CESEAREAN SECTION FOR INTRAPARTUM NON-REASSURING FETAL STATUS AND PREDICTION FOR NEONATAL ACIDEMIA AT BIRTH IN TIKUR ANBESA SPECIALIZED HOSPITAL, ETHIOPIA, 2021.

A PROSPECTIVE OBSERVATIONAL STUDY

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ACRONYM

AAU - Addis Ababa University

ACOG – American College of Obstetrics and Gynecology

BDec – Base Deficit of Extracellular Fluid

CI - Confidence Interval

CS – Cesarean Section

CSR – Cesarean Delivery rate

CTG – Cardiotocography

EDHS – Ethiopia Demographic and Health Survey

EFM – Electronic Fetal Monitoring

FHR – Fetal Heart Hate

FIGO - International Federation of Obstetrics and Gynecology

HIC – high income country

MCH – Maternal and Child Health

NICHD – National institute of Child Health and Human Development

NRFS – Non- reassuring Fetal Heart Rate Pattern

NRFS - Non- reassuring Fetal Status

PCO2 – Partial pressure of Carbon Dioxide

PO2 -Partial Pressure of Oxygen

RCOG – Royal College of Obstetrics and Gynecology

TASH – Tikur Anbesa Specialized Hospital

UCBGA – umbilical cord blood gas analysis

WHO - World Health Organization

ABSTRACT

Background: NRFS is leading indication for cesarean section. The risks of maternal morbidity and mortality associated with a caesarean section may not be reasonably justified by the degree of neonatal compromise at birth.

Objectives: This study was undertaken to evaluate prediction of clinical diagnosis of intrapartum NRFS for significant neonatal acidemia and short term adverse neonatal outcome.

Methods: Facility based prospective observation study where all the deliveries by cesarean section for NRFS over 2 months period were included. Fetal patterns prior to delivery were obtained from labor follow up chart and interpreted. The primary outcome was fetal acidemia (umbilical artery pH <7.20); short term neonatal morbidities were also assessed. Area under the receiver operating characteristic curves was used to assess the test characteristics of individual models for acidemia and neonatal morbidity. Population from historical cohort of similar study was used to calculate predictive ability of NRFS for fetal acidemia.

Results:

During this study period 228 deliveries occurred at the selected health facility and 98 women by cesarean section. From cesarean section 51% (50 of 98) were emergency and 56% (28 of 50) was done for NFS. Fetal bradycardia was the most common type of NRFS indicating emergency CS constituting 60% (15 of 25) of emergency CS.

The mean umbilical artery PH was 7.20±0.09 (SD) (range, 7.01-7.30). Incidence of acidemia was 32% (8 of 25), while pathologic acidemia (PH <7.10) account only for 20% (5 of 25). Although significant association was not found for all patterns of NRFS, fetal bradycardia seems non predictive for fetal acidemia with area under the curve of 0.41(OR 0.42, 95% CI (.075-2.36) P value 0.4) with PPV of 17.22%, while fetal tachycardia (AUC (.62), PPV 30.69) and MSAF (AUC (.68)) appears to have a fair prediction for fetal acidemia.

Conclusion:

None of NFS pattern had significant association with fetal acidemia and neonatal outcome. This may be due small sample size of this study and further study with large sample size is needed to establish existing association, if any.

1. INTRODUCTION

1.1. Background

Management of intrapartum non-reassuring fetal status by expediated cesarean delivery, common in obstetric practice, introduced into practice without randomized controlled trial. Some believe producing such evidence is unnecessary as non-reassuring fetal status is self-evident. To date all intrapartum fetal monitoring technique cited for poor positive predictive values for acidemia and harm may occur owing to unnecessary intervention. Intrapartum electronic fetal monitoring (EFM) introduced to market before consensus and its use leads to significantly greater rates of caesareans and operative vaginal deliveries in low risk patients without reducing perinatal mortality(1)(2). The occurrence of intrapartum significant fetal acidemia can be confirmed by a blood gas and acid-base assessment at delivery.

1.2. Statement of the Problem

Clinical diagnosis of intrapartum NRFS is not always correct and may result in unnecessary obstetric interventions to expedite the delivery of the fetus. There is no universally accepted method for diagnosis of NRFS and there is also inter and intra observer variation in interpreting of same finding(3). Appearance of an abnormal FHR tracing is not a reason to resort to prompt delivery; it is a reason to decide what may be causing the abnormalities, if fetal well-being can be ensured in the midst of non-reassuring patterns, and to attempt intrauterine resuscitation(4).

CS rates vary worldwide, ranging from approximately 10% in Sweden to about 80% in private-sector hospitals in Brazil(5). Overall cesarean delivery rate exceeded 32% in the United States in 2011, and exceeds 50% of all births in some US hospitals(6). While dystocia and prior cesarean delivery remain the leading indicators for such surgical intervention, the presence of a category II or III FHR in labor is a frequent indication as well(6). In one retrospective facility based study in Addis Ababa Ethiopia, overall CS rate was 38.7% (33.1% at TASH and 64.7% at the private MCH hospital) which higher than previous report(7).

Excessively high CSRs do not confer additional health gain and have raised concerns because of the important negative implications it has for health equity both within and across countries. The potential maternal and perinatal risks and costs associated with caesarean deliveries are

significant, especially where there was no medical indication. Evidence shows that caesarean delivery and maternal death are significantly and positively associated(8). A large population-based study from Canada found that the risk of severe maternal morbidities defined as hemorrhage that requires hysterectomy or transfusion, uterine rupture, anesthetic complications, shock, cardiac arrest, acute renal failure, assisted ventilation, venous thromboembolism, major infection, or in hospital wound disruption or hematoma—was increased threefold for cesarean delivery as compared with vaginal delivery (2.7% versus 0.9%, respectively)(9). Ill health related to poor socioeconomic and nutritional status is worsened by other co-morbidities(10).

So far most of the studies done on prediction of intrapartum fetal heart pattern for fetal asphyxia is in high income countries and uses CTG tracing pattern abnormality and neonatal adverse outcome and acidemia as an outcome. In LMIC countries such studies are limited to APGAR score and neonatal adverse outcome.

The purpose is to investigate the accuracy of clinical diagnosis of NRFS in setting where only base line fetal heartbeat abnormalities were used for diagnosis of NRFS using significant neonatal acidemia and short-term neonatal outcome as a measure.

1.3 Rationale of the Study

Rising CSRs demand evidence-based strategies safely to reduce unnecessary CS. Low positive predictive value of NRFS for adverse outcome, higher inter-observer variation of NRFS demand a safe mechanism to reduce CS. Umbilical cord blood gas and acid-base assessment are the most objective determinations of the fetal metabolic condition at the moment of birth. Determination of fetal UCBGA after cesarean section done for NRFS has got clinical importance to re-evaluate our clinical practice. So far, no study done to evaluate accuracy of clinical diagnosis of NRFS in this country using fetal acidemia. Only a few papers published in Africa. This is the first study done in this country and may help as an input for other large-scale studies on this topic.

2. LITERATURE REVIEW

2.1. Fetal Heart Rate Monitoring: an Evidence-free Zone

Historically, assessment of the FHR began with placing an ear on the pregnant woman's abdomen; progressed to use of the stethoscope, fetoscope, or handheld Doppler device for IA; and eventually transitioned to the use of EFM(11). There are two main modalities for FHR monitoring– Intermittent auscultation (IA) and continuous electronic monitoring using cardiotocography (CTG). Organizations and stakeholders like the World Health Organization, International Confederation of Midwives, and the International Federation of Gynecology and Obstetrics (FIGO) recommend that IA should be used to monitor uncomplicated (low-risk) pregnancies during labour and birth and for pregnancies in settings where no alternatives are available(12)(13).

