"TRANSCRANIAL DOPPLER EVALUATION OF CEREBRAL HEMODYNAMIC ALTERATION IN PRETERM NEONATES WITH EARLY ONSET SEPSIS - A ONE YEAR HOSPITAL BASED OBSERVATIONAL STUDY AT KLE DR. PRABHAKAR KORE HOSPITAL"

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Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"TRANSCRANIAL DOPPLER EVALUATION OF CEREBRAL HEMODYNAMIC ALTERATION IN PRETERM NEONATES WITH EARLY ONSET SEPSIS – A ONE YEAR HOSPITAL BASED OBSERVATIONAL STUDY AT KLE DR. PRABHAKAR KORE HOSPITAL"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

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LIST OF ABBREVIATIONS

GBS	Group B Streptococcus
MRSA	Methicillin-resistant S aureus
CONS	Coagulase Negative Staphylococci
HSV	Herpes simplex virus
VEONS	Very early-onset neonatal sepsis
EONS	Early-onset neonatal sepsis
LONS	Late-onset neonatal sepsis
PROM	Premature rupture of membranes
CBF	Cerebral blood flow
FIRS	Foetal inflammatory response syndrome
SIRS	Systemic inflammatory response syndrome
PVL	Periventricular leukomalacia
IVH	Intraventricular hemorrhage
TCD	Transcranial Doppler
ACA	Anterior communicating artery
MCA	Middle communicating artery
PCA	Posterior communicating artery
VA	Vertebral artery
ICA	Internal carotid artery
RI	Resistivity Index

PI	Pulsatility Index
PSV	Peak systolic velocity
EDV	End diastolic volume
LODS	Logistic organ dysfunction system
QSOFA	Quick Sequential Organ Failure Assessment
CSF	Cerebrospinal fluid
ICU	Intensive care unit
SVR	Systemic vascular resistance
RVO	Right ventricular output
LVO	Left ventricular output
SVC	Superior Venacava
sNSE	Serum Neuron Specific Enolase
NEC	Necrotising enterocolitis
RBC	Red blood cells
LR	Lindegaard Ratio
MFV	Mean Flow Velocity
APGAR	Appearance, Pulse, Grimace, Activity, Respiration

ABSTRACT

BACKGROUND: Diagnosis of early neonatal sepsis occurs between days 0 and 3 of neonatal life .In the first 24 hours of birth, 85% of infants with early-onset sepsis will show signs of illness. Development of sepsis has been linked to the ingestion of maternally acquired bacteria. There is a theoretical possibility of hegmatogenous and transplacental transmission from an infected mother, but cervicovaginal transmission is quite frequent.

A infant with a diagnosis of neonatal sepsis is at higher risk for complications and perhaps death. The purpose of this research is to assess the reliability of ultrasonographic Doppler prediction of cerebral blood flow velocities as a diagnostic marker of early-onset neonatal sepsis, since our understanding of early alterations to CBF in newborn sepsis is limited. In this study, cerebral blood flow was measured using trans cranial doppler ultrasound. Given that being born before 37 weeks of gestation is a risk factor for early-onset sepsis, we will include preterm neonates in our research if they have a history of exposure to at least two of the other risk factors of early onset sepsis.

We aimed to assess the alterations in doppler parameters of such neonates using trans cranial ultrasound so that the future adverse neurological outcomes can be prevented.

MATERIALS & METHODS: This research consisted of an observational study conducted at KLE's Dr. Prabhakar Kore Hospital & MRC, Belagavi, a medical facility over one year period,30 preterm babies who had risk factors of early onset sepsis & 30 normal (No risk factors for EONS) preterms were the subjects of the study who

underwent transcranial doppler evaluation. Beginning of the experiment will take place on January 1, 2021, and it will conclude on December 31, 2021

RESULTS: In our study, we discovered that ACA & MCA median PI was 0.85 & 0.76 respectively in the sepsis group and 1.51 & 1.43 respectively in the non sepsis group. The median ACA & MCA RI in the sepsis group was 0.4 & 0.33 respectively which is significantly lower than the median RI value of non sepsis group (0.74). Both the pulsatility index and the resistivity index were significantly reduced in the sepsis group. 63.33 % of our cases with sepsis had a vaginal birth as risk factor out of which 6 % had a prolonged delivery.33.33 % of our cases had PMRM as a risk factor which was also similar to the high percentage of PMRM. 26.67 % of our cases had meconium-stained liquor as a risk factor. On our study median APGAR score value of 7 was found in sepsis babies as compared to the a higher median APGAR score of 8 in non sepsis babies

CONCLUSION: A combined clinic-radiological approach to the neurological evaluation of premature newborns has allowed for recent advancements in the diagnosis and treatment of perinatal brain damage. In this study it was establishes that. Infants diagnosed with early-onset neonatal sepsis and those who were born prematurely had lower mean PI and RI values in the Anterior and in the middle cerebral arteries and also in our study we observed that vaginal mode of delivery, PROM, meconium stained liquor , prolonged labour were all risk factors in our sepsis group

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INTRODUCTION

Neonatal sepsis refers to a bloodstream infection caused by bacteria, viruses, or yeast that causes hemodynamic changes as well as other clinical signs and frequently results in severe mortality and morbidity. [1,2] The lack of a broadly agreed description of neonatal sepsis is one of several difficulties that persist despite years of clinical skill in the management of neonates diagnosed with or suspected of having sepsis[3]. However, infant sepsis has also been called SIRS (systemic inflammatory response syndrome) This is due to the fact that the clinical manifestations of sepsis can be produced by powerful pro-inflammatory cytokines [4,5]. The start of symptoms and the time of the sepsis episode are used to classify newborn sepsis as either early or late. Early-onset infections in infants often manifest during the initial seventy-two hours of life. In most situations, the mother will be the source of an early-onset infection because she will have passed it to her child vertically through the birth canal. Illnesses that don't show up until after birth or after the first three to seven days of life are considered "late-onset"[6].These diseases are associated with microorganisms picked up from either the hospital or the outside population [7]. Neonatal sepsis can be caused by an infection with any kind of microbe, including bacteria, viruses, and fungi (most commonly yeast) The most prevalent fungal infection is caused by yeast. Most cases of early-onset newborn sepsis have been attributed to Streptococcus agalactiae (GBS) and Escherichia coli [8]. Late-onset sepsis in neonates typically results in the isolation of coagulase-negative staphylococci in the neonatal intensive care unit [9]. Prematurity, gastrointestinal colonisation, and vascular catheterization have all been linked to the development of newborn infections. Given these results, it seems plausible that colonisation and infection may be avoided if transmission was prevented in a healthcare context [10].

One million infants are lost each year throughout the world due to neonatal sepsis. There is a high prevalence of morbidity and mortality in newborns nowadays, and a big reason for that is neonatal sepsis [11]. The danger of cerebral haemorrhage is raised when CBF is moderately elevated, while brain tissue is put at risk when CBF is moderately low. Preterm newborns are particularly vulnerable to oxidative stress of reperfusion injuries due to their immature oligodendrocytes, underdeveloped germinal matrix, and limited glial support Rapid vascular changes during the first few hours of a newborn's life have been linked to both acute and long-term morbidity, suggesting a role for CBF alterations in perinatal brain damage[12]. As an added bonus, a shift in CBF can be used as a early sign for EONS diagnosis. Infants born with very low birth weights, who subsequently experienced hypotension and varying cerebral blood flow velocities, have a higher risk of intraventricular haemorrhage [13].

Ultrasound Doppler examination is a real-time, generally risk-free, noninvasive, and sensitive approach for assessing these vascular alterations [14]. Cerebral blood flow (CBF) has been studied with Doppler ultrasound in order to aid in diagnosing if abnormalities in the cerebral circulation of neonates have occurred, which may cause injury to the brain and unfavourable results for development To ensure their utility in the early assessment and interpretation of changes in the hemodynamic state, it is crucial to verify the prediction validity of the cerebral blood flow measured by Doppler ultrasound [15]. Therefore, preterm newborns with EONS can receive the best clinical care possible if their illness is diagnosed as soon as possible. Hemodynamic stability, normotension, avoidance of activities that can further alter blood flow, and prompt initiation of anti-inflammatory therapy are all components of this care [16].

AIM AND OBJECTIVES

To assess the cerebral blood flow changes by transcranial Doppler ultrasound in preterm early onset sepsis neonates.

REVIEW OF LITERATURE

DEFINITIONS

The name "sepsis" has a Greek origin, "sepsis," which translates to "decomposition" /"decay." The original meaning of the English word stems from this Greek word. Hugo Schottmüller gave his definition of sepsis in 1914. He said that it was the presence of certain symptoms after the introduction of potentially harmful bacteria into the circulation [17]. Between the conferences that were conducted in 1992 and 2001 and the most recent meeting of the European Society of Intensive Care Medicine & the Society of Critical Care Medicine in February 2016, significant advancements were achieved in critical care medicine field. In this investigation, the Task Force compares the SIRS criteria against the LODS and qSOFA grading systems to see how they fare. In a clinical setting, the qSOFA score is calculated by taking into account the following components: You will get one point for every extra breath per minute that you take in excess of 22 (inclusive). You get an additional point since your systolic blood pressure is lower than 100 millimetres of mercury. Third, the patient's mental state has changed, and as a result, they get one point even though their score on the Glasgow Coma Scale is lower than 15. In the case that two out of these three conditions are fulfilled, there is a significant risk of serious organ malfunction and infection occurring. The following is the most recent and accurate definition of sepsis that has been supplied by the task force: Sepsis, often known as multi-organ failure induced by an infection, is a situation that requires immediate medical attention. Neonatal sepsis is referred to be "a clinical condition" by the International Pediatric Sepsis Association. This "clinical disease" is characterised by a severe infection and a systemic inflammatory response syndrome (SIRS). A patient's

temperature, heart rate (including any tachyarrhythmias, bradyarrhythmias, fast breathing, or the sudden need for mechanical ventilation), and blood count are all things that clinicians look at when attempting to identify SIRS in a patient (hematocrit)[3].

PATHOPHYSIOLOGY OF SEPSIS

Clinical symptoms that represent the presentation of an infection within 30 days of neonatal life can be termed as neonatal sepsis, whether or not bacteremia is present. A bacterial growth in either the blood or cerebrospinal fluid must be the cause of newborn sepsis, as per World Health Organization. A wide range of definitions have been offered by a variety of authors. Researchers Goldstein and Barnden say illness is a clinical state with life-threatening hemodynamic abnormalities that is marked by systemic infection. Pathogens (bacteria, viruses, and fungi) in typically germ-free body fluids (blood or CSF) cause these alterations in the first four weeks of a person's life (from birth onward). An infection of the bloodstream includes meningitis and pneumonia[18]. Gram-positive bacteria account for 62 percent of EONS cases, according to statistics from the American Neonatology Network; S. agalactiae is the germ suspected of causing the disease. Of the 37 percent of Gram-negative bacteria that cause EONS, E. coli makes up 29 percent, making up 29 percent of the total. Gram-positive bacteria, on the other hand, are to blame for 79% of late-onset neonatal sepsis, with CoNS accounting for 57% of the total and S. aureus accounting for 12%. Gram-negative microorganisms make for 19 percent of the total, and E. coli normally accounts for 7 percent of the total. Six distinct percentages of LONS cases are caused by fungi. Of the many bacteria found in countries in East Asia, the Pacific Rim, and South Asia, Pseudomonas and

Acinetobacter were the most often encountered. S. aureus infections were much fewer in East Asia and Latin America than in other locations[19].

Maternal and neonatal host characteristics, as well as the virulence of pathogens at various phases of infection, are the major causes of neonatal sepsis. Early-onset newborn sepsis risk factors include: a) prior pregnancy; b) prolonged membrane rupture (18 hours); c) premature membrane rupture; d) chorioamnionitis (maternal temperature of 38 degrees Celsius); e) urinary tract infection in the mother; f) GBS colonization in the mother's vagina; g) preterm birth; The following factors contribute to the development of late-onset newborn sepsis: An indwelling catheter; b) H2-receptor blocker; c) Breakage of the skin and mucosa; d) Prolonged antibiotic use; e) Invasive operations. Neonatal sepsis is more likely to occur if the following things happen to a newborn: As a result of prematurity, the fetus receives lower levels of maternal and specific antibodies, and the immune system is still developing. There are a vast range of environmental threats that infants face, and their immune systems are still developing. There are many factors that contribute to this, including the fact that babies in underdeveloped nations are more susceptible to infection than newborns in more developed countries. Approximately 68 percent of pregnant women in poor countries only partially utilize antenatal care facilities, and only 35 percent of moms in the least developed nations have been evaluated by qualified health staff. These figures are especially alarming because prenatal treatment can avert the vast majority of delivery problems. These practices have led to a lack of hygiene during and after delivery, as well as the cutting of umbilical cords with contaminated tools, as well as an avoidance of beneficial practices such as infant exclusive breastfeeding of in rural South Asian communities. Hospitals in the impoverished world lack basic sanitation facilities, which leads to infection spread and drug-resistant organisms development

said Ganatra and his colleagues. The safe storage of infectious waste in hospital settings also does not occur [20].

There are two main types of infection that can cause sepsis in neonates, one from the mother and the other from the hospital or medical staff or hospital equipment, the environment in which the infants are born after they are born. This is based on epidemiological features. Infections of this nature are known as "early-onset." Early Pregnancy or Pregnancy-Induced Diseases: Within the amniotic membranes, both the fetus and the surrounding environment are usually sterile. Amniotic fluid has an inhibitory effect on germ growth, although the membranes, placental tissue, and amniotic fluid provide physical protection for the fetus. Despite this, the fetus can still become infected directly or indirectly through the mother's blood. There's a chance that an amniotic fluid infection will spread to the mother's uterus due to the mother's vaginal flora being infected by the amniotic fluid, or there could be an unseen crack that heals and causes an infection within the amniotic sac. Premature labor can cause the membranes to rupture, which can cause this. A fetus' respiratory and digestive systems are at risk even before birth if it breathes in or swallows contaminated amniotic fluid. It is possible for newborns to develop skin and upper respiratory tract infections if they come into contact with the mother's bacteria in the cervix, vagina, or stool. Because newborns' skin is so thin, they may be more susceptible to infection because of a lack of physical barriers to protect them from microorganisms. Neonatals' lack of stomach acid renders them more vulnerable to invasive infections caused by bacteria that easily colonies the surroundings. Bacteria such as Salmonella spp., M. hominis, HClinfluenzae, S. pneumoniae, L. monocytogenes and others may cause neonatal sepsis by colonizing the mother's vaginal canal and causing infection, which can then spread to the baby. Either shortly

prior to or during childbirth, infectious organisms can infiltrate a mother's reproductive system through her external surroundings[21].

Fetal inflammation generated by neonatal sepsis leads to a phenomenon called foetal inflammatory response syndrome (FIRS) (FIRS). Newborns with mild EONS who have an inflammatory reaction after delivery may develop systemic inflammation response syndrome (SIRS). Severe sepsis-induced encephalopathy has been said to occur due to impaired cerebral autoregulation, disruption of blood-brain barrier and the direct damage due to oxidative stress or free radicals. It's conceivable that cytokines were released over the BBB or that it was destroyed. There is mounting evidence that astrocytes and microglia, when activated, may produce cytokines that contribute to the inflammatory response [22]. To induce excitotoxicity in the cerebral compartment, proinflammatory cytokines may alter glutamate absorption, produce free radical release, or boost formation of the vasodilator nitric oxide at the site of proinflammatory cytokine production. Premature, low-birth-weight, and asphyxiated infants now have a higher chance of surviving because of advancements in intensive care. Understanding of the extent of the brain damage sustained by these newborns has been greatly advanced by the combined clinical and radiographic approach to examining their nervous systems in recent years. The results have been improved medical precision for the benefit of patients[23].

