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DR LALAN BHARTI
President, NNF Delhi

DR KUMAR ANKUR
Secretary, NNF Delhi

DR NAVEEN PARKASH GUPTA
Chief Editor, Neo Clips

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Dear Esteemed Members,

Greetings from NNF Delhi!

It gives me a feeling of immense pleasure about the success of our Monthly Bulletin **NeoClips** (Neonatal Clinical Practice). This idea has emerged as a unique proposition from the minds of experienced neonatologists teaming up with young budding counterparts.

In this section, we are covering a few important topics like a review article on early intervention in preterm neonates to improve neurodevelopment outcomes and a case of congenital diaphragmatic hernia with Patau syndrome. My sincere congratulations to the NeoClips team for their continuing efforts in publishing this monthly bulletin.

With Best Regard

L Bharti

Dr. Lalan Bharti
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 monthly E- Bulleting from which was launched in February 2022 with the name of '***NeoClips' (Neonatal Clinical Practice)***. Every month it's getting better & better. And credit goes to the Chief editor Dr Naveen Gupta & their exceptional team. OSCE as system wise which would be very helpful for Neonatal fellow/Residents/Postgraduates. This month we have included some interesting topics like early intervention in preterm babies, an interesting case of twin anemia polycythemia sequence and an interesting xray image of two umbilical veins.

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. We hope you enjoyed reading previous issues of NeoClips.

As Editor I would like to start by thanking the editorial team for the effort and the authors for their contribution to this and previous issues.

In the fifth issue, we have covered some interesting topics.

The case report section covers twins with twin anaemia polycythemia sequence (TAPS).

Premature babies need an environment similar to an intrauterine one for their optimal growth and development. Early intervention for premature babies has been covered in the review section of the newsletter.

An interesting case of Patau syndrome with congenital diaphragmatic hernia has been covered in the picture of month.

The image section describes an interesting Xray of umbilical lines.

Neonatal endocrinology is covered in the OSCE section.

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

Successful Management of Monochorionic Twins with TAPS

Vikram Gupta[1], Kumar Ankur[1], Aparna Prasad[1], Keerti Khetan[2], Sanjeev Chetry[3]

[1]Department of Neonatology,
BLK MAX Superspeciality Hospital, Pusa Road,
New Delhi-110005

[2]Department of Obstetrics & Gynaecology,
BLK MAX Superspeciality Hospital, Pusa Road,
New Delhi-110005

[3]Department of Neonatology, Fortis Hospital, Noida

Presentation

A set of female twins were delivered to a 40 year old second gravida mother who was diagnosed to have monochorionic twins on the first trimester ultrasound. Subsequent ultrasound at 32 weeks of gestation revealed abnormal doppler changes i.e. increased SD ratio in one of the twins with the normal amniotic fluid level. The babies were delivered at 33 weeks of gestation by caesarean section in view of fetal distress. Twin 1 (recipient twin) was positioned in vertex position and twin 2 (donor twin) was positioned in breech position. They weighed 1800 grams (around 50th percentile) and 1440 grams (below 10th percentile) on the Fenton chart respectively. Both developed respiratory distress soon after birth and were managed with surfactant & short ventilation for 48 hours. Twin 1 was plethoric (Hb 26 gm/dl and Hct 80%) and twin 2 was pale (Hb 8.5 g/dl, Hct 25.9%). Twin 1 needed partial exchange transfusion for symptomatic polycythemia. Post exchange hematocrit was 65%. Twin II had high oxygen needs and was requiring ventilator support. She received a packed cell transfusion. During NICU stay, both twins tolerated feeding with gradual weight gain. The recipient twin developed moderate thrombocytopenia which recovered without any intervention by the 10th day of life. On 3rd week of life, twin I (recipient) and twin II (donor) have Hemoglobin of 21 and 10.5 gm/dl respectively.

Discussion

Monochorionic (MC) twins share a single placenta, characterized by the presence of vascular anastomoses, allowing blood to flow between the fetuses carrying a higher risk for severe complications. This is in contrast to dichorionic twins where each fetus has its own placenta and therefore own circulation. Twin-twin transfusion syndrome (TTTS) or Twin Anemia–Polycythemia Sequence (TAPS) can happen in up to 20% of cases due to unbalanced inter-twin blood flow. TTTS results from an imbalanced inter-twin blood flow that causes hypovolemia/oligohydramnios in the donor twin and hypervolemia/polyhydramnios in the recipient twin, so-called Twin oligohydramnios-polyhydramnios syndrome (TOPS) (1). The presence of TOPS is pathognomonic for TTTS. The pathogenesis of TTTS is based on large placental arterio-arterial or venovenous anastomoses with low resistance, allowing a large amount of blood to flow directly from the donor to the recipient (2).

TAPS was first described in 2006 by Robyr et al (3), as a chronic and slow inter-twin blood transfusion, characterized by large inter-twin Hb differences without signs of TOPS (4). Absence of oligohydramnios and polyhydramnios is an essential element in the diagnosis of TAPS. TAPS is of two types. Spontaneous TAPS refers to a type of chronic TTTS. It has been reported in 3 to 6 percent of previously uncomplicated third-trimester monochorionic diamniotic twins. Post-laser ablation TAPS refers to a

potential sequelae of use of laser ablation for treatment of TTTS. It occurs in 2 to 13 percent of such pregnancies, usually within one month but up to 17 weeks after the procedure.

In nursery, TAPS should be suspected if one twin is anemic (hematocrit <45 percent) and the other is polycythemic (hematocrit >65 percent). Postnatal diagnosis of TAPS is based on an intertwin hemoglobin difference ≥ 8.0 g/dL in conjunction with an intertwin reticulocyte ratio >1.7 (reticulocyte count of the donor twin divided by the reticulocyte count of the recipient twin) (4,5). In the indexed case, inter-twin hemoglobin difference was 17.5 g/dl and reticulocyte count ration was 14.7.

Neonates with TAPS have mainly short-term hematologic complications. Donor twins have chronic anemia with highly increased reticulocyte counts, reflecting chronic blood loss. A blood transfusion is often needed in the first 24 h of birth in 57–80% of cases. In contrast, recipients may be severely polycythemic and require partial exchange in 40–71% of cases (6). Risk of thrombocytopenia in TAPS recipient twins is also reported in recent case series which was also seen in our case, who had a nadir platelet count of 70,000 /mm^3 by 1st day of life and recovered spontaneously by 10th day of life, and cause being related to the polycythemia-hyperviscosity syndrome and mostly self limiting. The main cause is due to impaired production secondary to tissue hypoxia, secondary to slow splenic blood flow.

Key points

1. Twin anemia-polycythemia sequence (TAPS) may occur spontaneously or post-laser ablation for twin-twin transfusion syndrome (TTTS).
2. It is caused by slow unbalanced red cell transfusion across tiny placental anastomoses in monochorionic (MC) placentas that gradually leads to anemia in the donor twin and polycythemia in the recipient twin.
3. Amniotic fluid volumes remain normal.
4. TAPS has traditionally been diagnosed prenatally when the middle cerebral artery-peak systolic velocity (MCA-PSV) is >1.5 multiples of median (MoM) in one twin (suggestive of anemia) and <0.8 MoM in the other twin (suggestive of polycythemia.
5. Postnatal diagnosis of TAPS is based on an intertwin hemoglobin difference ≥ 8.0 g/dL in conjunction with an intertwin reticulocyte ratio >1.7

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Early intervention practices in neonatal intensive care unit

Dr (Prof.) Arti Maria[1], Dr Swati Upadhyay[2], Dr Nagaratna Vallomkonda[3]

1. Consultant & Head, Department of Neonatology, ABVIMS and Dr RML hospital,New Delhi.
2. Senior Conultant Neonatology, Max Superspeciality Hospital, Patparganj.
3. Early Interventionist, ABVIMS and Dr RML hospital, New Delhi.

