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Towards healthier mothers and newborns

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HIGHLIGHTS OF THE ISSUE

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FROM THE EDITOR

It is my greatest pleasure to introduce this inaugural issue of the Sri Lanka Journal of Perinatal Medicine (SLJPM).

The Sri Lanka Journal of Perinatal Medicine is the official journal of the Perinatal Society of Sri Lanka. This journal is unique in the fact that it brings together three core specialties of perinatal medicine - obstetrics, neonatology and community medicine.

It is an open access peer reviewed journal containing original research articles, expert reviews, and articles of interest to all involved in perinatal medicine. The journal follows the recommendations of the International Committee of Medical Journal Editors (ICMJE) as well as the guidelines of the Committee on Publication Ethics (COPE) and Principles of Transparency and Best Practice in Scholarly Publishing.

The mission of this journal is to disseminate vital and up to date research in areas relevant to perinatal medicine to all persons interested in perinatology medicine.

In keeping with other recognized journals, the SLJPM will soon be available through Journals on line. I believe that this will increase the scope of the Journal and make it available for a wider audience globally.

Dulanie Gunasekera
Editor in Chief

REACH AND COUNT EVERY PREGNANT MOTHER AND NEWBORN

Kaushalya Kasturiaratchi

Presidential Address 2020

REACH AND COUNT EVERY PREGNANT MOTHER AND NEWBORN

Kaushalya Kasturiaratchi [1]

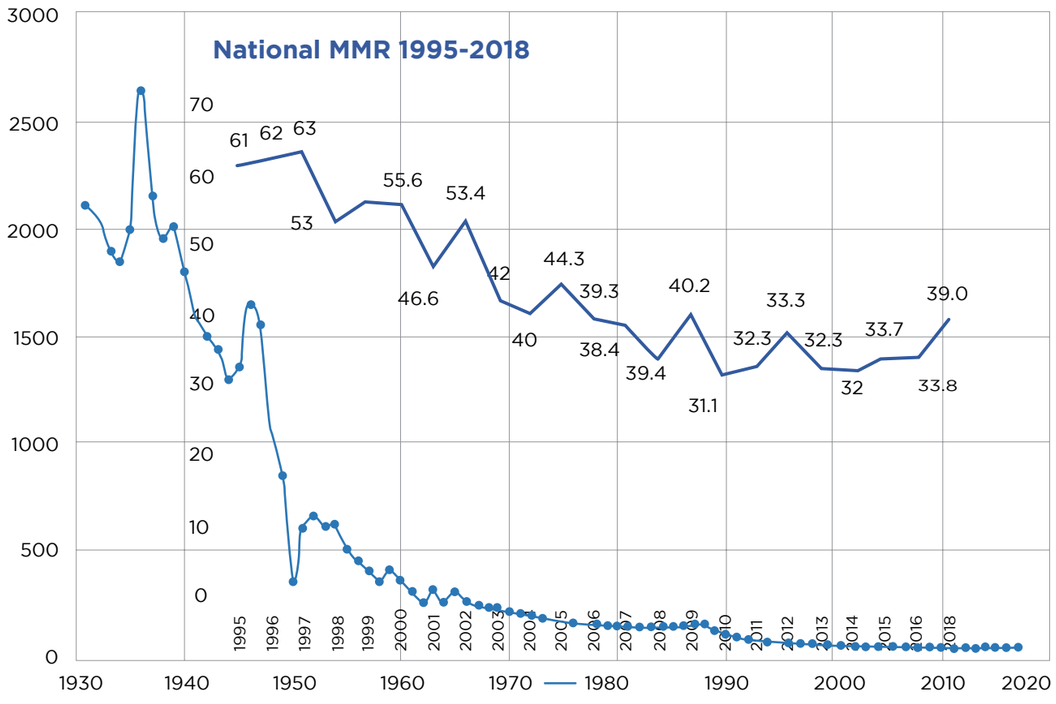
The term “Perinatal” refers to the period immediately before and after birth. The perinatal period is defined in diverse ways. According to many definitions, it starts at 20th to 28th weeks of gestation and ends 1-4 weeks after delivery. Perinatal health refers to the health of both the mother and the newborn during this specific period of time. The Sustainable Development Goals (SDGs) were set in 2015 by the United Nations General Assembly, and intended to be achieved by the year 2030. As you are aware, there are 17 SDGs and the goal applicable for health is the goal 3 i.e. “ensure healthy lives and promote wellbeing for all, at all ages”. This goal includes nine major targets and four sub-targets, and 14 indicators. Out of this gamut of targets, two indicators are relevant to maternal and newborn health. Those are the Maternal Mortality Ratio (MMR) and the Neonatal Mortality rate (NMR).

MMR in Sri Lanka has improved markedly over last several decades. However, it is stagnant over last 10 years around 30 deaths per 100,000 live births (LB) [Figure 1]. Therefore, fresh approaches need to be considered in achieving the country's target of < 10 deaths per 100,000 LBs in 2030.

Infant Mortality Rate too has significantly reduced over the years. So does the NMR and the still birth rates [Figure 2]. However, all these indicators have now reached a plateau and further reductions need fresh thinking and innovative approaches.

Given that the periods covered under MMR and NNMR are well within the perinatal period, it is obvious that, this period of time in the life of a mother and a newborn, will have a tremendous impact on their quality of lives. Therefore, the numerical figures that reflects their health such as Maternal Mortality Ratio and Neonatal Mortality Rate are not just statistical entities.

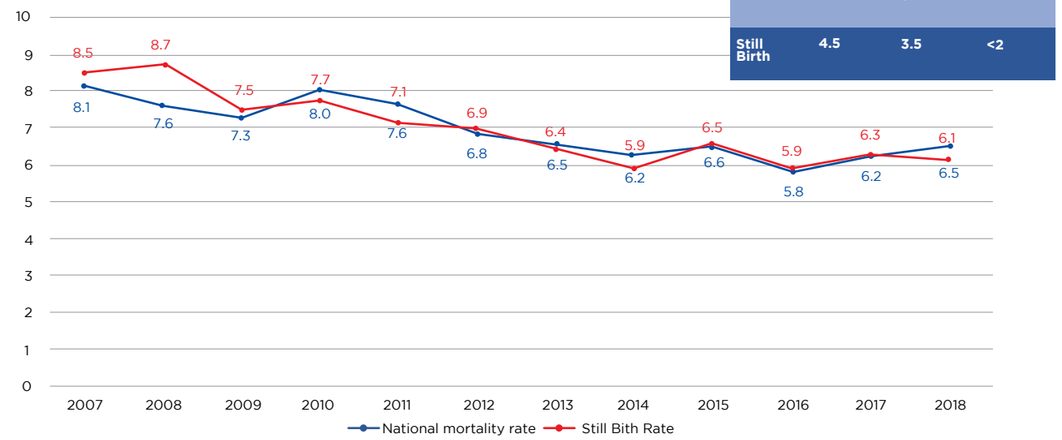
	2015	2020	2025	2030 (50G)
MMR	33.7	25	25	<10



Source : FHB

Figure1: Maternal Mortality Ratio change over the years in Sri Lanka

	2020	2025	2030 (5GD)
NMR	4.2	3.2	<2.2
Still Birth	4.5	3.5	<2



Source : FHB

Figure 2: Infant mortality and stillbirth rates in Sri Lanka

Apart from the influence on these indicators, this period of time, is an emotionally charged period, for the mother and her family. It is an important period for the medical team, as careful monitoring and provision of timely intervention becomes important, to ensure the welfare of both the mother and the newborn. During this period of time, medical teams should pay more focused attention on both mental and physical wellbeing of the mothers and newborns. Appropriate application of interventions, and collection of data by the programme managers is highly important to implement, cost effective evidence based interventions.

Considering this background, the theme introduced for for the year is "Reach and Count every pregnant mother and newborn". Beyond the ordinary meaning of the two terms, reach and count, there is little more technicality associated with these 2 words mentioned. Reaching in this instance means, evidence based interventions, introduction of new technologies and advance therapeutics, which you will realize, is beyond the ordinary reach out for these mothers. Such involves correct decision making, application of technology, and care for both the mother and the newborn. Similarly, counting refers to more intense type of identifying and collecting data with regard to status, progress and health outcomes of these mothers and newborns not necessarily limiting to clinical management but also to facilitate programme efficiency and proper health policy planning. Therefore, the theme for this year, encapsulates, wider multi disciplinary and an action oriented approach.

Having said all these, I would like to introduce what the new council and I as the President, propose that we achieve in the year 2020. Digitalization of perinatal health information, strengthening, perinatal psychiatry and an attempt to lower the cesarean section rates and promotion of normal vaginal deliveries. As these areas involve many

expertise, we would like to call upon, the members representing the different specialties to join hands with us to plan an execute the related activities. Very briefly, I would now like to elaborate on the three main thematic areas, selected for this year.

DIGITALIZATION OF PERINATAL CARE INFORMATION

Collection of health information in Sri Lanka has a long history that dates back to 1940s. Medical Statistics Unit of the Ministry of Health was established in mid 1950s and a comprehensive MCH information system covering the field health services, was started in early 1980s. Even though, we have a long history of collecting health information, the hospital information systems have not been fully developed to the expected levels, where as the Medical Officer of Health based field information systems have evolved tremendously over last 2 decades. More recently, the role of digital health in health system strengthening has been identified, as a valuable contribution, to advance the universal health coverage and other health aims of SDGs. Digital health interventions are expected to complement, and enhance health system functions, through accelerated exchange of information.

Digitalization of Medical Officer of Health based field MCH information system was initiated in 2017 by the FHB, covering all 6765 Public Health Midwife areas in the country and 4292 field health clinics in 354 Medical Officer of Health areas. Within three months, of implementation of the system, our team managed to achieve 100% coverage in all Public Health Midwife (PHM) areas and field clinics, enhancing the shift from totally paper based system to a web based electronic system. Each and every, PHM and field clinic data, is now entered into this system monthly. This web based system, was developed and implemented, not utilizing government or any other funds. It is a collective effort of the Health Informatics doctors and the public health doctors attached to the Monitoring & Evaluation Unit of the Family Health Bureau. For this system, the team won the Common wealth digital awards in 2 consecutive years 2017 and 2018 and was nominated for BMJ awards in 2017. In 2019, we won the eSwabimani digital awards and were nominated for the World Summit Awards.

Following this success story, we extended the electronic Reproductive Health Management Information system (eRHMIS) to hospital settings in mid 2019, to capture information from private hospitals in Sri Lanka. This was done in collaboration with the Perinatal Society of Sri Lanka and Perinatal Association of Private Hospitals in Sri Lanka. Having information from private sector was a long felt need of the country. Until now, we had no idea about the contribution of private hospitals in maternal and newborn health. This has been identified as a major deficiency in many instances, and recently during the application process, for WHO certification on elimination of mother to child transmission of HIV and Syphilis. This system is now running successfully covering all major private hospitals in Colombo and will be expanding further in 2020 to other districts in collaboration with the PSSL and Perinatal Association of Private Hospitals in Sri Lanka.

In addition, development and implementation of Neonatal ICU information system including an information system for tracking therapeutic cooling and nitric oxide therapies will be undertaken in the Level 3 and 3+ healthcare institutions during this year.

STRENGTHENING PERINATAL PSYCHIATRY

There is no time in the lifespan, that the statement “there is no health without mental health” rings truer than in the perinatal period. Pregnancy, and the arrival of a new baby is a challenging time for mothers. This period can be over shadowed by the appearance of mental illnesses associated with widespread stigma. Currently, not much attention has been paid to this aspect of mother’s health. There are many psychological issues identified in this period and they range from baby blues to perinatal depression to suicides. Available literature indicates that in Low and Middle Income Countries, an estimated 15-20% of females’ experience perinatal depression. Magnitude of the problem, varies from country to country and in a study done in Sri Lanka, it was shown to be 16.2% which is a considerable health burden. Mothers with perinatal depression are less likely to take care of themselves have threatened relationships with their partners and demonstrate impaired ability to work. They are less likely, to seek and receive antenatal care and also has a risk of committing suicides.

Perinatal mental disorders are associated with, increased risk of psychological and developmental disturbances in children. These mothers with psychiatric disorders, will find it difficult to bring up children, and there by causing physical, cognitive, social, behavioural and emotional developmental problems for their children. Higher rates of Low Birth Weights, malnutrition, stunting and other diseases have also been observed among these children. Negative effects can extend up to adolescent period causing adolescent depression, depressive disorders and poor social competencies. Suicides occupies, the one end of the spectrum of mental health disorders, during perinatal period. Globally, maternal suicides are a leading cause of maternal mortality across all income settings. Available information suggests prevalence of maternal suicides ranges from 0% in Vietnam to 23·08% in Argentina with an estimated global average of 1.68% of pregnancy-related deaths. In Sri Lanka, around 25 deaths are reported annually, with a rate of 8.3 per 100,000 LB in 2017 [Figure 3]. Currently, we do not take in to consideration, maternal suicides as a direct cause of maternal deaths. However, ICD MM necessitate, the counting suicides during pregnancy and postpartum period. If suicides are also included, there will be a further increase of MMR in SL.