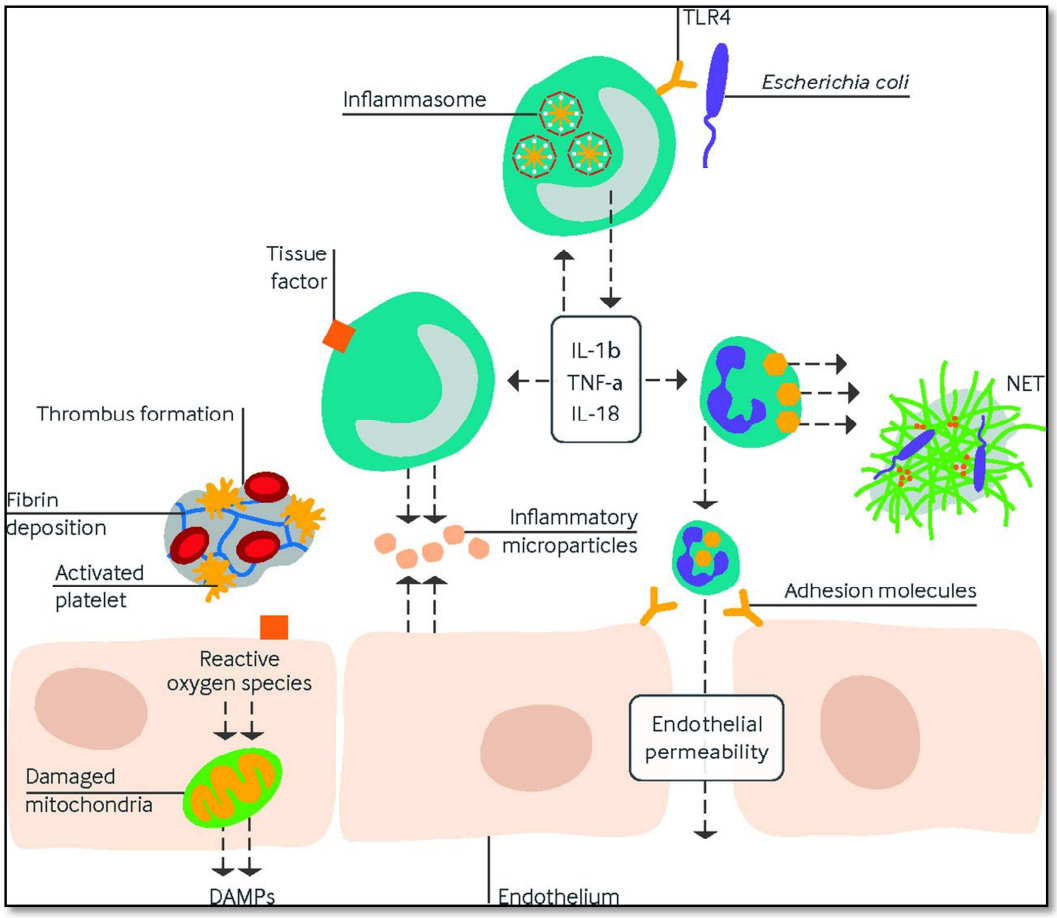


Figure 1: showing production & effect of inflammatory mediators on cell [32]

SEPSIS & HEMODYNAMICS

It has been shown that preterm infants with severe sepsis who get early volume assistance have left and right ventricular outputs similar to those of adult patients with similar conditions. This is quite close to the scenario seen in adult patients. Babies admitted to ICU with catheter-linked sepsis had higher cardiac index and lower SVR, according to the results of a recent research. However, babies diagnosed as having community-acquired sepsis were more likely to have a cardiac index that was either normal or low. Researchers Koert de Waal and his colleagues have published several publications on the hemodynamic presentation of sepsis in infants, but practically all of them have focused on group B streptococcus sepsis.

Koert de Waal's experiment included 20 babies. A birth weight of 995 g was typical for babies born at 27 weeks of pregnancy. Five of the patients who were undergoing the surgery did not successfully complete it. The 15 children who made it through the experience showed only minor disruptions in their blood flow patterns. Blood pressure and systemic vascular resistance (SVR) were increased between the first and most recent measurements. The five infants who did not survive had a lower flow, but a far higher SVR. When a premature kid has severe sepsis, their left and right ventricular outputs are usually rather high, but their stroke volume responses are usually only mild. The correlation between mortality and a decline in RVO or LVO is much more than 50% when compared to the value at the start of the research. Animal studies have shown that these people exhibit signs of organ ischemia, which is thought to result from reduced cardiac output. No accepted reference values for flow exist for preterm infants who have reached this stage of postnatal development. Researchers found that in stable preterm infants, there was a correlation between changes in RVO, LVO, and SVC flow compared to the value at the beginning of the trial and mortality. Patients with septic shock who are unable to recover normal cardiac function have a substantially higher risk of mortality. During initial weeks of life, preterm infants have inaccurate shortening fraction estimates due to aberrant wall motion and altered left ventricular geometry. The circulatory system collects this data. Cardiac output, which considers preload, contractility, and subsequent load, is an essential sign of cardiac dysfunction in premature infants. Presenting blood flow via the SVC in healthy preterm infants was only slightly greater than in post-transitional preterm children. The relatively normal blood flow via the SVC might be explained by compensatory mechanisms designed to maintain a consistent blood supply to the brain. When this factor is added to a mildly enhanced LVO, the inferior vena cava is

likely to receive more blood. The increased perfusion in the mesenteric area was observed in the cohort analysis conducted by Koert de Waal and colleagues, which included six patients with severe NEC. The infants that made it through the research showed no signs of aberrant blood flow. After the heart-lung machine has been turned off, blood flow should resume normally. These results suggest that the flow changes exclusively in infants who do not make it. Numerous preloaded neonates showed very slight variations in blood pressure and SVR. High doses of vasopressors were associated with a significant improvement in SVR in this cohort. Functional echocardiography is the only method developed so far to date that can give further insight into the hemodynamic conditions of newborns. This cohort demonstrates that there is substantial inter-individual heterogeneity in hemodynamic changes. Babies with septic shock should have a hemodynamic evaluation if their hypotension does not improve after receiving volume and dopamine therapy. The physician can tailor the patient's care to their specific hemodynamics with the use of functional echocardiography. Based on our experience, we know that the therapy that works for one person will not work for the other. When blood flow is diminished, it can be best to decrease the amount of vasopressor treatment while increasing the amount of afterload reduction. Additionally, this study suggests that it may be beneficial to increase the dosage of a powerful vasopressor in patients who have a high cardiac output but a low SVR [24 25].

TRANSCRIANIAL DOPPLER

USES OF TCD

Transcranial Doppler is increasingly being used as a diagnostic tool for assessing vascular and cerebrovascular abnormalities. Use of TCD ultrasonography allows for real-time, noninvasive, and minimally invasive assessments of cerebrovascular function.

When it comes to monitoring vascular changes at the bedside in response to treatment in the event of an acute cerebrovascular episode, TCD is the most time-efficient and user-friendly technique. Because of the ease with which this device may be used as a diagnostic tool, it is likely to see increased use in both clinical and academic settings for a wide variety of issues involving the cerebral arteries. This expansion is forecasted to happen in the not-too-distant future[26].

Subarachnoid haemorrhage and cerebral vasospasm, intracranial stenotic illness, acute ischemic stroke, sickle cell disease, and the identification of micro emboli are only few of the disorders that transcranial Doppler may help diagnose and treat. The three most common applications of TCD are as follows: (a) screening sickle cell disease children with higher stroke risk; (b) looking for symptoms of vasospasm after a subarachnoid haemorrhage; and (c) checking for a right-to-left shunt during an embolic stroke. The use of TCD in the follow-up of patients after neurosurgical procedures are additional areas where its use is being explored. Brain damage may be diagnosed with the use of TCD by measuring the intracranial pressure.

The Doppler examination has various benefits over other noninvasive examinations, including its mobility, precision, absence of ionising radiation, and

cost, in addition to its capacity to examine cranial architecture and CBF. Doppler tests should ideally be carried out in a manner that is both iterative and contemporaneous with therapy if one wishes to get the most possible benefit from them. Because of this, it is now feasible to make the most accurate diagnosis imaginable [27].

TCD DOPPLER PHYSICS

The Doppler Effect is a reference to the underlying notion that underpins the Doppler ultrasonography technique, as the name of this effect indicates. Christian Doppler was the first person to describe the Doppler Effect, which occurred in the middle of the 1800s. The red blood cell serves as a moving item in this demonstration, and the theory demonstrates how the frequency of a sound wave changes as it comes into contact with a moving object. When an ultrasonic probe is used, it will generate sound waves at a frequency that has been previously specified. As the sound wave passes through the tissue and comes into contact with a moving red blood cell, there is a change in frequency of the reflected back sound waves to the probe. On the basis of this information, the computer will be able to calculate the speed and direction of the red blood cell in respect to the probe. The Doppler angle is not the only factor that affects the accuracy of velocity estimates; other factors include (theta). The measurement of insonation and blood flow against one another in a straight line results in the formation of an angle. In order to do transcranial Doppler ultrasound, general vascular ultrasonography has to be performed at an angle that is less than sixty degrees [26].

The TCD ultrasonography makes use of the principle of Doppler effect. It is hypothesised that the Doppler probe's ultrasonic waves penetrate the cranium and gets reflected back by the RBCs inside the brain's capillaries. Combination of different

shifts in doppler frequency due to the laminar nature of the flow of blood determines the Doppler signal produced; as a result, a TCD monitor provides a spectrum representation of individual red blood cell velocities. This is because the resulting Doppler signal forms the basis for the TCD monitor. Thus, it is possible to quantify the blood flow velocity in the artery and other flow characteristics using spectral analysis. Included in this group are the following: From this spectrum analysis, we were able to calculate the time-averaged mean maximum velocity, peak systolic velocity, and end diastolic velocity (Vmean). Virtually every TCD gadget can compute and show Vmean as a smooth line chart of average speeds over time[26].

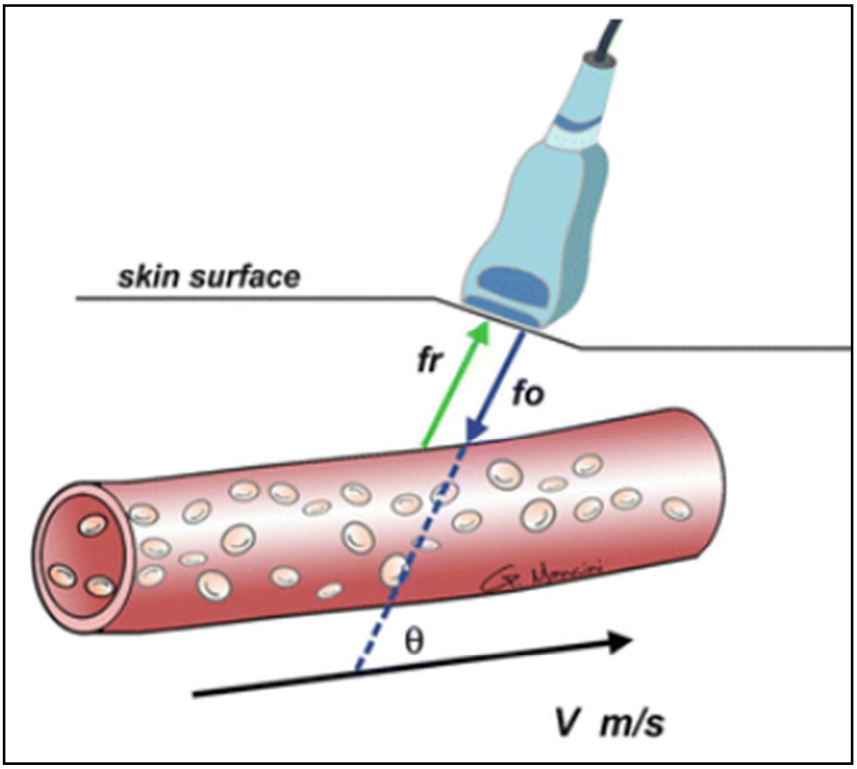


Figure 2. Doppler effect. The ultrasound transducer emits a sound wave pulse at a certain frequency, fo, which is reflected off the moving red blood cells back to the transducer at a different frequency, fr. This resulting frequency shift ($fd = fr - fo$) can be used in the Doppler equation to calculate the velocity of the flowing blood. The angle, θ, is the angle between the incident sound wave beam and the direction of the flowing blood [37]

Doppler probes with a higher operating frequency are utilised for extracranial studies; however, these probes cannot be used for intracranial measurements because waves of a higher frequency are unable to adequately permeate through the skull. These probes cannot be utilised for intracranial measurement due of their design. In addition to the use of a low frequency probe, evaluation of the cerebral arteries can only be achieved through specific acoustic windows.

Interrogation of intracranial vessels can be accomplished for a variety of purposes utilizing this technique. A low-frequency ultrasonic probe with a frequency range of 2 to 3 MHz is used in the initial step of the procedure. This is due to the fact that low-frequency sound waves are better able to penetrate thick tissues, such as the cranial bones in TCD. Most commonly, the power M-mode has been employed to display most of the conventional indicators (although colour Doppler can also be used). Knowledge of typical cerebral vascular anatomy and a few additional criteria are needed to recognize the vessels during an insonation of the cranium. At each stage of the identification procedure, the Doppler spectrum, target vessel depth, flow direction relative to the probe location, and the current Doppler window are all taken into account[26].

The following are some of the most often studied variables:

You can get an idea of how fast the blood is flowing through the brain if you insert in the PSV and EDV numbers into the following formula. EDV multiplied by two equals PSV./3

Resistive index is used to measure the resistance to blood flow. It is calculated as (PSV - EDV)/PSV

Ratio of Lindegaard: The LR is a number that is used to normalize the MCA velocity to the ICA. Divide the MCA's mean velocity by the ICA's mean velocity to get at the answer to this conundrum. With this ratio, it is possible to tell the difference between hyperemia and true vasospasm during a TCD research. If the patient's examination reveals an elevated velocity, it's possible that hyperemia is to blame for the elevated velocity. It is possible that the increased velocity is due to vasospasm when the MCA increases by more than the ICA. It is thought that a normal LR is less than 3, although mild, moderate, and severe vasospasm occur between 3.0 and 4.5, respectively, while severe vasospasm occurs larger than 6.0.

The following are typical arterial vasospasm-related velocity values:

Lindegaard Ratio of less than 3 and MFV of less than 120 cm/s are considered normal for the middle cerebral artery.

Lindegaard Ratio 3-4.5 indicates mild vasospasm, MFV between 120 and 150 cm/s.

The MFV is 150-200 cm/s, and the Lindegaard Ratio is 4.5-6.0 in patients with moderate vasospasm.

A Lindegaard Ratio of more than six indicates severe vasospasm.

MFV >80 cm/s in ACA= Vasospasm

MFV >85 cm/s in PCA= Vasospasm[26].

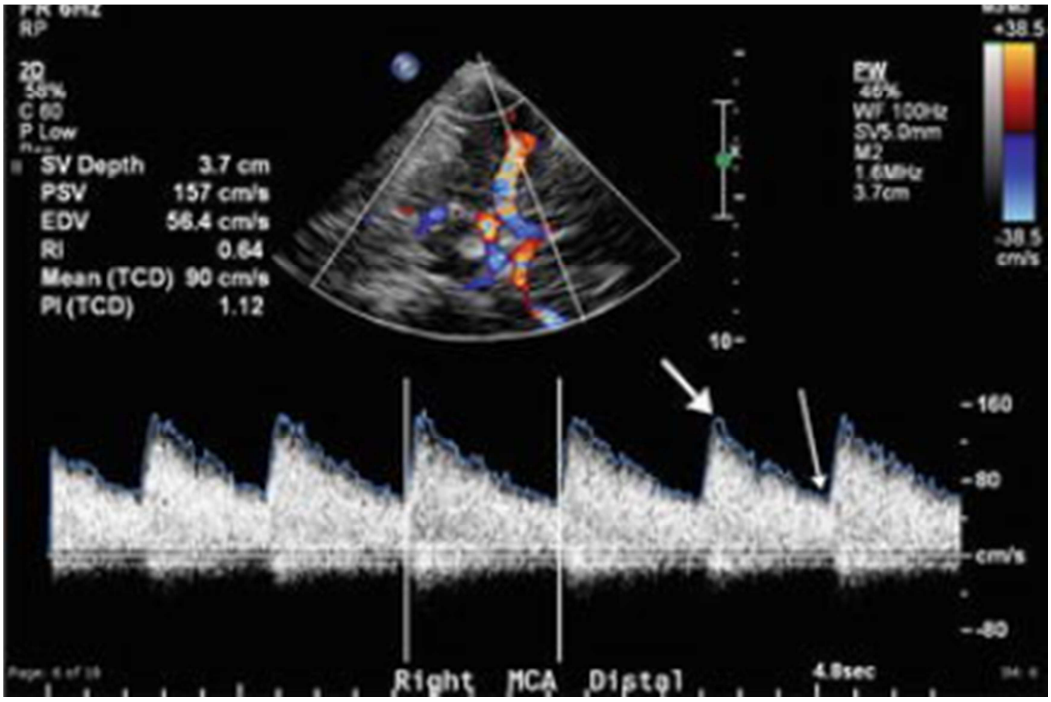


Figure3.Spectral Doppler waveform. The spectral Doppler waveform is a time/velocity curve that demonstrates the blood flow velocities over time within a defined sample window in the vessel being evaluated. The area below the curve or spectral line is called the spectral envelope or window. With turbulent blood flow, this window will "fill in" representing the myriad flow velocities associated with turbulent flow (as seen in this example). The spectral Doppler also can be used to measure peak systolic velocity (thick arrow) and end-diastolic velocity (thin arrow) from which the mean flow velocity and the resistive index can be calculated (table to left of CDF image). A waveform above the baseline (positive) indicates flow toward the transducer and a waveform below indicates flow away from the transducer[37]

ULTRASOUND ANATOMY & ACOUSTIC WINDOWS

The single most conventional acoustic window of TCD is anteriorfontanelle view

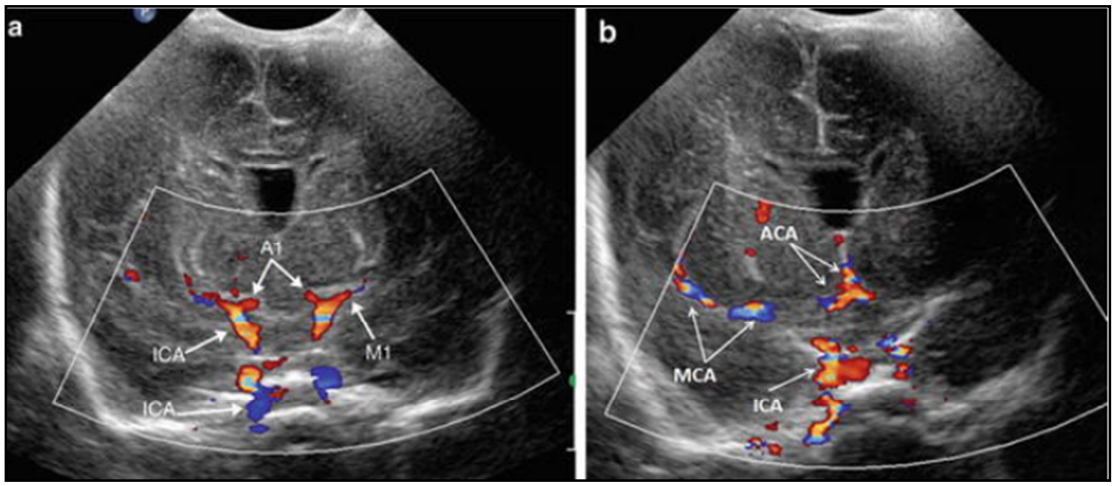


Figure 4. Coronal color Doppler flow imaging through the circle of Willis (a, b), utilizing the anterior fontanelle as an acoustic window, demonstrates the A1 segments of the anterior cerebral artery (ACA), M1 segments of the middle cerebral arteries (MCA), and the intracranial internal carotid artery (ICA) [37]

