Amnioinfusion for Meconium Stained Liquor at Chris Hani Baragwanath Hospital

A secondary analysis of local data from an international multicentre randomized trial

MMed Research Report

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DECLARATION

I, Etienne Nguekeng, declare here that the research report presented here is my own work.

It is submitted for the degree of Master of Medicine in Obstetrics and Gynaecology at the University of the Witwatersrand, Johannesburg.

It has not been previously submitted for degree or examination at this or any other educational institution.

Etienne Nguekeng.....

.....day of 2021

DEDICATION

I dedicate this research report to my late wife Leopoldine Nguekeng who passed on without seeing me complete the work. She gave me so much love, support and encouragement while I was undertaking this research project.

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I thank the following persons for making this research report possible:

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My family, for their support and for the sacrifices they have made to allow me to work towards my specialisation in Obstetrics and Gynaecology in South Africa.

ABSTRACT

Background

Passage of meconium-stained amniotic fluid (MSAF) during labour is associated, not only with fetal hypoxia, but with subsequent meconium aspiration syndrome. Amnioinfusion has been proposed as an effective treatment for reducing the risk of fetal or neonatal meconium aspiration, by diluting and washing out the meconium from the amniotic fluid in the uterus during labour.

Objective

This study was done to determine the effect of amnioinfusion on mode of delivery, meconium aspiration syndrome, and neonatal outcome at Chris Hani Baragwanath Hospital.

Methods

This was a secondary analysis of data collected at Chris Hani Baragwanath Hospital, as part of a large international Canada-based multicentre randomized controlled trial of amnioinfusion versus standard management (without amnioinfusion) in labours associated with passage of MSAF. The secondary data set of all women randomized at Chris Hani Baragwanath Hospital was analysed, comparing women who received amnioinfusion with those who received standard management. Chi-squared tests, and Fisher's exact tests where applicable, were used to make statistical comparisons.

Results

Data were available for analysis in 496 women. Standard management was done in 241 women, and amnioinfusion in 255. There were no statistically significant differences in caesarean section rate (38.0% v. 40.2% respectively; P= 0.61) or caesarean section rate for fetal distress (6.7%v.7.9%; P=0.60). There were no statistically significant differences in proportion of five-minute Apgar scores less than 7 (1.2% v.1.2%; P=1.0), neonatal admission (1.2% v. 1.6%; P=0.72), and neonatal ventilation (0.4% v 0.8%; P= 0.62). There was one neonatal death, from the amnioinfusion group. The neonatology care professionals

were unable to diagnose meconium aspiration with confidence in all cases and some neonatal ward data were missing, therefore results of this outcome were not available.

Conclusion

There were no significant differences in adverse outcomes between the amnioinfusion and standard treatment groups, although the sample size was not powered to determine statistically significant differences for uncommon outcomes such as meconium aspiration syndrome, neonatal ventilation and neonatal death. However, the incidence of adverse outcomes was low. There appeared to be no benefit for amnioinfusion in this secondary data analysis from Chris Hani Baragwanath Hospital.

LIST OF ABBREVIATIONS

AI:	Amnioinfusion
AAP:	American Academy of Pediatrics
CHBH:	Chris Hani Baragwanath Hospital
CRAMP:	Collaborative Randomised Amnioinfusion for Meconium Project
CTG:	Cardiotocography
HIV:	Human immunodeficiency virus
MAS:	Meconium aspiration syndrome
MSAF:	Meconium-stained amniotic fluid
PPHN:	Persistent pulmonary hypertension of the newborn

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1 INTRODUCTION AND LITERATURE REVIEW

The first intestinal discharge from a fetus or newborn is meconium, the fetal equivalent of faeces. If meconium is passed in the uterus, this may indicate a physiological or pathological process in pregnancy and labour. The greatest concern with the meconium staining of the amniotic fluid (MSAF) is the development of subsequent meconium aspiration syndrome (MAS) in the newborn.

1.1 Epidemiology

Intrauterine passage of meconium by the fetus, with the finding of MSAF at birth complicates about up to about 20% of all pregnancies worldwide, and the frequency is higher in women of African and South Asian descent (1). The frequency increases as gestational age advances, at 3%, 13% and 18% at 37,40 and more than 42 weeks respectively (2). In South Africa the frequency has been reported to be as high as 25% (3). While there has been a welcome decline in the incidence of MAS in developed countries, the condition remains a source of significant neonatal morbidity in low and middle income countries with limited resources for supervised birth and fetal monitoring. MAS reportedly complicates 1.7-35.8% of births associated with MSAF (2).

1.2 Modern understanding of meconium aspiration syndrome

1.2.1 Formation and composition of meconium

Meconium forms by 16 weeks of intrauterine life and is a thick, dark brown or green, but sterile and non-offensive component of the fetal intestinal lumen. It is composed of water, mucus, hair, bile and other solid elements such as shed fetal squamous cells (4). With ongoing gestation, the amount of meconium in the intestinal tract increases. The normal newborn usually passes the first meconium ‘stool’ within 24-48 hours after birth, but meconium passage in utero resulting in MSAF is not infrequent and may occur in the absence of any pathophysiological disorder (5). Typically, where a cause can be identified, intrauterine passage of meconium will occur where gestational age is advanced, or where there has been some degree of fetal hypoxic stress (6).