Analysis of Psychological autopsies of 409 maternal suicides from 2002 to 2017, have shown that More than 50% the suicides have occurred in antenatal period, majority in the first pregnancy, and 75% of mothers were below 30 years of age.

Currently, mothers are being screened for postpartum depression in field setting, however, the detection rates are very low.

What we intend to do regarding perinatal mental health during 2020 includes, integrating perinatal psychiatry services into the maternal care package, introduce mental health education sessions during antenatal period, enhancing self identification of depression and help seeking, community based interventions, using a reliable tool to identify mental health problems during pregnancy and following birth of the child, and training of healthcare workers to identify symptoms and signs of mental health problems, providing counselling about stress and providing effective psychological support with community engagement, enhancing family support is challenging unless paternity leave is provided to husbands for their active involvement during perinatal period.

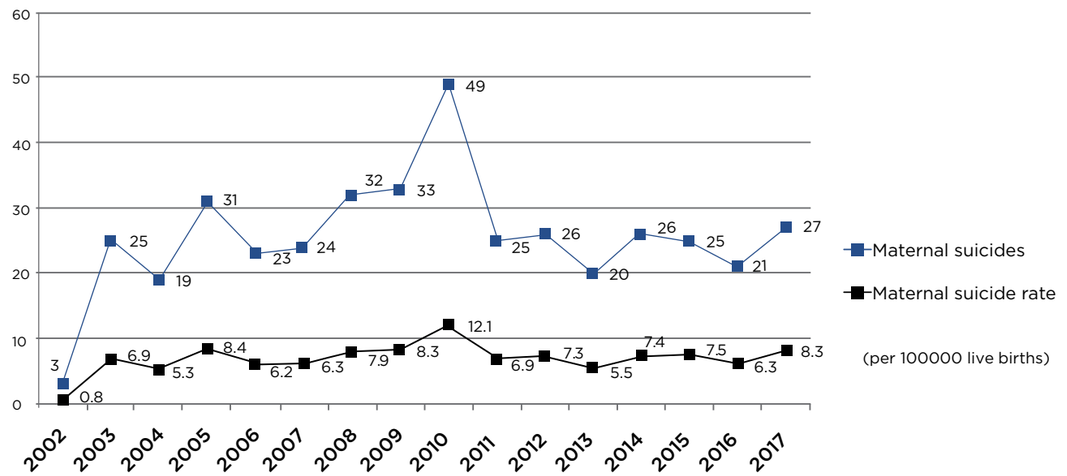
LOWERING THE RISING TRENDS IN CESAREAN SECTION RATES

Caesarean sections (CS) are the most common surgery worldwide, and it is a procedure that can save lives of women's and babies', when complications occur during pregnancy or child birth. The use of CS, for non-medically indicated reasons is a cause for concern because, the procedure is associated with considerable short-term and long-term adverse effects and rising health-care costs. Risks are progressively increasing as the number of previous caesarean deliveries, increases. Based on systematic reviews, WHO has concluded that CS rates of greater than 10% are not linked with lowering maternal and neonatal mortality rates. CS use is growing at an "alarming" rate globally, accounting for 21% of births being CS in 2015.

A series of papers published in the Lancet shows that CS rates above 10% to 15%, will not contribute for better health outcomes rather it indicates poor quality of service provision.

CS rates exceeds 40% in only 15 countries in the world and highest rate of 58.1% has been reported in Dominican Republic. In Sri Lanka, CS rates are increasing alarmingly and reaching the highest rates reported globally. In 2019, > 50% of CS rates are reported in 40 Medical Officer of Health areas. Highest being the Kurunegala Municipal Council with a rate of 67% in 2019. Nearly 40 hospitals in Sri Lanka, have reported, CS rates over 40% in 2018. Can we afford to have such increase is questionable? Efforts should be taken, to strengthen the clinical decision making, based on empirical evidence and following measures have been suggested by WHO to reduce high rates of Cesarean Sections. Application of Robson classification and assess the underline causes at the institution level, setting institutional targets, based on data and development of plan, for institution based action. Non clinical interventions, targeted at pregnant women, healthcare professionals, and community, aiming at reducing CSs. In addition to the activities, under the three themes, the following, have also being listed for 2020.

National Capacity building Programmes & Workshops specially aiming at building capacity of PHMs and Nurses. Capacity building on Positive experience in pregnancy, Respectful labour care, Pain control in labor, NICU Care and Breast feeding and completion of some of the last year's activities, developing a training module, and training programmes on therapeutic cooling and nitric oxide therapies, NICU module, and neonatal formulary initiated under Dr. Surantha Perera's Presidency.



Source : FHB

Figure 3: Numbers and rates of maternal suicides from 2002- 2017

PSSL will be working in collaboration with the Perinatal Association of Private Hospitals in Sri Lanka, Nurses Forum and the PHMs Forums during the year.

Additionally, PSSL will be working in collaboration with all other Academic Colleges to accomplish the activities under the three themes. Annual Scientific Sessions will be held from 11th to 12th November 2020 at Hotel Galadari.

To recapitulate, the theme for the next year is "Reach and count every mother and newborn, and we look at, the different aspects, that come under the two terms, "Reach and count". As mentioned before, these are tasks, can be implemented, by multi disciplinary teams, and I feel that the expertise available with the PSSL is optimal in developing these approaches.

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Sri Lanka

Oration

PERINATAL NEUROPROTECTION : CURRENT CONCEPTS AND FUTURE PERSPECTIVES

Axel Heep[1]

Professor Indrajee Amarasinghe Oration of the Perinatal Society of Sri Lanka Annual Scientific Congress of the Perinatal Society of Sri Lanka – 27th & 28th September 2019

THE BURDEN OF PERINATAL ASPHYXIA

Perinatal asphyxia is a major cause of childhood morbidity and neonatal mortality. The incidence of Hypoxic ischemic Encephalopathy (HIE) associated with perinatal asphyxia is 1-2/1000 in high income countries and 20/1000 in low-middle income countries (LMIC)1. In LMICs one in three infants suffering from severe perinatal asphyxia will died with one in two surviving infants suffering from significant brain injury and lifelong disability [2].

Improvement of Maternal and Child Health services in Sri Lanka has led to a steady decrease in neonatal mortality achieving the lowest infant mortality in South Asia[3]. The three major causes of neonatal mortality in Sri Lanka are Prematurity/ low birth weight, congenital malformations and asphyxia[4]. Asphyxia accounts for 14% of neonatal mortality in the country. Prevention of perinatal asphyxia related morbidity and mortality stands as a major target for improving Maternal and Child Health in Sri Lanka. Introducing a standardized protocol for active hypothermia treatment for the management of infants following asphyxia is an important step hereby.

PERINATAL MANAGEMENT AND RISK ASSESSMENT TO PREVENT ASPHYXIA

Identifying pregnancies at high risk of asphyxia event is an important focus of prevention strategies aiming to stratify perinatal management practice to potentially reduce asphyxia and its devastating consequences. In a recent study [5] we have presented an antepartum clinical score to identify women with high risk for having a baby with HIE. Parity, polyhydramnios, pre-rupture of membranes, gender, concerns about foetal growth and prematurity were co-variants of score, being strongly associated with risk of HIE, still birth, resuscitation or neonatal death. In this study elective delivery via caesarean section at 37 weeks of gestation following antenatal risk assessment was estimated to prevent 14% of HIE cases.

SPECIFIC VULNERABILITY OF THE EARLY BRAIN ON STRUCTURAL AND FUNCTIONAL DEVELOPMENT

During the development of the human brain neuron proliferation and cell migration are prerequisite for the structural brain development starting early at week 8-10 of foetal development[6]. The periventricular germinal matrix is a major site for neuronal stem cells, neuron proliferation and cell migration in the immature brain. Developmental processes including cell migration, cell branching, synaptogenesis and glia cell proliferation are highly active from 22 weeks of gestation onwards.

In addition to the structural immaturity of the developing brain, it has been demonstrated that the immature brain demonstrates a vulnerability to inflammation triggered by bacterial lipopolysaccharide, hypoxia-ischemia[7] and oxidative stress. Bacterial endotoxin acting in a synergistic way, sensitizing the immature brain aggravating hypoxic-ischemic injury [8,9].

The neuropathology of perinatal brain injury is marked by i) white matter injury including focal or diffuse parenchymal lesions, apoptotic cell death of immature oligodendrocytes and marked hypo-myelinisation; ii) grey matter injury demonstrating neuronal loss and impaired neuronal guidance and iii) “functional brain injury” demonstrating impaired structural and functional connectivity and pattern of brain plasticity on neonatal MRI studies[10].

SPECIFIC PATTERN OF PERINATAL BRAIN INJURY GERMINAL MATRIX – INTRAVENTRICULAR HAEMORRHAGE (GM-IVH) AETIOLOGY / PATHOPHYSIOLOGY

GM-IVH is a well described pattern of perinatal brain injury. The incidence of GM-IVH is directly related to prematurity and rarely occurs beyond 32 weeks of gestation.

In addition to the immaturity of the brain being the major predisposing factor for the development of GM-IVH further factors have been identified contributing in the pathophysiology of GM-IVH: i) impaired brain perfusion (hypoxia/ischaemia), ii) infection (chorioamnionitis) , iii) oxidative stress (lack of anti-oxidants) and iv) vascular anatomy (venous drainage).

The pattern of injury involves haemorrhage in the periventricular germinal matrix with extending blood in the ventricles and associated parenchymal lesions due to venous infarction / obstruction and inflammation triggered periventricular white matter injury.

CONSEQUENCES OF GM-IVH

The extend of GM-IVH described on trans-fontanelle cranial ultrasound is directly related to the acute and long-term consequences on cognitive and motor function outcome. Large GM-IVH consists of a 3-5-fold increased risk of major neurological disability in extremely preterm born infants and might lead to progressive post-haemorrhagic dilatation of the ventricular system (PHVD) with subsequent development of hydrocephalus in 40% of infants with PHVD[11].

“RISK REDUCTION AND OUTCOME IN GM-IVH”

Published meta-analyses illustrate 4 variables significantly associated with a risk reduction in development of GM-IVH in preterm infants: i) #Antenatal steroid application[12], ii) #Prophylactic indomethacin treatment for closure of patent ductus arteriosus[13], iii) #Delayed cord clamping[14] and iv) *Maternal vitamin K[15] (# risk reduction for IVH; *risk reduction for severe IVH).

MANAGEMENT OF SEVERE GM-IVH /POST HAEMORRHAGIC VENTRICULAR DILATATION (PHVD)

A severe complication in GM-IVH is the development of PHVD in cases with extended IVH (grade III bilateral or grade III plus parenchymal

lesion). A recently published RCT[16,17] compared different treatment thresholds for intervention in preterm infants with PHVD (defined by cranial ultrasound Ventricle Index (VI) parameter). This study confirmed that ultrasound guided assessment and decision on threshold in treatment resulted in early intervention (day 10 versus day 15 of life) by lumbar tap followed by insertion for ventriculostomy access device and daily CSF drainage (10 ml/kg) led to lowest reported ventriculoperitoneal shunt incidence so far reported for both group (19% versus 23%) and composite outcome (Death, need for VP shunt) and neurodevelopmental assessment (Bayley scales) at 24 month of life were significantly in favour for the early intervention group. A recently published observational clinical study on the management of PHVD[18] comparing ultrasound guided "early" treatment approach (mean first intervention day 13) as described in the RCT by de Vries et al.[16] with an management following clinical criteria for intervention (mean first intervention at day 47) described significant differences in need for shunt placement (20% versus 92%) and cognitive performance at 2 years (Bayley III scales Mental Developmental Index: 95 versus 68). Both studies provide evidence that early recognition and active management of GM-IVH is an essential and timely intervention in PHVD being associated with improved cognitive outcome and low incidence of need for shunt placement / development of hydrocephalus.

HYPOXIC ISCHAEMIC ENCEPHALOPATHY (HIE) AETIOLOGY / PATHOPHYSIOLOGY

The timing in the pathophysiology of perinatal asphyxia is associated with distinct pattern of neonatal encephalopathy and its clinical course and neurological outcome[19] Acute global brain injury pattern in HIE is typically characterised by low APGAR score, severe acidosis and clinical symptoms of moderate to severe encephalopathy following an uneventful pregnancy with regular foetal growth. An acute global brain injury pattern (deep grey matter / basal ganglia lesion) is frequently associated with acute intrapartum events (placental abruption; umbilical cord pathology).

The chronic hypoxic ischemic brain injury pattern ("watershed" lesions / chronic cortical injury) demonstrates a high incidence of maternal and antenatal recognized problems (Intra uterine growth restriction, long and difficult labour). Infants developing a watershed" lesions / cortical injury pattern are likely less compromised at birth but presenting with meconium aspiration, symptomatic hypoglycaemia or infection.

Infants suffering from acute global brain Injury pattern have a higher mortality rate and in up to 50% suffer from cerebral palsy and long-term sequel [20].

