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DR. PRADEEP KUMAR DEBATA

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President NNF Delhi

Dear NNF Delhi Members

Wish you all a happy and healthy new year on behalf of NNF Delhi. May this year bring new accolades to our most loved NNF Delhi branch.

It's a feeling of pride that we are coming with our new edition of NeoClips (Neonatal Clinical Practice) for the 2nd year. In this occasion, I am feeling privileged to congratulate our Editorial Board Members, chaired by Dr. T J Antony and our Editor in chief Dr. Naveen Parkash Gupta, who are working tirelessly, to make each edition of NeoClips to see the light.

NeoClips is the platform for the Neonatologist to publish their studies, review articles and their clinical experience as case reports which help adding to the current knowledge. I am thankful to the authors who are contributing with their research works for publication and request all our Esteemed Members to contribute their research works and experience in a big way to enrich it further.

We all, as Neonatologists, are contributing towards the better survival of neonates. Many national and international programs are being launched to decrease neonatal mortality and we are approaching our set target by reducing the deaths among extremely preterm and asphyxiated neonates. Is this enough? The mere survival of neonates is not the solution. I feel we have to rethink our current strategy not only to decrease neonatal mortality but also to have the intact survival of our children. In this year of 2023, let us all focus on the intact survival of neonates rather than just decreasing Neonatal mortality.

With Regards

Dr. Pradeep Kumar Debata
President, NNF Delhi

From Secretary's Pen

DR KUMAR ANKUR

Secretary, NNF Delhi

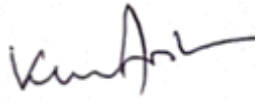
Dear friends,

Warm greetings from National Neonatology Forum, Delhi!

It gives me immense happiness to see the success of NNF Delhi's monthly E-Bulletin launched in February 2022 with the name 'NeoClips' (Neonatal Clinical Practice). Every month it's getting better & better. And credit goes to the Chief editor Dr Naveen Gupta & his exceptional team. Each system is covered separately in the OSCE section. This should be useful for our Neonatal Fellows/Residents and postgraduates. In the present issue, we have an interesting case of neonatal methemoglobinemia in case report section. The review is on oral colostrum as immune therapy in preterm babies.

We are requesting all the esteemed members to contribute to these E-bulletins. We shall be giving the due credits to all the contributors.

We eagerly look forward to your feedback and hope to give you an experience that you will cherish forever!



Dr. Kumar Ankur
Secretary, NNF Delhi

Editor's Desk

DR NAVEEN PARKASH GUPTA

Chief Editor, Neo Clips

Dear Friends,

Greetings from the NeoClips team.

As Editor, I would like to start by thanking the editorial team for the effort and the authors for their contribution to the current (10th issue) and previous issues.

We have covered some interesting topics in the present issue.

The case report covers an interesting case of Neonatal methemoglobinemia secondary to gastroenteritis.

Oral Colostrum has come up as a simple and novel intervention in premature babies to reduce nosocomial sepsis. The review article covers this important topic.

An interesting case of cleft lip and palate has been covered in the picture of the month.

The image section describes an ultrasound image of cystic periventricular leukomalacia in an extremely premature baby.

This issue OSCE is on a mixed bag which is having few interesting questions.

We hope that you will enjoy reading this issue. Please share your feedback with us. It will help us improve the journal.

Dr Naveen Parkash Gupta

A Newborn with Cyanosis and Diarrhoea

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Introduction

Case

Term (37 weeks) appropriate for gestational age male baby, born out of non-consanguineous marriage to primigravida mother with a birth weight of 2600 grams through normal vaginal delivery. The antenatal course was uneventful. The baby cried immediately after birth and was shifted to the mother. He was discharged on the second day of life. At home, he was receiving both breast and bottle feeds. He presented to us on the 15th day of life with a history of multiple watery loose stools for last 24 hours followed by fast breathing and cyanosis and nil urine output in last 12 hours. There was no history suggestive of high-grade fever and vomiting. There was no history suggestive of bluishness of skin or breathing difficulty or loose motions in these 15 days.

On examination, central cyanosis was present. Baby was in severe dehydration Pulse volume was low and extremities were cold. He was lethargic, less responsive to painful stimuli, tachycardic (HR 190/min), hypotensive (BP 30/16 mm Hg) and had acidotic breathing. His saturations were 85% on room air and there was no improvement in saturations with oxygen supplementation. His present weight was 2000 grams (23% weight loss from birth). The baby was intubated in delivery room and fluid boluses were started (20 ml/kg of Normal saline over 30 min) and was shifted to NICU on a transport ventilator. In NICU baby was kept on patient triggered ventilation (PTV) mode, and even on 100% oxygen his saturations were around 86%. Saturations remain in the range of 82-90% irrespective of FIO2 change.

Fluid resuscitation was started for severe dehydration. Cyanosis persisted even after stabilization. Blood pressure got normalized on inotropes. On IV cannulation, chocolate colored blood was noticed. Echocardiography was normal. Initial blood gas showed severe metabolic acidosis with pH 7.260, HCO3 – 9, BE = -15.4, lactate 5.1 mmol/l, PaO2 – 98 mm Hg. Methemoglobin levels in blood gas were 53.1%. G6PD levels were sent and the baby was started on intravenous methylene blue at 1mg/kg and ascorbic acid at 2mg/kg.

Rest blood reports suggested Hemoglobin of 16.5 gm/dl and his platelets and total leucocyte levels were normal. C Reactive protein levels were slightly raised (29 mg/L). Creatinine was slightly raised (Serum creatinine 1.5 mg/dl). Other kidney function tests were normal. Baby was started on antibiotics (Piperacillin, Tazobactam) after sending sepsis workup and stool examination.

After starting methylene blue, methemoglobin level fell down to 20% and significant clinical improvement was noticed in the form of improved saturations and sensorium. One more dose of methylene blue was given after a gap of 6 hours. Baby improved clinically and inotropes were weaned off in the next 24 hours. Methemoglobin level was 3% after 12 hours of methylene blue, repeat KFT was normal.

Loose stools continued post admission. Stool routine examination was normal, Stool for rotavirus antigen was negative, Stool culture grew Vibrio Cholerae which was sensitive to Piperacillin and Tazobactum and Amikacin which the baby already receiving apart from this single dose azithromycin was also given.

Tandem Mass Spectrometry (TMS) and Urine Gas Chromatography (GCMS) were normal. Blood culture was sterile.

Baby was extubated to room air post 72 hours of admission. He started accepting direct feeds and was discharged after 7 days of admission with weight of 2700 grams. At time of discharge parents were explained regarding danger signs and it was planned to rule out congenital methemoglobinemia in case of any recurrence.

Discussion:

Cyanosis, a bluish-purple discolouration of tissues due to increased concentration of deoxygenated hemoglobin in capillary bed usually result from respiratory and circulatory causes. Hemoglobinopathies like methemoglobinemia do lead to cyanosis in neonates. Central cyanosis appears when the amount of reduced hemoglobin is more than 5gms%. (1)

Methemoglobin is an altered state of hemoglobin in which heme iron is oxidized from ferrous form to ferric form. (2) Ferric form binds irreversibly to oxygen and it also increases oxygen affinity of other ferrous molecules in the heme tetramer thereby decreasing oxygen supply to tissues, eventually resulting in functional anemia and cyanosis. Normally, the ferric form is reduced back to ferrous form with the help of cytochrome b reductase (major pathway) or NADPH reductase (less common pathway). Infants are more prone than adults to develop methemoglobinemia owing to a higher proportion of fetal haemoglobin (which is easier to convert to methemoglobin) and lesser NADPH methemoglobin reductase activity (which converts methemoglobin to haemoglobin). (3) In methemoglobinemia, methemoglobin levels in the blood are increased and there is a decreased capability of red blood cells to oxygenate tissues. Hallmarks of methemoglobinemia are hypoxia, cyanosis and chocolate colored blood. (4)