Introduction - The quality of newborn care has improved by leaps and bounds over the last decade and is presently being measured against the yardstick of intact survival, rather than mere survival. For a baby born preterm or sick, the transition from a secure intrauterine environment to that of a rather hostile neonatal intensive care unit (NICU) environment after birth may be stressful and compound adversities for the developing brain. It is prudent that medical care of sick babies must be as close to the nurturing environment of the womb as possible, especially through the early critical period of brain development. This lies at the heart of the concept of early intervention.

'Early Intervention (EI), leveraging on experience-driven neuroplasticity, is defined as the introduction of a planned program timed early through the critical period of brain development in order to favourably alter the course of development. Beginning in the antenatal period, EI spans through the first 3 years of life. In the antenatal period, EI focuses on the identification of risk factors which can have adverse neuro-development outcomes; so that appropriate care can be delivered in the antenatal or postnatal period. For small and sick babies admitted to NICU, EI focuses on mitigating disability by providing positive sensorimotor experiences, developmentally supportive care (DSC), and few specific interventions which promote neurobehavioral maturation. EI practices vary across units and lack consistency and standardisation (1). In this review article, we discuss principles and practices of early intervention in the newborn care unit.

The concept of "critical period" and "neuroplasticity"

The period from around 22 weeks gestation through the first two years of life, is the "critical period" of brain development. The ongoing neural processes during this period are extremely sensitive to experience and sensory stimulation. Any biological or medical insult like intense, stressful, and unexpected sensory NICU surroundings, during this critical period, is detrimental to brain development that may affect neuro-outcomes adversely. During this period, the developing brain exhibits a remarkable capacity to reorganize and recover after injury. Sensorimotor experiences that minimise environmental stressors modify the organisation of neural circuits and impact functional recovery. Thus, early intervention (EI) and developmentally supportive care beginning in the NICU or newborn care unit (NBCU) not only prevent avoidable injury but also promote neuro-behavioural maturation of the growing brain due to unique neuroplasticity of the young brain during this critical period of development. (Fig 1)

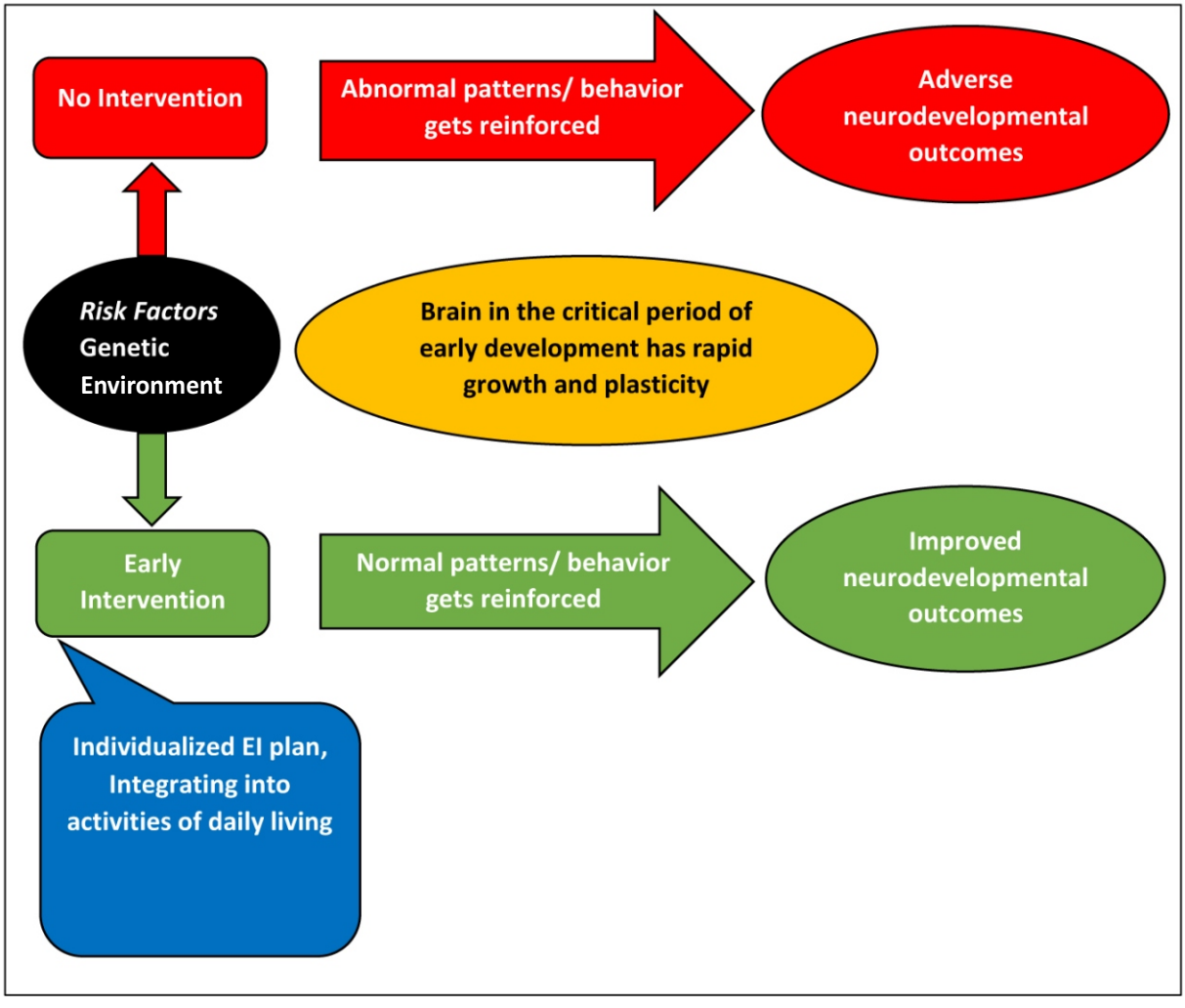

Fig 1. Conceptual framework and rationale of Early Intervention. Babies with genetic, medical or environmental risk factors are at increased risk of developing adverse neurodevelopmental outcomes in absence of early intervention and developmental care, as the abnormal patterns and behaviour get reinforced. However, if timely early intervention, leveraging on experience driven neuroplasticity, is provided to these babies, normal patterns and behaviour can be reinforced. This may help in mitigating adverse neurodevelopmental outcomes

Principles governing early intervention and developmentally supportive care

a. Gestational age-appropriate interventions: The timing and type of interventions prior to 40-44 weeks should mimic the intrauterine environment. Active interventions prior to term age can be a source of stress. The brain should not be overstimulated as overstimulation may be detrimental.

b. The interventions should preferably be delivered by parents with support from healthcare providers and therapists (2).

c. Any intervention should be guided by assessment and observation of the baby's behaviour:

i. Stress behaviours like back arching, finger splaying, startle, twitch, flailing, crying, gaze aversion or autonomic disturbances like changes in heart rate and Spo2.

ii. Self-regulatory behaviours like putting a fhand to mouth, foot bracing, sucking on tube, putting hands to face etc.

Impact of Early Intervention in NICU

Reports vary regarding the evidence of impact of early

intervention due to multiple reasons: marked heterogeneity among studies; difficulties in standardization; variability in sensory exposures, dosages, timing and outcome measures; and inclusion of multiple interventions implemented inconsistently and variably. A systematic review of the effectiveness of the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) did not show any beneficial effect on short-term medical and long-term neurodevelopmental outcomes (3). A recent systematic review including 13 studies showed that developmental care in preterm babies in NICU improved mental developmental index (MDI) and psychomotor developmental index (PDI) at 12 months of age and PDI at 24 months of age. However, the benefit was not detected at 24 months of age on MDI (4). Another systematic review on effect of motor interventions on outcomes in preterm babies showed positive effect on motor skills up to 24 months corrected age (5). Cochrane systematic review on early intervention programmes provided after discharge, demonstrated positive influence on cognitive and motor outcomes during infancy, with only cognitive benefits persisting into preschool age (1). Pineda et al have recently developed SENSE (Supporting and Enhancing NICU Sensory Experiences) program which includes intentional delivery of positive, age-appropriate sensory exposures by parents or a sensory support team every day of hospitalization (6).