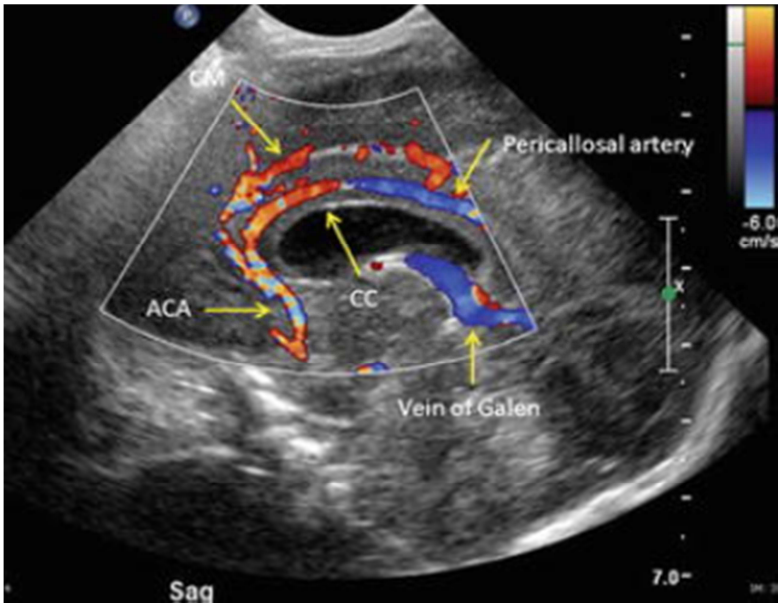


Figure5. Sagittal midline color Doppler flow imaging through the anterior fontanelle demonstrates the pericallosal artery, the callosomarginal artery (CM),the anterior cerebral artery (ACA), the vein of Galen, and the corpus callosum (CC) [37]

The four other most significant acoustic windows in the human skull are the transorbital, the submandibular, transtemporal window and the suboccipital windows. Every checkup needs to include measurements taken through all four TCD windows. The principal branches of the circle of Willis should also have their blood flow channels examined at different depths. Although the advantages provided by each window are unique and may not apply to all arteries or situations, it is still crucial that they be shown.

The transtemporal window is composed of the anterior, middle, and posterior windows. The ICA bifurcation may be detected via this window between 55 and 65 millimetres down. Typically, these measurements range from around 55 to 65 mm. Because of this, the ICA divides off into the ACA and MCA.

The great anatomical marker for finding the arteries that are a part of the anterior circulation is the terminal ICA since it acts as a connection point for the two main ICA branches. After it splits from the ICA, the MCA travels laterally and somewhat anteriorly, according to an examination conducted at depths ranging from 35 to 55 mm. After the ICA bifurcation, it will first migrate toward the middle, and later it will go toward the front. This may be seen at depths greater than 60 millimetres. According to the proposal, the Affordable Care Act need to be removed from the scope of the probe.

Insonation may be performed via the transtemporal window, which provides access to the posterior cerebral artery (PCA). PCA may be found at a depth of around 60 to 70 millimetres; this location is deeper than the ICA and MCA, which are located farther anteriorly. The proximal PCA, also known as the P1 segment, has flow that is directed toward the probe, while the distal PCA, also known as the P2 segment, has

flow that is directed away from the probe. No matter what time of day it is, the PCA will always display slower speeds than the MCA. People who have what's known as the "foetal PCA configuration". It is really necessary to be conscious of this fact[26].

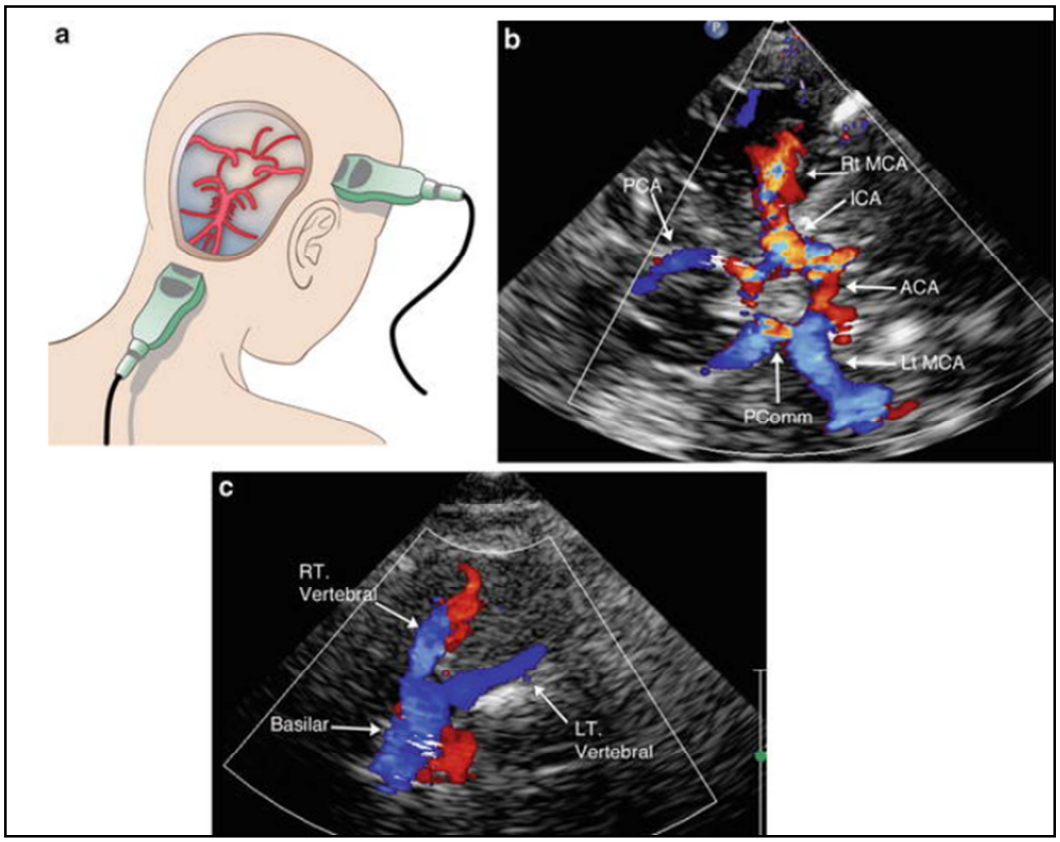


Figure 6.Transtemporaland transforaminal acoustic windows (a). The transducer is placed superior to the zygomatic arch and anterior to the external auditory canal or more cephalad above the earlobe for the transtemporal approach. For the transforaminal approach, the transducer is placed in the midline below the occiput and angled cephalad. Utilizing the transtemporal approach and color Doppler flow imaging, the circle of Willis can be visualized (b). The transforaminal approach allows visualization of the basilar and vertebral arteries (c) **ACA** ***anterior cerebral artery,*** **ICA** ***terminal internal carotid artery,*** **MCA** ***middle cerebral artery,*** **PCA** ***posterior cerebral artery,*** **PComm** ***posterior communicating artery***[37]

Examining the carotid syphon as well as the occular artery is possible when one makes use of the transorbital window. The probe is placed after closing the eyes of the patient. In order to avoid causing harm to the soft tissue, it is essential to use the least amount of energy possible and maintain the insonation at its shortest possible length. In order to insonate the carotid syphon, the probe has to be positioned at a depth of 55 to 70 mm pointing towards the ophthalmic canal. It is possible to distinguish between the various components of the syphon by paying attention to the direction in which the blood is moving. When it arrives to the syphon, flow normally travels away from it in its supraglenoid area, toward it in its infraclinoid region, and then toward the probe in its infraclinoid region. The genu contains a passageway that allows flow in both ways. Between 40 and 50 millimetres below the surface is where you'll find the ocular artery. It is of the utmost importance that the blood flow from the ocular artery be directed towards the probe.

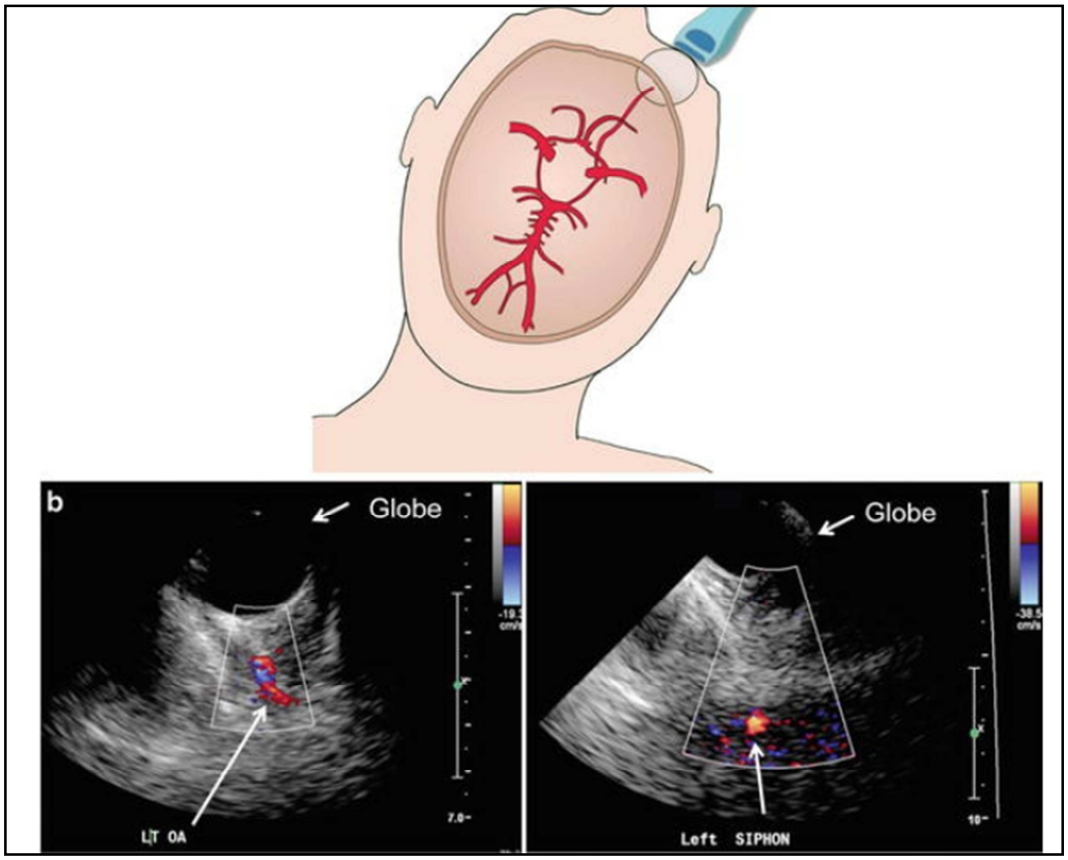


Figure 7: Transorbital acoustic window: The transducer is placed lightly on the closed eyelid (a) and utilizing the globe as an acoustic window, the ophthalmic artery and carotid siphon can be visualized by color Doppler flow imaging (b). OA ophthalmic artery

Basilar and vertebral arteries are insonated through the suboccipital window which is achieved by flexion of the patient's neck. Although this artery may be detected at a depth of up to 100 millimetres, it is far more likely to be discovered at a depth of 60 to 70 millimetres. Although it is possible to locate the basilar artery by positioning the probe in a medial direction, the most effective method for locating vertebral arteries is to insonate them at a depth of 80 to 115 mm while gradually shifting the probe to the side, as shown in the image. This is because the basilar artery is located more superficially than the vertebral arteries. Generally speaking, blood

flow in the vertebral arteries and at the apex of the basilar artery moves in the opposite direction to that of the probe.

Through a window located at the angle of your jaw that is between 40 and 60 millimetres deep, the distal internal carotid artery (ICA) may be located and identified. This is a point in the flow channel when the flow typically goes in the opposite direction of the probe[26].

Review of studies

Neonates with suspected sepsis were subjected to a variety of laboratory tests and classified into various categories, such as VEOS, EOS, and LOS, based on the age at which their symptoms first manifested themselves in a clinico-bacterial study conducted in Hubli, Karnataka, in 2000 by Shashikala S. Tallur et al. 64.87 percent in neonates with clinical suspicions of sepsis was found to have a positive blood culture test. Reduction in Infant mortality rate can be achieved by detection and treatment of signs and symptoms of sepsis as early as possible[28].

In 1987, Hiroko Yoshida and her colleagues in Japan conducted a study employing both transcranial Doppler and continuous wave Doppler to examine the skulls of newborns of various gestational ages. Findings showed a direct link between birth date and gender with that of that neonatal blood flow rates in the cerebral arteries. The velocities were found to be lesser in infants born at a younger gestational age[29].

When Rania H. Hashem and her colleagues did a case control study of premature Egyptian neonates with and without an EONS, they employed a Doppler ultrasound of the anterior and posterior chambers (ACA and MCA) to examine the

differences between the two groups. The PI and RI in the ACA and MCA arteries were shown to be lower in early-onset neonatal sepsis preterm infants. No statistical significance was found despite the fact that PSV was increased in sepsisneoanates. Only a small number of preterm infants died as a result of IVH during the course of the study. Doppler follow-up after the commencement of hemorrhage was unable to validate this information[30].

Ratnaparkhi CR et al. performed a cross-sectional analysis on neonates in a 2019 study in Nagpur, India. For each group of newborns, the risk variables and clinical suspicion of EONS were evaluated. Doppler ultrasound was used to assess the health of numerous brain vessels in both groups. In the ICA, MCA, and VA, there was evidence of decreased RI, increased PI, and increased EDV on either side. As an initial marker of SIRS, they found that CBF could be used to determine neonates who were at risk of developing EONS through their blood flow patterns. A poor APGAR score after 5 minutes was found to be statistically linked to EONS, according to the researchers. However, the long-term neurological prognosis of the newborns cannot be established because this is merely a one-time evaluation of CBF. Ratnaparkhi and her colleagues conducted a cross-sectional analysis on 123 babies over the course of two years as part of their research. Separation into two groups was performed on the neonates: those with EONS (group I) and those without (group II) respectively. Neonatal brain hemodynamics were studied using an ultrasonic Doppler examination in the first 72 hours of life. The internal carotid, middle cerebral and vertebral arteries on both sides were studied for Doppler indices and flow velocity. Study participants with EONS had lower RI, higher PSV & EDV values, and a more rapid progression to cardiovascular disease. They concluded that in babies with EONS, noninvasive

ultrasonography doppler testing can detect abnormal cerebral hemodynamics, in this study[31].

The prevalence of delays in neuromotor and cognitive development in children with neonatal sepsis is three times higher than in children without the condition. As a result of advancements in paediatric neurosonography, Doppler sonography may now be used to assess children's brain vascular architecture and perfusion. Rania Hashem's research used TCD to evaluate velocities and cerebral blood flow characteristics in preterm infants diagnosed with EONS. When compared to the control group, neonates with EONS had greater MCA and ACA peak systolic velocities and reduced resistance (RI and PI) as an early response to due sepsis induces early vasoconstriction. According to Sriparna et al the same Doppler findings were reported in babies with EONS within 24 hours after birth. These results suggest that an increase in CBF is a typical first response to sepsis. Koch et al. found that those with full-term chorioamnionitis had lower cerebral vascular resistance than controls, and this is in line with their results. TCD was conducted within 24 hours after delivery by Sriparna et al, but on day three following birth by Hashem. Septic preterm newborns in the hospital developed intraventricular hemorrhage, and three preterms died in the first month of follow-up ultrasound. Because there was no Doppler evaluation of the cerebral blood flow when IVH occurred, this assumption could not be confirmed as a marker of a change in cerebral blood flow in relation to IVH. Due to the cross-sectional nature of the study, the researchers were unable to follow changes in CBFV over time and determine whether or not they were linked to poor outcomes. Individuals in the sepsis group who died or acquired IVH had a greater CBF than those who survived normally, according to Sriparnaet al. For each parameter, a single

measurement was used instead of serial measurements, which would have tracked changes over time with higher accuracy[12].

In a case control research study conducted by Renmin Hospital, Wuhan University between January 1, 2019, and March 31, 2021 on 86 preterm neonates. Transcranial ultrasonography was used to analyse the hemodynamic modifications in the cerebral vasculature, and the results showed that EDV, MV, and PSV were all higher in the EONS group, while PI and RI were both lower. This was shown to be the case despite the fact that RI and PI were both lower. Because of this, it was deduced that inflammatory chemicals are released during the, the first phases of EONS which causes dilatation of cerebral arteries. This, in turn, reduces vascular resistance and pulsation, ultimately increasing blood flow. This increases the intraventricularhaemorrhage risk. It is possible that measuring IL-6 levels at very early stages helps to detect early-onset sepsis. However, the findings of this experiment demonstrated that the MV & EDV of ACA, in addition to the MV, PSV, & EDV of MCA and PCA, were more responsive compared to IL-6 concentrations[32].