1.2.2 How and why meconium is passed into the amniotic cavity

Passage of meconium into the amniotic cavity occurs commonly in the third trimester of pregnancy (1). Then, with development of fetal anal sphincter competence, external passage of intestinal contents reduces by 16 weeks of gestation, becoming most unusual between 20 and 34 weeks (1), and even infrequent up to term or post-term gestation (1). Passage of meconium in utero results directly from neural stimulation of the gastrointestinal tract or from fetal hypoxic stress (7). As term approaches, the gastrointestinal tract matures and the amount of meconium in the intestinal canal increases(8). Fetal head or cord compression, or hypoxia (resulting from maternal factors, placental dysfunction or intrapartum events), causes vagal nerve stimulation to induce bowel peristalsis and relaxation of the anal sphincter. This may lead to passage of meconium into the amniotic fluid and the finding of MSAF after the membranes rupture (9). Risk factors for meconium passage in utero include pre-eclampsia, oligohydramnios, post-term pregnancy and maternal substance abuse, such as cocaine or tobacco (10).

1.2.3 Effects on the fetus and meconium aspiration syndrome

Passage of a large amount of meconium may result in serotonin-induced vasoconstriction and necrosis of the umbilical vessels and the formation of thrombi, possibly resulting in fetal hypoxia. The frequency and clinical relevance of these effects however remains unclear (11). More typically, meconium in amniotic fluid can be aspirated in utero into the lungs during fetal gasping, but especially at or just after birth, when the infant takes its first breath through an upper airway loaded with thick MSAF (1). As the fetus makes breathing movements, the net flow of lung fluid is away from the lungs and into the trachea and upper airway. However, work in animal studies has shown that prolonged hypoxia, itself a possible cause of meconium passage, stimulates fetal gasping efforts, which may then lead to inhalation of amniotic fluid(1).Many centuries ago, Aristotle noted an association between MSAF and a sleepy fetal state or neonatal depression(12). MSAF still causes considerable concern to obstetricians, raising intrapartum risks and influencing clinical care decisions(13). Threats to neonatal well-being are related not only to underlying fetal hypoxia, but to postnatal MAS. This is a serious condition caused by irritation of the bronchial tree and alveoli by bile acids contained in meconium. In infants in whom MAS develops, there

is a small but not insignificant mortality risk, depending on severity of aspiration and resources available for care, amounting to an appreciable proportion of all perinatal deaths (14). The pathophysiology of MAS is discussed in more detail later.

Newborns that develop MAS frequently show classic stigmata of the postmaturity syndrome, such as long fingernails, skin peeling, subcutaneous wasting and a reduced amount of vernix. With increasing duration of exposure to intra-amniotic meconium, greater degrees of meconium staining of skin, nails and vernix are observed. Nails show staining (that cannot be washed off) after about 6 hours, and vernix after about 12 hours. About one-fifth to one-third of affected infants exhibit neurologic or respiratory depression at birth. MAS presents shortly after birth with cyanosis, expiratory grunting, nasal flaring, intercostal retraction, tachypnoea, barrel chest(resulting from trapping of air in the lungs), and clinical signs on auscultation of the chest; on chest radiographs, characteristic abnormalities are seen (2).

1.2.4 Pathophysiology of meconium aspiration syndrome.

MAS manifests primarily in the neonatal lungs, through three major pathways: 1) airway obstruction; 2) failure of surfactant activity; and 3) chemical pneumonitis. Airway obstruction by meconium plugs may be complete or partial, with consequent atelectasis or hyperdistention of alveoli (15). The latter may result in a ball-valve obstruction, leading to rupture of alveoli. Direct mechanical complications include pneumothorax, pneumomediastinum and pneumopericardium. The function of surfactant may fail because fatty acids (palmitic, stearic and oleic acid), which are normal constituents of meconium, inhibit the essential surface tension reducing properties of alveolar surfactant, resulting in widespread atelectasis. In addition, enzymes, bile salts and fats contained in meconium may induce a chemical pneumonitis, with diffuse inflammation of the lower airways and lung parenchyma. In severe cases, all of these adverse effects produce a signficant ventilation-to-perfusion mismatch (1,16). While the severity of lung damage usually correlates with the quantity of meconium aspirated into the lungs, it may also determined by the degree of fetal hypoxia and acidosis during labour (17). MAS and neonatal hypoxic-ischaemic encephalopathy frequently co-exist, and may be further complicated by multiple organ dysfunction or

failure. A secondary phenomenon in MAS is pulmonary hypertension, affecting 15 to 20% of affected newborns, resulting in persistent pulmonary hypertension of the newborn (PPHN) (18). Furthermore, meconium may adversely alter the natural antibacterial properties of amniotic fluid and thus potentially raise the risk of neonatal infection (19). Fetal skin irritation may also occur, and may present as erythema toxicum in the newborn.

1.2.5 Diagnosis

A clinical diagnosis of MAS relies on the finding of respiratory distress in a neonate born in the presence of MSAF, in the absence of any other explanation for the respiratory distress. The diagnostic criteria for MAS remain unclear, despite extensive research and literature, thus challenging the accuracy of diagnoses made. MAS is just one of many causes of neonatal respiratory distress. The differential diagnosis, irrespective of the presence of MSAF at birth, includes also congenital heart disease with pulmonary hypertension, congenital diaphragmatic hernia, idiopathic pulmonary artery hypertension, congenital pneumonia, neonatal sepsis, PPHN, surfactant deficiency, transient tachypnoea of the newborn and transposition of the great arteries. These conditions need to be ruled out while considering the diagnosis of MAS(20). The chest X-ray is the most important modality for confirming a diagnosis. The classical radiographic findings are over-distension of the lung with an underlying coarse patchy infiltrate. Yet, this imaging pattern often correlates poorly with the clinical presentation and severity of disease. Fetal blood gas measurements, while not specific for MAS, are important for assessing severity and need for specific therapies. The severity of the MAS appears less dependent on the amount of meconium obstruction and parenchymal damage than on the development of PPHN. The dilution of meconium does not make it less damaging in the lung tissue, with the imperative in such cases being better oxygenation of the lung rather than more washing or dilution of the meconium in the amniotic fluid (21,22).