There is no research to guide the optimal techniques for and timing of IA assessment of fetal heart activity, and most of the guideline recommendations were based on the techniques described in controlled trials that compared the effects of the Doppler vs. Pinard devices. Nor has any study assessed interpretations of intermittent auscultation finding, and few have assessed to what degree clinicians can describe FHR patterns detected by intermittent auscultation (14). Intermittent auscultation was successfully completed in only 3% of the cases. The most common reasons for unsuccessful intermittent auscultation included the frequency of recording and the requirements for recording(14).

Intrapartum cardiotocography (CTG) is besieged by controversies and myths, but will remain widely practiced(15). EFM was introduced into clinical practice before consensus was reached regarding standardized definitions of FHR patterns. This resulted in wide variations in the descriptions and interpretations of common FHR observations, and this lack of standardization was a major impediment to effective communication(3).

2.2. Physiology of Intrapartum Fetal Compromise (IFC) at Term

Unlike the adult, the fetus suppresses rather than increases respiratory drive during hypoxia, and this reaction is mediated by the brain and not by carotid chemoreceptor activation(16). Providing there is adequate time for placental and fetal reperfusion between contractions, these fetuses was able to withstand prolonged periods of intermittent hypoxia and avoid severe hypoxic injury(17).

Uterine contractions during term labor result in a rise in intrauterine pressure of up to 25 to 70 mm Hg,(18) compromising placental perfusion(19) and oxygenation(20). Although uterine contractions result in a decline in fetal PaO2 by approximately 25%,(21) the majority of appropriately grown, healthy, term fetuses are able to withstand the effects of this over a prolonged period of time. Indeed, normal fetuses can cope with a reduction in PaO2 of up to 50% (from a PaO2 above 20 mm Hg to as low as 10 -12 mm Hg) (22)(23) because of their high myocardial glycogen stores,(24)(25) the presence of vascular shunts, the increased oxygen affinity of fetal hemoglobin, and near-maximal basal cardiac output(25).

The cornerstone of the fetal defense against hypoxic injury lies in the peripheral chemoreflex, triggered in response to fetal hypoxia when uteroplacental perfusion declines by more than 50%.(26) (27)This has the sole aim of rapidly reducing oxygen consumption and centralizing blood flow to the critical organs needed for preservation of life and sensitive to hypoxic injury (the brain, heart, and adrenal glands).

Acute hypoxemia, detected by the carotid body chemoreceptors, stimulates the brain stem to increase both the parasympathetic and sympathetic outflow(27)(28). Parasympathetic tone predominates,(29) resulting in decrease in the FHB, prolonging end diastolic ventricular filling time, subsequently end diastolic volume. In addition, the reduction in FHR reduces myocardial oxygen consumption as well as allowing increased transit time of red cells through tissue beds (including the placenta), thereby permitting increased oxygen extraction from fetal hemoglobin and transplacental oxygen transfer to the fetal circulation. Increased sympathetic outflow induces profound peripheral vasoconstriction, resulting in hypertension and centralization of blood flow to critical organs as well as balancing the parasympathetic effects with a positive chronotropic effect, leading to a partial recovery in FHR(30)(31). Furthermore, peripheral vasoconstriction increases the descending aortic pressure, increasing right ventricular afterload that in turn encourages passage of blood from the right atrium, through the foramen ovale, into the left atrium and thereafter the left ventricle, (32) causing an increase in blood flow into the ascending aorta and cerebral and coronary circulations(33).

The initial neuronal triggered peripheral vasoconstriction is then maintained by humoral factors, including adrenal catecholamines, arginine vasopressin, cortisol, angiotensin II, and

neuropeptide Y, which prolong the redistribution of cardiac output, thus maintaining perfusion to critical organs(34)(35).

With uterine relaxation, there is rapid return of efficient placental gas exchange, restoring fetal PaO2 levels and removing lactate and carbon dioxide. In addition, the fetus is able to efficiently metabolize lactate (by oxidation and conversion to nonessential amino acids and lipids),(36) rapidly reversing the metabolic acidosis that occurs during the preceding contraction. These processes allow the autonomic fetal response to be reactivated during the next contraction, ensuring protection from the repeated hypoxic episodes that characterize labor(30).

It has now clear that fetal decompensation in labor occurs because of the infant's inability to respond to the peripheral chemoreflex to maintain cardiac output(30)(37). Intrapartum fetal compromise may occur when there is inadequate reperfusion time between contractions (eg, during uterine hyperstimulation) or when there is appropriate reperfusion time but suboptimal placental function to allow adequate oxygen transfer to the fetus(38)(39).

Women with pre-labor placental dysfunction are more likely to develop intrapartum fetal compromise. These fetuses are less likely to withstand intrapartum hypoxia due to lower glycogen stores before the onset of labor, limiting their ability to transition to anaerobic metabolism(40). As even short periods of hypoxia can quickly deplete cerebral and cardiac glycogen by up to 80%,(25) any limitation in placental transfer of nutrients and oxygen renders these fetuses vulnerable to intrapartum fetal compromise and injury. Progressive hypoxia in labor results in a further reduction of myocardial glycogen stores, impaired cardiac function, and, ultimately, profound systemic hypotension and irreversible multiorgan injury.

The magnitude of the hypoxic insult correlates with the fetal response. Siristatidis et al demonstrated that the "brain-sparing" response is only activated when fetal PaO2 falls below 37%(41). However, if the PaO2 falls below 30% for more than 2 minutes, this response fails altogether and significantly increases the risk of adverse perinatal outcomes(42).

2.3. Prediction and Association of NRFS with Acidemia

Acidemia at the time of birth is a risk factor for neonatal morbidity, including neurologic injury and mortality,(43)(44) and EFM promised to be a noninvasive tool to reduce adverse outcomes by identifying fetuses developing acidemia. Despite widespread adoption of the National

Institute of Child Health and Human Development (NICHD) category system, which EFM patterns predict acidemia remains unclear. Category II tracings, which are the most frequent seen in >80% of laboring women are quite variable in their significance and can include FHR patterns from the most benign to the most threatening(45). The variance in using NFHRP for indication of cesarean section may be directly related to the absence of defined management protocols for category II patterns.

During process of labor and vaginal delivery, with intermittent reductions in fetal oxygen delivery, results in the development of mild acidosis in almost all labors. Uncomplicated labour changes base excess by around 3 mmol/l overall(46). A normal second stage of labour changes it by around 1 mmol/l per hour(47). In contrast, base excess changes by around 1 mmol/l per 30 min during prolonged periods when there are repeated fetal heart rate decelerations.(48) The most profound fetal compromise, such as that associated with terminal bradycardia following acute uterine rupture, changes base excess by 1 mmol/l per 2–3 min.(46)

Original publications described the association between EFM patterns and fetal pH,(49)(50)(51) but not the ability of EFM to predict and prevent injury. A recent meta-analysis summarized the findings from 13 randomized controlled trials, comparing the ability of EFM to identify infants with acidemia and morbidity describe continuous CTG during labour is associated with reduced rates of neonatal seizures, but no clear differences in cerebral palsy, infant mortality, or other standard measures of neonatal wellbeing. However, continuous CTG was associated with an increase in caesarean sections and instrumental vaginal births(1). One recent prospective cohort study of 8580 women described Category I throughout the final 120 minutes was rare, occurring in 0.4% of patients, but all had a normal pH. The specificity of these EFM parameters for normal pH (always, mostly, and ever category I) were 64.4%, 57.7% and 65.8%, respectively. Moderate variability alone was not a significant independent factor to predict normal pH but presence of any acceleration in the 120 minutes prior to delivery was independently associated with a normal pH. Any 10-minute period of category III tracing was rare, but these women were significantly more likely to have infant acidemia at birth with sensitivity of 69.1% and specificity of 50.0%. The most predictive EFM feature was total deceleration area for acidemia and a combination of total deceleration area and any 10-minute period of baseline tachycardia for neonatal morbidity. predictive ability of specific patterns for acidemia and morbidity with the suggested NNT of

cesareans to prevent 1 case being 5 and 6, respectively.(52)