Providing early intervention in NICU: Rationale, evidence and practical aspects

Early intervention in NICU comprises largely of supportive positioning and handling, sensory environment stimulation and interaction, reducing pain and stress, protecting and promoting sleep, optimising nutrition, skin care and most importantly, family participatory care.

1. **Supportive Positioning and handling:** Aim of good positioning is to mimic third trimester fetal position by promoting flexion, midline orientation, good alignment, and support for movement.

Practice points for supportive positioning and handling:

- Contain the baby by swaddling, nesting, or other support to maintain a flexed posture with hands close to or touching the face, head in midline and neck slightly flexed. (Fig.2)
- Swaddling can be done by making oval or U-shaped nests with linen rolls. (Fig.2)

Fig 1. Containment of baby by nesting

- Exposure to varying positions- prone, supine, side lying and upright- should be done routinely, guided by the baby's condition and response. Critically sick babies may be nursed in the supine position for ease of access. Position may be changed every 4 to 6th hrly in relatively stable babies and this must be guided by the baby's response and comfort level in each position.
- For Gastroesophageal reflux disease (GERD): Baby should be kept in left lateral position after a feed and then in a prone position about half an hour later. Head end elevation by 30 degrees.
- For preventing plagiocephaly: Regular change in position, head supported in the midline, with the neck in a neutral position and slight chin tuck.
- Allow free unrestricted movements for some time

at defined intervals, such as before each diaper change.

- Validated objective tools like Infant Positioning Assessment Tool (IPAT; Philips Children's Medical Ventures) can be used as a bedside tool and guide to improve the developmental positioning of babies.
- In babies who develop tone abnormalities during the NICU stay, specific individualised interventions by trained neonatal therapists are provided to promote appropriate positioning and normal movement patterns

2. Sensory Environment- stimulation and interaction

a. Auditory: In NICU, ambient aberrant noise generated by various equipment, alarms and personnel induces stress, autonomic changes and sleep disruption, sensory neural damage, and contributes to language or auditory processing disorders.

Practice points for auditory intervention:

- Ambient noise should be < 45 dB. This can be achieved by holding quiet conversations at baby's bed, silencing the alarms promptly, avoiding use of headphones/ earphones/ mobile phones, handling doors and carts gently.
- Exposure to maternal sounds (reading/ talking/ singing to baby) should be started at around 28 weeks PMA, not before that.
- Exposure to music- classical/ womb sounds is optional and should be done only after 32 weeks.

b. Tactile: Largely four tactile interventions have been described in the literature. Kangaroo mother care (KMC), Gentle human touch (GHT), holding and massage.

Practice points for tactile intervention:

- Clustering of care: All non-urgent care giving activities should be clustered together to avoid unnecessary tactile exposure.
- KMC (Kangaroo Mother Care) and GHT (Gentle Human Touch) can begin prior to 32 weeks postmenstrual age (PMA). GHT involves placing one hand over the baby's head and another hand on the lower back and buttock for 10-20 minutes.
- Holding for a short duration can be started at 28 weeks PMA.
- Massage therapy involves gentle yet firm touch, stroking or rubbing the infant with a hand using light to moderate pressure, with or without oils. This should be done only after 32 weeks postmensutral age, and that too by trained personnel. This can be done for 15 minutes, 3-4 times/day.

c. Kinaesthetic: Kinaesthetic sensory exposure has been proposed to facilitate the normal evolution of general motor movements.

Practice point for kinesthetic intervention:

- Allow free unrestricted movements for some time at defined intervals, such as before each diaper change.
- Movement imitation therapy has been used in preterm babies with cramped synchronised movements. In this process, therapists or trained caregivers gently manoeuvre the baby's limbs to smoothen movements and mimic normal movement sequences as far as possible.

d. Gustatory and Olfactory: Marked alteration in the oro-gustatory environment due to differences in the composition of amniotic fluid and breast or formula milk, along with exposure to unpleasant odours, stressful procedures, and placement of orogastric/endotracheal tubes in preterm babies can lead to negative oral experiences and feed aversion.

Practice points for gustatory and olfactory intervention:

- Avoid opening pungent-smelling alcohol wipes or bottles near the infant and avoid strong-smelling oils for massage.
- Familiarise the neonate with breastmilk odour by placing the mother's breast pad nearby or

putting a small drop of breast milk on the tongue tip or lips.

- Keep maternal scent or breastmilk-soaked cloth near the baby.

e. Non-nutritive sucking (NNS) and oro-motor stimulation (OMS) facilitate a smooth transition to oral feeds in preterm babies.

Practice point:

- Start at 29 weeks of PMA in hemodynamically stable babies who have reached full OG feeds.
- Pacifiers can be used or sucking on an empty breast after expression of breast milk can be done.
- The Premature Infant Oral Motor Intervention (PIOMI) program describes five minutes stimulation program and involves assisted and resisted movements of oro-facial muscles; facilitated coordinated movement of cheeks, lips, gums, tongue and palate, and digital stroking of the same (7).

f. Vestibular: The fetus gets vestibular stimulation through maternal movements and gentle oscillations by amniotic fluid movement. Ex Utero, babies may have inappropriate vestibular experiences due to horizontal postures, the effect of gravity or rapid changes in position while handling. Lack of normal vestibular stimulation in early development can affect a general neurobehavioral organization and cause gravitational insecurities and deficits in balance and coordination.

Practice points for vestibular stimulation:

- Handle the babies gently, especially while turning or changing position.
- Care while changing a diaper: Do not lift the legs vertically up while changing a diaper.
- Swaddle the baby properly during transfers/ transport.
- Gently holding the baby and rocking can be initiated from 32-33 weeks PMA for a brief time initially, gradually increasing in frequency and duration by term age

g. Visual: Visual stimulation is potentially harmful to preterms prior to term equivalent age. The womb is dark, hence exposure to bright ambient lights is stressful for babies.

Practice points for visual intervention:

- Dim environment is encouraged until 32 weeks PMA.
- Cycling of light (12 hours on and 12 hours off with low intensity of 25-100 lux) should be initiated at 32 weeks PMA.
- Avoid direct and bright lights.
- Encourage visual attention through human interaction, starting at 36 weeks PMA
- Ambient lighting should be kept <646 Lux (60 fc)
- Intervention for cortical visual impairment (CVI): Visual stimulation exercises with the help of high contrast (black and white) pattern charts, reflective objects and closed yellow and red LED lights for babies who do not have basic visual functions such as fixation, smooth pursuit, and saccadic movements by term equivalent age. (Fig 3)

Fig 3. Intervention for Cortical visual impairment: Visual stimulation exercises with the help of closed yellow LED lights and high contrast (black and white) pattern charts for a term baby with hypoglycemic brain injury who did not have a fixation, smooth pursuit, and saccadic movements.

3. Reducing stress and Pain: Exposure to repeated painful procedures in early life can lead to altered brain development with impaired cognition, behaviour, and emotional regulation as well as altered pain perception in later life.

Practice points for pain management:

- Routine assessment and documentation of pain and stress with an established pain assessment tool like CRIES, NIPS (Neonatal infant pain score) or PIPP (Premature infant pain profile), should be done.
- According to level of pain involved, non-pharmacologic or pharmacological measures must be used prior to all stressful or painful procedures:
- Non-pharmacologic measures include swaddling, KMC, breastfeeding.
- Pharmacologic measures include oral sucrose, topical analgesics like EMLA, non-opioid analgesics like paracetamol or opioid analgesics like morphine or fentanyl.