1.3.Prevention of meconium aspiration

Preventing meconium aspiration should prevent MAS, and is based on early identification of risk factors for intrauterine meconium passage and appropriate management of MSAF as soon as it appears (23).

1.3.1. Antepartum period

Intrauterine meconium passage is more frequent with advanced, and especially post-term, gestation. Accordingly, the prevention of post-term pregnancy may reduce the risk of MSAF and consequent meconium aspiration and its complications. Cochrane systematic review evidence indicates that the risk MAS and its complications can be reduced by elective induction of labour before 41 weeks of gestation (24).

1.3.2 Intrapartum period, other than amnioinfusion

In theory, routine amniotomy early in labour should increase clinicians' ability to detect MSAF and to take appropriate action, but trials of early amniotomy versus leaving membranes intact have shown no reduction in incidence of subsequent MAS (25). Fetal heart rate monitoring and frequent observation of the amniotic fluid passing from the vagina also offer potential opportunities to prevent MAS, but these approaches have also not been proven to prevent MAS or to decrease MAS morbidity or mortality rates(25). In the 1990s, amnioinfusion (also known for managing other problems such as oligohydramnios and variable decelerations) emerged as an attractive and relatively simple method to reduce meconium aspiration. This is discussed in detail below.

1.3.3 Intrapartum amnioinfusion

Amnioinfusion (AI) is a technique where a thin, sterile, flexible plastic catheter is passed transvaginally into the uterus through the cervix. A saline solution is then run through the catheter into the uterine cavity. This may be done before or during labour. During labour, AI has been used most commonly in cases of MSAF and for variable fetal heart decelerations (26). Once an initial bolus of saline has been infused, a slow infusion is maintained to flow into the uterine cavity to replace some of the fluid that has drained, to effectively reduce the concentration of meconium in the amniotic fluid, if not to wash it out of the amniotic cavity completely. The theory then is that AI should prove effective in diluting the

meconium content in the amniotic fluid, thus mitigating against MAS and its complications. Given the relative ease of administration of the infusion, the method attracted considerable interest.

The early trials on AI were small studies that suggested that use of the technique was associated with fewer operative deliveries, less risk of fetal distress in labour and less MAS (27). In 1989, Sadovsky et al published a preliminary report on a randomized trail which suggested a significant protective effect of AI against MAS (28). These findings were supported in a randomised controlled trial done by Cialone et al, published in 1994(29), but the southern African studies CRAMP-1 and CRAMP-2 done in South Africa and in Zimbabwe made inconclusive findings with respect to MAS following AI (30,31). These two trials were performed in resource-constrained clinical environments with limited access to cardiotocography (CTG) monitoring and sophisticated neonatal care.

While complications occurring with AI are rare, the procedure may carry some risk. Complications that have been reported include endometritis, uterine overdistension, prolapse of the umbilical cord, and fetal heart rate abnormalities requiring stopping of infusion or delivery (32). Amniotic fluid embolism (a potentially fatal condition for the mother) has so far only been reported in five cases among the hundreds of thousands of women who have had AI (33,34). It is nevertheless still not possible to state with certainty that AI is not a cause of amniotic fluid embolism.

In 2000, Pierce et al published a systematic review and meta-analysis of trials on intrapartum AI for MSAF, with the conclusion that AI significantly improved neonatal outcome, lowered the caesarean section rate and showed no effect on the risk for postpartum endometritis (35). Hofmeyr et al, in a Cochrane systematic review, showed that AI done in cases of MSAF was associated with improved perinatal outcome, especially where there were resource constraints for intrapartum fetal surveillance (36). The authors however noted that the combined sample size of the trials was too small for robust estimation of the effects on rare but important outcomes, such as reduction of severe MAS or perinatal death, as well as rare but serious adverse effects of AI. Significant knowledge gaps remained, which

could only be filled by performing a large international multicentre randomised controlled trial. This trial was eventually undertaken and its results were published in 2005 by Fraser et al (7). This is the largest single randomised trial ever done on AI for MSAF. The trial was based in Canada and recruited about 2000 participants in 13 countries. These were women at 36 weeks or more of gestation, in labour, who were passing MSAF. One of the centres involved was Chris Hani Baragwanath Hospital (CHBH) in Soweto, Johannesburg, and the results from this hospital will be presented in this research report. The women worldwide were randomly allocated to AI or to the current care at their institution (care excluding AI). The main finding of the trial was that AI failed to reduce the risk of MAS or perinatal mortality, or any maternal adverse indicator. MAS or infant death occurred in 44 infants (including 5 deaths) from the AI group while MAS or infant death occurred in 35 infants (also including 5 deaths) in the non-AI group. This contradicted the results of the previous trials and meta-analyses. The trial results therefore challenged previously accepted conclusions about the efficacy of AI, and forced clinicians to reconsider the guidelines that had been developed in response to the results of earlier trials supporting efficacy of AI.