Methemoglobinemia is of 2 types: Congenital and acquired. Congenital methemoglobinemia is of 3 types: Type 1, II and Hemoglobin M disease (HbM). In type I there is deficiency of enzyme NADH cytochrome b5 reductase (cyb5r) in red blood cells. Babies usually present with cyanosis which is easily treated by methylene blue or a combination of vitamin C and riboflavin. (5) Although the cyanosis recurs, the disease course is so mild for most babies and children diagnosed to have a normal life expectancy. Type II, however, is more serious and is characterized by a deficiency in membrane-bound cyb5r3 in all cells, which may impair fatty acid synthesis. (6) Symptoms include ongoing cyanosis, cognitive impairment, microcephaly, dystonia, and movement disorders. Infants born with type II disease usually have a shortened lifespan; most die in the first year of life. (7) HBM disease is the result of mutations in the globin gene and is associated with a benign course. All forms of congenital methemoglobinemia respond to methylene blue treatment except HBM type. (8)

Acquired methemoglobinemia can be because of endogenous and exogenous causes. Use of aniline dyes (to wash diapers), drinking well water (contains nitrites), nitric oxide to treat persistent pulmonary hypertension, nitro and benzo compound can lead to acquired methemoglobinemia. (9)

Acute diarrheal illness in children has been recognized as a cause of acquired methemoglobinemia when no exogenous exposure or congenital deficiency can be documented. Acquired methemoglobinemia has been associated with diarrhoea or infection secondary to nitrite-forming bacteria (Escherichia coli), serious acidosis and hyperchloremia. Some authors have suggested impaired reduction of methemoglobin secondary to acidosis as a necessary component to produce methemoglobinemia. However, no consistent correlation between methemoglobin levels and severity of acidosis was seen. (10)

Key points:

1. Fixed SpO2 around 85% may point towards hemoglobinopathies (methemoglobinemia being most common) in a case of central cyanosis.
2. Methemoglobinemia can be congenital or acquired. Usually, it responds to methylene blue except when there is complete absence of NADPH reductase.
3. Diarrhoea in neonates can lead to acquired methemoglobinemia (though less common)

References:

1. Elboraee MS, Clarke G, Belletrutti MJ, Escoredo S. HbM methaemoglobinaemia as a rare case of early neonatal benign cyanosis. Case Reports 2015;2015.
2. Kuiper-Prins E, Kerkhof GF, Reijnen CG, van Dijken PJ. A 12-day-old boy with methemoglobinemia after circumcision with local anesthesia (lidocaine/prilocaine). Drug Saf Case Rep 2016;3(1):12
3. Yip L, Spyker DA. NADH-methemoglobin reductase activity: adult versus child. Clin Toxicol (Phila) 2018;56(9):866–8.
4. Bayat A, Kosinski RW. Methemoglobinemia in a newborn: a case report. Pediatr Dent 2011;33(3):252–4.
5. Lorenzo FRt, Phillips JD, Nussenzveig R, et al. Molecular basis of two novel mutations found in type I methemoglobine- mia. Blood Cells Mol Dis 2011;46(4):277–81
6. Kedar PS, Warang P, Ghosh K, Colah RB. Severe mental retardation and recessive congenital methemoglobinemia in three Indian patients: compound heterozygous for NADH- cytochrome b5 reductase gene mutations. Am J Hematol 2011;86(3):327–9.
7. Ewenczyk C, Leroux A, Roubergue A, et al. Recessive heredi- tary methaemoglobinaemia, type II: delineation of the clinical spectrum. Brain 2008;131(Pt 3):760–1
8. Rangan A, Savedra ME, Dergam-Larson C, et al. Interpreting sulfhemoglobin and methemoglobin in patients with cyanosis: an overview of patients with M-hemoglobin variants. *Int J Lab Hematol*. 2021;43:837-844.
9. Bloom John C, Schade Andrew E, Brandt John T. Toxic responses of the blood. In: Klassen Curtis D, Casarett, Doull's, (eds). The Basic Science of Poisons, 8th ed., New York: McGraw-Hill Educcation, 2013. pp. 529–52.
10. Greer FR, Shannon M, American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Committee on Environmental Health . Infant methemoglobinemia: the role of dietary nitrate in food and water. *Pediatrics*. 2005;116(3):784-786

A Brief Overview of Colostrum Oral Immune Therapy in Neonates

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Background

With the advancement in newborn care, the survival of very low birth weight infants has improved significantly in the past few decades. With better survival rates, the focus has shifted from survival to "intact survival." Intact survival here refers to survival without major morbidities like late-onset sepsis (LOS), including meningitis, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH) and Bronchopulmonary dysplasia (BPD). Therefore, the practices in neonatal care should be directed towards intact survival.

A close look into the pathogenesis of these morbidities (sepsis, NEC, ROP, BPD) suggests that these are associated with/caused by cytokine storm characterized by increased pro-inflammatory cytokines (IL-1, IL-6, IL-8, Tumor necrosis factor, etc.) with a concomitant reduction in protective cytokines (IL-2, IL-17, sIgA, Lactoferrin, etc.) (Figure 1) (1). Therefore, there is a need for evidence-based strategies to maintain the delicate balance between pro- and anti-inflammatory cytokines. Colostrum or Mother's own milk (MOM) is rich in anti-inflammatory properties. Colostrum is a rich source of secretory immunoglobulins (sIgA), Lactoferrin, and human milk oligosaccharide (HMO). The cytokines in the mother's milk stimulate the oropharyngeal mucosa-associated lymphoid tissue (OMALT) of the neonates and activate the immune cascade to provide anti-infective, anti-inflammatory, and immunomodulatory actions against bacterial, viral, and fungal infections.

Unfortunately, in the first few days of life (when the vulnerability to infections is at its peak), breastmilk feeding might not be possible due to neonatal sickness or prematurity. Even if fed, they are on predominant gavage feeds, bypassing OMALT. Therefore, with conventional feeding methods, it might not be possible to fully harness the immune properties of the colostrum or MoM, personalized nutrition for the baby.

What is Oral Immune Therapy?

Oral immune therapy (OIT) or colostrum oral immune therapy (COIT) refers to oral/oropharyngeal application of a tiny amount of colostrum or mother's milk (typically 0.2 mL) with the help of an insulin syringe or sterile cotton swab in order to stimulate lymphoid tissue of oral mucosa '(6,7). This strategy helps harness the immune benefits of colostrum/ MoM while babies can't be fed orally. The rationale for using this small amount is to stimulate the OMALT by painting the mucosa without letting the baby swallow.

Colostrum oral immune therapy (COIT) was invented and popularized by Nancy Rodriguez in 2011. It uses MoM only but in a different and structured way. Most authors have suggested the following protocol to ensure uniformity in clinical practices and clinical trials (2,4,5,7).

***a) Steps of Oral Immune Therapy*:**

Various steps included in the therapy are as follows:

a. Collect colostrum from mothers from the first day itself. Kindly make sure that appropriate hand hygiene measures are taken while expressing milk.

b. Depending on the volume, this collected colostrum can be administered fresh (preferred) or stored. The stored colostrum must be pre-warmed before use.

c. Take 0.2 mL of colostrum with the help of a tuberculin syringe or dip the swab stick well into the colostrum so that it absorbs colostrum

completely and is not dribbling. Approximately 14 drops of colostrum are enough to meet the 0.2 mL requirement.

d. Apply 0.1 mL on each oral mucosa and oropharynx side in gentle strokes. This procedure generally takes 1-2 minutes.

e. While applying these strokes, the baby should be monitored for changes in heart rate, apnea, desaturations etc. Until now, none of the trials reported any adverse effects related to the application, but being a relatively new strategy is advisable to monitor the baby. The procedure should be stopped in case of any adverse event.

b) Eligibility for Oral Immune Therapy

All infants not on oral feeds, irrespective of gestational age, weight, and sickness with no contraindication for milk (like IEMs), are eligible for OIT. A few doctors and nurses might be concerned about applying OIT in Extremely low-birth babies on mechanical ventilation and inotropes. However, many RCTs enrolled such neonates and did not observe any difference from those of larger neonates. Infact, this is suggested as one of the interventions to prevent ventilator-associated pneumonia in neonates.

c) When to Initiate

COIT can be initiated as early as possible. Earlier colonization of the oral cavity with friendly bacteria (Bifidobacterium, etc.) improves the long-term outcome. Human milk oligosaccharides in colostrum and MoM increase the concentration of Bifidobacterium, whereas sIgA and Lactoferrin reduce the colonization of harmful bacterium like Enterobacteriaceae. Therefore, early initiation with colostrum is likely to improve the outcomes.

d) Frequency of Oral Immune Therapy

There are no evidence-based recommendations to best guide the frequency. However, most studies used 2-3 hours frequency per their unit's feeding schedule. While deciding frequency, it should gel with the unit's feeding schedule to make it easy for nurses to follow. In this way, it might improve adherence to the therapy.

e) Duration of Oral Immune Therapy

Various studies have given therapy for a variable duration ranging from 48 hours until the oral feeds are initiated. Again, there are no evidence-based recommendations to guide the duration of therapy. However, many authors prefer to administer it until oral feeds are started, as until then, OMALT remains unexposed to the milk (1,2).