Mohammed S El Shimy et al. from Ain Shams University Hospitals conducted another study between December 2014 and December 2016 on 200 newborns with EONS risk factors to determine whether or not the ratio of the mean flow velocities in the internal carotid artery (ICA) and the middle cerebral artery (MCA) could predict neurodevelopmental disabilities in the immediate postnatal period. At 6 months of age, they were evaluated using Griffiths Mental Developmental Scale after having their PSV, EDV, RI of ACA & MCA recorded on Day 1 of life. In this study, researchers observed that CBFV was higher in the sepsis group than the no-sepsis group, and that ACA RI values below 0.61 was associated with a higher risk of

developing encephalopathy in them. Low RI & PI and high MCA PSV were identified within 24 hours of delivery in EONS neonates, which is consistent with the work of, Basu et al. Furthermore, the cNSE levels were found to be greater in sepsis neonates. Researchers concluded that both of these measures are useful indicators of sepsis-related damage to the brain's blood vessels[33].

All these studies, reached a common consensus that in addition to the routine EONS transcranial sonography screening of preterm babies, a Doppler examination be performed in order to examine their cerebral hemodynamic state and to detect any increase in blood flow early on. In addition to the early administration of anti-inflammatory drugs, preterm neonates with EONS may benefit from clinical care such as establishing hemodynamic stability, maintaining normotensive state, and refraining from activities that could further affect blood flow.

METHODOLOGY

STUDY DESIGN: This research consisted of an observational study conducted at KLE's Dr. Prabhakar Kore Hospital & MRC, Belagavi, a medical facility over one year period, 30 preterm babies who had risk factors of early onset sepsis & 30 normal preterms were the subjects of the study . Beginning of the experiment will take place on January 1, 2021, and it will conclude on December 31, 2021.

METHOD OF DATA COLLECTION: All of the participants' parents will be asked to sign a written agreement stating that they have been made aware of the nature of the research that is being undertaken on their children as part of the study that will be conducted.

Transcranial Doppler (TCD) ultrasound was used to assess blood flow of cerebral vessels MINDRAY system with high-frequency transducer operating at 7.5-12 MHz and a sector array probe operating at 2-6 MHz was used to conduct each ultrasound exam. During TCD and TCU, the newborn will not be removed from the incubator for any reason to maintain a normotensive environment. Babies are examined with their heads tilted to the side while lying supine. In an attempt to prevent hypothermia, the examination will only need a minimal quantity of gel to be applied.

By placing a transverse probe on the patient's anterior fontanelle and listening to the echoes it creates, we may insonate the middle cerebral artery (coronal position). Putting the beam in the trans-fontanelle position tilts it so that the front side is towards the user. Beam insonation may be performed on the first and second MCA segments

thanks to the beam's forward position (M1 & M2). We want to use colour Doppler to investigate the MCA, that enters the Sylvian fissure laterally.

The trans-fontanelle method will be used with the probe lying in a longitudinal position on the patient's forehead to insonate ACA (sagittal position). Trans-fontanelle technique involves angling ultrasound beam such that it passes in front of the patient's skull. As the beam is aimed towards the front of the ACA, it will be able to insonate segments 1 and 2 of the ACA (A1 & A2). Color Doppler will be used in the study of the corpus callosum, and ACA.

A 60-degree angle will be used for the spectral wave analysis. Throughout the inquiry, we will maintain a constant sample volume, gain, and power. Resistance and pulsatility values will be determined using hand calculations.

Algorithm for calculating the best possible size of a sample from the data provided:

The formula for the smallest possible sample size that can be produced from these data.

$$n = \frac{z_\alpha{}^2 P(1-P)}{d^2}$$

The P variable represents the prevalence, and the d variable represents the expected difference in prevalence between the two groups.

The value of z is related to the significance of anything. z = 1.96, statistically significant at the 5% level.

If P = 64.873 and d = 15% of P = 9.73%, then the required sample size is forty.

The number of people that took part in the research will be increased to sixty so that more accurate conclusions can be drawn from it.

SAMPLING METHOD: Sampling according to predetermined inclusion and exclusion criteria

All peterms are eligible for the study. In our study we have divided the preterms into two groups: Sepsis group & non sepsis group (Normal preterms with no sepsis risk factors)

INCLUSION CRIETRIA (For sepsis group)

In our sepsis group, we will include preterm children who have a history of exposure to at least two of the following risk variables in our study because preterm nature of the infant (less than 37 weeks of gestational age) is in itself a risk factor of early-onset sepsis.

- Meconium stained amniotic fluid
- Rupture of the membranous structure that lasts for more than twenty-four hours.(PMRM)
- Prolonged/assisted labour

Blood tests have to fulfil at least two of the following requirements: the white blood cell count (WBC) must be either below 5,000 or over 20,000 x 109 cells/L; the international normalised ratio (I/T) must be larger than 0.2; and the platelet count (PCV) must be below 100,000 x 109 cells/L.

Patients who presented with the following signs and symptoms in clinical practise were considered to have:

Respiratory Problem:

1. Tachypnea
2. A significantly higher prevalence of apnea
3. A surge in desaturations

Metabolism Changes:

1. Hypothermia
2. Metabolic acidosis.
3. Excessive body heat
4. Glucose Instability
5. Feeding Intolerance

Neurologic Changes:

1. Lethargy
2. Hypotonia

EXCLUSION CRITERIA (For both sepsis & non sepsis group):

1. Newborns who are dependent on mechanical ventilation and are hemo dynamically unstable at the time of the CBF assessment.
2. Term infants

Examining the Data in Detail

In light of the fact that this is an observational study, the following is how we will approach the data analysis.

The data is divided into two categories based on some qualitative metric, hence to compare the continuous variables, statistical tests like student's unpaired t

test will be used. The median value will serve as a proxy for discrete variables going forward.

The categories are going to be analysed further by using rates, ratios, and percentages. To investigate the degree of correlation that exists between the variables of interest (result, clinical, and demographic), the Chi-square test will be used.

In order to illustrate the contrast, we will utilise the proper visuals.

Results with p value less than 5%.will be considered significant

RESULT AND INTERPRETATION

Variable list

Gestational age (sepsis group)

APGAR score (sepsis group)

PO2 (sepsis group)

PCO2 (sepsis group)

HCO3 (sepsis group)

Gestational age (non sepsis group)

APGAR score (non sepsis group)

PO2 (non sepsis group)

PCO2 (non sepsis group)

HCO3 (non sepsis group)

Resistivity Index of Middle Cerebral Artery (sepsis group)

Pulsatility Index of Middle Cerebral Artery (sepsis group)

Resistivity Index of Anterior Cerebral Artery (sepsis group)

Pulsatility Index of Anterior Cerebral Artery (sepsis group)

Resistivity Index of Middle Cerebral Artery (non sepsis group)

Pulsatility Index of Middle Cerebral Artery (non sepsis group)

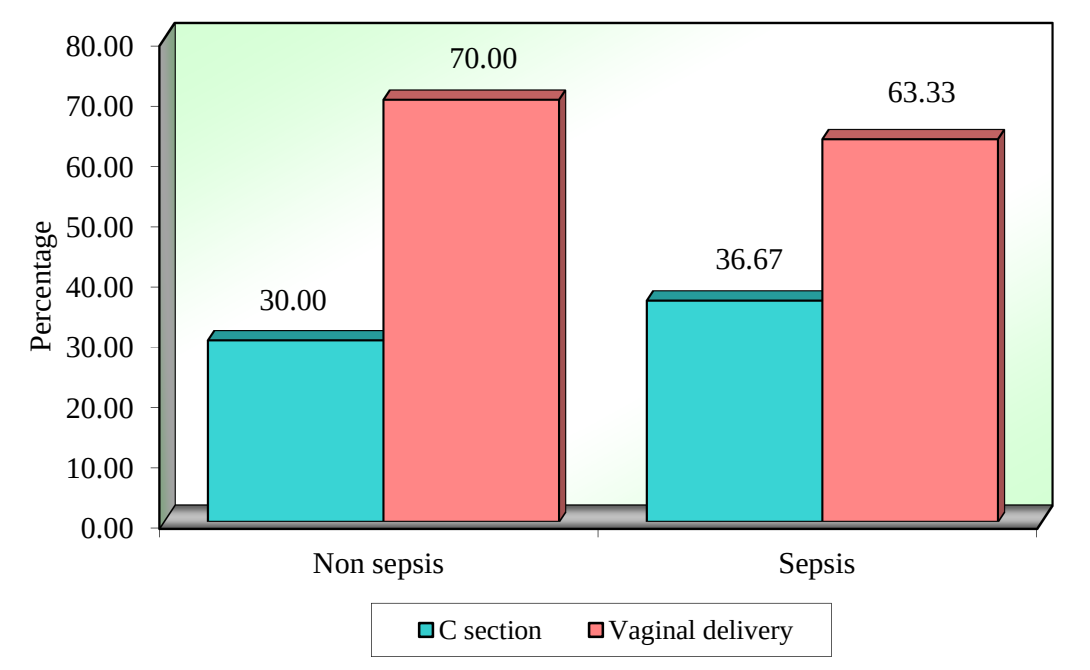
Resistivity Index of Anterior Cerebral Artery (non sepsis group)

Pulsatility Index of Anterior Cerebral Artery (non sepsis group)

Table 1: Comparison of sepsis & non sepsis group according to types of delivery

Type of delivery	Non sepsis	%	Sepsis	%	Total	%
C section	9	30.00	11	36.67	20	33.33
Vaginal delivery	21	70.00	19	63.33	40	66.67
Total	**30**	**100.00**	**30**	**100.00**	**60**	**100.00**
Chi-square=0.3000, p=0.5840						

Figure 1: Comparison of sepsis & non sepsis group according to types of delivery



Interpretation: The above table and figure indicates that, in case of no-sepsis group total 30 patients among them, 9 (30%) patients had c section delivery and remaining 21 (70%) patients had vaginal type delivery likewise, in case of sepsis group total 30 patients among them, 11 (36.67%) patients had c section delivery and remaining 19 (63.33%) patients had vaginal type delivery.

While in case of total 60 patients among them, 20 patients (33.33%) patients had c section delivery and remaining 40 (66.67%) patients had vaginal type delivery.

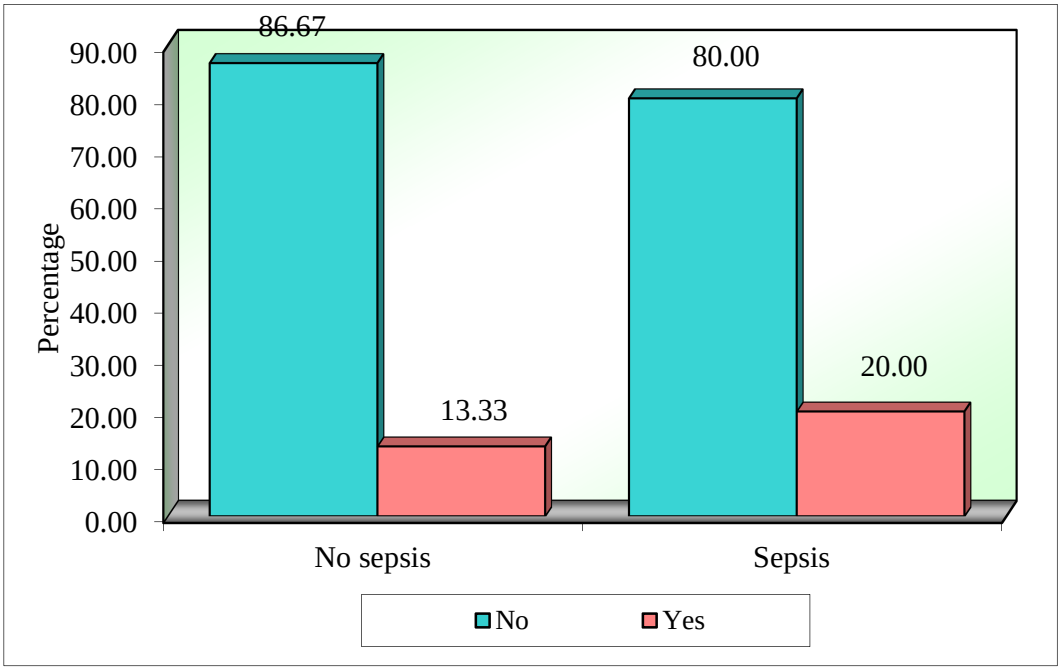
Majority of women' in both groups had vaginal delivery as compared to c section.

While looking for significant level chi square value is (0.3000) which was non-significant (0.5840 %) it means no significant difference between sepsis and no sepsis group.

Table 2: Comparison of sepsis & non sepsis group according to prolonged delivery status

Prolonged delivery	Non sepsis	%	Sepsis	%	Total	%
No	26	86.67	24	80.00	50	83.33
Yes	4	13.33	6	20.00	10	16.67
Total	**30**	**100.00**	**30**	**100.00**	**60**	**100.00**
Chi-square=0.4800, p=0.4880						

Figure 2: Comparison of sepsis & non sepsis group according to prolonged delivery status



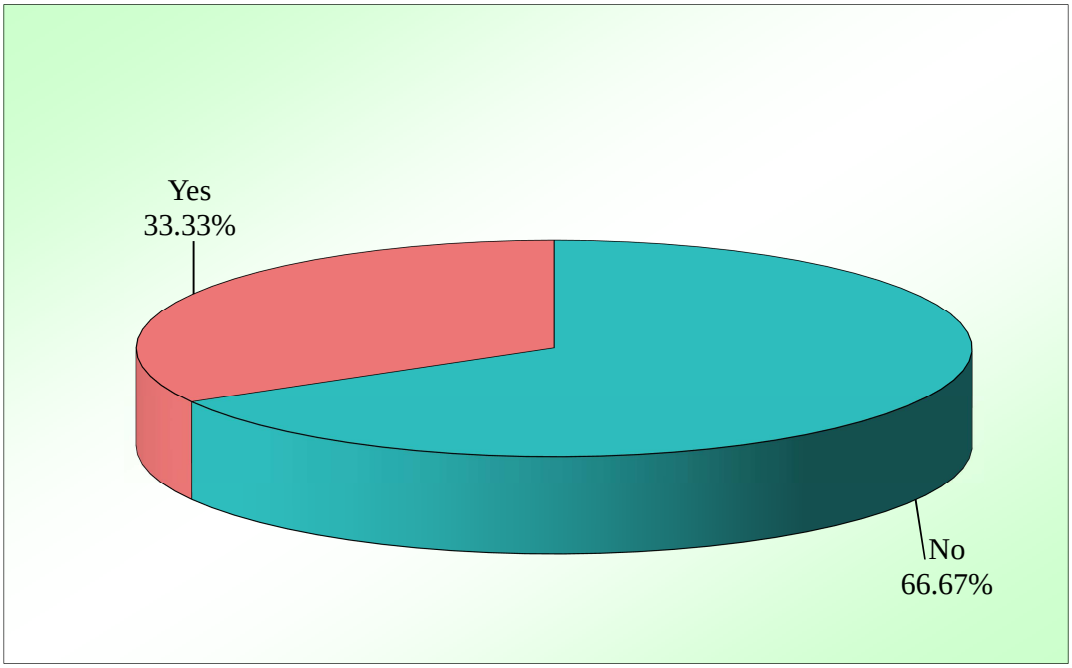
Interpretation: The above table and figure indicates that, in case of no-sepsis group total 30 4 (13.33%) patients had prolonged delivery likewise, in case of sepsis group out of 30 patients 6 (20%) patients had prolonged delivery.

While looking for significant level chi square value is (0.4800) which was non-significant (0.4880 %) it means no significant difference between sepsis and no sepsis group.