The authors of the multicentre trial explained their results with the contention that that AI does not work to prevent MAS because meconium aspiration has likely already occurred before the intervention. They concluded that AI could not be recommended as treatment of MSAF. The authors stated their belief that AI was an intervention that had never been rigorously evaluated, and that given the trial results, the clinical focus in MSAF should be on preventing intrapartum fetal hypoxia. They recommended, for example, that babies be delivered before they are likely to pass meconium (<42 weeks of gestation).
A further meta-analysis, published by Xu et al in 2007(37), included results of the Canada-based multicentre trial. The authors acknowledged that AI appeared to be of little value, except possibly in areas where there is limited intrapartum fetal surveillance. It was recommended that further trials on AI be done in such environments.

Another Cochrane systematic review and meta-analysis was performed by Hofmeyr et al (17) in 2010, and reported on 13 studies with 4143 patients, divided into clinical settings where there were limited

facilities, and clinical settings where modern peripartum surveillance was available. The authors found that in clinical settings with sufficient fetal intrapartum surveillance, for AI: 1) no significant decreases in primary outcomes (MAS, other severe perinatal morbidity, perinatal mortality or maternal morbidity); 2) a decrease in caesarean section rate for the indication of fetal distress; 3) a reduced finding of meconium distal to the newborn vocal cords; and 4) a reduced need for neonatal ventilation and neonatal unit admission. Then, in settings with limited intrapartum surveillance, the authors found, for AI: 1) a reduced caesarean section rate; and 2) a reduced requirement for neonatal admission and neonatal ventilation. The authors concluded that AI was associated with measurable improvement in newborn outcomes, but this benefit was restricted to settings with limited facilities for intrapartum surveillance. They concluded that AI was ineffective in settings with available peripartum surveillance, or that the benefits of AI in those settings were masked by other strategies to optimise neonatal outcomes.

1.3.4 Intrapartumsuctioning

Pharyngeal suctioning done routinely before delivery in cases of MSAF, using a De Lee catheter, was first described by Carson et al (38). This was for a long time the recommended standard at birth accompanied by MSAF (4-7). Such suctioning needs to be done as soon as the newborn's face becomes accessible after crowning and extension of the head, before delivery of the trunk and before the first breath has been taken(15). Unfortunately, even when these methods are used appropriately, MAS may still occur (16). A randomized controlled trial performed in Argentina cast doubt on the value of intrapartum suctioning, finding that it did not prevent MAS (39). Routine intrapartum suction for MSAF has now been largely abandoned.

1.3.5 Postpartum suctioning

The American Academy of Pediatrics recommends endotracheal suctioning with a meconium aspirator under direct vision with a laryngoscope for the non-vigorous infant, and non-suctioning for the vigorous infant (40.41). And with regard to AI, Garcia-Prats et al state that suctioning versus non-suctioning of the non-vigorous infant confers no benefits in both AI and non-AI groups of infants after delivery (1). There

is insufficient evidence to support that routine endotracheal suctioning is beneficial in these circumstances, thus justifying the thinking that infants need more oxygenation and not less meconium. Routine suctioning for all cases of MSAF in order to prevent harm in fact delays the establishment of sustained ventilation, and carries all the complications of endotracheal intubation. New borns in good condition at birth who are born in the presence of MSAF, that have undergone suctioning, do not have any benefits as compared to vigorous infants that did not have suctioning. These formerly vigorous infants are at risk of developing transient bradycardia, stridor and laryngospasm (26,42).The evidence shows that tracheal suctioning is not superior to routine resuscitation in vigorous term infants and that it may itself result in complications (40,41).

Specifically, the Neonatal Resuscitation Program recommends that intubation and endotracheal suctioning should be done after birth only for infants that are not vigorous, meaning those with depressed respirations, hypotonia or with bradycardia (below 100 beats per minute).

1.3.6 Management of meconium aspiration syndrome

Detailed discussion falls out of the scope of this research report, and has been reviewed by Vain et al. (23). Only a brief summary is given here. The care of patients with MAS is supportive for lung and cardiovascular function, with no definitive therapy demonstrated as yet. Meconium inactivates surfactant function, displacing surfactant from the alveolar surface. Infants born after having had MSAF and presenting with evidence of respiratory distress should be referred and admitted for special neonatal care and, if necessary, to an intensive care unit, to be provided with respiratory supportive therapy. Therapies effective in managing MAS include artificial ventilation, surfactant, steroids, antibiotics, nitric oxide and opioids. Other causes of respiratory distress must be considered. Close monitoring of temperature, oxygenation, pH, blood glucose, perfusion and blood pressure is necessary. A multidisciplinary approach should include, where possible, care from a paediatric cardiologist and neurologist, as well as a dietician given the difficulties of feeding associated with MAS.

2 BACKGROUNDFOR THIS RESEARCH

2.1 Motivation

There remains uncertainty about the potential role of AI in settings with limited capacity for peripartum surveillance, specifically fetal heart rate monitoring. The multicentre trial published by Fraser et al (7) included a large number of women randomized at CHBH. The trial data from CHBH have not yet been analysed separately nor published, and may provide different results from those of the trial as whole. There are several reasons why the results may differ. The ratio of midwives to parturient women was at the time of trial (and still is) inadequate, limiting clinical surveillance of patients during labour (personal communication, Prof E Buchmann) and thus differing from the other trial sites. Intermittent auscultation of the fetal heart rate by midwives has been a logistical challenge, and CTG for fetal monitoring was in short supply at the turn of the millennium. An example of a problem encountered is that oxytocin administration is not sufficiently supervised, sometimes leading to unnecessary caesarean sections being performed for poor progress in labour. CHBH is an environment with limited peripartum surveillance and may, as such, provide useful data and trends to assist with compilation of clinical guidelines for such settings.