The pathophysiology of an acute global HI event follows a time course that is well described by the changes in cerebral blood flow[20]. Initial cerebral ischaemia/reperfusion and resuscitation is followed by a prolonged phase of hypoperfusion (» latent phase) which lasts for 1-6 to 24h. It is followed by local hyper-perfusion and secondary cellular damage in the penumbra (» Secondary "energy failure" phase 6 to 24 h to days). The restorage of normal brain perfusion is called tertiary phase and lasts from weeks to years. MRI spectroscopy enables to study the underlying biochemistry of molecular injury cascades involved during the time course. Taken from experimental studies it has become apparent that the major aim following resuscitation is the recovery of oxidative metabolism and recovery of mitochondrial injury / "Secondary energy" loss during the Latent phase [21].

ACTIVE HYPOTHERMIA TREATMENT

A positive effect of active hypothermia treatment in neonates suffering from severe asphyxia was first described in 1958 by B. Westin and colleagues [22] in a study including 10 severely asphyxiated infants immersed in 23-28° Celsius cold water presenting with intact survival of 9/10 at 16-24 months of life.

Following extensive experimental studies in the 1990th several RCTs comparing moderate hypothermia versus normothermia in infants with moderate to severe HIE demonstrated were performed. The metanalysis[23] including results of 3 of the 10 trials (n=767 infants) demonstrated significant benefit for active hypothermia treatment in neonates born from 36 weeks' gestation (starting less 6 h after birth and cooling at 33.5° Celsius) on neurological outcome and significant reduced mortality following hypothermia treatment analysing data from all included infants (n=1320 infants). Since, further studies have been performed in different clinical settings presenting differences in mortality rates and disability scores recognized.

Active hypothermia treatment trials performed in LMIC countries often demonstrate disappointing results compared to studies performed in high income countries (HICs)[24]. Simply translating results and strategies from hypothermia trials performed in HICs into management in LMICs have failed. To some degree, the differences observed might be explained by less availability of antenatal care and thereby recognition of time course of foetal distress, as well as by the difference in the incidence of unrecognized perinatal infections or other health conditions. Importantly, the incidence of Group B streptococcal infection in neonates with HIE is increased and significantly associated with mortality compared with HIE alone[25]. Perinatal infection / chorioamnionitis predisposes to direct injury of the developing brain. A study from Uganda[26] involving neonates with neonatal encephalopathy reported a high incidence of pathogenic bacterial species detected (8.9 %) in comparison to unwell neonates admitted for a different reason (2.0 %).

ACTIVE HYPOTHERMIA TREATMENT: CLINICAL SETTING

Active hypothermia treatment should be offered to neonates presenting with moderate to severe clinical sign of HIE. Currently it is advised to perform active hypothermia in infant born from 36 weeks' gestation onwards starting immediately after birth until less 6 h - "latent phase" - after birth targeting a body core temperature of 33.5° Celsius. Infants will particularly benefit, if hypothermia is started within first 3 hours of life [27].

Active hypothermia treatment should be applied using automated devices for whole body cooling. The use of active cooling achieves target temperature in a shorter period and maintains better temperature stability compared to passive cooling setting[28]. Manual low-technology cooling devices have been applied in low cost setting. However non-automated cooling settings require high degree of observation and care to perform cooling in a safe - constant temperature - clinical setting [24]. In addition to hypothermia treatment, it is important to address hypoglycaemia, seizures

and suspected infection appropriately in neonatal HIE [29]. In view of a high incidence of non- visible "electrical" seizure activity, it is advisable to include monitoring of brain activity using cerebral function monitors (Amplitude integrated EEG) for early recognition and course of impaired brain function (low voltage activity) under treatment and management of seizure activity.

THE ROLE OF NEUROIMAGING IN HIE

Structural neonatal MRI has been introduced to study the brain injury pattern in neonatal encephalopathy. The British Association for Perinatal Medicine[30] has published a framework for neonatal MRI studies in term infants with acquired brain injury, encephalopathy or seizures. MRI is useful in aiding prediction of neurological[19] and neurodevelopmental outcome in neonates with hypoxic-ischaemic encephalopathy (HIE). neonates with clinical signs of acquired brain injury, neonatal encephalopathy (NE) or seizures should undergo neuroimaging.

OUTLOOK ON MANAGEMENT OF HIE PHARMACOLOGICAL NEUROPROTECTION

Experimental work and clinical studies have been performed aiming to augment neuroprotection adding pharmacological intervention to active hypothermia treatment. Targets for pharmacological neuroprotection along the basic pathophysiological mechanisms are restorage of cellular energetics and mitochondrial function, counteracting pathophysiological cascades during reperfusion / re-oxygenation, anti-inflammation and cell death (apoptosis/necrosis) as well augmenting endogenous repair mechanism [31].
Drug targets for neuroprotection that so far have been studied in randomized clinical trials are: Melatonin[32,33], Erythropoietin[34] and Xenon[35] Currently studies are focussing of inclusion criteria for active hypothermia treatment in view of delayed start of hypothermia treatment > 6 hours of life and including infants born less 36 weeks of gestation and identifying the additional risk of perinatal infection (GBS) on the outcome.

REMOTE ISCHAEMIC PRECONDITIONING (RIC)

In 1993 it was first described by K. Przyklenk and colleagues that: "brief ischemia in vascular bed also protects remote, myocardium from subsequent sustained coronary artery occlusion" Since, RIC has been extensively studied in adult myocardial ischaemia and stroke. RIC is a simple applicable non-invasive technique for example inflating and deflating blood pressure cuff placed on the upper arm. An activation of afferent neuronal pathways is observed within the remote organ and blood-borne protective factor(s), appearing to recruit intracellular signalling pathways to promote immune modulatory effects, increase local blood flow and augmenting cellular repair mechanisms within the target organ[20]. In neurological hypoxic ischemic conditions, RIC has been shown to reduce stroke infarct size in the adult and in a neonatal model of HIE experimental studies, confirm the effect of RIC performed at onset of reperfusion preserving cell metabolism and reducing apoptosis in the white matter[37,38]. Further experimental work and clinical studies are needed to confirm a possible neuroprotective benefit in infants treated for HIE.

ACTIVE CELL TREATMENT AND EXTRACELLULAR VESICLES

Cell based therapy for perinatal brain injury are currently strongly looked at[38,39]. Clinical trials have been set up to study the potential of stem cell (SC) therapy in infants at risk of developing cerebral palsy following perinatal brain injury. These studies focus on the major caused of perinatal brain injury discussed earlier (GM-IVH[40] ; HIE[41]). Both conditions are associated with increased risk of development of long-term neurological sequel in particular cerebral palsy and cognitive disability.

The human umbilical cord blood contains of a variety of SC types (Mesenchymal stem cells, endothelial progenitor cells, haemopoietic SCs) that have been studied in view of active cell therapy[39]. Umbilical cord stem cells are easily to be obtained and ready availability in acute injury. Mesenchymal SC from umbilical cord have a low immunogenicity and exhibit a greater proliferative activity than mesenchymal SC from the bone marrow.

There are two goals for active cell therapy in perinatal brain injury: First replacement of lost cells and second supporting endogenous mechanism via cell based molecular signalling supporting cells in the injured areas to survive by regulating inflammation and active cell death, supporting neurogenesis and myelination. The effect of cell replacement is expected to be small (5-10%) compared to the expected effect of transplanted SCs from molecular (paracrine) signalling (90-95%). Experimental studies[42] have shown that mesenchymal stem cell derived extracellular nanoparticles containing gene encoding microRNA ameliorate inflammation induced preterm brain injury. It appears that a given neuroprotective effect of active cell treatment is less about the cell but more about the molecular signalling via extracellular vesicles orchestrating restoration and repair of brain structure, attenuating inflammation, reactive astrogliosis and promoting myelinisation following acute brain injury.

CONCLUSION

Antenatal recognition of perinatal risk, prevention of prematurity and excellent perinatal management are keys to neuroprotection in neonates. It is important to recognize that the immature brain demonstrates specific vulnerability during development. Perinatal inflammation or infection are important confounders in hypoxic-ischaemic perinatal brain injury. Post haemorrhagic hydrocephalus is a severe complication following germinal matrix-intraventricular haemorrhage in preterm born infants less 32 weeks requiring early recognition and active management. Active hypothermia treatment is the corner stone of current management of HIE. For the future specific pharmacological interventions and active cell therapy are under investigation whether to provide additional neuroprotective effect in infants with HIE.

REFERENCES

01. Lawn, Joy, Shibuya, Kenji & Stein,Claudia. (2005). No cry at birth: global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths. Bulletin of the World Health Organization, 83(6), 409 - 417. World Health Organization.

02. Ellis M, Manandhar N, Shrestha PS, Shrestha L, Manandhar DS, Costello AM. Outcome at 1 year of neonatal encephalopathy in Kathmandu, Nepal. Dev Med Child Neurol. 1999 Oct;41(10):689-95. doi: 10.1017/s 0012162299001413. PMID: 10587046

03. Firoz T, Ateka-Barrutia O, Rojas-Suarez JA, Wijeyaratne C, Castillo E, Lombaard H, Magee LA. Global obstetric medicine: Collaborating towards global progress in maternal health. Obstet Med. 015 Sep;8 (3):138- 45. doi: 10.1177/1753495X15595308. Epub 2015 Aug 27. PMID: 27512469

04. Rajindrajith S, Mettananda S, Adihetti D, Goonawardana R, Devanarayana NM. Neonatal mortality in Sri Lanka: timing,causes and distribution. J Matern Fetal NeonatalMed. 2009 Sep;22(9):791-6. doi: 10.3109/14767050902994549. PMID: 19526423

05. Odd D, Heep A, Luyt K, Draycott T. Hypoxic-ischemic brain injury: Planned delivery before intrapartum events. J Perinatal Med 2017;10(4):347-353. doi: 10.3233/NPM-16152.

06. Lagerkrantz H , Hanson MA, Ment LR, Pebbles DM. The Newborn Brain 2nd Ed., 2010. Cambridge University Press New York, USA

07. Back SA, Han BH, Luo NL, Chricton CA, Xanthoudakis S, Tam J, Arvin KL, Holtzman DM. Selective vulnerability of late oligodendrocyte progenitors to hypoxia-ischemia. J Neurosci 2002 Jan 15;22(2):455-63. doi: 10.1523/JNEUROSCI.22 -02-00455. 2002.

08. Martinello KA, Meehan C, Avdic-Belltheus A, Lingam I, Ragab S,Hristova M, Tann CJ, Peebles D, Hagberg H, Wolfs TGAM, Klein N, Tachtsidis I, Golay X, Kramer BW, Fleiss B, Gressens P, Robertson NJ. Acute LPS sensitization and continuous infusion exacerbates hypoxic brain injury in a piglet model of neonatal encephalopathy. Sci Rep. 2019 Jul 15;9(1):10184. doi:10.1038/s41598-019-46488-y.

09. Eklind S, Mallard C, Leverin AL, Gilland E, Blomgren K, Mattsby-Baltzer I, Hagberg H. Bacterial endotoxin sensitizes the immature brain to hypoxic–ischaemic injury.Eur J Neurosci 2001 Mar;13(6):1101-6. doi: 10.1046/j.0953816x.2001.01474.x.

10. Stoecklein S, Hilgendorff A, Li M, Förster K, Flemmer AW, Galiè F,Wunderlich S, Wang D, Stein S, Ehrhardt H, Dietrich O, Zou Q, Zhou S, Ertl-Wagner B, Liu H.Variable functional connectivityarchitecture of the preterm human brain: Impact of developmental cortical expansion and maturation. Proc Natl Acad Sci U S A. 2020 Jan 14;117(2):1201-1206. doi: 10.1073/pnas.1907892117. Epub 2019 Dec 30.

11. Adams-Chapman I, Hansen NI, Stoll BJ, Higgins R, NICHD Research Network. Neurodevelopmental outcome of extremely low birth weight infants with posthemorrhagic hydrocephalus requiring shunt insertion. Pediatrics 2008 May;121(5):e1167-77. doi: 10.1542/peds.2007-0423. Epub 2008 Apr 7.

12. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2017 Mar 21;3 (3):CD004454. doi: 10.1002/14651858. CD004454.pub3.

13. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev. 2010 Jul 7;2010(7):CD000174.doi: 10.1002/14651858.CD000174.pub2.

14. Rabe H, Gyte GM, Díaz-Rossello JL, Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev. 2019 Sep 17;9(9):CD003248. doi: 10.1002/14651858.CD003248.pub4.

15. Crowther CA, Crosby DD, Henderson-Smart DJ. Vitamin K prior to preterm birth for preventing neonatal periventricular haemorrhage. Cochrane Database Syst Rev. 2010 Jan 20;2010(1):CD000229. doi: 10.1002/14651858.CD000229.pub2.

16. de Vries LS, Groenendaal F, Liem KD, Heep A, Brouwer AJ, van ‘t Verlaat E, Benavente-Fernández I, van Straaten HL, van Wezel-Meijler G, Smit BJ, Govaert P, Woerdeman PA,Whitelaw A; ELVIS study group. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2019 Jan;104(1):F70-F75. doi:10.1136/archdischild-2017-314206. Epub 2018 Feb 10.