Table 3: Status of PROM in sepsis group

Status of PROM	Number	Percentage
No	20	66.67
Yes	10	33.33
Total	**30**	**100.00**

Figure 3: Status of PROM in sepsis group



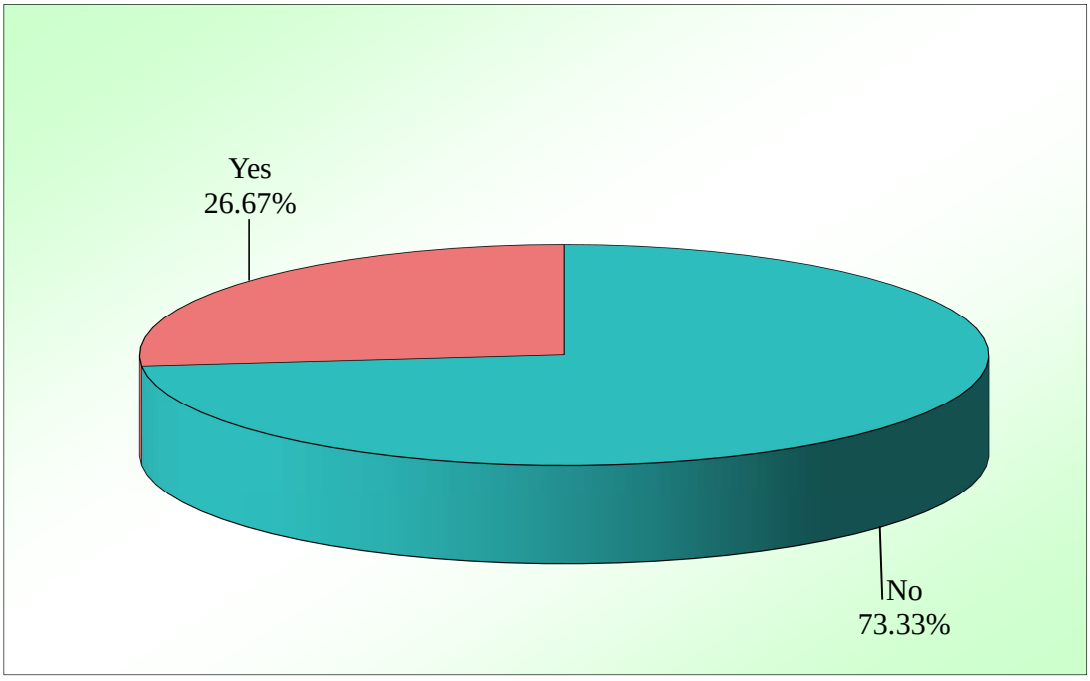
Interpretation: The above table and figure indicates that, in case of sepsis group among total of 30 patients 20 (66.67%) had PMPR

Majority of women had PMPR

Table 4: Status of Meconium stained liquor in sepsis group

Status of Meconium stained liquor	Number	Percentage
No	22	73.33
Yes	8	26.67
Total	**30**	**100.00**

Figure 4: Status of Meconium stained liquor in sepsis group

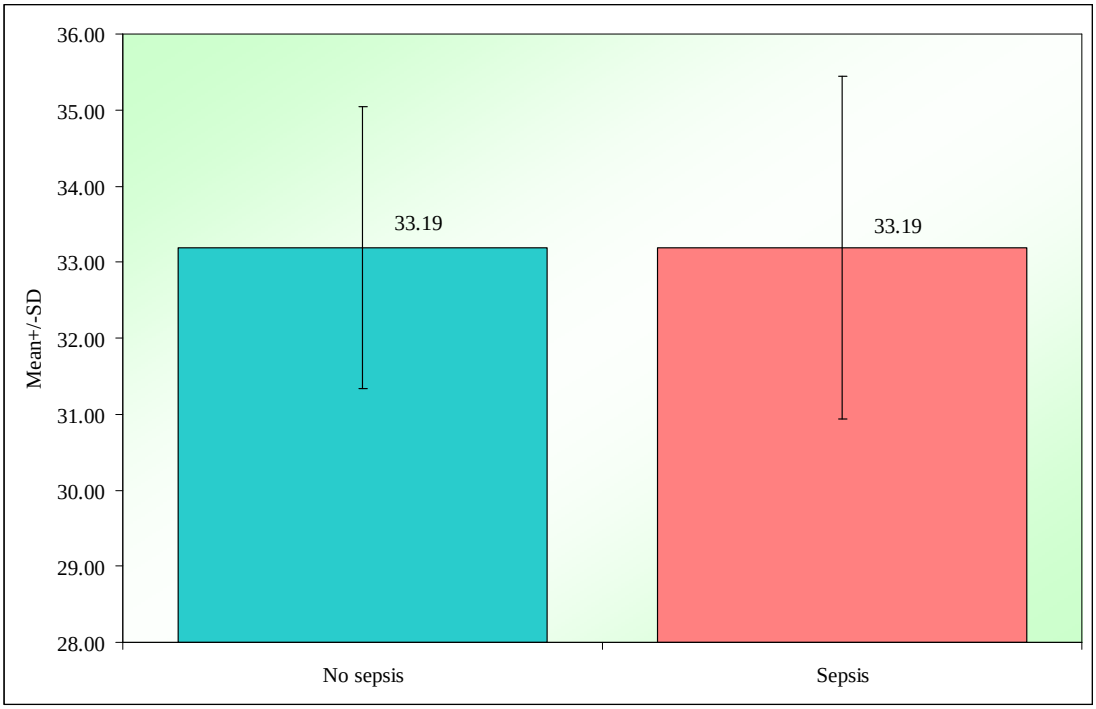


Interpretation: The above table and figure indicates that, in case of sepsis group out of 30 remaining 8 (26.67%) patients had Meconium stained liquor.

Table 5: Comparison of sepsis & non sepsis group with mean gestational age (in weeks) by independent t test

Groups	Mean	SD	Median	t-value	P-value
Non sepsis	33.19	1.86	33.45	**0.0000**	1.0000
Sepsis	33.19	2.25	33.80		

Figure 5: Comparison of sepsis & non sepsis group with mean gestational age (in weeks) by independent t test



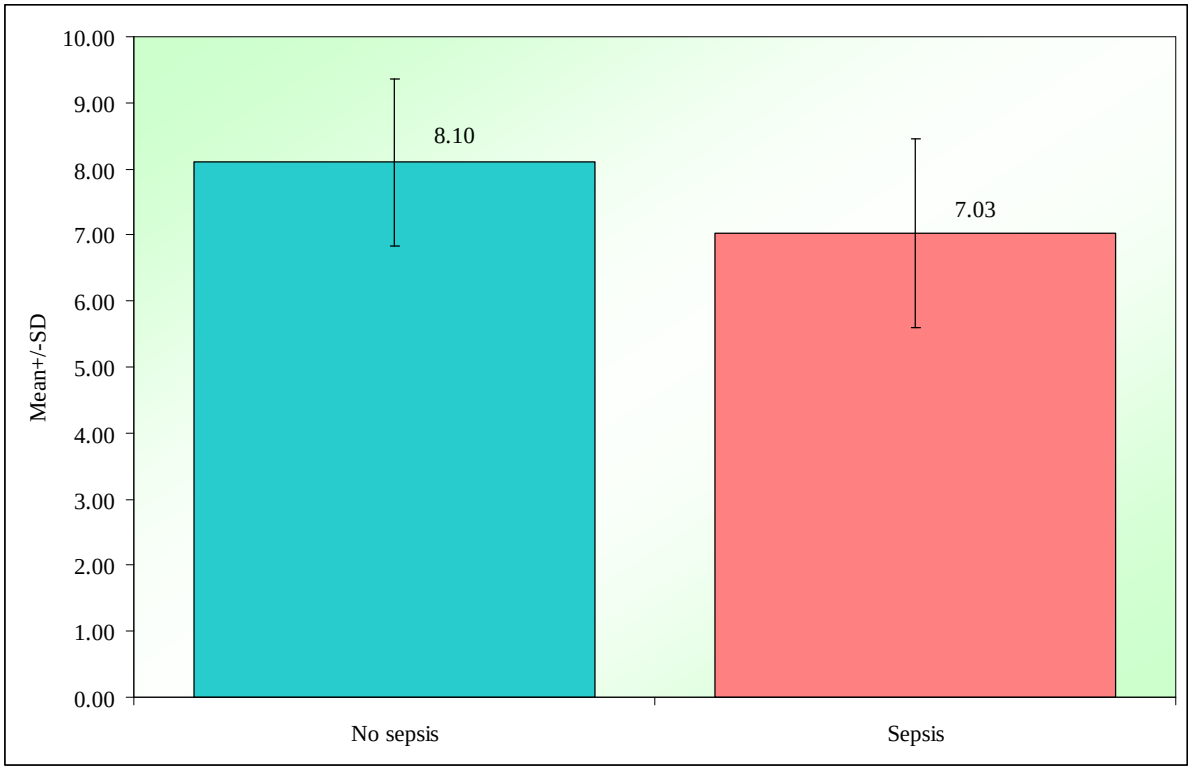
Interpretation: The above table and figure indicate that, in case of mean gestation age variables, descriptive statistics in that higher mean (33.19), SD (2.25) and median (33.80) in sepsis group.The independent t test (0.0000) which indicate that, non-significant value which means non-significant mean difference was observed between sepsis and non-sepsis group for gestation age.

Table 6: Comparison of sepsis & non sepsis group with mean APGAR scores by independent t test

Groups	Mean	SD	Median	t-value	P-value
Non sepsis	8.10	1.27	8.00	**3.0607**	0.0033*
Sepsis	7.03	1.43	7.00		

***p<0.05**

Figure 6: Comparison of sepsis & non sepsis group with mean APGAR scores by independent t test



Interpretation: The above table and figure indicate that, in case of mean APGAR scores variables, descriptive statistics in that higher mean (8.10) and median (8.00) were observed in non sepsis group, while higher SD (1.43) was observed in sepsis group.

The independent t test (3.0607) which was highly significant at less than 1% which indicate that, highly significant value which means significant mean difference was observed between sepsis and non-sepsis group for APGAR scores.

Table 7: Comparison of sepsis & non sepsis group with mean PO2, PCO2, HCO3 values by independent t test

Variables	Groups	Mean	SD	Median	t-value	P-value
PO2	**Non sepsis**	79.02	5.77	78.40	**1.9066**	0.0615
	Sepsis	76.01	6.43	73.60		
PCO2	**Non sepsis**	40.25	4.31	39.95	**2.0789**	0.0421*
	Sepsis	38.00	4.07	37.40		
HCO3	**Non sepsis**	22.30	3.63	22.25	**1.8002**	0.0770
	Sepsis	20.65	3.44	20.60		

***p<0.05**

Figure 7: Comparison of sepsis & non sepsis group with mean PO2 values by independent t test

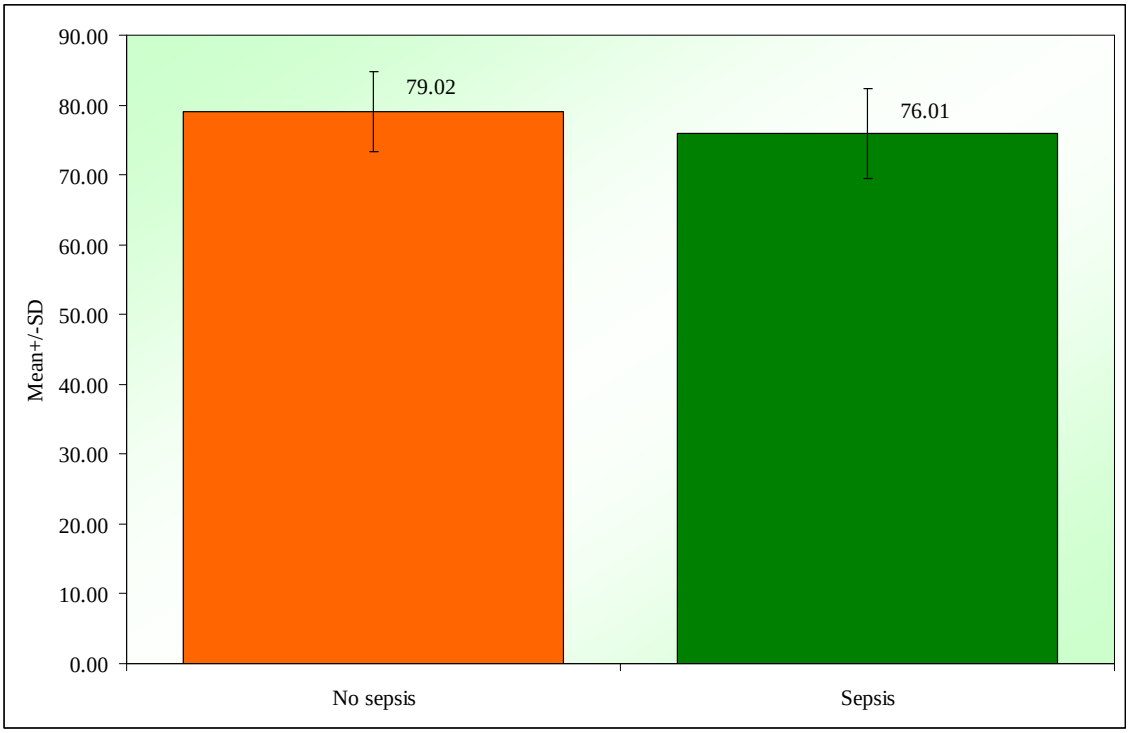


Figure 8: Comparison of sepsis & non sepsis group with mean PCO2 scores by independent t test

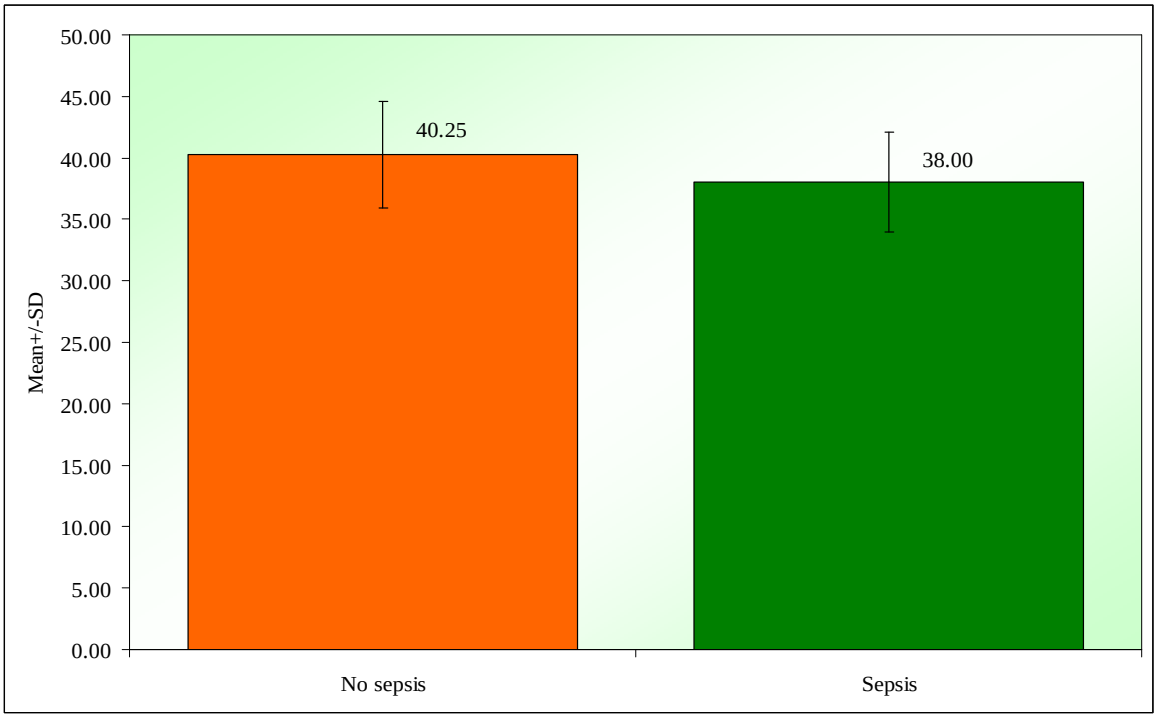
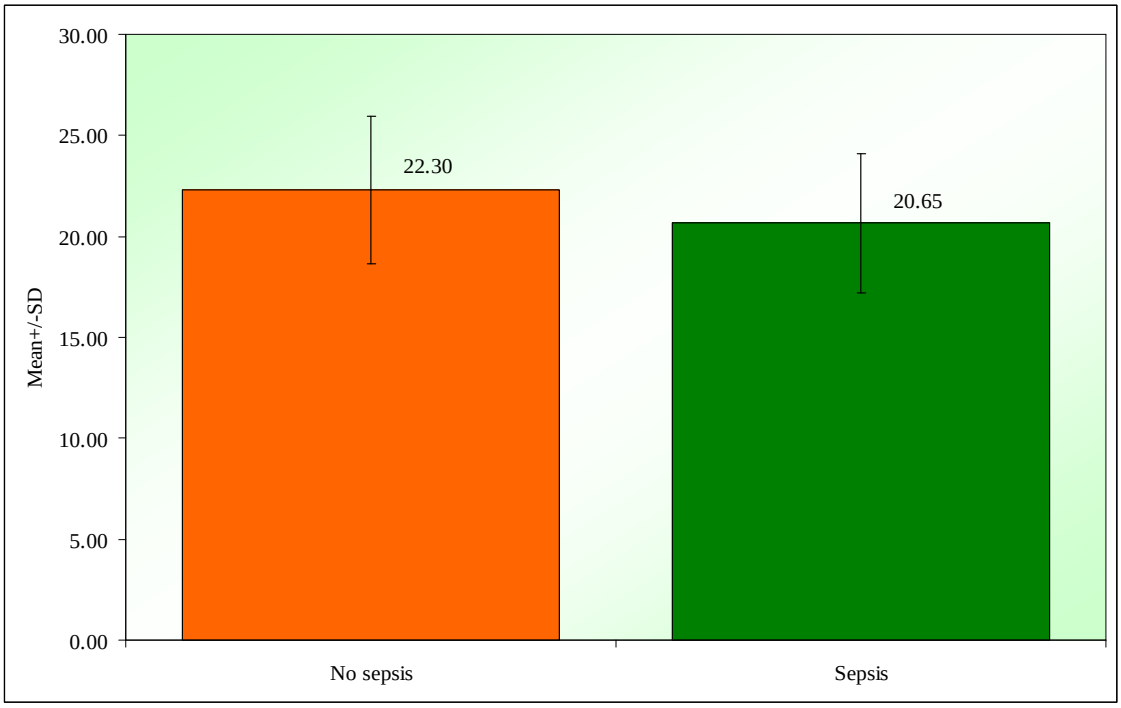


Figure 9: Comparison of sepsis & non sepsis group with mean HCO3 values by independent t test



Interpretation: The above table and figure indicate that, in case of mean PO2 variable, descriptive statistics in that higher mean (79.02) and median (78.40) were observed in no sepsis group, while higher SD (6.43) was observed in sepsis group. Whereas, in case of mean PCO2 variable, descriptive statistics in that higher mean (40.25), median (39.95) and SD (4.31) was observed in no sepsis group. While in case of mean HCO3 variable, descriptive statistics analysis in that higher mean (22.30), median (22.25) and SD (3.65) was observed in no sepsis group.