Effect of Oral Immune Therapy on Cytokine Profile

As the basis of OIT therapy was improved cytokine profile, initial studies mainly focussed on change in cytokine profile. Various body secretions, namely Saliva, Urine, tracheal secretions, and stool, have been used for measuring cytokine concentrations. Some studies have shown increased sIgA and Lactoferrin on body secretion with OIT application (1,2,5). However, few did not find any significant differences between the two groups, more so beyond the first few days of life. The overall profile suggests that OIT might be associated with improvement in cytokine profile in the initial few days. However, its effect doesn't last long, particularly if applied for a shorter duration. This area is still under research and requires further studies.

Effect of Oral Immune Therapy on Clinical Outcomes

More than 20 randomized controlled trials compared the colostrum group (COIT) with a placebo or routine care except COIT. A recent systematic review of 17 RCTs enrolling 4106 preterm infants indicates the clinical benefits too (1). In this systematic review and meta-analysis, the authors did not observe a statistically significant difference between groups in the incidence of necrotizing enterocolitis (NEC) stage 2 or higher (RR = 0.65; 95%CI, 0.36-1.20; 1089 participants in 12 trials). However, they observed that OIT significantly reduced the incidence of sepsis (RR = 0.72; 95%CI, 0.56-0.92; 1511 participants in 15 studies) and any stage of NEC (RR = 0.58; 95%CI, 0.37-0.92; 1616 participants in 16 trials). Also, infants in the OIT group achieved full enteral feeds 1.75 days sooner (95%CI, 0.3-3.2 days; 1580 participants in 14 studies) and had higher weight at discharge (MD = 43.9 g; 95%CI, 3-85 g; 569 participants in 3 studies). Based on this evidence, the authors concluded that there is low certainty to suggest that OIT might have a beneficial effect on NEC (any stage), sepsis, and time to full

enteral feeds. As the intervention does not include any additional cost (may involve minimal) or human resources, and no harm is reported with the therapy, the authors suggest routine use of OIT in preterm neonates, more so in countries where the burden of sepsis and NEC is high. This systematic review also includes studies from India, suggesting beneficial effects on intact survival. Moreover, this therapy involves stimulation of oral mucosa, which has been shown to improve feeding outcomes independently.

Challenges in Routine Clinical Practice

Though evidence suggests the beneficial effects of OIT on various critical neonatal outcomes, it has not gained popularity. Only a few units have protocol to use OIT in all eligible babies. Many clinicians are still hesitant or unable to implement it (9). The common implementation challenges include the non-availability of colostrum, lack of experience in extremely premature infants, and fear of aspiration or apnea in ventilated neonates. Also, due to non-availability of colostrum round the clock might lead to frequent missed doses, hence limiting the benefits.

Possible Solutions for Improving Adoption of Oral Immune Therapy

First and foremost is ensuring the colostrum availability from the first day of life. In most trials, many infants were excluded because of this reason. The efforts to improve colostrum expression are the same as the measures are routinely taken to improve early breastmilk expression. Mothers should be counseled from the antenatal period regarding the early expression of colostrum and not to discard it, irrespective of its quantity. For this purpose, counseling by lactation nurses and early use of breast pumps are found useful. A few quality improvement studies have shown that efforts to improve the uptake of OIT in their unit lead to increased overall breastmilk feeding rates (1,9). This increase in MoM intake was not limited to the hospital stay but rather persisted during follow-up also.

In case colostrum or MoM is unavailable, few studies have used donor human milk (DHM). Though we are not sure whether the effects are the same as that of MoM, theoretically, it should also provide some benefits of human milk-led stimulation of MALT tissue.

Early involvement of the mother and other family members might pave the way for successful implementation. Therefore, explaining the potential benefits and use of even tiniest amount of colostrum might help them better express colostrum. Being a new therapy, the nurses and doctors need to be trained in OIT application. Though in our experience, it doesn't take long, its compliance drastically improves once they learn. Finally, is the need for a written, structured policy for using OIT. Success is unlikely unless a unit has a structured approach on the indication, when to start, dose, duration, etc.

Conclusion

Oral Colostrum Immune Therapy can reduce sepsis and NEC in fragile neonates without significant additional resources or harm. There is a need for quality improvement initiatives to understand the barrier to its implementation in local setup and to address those barriers systematically.

References

1. Kumar J, Meena J, Ranjan A, Kumar P. Oropharyngeal application of colostrum or mothers own milk in preterm infants: a systematic review and meta-analysis. Nutr Rev. 2023 Jan 30;nuad002.
2. Sudeep KC, Kumar J, Ray S, Dutta S, Aggarwal R, Kumar P. Oral Application of Colostrum and Mothers Own Milk in Preterm Infants-A Randomized, Controlled Trial. Indian J Pediatr. 2022 Jun;89(6):579-586.
3. Aggarwal R, Plakkal N, Bhat V. Does oropharyngeal administration of colostrum reduce morbidity and mortality in very preterm infants? A randomised parallel-group controlled trial. J Paediatr Child Health. 2021 Sep;57(9):146772.
4. Glass KM, Greecher CP, Doheny KK. Oropharyngeal Administration of Colostrum Increases Salivary Secretory IgA Levels in Very Low-Birth-Weight Infants. Am J Perinatol. 2017;34(14):138995.
5. Lee J, Kim HS, Jung YH, Choi KY, Shin SH, Kim EK, et al. Oropharyngeal colostrum administration in extremely premature infants: an RCT. Pediatrics. 2015 Feb;135(2):e357-366.

6. Rodriguez NA, Meier PP, Groer MW, Zeller JM, Engstrom JL, Fogg L. A pilot study to determine the safety and feasibility of oropharyngeal administration of own mothers colostrum to extremely low-birth-weight infants. Adv Neonatal Care Off J Natl Assoc Neonatal Nurses. 2010 Aug;10(4):20612.

7. Rodriguez NA, Groer MW, Zeller JM, Engstrom JL, Fogg L, Hongyan D, et al. A randomized controlled trial of the oropharyngeal administration of mothers colostrum to extremely low birth weight infants in the first days of life. Neonatal Intensive Care [Internet]. 2011 Jul [cited 2021 Dec 3];24(4):315. Available from: https://nicmag.ca/pdf/NIC-24-4-JA11-web.pdf

8. Rodriguez NA, Vento M, Claud EC, Wang CE, Caplan MS. Oropharyngeal administration of mothers colostrum, health outcomes of premature infants: study protocol for a randomized controlled trial. Trials. 2015 Oct 12;16:453.

9. Wetzel CM, Davis L, Grohler N, Oprondek D, Ruff D, Lowery K, et al. A Quality Improvement Project to Improve the Use of Mothers Own Milk (MOM) With Precision Oropharyngeal Therapy. Adv Neonatal Care Off J Natl Assoc Neonatal Nurses. 2020 Apr;20(2):E1930.