It is commonly accepted clinically that the deeper the decelerations the greater the likelihood of acidemia and/or depression but total deceleration area has the best predictive power for identifying newborn acidemia. A small study by Tranquilli et al, correlated the total deceleration area to umbilical artery pH values and found an umbilical artery pH of less than 7.1 following 25 minutes of FHR of 80 bpm, 13 minutes for an FHR of 70 bpm, 8 minutes for an FHR of 60 bpm, 6 minutes for an FHR of 50 bpm, and only 5 minutes for an FHR of 40 bpm. The positive predictive value was 78.5% and the negative predictive value was 68.4%(53).

In presence sentinel event such as uterine rupture, placental abruption, cord prolapse, shoulder dystocia, maternal hypotension, amniotic fluid embolism, vasa previa, and other causes sudden bradycardia may occur. In general, if the FHR remains above 80 bpm, variability was retained and both coronary and cerebral oxygenation was preserved(54). In contrast, when the FHR falls below 80 bpm, the variability will diminish rapidly as a metabolic acidemia accumulates. In this scenario, the fetus rapidly becomes unable to maintain circulation.

2.4. Respiratory and Metabolic Acidosis

Normal fetal metabolism results in the production of acids that are buffered to maintain extracellular pH within a critical range. The major buffers utilized by the fetus for neutralizing hydrogen ion production are plasma bicarbonate and hemoglobin(55). The fetus produces carbonic acid (H_2CO_3) during aerobic glycolysis. H_2CO_3 dissociates to water and CO_2, which readily diffuses across the placenta. Retention of CO_2 (hypercarbia) leads to respiratory acidemia (low pH with high PCO_2 and normal bicarbonate concentration).

When adequate fetal oxygenation does not occur, metabolism proceeds along an anaerobic pathway with production of organic acids, such as lactic acid and ketoacids. In contrast to carbonic acid, organic acids are not readily excreted or metabolized and are cleared very slowly across the placenta; therefore, they accumulate in the fetus. Mixed acidemia (low pH with low bicarbonate concentration and high PCO_2) or metabolic acidemia (low pH with normal PCO_2 and low bicarbonate concentration) develops when accumulation of organic acids depletes the buffer system to critically low levels of buffers.

As pH represents the inverse logarithm of the hydrogen ion concentration, it does not change linearly with hydrogen ion concentration. During periods of reduced organ oxygen delivery, cellular responses to hypoxia and ischemia result in the accumulation of lactic acid in proportion to the degree and duration of the hypoxic stress; but pH, being an exponential function and affected by changes in carbon dioxide and lactate, has limited use for quantitating the degree of accumulated metabolic acidosis and tissue ischemia. In contrast, base deficit, a calculated value derived from the measured values of pH and Pco2 in blood, does have a linear relationship to the accumulation of lactic acid and, thus, also correlates with the risk of newborn neurologic injury, especially when it becomes severe (base deficit greater than 12 mmol/L)(56). An umbilical artery base deficit ≥12 mmol/L, which is >2 standard deviations above the mean(57), is commonly accepted as a reasonable threshold for predicting an increased risk of moderate or severe newborn complications(46)(58)(59). A base deficit of 12 to 16 mmol/L is associated with an increase in infant mortality, moderate to severe neonatal encephalopathy, multiorgan failure, and long-term neurologic dysfunction(60)(61).

Because lactic acid (lactate) is the product of anaerobic metabolism and, in contrast to base deficit, is a measured product and not an estimate, it therefore, might provide improved precision in prediction of neonatal outcome. However, large studies of umbilical cord blood lactate levels are few and the variation in mean values surprisingly large, ranging from 2.55 mmol/L to 4.63 mmol/L(62). The large variation in mean values may be because of the differences in calibration in blood gas meters. Therefore, the use of cord blood lactic acid as an index of fetal metabolic status is less well defined than the base deficit.

2.5. Fetal Acidosis and Adverse Events for Infants

Perinatal asphyxia is a major cause of neonatal and childhood morbidity and mortality and has been associated with neonatal death(63); hypoxic ischaemic encephalopathy and seizures; intraventricular haemorrhage(64); cerebral palsy; and delayed development. Perinatal asphyxia is predicated by fetal acidosis, determined by umbilical cord pH at birth(65).

Various methods have been devised for evaluation of a newborn's condition, of which a commonly used method is Apgar scoring. However, this is not appropriate for evaluation of birth asphyxia as it may be influenced by a variety of factors including, but not limited to, fetal maturity or malformations, maternal medications and infection or another fetal status(62)(66).

Similar to in utero cord compression-induced bradycardia, umbilical cord clamping at birth induces a marked bradycardic response. Thus, newborn heart rate is often low and sometimes undetectable, despite a normal FHR just before delivery(56). The neonatal acid-base state mainly evaluates the fetal condition during labor, whereas the Apgar score evaluates fetal well-being in pregnancy and in labor. Umbilical cord blood is the most objective method(67).

The fetal brain is particularly sensitive to hypoxic injury and oxidative stress due to its high rate of oxygen consumption, lack of glucose stores, high lipid content (rendering neurons susceptible to lipid peroxidation),(68)(69) and relatively low concentrations and activity of antioxidant enzymes.(70). The mechanisms of hypoxic cerebral damage are complex and not entirely mediated by the initial hypoxic insult but are compounded by injuries occurring during the reperfusion phase (71) due to toxicity from reactive oxygen species and excessive stimulation of N-methyl-D aspartate-type glutamate receptors(72),(73). Indeed, the severity of the secondary injury occurring during the reperfusion phase correlates best with the severity of neurodevelopmental disability at ages 1 and 4 years(74). There is a strong association between hypotension and hypoxia with fetal injury, particularly neuronal damage and fetal death(75). During hypoxia, blood flow to the cerebral hemispheres is reduced, whereas perfusion to the basal ganglia, thalamus, and brainstem is increased(76). Animal studies suggest that, even if the total duration of hypoxia is the same, repeated severe episodes cause greater neurologic injury than a single severe prolonged event(77). In addition, the pattern of neuronal damage is further influenced by the pre-labor metabolic and growth status of the fetus, as well as metabolic and nutritional status of the mother(78).

Umbilical cord blood gas and acid-base assessment are the most objective determinations of the fetal metabolic condition at the moment of birth. ACOG recommend Cord blood gas and acid-base assessment should be done in circumstances of cesarean delivery for fetal compromise, low 5-minute Apgar score, severe growth restriction, abnormal fetal heart rate tracing, maternal thyroid disease, intrapartum fever, or multifetal gestation(79).

With regard to the correlation with umbilical cord blood gases and long-term outcomes, a systematic review of 51 studies of term infants correlating neonatal mortality, HIE, and cerebral palsy documented a graded increase in risk of perinatal mortality and morbidity with increasingly acidemic status at birth(60). Moderate and severe newborn encephalopathy,

respiratory complications, and composite complication scores increase with an umbilical arterial base deficit of 12–16mmol/L. Moderate or severe newborn complications occur in 10% of neonates who have this level of acidemia and the rate increases to 40% in neonates who have an umbilical arterial base deficit greater than 16mmol/L at birth(58). Poor condition at birth and all adverse outcomes increased with worsening acidosis. The correlation with umbilical artery pH and cerebral palsy was much weaker, with seven studies showing non-significant increases in risk at various degrees of acidosis (for pH less than 7.0 to pH less than 7.2). However, when subjected to meta-analysis, the OR for cerebral palsy with umbilical artery acidemia was significantly but moderately increased (80).