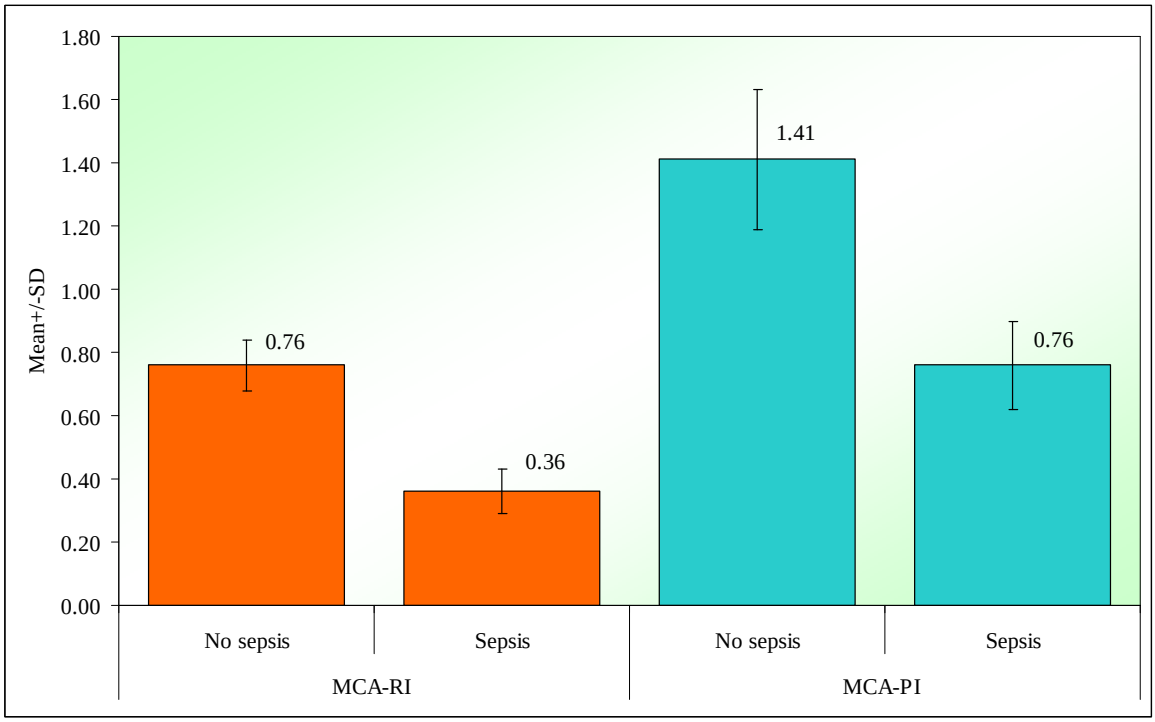
The independent t test (2.0789) which was significant at less than 5% which indicate that, significant value which means significant mean difference was observed between sepsis and non-sepsis group for PCO2. While the independent t tests for PO2 (1.9066) and HCO3 (1.8002) which was non- significant which indicate that, non-significant mean difference was observed between sepsis and non-sepsis group for PO2 and HCO3.

Table 8: Comparison of sepsis & non sepsis group with mean MCA-RI & MCA-PI values by independent t test

Variables	Groups	Mean	SD	Median	t-value	P-value
MCA-RI	**Non sepsis**	0.76	0.08	0.74	**20.4456**	0.0001*
	Sepsis	0.36	0.07	0.33		
MCA-PI	**Non sepsis**	1.41	0.22	1.43	**13.7251**	0.0001*
	Sepsis	0.76	0.14	0.76		

***p<0.05**

Figure 10: Comparison of sepsis & non sepsis group with mean MCA-RI & MCA-PI values by independent t test



Interpretation: The above table and figure indicate that, in case of mean MCA-RI variable, descriptive statistics in that higher mean (0.76), median (0.74) and SD (0.008) was observed in no sepsis group. Whereas, in case of mean MCA-PI variable, descriptive statistics analysis in that higher mean (1.41), median (1.43) and SD (0.22) was observed for no sepsis group.

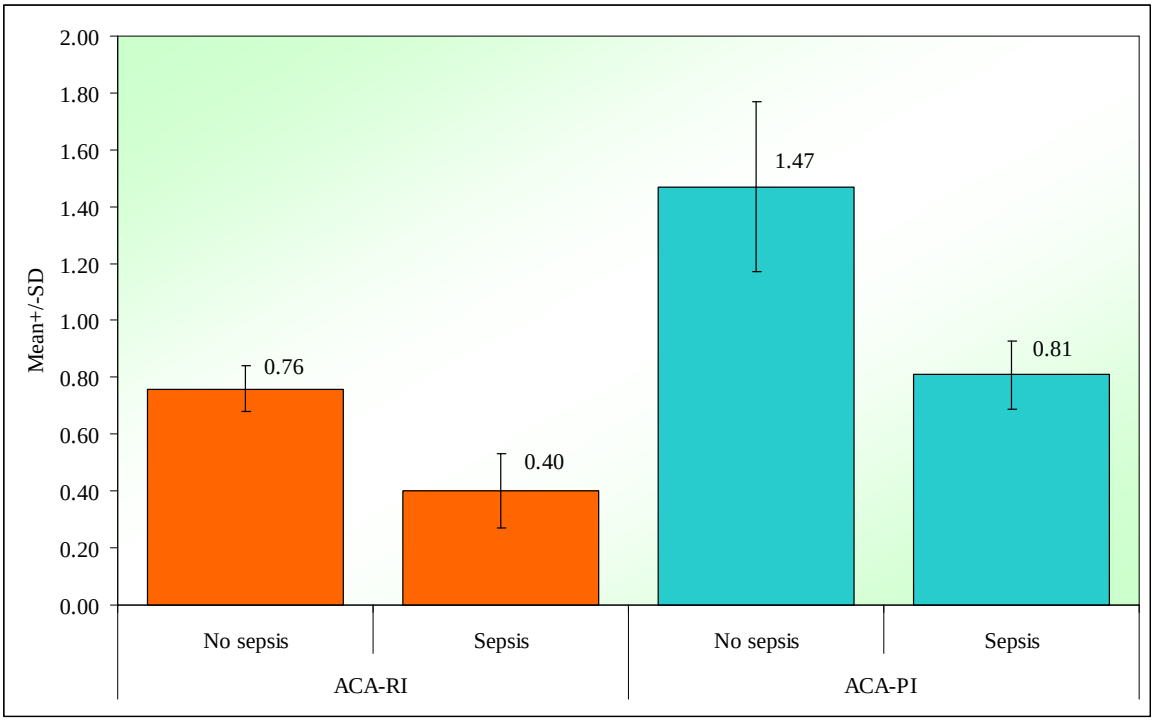
The independent t test for MCA-RI (20.4456) and MCA-PI (13.7251) which was highly significant at less than 1% which indicate significant mean difference was observed between sepsis and non-sepsis group for MCA-RI and MCA-PI variable.

Table 9: Comparison of sepsis & non sepsis group with mean ACA-RI & ACA-PI values by independent t test

Variables	Groups	Mean	SD	Median	t-value	P-value
ACA-RI	**Non sepsis**	0.76	0.08	0.74	**12.3446**	0.0001*
	Sepsis	0.40	0.13	0.40		
ACA-PI	**Non sepsis**	1.47	0.30	1.51	**11.1977**	0.0001*
	Sepsis	0.81	0.12	0.85		

***p<0.05**

Figure 11: Comparison of sepsis & non sepsis group with mean ACA-RI & ACA-PI values by independent t test



Interpretation: The above table and figure indicate that, in case of mean ACA-RI variable, descriptive statistics in that higher mean (0.76), median (0.74) in no sepsis group and maximum SD (0.13) was observed in sepsis group. Whereas, in case of mean ACA -PI variable, descriptive statistics analysis indicate that higher mean (1.47), median (1.51) and SD (0.30) was observed for no sepsis group.

The independent t test for ACA -RI (12.3446) and ACA -PI (11.1977) which was highly significant at less than 1% which indicate that significant mean difference was observed between sepsis and non-sepsis group for ACA -RI and ACA –PI variable.

DISCUSSION

Due to advancements in critical care, more babies are making it through their first year of life despite being born prematurely and with a low birth weight. A combined clinic-radiological approach to the neurological evaluation of premature newborns has allowed for recent advancements in the diagnosis and treatment of perinatal brain damage. It has improved our knowledge of the origin and course of the brain lesions, allowing for more precise medical intervention that may have a positive effect on clinical outcome. In order to better diagnose EONS, researchers have been looking at the possible connection between risk factors for neurodevelopmental disorders and alterations in cerebral blood flow (CBF). The risk of neuromotor and cognitive deficits in children diagnosed with neonatal sepsis was shown to be three times higher than in children without the diagnosis

Correlation of Doppler indices

In our study, we discovered that ACA & MCA median PI was 0.85 & 0.76 respectively in the sepsis group and 1.51 &1.43 respectively in the non sepsis group. The median ACA & MCA RI in the sepsis group was 0.4 & 0.33 respectively which is significantly lower than the median RI value of nonsepsis group (0.74). Both the pulsatility index and the resistivity index were significantly reduced in the sepsis group.

Our findings were consistent with those of prior research conducted by Rania H. Hashem. Doppler ultrasonography was utilised to examine the ACA and MCA in a group of premature infants in his case-control research from 2017. Their study had concluded that a lower ACA and middle cerebral artery PI and RI were seen in

preterm neonates with early-onset neonatal sepsis[30].Our study alsoagreed with the study of Sriparna et al. that detected significantly lower resistance (RI and PI) in all the three major cerebral vessels (ICA, MCA and vertebral artery(VA))documented within24hr of birth in neonates with EONS.

Similar study results where also shown in cross-sectional study carried out in 2019 by Ratnaparkhi CR and colleagues in Nagpur 31, India in which Newborns' cerebral arteries were analysed using Doppler ultrasonography, and those with risk characteristics or clinical suspicion of EONS showed low RI & PI values in the ICAs, MCAs, and VAs of both sides.

Correlation of clinical risk factors

63.33 % of our cases with sepsis had a vaginal birth as risk factor out of which 6 % had a prolonged delivery which might be due to the fact that maternal vaginal tract harbours a variety of organisms so vaginal delivery carries a the risk of direct transmission of infection &prolonged labour will further increase the risk due to proloned exposure of the neonate to these sepsis causing organisms. The same result was observed in a systemic review & meta analysis conducted by Shruti Murthy et al in 2018 on risk factors of neonatal sepsis in Indian population[34].

33.33 % of our cases had PROM as a risk factor which was also similar to the high percentage of PROM in a study by Fedaa Noah Noah, et al in 2019 at Latakia, Syria and also another study of Asia Jabiri in Tanzania . This maybe due to the fact that PMRM may increase risk of ascending infections in fetus[35].

26.67% of our cases had meconium-stained liquor as a risk factor which again correlated with studies Fedaa Noah Noah, et al in which 13 % of their cases had the

same risk factor and also few other studies by Getabelw in Ethiopia and Saleh in Lattakia who observed, 7%, and 10% of their cases had the same risk factor respectively. This may be due to the fact that presence of meconium in amniotic fluid can inhibit the bacteriostatic properties in it and thus can promote the growth of sepsis causing bacterias[35].

On our study median APGAR score value of 7 was found in sepsis babies as compared to the a higher median APGAR score of 8 in non sepsis babies, it had established in previous studies like that of Jimba Jatsho et al at Bhutan National hospital in 2016 that preterm neonates with a low APGAR score at birth are more prone to develop sepsis as low APGAR score indicates the inability of the neonate to acclimatize to the external postnatal environment[36].

CONCLUSION

a. Infants diagnosed with EONS have increased CBF compared to healthy neonates.

b. Infants diagnosed with early-onset neonatal sepsis and those who were born prematurely had lower mean PI and RI values in the anterior and in the middle cerebral arteries.

c. According to the findings of our research, the median MCA PI was 0.78 in the group that had sepsis, whereas it was 1.8 in the group that served as a control. The median resistivity index (RI) in the sepsis group was 0.401, which is also significantly lower than the value that was seen in the non sepsis group (0.800).

d. Also in our study we observed that vaginal mode of delivery, PROM, meconium stained liquor, prolonged labour were all risk factors in our sepsis group

e. CBF assessment by Doppler ultrasound examination may be utilised in the first few hours after delivery; it is a noninvasive portable tool with prompt diagnostic and good prognostic value.

- It is possible that this kind of study might be seen as a supplement to the many blood tests that are carried out in laboratories
- It uses non-ionizing radiation, it is accurate, it is cost-effective, and it can perform serial and repeated examinations, which are all advantages that make it an excellent tool for neuroimaging.
- Other advantages include the ability to detect early signs of sepsis and to begin treatment at an earlier stage.

SUMMARY

- Neonates with blood that has been tainted by bacteria, viruses, or yeast are at risk for developing a life-threatening infection called neonatal sepsis. The physiological and molecular processes behind sepsis-induced encephalopathy remain poorly understood. Potential causes include free radicals, oxidative stress, and cytokines, which cause inflammation, and a deficit in the brain's autoregulation.
- Babies that contract infections within day 3 of life are said to have "Early Onset Neonatal Sepsis." Babies born with septic shock, bacterial meningitis, or bacteremia fall under this category.Acute and chronic complications may occur due to cerebral blood flow changes during the neonatal period. Real-time, risk-free, noninvasive, and sensitive, ultrasound Doppler testing can detect these vascular changes. Due to insufficient intrapartum and postnatal infection control methods, newborns in underdeveloped nations have an increased chance of contracting an illness.
- This observational study, which lasted for a whole year took place in a hospital. Included in the trial were premature babies who had early onset sepsis risk factors and were being cared for at KLE's Dr. Prabhakar Kore Hospital and MRC in Belagavi.
- Our study's sample of sixty patients comprised neonates who were born prematurely and who fitted into our inclusion & exclusion criterias. This is in addition to the fact that gestational age less than 37 weeks is in itself a risk factor for early-onset sepsis.

- After obtaining informed consent from the parent, a MINDRAY system with a high-frequency linear array transducer operating at 7.5-12 MHz and a sector array probe operating at 2-6 MHz to conduct transcranial Doppler ultrasound examination on these neonates in suitable acoustic windows
- Infants who experienced early-onset neonatal sepsis and were born preterm exhibited decreased PI and RI in the ACA and MCA vessels.
- Also in our study we observed that vaginal mode of delivery, PROM, meconium stained liquor, prolonged labour were all risk factors in our sepsis group

LIMITATIONS OF STUDY

- Small sample size, when compared to the vast prevalence of early onset sepsis in our Indian population, especially in those belonging to low socioeconomic group
- Lack of follow up and confirmation of a negative or positive neurological neurological outcome in the neonates in view of the doppler results.

SCOPE FOR FUTURE STUDIES

- Larger sample size so that more accurate representation of sepsis patients
- Frequent sonographic & clinical follow up of the patients so that the neurological outcomes are monitored

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ANNEXURE – I - WRITTEN INFORMED CONSENT

TITLE OF THE STUDY: "TRANSCRANIAL DOPPLER EVALUATION OF CEREBRAL HEMODYNAMIC ALTERATION IN PRETERMS WITH EARLY ONSET NEONATAL SEPSIS- A ONE YEAR HOSPITAL BASED OBSERVATIONAL STUDY AT KLE DR. PRABHAKAR KORE HOSPITAL''

INVESTIGATOR: DR.

GUIDE: DR.

INTRODUCTION AND PURPOSE: Cerebral blood flow (CBF), by Doppler Ultrasound, has been studied mainly to help detect whether alterations have occurred in the neonatal cerebral circulation that could result in brain damage and adverse developmental outcomes. Establishment of the predictive validity of the cerebral blood flow measured by Doppler ultrasound is essential to ensure their usefulness in the early assessment and interpretation of hemodynamic changes in neonates. Studies on cerebral blood flow in neonatal sepsis is of concern because, the brain of the newborn is highly susceptible to blood flow fluctuations. Moderately elevated CBF can increase the chances of cerebral hemorrhage where as moderate decrease can expose the brain to ischemic damage.

PROCEDURE: "Consent will be taken from the parent and the usg of the neonatal head will be performed by using various probes and Doppler studies will also be done to check any changes in the flow resitances in the various blood vessels supplying the brain in order to detect early changes of any sepsis which will be in the form of derrangement of resistances in the blood vessels. The study will be done at Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi and is

being conducted by **Dr. _____,** Post graduate in Radio diagnosis at J. N. Medical College Belagavi, Karnataka, under the guidance of **Dr. _____,** Professor, Dept. of Radio diagnosis, and **Dr. _____ M.D.,** principal and professor of Paediatrics, J. N. Medical College, Belgaum.

We request you to allow the participation of your baby in this study as he/she is eligible to be included. During the study you will be asked questions regarding your present and past medical and obstetric history and your baby's medical history and you will be required to answer to the best of your knowledge. Your baby will also have to undergo an ultrasound of the cranium.

If you agree for the participation of your baby in the study, please furnish the details pertaining to the study.

BENEFITS:

- Early detection of neurological abnormalities in early onset sepsis neonates

RISKS:

- No risk to the patient has been documented from ultrasound imaging of the cranium earlier.

ALTERNATIVES: If the parents are not willing for their baby to take part in the study, the child's treatment or any other further investigations the he/she wants to undergo, in future, in KLE will not be affected by their decision.