17. Cizmeci MN, Groenendaal F, Liem KD, van Haastert IC, Benavente-Fernández I, van Straaten HLM, Steggerda S, Smit BJ, Whitelaw A, Woerdeman P, Heep A, de Vries LS; ELVIS study group. Randomized Controlled Early versus Late VentricularIntervention Study in Posthemorrhagic Ventricular Dilatation: Outcome at 2 Years. J Pediatr. 2020 Aug 12:S0022-3476(20)30996-3. doi: 10.1016/j. jpeds.2020.08.014.

18. Leijser LM, Miller SP, van Wezel-Meijler G, Brouwer AJ, Traubici J,van Haastert IC, Whyte HE, Groenendaal F, Kulkarni AV, Han KS, Woerdeman PA, Church PT, Kelly EN, van Straaten HLM, Ly LG, de Vries LS. Posthemorrhagic ventricular dilatation in preterm infants: When best to intervene? Neurology. 2018 Feb 20;90(8):e698-e706. doi: 10.1212/ WNL.0000000000004984. Epub 2018 Jan 24.

19. Martinez-Biarge M, Diez-Sebastian J, Kapellou O,Gindner D, Allsop JM, Rutherford MA, Cowan FM. Predicting motor outcome and death in term hypoxic-ischemic encephalopathy. Neurology 2011 Jun 14;76(24):2055-61. doi: 10.1212/ WNL.0b013e31821f442d.

20. Hassell KJ, Ezzati M, Alonso- Alconada D, Hausenloy DJ, Robertson NJ. New horizons for newborn brain protection:enhancing endogenous neuroprotection. Arch Dis Child Fetal Neonatal Ed. 2015 Nov;100(6):F541-52. doi: 10.1136/archdischild-2014-306284. Epub 2015 Jun 10.

21. Millar LJ , Shi L , Hoerder-Suabedissen A, Molnár Z. Neonatal Hypoxia Ischaemia: Mechanisms, Models, and Therapeutic Challenges. Front Cell Neurosci. 2017 May 8;11:78. doi: 10.3389/fncel.2017.00078. eCollection 2017.

22. Westin B, Miller JA Jr, Nyberg R, Wedenberg E. Neonatal asphyxia pallida treated with hypothermia alone or with hypothermia and transfusion of oxygenated blood. Surgery. 1959 May;45(5):868-79.

23. Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M,Strohm B, Thoresen M, Whitelaw A, Azzopardi D. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data BMJ. 2010 Feb 9;340:c363. doi: 10.1136/bmj.c363.

24. Montaldo P, Pauliah SS, Lally PJ,Olson L, Thayyil S. Cooling in a low-resource environment: lost in translation. Semin Fetal Neonatal Med. 2015 Apr;20(2):72-9. doi: 10.1016/j.siny.2014.10.004. Epub 2014 Oct 31.

25. Tann CJ, Martinello KA, Sadoo S, Lawn JE, Seale AC, Vega-Poblete M, Russell NJ, Baker CJ, Bartlett L, Cutland C, Gravett MG, Ip M, Le Doare K, Madhi SA, Rubens CE, Saha SK, Schrag S, Sobanjo-Ter Meulen A, Vekemans J, Heath PT; GBS Neonatal Encephalopathy Investigator Group.

Neonatal Encephalopathy With Group B Streptococcal Disease Worldwide: Systematic Review, Investigator Group Datasets, and Meta-analysis. Clin Infect Dis. 2017 Nov 6;65(suppl_2): S173-S189. doi: 10.1093/cid/cix662.

26. Tann CJ, Nkurunziza P, Nakakeeto M, Oweka J, Kurinczuk JJ, Were J, Nyombi N, Hughes P, Willey BA, Elliott AM, Robertson NJ, Klein N, Harris KA. Prevalence of bloodstream pathogens is higher in neonatal encephalopathy cases vs. controls using a novel panel of real-time PCR assays. PLOS One. 2014 May 16;9(5):e97259. doi: 10.1371/journal.pone.0097259. eCollection 2014.

27. Thoresen M, Tooley J, Liu X, Jary S, Fleming P, Luyt K, Jain A, Cairns P, Harding D, Sabir H. Time is brain: starting therapeutic hypothermia within three hours after birth improves motor outcome in asphyxiated newborns. Neonatology. 2013;104(3):228-33. doi:10.1159/000353948.Epub 2013 Sep 12.

28. Goel N, Mohinuddin SM, Ratnavel N, Kempley S, Sinha A. Comparison of Passive and Servo-Controlled Active Cooling for Infants with Hypoxic-Ischemic Encephalopathy during Neonatal Transfers. Am J Perinatol. 2017 Jan;34(1):19-25. doi: 10.1055/s-0036-1584151. Epub 2016 May 16.

29. Paul SP, Abdelrhim H, Heep A. Management of Hypoxic-ischemic Encephalopathy. Ind J Pediatr. 2015 Jun;82(6):493-6. doi: 10.1007/ s12098-014-1592-3.Epub 2014 Oct 23.

30. British Association of Perinatal Medicine (BAPM). BAPM standards for fetal and neonatal MRI 8th February 2016. Downloaded 24/11/2020 from: https://www.bapm.org/resources/33-fetal-neonatal-brain-magnetic-resonance-imaging-clinical-indications-acquisitions-and-reporting

31. Fan X, Kavelaars A, Heijnen CJ, Groenendaal F, van Bel F. Pharmacological Neuroprotection after Perinatal Hypoxic-Ischemic Brain Injury. Curr Neuropharmacol.2010 Dec;8(4):324-34. doi: 10.2174/157015910793358150.

32. Aly H, Elmahdy H, El-Dib M,Rowisha M, Awny M, El-Gohary T, Elbatch M, Hamisa M, El-Mashad AR. Melatonin use for neuroprotection in perinatal asphyxia: a randomized controlled pilot study. J Perinatol. 2015 Mar;35(3):186-91. doi:10.1038/jp.2014.186. Epub 2014 Nov 13. PMID: 25393080

33. D'angelo G, Cannavò L, Reiter RJ,Gitto E. Melatonin Administration from 2000 to 2020 to Human Newborns with Hypoxic-Ischemic Encephalopathy. Am J Perinatol. 2020 Oct 31. doi: 10.1055/s-0040-1719151. Online ahead of print.

34. Oorschot DE, Sizemore RJ, Amer AR. Treatment of Neonatal Hypoxic-Ischemic Encephalopathy with Erythropoietin Alone, and Erythropoietin Combined with Hypothermia: History, Current Status, and Future Research. Int J Mol Sci. 2020 Feb 21;21(4):1487. doi: 10.3390/ijms21041487.

35. Azzopardi D, Robertson NJ, Bainbridge A, Cady E, Charles-Edwards G, Deierl A , Fagiolo G, Franks NP, Griffiths J, Hajnal J, Juszczak E, Kapetanakis B, Linsell L, Maze M, Omar O, Strohm B , Tusor N,Edwards AD. Moderate hypothermia within 6th of birth plus inhaled xenon versus moderate hypothermia alone after birth asphyxia (TOBY-Xe): a proof-of-concept, open label, randomised controlled trial. Lancet Neurol. 2016 Feb;15(2):145-153. doi: 10.1016/S1474-4422(15)00347-6. Epub 2015 Dec 19.

36. Drunalini Perera PN, Hu Q, Tang J, Li L, Barnhart M, Doycheva DM, Zhang JH, Tang J. Delayed remote ischemic postconditioning improves long term sensory motor deficits in a neonatal hypoxic ischemic rat model.PLoS One. 2014 Feb 28;9(2):e90258. doi: 10.1371/journal.pone.0090258. eCollection 2014.

37. Ezzati M, Bainbridge A, Broad KD, Kawano G, Oliver-Taylor A, Rocha-Ferreira E, Alonso-Alconada D, Fierens I, Rostami J, Jane Hassell K, Tachtsidis I, Gressens P, Hristova M, Bennett K, Lebon S, Fleiss B, Yellon D, Hausenloy DJ, Golay X, Robertson NJ. Immediate remote ischemic postconditioning after hypoxia ischemia in piglets protects cerebral white matter but not grey matter. J Cereb Blood Flow Metab. 2016 Aug;36(8):1396-411. doi: 10.1177/0271678X15608862. Epub 2015 Oct 8.

38. Zhu D, Wallace EM. Cell-based therapies for the preterm infant. Mesenchymal stem cell derived extracellular vesicle ameliorate inflammation induced preterm brain injury. Cytotherapy 2014; 16:1614-1628.

39. Titomanlio L, Kavelaars A, Dalous J, Mani S, El Ghouzzi V, Heijen C, Baud O, Gressens P. Stem cell therapy for neonatal brain injury: Perspectives and challenges. Ann Neurol 2011; 70: 698-712.

40. Malhotra A, Novak I, Miller SL, Jenkin G. Autologous transplantation of umbilical cord blood-derived cells in extreme preterm infants: protocol for a safety and feasibility study. BMJ Open. 2020 May 11;10(5): e036065. doi: 10.1136/bmjopen-2019-036065.

41. Masahiro Tsuji, Mariko Sawada, Shinichi Watabe, Hiroyuki Sano, Masayo Kanai, Emi Tanaka, Satoshi Ohnishi, Yoshiaki Sato, Hisanori Sobajima, Takashi Hamazaki, Rintaro Mori, Akira Oka, Hiroyuki Ichiba, Masahiro Hayakawa, Satoshi Kusuda, Masanori Tamura, Makoto Nabetani, Haruo Shintaku. Autologous cord blood cell therapy for neonatal hypoxic-ischaemic encephalopathy: a pilot study for feasibility and safety. Sci Rep. 2020; 10: 4603. Published online 2020 Mar 12. doi: 10.1038/s41598-020-61311-9.

42. Drommelschmidt K, Serdar M, Bendix I , Herz J, Bertling F ,Prager S , Keller M, Ludwig AK ,Duhan V ,Radtke S, de Miroschedji K , Horn PA ,van de Looij Y, Giebel B ,Felderhoff-Müser U. Mesenchymal stem cell-derived extracellular vesicles ameliorate inflammation-induced preterm brain injury Brain Behav Immun. 2017 Feb;60: 220-232. doi: 10.1016/j.bbi.2016.11.011. Epub 2016 Nov 12.

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REDUCING THE BURDEN OF PREMATURITY – THE OBSTETRIC PERSPECTIVE

Sanath Lanerolle[1], RMDB Ranatunga[2]

Review Article

REDUCING THE BURDEN OF PREMATURITY – THE OBSTETRIC PERSPECTIVE

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INTRODUCTION
DEFINITION AND PREVALENCE

'Preterm or Premature Birth' is defined as birth occurring before completion of 37 weeks or 259 days since the first day of the last menstrual period of the mother.[1] Every year, an estimated 15 million babies (more than one in ten births) are born preterm worldwide, and this number is rising.[2] In Sri Lanka, approximately 24,500 babies are born prematurely each year.[3] Efforts by obstetricians and neonatologists have led to significant advances in reducing preterm birth and improving outcomes.

THE BURDEN OF PRETERM BIRTH

Prematurity has been the leading cause of neonatal mortality worldwide for at least a decade and has now become the second leading cause of childhood mortality up to five years of age.[2]

The global neonatal mortality rate (per 1000 live births) has come down from 18.3 in 2016 to 17 in 2019. When comparing the statistics in Sri Lanka for the years 2016 and 2019, the neonatal mortality rate (per 1000 live births) has gone up from 5.8 (2016) to 7 (2019)[4]. Similarly, the infant mortality rate (per 1000 live births) in Sri Lanka was 8.2 in 2016 and increased to 10.1 in 2019.[4] Around 75% of deaths of children below 5 years occur during the first four weeks (28 days) of life. Of these, more than one-third are due to preterm births[4], making it the leading cause of neonatal death in Sri Lanka as well.

The preterm babies comprise a large portion of the admissions to the neonatal intensive care units. Those who survive are at increased risk of life-long disabilities including cerebral palsy, intellectual and learning disabilities, chronic broncho-pulmonary disease, and vision and hearing impairment. Fifty percent of long-term neurological morbidity in high-income nations is linked directly to preterm delivery. In addition, preterm birth poses a threat to maternal mental health with evidence of higher risk for post-partum depression.[5] These complications exert a huge impact on the affected families and the healthcare and educational systems of a country.

Prolonging pregnancies even for a few weeks significantly reduces risks for the new-born, since gestational age is the essential determinant of most perinatal outcomes.[6]

RISK FACTORS, PREDICTORS AND OUTCOMES

Preterm birth is a syndrome with a variety of causes. It can be basically categorized according to the gestational age.[2]

Extremely preterm (less than 28 weeks)
Very preterm (28 to 32 weeks)
Moderate preterm (32 to 34 weeks)
Late preterm (34 to 37 weeks)[7]

For a better understanding of risk factors and management, preterm birth can also be classified with the clinical subtype:
Spontaneous preterm birth (SPB)
Provider-initiated preterm birth (PIPB)

The pathophysiological mechanisms that underlie preterm labour are poorly understood but it is suggested that a host of multiple factors trigger the pathogenic processes leading to a final common pathway for the initiation of uterine contractions that will lead to SPB.[6] Unmodifiable risk factors for SPB include a shortened cervix less than 25mm before 28weeks (Risk rate is 6.19 for the length of 26mm or less) and a history of preterm delivery (1.5 to 2 fold risk of subsequent preterm delivery).[8] Age at pregnancy and pregnancy spacing, multiple pregnancies, infection, underlying maternal chronic medical conditions, level of maternal nutrition and lifestyle, maternal psychological health, and genetics are also recognized as contributors.