4. Promoting and Protecting sleep: Undisturbed sleep is essential for weight gain and optimal brain growth. All non-emergent care giving activities should be provided during wakeful states.

Practice points:

- Provide non-emergent care giving activities during wakeful states.
- Cluster care: All non-urgent care giving activities should be clustered together to avoid unnecessary tactile exposure.
- Provide care giving activities that promote sleep (i.e., facilitative tuck, swaddling, and skin-to-skin care)
- Light and sound levels to be maintained within the recommended range.
- Use cycled lights to support nocturnal sleep and facilitate development of circadian rhythm.

5. Skin care: Optimal skin care is important to prevent skin injury and subsequent infection.

Practice points for skin care:

- Validated tools like Neonatal Skin Condition Score (NSCS) and Neonatal Skin Risk Assessment Scale (NSRAS) can be used to document and monitor skin integrity. Assessment and documentation of skin integrity must be done by nursing staff at least once per shift.
- Protective skin dressing like Duoderm/ Tegaderm to be applied at sites of frequent taping.
- Gentle application as well as the removal of adhesive products. Use saline or lubricant while removing the adhesives. Never pull out the dressing forcefully.
- Change probe position in every shift to avoid skin burns.

6. Nutrition: Human milk has a positive impact on preterm infant neurodevelopmental outcomes. All efforts should be made to start enteral feeding in small and sick babies as early as possible, with expressed breast milk or donor human milk.

Practice points for optimising nutrition:

- Early enteral nutrition to be started as early as possible.
- For increasing expressed breast milk availability in NICU, ensure:
- Maternal motivation
- Early and frequent expression of breast milk
- KMC and maternal involvement in baby care
- Management of maternal pain if any.
- Galactagogues if required.

7. Partnering with parents and Families (Family Participatory Care): Care for the small and sick neonates must be delivered by parents and supported by healthcare providers. Vanderveen et al reported that this resulted in improved neurodevelopment at 12 months, with positive effects persisting till 36 months of age (8).

Practice points for family participatory care:

- Parents should have 24 hours access to their baby in NICU, and the healthcare team should assess their emotional and physical wellbeing; and their evolving competence and confidence in handling their baby.
- Ensure daily communication with parents, at least once. The communication can be virtual or telephonic in case the family is unable to visit the baby in NICU on some days.
- Embrace the family as a decision maker and collaborator for baby care in NICU.
- Train the parents using structured modules on hand hygiene, activities like KMC, holding, feeding, dressing, diapering, singing etc., handling the baby, baby care in NICU and care at home post-discharge.

Conclusion:

- Care of sick babies in the NICU must be as close to the nurturing environment of the womb as possible, especially through the early critical period of brain development.
- Early developmental interventions in NICU, with a preventive focus, may improve outcomes in high-risk neonates.
- These interventions must be gestational age appropriate and should be guided by the baby's response. Overstimulation is detrimental and should be avoided.
- These interventions are best provided by family and healthcare workers in collaboration.
- Further research is required to determine which interventions are most effective in improving cognitive and motor outcomes and to discern the long-term effects of these interventions.

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Neonate with Congenital diaphragmatic hernia and facial dysmorphism

Dr Neha Israni[1], Dr Naveen Parkash Gupta[2], Dr Shandip Sinha[3], Dr Anil Batra[2]

1. Associate Consultant, Rosewalk hospital, Delhi.
2. Neonatologist, Madhukar Rainbow Children's Hospital, Delhi
3. Pediatric Surgeon, Mahdukar Rainbow Children's Hospital, Delhi.

Clinical presentation: A term baby girl weighing 3600 grams born through caesarean section developed respiratory distress soon after birth, with cyanosis and saturations below 80% in room air. The baby was started on CPAP and referred to our unit where the baby had to be intubated and ventilated. Her initial Xray showed left sided congenital diaphragmatic hernia (Figure 1). The pediatric surgery team was involved and she was operated on second day of life. Intraoperatively the defect was noted to be in the left Postero-lateral aspect of the diaphragm with spleen and stomach as contents which were reduced, sac excised and defect closed.

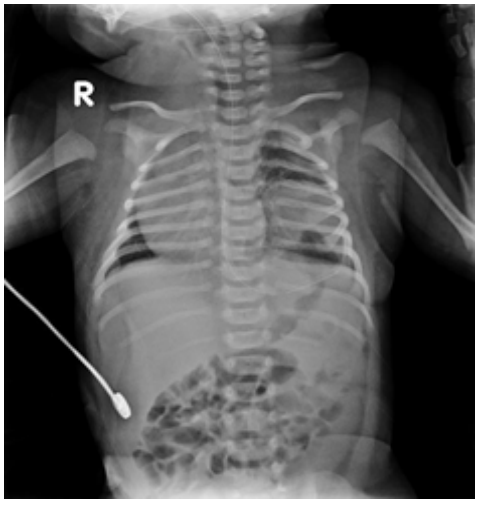

Fig.1. Xray chest and abdomen showing left side congenital diaphragmatic hernia

Baby also had features of dysmorphism in form of microcephaly, down slanting forehead, low set ears, high arched palate, bilateral post axial polydactaly, with rocker bottom feet (Figure 2).

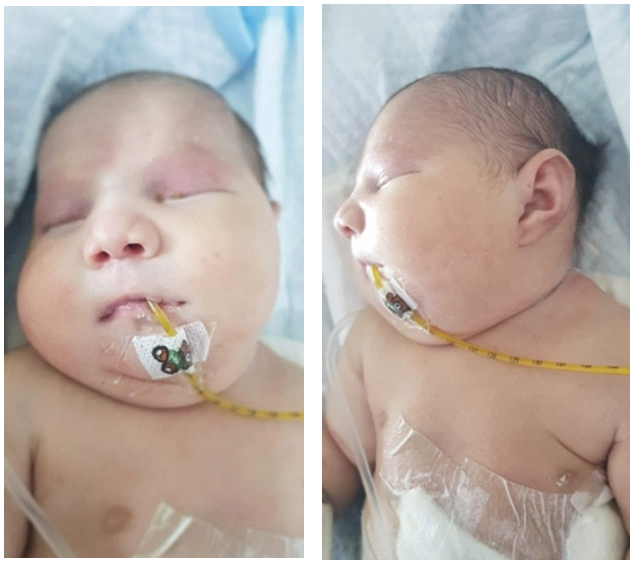

Fig. 2. Facial dysmorphism

Diagnosis: Chromosomal microarray revealed trisomy 13.

Course: The child was weaned off respiratory support by day 8 of life and was discharged home on day 15 of life.

Review of Literature:

Congenital Diaphragmatic Hernia (CDH) can be isolated or associated with malformations or can be syndromic. Isolated CDH is the only birth defect in 60% of the cases while non-isolated accounts for the rest of 40%. Bilateral CDH has a higher incidence of associated anomalies than unilateral ones.

The associated malformations are heterogeneous and can be a cardiovascular, pulmonary, central nervous system, genitourinary, and musculoskeletal. Chromosomal abnormalities have been implicated in

~ 15% of the cases of CDH of which trisomy 18, trisomy 21 and Pallister-Killian syndrome (Isochromosome 12 p) are the most common ones.

Trisomy 13 is one of the common trisomies and occurs in 1 in 5000 total births. The syndrome typically has intrauterine growth restriction with microcephaly, anophthalmia, midline facial defects like cleft lip and palate, limb defects and alobar holoprosencephaly. Few cases of Congenital Diaphragmatic Hernia in association with Trisomy 13 have been reported in literature (1,2).