Another local factor that may modify outcomes related to intrapartum meconium passage is the reported taking of African traditional medicines, for example *isihlambezo*, by pregnant women close to term. This has been associated with meconium passage by the fetus during labour(43). It is not known if the local use of traditional medicine differs from areas where previous research on AI was done, such as in the CRAMP-1 and CRAMP-2 studies.

It was therefore considered appropriate to perform a secondary analysis of CHBH data from the Canada-based multicentre Amnioinfusion for Meconium trial. The purpose was to determine if local data from the secondary analysis differed from the results of the large trial.

3 AIM AND OBJECTIVES

The objectives of this study were to determine the clinical effects of AI done for MSAF in women at CHBH as part of the international multicentre trial published in 2005 (7), specifically on:

- Mode of delivery
- Five-minute Apgar score
- Admission to the neonatal care unit
- Need for neonatal ventilation
- Incidence of MAS
- Neonatal death

4 METHODS

This was a secondary analysis of data collected at CHBH for the Canada-based international multicentre randomised single-blinded non-placebo controlled trial (7). At all sites worldwide, AI was compared with standard (non-AI) management for MSAF during labour.

4.1 Study population

Inclusion criteria were:

- Ruptured membranes with drainage of thick (particulate) MSAF
- Single live fetus with cephalic presentation
- Gestational age of 36 weeks or more
- Women in labour with cervical dilation of 2-7cm
- No indication for urgent delivery, for example, suspected fetal distress because of abnormal CTG or obvious cephalopelvic disproportion. (The presence of early or variable decelerations was not an exclusion criterion.)

Exclusion criteria were:

- Suspected major fetal abnormality
- Placenta praevia or vaginal bleeding
- Known or suspected seropositive for human immunodeficiency virus (HIV). At the time of the trial, HIV testing was not routine at CHBH. Subjects whose HIV status was unknown were not excluded from the trial
- Known or suspected active Hepatitis B or C infection
- Active genital herpes
- Polyhydramnios
- Previous uterine incision
- Inability to comprehend the consent form or refusal to participate in the trial.

4.2 Randomisation

A centralized randomisation service was based in Canada for all participating centres, including the one at CHBH. Using this service, participants were allocated randomly at a ratio of 1:1 to either AI or usual hospital care. Women were recruited and randomized at times when the researcher was present and available to randomize participants in the labour unit. A pre-randomization CTG was performed on all women recruited. One obstetrician, blinded to trial allocation, interpreted all CTG tracings, categorised in the 30 minutes before randomization as follows:

- Less than three variable decelerations (defined as a decrease in fetal heart rate ≤15 beats below the baseline for ≥15 seconds (for inclusion)
- Three or more variable decelerations as above with no other abnormalities for provisional exclusion
- Both of the above conditions were considered to be of insufficient severity to justify immediate clinical intervention
- Where there was significantly reduced fetal heart rate variability, with prolonged or late decelerations, this was deemed as sufficient reason for emergency intervention (intrauterine resuscitation with consideration for urgent delivery), therefore such participants were not eligible for randomization.

4.3 Amnioinfusion and clinical care

Participants that were allocated to AI underwent the procedure as soon as possible after randomization. The researcher introduced a sterile catheter 30 cm through the cervix and infused 800 mL of sterile saline at room temperature into the amniotic cavity from a 1 L infusion bag, without an infusion pump (by gravity). The infusion rate was regulated at about 20 mL per minute for about 40 minutes. Use of an additional litre of saline was allowed up to a total infusion of 1500 mL. The researcher assessed uterine pressure and tenderness every 15 minutes by clinical palpation, for signs of hyperstimulation or overdistension. Ultrasonography to assess amniotic fluid volume (polyhydramnios) was done if the uterus failed to relax between contractions. Both AI and usual care groups underwent CTG monitoring. There was no restriction on using oxytocin augmentation if this was clinically indicated, as long as the CTG tracing showed no evidence of evolving fetal hypoxia. At the time of delivery, the attendant

midwife or doctor performed careful oral and pharyngeal suctioning before the shoulder delivered, and this was repeated after delivery. Laryngoscopy and intubation with tracheal suction was only performed for infants with signs of respiratory depression and in need of ventilation as part of neonatal resuscitation, as determined by the clinicians on duty.

4.4 Outcome measures and data analysis

The primary outcomes of interest were:

- Mode of delivery
- Five-minute Apgar scores
- Admission to the neonatal unit
- Need for neonatal ventilation
- Moderate or severe MAS
- Neonatal death

MAS in this study was defined as respiratory distress in the first 60 minutes of life in the presence of MSAF. MAS categories were grouped as severe (requiring ventilation) or moderate (not requiring ventilation, but needing oxygen for at least 48 hours at oxygen saturation of 40% or more). A neonatal paediatrician, blinded to the trial allocation (AI or standard care), made the clinical assessment of severity and diagnoses of MAS, if applicable. Chest radiographs were used to assist in the diagnosis.

4.5 Participants at Chris Hani Baragwanath Hospital

The CHBH participants in the Canadian-based AI trial were recruited from April1999 to June 2000. The research Medical Officer (Dr E Nguekeng) performed randomization and data collection for all subjects recruited to the trial at this institution. This was a secondary analysis of data from the CHBH subgroup of recruited women. About 500 women were randomized at CHBH and this was the sample size for the secondary analysis. The study methods, as applied to this secondary analysis, are described below.