PIPB is defined as induction of labour or elective caesarean birth before completion of 37 weeks of gestation for maternal or foetal indications. Increasingly high numbers of PIPB are seen among middle and high income countries but seen less in the countries with the highest burden of PTB.[7]

There is not a single or combined screening method for preterm birth with high sensitivity which will truly identify the women at risk for preterm birth while also with high specificity to prevent unnecessary interventions and high treatment costs.

The maternal history, health condition, and socio-demographic factors need to be taken into consideration. The measurement of cervical length is the most cost-effective method that is used in clinical practice. Bedside tests have also been developed for detecting markers like foetal fibronectin, insulin-like growth factor binding protein-1 (IGFBP-1), interleukin-6, and placental alpha-macroglobulin-1.

The major clinical outcomes that are important to preterm infants are survival and normal long-term neurodevelopment.(Figure 1)

PREVENTION OF PRETERM BIRTH

Interventions aimed at preventing preterm birth can be classified as primary, secondary, or tertiary prevention. Primary prevention involves the provision of interventions before and between pregnancies which enhance the mother's health and reduce risks of her or the baby succumbing to preventable adverse pregnancy conditions.[6] The main aim of primary prevention is to identify and improve women's health or pregnancy outcomes through various interventions.

The main aim of secondary prevention involves interventions directed towards early detection of pregnant women at risk of preterm labour and helping them to prolong their pregnancy to term. Tertiary prevention mainly aims to minimize complications of prematurity.

Antenatal therapies with insufficient evidence of benefit include screening and treatment of asymptomatic women for lower genital tract infection, treatment for periodontal disease, bed rest and relaxation or stress reduction.

PRECONCEPTION CARE

The WHO report 'Born Too Soon' emphasizes on several preconception care measures to prevent premature birth. Promoting family planning to minimize teenage pregnancy and better interpregnancy spacing, lifestyle modification with cessation of smoking, healthy food and

IMPACT		FREQUENCY IN SURVIVORS:
PHYSICAL EFFECTS	Visual impairment Blindness /myopia Hypermetropia and myopia	One fourth of extremely preterm affected
	Hearing impairment	Up to about 10% of extremely preterm
	Chronic lung disease of Prematurity (From reduced exercise tolerance to requirement for home oxygen)	Up to 40% of extremely preterm
	Long term cardio vascular disorders and NCDs such as hypertension, reduced lung function, asthma, growth failure in infancy accelerated weight gain in adolescence	Full extent of burden still not known
NEURO-DEVELOPMENTAL/ BEHAVIORAL EFFECTS	Mild Disorders of executive Functioning Specific learning impairment, dyslexia, reduced Academic achievement	
	Moderate to severe Global development delay/ cerebral palsy	Depend on gestational age and quality of care
	• Psychiatric/behavioral sequelae: attention deficit hyperactivity disorder, increased anxiety and depression	
ECONOMIC AND SOCIETAL EFFECTS	• Impact on health service Intergenerational Psychosocial, emotional and economic, Cost of care, risk of preterm birth in offspring	Varying with medical risk factor, disability, socioeconomic Status

Figure 1: Long-term impact of preterm birth on survivors[2]

micronutrient supplementation, and optimization of pre-pregnancy weight are the cost-effective strategies. Education for girls and women, economic empowerment, screening for mental and medical health conditions, pre-conception surgical interventions to normalize uterine anomalies, partner education to reduce domestic violence are also essential in building a healthy environment for future mothers. Prevention, screening, and management of sexually transmitted diseases (eg: HIV, Syphilis) and teenage HPV vaccination should be taken care of at the community level.[2]

ANTENATAL CARE

Enhanced antenatal care for the prevention of PTB focuses on the management of pregnancies with potential risk. The mother should be educated regarding early warning signs, possible complications of the pregnancy, healthy behaviour, and the necessity of regular antenatal care visits. Health care providers must be competent in identifying pregnancies with a higher risk for PTB and the requirement for multidisciplinary care.

REDUCING MULTIPLE PREGNANCIES

The rate of PTB is about 10% in twin pregnancies compared to the 1-2% in singletons.[9] Mothers with multiple foetuses require close monitoring and cervical length assessment. Regulation of assisted reproductive techniques (ART), such as adopting the single embryo transfer policy by the Human Fertilization and Embryology Act in the UK[10] would pave the way to reduce multiple pregnancies. Although there are no such regulations in Sri Lanka at the present, with the advances of technology similar laws and acts would be a necessity.

REDUCING MATERNAL INFECTIONS

Maternal infections generally play a significant role in the pathogenesis of preterm labour. It is reported that 80% of women presenting with preterm labour before 30 weeks had evidence of amniotic fluid infection.[11] Persistent or recurrent intrauterine infections probably explain many repetitive spontaneous preterm births. Various studies and trials revealed conflicting results on the benefit of prophylactic antibiotics[12] and some suggest benefit of reducing infections is only applicable to women with a previous history of preterm labour and positive screen for bacterial vaginosis.

OPTIMIZING TREATMENT OF MEDICAL DISORDERS

Complications of medical disorders are a common cause of iatrogenic preterm labour. Optimization of antenatal care with the use of medications and behavioural therapy may reduce the need for early delivery. High-risk pregnancies associated with diabetes mellitus, hypertension, autoimmune, reno-vascular, connective tissue and endocrine disorders are best managed in dedicated clinics in which additional treatment and monitoring can be provided to reduce the risk of complications.[6]

CERVICAL LENGTH SCREENING AND CERCLAGE

Generally, preterm delivery is highly unlikely where the cervical length is greater than 3 cm and highly likely when it is less than 1.5 - 2.0 cm. The RR of preterm delivery increases with decreasing cervical length[8]. Universal screening for cervical length is controversial due to concerns about its cost-effectiveness and the availability of quality imaging for all patients.

RCOG recommends prophylactic cervical cerclage, if the cervical length is 25mm or less detected by the cervical assessment of a transvaginal ultrasound scan carried out between 16 and 24 weeks of gestation for who have had either preterm prelabour rupture of membranes (P-PROM) in a previous pregnancy or a history of cervical trauma. If prophylactic cerclage is used, a plan for its removal must be ensured[13].

PROGESTERONE PROPHYLAXIS

Antenatal progesterone therapy is one of the most effective measures in reducing the risk of preterm delivery, neonatal morbidity, and mortality in women with single gestation with a history of spontaneous preterm delivery. Progesterone is secreted by corpus luteum for the maintenance of early pregnancy until when the placenta takes over this function approximately between 7-9 weeks. Progesterone appears to help maintain uterine quiescence by inhibiting myometrial contraction through the modulation of cytokine production and inhibiting the expression of contraction associated protein genes within the myometrium. In a randomized controlled study, treatment with vaginal progesterone showed less frequency of spontaneous delivery before 34 weeks of gestation in the progesterone group than in the placebo group (19.2% vs. 34.4%)[14]. Progesterone is not beneficial in multiple gestation pregnancies. Prophylactic vaginal progesterone is considered for women who have either a history of spontaneous preterm birth (up to 34+0 weeks of pregnancy) or mid-trimester loss (from 16+0 weeks of pregnancy onwards) or results from a transvaginal ultrasound scan carried out between 16+0 and 24+0 weeks of pregnancy that show a cervical length of 25 mm or less. When using vaginal progesterone, treatment to be commenced between 16+0 and 24+0 weeks of pregnancy and continued until at least 34 weeks[13].

CERVICAL PESSARY

The main aim of inserting a pessary is to produce a more acute cervical angle relative to the uterus, thereby preventing the direct pressure over the cervix and foetal membranes at the level of the internal cervical opening. Utilization of cervical pessary for the prevention of preterm labour is a recent phenomenon and more evidence to assess its potential clinical efficacy is required. Despite the conflicting results provided by the clinical trials, they are good alternatives to cerclage and progesterone supplementation, especially for developing countries. It is also suggested that the use of cervical pessary is superior to the expectant management for the prevention of preterm labour in women with a singleton pregnancy with a short cervix[15].

CERVICAL CERCLAGE OR PROGESTERONE?

A metanalysis in 2018 including five trials each comparing vaginal progesterone vs placebo and cerclage vs no cerclage revealed that vaginal progesterone and cervical cerclage are equally effective for the prevention of PTB <35 weeks of gestation, in women with singleton pregnancies, previous PTB and short cervix. There was a significant reduction in perinatal morbidity and mortality as well[16]. The treatment of choice will be determined by the preference of the physician and the patient, adverse effects, and the cost-effectiveness.

EVALUATION OF PATIENTS WITH PRETERM LABOUR

Preterm labour is diagnosed when a mother with less than 37 completed weeks of the gestational period has regular uterine contractions that are followed by progressive cervical dilation and effacement. It is essential to determine if the patient is in true labour or if the delivery is imminent. Less than 10% of women with a clinical diagnosis of preterm labour will deliver within seven days of initial presentation[17].

A distinction between the clinical presentation of both preterm labour (PTL) and preterm pre-labour rupture of membranes (P-PROM) could be difficult and vary. The diagnosis that is often made based on the clinical findings could be unreliable, thus many studies have suggested the use of transvaginal ultrasound cervical length assessment (CL), oncofoetal fibronectin test (ofFN), the Actim Partus test, Amnisure, and Nitrazine in improving the diagnosis.

It is of utmost importance to conduct an initial assessment of women with preterm contractions to find out the likelihood of the patient delivering prematurely. A comprehensive algorithm to follow for preterm labour assessment is also available for further reference at http://www.marchofdimes.org/pdf/nevada/nv-Preterm-Labor-Assessment-Toolkit.pdf [18].

The diagnosis of P-PROM is made by observing the pooling of amniotic fluid by a sterile speculum examination. If the pooling is not observed, the NICE guidelines (2020) advise performing phosphorylated insulin like growth factor binding protein 1 test (PIGFBP-1; used in Actim Partus test) or placental alpha macroglobulin I test (PAMG-1; Amnisure test) of vaginal fluid. It is suggested not use Nitrazine test to diagnose P-PROM[13].

Diagnosis of preterm labour for women with intact membranes should follow the clinical assessment which includes clinical history taking and sterile speculum examination. If it is suggestive of preterm labour and she is 29+6 weeks or less, a treatment plan for preterm labour is to be followed. If she is 30 weeks or more, the likelihood of birth within 48 hours is determined with transvaginal ultrasound measurement of cervical length or foetal fibronectin test[13].

A risk prediction tool (combining quantitative foetal fibronectin, cervical length, and past obstetric history) for both symptomatic and high-risk asymptomatic women has been developed to provide an individualized estimate of preterm delivery[19].

Up-to-date algorithm for diagnosis and management of preterm labour is also available for further reference[20].

MANAGEMENT OF PRETERM LABOUR

Management of preterm labour begins with a comprehensive history, examination, and investigations, collaboratively aimed at determining the diagnosis and excluding the fetomaternal complications that require imminent delivery. Despite great medical advances in managing prematurity, finding the best strategy to minimize the preterm birth rate and to improve neonatal outcomes is still debatable. Exclusion of the conditions associated with expedited delivery allows adjunct tests (such as cervical length measurement, foetal fibronectin) to be utilized and to initiate targeted use of therapies to improve neonatal outcomes[20].

Treatment modalities for the management of preterm labour include; antenatal corticosteroid therapy, cervical cerclage, tocolysis, antibiotics, administration of magnesium sulphate, use of cervical pessary, and foetal monitoring. The current dilemma related to management perspective is not in deciding the best treatment modality but determining which is better for the patient and the physician with less adverse events and best cost-effectiveness.

ANTENATAL CORTICOSTEROID THERAPY

The use of corticosteroids is associated with a significant reduction in neonatal morbidity and mortality. It is associated with enhanced foetal lung maturation, reduction in respiratory distress syndrome, necrotizing enterocolitis, intraventricular haemorrhage, and neonatal ICU admissions[17]. It is recommended to offer maternal corticosteroids to women between 24 and 33 weeks of pregnancy and to consider for women between 34 and 35 weeks who are in suspected or diagnosed or established preterm labour. The optimal benefit of corticosteroid therapy is said to be achieved between 24 – 34 weeks of gestation, but the results of the Epicure study have shown reduced neonatal mortality and improved neurodevelopment with deliveries between 22 – 24 weeks as well[6].

The RCOG Green Top guidelines state, ‘Although there are limited data to support the use of antenatal corticosteroids in multiple pregnancy, the overall improvement in outcomes in singleton foetuses would suggest that steroids could be beneficial in multiple pregnancy’[21]. Repeated doses of corticosteroids are not encouraged since there is a concern regarding an increased risk of cerebral palsy. According to the RCOG guidelines ‘Antenatal corticosteroid use reduces neonatal death within the first 24 hours and therefore should still be given even if delivery is expected within this time’[21] as a rescue therapy.