2.6. Umbilical Cord Blood Acid-base State: What is Pathologic?

Values for umbilical arterial and venous pH and Pco2 at delivery have been widely reported. In a study of normal term vaginal deliveries, mean umbilical arterial values were pH 7.28 ± 0.05, Pco2 49.2 ± 8.4 mm Hg, Po2 18.0 ± 6.2 mm Hg, and bicarbonate 22.3 ± 2.5mEq/L(81). Note that pH, Po2, and Pco2 data may be the result of rapid and acute changes in placental gas transfer, resulting in the broad range of normal values. In contrast, base deficit reflects the long term metabolic fetal acid–base status. Based on a study retrospective cohort study of 3522 term, singleton, non-anomalous neonates with 5-minute Apgar scores of ≤7, the overall incidence of an umbilical artery pH ≤7.0 was 0.5% of umbilical artery cord pH ≤ 7.1 was 3.4% of base excess ≤ -12mmol/L was 1.4%, and of base excess ≤ -10mmol/L was 4.0%. After other factor controlled, it was determined that neonates with a pH of ≤7.0, despite an Apgar of >7 at 5 minutes, had a statistically significant increased risk of RDS and NICU admission with an adjusted odds ratio (aOR) of 6.5 (95% CI, 2.9-14.3) and 10.8 (95% CI, 6.8-17.4) respectively. A base excess of ≤ -12mmol/L was associated with a statistically significant increase in MAS (aOR, 4.2; 95% CI, 2.1-8.4), neonatal sepsis (aOR, 4.7; 95% CI, 1.9-12.1), RDS (aOR, 2.2; 95% CI, 1.1-4.4), and NICU admission (aOR, 2.9; 95% CI, 2.0-4.4). Similar trends were also seen with a base excess of ≤ -10mmol/L.

It is unhelpful to define pathological acidosis statistically, using deviation from the normal population values. This is because acidosis is generally tolerated by the fetus without sequelae until it becomes very severe. It is more clinically relevant to define pathological acidosis as the threshold at which the incidence of adverse clinical events starts to correlate strongly(82).

Although fetal acidemia has been classically defined as an umbilical artery pH of <7.20, significant or pathologic fetal acidemia has been defined as an umbilical artery pH of <7.00(83). But more recent data shows small absolute risk of an adverse neurological outcome start significantly increased below 7.10(84).

2.7. Umbilical Artery Blood Sampling

Sampling from the umbilical artery is more challenging than from the vein because the former has a smaller lumen, a thicker wall, and contains less blood. For this reason, it may be easier to sample the artery first because the distended vein may provide some support to the artery. If the placental vessels are sampled, the smaller, thicker-walled arteries almost always cross over the larger thinner-walled veins on the chorionic plate. If there is any question, the vessels can be traced to the umbilical cord where they become more apparent(85). Both arterial and venous gases should be measured for as 25% of the time the venous, not arterial, is sampled in error(86).

Immediately after delivery of the neonate, a segment of umbilical cord should be double-clamped and divided. A clamped segment of cord will remain stable for pH, PO2, and PCO2 analysis for at least 60 minutes. A cord blood sample in a heparin flashed syringe is stable for up to 60 minutes. Base deficit values may increase by 1.2mmol/L in 20 minutes and by 4.5mmol/L in 60 minutes(87). Lactate values can increase by 40% within 20 minutes and by 245% in 60 minutes, therefore if warranted by the condition of the neonate, blood should be drawn from an artery and a vein in the clamped cord segment and should be sent to the laboratory for blood gas analysis, including pH, PO2, PCO2, and base deficit, preferably within 20 minutes. If blood gas analysis is expected to take longer than 20 minutes, the syringe should be stored on ice. In all such cases, base deficit and lactate values should be interpreted with caution (88). Exposure of arterial or venous samples to air tends to increase the PO2 and decrease the PCO2 toward atmospheric values (31, 38, 39).

The median (range) arteriovenous difference in pH was 0.09 (0.02–0.49) units, and in PCO2 was 1.9 (0.5–9.9). The minimum venous-arterial pH difference of PH .02 and PCO2 of 0.5 used to differentiate sampling error. In Westgate et study, very large arterial–venous differences existed (0.02–0.49 for pH, 0.5–9.9 kPa for PCO2, and 11.8–9.7 for base excess); therefore, a normal venous pH is unable to exclude the possibility of significant arterial acidosis. (89). Moreover,

differences in pH and base excess may provide some information about the time course of acidosis because a large arterial–venous base excess difference may indicate an acute event, whereas a small arterial–venous base excess difference is more likely to indicate a chronic acidosis course(89).

Restriction of umbilical blood flow causes a progressive widening of the difference between umbilical arterial and venous blood gas values. Martin et al showed that term infants with nuchal cords have larger differences in umbilical venous and arterial pH, PCO2 and PO2 than those without evidence of cord compression(90). In contrast, arterial to venous differences are small where there is impairment of the maternal perfusion of the placenta, such as in cases of abruption(91).

2.8. Management of NRFS

As discussed in previous section FHR changes that are considered non reassuring are not specific reflections of fetal acid-base status, and therefore many fetuses with these FHR patterns have normal, healthy acid-base values. These limitations present challenges to health care providers as they assess fetal status during labor and intervene to promote fetal well-being based on EFM data.

Principal management options for variant fetal heart rate patterns consist of identifying and correcting any fetal insult, if possible. But response will vary given based on the clinical situation, classification of findings, and monitoring method being used.

Initiating intrauterine resuscitation is often the first response for abnormal findings. Action include: Removing vaginal prostaglandin/ stop or decrease oxytocin, changing maternal position to left or right lateral, checking maternal vital signs, including differentiation of maternal heart beat from FHR, asking woman to modify or pause pushing efforts in the active second stage of labour, improving maternal hydration, with an intravenous fluid bolus, only if indicated (i.e., maternal hypovolemia and/ or hypotension), performing vaginal examination to rule out cord prolapse and assess progress, tocolysis in the presence of tachysystole, considering amnioinfusion in the presence of complicated variable decelerations, providing supportive care to reduce maternal anxiety (to lessen catecholamine impact) and proving oxygen by mask only when maternal hypoxia and/or hypovolemia is suspected/confirmed(92).

Category III tracing is considered abnormal because studies have demonstrated that these findings are associated with an increased risk of fetal hypoxic acidemia, which can lead to cerebral palsy and neonatal hypoxic ischemic encephalopathy(56). A retrospective case-control study in Shanghai, China, Women delivered a singleton, non-anomalous infant at ≥36 weeks' gestation diagnosed with neonatal hypoxic ischemic encephalopathy (NE), Category II FHR tracings were observed in 89% of women prior to delivery and were not independently associated with NE. Notably, a category III FHR was observed in 17.4% of women in the NE group compared with 0.9% of women in the control. Bradycardia, minimal/absent variability, late decelerations, and prolonged decelerations were independently associated with NE, whereas accelerations were protective. Similar findings were found when the cases were limited to NE with arterial cord pH <7.1 and in a subgroup analysis of women with category II tracings(93).