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2. Jain A, Kumar P, Jindal A, SarinYK. Congenital Diaphragmatic Hernia in a Case of Patau Syndrome: A Rare Association, Journal of Neonatal Surgery 2015 Apr-Jun; 4(2): 20

Image Section

Dr Pinaki Dutta[1], Dr Naveen Parkash Gupta[2], Dr Swetha K[1], Dr Devendra Singh[1]

1. NNF fellow, Madhukar Rainbow Children's Hospital, Delhi
2. Neonatologist, Madhukar Rainbow Children's Hospital, Delhi

Clinical Presentation – Extreme preterm (25 weeks), appropriate for gestational age baby delivered through caesarean section. The baby was intubated in the delivery room and he was ventilated. Umbilical lines were inserted and surfactant was administered. On the X-ray abdomen, 2 catheters were visible (one catheter tip at T11 and other catheter tip at T7), the downward course of the umbilical arterial line was not clearly visible due to loops created over the abdomen to fix the lines.

Suspicion: Two umbilical venous lines (Either two catheters have been inserted through a single umbilical vein or there are two umbilical veins)

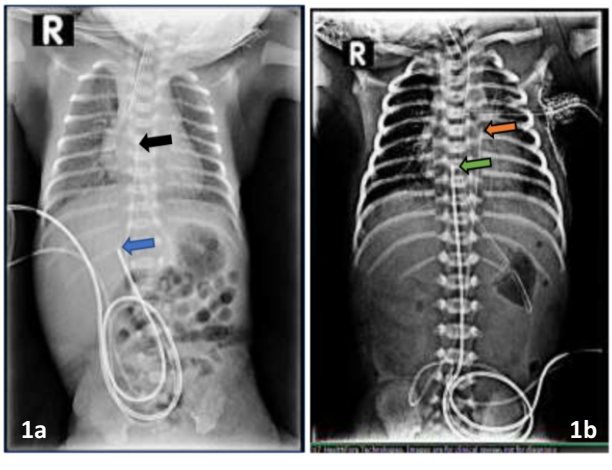

Fig. 1 a : X-ray showing two catheters in indexed case (Black arrow denotes catheter tip at level of T7 vertebra which was initially thought to be UAC and blue arrow denotes catheter tip at T11 vertebrae). 1 b shows the normal course of the umbilical artery and vein (as reference for comparison, the orange arrow denotes the UAC tip and the green arrow denotes UVC tip)

Course –On point of care sonography(POCUS), one catheter tip (T7 on x-ray) was seen in the right atrium (seems UVC) and the other catheter tip (T11 on x-ray) was seen in the liver (Figure 2). No central line catheter was seen in the descending aorta either in low lying or normal position. Fluid was seen flowing in inferior vena cava on flushing both the catheters thereby confirming the possibility of two umbilical veins. Umbilicus was inspected for the number of openings. There were 3 openings and two catheters were inserted in two different vessels (Figure 3). The loops over abdomen were straightened and the Xray abdomen was repeated (both anteroposterior and lateral view) (Figure 4a,4b). On screening antenatal records, antenatal ultrasound mentioned 3 vessel cord. The baby was screened for other congenital anomalies. No associated anomalies were found.

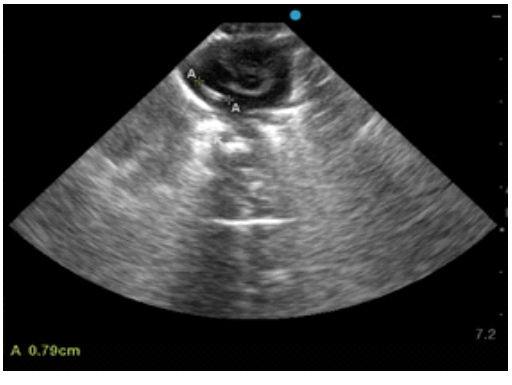

Fig. 2 : POCUS showing one catheter tip (black arrow) in the right atrium

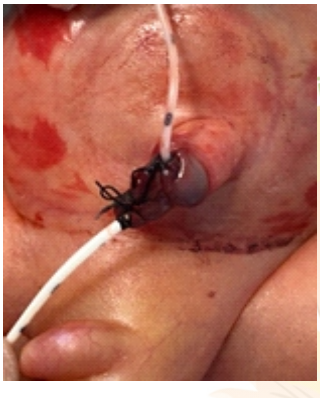

Fig. 3: On visual inspection, 2 catheters have been put through 2 different openings

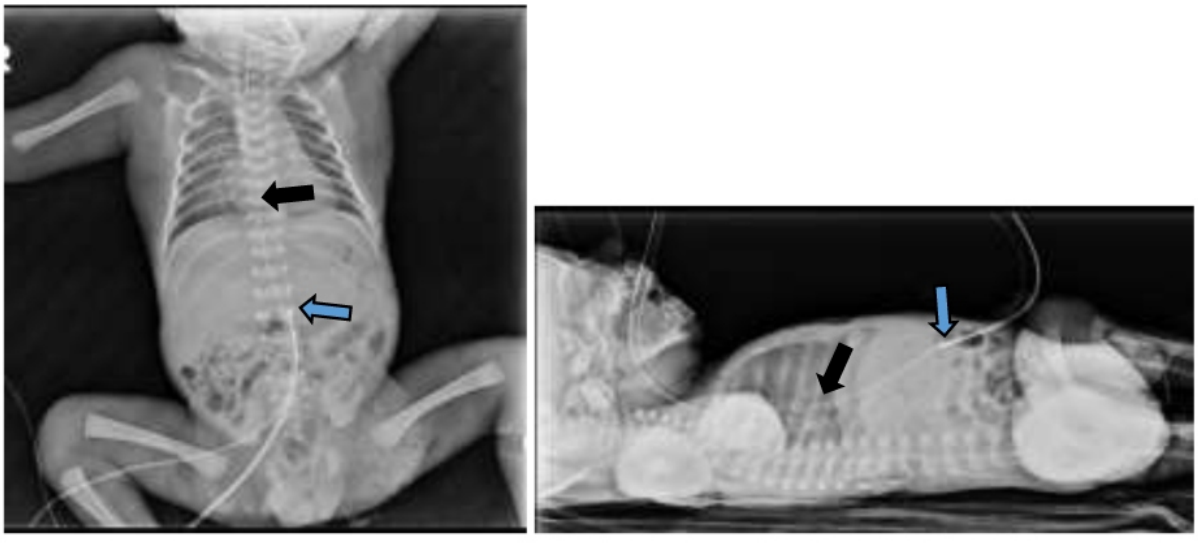

Fig. 4: Anteroposterior and cross-table lateral views demonstrating two umbilical veins (Black and blue arrow denote two catheter tips). Note both catheters are following the same course.

Diagnosis – Single umbilical artery with 2 umbilical veins (Type 3)

Discussion: Single umbilical artery is of 4 types. Type 3 is rare. The umbilical cord contains three patent vessels, one artery of allantoic origin and two veins. The veins arise from the left umbilical vein and a persistent anomalous right umbilical vein. Normally it is associated with other anomalies and poor prognosis (1,2).

Key points:

1. It is important to trace course of umbilical lines on Xray
2. Two umbilical veins are uncommon but do look for them.
3. In case of any confusion, cross table lateral view should be done in addition to anteroposterior view.
4. POCUS is gaining importance these days and is a handy tool to locate line tips.
5. Neonates with a single umbilical artery should be screened for other associated anomalies.