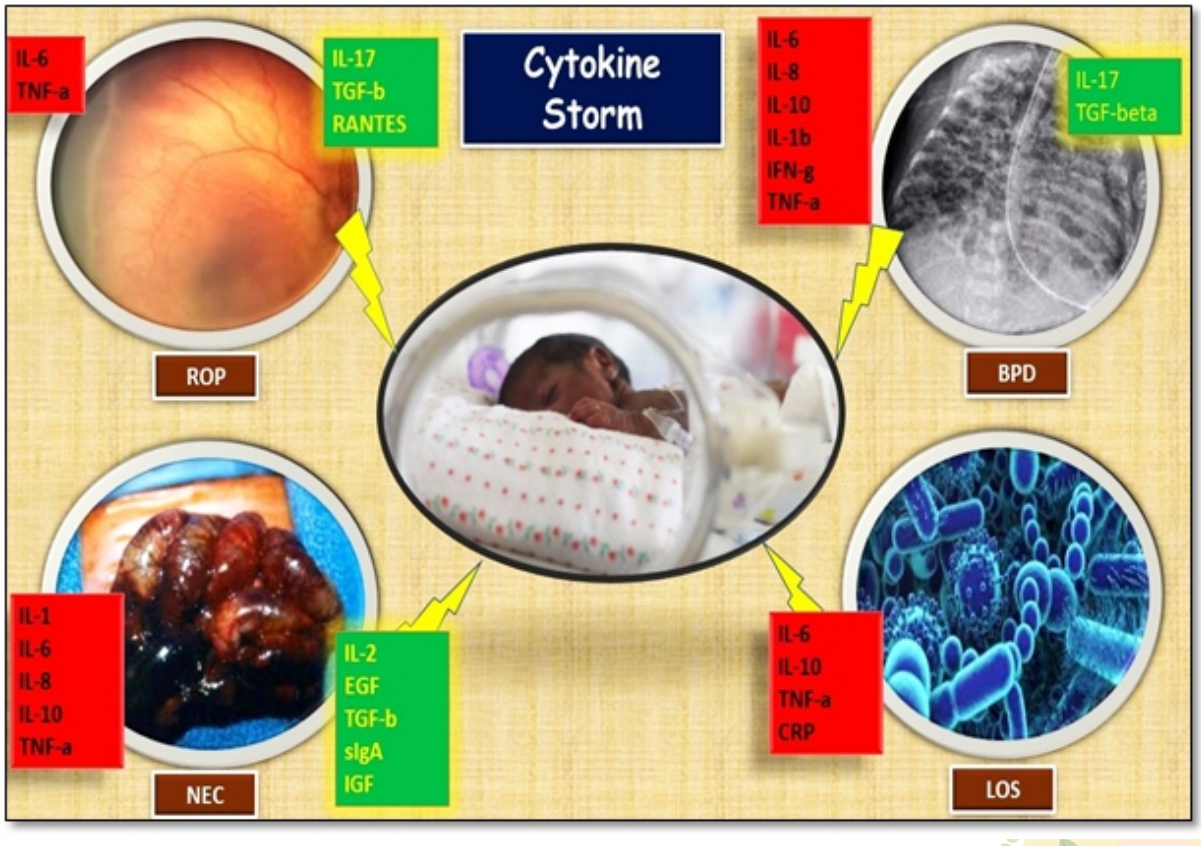

Fig 1: Cytokine profile in various neonatal morbidities

Feeding appliance for a neonate with severe cleft lip and palate

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Clinical presentation: A full term appropriate for age female neonate (birth weight 3163 grams) was delivered to a young healthy primigravida mother with uneventful pregnancy by an emergency caesarean section through meconium-stained amniotic fluid at a peripheral health centre. The neonate was noted to have a severe grade of cleft lip and cleft palate (CL/CP) at birth (figure 1A). Baby was referred to our center for further management.

Assessment: Neonate had a cleft lip on the left side with bilateral cleft palate extending up to the soft palate. Uvula was not bifid. It was categorised as group III CL/ CP. Echocardiography and ultrasonography of the renal system done to rule out concealed anomalies were reassuring.

Final Diagnosis: Isolated non-syndromic group III CL/ CP

Management: A customised feeding appliance was fabricated by the dental surgeon in two different thicknesses after obtaining the oral impressions (Fig 1). Feeding appliance once positioned over the hard palate area, baby was able to control the flow of milk expressed through mother's breast as well as feeding bottle.

Course during NICU stay: Baby was initially managed with gavage feeds as she had respiratory distress, the clinical and radiological diagnosis being consistent with transient tachyponea of the newborn. Once the tachypnea settled and the feeding appliance was ready, she was transitioned to oral feeds. The infant was able to feed well orally without any regurgitation or breathing difficulty. The family was trained regarding the use of feeding appliance. The mother was able to effectively breastfeed with the appliance on. Surgical timing and sequence of intervention was explained to the family. She was discharged home after feeding training and with consistent weight gain after the initial loss.

Discussion: Cleft lip and palate are amongst the most common congenital anomalies worldwide with an estimated incidence of 0.8 to 1.7 cases per 1,000 live births and exhibits a multi-factorial etiology. (1) CL/CP affects several functions, primarily feeding, swallowing, ventilation, facial growth, dentition, hearing, and speech as well as impacts the caregivers socially, psychologically and financially. (2) Neonates born with both cleft lip and palate suffer from oro-naso-pharyngeal incompetency. Due to oro-nasal communication, neonates born with cleft lip and palate, on one side, are unable to generate the negative pressure necessary for suckling and on the other hand, cannot compress the nipple between the tongue and hard palate to squeeze out milk. (2) This makes the infant unable to swallow milk, which in turn regurgitates out through the nose.

Treatment of these patients involves a multidisciplinary team (MDT) approach from birth into adulthood, involving a neonatologist, dental surgeon, pediatric surgeon, speech therapist, occupational therapist, and audiologist. Feeding difficulties should be assessed and intervened at the earliest, as it is the most critical aspect of the initial management after stabilisation. The simplest and immediate functional, non-surgical solution for this congenital anomaly is a feeding appliance, also referred to as an obturator. A 'Feeding appliance' is a customised prosthetic aid, designed to create a seal between the oral and the nasal cavity. This feeding appliance helps to serve two purposes. It not only creates a barrier between the oral and nasal cavities, but also helps in creating a negative intraoral pressure during suckling by providing a contact point to oppose the breast or nipple during suckling and thus helps the

infant to express milk effectively.

Such feeding appliances can be easily fabricated by dental surgeons who make a rubber base impression intraorally to record the details of the deformed tissues (Fig. 1B) which is poured with plaster to create a cast in the laboratory (Fig. 1C, 1D). This cast is used to fabricate the feeding appliance made with ethylene vinyl acetate using the pressure moulding technique (Fig 1E). Before inserting the appliance into the infant's mouth, it is inspected thoroughly to eliminate any sharp edges and is usually attached with a floss thread (Fig 1F) to facilitate easy retrieval for cleaning and prevent the unfortunate incidence of swallowing the appliance. A feeding appliance can function effectively till the cleft is surgically repaired and heals completely during infancy. In the case of postoperative palatal fistulas, a modified obturator is still indicated till the salvage surgical repair is planned.

Key points

- A thorough medical assessment should be done to determine the nature of the cleft and any associated concealed anomalies or co-morbidities
- An appropriate feeding plan should be initiated as soon as possible in discussion with a dedicated MDT of specialists
- Family should be integrated into the planning of individualised road map of surgical as well as non-surgical care.
- The support of parents by experienced professionals from various sub-specialities and allied health services can help in the establishment of adequate feeding
- Regular follow-up with MDT is essential to ensure adequate long-term growth and development

References

1. Mossey PA, Little J. Epidemiology of oral clefts: an international perspective. In: Wyszynski DF, editor. *Cleft lip and palate: from origin to treatment.* New York: Oxford University Press; 2002. pp. 127–158
2. Reid J. A review of feeding interventions for infants with cleft palate. Cleft Palate Craniofac J 2004;41:268-78.

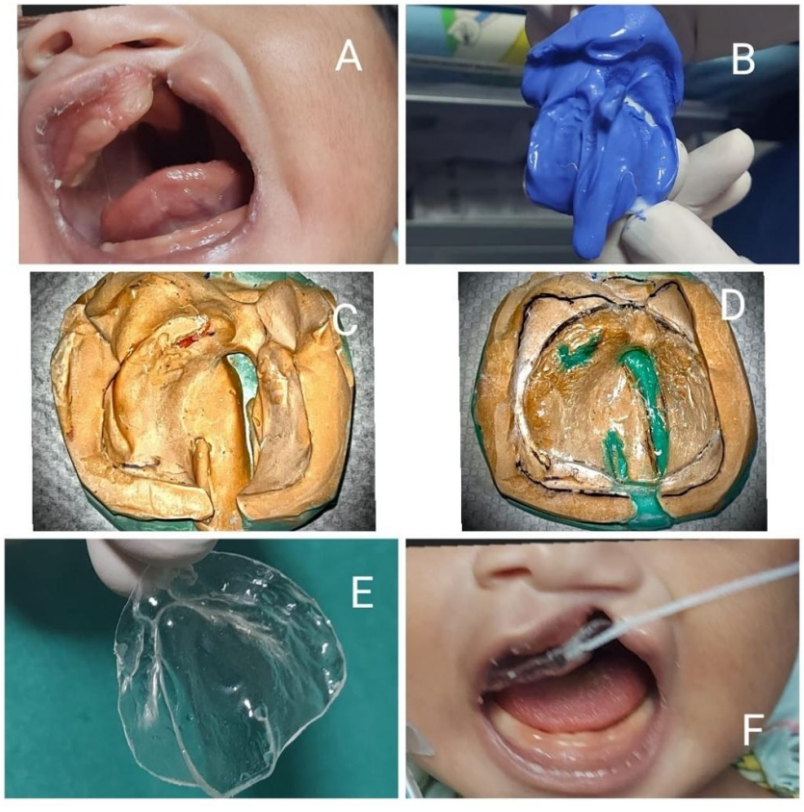

Fig 2: Representation of the feeding appliance during its fabrication from the NICU to the laboratory steps for a neonate with severe grade CL/CP