3. STUDY OBJECTIVE

3.1. General Objective

- ✓ This study is designed determine the predictive ability of clinical diagnosis of NRFS indicating caesarean section (CS) for fetal acidemia at birth and short-term neonatal adverse outcome.

3.2. Specific Objectives

- ✓ Determine the incidence of acidemia in neonates delivered by CS for NRFS
- ✓ Examine association of NRFS with fetal acidemia at birth and short-term neonatal outcome
- ✓ Measures predictive ability of clinically diagnosed NRFS for fetal acidemia and short-term neonatal adverse outcome.

4. METHODOLOGY

4.1. Study Design and Study Setting

Facility based prospective cohort study was conducted to assess prediction of clinical diagnosis of NRFS for fetal acidemia and short-term neonatal adverse outcome, from January Aug 1, 2020, to April 31,2021 at Tikur Anbessa Specialized Hospital (TASH). TASH is national referral and teaching hospital affiliated to college of health sciences, Addis Ababa University, with approximately 5,000-6,000 deliveries conducted annually. The Obstetrics department at TASH is staffed by midwives, intern doctors, residents, and specialists. There are two operating theatres for obstetrics which is available 24 hours a day. Population from historical cohort of similar study was used to calculate predictive ability of NRFS for fetal acidemia.

4.2. Population

- ✓ **Source population**

All mothers who delivered in the selected health facilities in the months of the study period.

- ✓ **Study population**

All newborns delivered by emergency caesarean section for NRFS during study period.

4.3. Inclusion and Exclusion Criteria

A laboring woman was eligible if GA is $\geq$ 37 weeks, cephalic presentation, active labor established, no gross anomalies, delivered by cesarean section for NRFS, was able to give written informed consent. Mothers with multiple pregnancy were excluded. Incomplete and conflicting documentation were excluded from study.

4.4. Sample Size Determination and Sampling Technique

- ✓ **Sample size determination**

Nonprobability consecutive sampling method was used.

Sample size **n** for independent cohort studies calculated as

$$n = \frac{\left[Z_{\alpha}\sqrt{(1+1/m)\bar{p}(1-\bar{p})} + Z_{\beta}\sqrt{p_0(1-p_0)/m + p_1(1-p_1)}\right]^2}{(p_0 - p_1)^2}$$

β = 1 – power, m is the number of control subjects per experimental subject, p0 is the probability of event in controls, p1 is the probability of event in experimental subjects, and Zp is the standard normal deviate for the probability p.

- ✓ P1 = 27.3%, incidence of acidemia in mild fetal bradycardia and Po =1.3% incidence of acidemia in normal fetal heart rate (94).
- ✓ n = 56 Exposed 28 and non-exposed 28 was required for analysis.
- ✓ For non-exposed, historical cohort from similar study (94) was used to calculate predictive ability of NRFS for fetal acidemia

✓ **Sampling technique**

All mother admitted to labor ward or having active labor before admission to labor ward included in study. The diagnosis of NRFS was based on persistent fetal heart rate abnormalities detected by either EFM, intermittent auscultation or presence of meconium.

Maternal demographic profile, specific types of abnormal fetal heart rate tracing that prompted cesarean section, decision to delivery interval, types of anesthesia, duration of labor, stage of labor, liquor status, was documented. Immediate neonatal outcome: the birth weight, Apgar score at 5 minutes, the umbilical artery acid base blood gas analysis (PH, base deficit, lactate), adverse neonatal outcome was recorded.

4.5. Study Variables

The primary outcome was fetal acidemia, defined as an umbilical arterial cord gas measurement of PH <7.20 or and base deficit greater than 8mmol/l. Secondary outcomes included neonatal composite morbidity, which include any of the following: Apgar score at 5^{th} minute ≤ 7, respiratory distress, birth asphyxia, NICU admission, need for respiratory support, seizure, death. The primary exposure of the study was NRFS before delivery.

In exposed cohort, the following comparison were made between those with acidemia and non-acidemic group. 1. Demographic parameters: maternal age, gestational age, and parity. 2. Pregnancy and obstetrics characteristics: hypertensive disorders, diabetic disorder, cardiac

disease, respiratory disease, oligohydramnios (single deepest amniotic fluid pocket ≤ 2cm), liquor status, and suspect intra-uterine growth restriction (IUGR), Prior cesarean delivery, induction of labor. 3.Delivery characteristics and complications: birth weight, Apgar score at 5^{th} minute, respiratory distress, birth asphyxia, NICU admission, need for respiratory support, seizure, early neonatal death.

4.6. Data Collection Procedure

During caesarean, at birth of baby, about 10 cm of umbilical cord segment was double clamped, divided and 2 ml of blood samples are obtained in heparin flushed syringes by trained midwife and operation theatre room nurses, then sample immediately covered, and analysis done within 10minute by trained residents. All residual air was ejected upon sampling and analyzing. Blood was mixed throughout and checked for clot before inserting into fill port. Calibrant fluid pack checked for expiration and used only for 30 days and replaced after 30 days. Cartridge kept at 4 - 15 Celsius and fill port and electrical contact kept out of touch.

EDAN blood gas analyzer was used for measurement and standard calibration was done every month by biomedical engineer. EDAN blood gas analyzer was a validated ABGA against standard blood gas analyzer.

Fetal heart rate records of these patients were retrieved from the health records and analyzed.

Pre-structured data collection sheets were used, and data extracted from the files, history taken from mother and operating physician and filled manually.

4.7. Data Quality Control

Data was entered after thorough scrutiny and validation of any information that may have been incomplete or conflicting. In order to avoid double participant recruitment, the participants' medical registry number was entered into a register upon recruitment for serialization. This register was counter-checked daily for any double entries and if it was so discovered, one of the data collection sheets was withdrawn and discarded and the serialization rectified before recruitment is continued.

4.8. Operational Definitions

- ✓ Clinical diagnosis of NRFS –
    - Persistent fetal tachycardia – is defined as a baseline heart rate greater than 160bpm for at least 10 minutes
    - Persistent fetal bradycardia - is defined as a baseline heart rate less than 120bpm for at least 10 minutes.
    - Severe fetal bradycardia - defined as a baseline heart rate less than 80bpm
    - Fetal tachycardia - include persistent fetal tachycardia, and fetal tachycardia with abruptio placentae.
    - Fetal bradycardia - severe fetal bradycardia, persistent fetal bradycardia, bradycardia plus abruption
    - Meconium-stained amniotic fluid – MASF and tachycardia, MASF and bradycardia
- ✓ Fetal acidemia
    - Mild - umbilical artery pH 7.19 -7.16 or base deficit 8 to 12
    - Moderate - umbilical artery pH 7.15 – 7.11, or base deficit 12 to 16
    - Severe/ Pathologic acidemia - umbilical artery pH $\leq$ 7.10 or base deficit > 16
- ✓ Active labor - onset painful contractions and cervical dilation of 3 to 4 cm or greater

4.9. Data Processing and Analysis Procedures

Data was entered and analyzed using SPSS 20 version. The associations between baseline prenatal and intrapartum factors with intrapartum fetal heart rate patterns characteristics were analyzed by fisher exact test due to small sample size (when X-square test used, some cell has expected count less than 5). Adjusted odds ratios were obtained using logistic regression analysis adjusted for baseline differences in maternal age, parity, induction of labor, birth weight, and hypertensive disorders. Multivariable models were constructed to control for confounders; Odds ratio (OR) and 95% confidence intervals (CI) were calculated, $p \leq 0.05$ was considered statistically significant.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using historical cohort for comparison.

4.10. Risks and Benefits

There was no special benefit provided for a mother and neonatal NICU referral was only based on clinical decision. The only potential risk is that of data being seen by people not on the study team. The study team will not collect any identifying information about participants.