4.6 Secondary data sheet

A secondary data sheet was drawn up for this analysis, based on the information that was available to the researcher in the secondary data set (Appendix 2). The data sheet included, in addition to the above primary outcomes, the following:

Clinical and demographic variables:

- Maternal age
- Gestational age
- Maternal weight
- Maternal height
- Dilatation of the cervix at the time of randomization (duration of ruptured membrane was mentioned for prophylactic antibiotic therapy purpose)
- Presence of pregnancy-induced hypertension
- Time from randomization and AI to delivery in hours
- Induction of labour
- Augmentation of labour
- Birth weight

Obstetric and maternal adverse outcomes:

- Antepartum haemorrhage
- Cord prolapse
- Uterine hyperstimulation (≥ 6 contractions in 10 minutes)
- Amniotic fluid embolism
- Uterine rupture
- Coagulopathy
- Intensive care unit admission
- Maternal death

- Postpartum pyrexia ≥38 degrees Celsius
- Postpartum haemorrhage requiring blood transfusion

Neonatal adverse outcomes:

- Hypoglycaemia
- Seizures
- Birth trauma (fractures, or haematomas requiring surgery or blood transfusion)
- Peripheral nerve palsy

Data were analysed with Epi-Info software. Participants allocated to the AI group were compared with those receiving standard care. Summary measures used for categorical variables were frequencies and percentages, and for continuous variables, means ± standard deviations, and medians with ranges and interquartile ranges. For comparison of frequencies, Chi-squared or Fisher's exact tests were used. For comparison of frequency distributions, Students' t-test or non-parametric (Mann-Whitney) tests were used. Statistical significance was accepted at $p< 0.05$.

4.7 Chris Hani Baragwanath Hospital ethical considerations

Conduct of the Canada-based multicentre trial at CHBH was approved by the Human Research and Ethics Committee at the University of the Witwatersrand. Written informed consent was obtained from all participants. Permission to undertake this secondary analysis was granted by the same committee. The approval number was M081024 (Appendix 1).

4.8 Funding

Data capturing was conducted by the researcher and processed with the help of the supervisor. The researcher incurred all costs concerned with the study.

5 RESULTS

The results of 499 women were available for this secondary analysis, but three were excluded because their allocation to intervention or control groups had not been noted. Analysis was therefore done on 496 women, of whom 241 (48.6%) underwent AI.

Data were incomplete for most of the variables and this is shown in the tables with the totals given of the numbers with available data. The mean age of the women was 25.9 ± 6.0 years, and the mean gestational age at the time of birth was 39.3±1.5 weeks. Parity was recorded for only 194 women. Labour was induced in 25 of 490 women (5.7%). The median cervical dilatation at the time of randomization was 5 cm, with a range of 2-7cm. The AI and control groups were comparable at the time of randomization, except that there were significantly fewer labour inductions and women with pregnancy-induced hypertension in the AI group (Table 1).

Maternal outcomes did not differ significantly between AI and control groups (Table2). However, there was a trend to more cases of postpartum pyrexia (4 vs. 1; P=0.20) and postpartum haemorrhage (7 vs. 2; P=0.07) in the AI group. There were no instances of cord prolapse, antepartum haemorrhage, uterine hyperstimulation, amniotic fluid embolism, uterine rupture, peripartum hysterectomy, maternal coagulopathy, maternal admission to intensive care unit or maternal death in either of the groups.

Neonatal outcomes did not differ significantly between the AI and control groups (Table 3). Meconium aspiration was not accurately recorded by the neonatal unit staff. However, all seven admissions to the unit were for respiratory distress or ‘asphyxia’. There was one neonatal death, in the AI group. The details of the death were not available in the secondary data set. There were no newborns with recorded hypoglycaemia, seizures, birth trauma, or peripheral nerve palsy.

Table 1.Comparison of amnioinfusion and control groups in terms of obstetric variables at the time of randomization; n (%), mean±standard deviation, median (range).

	No Amnioinfusion	Amnioinfusion	P value
Mean age in years (n=496)	25.5±6.0	26.3±6.0	0.14
Mean weight in kg (n=481)	78.7±14.4	78.0±14.0	0.62
Mean height in cm (n=458)	157.7±7.3	158.2±6.7	0.44
Mean gestational age in weeks (n=488)	39.3±1.4	39.2±1.5	0.64
Induction of labour (n=490)	20 (7.9%)	8 (3.4%)	0.03
More than three variable decelerations (n=495)	79 (31.1%)	75 (31.1%)	1.0
Median cervical dilatation in cm (n=495)	5 (2-7)	5 (2-7)	0.18
Pregnancy-induced hypertension (n=485)	22 (8.8%)	10 (4.2%)	0.04

Table 2.Comparison of maternal outcomes between amnioinfusion and control groups; n (%).

	No Amnioinfusion	Amnioinfusion	P value
Interval to birth < 3 hours (n=487)	115 (45.6%)	108 (46.0%)	0.94
Oxytocin augmentation (n=486)	7 (2.8%)	3(1.3%)	0.34
Caesarean delivery (n=496)	97 (38.0%)	97 (40.2%)	0.61
Postpartum pyrexia (n=493)	1 (0.4%)	4 (1.7%)	0.20
Postpartum haemorrhage (n=491)	2 (0.8%)	7 (2.9%)	0.07

Table 3.Comparison of neonatal outcomes between amnioinfusion and control groups; n (%), mean±standard deviation.