Betamethasone 12 mg given intramuscularly in two doses or dexamethasone 6 mg given intramuscularly in four doses are the steroids of choice to enhance lung maturation[21].

RESCUE CERVICAL CERCLAGE

In a study conducted in women with prolapse of the amniotic sac during live pregnancies between the 17+0 and 26+0 weeks of gestation, the following results were noted. With emergency cerclage, the pregnancy was prolonged by 41 days with an outcome of 72% live births as opposed to the pregnancy prolongation of 3 days and only 25% of live births resulting with the conservative therapy (including bed rest, tocolysis, and antibiotics)[22].

It is recommended to consider rescue cerclage for women between 16 and 27+6 weeks of pregnancy with a dilated cervix and exposed, unruptured foetal membranes, while contraindicated when there are signs of infection, active vaginal bleeding, or uterine contractions[13].

TOCOLYSIS

Tocolytic agents are medicines that are given to women in preterm labour to prolong pregnancy for at least 48 hours to enable administration of antenatal corticosteroids, magnesium sulphate, or

buy more time for maternal transport to a tertiary care facility.

Tocolytics in common use include calcium channel blockers (Nifedipine), oxytocin receptor antagonists (Atosiban), and cyclooxygenase inhibitors (Indomethacin). Betamimetics (Eg: Ritodrine) associated with severe maternal side effects are no longer recommended.

It is recommended to offer Nifedipine for tocolysis for women between 26 and 33 weeks of pregnancy who have an intact membrane and are in suspected preterm labour. It is suggested to offer Atosiban for tocolysis if Nifedipine is contraindicated[23].

ANTIBIOTICS

Preterm labour is associated with intrauterine bacterial infection and it is more evident before 32weeks of gestation. Several reviews and meta-analyses conducted to determine the effectiveness of the use of prophylactic antibiotics found out that there was no benefit of its use especially, with intact membranes. It is further suggested that babies exposed to antenatal Co-amoxiclav had an increased risk of cerebral palsy[12].

It is recommended to use a combination of clinical assessment and tests (C reactive protein, white blood cell count, and measurement of foetal heart rate using cardiotocography) to diagnose intrauterine infection (chorioamnionitis) in women with P-PROM. Further, it is suggested to offer oral Erythromycin 250mg 4 times a day (or oral Penicillin) for a maximum of 10 days for women with P-PROM or until she is in established labour[13].

MAGNESIUM SULPHATE

Administration of antenatal magnesium sulphate has been shown to decrease the occurrence and severity of cerebral palsy in infants due to its neuroprotective effect.[24] It is recommended to offer intravenous magnesium sulphate for women between 24 and 29 +6 weeks of pregnancy and to consider it for women between 30 and 33+6 weeks of pregnancy, who are in established preterm labour or having a planned preterm birth within 24 hours.

Magnesium sulphate is given as a 4g bolus over 15minutes, followed by 1g per hour until the birth or for 24 hours. It is also advised to monitor clinical signs of magnesium toxicity (bradycardia, hypotension, respiratory depression, hyporeflexia, and decreased urine output) at least every 4 hours[13].

ANTENATAL AND INTRAPARTUM FOETAL MONITORING

The monitoring options for a patient in established P-PROM include foetal heart rate monitoring, foetal scalp electrodes, and foetal scalp blood sampling.

It is recommended to offer women in established preterm labour (but with no other risk factors), a choice of foetal heart rate monitoring using either cardiotocography using external ultrasound or by intermittent auscultation. If it is not possible to monitor foetal heart rate using the above methods it is advisable to discuss with the women between 34 and 36+6 weeks of pregnancy, the possible use of a foetal scalp electrode. The possibility of using foetal scalp blood sampling between 34 and 36+6 weeks of pregnancy can be considered if the benefits are likely to outweigh the potential risks[13].

MODE OF BIRTH AND TIMING OF CORD CLAMPING

It is recommended discussing the risks and benefits of caesarean delivery and vaginal birth with women in suspected, diagnosed, or established preterm labour and women with P-PROM. Caesarean delivery could be considered for women in suspected, diagnosed, or established preterm labour between 26 and 36+6 weeks of pregnancy with breech presentation. Clamping of the cord should be done between 30 seconds to 3 minutes following delivery with the baby positioned at or below the level of the placenta. If a preterm baby needs to be moved away form mother for resuscitation or in a significant maternal bleeding, milking of the cord is considered followed by clamping as soon as possible[13].

PRACTICE POINTS AND RECOMMENDATIONS

01. Preterm birth is a health issue with a significant burden due to the high rate of neonatal morbidity and mortality associated with prematurity. Gestational age of delivery is the main determining factor of the foetal outcome hence prolonging pregnancies even for a few weeks reduces risks for the new-born.

02. The risk of recurrence of preterm birth mainly depends on the associated specific condition which necessitated the previous early delivery.

03. There is not a single or combined screening method with high sensitivity and specificity for early identification of preterm birth.

04. Primary prevention initiated during the period of preconception is the most effective step in reducing the incidence of preterm labour.

05. The risk of PTB is inversely related to the length of the cervix. Natural progesterone decreases the risk by 50%, in singleton pregnancies with a short cervix with statistically significant reduction in the risk of respiratory distress syndrome, low birth weight, and fewer admissions to the neonatal intensive care unit.

06. The risk estimation for preterm delivery can be improved by ransvaginal cervical length assessment combine with the detection of fetal fibronectin in the cervicovaginal secretions.

07. Vaginal progesterone and cervical cerclage are equally effective for the prevention of preterm labour in women with singleton pregnancies. However, there is no adequate evidence that progesterone is effective in preventing preterm deliveries in multiple pregnancies. Therefore, further research is needed to clarify this association.

08. Antenatal corticosteroids (either B etamethasone or Dexamethasone) and Magnesium sulphate due to their associated reduction in neonatal mortality and morbidity, play a major role in the treatment of preterm labour.

REFERENCES

01. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. Acta Obstet Gynecol Scand. 1977;56(3):247–53.

02. WHO | born too soon: The global action report on preterm birth. 2013; Available from: https://www.who.int/pmnch/media/news/2012/ preterm_birth_report/en/

03. World Health Organization, Sri Lanka launches innovative method to track health of premature babies. 2017; Available from: http://origin.searo.who.int/srilanka/areas/child_adolescent_ health/sri-lanka-launches-method-to-track-health-of-premature-babies/en/

04. Statistics. Gov.lk. Available from: http://fhb.health.gov.lk/index.php/en/statistics

05. Vigod SN, Villegas L, Dennis C-L, Ross LE. Prevalence and risk factors for postpartum depression among women with preterm and low-birth-weight infants: a systematic review: Risk of postpartum depression in mothers of preterm and low-birth-weight infants. BJOG. 2010;117(5):540–50.

06. Appiah-Sakyi K, Konje JC. Prevention of preterm labour. Obstetrics-gynaecology-journal.com. 2015. Available from: https://www.obstetrics-gynaecology-journal.com/article/S1751-7214(15)00121-9/

07. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162–72.

08. Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, et al. The length of the cervix and the risk of spontaneous premature delivery. N Engl J Med. 1996;334(9):567–73.

09. Sebire NJ, Snijders RJ, Hughes K,Sepulveda W, Nicolaides KH.The hidden mortality of monochorionic twin pregnancies. Br J Obstet Gynaecol. 1997;104(10):1203–7.

10. Human Fertilisation and Embryology Act 2008.Available from:https:// www.legislation.gov.uk/ukpga/2008/22/contents

11. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75–84.

12. Kenyon S, Pike K, Jones D, Brocklehurst P, Marlow N, Salt A and Taylo, D. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial [Internet]. Thelancet.com. 2008. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)61203-9/fulltext

13. Overview | Preterm labour and birth | Guidance | NICE.; Available from: https://www.nice.org.uk/guidance/ng25

14. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH, Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007;357(5):462–9.

15. Abdel-Aleem H, Shaaban OM, Abdel-Aleem MA. Cervical pessary for preventing preterm birth. Cochrane Database Syst Rev. 2013;(5):CD007873.

16. Harris M. Progesterone or cerclage in preterm prevention in women with previous preterm birth and short cervix? - the ObG project. Obgproject.com. 2018. Available from: https://www.obgproject.com/2018/04/19/progesterone-cerclage-preterm-prevention-women-previous-preterm-birth-short-cervix

17. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics.Practice bulletin no. 171: Management of preterm labor. Obstet Gynecol. 2016;128(4):e155–64.

18. Hurt KJ. Webinar: Preterm Labor Assessment and Management Guidelines [Internet]. Cha.com. Available from: https://cha.com/wp-content/uploads/2017/03/MoD-Preterm-Labor-Assessment-Toolkit-Overview-003.pdf

19. QUiPP: A tool to predict spontaneous preterm birth. Quipp.org.; Available from: https://quipp.org/

20. UpToDate. Uptodate.com.; Available from: https://www.uptodate.com/contents/preterm-labor-clinical-findings-diagnostic-evaluation-and-initial-treatment.

21. Antenatal corticosteroids to reduce neonatal morbidity (green-top guideline no. 7). Org.uk.; Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg7/

22. Stupin JH, David M, Siedentopf J-P, Dudenhausen JW. Emergency cerclage versus bed rest for amniotic sac prolapse before 27 gestational weeks. A retrospective, comparative study of 161 women. Eur J Obstet Gynecol Reprod Biol. 2008;139(1):32–7.

23. Mackeen AD, Seibel-Seamon J, Muhammad J, Baxter JK,Berghella V.Tocolytics for preterm premature rupture of membranes. Cochrane Database Syst Rev. 2014;(2):CD007062.

24. Europepmc.org.; Available from: https://europepmc.org/article/med/19461430

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Current Practice

GUIDELINES FOR ASSESSMENT AND INITIATION OF THERAPEUTIC HYPOTHERMIA (COOLING) TREATMENT FOR MODERATE OR SEVERE HYPOXIC ISCHAEMIC ENCEPHALOPATHY

Surantha Perera[1], Amit Gupta[2]

AIMS OF THE GUIDELINE

- To ensure that babies with suspected HIE are appropriately assessed to see whether therapeutic hypothermia (cooling) is appropriate.
- To ensure that cooling is initiated in a safe and timely manner.
- To outline the care pathway for ongoing cooling treatment.

INTRODUCTION

Neonatal encephalopathy has an incidence of approximately 3/1000 births, with hypoxic ischaemic encephalopathy occurring in approximately 1.3-1.7/1000[1] and more specifically, moderate-severe HIE occurring in approximately 1.0-1.5/1000 live births in the UK[1,2]. The risk of death or severe handicap in survivors of moderate or severe HIE is approximately 25 and 75% respectively[3], and children without cerebral palsy are at increased long-term risk of cognitive and behavioural problems as well as motor deficits[4].

A recent Cochrane Review that included 11 trials on therapeutic hypothermia such as the UK total body cooling trial (TOBY) and US National Institute of Child Health and Human Development (NICHD) trial, confirmed that therapeutic hypothermia reduces death and disability at 18 months of age and improves neurodevelopmental outcomes in survivors with a number needed to treat of 7-11, depending on the outcome measured[5]. Other meta-analysis have confirmed this finding and showed that the number needed to treat for survival with normal neurological function at 18 months is 7 (95% CI 5-11) [6] and 8 (95% CI 5- 17)[7], respectively. Recently published longer-term data at the age of 6-7 years by the TOBY and NICHD groups showed a benefit of therapeutic hypothermia for reduction of death and improvement of neurodevelopmental outcome up to school age[8,9]. Clinically significant adverse events attributed to cooling are uncommon and the benefits of therapeutic hypothermia outweigh the possible short-term adverse effects[5].

Therapeutic hypothermia is now standard of care in selected neonates with HIE and is supported by NICE and BAPM[10,11].

CRITERIA FOR COOLING

- Cooling should be considered in all infants that meet criteria A and B (Table1).
- Criteria B can be assessed and recorded shortly after delivery. However, the baby should be reassessed when the patient is more than 30 minutes old to allow time for spontaneous recovery post resuscitation.
- Where an infant meets criteria A; but it is not possible to assess criteria B (e.g. paralyzing agents have been used prior to clinical neurological assessment), cooling should be commenced and the aEEG should be used to assess ongoing need for cooling.

Initiation of cooling should not be delayed if aEEG is not readily available.

TABLE 1 : CRITERIA FOR COOLING

CRITERIA - A	CRITERIA - B
Infants ≥36 completed weeks gestation admitted to NICU with at least one of the following: • Apgar score of ≤5 at 10 minutes after birth • Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth • Acidosis within 60 minutes of birth (defined as any occurrence of umbilical cord, arterial or capillary pH <7. • Base Deficit ≥16 mmol/L in umbilical cord or any blood sample (arterial, venous or capillary) within 60 minutes of birth	Seizures (clinical or subclinical*) or moderate to severe encephalopathy, consisting of: • Altered state of consciousness (reduced or absent response to stimulation) AND • Abnormal tone (focal or general hypotonia, or flaccid) AND • Abnormal primitive reflexes (weak or absent suck or Moro response) ** Subclinical seizures are those which are detected on amplitude integrated EEG (aEEG) but there are no clinical signs apparent.*

COOLING OUTSIDE TRIAL GUIDELINES

Evidence for cooling outside the above guidelines is weak or unavailable. However, there are circumstances where there may be theoretical benefits for cooling in certain other patients[12-14]. Cooling in these circumstances should only be instigated following discussion with the cooling centre.

