not available

Gender: Male Female

Date of birth: [___][___] / [___][___] / 201[___]

Time of birth: [___][___] h [___][___]

Birth weight: [___][___][___][___] grams Not available

Apgar score:

1 min [___][___] Not done/unknown

5 min [___][___] Not done/unknown

Maternal outcome:

Discharged home after routine postnatal observations [] Yes [] No

Admitted to wards for complications [] Yes [] No

Reason for admission……

Chorioamnionitis? [] Yes [] No

Endometritis? [] Yes [] No

Died [] Yes [] No

Cause of death……..

_____Infant Outcome:

Did newborn require resuscitation immediately post-delivery? [] Yes [] No

Supplemental oxygen [] Yes [] No

Continuous positive airway pressure [] Yes [] No

Bag/mask ventilation [] Yes [] No

Endotracheal intubation [] Yes [] No

Chest compressions [] Yes [] No

Intravenous fluids [] Yes [] No

Epinephrine [] Yes [] No

Bicarbonate [] Yes [] No

Use of Narcan [] Yes [] No

Suctioning for meconium [] Yes [] No

Chest X-ray done [] Yes [] No

Outcome:

Discharged home with mother [] Yes [] No

Discharged home to family (mother still admitted/died) [] Yes [] No

Admitted to neonatal ward [] Yes [] No

Reason for admission: ……..

MAS [] Yes [] No

TTTN [] Yes [] No

Respiratory distress [] Yes [] No

Died after delivery [] Yes [] No

Cause of death: ……

3.2 ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Relebogile Sekele

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M171033

NAME: (Principal Investigator)	Dr Relebogile Sekele
DEPARTMENT:	Obstetrics and Gynaecology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Meconium Stained Amniotic Fluid and Its Effects on the Early Maternal and Neonatal Outcomes
DATE CONSIDERED:	27/10/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Yasmin Adam and Dr Clare Cutland
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/10/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in October and will therefore be due in the month of October each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

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