References:

1. Persutte WH, Hobbins J. Single umbilical artery: a clinical enigma in modern prenatal diagnosis. Ultrasound Obstet Gynecol 1995; 6:216.
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BMC Pediatrics

RESEARCH Open Access

Oral versus intravenous sildenafil for pulmonary hypertension in neonates: a randomized trial

Chinmay Chetan[1,2], Pradeep Suryawanshi[2*], Suprabha Patnaik[2], Naharmal B. Soni[3], Chandra Rath[4], Prince Pareek[2], Bhvya Gupta[5], Reema Garegrat[2], Arjun Verma[2] and Yogen Singh[6]

Reviewed by
Dr Sidharth Nayyar
Senior Consultant, Neonatology and Pediatrics, Cloudnine Hospital, Faridabad

Research Question- Does Oral Sildenafil have comparable efficacy and lesser side effect profile when compared to IV Sildenafil for treatment for mild to moderate Neonatal Pulmonary Hypertension.

Hypothesis

Population	**Neonates more than 35 weeks' gestational age with Pulmonary arterial pressure (PAP) > 25 mm Hg measured by echocardiography, within 72 h of birth.**
Intervention	**Oral Sildenafil (6-hourly oral sildenafil at 1 mg/kg/dose).**
Control	**IV Sildenafil (loading dose of 0.4 mg/kg of sildenafil over 3 h followed by continuous infusion of 1.6 mg/kg/day).**
Outcome	**Time taken for PAP to decrease below 25 mm Hg.**

METHODS

- **Design:** Open Labelled, Parallel, Randomized controlled trial
- **Allocation/ Randomization:** Neonates were randomly assigned using computer-generated numbers to either the oral or the IV sildenafil group in 1:1 ratio
- **Blinding:** Neither clinicians nor parents could be blinded to study
- **Setting:** level III neonatal intensive care unit (NICU) in an urban academic medical centre in Pune,India
- **Patients:** 40 infants

Inclusion criteria: Late preterm and term infants with Pulmonary arterial pressure (PAP) > 25 mm Hg on echocardiography within 72 h of birth were enrolled

Exclusion criteria: Neonates with congenital heart disease (except patent ductus arteriosus, patent foramen ovale, atrial septal defect, or a single muscular ventricular septal defect of < 4 mm size), congenital diaphragmatic hernia, any lethal congenital anomaly, or with any contraindication for oral or IV sildenafil (systemic hypotension, necrotizing enterocolitis [NEC], or gastrointestinal bleeding), were excluded.

Sample size Researchers aimed to enrol a sample size of 40 patients based on likely enrollment rates in their nursery over the 2-year period as a pilot trial.

Echocardiographic evaluation All late preterm and term infants admitted in NICU, on nasal oxygen, non-invasive respiratory support or invasive respiratory support were screened for pulmonary hypertension by echocardiography every 24 h during the first 72 h

after birth. Echocardiography was done on a Siemenes Acuson X 300 machine using a neonatal probe (4–8 Hz transducer). Pulmonary pressures were measured by tricuspid regurgitation velocity.

Intervention- After taking written informed consent from parents neonates were randomly assigned to one of the groups. Babies in the oral sildenafil group were started on 6-hourly oral sildenafil at 1 mg/kg/dose. Babies in the IV group were given a loading dose of 0.4 mg/kg of sildenafil over 3 h followed by continuous infusion of 1.6 mg/kg/day. After starting Sildenafil, functional echocardiography was repeated every 12 h until PAP dropped to < 25 mmHg. Sildenafil was tapered when PAP reached < 25 mmHg and stopped within 4 days according to the hospital protocol. During tapering, echocardiography was done every 24 h. In case of rebound increase in PAP to > 25 mm Hg, Sildenafil was increased back to its original dose.

RESULTS

Forty patients were enrolled. The baseline characteristics of neonates in both groups were similar except for APGAR scores at 1 min and 5 min, with oral group having lower score [MEDIAN (IQR) 5.00 (4.00- 7.00) and 7.00 (6.00- 8.00)] compared to IV group [MEDIAN (IQR) 7.00 (6.00–8.00) and 9.00 (8.00–9.00)] respectively. Time taken for PAP to decrease below 25 mm was not statistically different between the oral and intravenous groups. Systemic hypotension occurred in 4 neonates of the intravenous group but none in the oral group.

Conclusion: Oral and intravenous sildenafil had equal efficacy at reducing PAP in neonatal pulmonary hypertension, albeit intravenous sildenafil use was associated with a greater complication rate.

Reviewer's Comments-

With the advancement in the field of neonatology, managing neonates with PPHN is becoming more protocol and evidence based. We nowadays have iNO and ECMO support especially in high income settings for managing cased of severe PPHN.[1] But in cases of Mild to moderate PPHN in low resource settings, we need to rely on various pumonary vasodilators (Milrinone and Sildenafil).[2] Sildenafil has been used in cases of neonates with PPHN without cardiac compromise.[3] Both Oral[4] and IV[5] sildenafil have been used, with IV sildenafil causing side effects which include systemic hypotension. This trial evaluated the efficacy and safety of oral sildenafil against IV sildenafil. Oral sildenafil was found to be comparable to IV in terms of efficacy when PPHN was mild to moderate.

Strengths of study – In developing world where intravenous sildenafil is not readily available, comparing oral vs intravenous is a nice idea.

Limitations –

1. Pulmonary vasodilators are normally started based on oxygenation index in case of PPHN. Entry criteria is based on PAP. Severe cases of PPHN are not included. So we can't replicate findings of study in day-to-day clinical practice where we are starting pulmonary vasodialtors in case of PPHN based on oxygenation index.
2. No apriori sample size was calculated.
3. The cut off of 25 mm Hg as inclusion criteria and the response to sildenafil as time taken for the pressures to reduce below 25 mm Hg may overlap with the normal physiology, and actual drop in pulmonary pressures might be due to improvement in lung disease rather than sildenafil administration.

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3. Kelly LE, Ohlsson A, Shah PS. Sildenafil for pulmonary hypertension in neonates. Cochrane Database Syst Rev. 2017;8:CD005494
4. Hussain AS, Ali R, Ahmed S, et al. Oral Sildenafil Use In Neonates With Persistent Pulmonary Hypertension Of Newborn. J Ayub Med Coll Abbottabad. 2017;29(4):677–80.
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QUESTIONS

Dr Swati Upadhyay
Senior Consultant Neonatology
Max Superspeciality Hospital, Patparganj, Delhi

Dr Ranjani Updahyay
Associate Consultant
Department of Neonatology
Madhukar Rainbow Children's Hospital, Delhi

Question .1.

4 hours old term small for gestational age (SGA) baby boy born with a birth weight of 1800 grams to 27 years old primigravida mother was admitted with poor feeding and lethargy. Blood sugar was 25 mg/dl. Dextrose 10% bolus was given, followed by continuous infusion with glucose infusion rate (GIR) of 6 mg/kg/min. His blood sugars remained less than 40 mg/dl and GIR was increased in stepwise manner to 12 mg/kg/min. Hydrocortisone was added. There was no history of perinatal asphyxia and no risk factors for early onset neonatal sepsis. Mother wasn't receiving any drugs apart from routine supplementation. There were no visible external malformations and no organomegaly. The family history was unremarkable.

a. What do you think is underlying cause of hypoglycemia in this case and how would you investigate this baby further?

b. Enumerate diagnostic criteria for hyperinsulinemic hypoglycemia?

c. Baby had elevated insulin levels (sample was taken at time when RBS was 32 mg/dl). His free fatty acid and ketone levels were low. His GIR needs were 15 mg/kg/min to maintain blood sugars in normal range. Lactate and ammonia were within acceptable range; urine ketones and sepsis work-up were negative.

i. What will be your drug of choice in this scenario?

ii. What is its mechanism of action?

iii. What is the recommended dose?

iv. What are the adverse effects of this drug?

d. In spite of diazoxide hypoglycemia persisted. What other drugs would you consider in this baby?

e. What genetic work up would you plan for this baby?

Question .2.