	No Amnioinfusion	Amnioinfusion	P value
Mean birth weight in g (n=435)	3132±383	3119±422	0.74
Five-minutes Apgar score <7 (n=496)	3 (1.2%)	3 (1.2%)	1.0
Requirement for early intubation (n=485)	2 (0.8%)	4 (1.7%)	0.32
Neonatal admission (n=485)	3 (1.2%)	4 (1.6%)	0.72
Neonatal ventilation (n=486)	1 (0.4%)	2 (0.8%)	0.62
Neonatal death (n=487)	0 (0.0%)	1 (0.4%)	0.49

6 DISCUSSION

6.1 Interpretation of findings

This secondary analysis of data from the Canada-based multicentre trial found no evidence to suggest that AI affected the overall caesarean section rate or caesarean section rate for fetal distress. Compared with standard care, AI was not associated with any maternal adverse effects, although there was a non-significant trend to a higher frequency of postpartum pyrexia and haemorrhage. The mechanism of such complications is unclear, although it could be speculated that postpartum pyrexia was the result of instrumentation and subsequent ascending uterine infection. The affected women however suffered no severe morbidity.

The primary neonatal outcomes did not differ between the two groups. However, this secondary analysis was not sufficiently powered to detect significant differences in uncommon outcomes, such as MAS, neonatal ventilation and neonatal death. It is problematic, as was the case at CHBH, that the diagnosis of MAS is difficult to distinguish clinically from neonatal congenital pneumonia. However, MAS is uncommon, and the need for ventilation was rarely required, being used in only three newborns (0.6%).

The AI and standard treatment groups were not comparable with respect to induction of labour and the presence of pregnancy-induced hypertension, both of which were significantly more frequent in the control group. This should theoretically place the control group at increased risk for neonatal complications. Yet, this group did not suffer more complications, thus strengthening the case for stating that AI had no beneficial effects.

These results are in keeping with the amalgamated data from the Canada-based multicentre AI trial (7). Some of the major results of the trial are shown in Table 4. There is a trend to lower rates of poor neonatal outcomes in the CHBH secondary analysis. For example, only three newborns (0.6%) required ventilation compared with 3.0% in the larger trial. This is difficult to explain, although it can reasonably be suggested that the threshold for neonatal ventilation is higher at CHBH because of pressure on scarce

neonatal intensive care resources. However, it does appear that newborns at CHBH were generally in better condition at birth, with five-minute Apgar scores of less than 7 being recorded less frequently. The caesarean section rate at CHBH was also higher than in the trial overall, possibly because CHBH is a referral centre that excludes many normal births that happen in the surrounding primary care facilities. Even given the sample differences at CHBH, there is no evidence from this secondary analysis that AI is any more or less beneficial at CHBH than it is elsewhere. The frequencies of respiratory complications and MAS did not differ between the AI and control groups.

One area in which there is difficulty with applying the results of this secondary analysis to current intrapartum care practice at CHBH, is electronic fetal monitoring. The randomized trial protocol demanded, and obtained, continuous electronic monitoring in all participants. Unfortunately, the hospital cannot currently guarantee such monitoring in all labours at risk for fetal distress, for example, in those who have passed meconium during labour. Therefore, CHBH, out of the research setting, may fall into the category of facilities with limited intrapartum fetal surveillance, where, as has been discussed above, AI may be of value (30, 31).One of the problems with this would be that in such low-resource environments the cost of AI (equipment, skilled staff) is also a consideration. The conduct of any further trials, with cost-effectiveness outcomes, in such environments is therefore warranted. AI has costs, although these have not been calculated in environments such as CHBH. The costs are in skills, time and equipment. Given the failure of this secondary analysis or any of the meta-analyses to find significant benefits for the procedure in MSAF, it would be unwise to incur these additional costs currently. Another consideration in benefit and risk of AI is the high HIV seroprevalence at CHBH, until recently at about 30% (44). There are insufficient data to justify the use of AI in a high-prevalence HIV infection setting.

Table 4.Frequencies of key outcomes in the Canada-based multicentre amnioinfusion trial; n(%) (none statistically significantly different at P<0.05)(7).

	No Amnioinfusion (n=989)	Amnioinfusion(n=986)
Caesarean section	287 (29.0%)	314 (31.8%)
Five-minute Apgar score <7	29 (2.9%)	26 (2.6%)
Need for intubation at birth	19 (1.9%)	19 (1.9%)
Need for ventilation	29 (2.9%)	31 (3.1%)
Meconium aspiration syndrome	35 (3.5%)	44 (4.5%)
Neonatal death	5 (0.5%)	5 (0.5%)

6.2 Limitations

This secondary analysis was necessarily limited by a sample size deficiency, although the total of just under 500 participants would have been enough to detect differences in frequently recorded outcomes. The analysis also suffered from a lack of detail in the secondary data set. It was impossible to determine, for example, the cause of the one neonatal death, which occurred in the AI group. The difficulty with diagnosing MAS is unfortunate as this should be the ultimate indicator for the efficacy of AI.

Women who were HIV infected were excluded in this trial. The possible effects of the AI procedure on mother-to-child transmission are unknown, although it seems likely that AI would not increase the risk of intrapartum mother-to-child transmission in women whose viral loads are suppressed. Currently the maternal HIV seroprevalence rate at CHBH is close to 30%. Consideration of this factor would discourage the use of AI at CHBH; however, the introduction of antiretroviral therapy has significantly reduced the maternal mortality ratio and the risk of MTCT (44,45).