4.11. Ethical Consideration

Ethical approval to conduct the study was obtained from the Department Research and Publication Committee, Addis Ababa University, College of Health Sciences, and permission was obtained from the medical directors of the respective hospitals. This study does not pose any ethical issues of significance; however, confidentiality was ensured by collecting the data within the wards and no names was recorded on the data collection sheets. The information obtained from the records was used only for the purpose of this study.

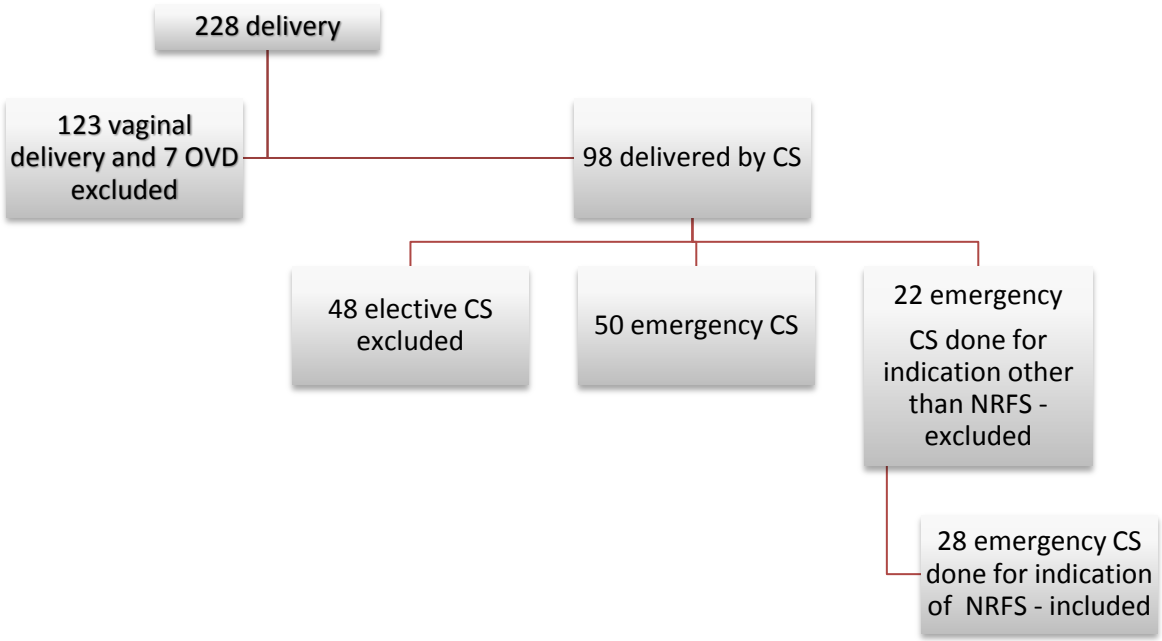
4.12. Dissemination Plan

The results of the study will be presented to Department of Gynecology and Obstetrics, AAU. Findings will also be presented on different conferences and professional society meetings. Attempts will be made to publish in peer reviewed and reputable national and international journals.

5. STUDY RESULTS

5.1. Study population

Overall, 228 deliveries occurred at the selected health facility during the study period. From these 123 women delivered vaginally, 7 women delivered by operative vaginal delivery and 98 women by cesarean section. Of those women delivered by cesarean section 48 were elective and 50 CS were done on emergency base. From women delivered by emergency cesarean section, 28 were for NRFS. Women delivered by operative vaginal delivery and those delivered by spontaneous vaginal delivered excluded. Women who have incomplete recording excluded. Finally, 28 women for whom cesarean section done for non-reassuring fetal status done included in this study. From 28 NFS for which sample taken for acid gas analysis, three sample was disqualified due to sampling error and finally 25 cord blood acid base gas result was subjected to final analysis



5.2. Characteristics of the population in the study

- ✓ **Maternal demographic character**

Base line maternal demographic character and newborn listed in Table 1. Mean maternal age was 25.64yr (SD 3.8). 72% (18/25) of women were nullipara and remaining were primiparous. Mean gestation age was 40.12 weeks (SD 1.48). 12% (3/25) of women gestation age were early term, 36% (9/25) full term, 36% (9/25) late term and 16% (4/25) were post term. 36% (9/25) women has pregnancy related antepartum and/or intrapartum complication.

Table 1: Obstetric Characteristics of Study Participants

Variable	Categorized	Percentage %
Age in years	<18	4 (1/25)
	18 – 34	96 (24/25)
Parity	Nullipara	72 (18/25)
	Primipara	18 (7/25)
GA in weeks	Early term	12 (3/25)
	Full term	36 (9/25)
	Late term	36 (9/25)
	Post term	16 (4/25)
Medical Comorbidity	RVI	8 (2/25)
	None	92 (23/25)
Pregnancy complication	APH	12 (3/25)
	Oligohydramnios	8 (2/25)
	PIH	12 (3/25)
	Chorioamnionitis	4 (1/25)
	No complication	64 (16/25)

- ✓ **Labor character**

Almost three-fourth of the participants labour were established spontaneously and 84% of them at latent phase of labour at time of decision for cesarean section. 16% of women received oxytocin augmentation. About two fifth of had a prolonged membrane rupture (>12 hours) and

52% of women had MSAF liquor status at delivery. Mean duration of labor was 14.68hr ±7.73(SD) (range, 4 to 28hr).

During this study period, the most common cited indication for cesarean section was NRFS constituting 56% (14 of 25) of emergency cesarean section. 52% (13 of 25) of emergency cesarean section done for mother at gestational age greater or equal to 41weeks. The most common type of NRFS indicating cesarean section were fetal bradycardia constituting 60% of indication. Only one woman received general anesthesia and all other delivered under spinal anesthesia. Mean time of decision to delivery time were 41.92minute (SD 19.71) while 32 % (8/25) of women delivered with 30minute of decision while 68% of at time greater than 30minute.

Table 2: Labor characteristics

		Percentage
Onset of labor	Spontaneous	72 (18/25)
	Induced	28 (7/25)
Stage of labor	LFSL	72 (18/25)
	AFSL	28 (7/25)
Labor argumentation	Yes	16 (4/18)
	No	56 (14/18)
Duration of labor	< 28hr	96 (23/25)
	≥ 28hr	4 (2/25)
Liquor status	Clear	40 (10/25)
	MSAF	60 (15/25)
Duration of ROM	<12hr	64 (16/25)
	≥ 12hr	36 (9/25)
Indication for CS delivery	Bradycardia plus	60 (15/25)
	MSAF plus	20 (5/25)
	Tachycardia plus	20 (5/25)
Decision to incision time in minute	<30 min	32 (8/25)
	≥30min	68 (17/25)

5.3. Neonatal Outcome

Fifty six percent of the study participants had delivered female child and 92% of newborn were in normal birth weight range. Mean birth weight of neonates were 3284gm ±471.42 (SD). None of newborns had an 5th minute APGAR of less than 7. Eight neonates had NICU referral, and five neonates were admitted. Two of admitted neonate had respiratory distress, one had stage 1 PNA and two with neonatal sepsis and respiratory distress. Other 4 neonate evaluated and returned to the mother. There was no neonatal death.