A: infant with CL/CP group III

B: impression of the defect made with rubber base impression material to record the details of the deformed tissues

C: Final impression

D: Master cast

E: Transparent thin feeding appliance made of ethylene vinyl acetate by using pressure moulding technique

F: Feeding appliance placed in the oral cavity of the newborn attached with floss

Premature baby with White matter injury

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Case: Very preterm twin -2 born at 29wk with a birth weight of 890 grams. The baby had respiratory distress (required surfactant through LISA, CPAP, and ventilatory support till DOL 40). Baby received dexamethasone to facilitate extubation. Screening ultrasound brain on 3rd and 10th day of life was normal. Ultrasound brain done on DOL 40 revealed white matter injury (Figure 1). Baby stayed in NICU for 7 weeks and was discharged at 36wk of PMA.

Diagnosis – Grade 3 Periventricular leukomalacia

Course – Developmentally supportive care was continued and was discharged on 50th day of life on full feeds. On follow up baby is gaining weight well and milestones are normal so far (baby is presently 3 months corrected age).

Condition –

Periventricular leukomalacia (PVL) is the predominant form of brain injury and a leading cause of cerebral palsy and cognitive deficits in preterm. White matter injury (WMI) is the most common form and may be present to some degree in up to 50% of very low birth weight infants. (1) With advances in neonatal care cystic PVL is rare and diffuse white matter injury is more common. (2) The prevalence of white matter injury in preterm is 39.6% (< 28 weeks GA), 27.4% (<32 weeks) and 7.3%(<37wk). (3) Neuropathologically PVL are of 2 types focal and diffuse, focal component usually located deep in cerebral white matter characterised by localised necrosis of all cellular elements and subsequent cyst formation, diffuse component is less severe cell-specific diffuse injury to oligodentrites. Diagnosis of focal component PVL is made by cranial USG. However, the diffuse component of the lesion is invisible on USG, and DWI MRI has been shown to identify this lesion (4).

De Vries et al described a grading for PVL (5)

(1) periventricular densities persisting>7days

(2) localised cysts beside the external angle of lateral ventricle

(3) extensive cysts in frontoparietal and occipital periventricular white matter (cystic PVL)

(4) extensive cysts in subcortical white matter (cystic subcortical leukomalacia).

Prevention- Avoidance of factors that may lead to cerebral ischemia even in presence of intact autoregulation can lead to prevention of PVL (6)

- Severe hypotension,
- Marked hypocarbia (PCO2<35mmhg)
- Prevention of infection by giving antibiotics to the mother if chorioamnionitis is present.
- Control of cascade of free radical injury

Outcome- Cystic PVL carries a bad neuromotor outcome. In a followup study done on 52 preterm babies with PVL (diagnosed on ultrasound brain), 17 babies had Grade 1 PVL, 20 had Grade 2 and 15 had Grade 3. (7). All 15 (100%) children with PVL-3 developed cerebral palsy with additional visual perceptual dysfunctions and epilepsy. PVL-2 and PVL-3 have a greater risk for severe neurodevelopmental disorders. (7)

References:

1. Volpe, J. J. Cerebral white matter injury of the premature infant-more common than you think. Pediatrics 112, 176–180 (2003).
2. Hamrick, S. E. G. et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: the role of cystic periventricular leuko- malacia. J. Pediatr. 145, 593–599 (2004).
3. Romero-Guzman, G. J. & Lopez-Munoz, F. Prevalence and risk factors for peri- ventricular

leukomalacia in preterm infants. A systematic review. Rev. Neurol. 65, 57–62 (2017).

4. Volpe JJ 2001 Neurology of the Newborn. WB Saunders: Philadelphia, pp217–497
5. 5de Vries LS, Eken P, Dubowitz LMS*(1992) The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res 49:1–6.*
6. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res.* 2001;50(6):712–719.
7. Resić B, Tomasović M, Kuzmanić-Samija R, Lozić M, Resić J, Solak M. Neurodevelopmental outcome in children with periventricular leukomalacia. Coll Antropol. 2008 Jan;32 Suppl 1:143-7.

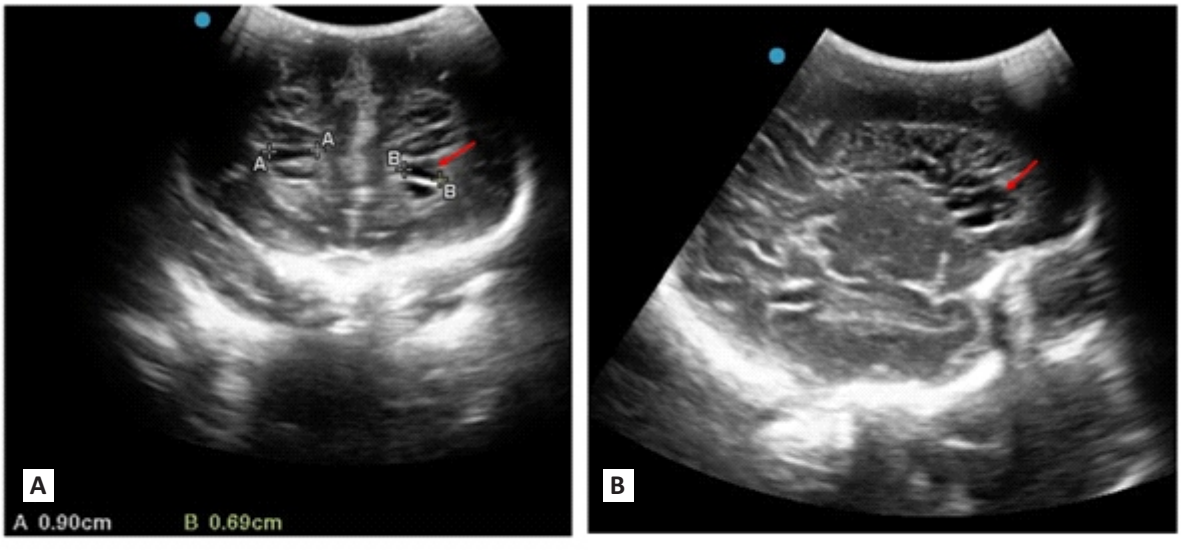

Fig.1. : (A) Coronal view at level of frontal lobe revealing multiple cysts (red arrows) bilaterally (Grade 3 PVL) giving honeycomb appearance. (B) Sagittal view in same baby at level of frontal lobe.

Journal Scan

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JAMA Network Open

Original Investigation | Pediatrics

Association of Fluid Balance With Short- and Long-term Respiratory Outcomes in Extremely Premature Neonates
A Secondary Analysis of a Randomized Clinical Trial

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Objective

- To describe fluid balance in Extremely low gestational age neonates (ELGAN) in the first 14 days of life
- To evaluate the association of fluid balance with the need of mechanical ventilation on day 14 of life
- To study the association of fluid balance with BPD

Hypothesis: More positive fluid balance in the first 14 days of life would be associated with increased need of mechanical ventilation on day 14 of life.

Methods

Design: Secondary analysis of Randomized controlled trial

Settings: Phase 3 placebo controlled RCT of erythropoietin in 19 academic centre and 30 NICUs in US from December 1 2013 to September 31 2016.

Inclusion criteria

- Gestational age 24 to27 $^{6/7}$ weeks
- Enrolment at <24 hrs of age
- Arterial/venous access

Exclusion criteria:

- Major life-threatening anomalies
- Hematologic crises (DIC, hemolysis)
- HCT >65%
- Hydrops, congenital infection

Fluid balance definition:

Daily weight, total fluid intake and output for the first 14 days were recorded when available. Fluid balance was obtained by comparing daily weight with birth weight.