Examples would include:

- Infants who fulfil criteria A+B but are between 6-12 hours old.
- Preterm infants, 33+weeks or more,who have suffered an acute asphyxia event and fulfil criteria A+B above.
- Acute postnatal collapse with a neurological examination consistent with a diagnosis of acute encephalopathy.
- Early prolonged or recurrent seizures (within 12 hours of birth).
- Infants who fulfil criteria A but only partially fulfil criteria B.

CONTRAINDICATIONS TO COOLING

There are no absolute contraindications to cooling infants who meet the criteria above except where there are other life-threatening congenital abnormalities present. Relative contra-indications include:

- Suspected significant haemorrhage or thrombosis (NB although hypothermia prolongs bleeding time, trials did not

demonstrate differences in complications related to abnormal clotting).

- Surgical conditions likely to be associated with significant blood loss.

- Severe PPHN - Cooling may produce adverse respiratory or cardiovascular effects. However, trials found no difference in the prevalence of PPHN between cooled patients and control groups.

AMPLITUDE INTEGRATED EEG (aEEG) ASSESSMENT

The aEEG (also known as Cerebral Function Monitor –CFM) is a single or dual channel time compressed and filtered EEG providing information on overall electrical activity in the brain.

- The amplitude integrated EEG (aEEG or CFM) must be recorded in all infants treated with cooling but cooling should not be delayed until the aEEG is initiated.

- A normal aEEG record indicates a high probability of normal outcome, and clinicians may consider that treatment with cooling is not required.

- Rewarming following active cooling may be considered if the clinical examination is normal and the CFM normalizes within the first 6 hours. However, ongoing neurological examination and CFM recording should occur during rewarming and if any signs of deterioration occur the patient should be re-cooled for the full 72 hours.

  Apparent improvement of the aEEG AFTER 6 hours of age is NOT an indication for discontinuing cooling.

- A copy of the initial CFM traces should be sent with the baby to the cooling centre.

- IV anticonvulsant therapy may cause transient suppression of EEG activity. Ideally the aEEG should be performed before administering anticonvulsant therapy.

VENTILATION

- Most infants treated with cooling will initially require mechanical ventilation as a consequence of their encephalopathy/ anticonvulsant medication.

- Ventilatory care should be managed according to local protocol

- Bolus doses of paralysis should be used if required rather than infusions to prevent drug accumulation.

- Blood gases will guide ventilatory requirements; particular care should be taken to ensure normocapnia. The infant's temperature should be inputted into the blood gas machine so that the appropriate adjustment is performed.

- Ventilator gases should be warmed and humidified in the normal way.

- More frequent suctioning may be necessary as secretions tend to be more viscous when cold. Vary positioning 6 hourly, Chest physio as indicated.

CARDIOVASCULAR SUPPORT

- Most infants with a rectal temperature of 33-34^{o}C will have a heart rate around 100 bpm and a mean blood pressure greater than 40 mmHg.

- Treatment with volume replacement and inotropes should be considered if the mean arterial blood pressure is less than 40 mmHg.

ANALGESIC AND SEDATIVE THERAPY

- Stress may have adverse effects in asphyxiated infants and may influence the therapeutic effect of hypothermia. Signs of distress include tachycardia, facial grimacing and irritability. A heart rate consistently above 110 bpm in cooled infants suggests that the infant is distressed (exclude hypotension/ hypovolaemia and other causes of pain).

- Ventilated infants should be sedated with intravenous morphine as per local unit guidelines.

- Non-ventilated infants will also require morphine therapy, commenced at 10 mcg/kg/ hr. Respiratory function must be monitored in these infants. There should be a low threshold for commencing ventilation, if required, in order to give adequate sedation/pain relief.

FLUID & ELECTROLYTE MANAGEMENT

- Renal function is commonly impaired following severe perinatal asphyxia and fluids should be restricted.

COAGULATION

- Send platelet count and clotting at the start of cooling. If there are clinical signs of increased bleeding tendency, treat babies with FFP without waiting for lab results.

SEPSIS

- Antibiotic therapy may be given if clinically indicated. Gentamycin and other aminoglycosides should be avoided as there is a higher risk of toxicity

SEIZURES

- The management of seizures should be as usual

- In general, symptomatic seizures or frequent subclinical (>3/hr) seizures seen on aEEG/ CFM should be treated with anticonvulsants.

- Cooling may affect the metabolism of several drugs, including anticonvulsants and sedatives, and toxic drug levels may occur even with normal doses.

REFERENCES

01. Kurinczuk JJ, White-Koning M,Badawi N.Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev 2010; 86(6):329-38

02. Azzopardi D, Strohm B, Linsell L,Hobson A, Juszczak E, Kurinczuk JJ, Brocklehurst P, Edwards AD. Implementation and conduct of therapeutic hypothermia for perinatalasphyxia encephalopathy in the UK – analysis of national data. PLoD One 2012;7(6): e38504

03. Marlow N, Rose AS, Rands CE,Draper ES.Neuropsychological and educational problems at school age associated with neonatal encephalopathy. Arch Dis Child Fetal Neonatal Ed2005;90 (5):F380-F387.

04. De Vries LS, Jogmans MJ. Long-term outcome after neonatal hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed 2010; 95:F220-F224

05. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy (Review). Cochrane Database of Systemic Reviews 2013

06. Tagin MA, Woolcott CG, Vincer MJ, Whyte RK, Stinson DA. Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy. Arch Pediatr Adolesc Med. 2012; 166(6):558-566

07. Edwards AD, Brocklehurst P, Gunn AJ, Halliday H Juszczak E, Levene M, Strohm B, Thoresen M, Withelaw A, Azzopardi D. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic- ischaemic encephalopathy: synthesis and meta-analysis of trial data. BMJ 2010; 340:c363

08. Azzopardi D et al. Effect of Hypothermia for Perinatal Asphyxia on Childhood Outcomes. N Engl J Med 2014;371:140-9

09. Shankaran S et al. Childhood Outcomes afterHypothermia for Neonatal Encephalopathy. N Engl J Med. 2012;366(22):2085-2092

10. NICE Interventional Procedure Guidance 347. Therapeutic Hypothermia with intracorporeal temperature monitoring for hypoxic Perinatal brain injury. May 2010

11. British Association of Perinatal Medicine. Position Statement on Therapeutic Cooling for Neonatal Encephalopathy. July 2010

12. Hall NJ, Eaton S, Peters MJ, Hiorns MP, Alexander N, Azzopardi DV, Pierro A. Mild controlled hypothermia in preterm neonates with advanced necrotizing enterocolitis. Pediatrics 2010; 125(2): e300-8.

13. Smit E, LiuX, Cowan F, Thoresen M. Cooling neonates who do not fulfil the standard cooling criteria – short and longterm outcomes. Acta Paediatr 2015; 104(2):138-45

14. Austin A, Shanmugalingam S, Clarke P. To cool or not to cool? Hypothermia treatment outside trial criteria. Arch Dis Child Fetal Neonatal Ed. 2013; 98(5): F451-3.

(Adapted from John Radcliffe University Hospital, Oxford, NICU Guidelines)

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Picture Story

A CASE OF INCONTINENTIA PIGMENTI IN A NEW BORN

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Key words: Incontinentia Pigmenti, new born, skin manifestations

INTRODUCTION:

Incontinentia pigmenti (IP) is a rare neuroectodermal dysplasia with an estimated incidence of 0.7 cases per 100,000 births[1]. Up to date approximately 1,200 cases have been reported in scientific literature[2]. IP has a multisystemic involvement where the skin manifestations are the hall mark and could be seen even at birth.

We present a baby girl with typical skin manifestations of IP seen at birth.

CASE REPORT:

A baby girl was born to healthy non-consanguineous parents at term via assisted vaginal delivery.Erythematous linear streaks and plaques of vesicular eruptions with hyperpigmentation arranged in a linear configuration, were mainly seen on the limbs and the trunk (Figure 1 & 2). Lesions were more pronounce on the flexor aspect of the lower limbs (Figure2)

There was a history of premature rupture of membranes for 16 hours without other risk factors for sepsis. Baby was born with a birth weight of 3.08 kg (median to -1SD) with normal Apgar scores. Her length and occipitofrontal circumference were 50 cm s (median) and 33 cm s (-1SD) respectively. There was no scaring alopecia, nail dystrophy or skeletal abnormalities. Neurological examination including tone, reflexes, fontanellae and primitive

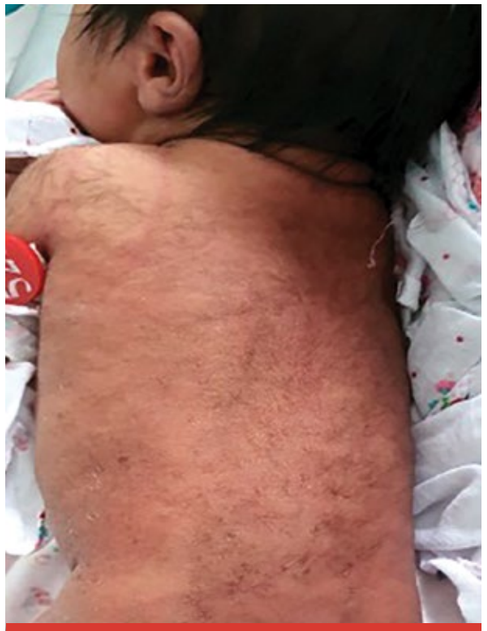

Figure 1: Hyperpigmentation in a liner configuration on the trunk

reflexes were normal. Formal eye examination revealed abnormal palpebral and conjunctival dilated vessels with occasional pigmentation.No retinal vasculature abnormality, arteriovenous malformations or lens opacity were noted. A grade-2 ejection systolic murmur was found. Rest of the system examination was unremarkable.

She was the second born with a healthy developmentally normal female sibling. There weren't any miscarriages or similar conditions, bulbous dermatosis, severe allergic reactions and neurological disorders in the family. Mother's venereal disease screening was negative and she

Figure 2: Erythematous linear streaks and plaques of vesicular eruptions with hyperpigmentation in a linear configuration mainly affecting the lower limbs.

did not have any lesions suggestive of herpes simplex infection. A diagnosis of IP was made on clinical grounds with the presence of typical neonatal rash with ocular manifestations. Skin biopsy was not performed. Mother did not show any features of IP.

Skin lesions were managed with topical antibiotic preparations and aqueous cream. Baby was discharged on day 3 of life after counseling the parents and with a plan for follow up including routine eye, neurological examinations and a plan for dental referral in future. Chromosomal and genetic testing was not done due to financial constraints.

DISCUSSION:

IP is an ectodermal dysplasia where skin and its appendages, endovasculature and central nervous system (CNS) are affected. IP is typically identified by its unique skin manifestations that appear in four stages and is the first notable clinical manifestation. Vesiculobullous lesions are noted on torso and extremities from birth to 2 weeks which proceed to verrucous hyperkeratotic papules. Classical whorls and streaks of brown pigmentation following lines of Blaschko are seen from late infancy to puberty. The fourth stage is manifested by adolescence which comprises of pale, hairless, atrophic patches and/or hypopigmentation. Vertex alopecia is the commonest hair manifestation of IP[3]. Prevalence of nail dystrophy in IP is uncertain and may regress with time. Dental anomalies which include partial/ total adonentia, pegged and conical teeth are the mostly seen non-cutaneous manifestation[3]. CNS manifestations include infantile spasms, seizure disorder, spastic paralysis, learning disabilities and microcephaly.

IP is an X-linked dominant genetic disorder caused by a mutation in the IKBKG (NEMO) gene which codes for proteins preventing cellular apoptosis[4]. Affected hemizygous male foetuses demise in utero, but males with milder forms of gene mutation, mosaicism and XXY karyotype may survive[2]. The diagnosis of IP is mainly based on clinical evaluation. Molecular genetic testing is also available. Skin biopsy may be helpful in females with questionable findings in resource poor settings. Diagnostic criteria are being brought up by Mini S et al which includes any stage of skin manifestations of IP as the major criterion. The minor criteria consist of non-cutaneous anomalies and multiple male miscarriages[5]. Histopathological findings of IP are also considered as a minor criterion[5]. Presence of IKBKG mutation and presence of a relative with IP are also considered in making a diagnosis[5]. Ophthalmological evaluation by a paediatric ophthalmologist is a must. Repeated eye evaluations and fluorescein angiograms are needed since the eye manifestations are severe but be effectively treated with early identification. A thorough examination of skin and its appendages and a detailed neurological examination is warranted on follow up. MRI brain with or without angiography and electroencephalography are indicated if seizures, neurological abnormalities or retinal changes are present. A detailed evaluation of the mother is important since in some, manifestations can be very mild and missed.