6.3 Conclusion

The results of this secondary analysis of CHBH findings on AI, as a subgroup of the multicentre randomized trial, concur with the overall trial results that there were no benefits in intervening with AI to prevent MAS. However, while CHBH is an institution with limited resources for surveillance, CTG monitoring was provided for all recruited participants and conclusions on these results with respect to limited peripartum surveillance cannot be made.

Given the lack of evidence for benefit of AI for MSAF, the costs involved, and the unanswered question of HIV infection and associated adverse effects, the use of the procedure cannot be currently justified at CHBH or at similar institutions in South Africa. The use of close intrapartum surveillance (continuous CTG, or at least frequent intermittent CTG) of fetuses that have passed meconium must be ensured to identify those with developing subacute hypoxia.

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APPENDIX 1. ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Nguekeng

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M081024**
PROJECT	Amnioinfusion for Meconium Stained Liquor at CH Baragwanath Hospital secondary Data analysis
INVESTIGATORS	Dr E Nguekeng
DEPARTMENT	Obstetrics & Gynaecology
DATE CONSIDERED	08.10.31
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08.11.03 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof EJ Buchmann

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 2. STUDY DATA SHEET

AMNIOINFUSION STUDY

Information sheet number:

MOTHER

Identification Number:

Case or control:

1) Baseline Characteristics

Age :

Weigh on admission:

High on admission:

Parity:

Gestational age:

Labour:

Dilatation on randomization:

Time from Amnioinfusion / Randomisation to delivery:

2) Delivery

Mode of delivery:

Indication for C/S

3) Complications

Fever in labour:

Fever after delivery:

Uterine rupture:

Amnioticfluid embolism:

Cord prolapsed

APH:

PPH:

DIC:

Pulmonary eodema:

ICU admission:

BABY

Birth weight:

Apgar 5:

Suctioning:

Intubations:

Admission:

Ventilation:

Death:

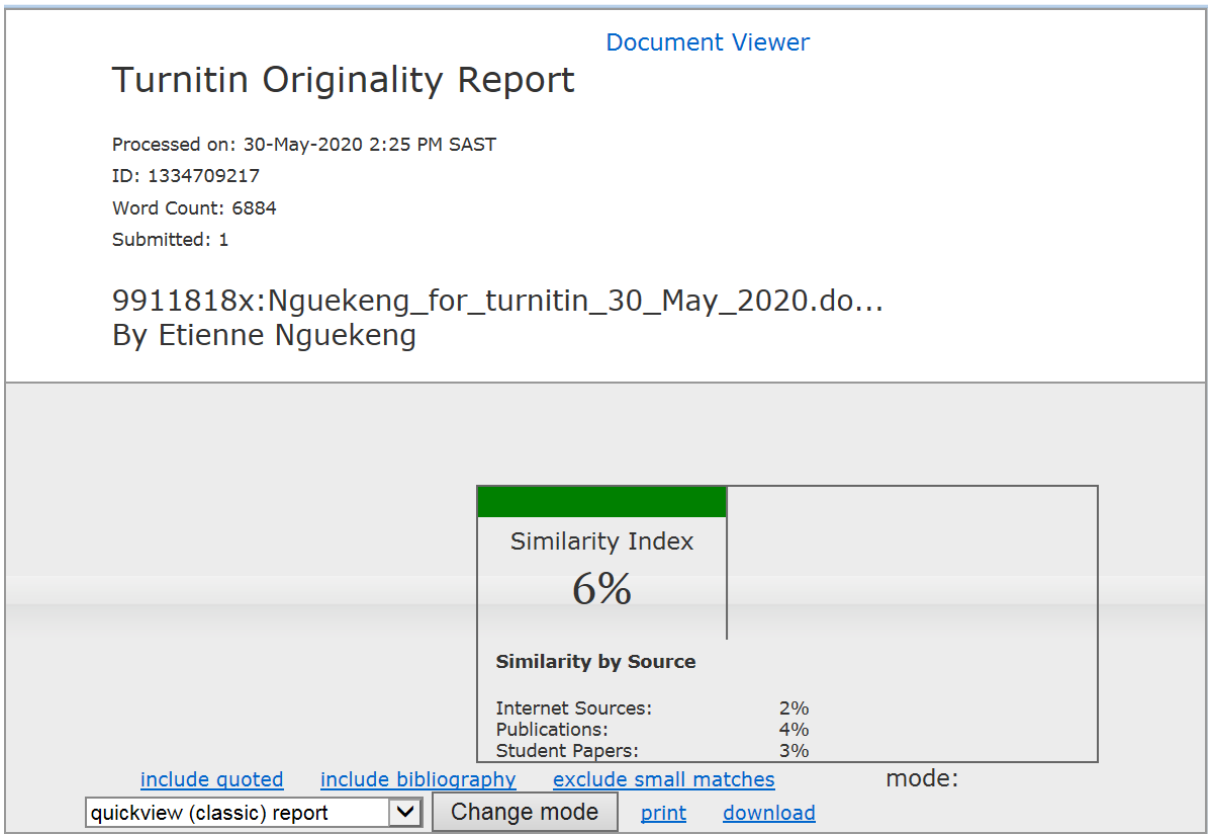
NB: O = (control group, spontaneous labour, non intubations, non admission, non ventilation, non death,non C/S delivery).

1 = (amnioinfusion group, induction of labour, intubations, admission, ventilation, death,[C/S delivery:1=FD,2=NP,3=other])

Completed hours to delivery:0-1h=0,1-2h=1,2-3h=2,>3h=3.

1

Appendix 3. Plagiarism report: Turnitin



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