Fluid Balance = [(Daily Weight − Birth Weight) / Birth Weight] × 100.

Fluid balance was calculated in the following 5 ways:

1. Maximum percentage of weight gain (Peak positive fluid balance)
2. Maximum percentage of weight loss (peak negative fluid balance)
3. Percentage weight change on postnatal Day 3
4. Percentage weight change on postnatal day 7
5. Time to regain birth weight

Acute kidney injury (AKIN) was defined using neonatal-modified KDIGO serum creatinine criteria only.

Outcome:

Primary- Invasive ventilation (conventional or HFOV)

Secondary- Death between day 14 to 36 weeks of life or BPD

BPD was defined as per Jensen criteria with severe BPD defined as the need of more than 30% FiO2 or the need of positive pressure at 36 weeks of life.

Statistical analysis- Fisher exact or chi-square was used for categorical variables. T-test was used for continuous and Wilcoxon Rank test for ordinal variables. The relation between fluid balance variables and outcomes of interest was done using unconditional logistic regression. Sensitivity analysis was done for excluded infants.

Results:

Of eligible 923 neonates, 874 were analysed with the mean birth weight being 801 (188) grams. Acute kidney injury occurred in 39.4%, NEC in 10.4%, PDA in 41.5%, IVH in 36.4% and 66% had BPD.Median peak positive fluid balance was 11.1% (IQR 4-20%) occurring on day 13 postnatally. 10.6% of neonates never dropped below their birth weight. The median (IQR) peak negative fluid balance was 10% (-15 to -6) occurring on postnatal day 3. 52.4% of neonates were ventilated on day 14 of life. These were most likely to be born at lower gestational age, had less birth weight, less APGAR, needed vasopressors and had acute kidney injury.

Median peak positive balance was higher in neonates needing ventilation on day 14 compared with those not needing ventilation. (15 vs 8, p<.001). Also, neonates with more negative fluid balance on day 3 of life were less likely to be ventilated (5 vs 8%, p<001). Contrary results were noted on day 7 of life with more negative fluid balance on the day associated with increased risk of ventilation on day 7 of life. (4 vs 1%, p<.001)

Neonates who regained birth weight earlier were more likely to be ventilated. For each 10% increase in peak positive fluid balance, there was 103% increased odds of mechanical ventilation at day 14 of life. In the multivariable analysis for every 10% increase in peak positive fluid balance, there was no significant change in the odds of severe BPD/death.

Reviewers comments:

Optimisation of fluid balance in the early neonatal period is of utmost importance in the management of ELGANs with fluid overload linked to neonatal morbidity and mortality. (1,2) Present study showed that peak positive fluid balance in the first 2 postnatal weeks and on postnatal day 3 is associated with increased need of mechanical ventilation at day 14 as well as BPD. Avoiding fluid overload of more than 5 % in the first 2 postnatal weeks may be an important consideration while managing fluid intakes in such critically ill neonates. Fluid balance >5% increased the odds of mechanical ventilation 2 fold. There is a paucity of multicentric data which has looked at fluid balance and its association with short and long-term respiratory outcomes.(3,5,6) Large multicentre prospective studies ideally a randomized controlled trial need to be conducted to further study fluid balance and long and short-term neonatal respiratory outcomes and also look at impact of fluid status beyond the initial 2 weeks.

Strengths of study:

High-quality data were collected in a large prospective multicentre study which allowed for a detailed analysis of impact of fluid balance on respiratory outcomes.

Limitation of study:

Since this is a retrospective secondary analysis, differences in clinical practice in various NICUs which may have resulted in changes in weight pattern could not be captured. The PENUT database collected weight only in the first 2 weeks so the impact of fluid status in subsequent weeks could not be determined. The findings were based on clinically available weights and most laboratory values which had no uniform protocols.

References:

1. Starr MC, Griffin R, Gist KM, Segar JL, Raina R, Guillet R, Nesargi S, Menon S, Anderson N, Askenazi DJ, Selewski DT; Neonatal Kidney Collaborative Research Committee. Association of Fluid Balance With Short- and Long-term Respiratory Outcomes in Extremely Premature Neonates: A Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open. 2022 Dec 1;5(12):e2248826.
2. Selewski DT, Gist KM, Nathan AT, Goldstein SL, Boohaker LJ, Akcan-Arikan A, Bonachea EM,

Hanna M, Joseph C, Mahan JD, Mammen C, Nada A, Reidy K, Staples A, Wintermark P, Griffin R, Askenazi DJ, Guillet R; Neonatal Kidney Collaborative. The impact of fluid balance on outcomes in premature neonates: a report from the AWAKEN study group. Pediatr Res. 2020 Feb;87(3):550-557.

3. Selewski DT, Akcan-Arikan A, Bonachea EM, Gist KM, Goldstein SL, Hanna M, Joseph C, Mahan JD, Nada A, Nathan AT, Reidy K, Staples A, Wintermark P, Boohaker LJ, Griffin R, Askenazi DJ, Guillet R; Neonatal Kidney Collaborative. The impact of fluid balance on outcomes in critically ill near-term/term neonates: a report from the AWAKEN study group. Pediatr Res. 2019 Jan;85(1):79-85.
4. Basu RK, Wheeler DS. Kidney-lung cross-talk and acute kidney injury. Pediatr Nephrol. 2013 Dec;28(12):2239-48.
5. Jetton JG, Boohaker LJ, Sethi SK, Wazir S, Rohatgi S, Soranno DE, Chishti AS, Woroniecki R, Mammen C, Swanson JR, Sridhar S, Wong CS, Kupferman JC, Griffin RL, Askenazi DJ; Neonatal Kidney Collaborative (NKC). Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Health. 2017 Nov;1(3):184-194.
6. Sutherland SM, Zappitelli M, Alexander SR, Chua AN, Brophy PD, Bunchman TE, Hackbarth R, Somers MJ, Baum M, Symons JM, Flores FX, Benfield M, Askenazi D, Chand D, Fortenberry JD, Mahan JD, McBryde K, Blowey D, Goldstein SL. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. Am J Kidney Dis. 2010 Feb;55(2):316-25.

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Question 1.

Rh Blood Group System

a. What are some Rh blood group antigens?

b. What is the prevalence of Rh D-negative blood group among Indians?

c. What is the critical titre in this context and what is the next step of management, once the critical titre has been reached?

d. What is the indication of intrauterine transfusion (IUT) and what is the ideal GA between which this should be performed?

Question 2.

Non-Invasive Prenatal Testing (NIPT)

a. What is cell free DNA (cfDNA)?

b. What minimum percentage of total circulating cfDNA should be derived from the fetal-placental unit for successful testing?

c. Enumerate few factors that can result in low fetal fraction

d. What is the limitation of non invasive prenatal test (NIPT)

Question 3.

Administering Antenatal Steroids (ANS)

a. What are the evidence-based benefits of administering antenatal steroids (ANS) in preterm neonates?

b. Briefly describe the results of the ACTION 1 trial.

c. Briefly describe the results of the ASTEROID trial.

d. Why is dexamethasone preferred over betamethasone in the Indian scenario?

Question 4.

Aneuploidy Screening During Pregnancy

a. What is the indication for offering aneuploidy screening during pregnancy?

b. What is the risk of recurrence of Down syndrome, because of non disjunction, in a mother who is <35 years of age.

c. Enlist the group of candidates in whom diagnostic testing for aneuploidy should be offered

d. Name the components of the combined test and quadruple marker test

Question 5.

Neuroprotective Effects of Magnesium Sulfate

a. What are the different mechanisms for the neuroprotective effects of magnesium sulfate?

b. Where should we consider administering this drug antenatally?

c. What is the evidence available for efficacy of use of antenatal $MgSO_4$ for neuroprotection?

d. What are the different parameters which needs to be monitored while administering this drug?

Question 6.

Common Complications Associated with Twin Pregnancy

a. What are the common complications associated with twin pregnancy?

b. What results in conjoint twins?

c. What is TTTS and how it is diagnosed?

d. What are the management options for TTTS?

Question 7.

Meningomyelocele

a. What causes meningomyelocele to occur?

b. What are the risk factors for open neural tube defects?

c. What is the risk of recurrence of neural tube defect?

d. What is the role of fetal surgery in MMC?

Question 8.