29 years old primigravida mother delivered a term female baby at 38 weeks gestation with weight 3.2 kg. Routine cord blood TSH screening showed TSH levels of 90 mIU/L.

a. How will you proceed?

b. Repeat venous sampling was done at 72 hours of life. Repeat TSH was 100 mIU/L and free T4 was low (0.2 ng/dl). Suspecting congenital hypothyroidism, what additional tests will you perform?

c. What is the time frame within which ultrasound and radionuclide scan can be done in babies with congenital hypothyroidism?

d. USG of thyroid gland showed small gland in this baby and thyroid scan showed absent uptake. What is the most probable diagnosis?

e. How would you initiate and titrate treatment in this baby? When would you repeat thyroid function tests after starting treatment?

f. How would you plan long-term follow-up for this baby?

g. What are the current criteria for initiation of levothyroxine therapy in term newborns based on confirmatory venous sample results after newborn screening?

h. When should screening for congenital hypothyroidism (CH) be done in preterm babies?

Question .3.

A preterm 26-week male baby boy with birth weight 700 gm is admitted in your NICU. Baby is now 4 weeks old and is still on HHHFNC support (25% Fio2 and 4 l/min Flow). He had a stormy initial course, required invasive ventilation for 2 weeks and had suspect NEC warranting parenteral nutrition for 15 days. Calcium and vitamin D was added in milk once baby reached full feeds. He also received a course of post-natal steroids and diuretics for evolving bronchopulmonary dysplasia (BPD).

a. When would you start evaluating this baby for metabolic bone disease? What lab tests would you use for screening and what are the cut-off values for diagnosing metabolic bone disease (MBD)?

b. What risk factors in this baby put him at a higher risk for developing the metabolic bone disease?

c. This baby had a serum phosphorus level of 3 mg/dl and alkaline phosphatase (ALP) of 1200 IU/L, despite optimal Ca and P supplementation. How would you investigate this baby further?

d. On further evaluation, the baby had serum parathormone (PTH) of 150 pg/ml and tubular reabsorption of phosphorus (TRP) of 70%. Vitamin D levels were low. What would be your interpretation and how would your management change?

e. What is the current recommendation for Calcium, Phosphate and Vit D supplementation in preterm VLBW babies? Upto what age is fortification indicated?

Question .4.

A multigravida mother with gestational diabetes mellitus (GDM), with poor glycemic control during pregnancy delivered a male baby with weight 4.5 kg. There was no history of perinatal asphyxia and no risk factors for early-onset neonatal sepsis. The baby was started on feeds. On screening, blood sugars were with in normal range. He has an epidose of mulifocal clonic seizure at 24 hours of life. RBS was 64 mg/dl. Baby was shifted to NICU and stabilized. Baby remained hemodynamically stable.

a. Enumerate possible reasons for seizure in this baby?

b. This baby had a Calcium level of 6 mg/dl. How would you manage the baby?

c. Despite adequate treatment with IV calcium, the baby had another seizure on 3rd day of life. You repeated calcium levels and they were still 6.1mg/dl. What will be your next step in managing this baby?

d. What other systemic and metabolic complications can occur in this baby? What are the long-term complications which can occur in infants of diabetic mothers?

e. What are the current recommendations on the timing of delivery in pregnant women with GDM?

f. This mother is concerned regarding her own follow-up and risk of developing diabetes. What are the current ACOG recommendations for follow-up of women with GDM?

Question .5.

A 30-days old baby boy is admitted with complaints of poor feeding, vomiting and lethargy. On examination, the baby is dehydrated, dull and has hypotonia. There is no history of diarrhoea. The mother reported that she had been giving supplements as advised to the baby. His HR is 160/min, RR is 58/min, and spo2 is 100% on room air. RBS is 80 mg/dl. IV fluids and antibiotics are started, and investigations are sent.

The lab tests are as follows: Hb 15 g/dl, TLC 6000, Platelet count 4 lakh, CRP Negative, Sodium 140 mEq/l, Potassium 4.5 mmol/l, pH 7.38, Calcium 17 mg/dl.

a. What is your diagnosis?

b. What are the common causes of this condition in neonates?

c. What medication history would you particularly ask from mother?

d. How would you evaluate this baby further?

e. Upon checking the medications, you find that child has been receiving 0.5 ml/day of a cholecalciferol preparation containing 60,000 Units/ 5 ml, instead of standard formulation. The baby had suppressed PTH levels and Vitamin D level > 100 ng/ml. What is your diagnosis? What would be your line of management?

Question .6.

A girl child is delivered at 38 weeks of gestation to 27 years old primigravida mother with Grave's disease. She was diagnosed to have Grave's disease at 24 years of age and had received treatment in form of oral medications, followed by radioactive ablation of thyroid gland. Subsequently, she received thyroxine and had remained euthyroid throughout pregnancy.

a. How would you evaluate the baby? Is this baby at risk of developing hyperthyroidism despite maternal thyroid gland ablation and adequate treatment? If yes, then why?

b. On day 4 of life, the baby was noticed to have tachycardia and irritability. Baby's free T4 was 7 ng/dl and TSH was 0.1 mIU/ml. What drugs would you use for managing this baby? What doses would you use?

c. What are the current recommendations for antenatal evaluation of mothers with history of Grave's disease?

d. Which drugs are used for antenatal treatment of maternal and fetal hyperthyroidism? What are the potential adverse effects of these drugs?

e. Which drug is preferred for treatment of hyperthyroidism in lactating women?

Question .7.

A term born SGA baby boy, presented on day 26 of life with weight loss, vomiting and dehydration. He was admitted and IV fluids and antibiotics were started. Blood sugar levels on admission were 400 mg/dl and remained high even on subsequent readings.

a. How do you define neonatal hyperglycemia? What are the common causes of neonatal hyperglycemia?

b. What treatment would you initiate for hyperglycemia? What are the current suggested operational thresholds at which treatment for hyperglycemia should be initiated?

c. How would you diagnose neonatal diabetes mellitus (NDM)?

d. What is the etiology of NDM? What treatment options are available for NDM?

e. This baby required insulin during the hospital stay and blood sugars normalized. Insulin was gradually stopped. Post-discharge, this baby had recurrent infections, dermatitis, persistent diarrhoea and required re-initiation of insulin for hyperglycemia. Which syndrome would you suspect? What genetic defect is involved in this syndrome?

Question .8.

A 12-day old neonate is admitted with complaints of lethargy, vomiting and poor feeding. The baby was born at 38 weeks and had a birth weight of 3 kg. On examination, the baby was dehydrated, had feeble pulses with prolonged CFT and mean BP of 35 mm Hg. Head to toe examination revealed findings as shown in Fig 1. There was hyperpigmentation in the umbilical and genital regions. Palpation of genitals revealed “empty scrotum”. RBS was 40 mg/dl. Blood gas revealed metabolic acidosis. Sodium levels were 120 meq/l and potassium levels were 7.8 meq/l.

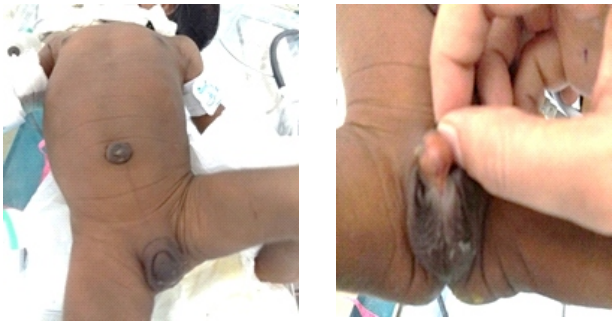


Fig 1. Empty scrotum and hyperpigmented genitals and umbilical regions

a. What would be your provisional diagnosis?

b. How would you confirm your diagnosis and investigate this baby?

a. This baby had markedly elevated 17-OHP levels and low cortisol levels. Other adrenocortical hormones were within range. USG pelvis showed Mullerian structures. FISH analysis suggested 46 XX pattern. What would be your final diagnosis and

c. How would you manage this baby immediately and thereafter?

d. What factors would you consider while assigning sex of rearing in this baby?

e. How would you plan follow up for this baby and what instructions would you give to parents for intercurrent illnesses?

f. What is the current consensus on the timing of genital surgery in these babies?

g. What is the current consensus on prenatal dexamethasone administration to pregnant women with a prior CAH-affected child?