VOLUNTARY PARTICIPATION/WITHDRAWAL: Taking part in this study is voluntary. I may choose for my child not to take part in this study, or if I decide for him/her to take part I can later change my mind and withdraw my child from the study. My decision will not change the present or future health care or other services that my child receives. The study doctor or the sponsor may stop my child's participation in this study. I will tell of any important new findings that may change my willingness to continue to take part. If I choose for my child to not to take part in the study I will receive the standard treatment for patients with my child's condition.

COSTS: NIL

PAYMENT FOR PARTICIPATION: No incentive will be paid to you for allowing your child to participate in this study.

COMPENSATION: In the event that my child becomes injured as a result of taking part in this study, treatment whatever available at KLE charitable hospital, Belagavi, will be offered to him/her. No reimbursement, compensation or free medical care is given.

CONFIDENTIALITY: All information collected about my child during the course of the study will be kept confidential to the extent permitted by the law. The code numbers will identify him/her in this research record. Information from this study may be published but his/her identity will be confidential in any publication.

QUESTION: If any enquiries in the future or in case of research related injury illness, you may contact following person.

Dr. Harsha Hegde
Chairperson, J.N. Medical college institutional ethical committee for human subjects research, ICMR, national institute of traditional medicine Belgaum
Ph. No: 0831-2473777, Ext. 1529 Mob- 9480422500

CONSENT TO PARTICIPATE IN RESEARCH STUDY:

1. I understand that my child will be participating in the study, which includes ultrasound of the cranium.

2. I confirm that I have read and understood the information in the patient information sheet. Procedure is explained to me in detail along with information about the advantages and disadvantages of my child taking part in the study. I have been given the opportunity to discuss all aspects of the trial, to ask questions and hereby consent my child to participate in the trial outlined above.

3. I understand that the decision to take part in this study is completely voluntary and I am aware that I can choose to withdraw my child from the study at any point of time.

4. I consent to the photographing or recording of the procedure to be performed including appropriate portions of my child's body, for medical, scientific or educational purposes provided his/her identity is not revealed in the pictures or by the descriptive texts accompanying them.

5. I understand that there is no significant risk involved in the test that would be done in this study.

6. No guarantee or assurance has given by anyone as to the results that may be obtained.

7. My signature on this form signifies that I have willingly decided for my child's participation after understanding the above information.

Participant's Name/ legally authorized_____

Representative Signature_____

Name and signature of witness_____

Name and signature of interviewer _____

Date:

Place:_____

ANNEXURE – II - PROFORMA FOR DATA COLLECTION

NAME OF THE PATIENT: _____

GESTATIONAL AGE:_____

IP NO_____

MOBILE NUMBER: _____

GENDER: M / F

ADDRESS: HOUSE NO.: _____

WARD/GALLI: _____

VILLAGE _____ TALUK:_____ DISTRICT: _____

PH NO.:_____

MATERNAL RISK FACTORSRISK FACTOR

	PRESENT	ABSENT
FOUL SMELLING LIQUOR		
MECONIUM STAINED LIQUOR		
PROM		
PROLONGED LABOUR		
INSTRUMENTAL DELIVERY		

NEONATAL RISK FACTORS

1. LAB INVESTIGATIONS
    - PLATELET COUNT-
    - TOTAL LEUKOCYTE COUNT-

2. RESPIRATORY SYMPTOMS

	PRESENT	ABSENT
TACHYPNEA		
H/O DESATURATION		

3. METABOLIC CHANGES

	PRESENT	ABSENT
HYPOTHERMIA		
METABOLIC ACIDOSIS		

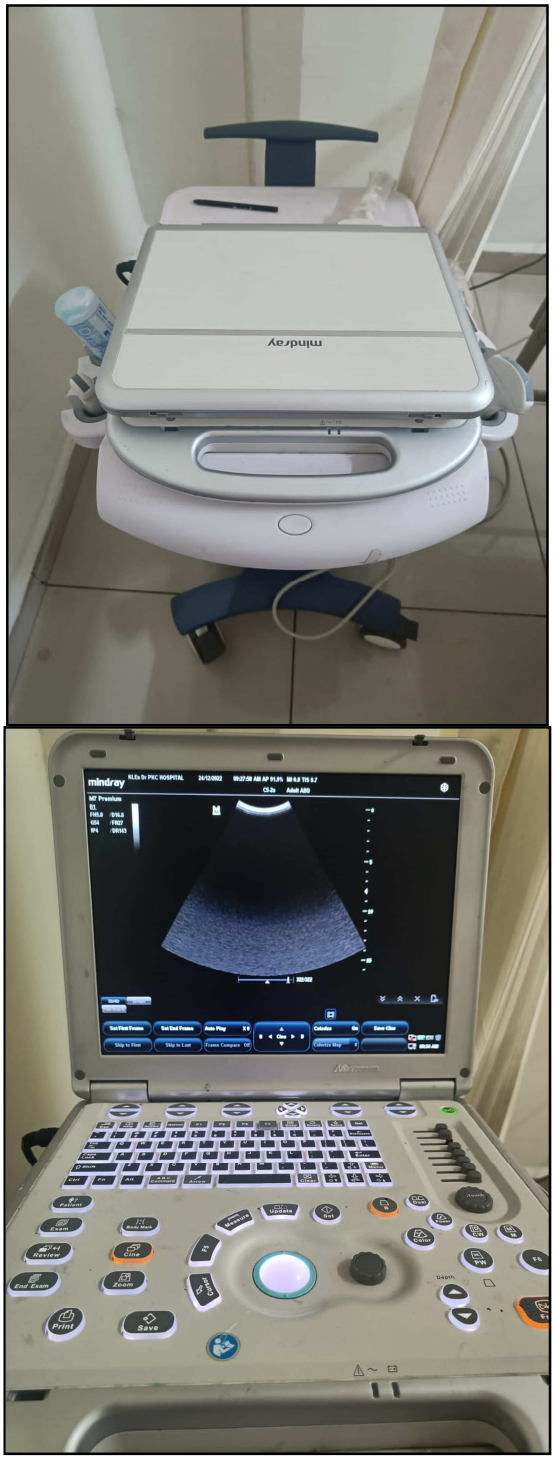
4. NEUROLOGICAL ACTIVITY

	PRESENT	ABSENT
HYPOTONIA		
DECREASED ACTIVITY		

USG FINDINGS

	RI	PI
MCA		
ACA		

ANNEXURE – III - LIST OF FIGURES



PHILIPS MINDRAY portable USG machine used for the study

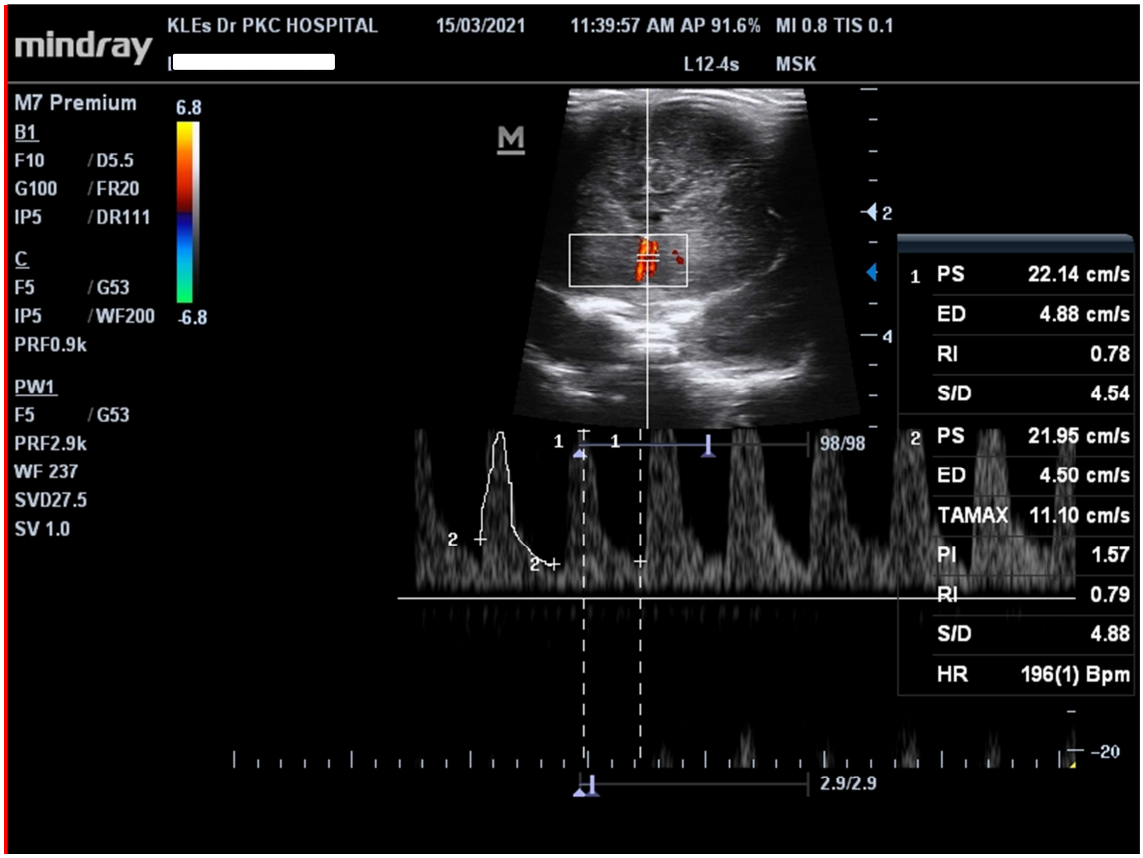
Small curvilinear transducer used for cranial ultrasound

.

High frequency linear array transducer used for the study.

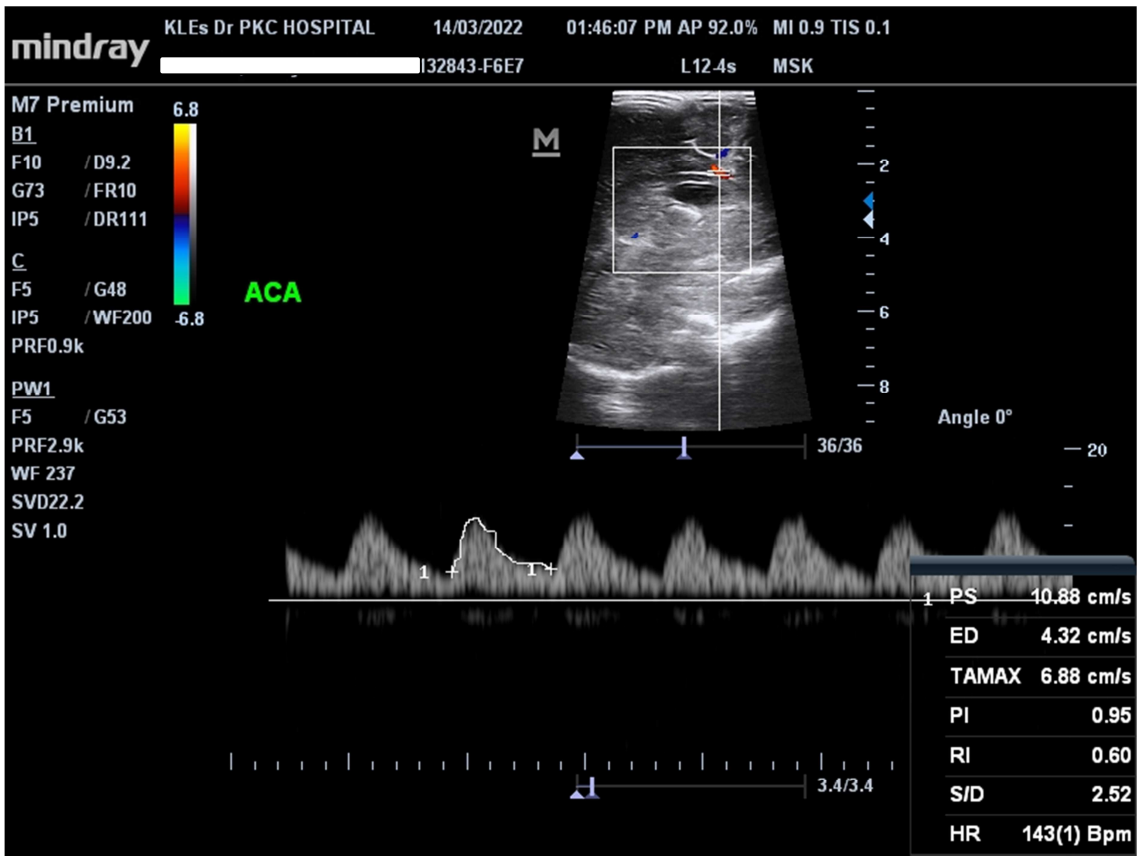
PHOTOGRAPHS OF CASES

Case 1: 32 weeks preterm in the non sepsis group, delivered via C-section



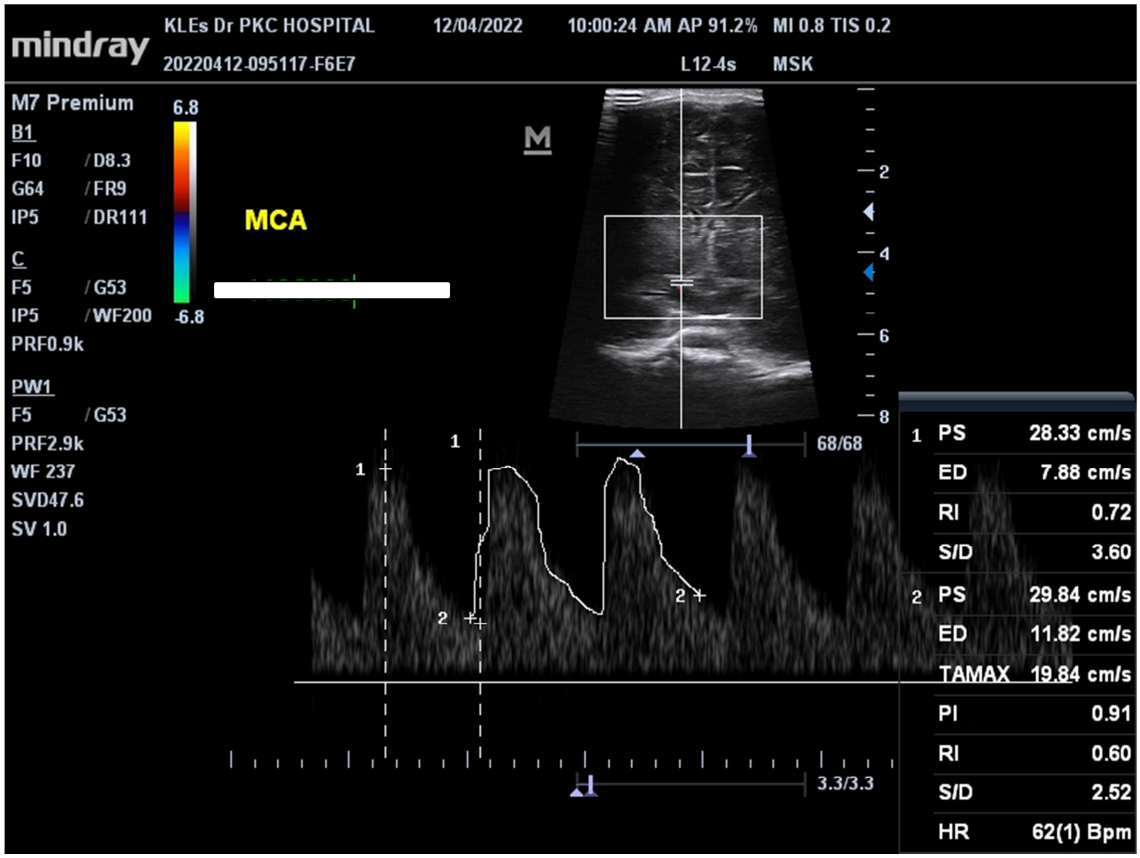
Doppler MCA spectral waveforms showing Normal RI (0.7) & raised PI (1.5) values

Case 2: A 34 weeks preterm in the non sepsis group, delivered via vaginal delivery