Fetal Hydronephrosis

a. Name systems that have been developed to diagnose and grade the severity of fetal hydronephrosis.

b. What are the factors on which SFU grading of fetal hydronephrosis is based upon.

c. What is the most common etiology behind fetal hydronephrosis?

d. What are the other features besides B/L HDN indicative of Posterior uretheral valve (PUV)?

e. What is the criterion to define ureter and bladder enlargement on antenatal USG?

Question 9.

Hydrops Fetalis

a. What is the diagnostic criterion for hydrops fetalis based on antenatal USG?

b. Name the most common cause of non immune hydrops fetalis (NIHF)

(i) Which is the most common aneuploidy a/w NIHF

(ii) Which is the most common infection a/w NIHF

(iii) Which is the most common IEM a/w NIHF

c. Enlist the poor prognostic markers a/w hydros fetalis

d. What is mirror syndrome?

Question 10.

Anti-Ro and Anti-La Antibodies

a. Where do we warrant a prenatal screening for anti-Ro and anti-La antibodies?

b. What is the most vulnerable period during gestation to develop heart block in cases where mother was tested positive for Ro and La antibodies?

c. How do we measure mechanical PR interval?

d. Which is the drug suggested to decrease the risk of foetus developing cardiac neonatal lupus (NL) when there is a prior history of cardiac NL in a sibling?

Answer 1.

Rh Blood Group System

a. The Rh blood group system consists of over 50 antigens, but the most common antigens that induce antibodies are D, C, c, E, and e. There is no d antigen, but C and c and E and e are alternate alleles with co-dominant expression.

b. The prevalence of Rh D-negative blood group among Indians is about 5%. This means that about 1 in 20 Indians is Rh D-negative.

c. The critical titre is the titer associated with a risk for the development of severe anaemia and hydrops fetalis. When the critical titer is reached or exceeded, the fetus is at risk for developing severe anemia. The next step of management is to perform Doppler velocimetry of the middle cerebral artery. MCA-PSV identifies fetuses that are likely to be severely anemic. If the MCA-PSV is >1.5 MoMs for gestational age, fetal blood is obtained by cordocentesis for haemoglobin determination. If the fetal haemoglobin is more than two standard deviations below the mean value for gestational age, an intrauterine transfusion is performed.

d. The indication of intrauterine transfusion (IUT) is severe fetal anemia due to Rh alloimmunization. The ideal GA for IUT is between 18 and 35 weeks of gestation. Before 18 weeks, the small size of the relevant anatomic structures poses technical challenges. After 35 weeks, IUT is considered riskier than delivery followed by postnatal transfusion therapy.

Answer 2.

Non-Invasive Prenatal Testing (NIPT)

a. Cell-free DNA (cfDNA) is DNA that is found in the blood plasma. It is released from cells throughout the body, including from the placenta. NIPT is a type of prenatal test that uses cfDNA to screen for genetic disorders in the fetus.

b. A minimum of 3 to 4 percent of the total circulating cfDNA should be derived from the fetal-placental unit for successful testing. If the percentage of cfDNA is lower than this, the test may not be accurate.

c. Factors that can result in low cfDNA fraction include:

- Early gestational age
- Suboptimal sample collection
- Maternal obesity
- Trisomy 18

d. NIPT is a screening test, not a diagnostic test. This means that it can only tell you if there is an increased risk of your baby having a genetic disorder. If the test results are positive, you will need to have a diagnostic test, such as amniocentesis or chorionic villus sampling, to confirm the diagnosis.

NIPT also has some limitations:

- It is not 100% accurate. There is a small chance that the test will give a false positive or false negative result.
- It cannot detect all genetic disorders. NIPT only tests for a limited number of genetic disorders, including Down syndrome, trisomy 18, and trisomy 13.
- It is not available to everyone. NIPT is not covered by all insurance plans, and it can be expensive.

Despite these limitations, NIPT is a valuable tool for prenatal screening. It can help to identify babies who are at risk for genetic disorders, so that parents can make informed decisions about their care.

Answer 3.

Administering Antenatal Steroids (ANS)

a. Antenatal steroids (ANS) are a type of corticosteroid that is given to pregnant women who are at risk of delivering preterm. ANS have been shown to reduce the risk of several

complications in preterm babies, including:

- Respiratory distress syndrome (RDS)
- Necrotizing enterocolitis (NEC)
- Intraventricular hemorrhage (IVH)
- Need for mechanical ventilation

b. The ACTION 1 trial was a randomized controlled trial that compared the use of dexamethasone to placebo in women at risk of delivering preterm between 26 and 33+6 weeks of gestation. The trial found that dexamethasone was associated with a lower risk of neonatal death or stillbirth without increasing the risk of maternal bacterial infection.

c. The ASTEROID trial was a randomized controlled trial that compared the use of dexamethasone to betamethasone in women at risk of delivering preterm (< 34 weeks gestation). The trial found that there was no difference in the risk of death or neurosensory disability at 2 years of age between the two groups.

d. Dexamethasone is preferred over betamethasone in the Indian scenario for several reasons. First, the salt available in India is pure betamethasone sodium phosphate containing no acetate. Second, dexamethasone is cheaper than betamethasone. Third, dexamethasone remains stable even at room temperature.

Answer 4.

Aneuploidy Screening During Pregnancy

a. The American College of Obstetricians and Gynecologists (ACOG) recommends offering aneuploidy screening to all pregnant individuals in early pregnancy. Aneuploidy screening is a test that can be used to assess the risk of a fetus having a chromosomal abnormality, such as Down syndrome, trisomy 18, or trisomy 13.

b. When the mother is <35 years of age at the time of diagnosis of nondisjunction trisomy 21, the risk of recurrence is approximately 1 per cent, which is higher than the maternal age-related risk of Down syndrome for this age group. When the mother is ≥ 35 years of age at the time of diagnosis of nondisjunction trisomy 21, the risk of recurrence is the maternal age-related risk.

c. Candidates for diagnostic testing for aneuploidy include:

- Positive screening test for one of the common trisomies or other identified chromosomal abnormalities.
- Previous pregnancy complicated by fetal trisomy.
- At least one major or two minor fetal structural anomalies in the current pregnancy.
- A chromosomal translocation, inversion, or aneuploidy, or a partner with one of these abnormalities.
- A desire to have the most reliable information about the fetal karyotype.

d. The combined test includes both sonographic determination of nuchal translucency (NT) and determination of biochemical markers associated with aneuploidy: pregnancy-associated plasma protein A (PAPP-A) and free-beta or total human chorionic gonadotropin (hCG). In most patients, both ultrasound and biochemical marker screening are performed at 11+0 to 13+6 weeks of gestation. However, some protocols allow for earlier collection of the serum sample (beginning at 9+0 weeks) with the ultrasound performed later (10+3 to 13+6 weeks).

The quadruple test measures the level of the biochemical markers alpha-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and dimeric inhibin A (DIA) in maternal serum. Maternal serum AFP and uE3 levels are, on average, reduced by 25 to 30 percent in pregnancies affected by Down syndrome, and hCG and DIA levels are, on average, twice as high as those in unaffected pregnancies. The quadruple test is ideally performed at 15+0 to 18+6 weeks of gestation but can be done as late as 22+6 weeks.

Answer 5.

Neuroprotective Effects of Magnesium Sulfate

a. Magnesium sulfate has several neuroprotective effects, including:

- Stabilization of cerebral circulation by stabilizing blood pressure and normalizing cerebral blood flow.

- Prevention of excitatory injury by stabilization of neuronal membranes and blockade of excitatory neurotransmitters, such as glutamate.
- Protection against oxidative injury via antioxidant effects.
- Protection against inflammatory injury via anti-inflammatory effects.

b. Magnesium sulfate is indicated for antenatal neuroprotection in women at high risk of preterm birth (<32 weeks) within 24 hours.

c. The Cochrane meta-analysis of magnesium sulfate for women at risk of preterm birth for neuroprotection of the fetus found that it was associated with a significant reduction in the risk of "any cerebral palsy" (RR 0.68, 95% CI 0.54-0.87) and substantial gross motor dysfunction (RR 0.61, 95% CI 0.44-0.85).

d. The following parameters need to be monitored while administering magnesium sulfate:
- Urine output
- Deep tendon reflexes
- Respiration rate
- Blood pressure
- Electrocardiogram (EKG)
- Magnesium levels

Answer 6.