Table 3: Neonatal outcome character

Variables	Categorized	Percentage
Sex of newborn	Male	44 (11/25)
	Female	56 (14/25)
Birth weight	2500 – 3999	88 (22/25)
	≥4000	12 (12/25)
5th minute APGAR	≥7	100
NICU admission	Yes	32 (8/25)
	No	68 (17/25)
Duration in NICU	<48hr	20 (5/25)
	>48hr	12 (3/25)
Respiratory distress	Yes	8 (2/25)
	No	92 (23/25)
PNA occurrence	Yes	4 (1/25)

- ✓ **Umbilical artery cord blood gas analysis result**

In this study, umbilical arterial acidemia (pH of <7.20) occurred in 8 infants 32%and 17 (68%) had a pH ≥7.20. From those with acidemia 37.5% (3 of 8) had mild acidemia and 62.5% (5 of 8) had pathologic acidemia. The mean umbilical artery PH was 7.20±0.09(SD) (range, 7.01-7.30). When base deficit taken into consideration 16 infants had normal base deficit while 7 newborns had mild acidemia and 2 had moderate acidemia. Mean and median values of measured acid blood gas analysis summarized in table 6 and classified based on severity of acidemia in table 5.

Table 4" Umbilical artery cord blood gas analysis result

		Percentage
PH	Mild acidemia	12 (3/25)
	Moderate acidemia	0
	Pathologic acidemia	20 (/25)
	No acidemia	68 (17/25)
Base deficit	< 8	64 (16/25)
	8.01 -12	28 (7/25)
	12.01 – 15.99	8 (2/25)
	≥ 16	0

Table 5: Mean and median values of umbilical artery acid base and blood gas values

	Mean	SD	5^{th} percentile	Median	95^{th} percentile
PH	7.20	0.09	7.01	7.24	7.29
HCO3	21.60	3.70	17.52	20.90	32.29
PCO2	54.82	11.47	37.39	55.80	71.95
Base deficit	7.14	2.79	3.04	7.50	12.62
Lactate	35.00	16.99	17.23	28.20	71.16

5.4. Association and prediction

Fisher exact test of association was conducted to identify an association between fetal acidemia or neonatal comorbidity and categorical variables. Binary and multiple logistic regression analysis was done to see association of variables and control confounders. There was no significant association any type of NRFS and fetal acidemia. Fetus with acidemia had 7.8 times higher ICU admission when compared to non acidemic fetus but it didn't reach significant level (aOR, 5.029; 95% CI, 1.112–11.283), P-value 0.061.

Area under the receiver operating characteristic curves (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) estimated the discriminative efficiency of NRFS patterns, alone or in combination, to predict acidemia and morbidity. Fetal

bradycardia had lost prediction ability for acidemia with area under the curve (AUC) (0.41), PPV 17.22%, while fetal tachycardia (AUC (.62), PPV 30.69) and MSAF (AUC (.62)) had fair prediction for fetal acidemia.

Table 6: Fisher exact test for categorical variable association with fetal acidemia

Variable			Fetal acidemia		
	Categorized	Frequency	Frequency	OR	P value
Parity	Nullipara	18	6 of 18		1.00
	Primipara	7	2 of 7		
Gestational age in Weeks	Early term	3	2 of 3		0.505
	Full term	9	2 of 9		
	Late and post term	13	4 of 13		
Medical comorbidity	Yes	2	1 of 2		1.00
	No	23	7 of 23		
Stage of labor	Latent	21	7 of 21		1.00
	Active	4	1 of 4		
Onset of labor	Spontaneous	18	6 of 18		1.00
	Induced	7	2 of 7		
Oxytocin Augmentation	Yes	4	0		0.307
	No	14	6 of 14		
Total duration of labor	< 28hrs	23	7 of 23		1.00
	≥28hrs	2	1 of 2		
Duration of ROM	<12hr	17	7 of 17		0.236
	≥12hrs	8	1 of 8		
Complication in pregnancy	Yes	6	3 of 6		0.344
	No	19	5 of 19		
Liquor status at delivery	Clear	10	1 of 10	3.707	0.088
	MSAF	15	8 of 15		
Type of anesthesia	General	1	1		0.320
	Spinal	24	7 of 24		
Indication for	Bradycardia plus	15	3 of 15		0.354

cesarean section	Tachycardia plus	5	2 of 5		
	MSAF plus	5	3 of 5		
Decision to incision time	< 30 minutes	9	1 of 9		0.182
	≥30 minutes	16	7 of 16		
Sex of the neonate	Male	11	4 of 11		1.00
	Female	14	4 of 14		
Birth weight	Normal birth weight	22	6 of 22	.	0.231
	Macrosomia	3	2 of 3		
Neonatal comorbidity	Yes	8	5 of 8	5.029	0.061
	No	17	3 of 17		

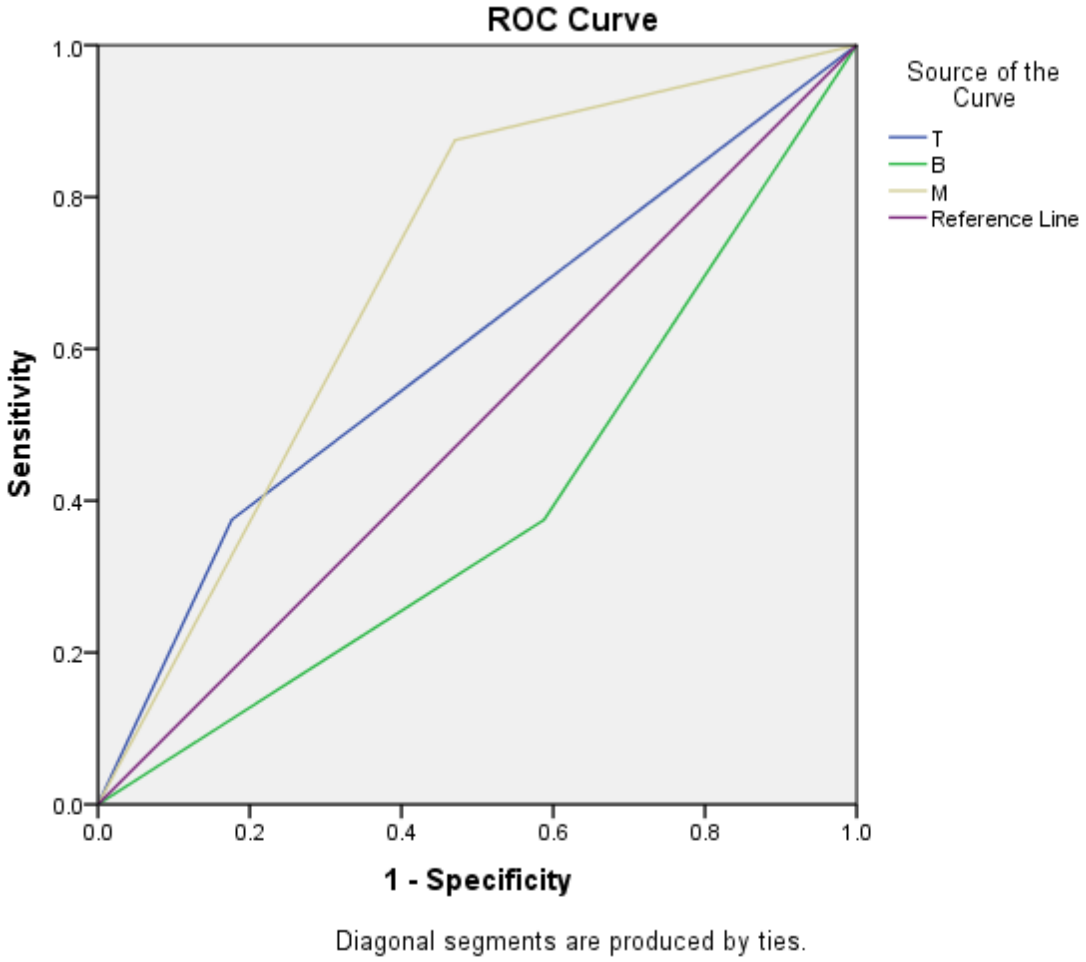
Table 7: Fisher exact test for neonatal comorbidity

Chi-square test of association	Neonatal comorbidity vs.
Parity	0.640
Gestational age in Weeks	0.284
Medical comorbidity	1.00
Stage of labor	1.00
Onset of labor	1.00
Oxytocin Augmentation	0.307
Total duration of labor	1.00
Duration of rupture of membranes	0.362
Obstetric complication	0.624
Liquor status at delivery	0.402
Type of anesthesia	0.32
Indication for cesarean section	1.00
Sex of the neonate	0.695
Birth weight	1.00

Table 8: Predictive ability of NRFS pattern for fetal acidemia

NB - 1.3% incidence of acidemia in normal fetal heart rate in historical cohort study were used to calculate PPV.