Treatment is purely supportive[6]. Skin manifestations may disappear with growth. In newborn a local antiseptic can be used for vesiculo-bullous lesions to prevent secondary infections. Topical corticosteroids may be used to control the inflammation when it is severe. To prevent skin inflammation and pigmentation photoprotective measurements are recommended. Laser treatment should be avoided on hyperpigmented lesions since it results in recurrent cutaneous inflammation. Retinal neovascularization is treated with cryotherapy and laser photocoagulation to prevent retinal detachment. Appropriate rehabilitation is needed when developmental delay and/or intellectual disabilities are present. Since dental anomalies may interfere with feeding and speech, timely interventions are important. Genetic counselling is a key aspect in management.

REFERENCES:

01. Fusco F, Paciozlla M, Conte MI, Pescatore A, Esposito E, Mirabelli P, et al. Incontinentia pigmenti: report on data from 2000 to 2013. Orphanet J Rare Dis. 2014;9:93

02. National Organization for Rare Disorders [home page on the internet].Danbury. Available from https://rarediseases.org/rare diseases/incontinentia-pigmenti/

03. Landy SJ, Donnai D. Incontinentia pigmenti (Bloch-Sulzberger syndrome). J Med Genet 1993;30:53-9.

04. Berlin AL, Paller AS, Chan LS. Incontinentia pigmenti: a review and update on the molecular basis of pathophysiology. J Am Acad Dermatol.2002;47(2):169-190. doi:10.1067/mjd.2002.125949

05. Mini S, Trpinac D, Obradovi M. Incontinentia pigmenti diagnostic criteria update. Clin Genet. 2014;85(6):536-542. doi:10.1111/ cge.12223

06. National Foundation For Ectodermal Dysplasia-Incontinentia pigmenti [home page on the internet]. https://www.nfed.org/learn/ types/incontinentia-pigmenti/

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Picture Srory

A RARE CASE OF DIPHALLIA ASSOCIATED WITH ANORECTAL AND VERTEBRAL MALFORMATIONS

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Key words: Diphallia, Congenital malformation

INTRODUCTION

Diphallia is a rare urogenital tract malformation characterized by complete or partial penile duplication with an estimated incidence of 1 per 5 to 6 million live births.[1] First case was published in 1609 and till now only around 100 cases have been reported worldwide.[1]

Diphallia is often associated with multiple anomalies such as anorectal malformations, urinary tract abnormalities, vertebral deformities, bladder or cloacal extrophy and congenital heart diseases. In severe cases pubic symphysis diastasis, imperforated or duplicated anus, recto sigmoidal duplication and inguinal hernia may be observed.

It is proposed that diphallia occurs between 23rd to 25th days of gestation when environmental precipitants like drugs, infections, chemical stress impair the normal function of the caudal cell mass of the mesoderm.[1,3]

CASE REPORT

A baby boy was born to a 29 year old mother in her third pregnancy with two healthy living children. There were no antenatal complications and her ultra sound scan including anomaly scan did not reveal any significant fetal anomalies. Baby was delivered by elective caesarian section due to past section at 37 weeks of period of gestation. Baby was born in good conditions and his APGAR scores were 8,9,10 at 1 minute, 5 minutes and 10 minutes respectively. Baby weighed 2.9 kg, had a length of 45cm and OFC of 34cm.

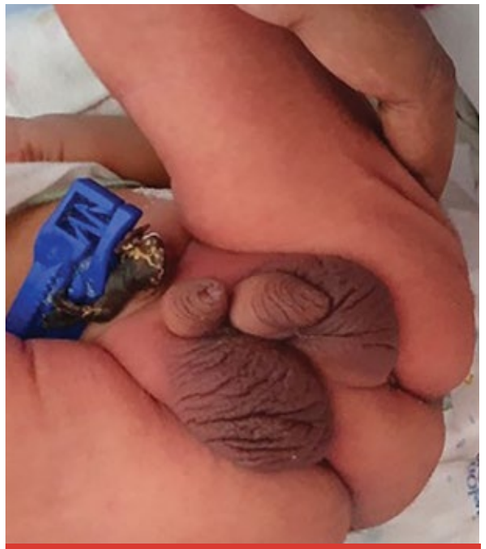

Figure 1: Diphallia (Anterior view)

Figure 2: Following exploratory laparotomy and colostomy creation

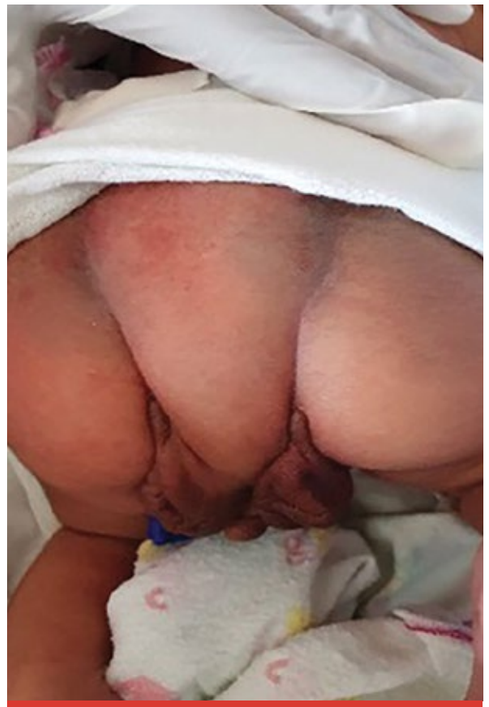

Figure 3: Diphallia (Posterior view)

During the inspection complete penile duplication, bifid scrotum with bilateral undescended testes and duplicated dimple like anal margins with imperforation were noted. In addition a soft tissue swelling was found over the sacral spine without any external deformities. (figure 1,2) However bilateral lower limb movements were persevered. Apart from above anomalies rest of the neonatal examination was normal.

Ultra sound scan KUB (kidney, ureters and bladder) revealed a cross fused left sided renal ectopia and right sided testes was visualized in inguinal canal but left side testes was not identified. Ultra sound scan of spine showed possible tethered cord with distal diastomatomyelia. Chest X-ray and 2D Echocardiogram were normal. Baby is awaiting for MRI brain and spine. Free urinary flow was noted during catheter insertion of both urethral openings.

Baby has undergone exploratory laparotomy and colostomy creation under general anesthesia in day 2 of life. He is presently awating multidisciplinary review.

DISCUSSION

Diphallia is a rare congenital abnormality. Extensive investigations are needed in all cases to identify associated other congenital malformations. Treatment should always be individualized according to the degree of penile duplication and extend of the associated anomalies[2].Management of these patients will be a challenge for the Multi-disciplinary team.

REFERENCES

01. Frolov A, Tan Y, Rana MW, Martin J R . A rare case of human diphallia associated with hypospadias. Case reports in urology. 2018 Jun 13;2018.

02. Gyftopoulos K, Wolffenbuttel KP, Nijman RJ. Clinical and embryologic aspects of penile duplication and associated anomalies. Urology. 2002 Oct 1;60(4):675-9.

03. Kundal VK, Gajdhar M, Shukla AK, Kundal R. A rare case of isolated complete diphallia and review of the literature. Case Reports. 2013 Feb 13;2013:bcr2012008117.

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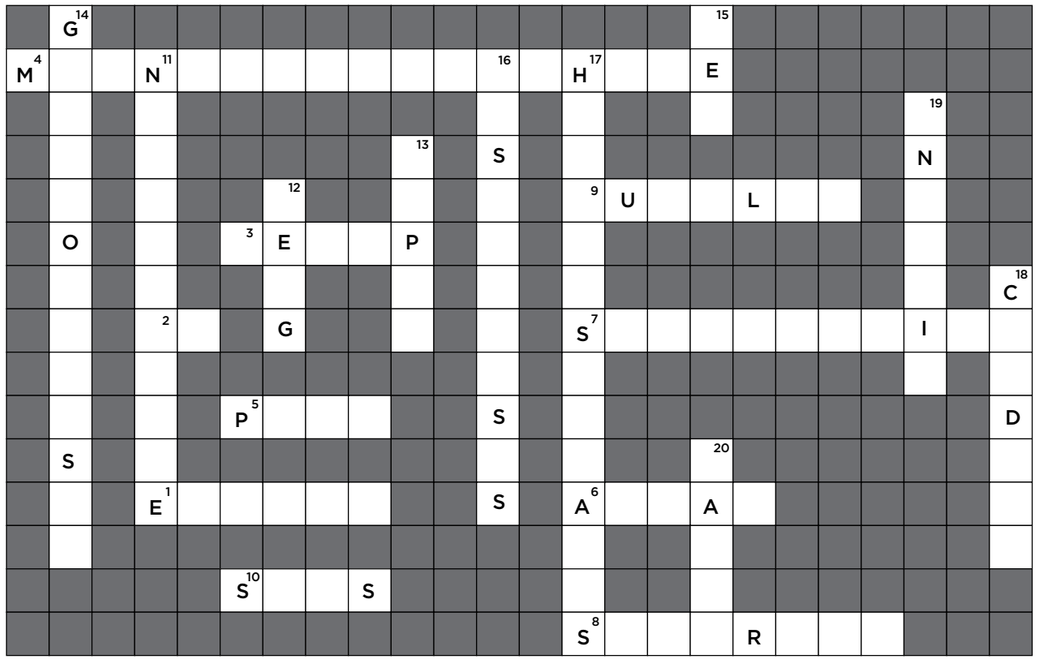

Across

1. Trisomy 18
2. Calculated to determine ECMO
3. A condition associated with Pre-eclampsia
4. A medication used in preterm labour and eclampsia
5. Occurs due to ascending infection in pregnancy
6. It is an assessment done at the birth
7. Lack of folic acid causeS this
8. A group of clinical symptoms which occur consistently
9. Intrauterine infection causing heart disease
10. provides better view of the woman cervix

Down

11. Potent pulmonary vasodilator
12. Gold standard for monitoring neonatal convulsions
13. Maternal illness causes heart block in newborn
14. A Birth defect in which babies' intestines extend outside of the abdomen
15. In this condition gas is seen in the intestinal wall
16. preterm meconium stained liquor seen in this condition
17. Associated with Parvo virus B19
18. Commonest vaginal infection during pregnancy
19. Occurs commonly due to Iron deficiency in pregnancy
20. Heart shadow of figure of eight seen in CXR of a newborn

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ORGANIZATION AS AUTHOR

Diabetes Prevention Program Research Group. Hypertension, insulin & proinsulin in participants with imp. tolerance. Hypertension. 2002;40(5):679-86. https://doi.org/10.1161/01.HYP.0000035706.28494.09 PMid: 12411462 PMCid: PMC2516377Both personal authors and an organization as author Vallancien G, Emberton M, Harving N, van Moorsel RJ; Alf-One Study Group. Sexual dysfunction in patients suffering from lower urinary tract symptoms. J Urol. 2003;169(6):2257-61. https://doi.org/10.1097/01.ju.0000067940.76090.73 PMid: 12771764

NO AUTHOR GIVEN

21st century heart solution may have a sting in the tail. BMJ.2002;325(7357):184. https://doi.org/10.1136/bmj.325.7357.184

VOLUME WITH SUPPLEMENT

Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for migraine and in comparison with sumatriptan. Headache. 2002;42Suppl 2:S93-9. https://doi.org/10.1046/j.1526-4610.42.s2.7.x PMid: 12028325

ISSUE WITH SUPPLEMENT

Glauser TA. Integrating clinical trial data into clinical practice. Neurology. 2002;58(12 Suppl 7):S6-12. https://doi.org/10.1212/WNL.58.12_suppl_7.S6 PMid: 12084862
BOOKS AND OTHER MONOGRAPHS
PERSONAL AUTHOR(S)

Murray PR, Rosenthal KS. Medical microbiology. 4th ed. St. Louis: Mosby;2002.

EDITOR(S), COMPILER(S) AS AUTHOR(S)

Gilstrap LC 3rd, Cunningham FG, VanDorsten JP, editors. Operative obstetrics. 2nd ed. New York: McGraw 2002.

CHAPTER IN A BOOK

Weinstein L, Swartz MN. Pathologic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, editors. Pathophysiology of disease. Phoenix: Saunders; 1975. p. 450-55.

CONFERENCE PROCEEDINGS

Harnden P, Joffe JK, editors. Germ cell tumours V. Proceedings of the 5th Germ Cell Conference

Sep 13-15; Leeds, UK. New York: Springer; 2002.

CONFERENCE PAPER

Christensen S, Oppacher F. An analysis of computational effort statistics for gene programming. In: Lutton E, Miller J, Ryan C, editors. Genetic programming. Euro GP 2002: Proceedings of the Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

ELECTRONIC MATERIAL

CD-ROM

Anderson SC, Poulsen KB. Anderson's electronic atlas of haematology [CD-ROM]. Phoenix: lippincott Will 2000.

WEBSITES

Preminger GM, Tiselius HG, Assimos DG, et al. Guideline for the management of ureteral calculi. American Urological Association, 2007. http://www.auanet.org/education/guidelines/ureteralcalculi (accessed on Feb 20, 2011)

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