Common Complications Associated with Twin Pregnancy

a. The common complications associated with twin pregnancy include:
- Preterm birth
- Growth restriction
- Congenital malformations
- Placental vascular anastomosis

b. Conjoined twins occur when monozygotic (MZ) twins fail to separate into two individuals as division occurs at or after day 13 post-fertilization.

c. Twin-twin transfusion syndrome (TTTS) results from unbalanced blood flow caused by artery-to-vein anastomoses, which are present in the placenta of the majority of monochorionic multiple pregnancies. With preferential blood flow in severe cases, one twin becomes the donor and the other is the recipient, which may result in wide discordance in fetal growth. The prenatal diagnosis of TTTS is based upon ultrasonographic evidence of a single MC placenta with twin oligohydramnios/polyhydramnios sequence, after exclusion of other disorders of discordant amniotic fluid volume. The maximum vertical amniotic fluid pockets for oligohydramnios and polyhydramnios are usually defined as <2 cm and >8 cm, respectively.

d. The three primary approaches to management of TTTS are:

. Expectant management: This is a non-interventional approach that involves monitoring the pregnancy and intervening only if complications arise.

. Fetoscopic laser ablation of anastomotic vessels: This is a minimally invasive procedure that involves the use of a laser to ablate the blood vessels that are causing the unbalanced blood flow.

. Amnioreduction: This is a procedure that involves draining excess amniotic fluid from the sac of the recipient twin.

Answer 7.

Meningomyelocele

a. Myelomeningocele is caused by a failure of primary neurulation (failure of the spinal neural tube to close normally by 28 days after conception). The central nervous system (CNS) initially appears as a plate of thickened ectoderm, called the neural plate, at the beginning of the third week of embryonic life. The lateral edges of the neural plate become elevated to form the neural folds. These folds subsequently become further elevated, approach each other, and fuse to form the neural tube. The fusion begins in the cervical region and proceeds in both the cephalad and caudal directions.

b. The risk factors for open neural tube defects (NTDs) include:
- Folate deficiency
- Genetic syndromes (Meckel Gruber syndrome,

Roberts syndrome, trisomy 13 and 18)

- Hyperthermia in the first trimester
- Amniotic band sequence
- Pre-gestational diabetes
- Obesity

c. The risk of recurrence for isolated NTDs is approximately 2 to 4 percent with one affected sibling. With two affected siblings, the risk is approximately 10 per cent.

d. Fetal surgery for myelomeningocele repair arrests leakage of spinal fluid from the back and might, therefore, prevent or reverse herniation of the hindbrain (Chiari II malformation) and hydrocephalus and their adverse sequelae. The safety and efficacy of fetal surgery for repair of open spina bifida were evaluated in the seminal Management of Myelomeningocele Study (MOMS) trial, conducted from 2003 to 2010 showed decreased need of CSF shunting and improved motor development and function.

Answer 8.

Fetal Hydronephrosis

a. Several systems have been developed to diagnose and grade the severity of fetal hydronephrosis. These include:

- Renal pelvic diameter (RPD)
- Society of Fetal Urology (SFU) criteria
- Urinary tract dilation (UTD) classification system

b. The SFU grading of fetal hydronephrosis is based upon the degree and site of pelvic dilation, number of calyces seen, and the presence and severity of parenchymal atrophy.

- Grade 0 – Normal examination with no dilation of the renal pelvis
- Grade I – Mild dilation of the renal pelvis only
- Grade II – Moderate dilation of the renal pelvis including a few calyces
- Grade III – Dilation of the renal pelvis with visualization of all the calyces, which are uniformly dilated, and normal renal parenchyma
- Grade IV – Similar appearance of the renal pelvis and calyces as grade III, plus thinning of the renal parenchyma

c. The most common etiology behind fetal hydronephrosis is posterior urethral valve (PUV). Other causes include:

- Ureteropelvic junction obstruction (UPJO)
- Vesicoureteral reflux (VUR)
- Bilateral renal agenesis
- Multicystic dysplastic kidney (MCDK)
- Prune belly syndrome

d. Other features besides bilateral hydronephrosis indicative of PUV include:

- Dilated bladder
- Thickened bladder wall
- Keyhole sign (dilated posterior urethra)

e. The criterion to define ureter and bladder enlargement on antenatal USG is:

- Ureters: Any visible ureter on ultrasonogram is considered dilated ureter.
- Bladder: Bladder enlargement can be defined as a sagittal diameter (measured in mm) of 2 plus the gestational age (GA) (weeks). So, for a fetus that is 24 weeks GA, bladder enlargement would be defined as a sagittal diameter ≥ 26 mm.

Answer 9.

Hydrops Fetalis

a. The prenatal diagnosis of hydrops fetalis is based on ultrasound examination that shows two or more of the following fetal findings:

- Ascites
- Pleural effusion
- Pericardial effusion
- Generalized skin edema (skin thickness >5 mm)

b. The most common cause of non immune hydrops fetalis (NIHF) is cardiovascular abnormality.

i. The most common aneuploidy associated with NIHF is monosomy X (Turner syndrome), which accounts for 42 to 67 percent of aneuploid cases.

ii. Parvovirus B19 is the most common infection associated with hydrops.

iii. Lysosomal storage disorder is the most common IEM a/w hydrops fetalis.

c. Poor prognostic markers associated with hydrops fetalis include:
   - Early onset of hydrops
   - Pleural effusions and polyhydramnios prior to 20 weeks of gestation
   - Presence of aneuploidy or major structural malformation

d. Mirror syndrome (also called Ballantynes syndrome) refers to a condition of generalized maternal edema, often with pulmonary involvement, that "mirrors" the edema of the hydropic fetus and placenta. Although usually associated with NIHF, it can also occur with immune-mediated hydrops. The pathogenesis has not been firmly established, but at least in some cases, the hydropic placenta increases production of soluble fms-like tyrosine kinase (sFlt1), which is an important mediator of maternal endothelial and vascular abnormalities in preeclampsia.

Answer 10.

Anti-Ro and Anti-La Antibodies

a. Prenatal screening for anti-Ro/SSA and anti-La/SSB antibodies is warranted for individuals at risk of having a pregnancy complicated by neonatal lupus (NL) which includes those with systemic lupus erythematosus (SLE), Sjögren syndrome, rheumatoid arthritis, mixed connective tissue disease, an undifferentiated autoimmune disease, or NL with cutaneous and/or cardiac manifestations in a previous pregnancy.

b. The most vulnerable period for the fetus is during the period from 18 to 24 weeks gestation. Normal sinus rhythm (NSR) can progress to complete block in seven days during this high-risk period. New onset of heart block is less likely during the 26th through the 30th week, and it rarely develops after 30 weeks of pregnancy.

c. Pulsed-Doppler fetal echocardiography measures the mechanical PR interval from the onset of atrial contraction [initiation of mitral valve movement] to ventricular contraction [aortic pulsation].

d. Hydroxychloroquine. It is an antimalarial drug that inhibits nucleic acid ligation of endosomal Toll-like receptors (TLRs) by preventing endosomal acidification or direct binding to nucleic acids. Data suggests that it may also decrease the risk of the fetus developing cardiac-NL when there is a prior history of cardiac-NL in a sibling. The efficacy in the setting of prior cutaneous-NL is not known.

Instructions for Authors

Review Article	**The article should be approximately 2-3 pages long with a word count of 2000-2500 words. Author should summarize key practice points at the end. Please include 5-6 references as suggested reading.**
Case Report	**This would be a summary of the case discussed in that months clinical meeting. Interesting cases even if not presented may also be submitted. It should include the clinical presentation and a brief discussion about the condition. Word count should be 1000-1500. Please include 2-3 references at the end.**
Journal Scan	**Some recent research paper of interest to pediatricians and neonatologists. The structure should include Introduction, Research question, Hypothesis, Methods, Results, Limitations and strengths of study, Reviewers comments. Word count should be approximately 1000 words. Please include 2-3 references if needed at the end.**
Picture of Month	**An interesting case related to neonatal practice. It should have a brief case history and a commentary, all fitting on one page along with the pictures.**
Image section	**Any interesting Xray, Ultrasound, CT or MRI of clinical interest. Brief clinical presentation and about the condition should be summarized on one page along with image.**
OSCE	**About 10-12 questions would be included in this section along with answers.**

Contact Us

On behalf of committee, I request all members of NNF, Delhi to actively contribute to various sections of the newsletter.

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