Type of NRFS	OR 95% CI	P value	AUC 95% CI	Sensitivity %	Specificity %	PPV	NNP
Bradycardia	0.42 (.075-2.36)	0.411	.41(.18-.64)	23.1	58.3	17.22	66.88
Tachycardia	2.8(.42-18.69)	0.344	.62(.35-.89)	50	73	30.69	85.92
MSAF	7.87(.79-78.67)	0.088	.68(.47-.90)	46.7	90	-	-



6. DISCUSSION

Intrapartum fetal monitoring is being used universally both in low income and high-income country. Appearance of an abnormal FHR tracing is not a reason to resort to prompt delivery; it is a reason to decide what may be causing the abnormalities, if fetal well-being can be ensured in the midst of non-reassuring patterns, and to attempt intrauterine resuscitation(2). Fetus usually with stand intermittent hypoxia (17) (21) (23) (34) and intermittent fetal heartbeat abnormality should not an indication for cesarean section. In this study most common cited indication for emergency cesarean section was NRFS constituting more than half of emergency CS and for 28.5% of all CS. Contribution of NRFS for CS in our study is comparable to annual cesarean section audit done at this hospital (30.6%)(95) but higher than report from United Kingdom and reports from other studies(10%)(96).

More than half of NFS for which cesarean section done was at gestational age of greater than 41 weeks. This finding is consistent with ARRIVAL trial which shows expectant management of pregnancy beyond 39weeks was associated with higher rate of cesarean section(97). Though there was no significant association between fetal acidemia and gestational age delivery, late term and post term may contribute to increased rate of cesarean section in this study.

In this study incidence of fetal acidemia (PH <7.20) for all type NFS was 32% (8 of 25). The incidence of pathologic acidemia, (PH <7.10), was 20% (5 of 25) which is lower than incidence of acidemia of NRFS in other study (53%) (51). In our study, base excess of mild to moderate range acidemia found in 36% (9 of 25) of neonate. Lower proportion of fetal acidemia in a newborn with NRFS when compared to other study may indicate physician's lower threshold in deciding for CS for mild form of NRFS which can be managed conservatively and associated higher rate of emergency CS for NRFS. But further study with adequate sample size is needed.

There are various methods of newborn's condition evaluation at birth and, APGAR scoring is the most commonly used method. Evaluation of newborn by APGAR score is limited because it is influenced by a factor not related to birth asphyxia and relatively it is subjective (62) (66). In our APGAR scoring was left for treating physician and study all newborn had a 5^{th} minute APGAR score of greater than 7. Incidence of pathologic acidemia in new born with 5^{th} minute APGAR greater 7 in one prospective study (98)was 3.4% and which very lower than in our finding. This may explain highly subjective scoring of APGAR in our study. Neonates with reassuring

APGAR scores have a residual risk of neonatal acidemia that is associated with higher rates of adverse outcomes (98), though not significant our study shows higher ICU admission.

Fetal acidemia is associated with gestational age at birth, oxytocin stimulation, meconium stained amniotic fluid, use of spinal anesthesia, NRFS and maternal comorbidity at birth (99)(100) (51). In our study was no significant association between fetal acidemia with type of NFS, parity, gestational age, duration of labor, duration of rupture of membrane, liquor status and maternal comorbidity. Though it was not significant, risk of newborn acidemia with MSAF, delayed delivery (>30minute of decision to delivery), prolonged rupture of membrane(>12hours) was higher by 7.9, 6.2 and 3.8 times respectively.

Newborn with acidemia at birth has significant association with ICU admission, intubation, MAS, seizure and birth asphyxia(41) (84) (98). In this study was no significant association between fetal acidemia fetal ICU admission, respiratory distress, sepsis, and perinatal asphyxia. Fetus with acidemia had 7.8 times higher ICU admission when compared to non acidemic fetus but it didn't reach significant level

Study comparing base line heart rate change with fetal acidemia is limited. In evaluation abnormal EFM pattern for fetal acidemia (51), total deceleration area was most discriminative of acidemia (area under the receiver operating characteristic curves, 0.76). Cahil AG also found base line tachycardia had AUC of 0.80 and repetitive late decelerations had 0.78. In this study fetal bradycardia was the most common type of NRFS (60%) indicating CS, but its' AUC was 0.41(OR 0.42, 95% CI (.075-2.36)) for acidemia which means discriminative capacity of fetal bradycardia for acidemia is totally lost (≤ 0.5) and actually predicting non acidemic fetus as acidemic. Though small sample size this study failed to identify significant association of fetal bradycardia with acidemia, discriminative ability loss of fetal bradycardia for acidemia may contribute to higher rate of unnecessary cesarean section. Both fetal tachycardia and MSAF has discriminative ability of clinical importance (≥ 0.6). Calculated area under the curve for fetal tachycardia was 0.62 (OR 2.8, 95% CI (.42-18.69)) with sensitivity, specificity and PPV of 50%, 73% and 30.69% respectively while MSAF has AUC of 0.68 (OR 7.87, 95% CI (.79-78.67)) with sensitivity and specificity 46.7% and 90%.

7. LIMITATIONS OF THE STUDY

The limitations of our study include a lack of objectivity in the diagnosis of fetal heart rate abnormality as intermittent auscultation of fetal heart rate used in most case. Due to the high cost of analysis, sampling was restricted to umbilical artery and sample from umbilical vein was not taken for validation of correct sampling. For same reason, control sample from reassuring fetal status and normal vaginal delivery was taken from historical cohort of similar population under different setup.

There is also controversy that acidemia is not intended outcome and its use gold diagnostic test is controversial. In this study maternal outcome was also not measured. There was also an interruption of data collection in between due to some logistic and administrative issue and sample selection bias is possible. Finally, most participant in this study were at latent first stage of labor at time of indicated cesarean delivery and fetus at latent first stage of labor thought to be less acidemic than if cesarean section done at second stage of labor.

8. STRENGTHS OF THE STUDY

It is first attempt to objectively assess accuracy of clinical diagnosis of NRFS using fetal acidemia which is mostly used as gold standard measurement. This study was prospective and all-important information was obtained for analysis

9. CONCLUSION

NFS was leading cause of emergency cesarean section but only 20% of fetus had pathologic acidemia. There is no significant association between maternal demographic and labor character with fetal acidemia. None of NRFS pattern had significantly association with fetal acidemia and fetal outcome. Fetal bradycardia had no discriminative ability for acidemia while fetal tachycardia and MSAF had fair prediction for fetal acidemia. Non-significant association of all type NFS with fetal acidemia may be due small sample size of this study and further study with large sample size is needed to establish existing association in this set up, if any.

10. RECOMMENDATIONS

Further study with large sample size and good control is needed to see correlation between clinical diagnosis of NRFS and fetal acidemia.

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