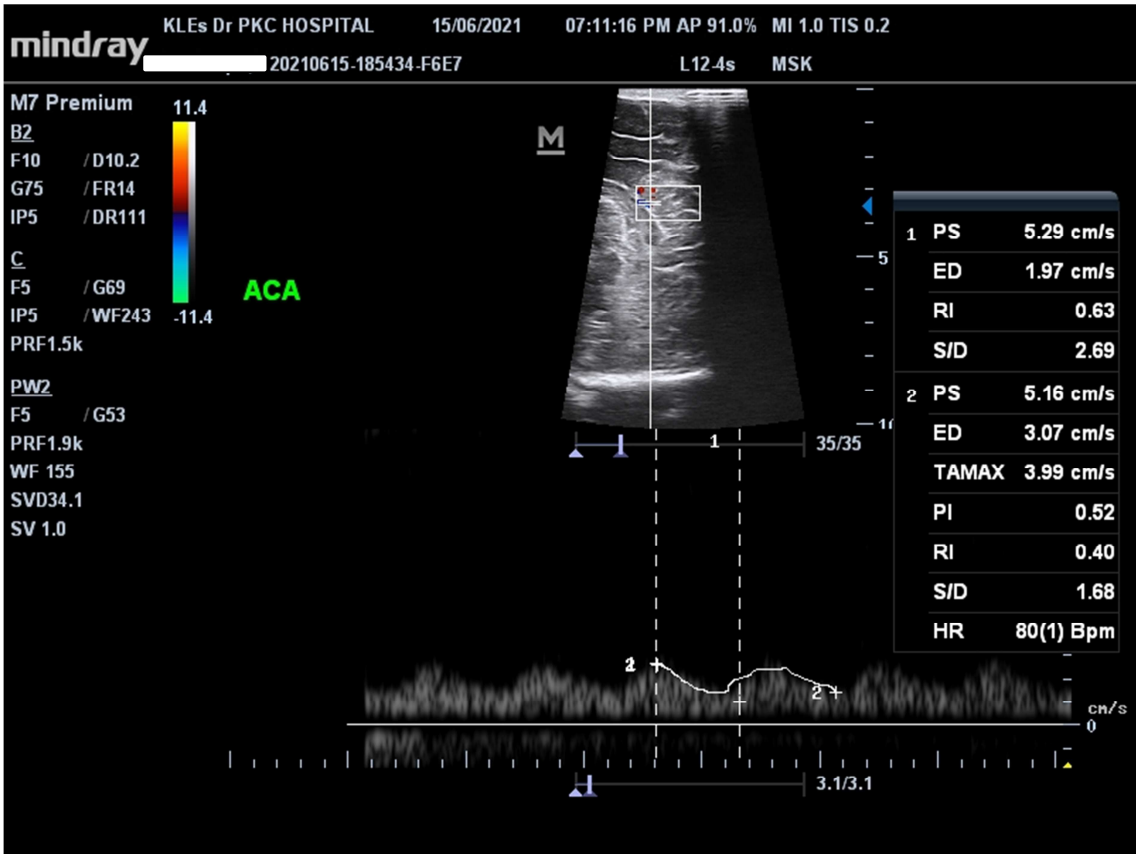
Doppler ACA spectral waveforms showing Normal RI (0.6) & PI (0.95)values

Case 3: A 30 weeks preterm in the non sepsis group, delivered via vaginal delivery



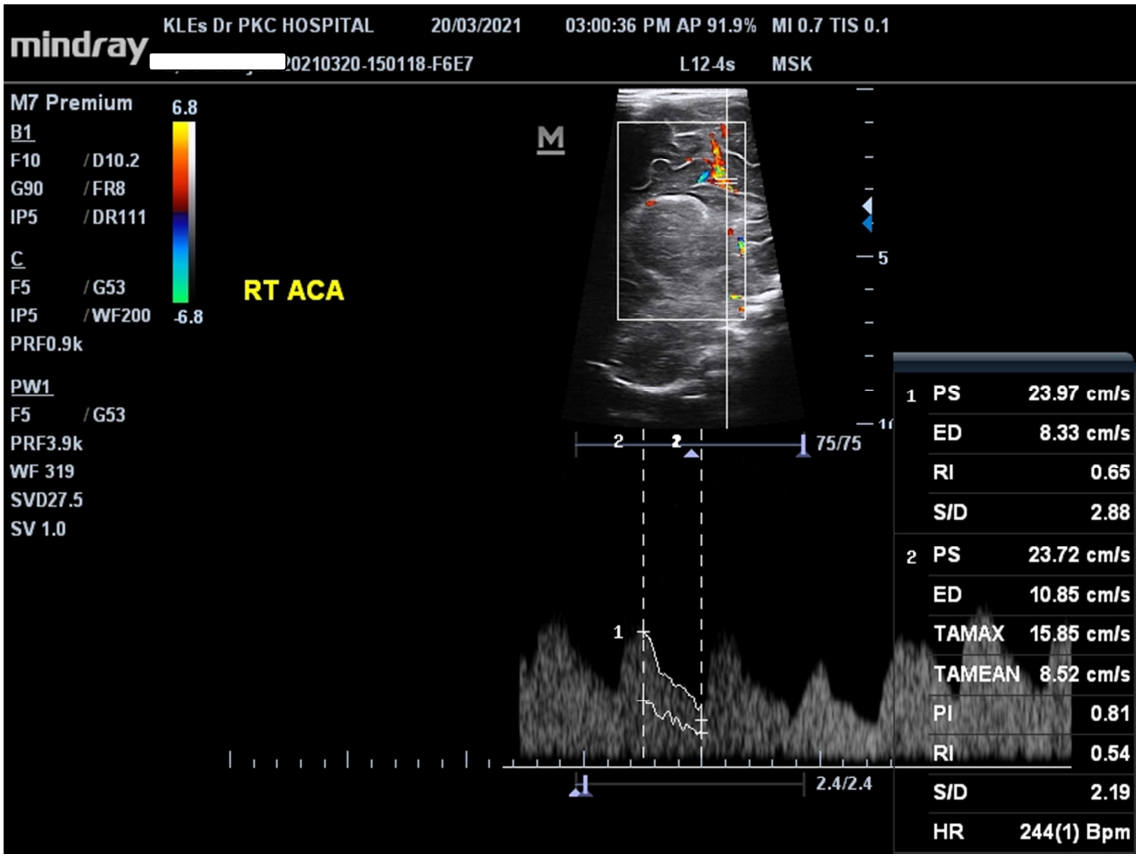
Doppler MCA spectral waveforms showing Normal RI (0.6) & PI (0.9)values

Case 4 : A 28 weeks preterm from the sepsis group with risk factors of PROM & meconium stained liquour



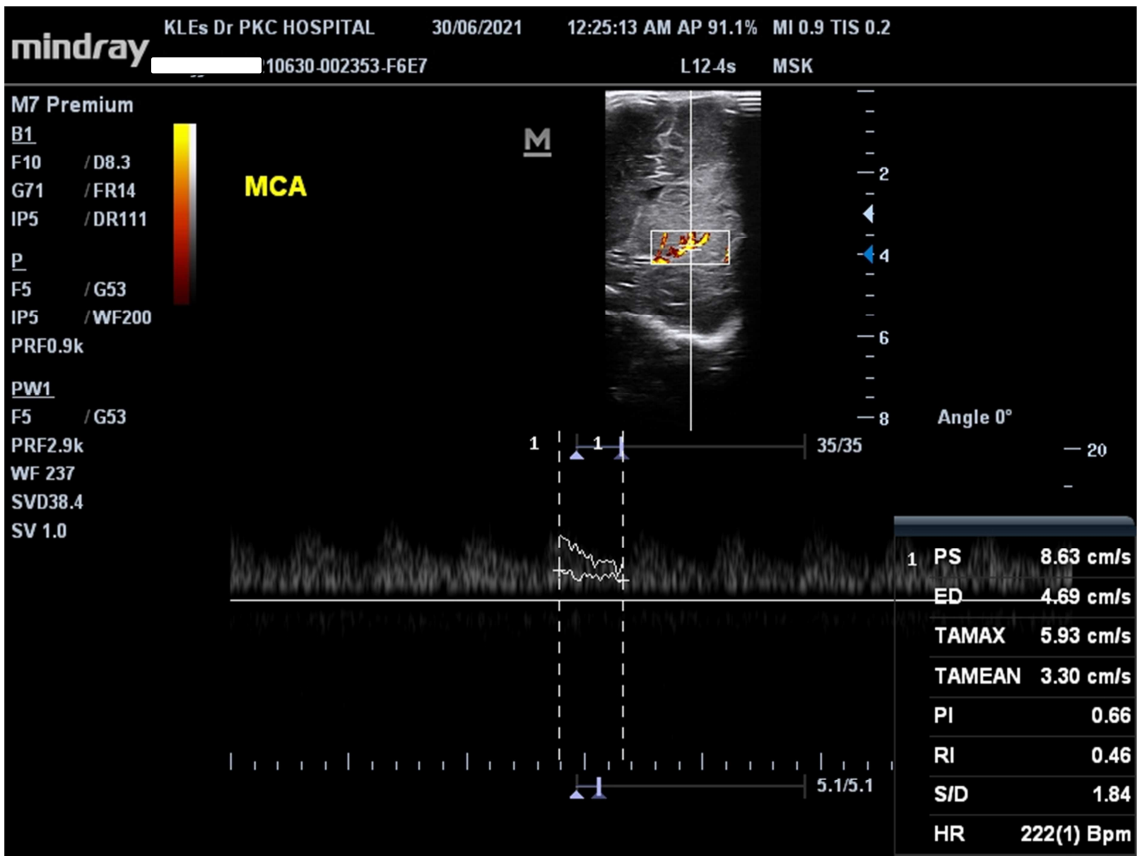
Doppler ACA spectral waveforms showing low RI (0.4) & PI (0.5)values

Case 5: A 30 weeks preterm from the sepsis group , delivered via vaginal delivery with risk factors of PROM & prolonged labour



Doppler ACA spectral waveforms showing low RI (0.5) &normal PI (0.8)values

Case 6: A 32 weeks preterm from the sepsis group , delivered via vaginal delivery with risk factors of prolonged labour



Doppler MCA spectral waveforms showing low RI (0.4) & PI (0.6)values

ANNEXYRE – IV - MASTERCHART

		Risk factor					Clinical laboratory data					MCA		ACA	
No	Groups	Type of delivery	Prolonged delivery	PMRM	Meconium stained liquor	Groups	Gestational age (in weeks)	Apgar score	PO2	PCO2	HCO3	RI	PI	RI	PI
1	Sepsis	Vaginal delivery	No	Yes	Yes	2	31.0	6.0	71.1	31.0	16.4	0.5	0.9	0.5	0.6
2	Sepsis	C section	Yes	No	No	2	32.2	7.0	82.3	42.2	22.1	0.3	0.8	0.3	0.8
3	Sepsis	Vaginal delivery	No	No	No	2	30.5	8.0	73.7	35.6	18.4	0.3	0.6	0.2	0.9
4	Sepsis	Vaginal delivery	No	Yes	No	2	34.6	7.0	75.4	44.9	22.2	0.3	0.8	0.5	0.8
5	Sepsis	Vaginal delivery	No	No	No	2	36.5	5.0	73.4	36.5	16.5	0.4	0.5	0.5	0.9
6	Sepsis	Vaginal delivery	No	No	Yes	2	28.6	6.0	89.4	38.2	17.8	0.3	0.5	0.3	0.7
7	Sepsis	Vaginal delivery	No	No	No	2	30.2	7.0	71.9	40.0	19.0	0.4	0.9	0.2	0.9
8	Sepsis	C section	No	Yes	No	2	33.4	7.0	84.5	32.0	20.5	0.4	0.7	0.4	0.9
9	Sepsis	Vaginal delivery	Yes	No	No	2	32.5	6.0	87.7	44.1	19.0	0.3	0.9	0.5	0.8
10	Sepsis	Vaginal delivery	No	No	No	2	34.3	6.0	73.2	36.3	16.6	0.3	0.9	0.3	0.6
11	Sepsis	C section	No	No	No	2	34.5	5.0	84.8	38.6	15.1	0.4	0.8	0.2	0.8
12	Sepsis	Vaginal delivery	No	Yes	Yes	2	35.5	7.0	65.8	36.1	16.5	0.4	0.6	0.5	0.5
13	Sepsis	Vaginal delivery	No	No	No	2	34.0	6.0	73.4	43.8	18.0	0.3	0.8	0.5	0.5
14	Sepsis	C section	No	Yes	Yes	2	32.4	5.0	78.6	36.5	19.4	0.3	0.9	0.3	0.9
15	Sepsis	Vaginal delivery	No	No	No	2	34.5	7.0	84.3	39.4	20.7	0.4	0.8	0.2	0.7
16	Sepsis	Vaginal delivery	Yes	No	No	2	35.2	6.0	86.3	32.5	21.9	0.5	0.9	0.4	0.9
17	Sepsis	C section	Yes	No	No	2	33.6	8.0	75.7	35.7	22.9	0.3	0.7	0.5	1.1
18	Sepsis	C section	No	Yes	No	2	28.5	10.0	65.3	39.0	23.8	0.3	0.9	0.3	0.9
19	Sepsis	Vaginal delivery	No	No	No	2	35.5	7.0	73.5	42.5	24.6	0.3	0.9	0.6	0.8
20	Sepsis	Vaginal delivery	No	No	Yes	2	33.0	10.0	82.5	45.1	25.2	0.4	0.7	0.5	0.8
21	Sepsis	C section	No	No	No	2	34.5	9.0	70.2	42.9	25.5	0.4	0.6	0.6	0.8
22	Sepsis	C section	Yes	Yes	Yes	2	36.4	7.0	74.6	33.9	25.7	0.5	0.7	0.4	0.8
23	Sepsis	Vaginal delivery	No	Yes	No	2	34.5	6.0	72.0	38.0	25.5	0.3	0.5	0.2	0.9
24	Sepsis	Vaginal delivery	No	No	No	2	35.3	7.0	70.0	42.3	25.1	0.4	0.5	0.4	0.9

25	Sepsis	C section	No	No	No	2	32.4	7.0	69.8	36.7	24.3	0.3	0.9	0.5	0.9
26	Sepsis	Vaginal delivery	No	Yes	No	2	30.4	8.0	73.5	34.3	23.2	0.3	0.7	0.4	0.9
27	Sepsis	Vaginal delivery	No	No	Yes	2	29.5	6.0	70.9	36.8	21.7	0.3	0.8	0.2	0.9
28	Sepsis	C section	Yes	No	No	2	35.5	6.0	78.2	35.0	19.8	0.4	1.0	0.5	0.9
29	Sepsis	C section	No	Yes	Yes	2	32.3	9.0	75.9	38.6	17.5	0.3	0.9	0.5	0.9
30	Sepsis	Vaginal delivery	No	No	No	2	34.4	10.0	72.5	31.4	14.7	0.4	0.8	0.6	0.9
31	non sepsis	Vaginal delivery	No			1	34.0	10.0	73.1	34.3	18.4	0.9	1.1	0.9	0.8
32	non sepsis	C section	No			1	33.2	7.0	92.3	46.2	24.1	0.8	1.5	0.8	1.5
33	non sepsis	Vaginal delivery	No			1	32.5	8.0	76.7	39.6	22.4	0.6	1.4	0.6	1.4
34	non sepsis	Vaginal delivery	No			1	32.6	7.0	73.4	34.9	26.2	0.8	1.6	0.8	1.8
35	non sepsis	Vaginal delivery	No			1	34.5	8.0	75.4	38.5	18.5	0.9	1.4	0.9	1.8
36	non sepsis	Vaginal delivery	No			1	34.6	9.0	80.4	39.2	19.8	0.8	1.7	0.8	1.7
37	non sepsis	Vaginal delivery	No			1	28.2	7.0	78.9	42.0	20.0	0.9	1.4	0.9	1.5
38	non sepsis	C section	No			1	33.4	7.0	83.5	34.0	20.5	0.7	1.4	0.7	1.5
39	non sepsis	Vaginal delivery	Yes			1	30.5	10.0	80.7	39.1	21.0	0.9	1.4	0.9	1.6
40	non sepsis	Vaginal delivery	No			1	35.3	8.0	78.2	40.3	16.6	0.9	1.6	0.9	1.8
41	non sepsis	Vaginal delivery	No			1	32.5	9.0	64.8	45.6	16.4	0.8	1.3	0.8	1.0
42	non sepsis	Vaginal delivery	No			1	36.5	7.0	75.8	39.1	18.1	0.6	1.2	0.6	1.0
43	non sepsis	Vaginal delivery	No			1	33.0	6.0	70.4	33.8	19.8	0.8	0.8	0.8	0.9
44	non sepsis	C section	No			1	31.4	8.0	76.6	40.5	21.5	0.8	1.4	0.8	1.5
45	non sepsis	Vaginal delivery	Yes			1	30.5	7.0	79.3	36.4	23.1	0.8	1.5	0.8	1.6
46	non sepsis	Vaginal delivery	No			1	34.2	6.0	76.3	38.5	24.6	0.7	1.2	0.7	1.4
47	non sepsis	C section	No			1	34.6	8.0	77.7	40.7	26.0	0.7	1.5	0.7	1.8
48	non sepsis	Vaginal delivery	No			1	34.5	10.0	72.3	42.4	27.1	0.7	1.4	0.7	1.7
49	non sepsis	Vaginal delivery	No			1	33.5	7.0	76.5	44.5	28.1	0.7	1.2	0.7	1.5
50	non sepsis	Vaginal delivery	Yes			1	36.0	10.0	86.5	46.1	28.8	0.7	1.2	0.7	1.4
51	non sepsis	C section	No			1	33.5	9.0	88.2	42.9	26.3	0.8	1.4	0.8	1.6
52	non sepsis	C section	No			1	32.4	7.0	78.6	34.9	26.4	0.7	1.8	0.7	1.8
53	non sepsis	Vaginal delivery	No			1	33.5	9.0	79.8	48.0	20.8	0.7	1.6	0.7	1.6
54	non sepsis	Vaginal delivery	No			1	34.3	7.0	82.4	42.3	23.7	0.7	1.4	0.7	1.4
55	non sepsis	C section	No			1	35.4	7.0	89.8	46.7	22.7	0.7	1.7	0.7	1.7

56	non sepsis	Vaginal delivery	Yes			1	32.4	8.0	77.5	44.3	26.3	0.7	1.5	0.8	1.5
57	non sepsis	Vaginal delivery	No			1	34.5	8.0	80.9	42.8	24.4	0.7	1.4	0.8	1.4
58	non sepsis	C section	No			1	30.5	10.0	78.2	38.8	22.1	0.7	1.6	0.7	1.6
59	non sepsis	C section	No			1	33.3	10.0	85.9	39.6	19.3	0.7	1.0	0.7	0.8
60	non sepsis	Vaginal delivery	No			1	30.4	9.0	80.5	31.4	15.9	0.7	1.6	0.7	1.5