Question .9.

A 3-week-old baby boy is referred to you with a history of recurrent hypoglycemia and persistent jaundice. The child was born full term and had birth weight of 2 kg. The antenatal period was uneventful, except for the absent cavum septum pellucidum in antenatal scans. Family history was unremarkable and there was no history of consanguinity. On examination, the baby was hemodynamically stable. He had a midline cleft lip, hypospadias, micropenis and icterus till legs.

a. What would you suspect? What hormonal deficiencies is the baby expected to have?

b. On lab evaluation, the baby had conjugated hyperbilirubinemia, mildly raised transaminases, low stimulated cortisol levels, low free T4 levels and TSH levels. Other pituitary hormones were normal. How would you manage this baby?

c. What associated CNS anomalies you may find in the MRI Brain of this baby?

d. How would you diagnose neonatal growth hormone deficiency? Is there any role of GH stimulation test in newborns?

e. What is the ideal time to evaluate this baby for central hypogonadism associated with hypopituitarism?

Question .10.

A baby is delivered at 39 weeks of gestation to a primigravida mother. The baby has small phallus with separation of the scrotal sac, penoscrotal hypospadias and single palpable testis. The antenatal period was uneventful.

a. In which babies would you suspect DSD?

b. What is the external masculinization score?

c. What important points would you elicit in antenatal and family history?

d. Which disorder of sex development is this baby likely to have?

e. What are the causes of 46 XY DSD?

f. Parents were apprehensive and therefore FISH was sent while Karyotype results were awaited. FISH detected Y chromosome material. How would you further evaluate the baby? At what age would you do biochemical and hormonal evaluation?

Answer 1.

a. Blood should be taken at time of hypoglycemia (critical samples) and sent for plasma glucose, serum insulin, serum cortisol, serum free fatty acids (FFA), serum Beta-hydroxybutyrate (BOHB), serum HCO3, lactate.

b. Diagnostic criteria for hyperinsulinemic hypoglycemia (1).

At time of hypoglycemia (RB < 50 mg/dl):

Insulin level 2 microIU/ml (Normally insulin levels should be undetectable in blood at time of hypoglycemia, so any detectable level of insulin at time of hypoglycemia can be taken as abnormal also)

Beta Hydroxy butyrate < 1.8 mmol/l

FFA < 1.7 mmol/l

Glucose rise 30 mg/dl after glucagon administration

Insulin like growth factor binding protein (IGFBP) </= 110 ng/ml

Low ketone and low FFA levels suggest insulin-mediated hypoglycemia. Low ketones and increased FFA levels suggest fatty acid oxidation defects.

If GIR need is more than 12 mg/kg/min in absence of sepsis, hyperinsulinemia is likely etiology of hypoglycemia

c. i) Diazoxide

ii) Binds to SUR1 subunit. It is a potassium channel opener.

ii) 5-20 mg/kg/day in 3 divided doses orally

iii) Fluid retention, hyponatremia, hypertrichosis, cardiac toxicity, rarely eosinophilia, leukopenia, hypotension

d. Octreotide, Nifedipine, and Sirolimus are other drugs which can be used in hyperinsulinemic hypoglycemia if there is no response to Diazoxide.

e. Genetic studies for mutational analysis of ABCC8/ KCNJ11 genes

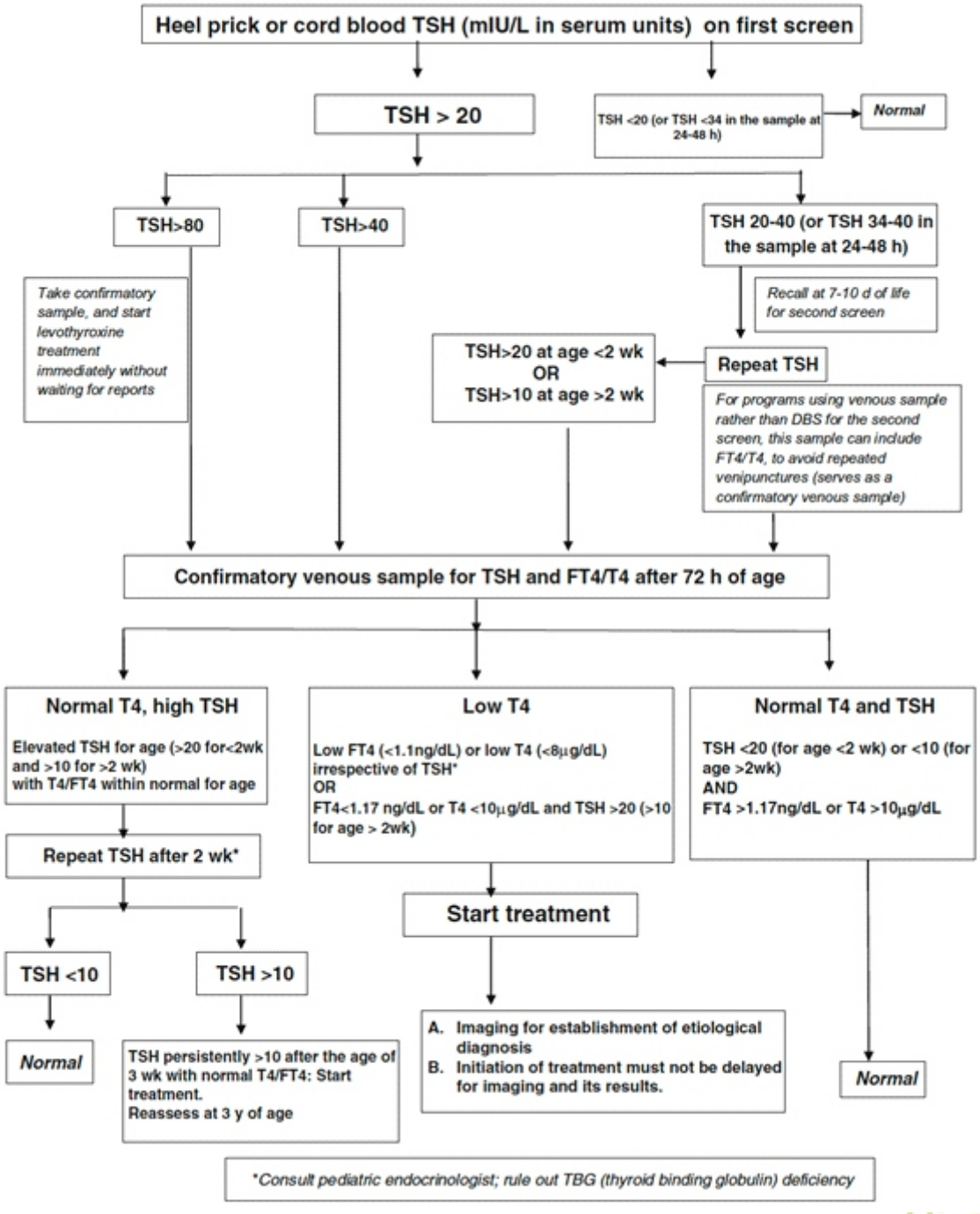
Answer 2.

a. Infants with TSH values above certain levels on the initial newborn screen, usually >30 mIU/L in serum units (equivalent to >15 mIU/L in whole blood units), are recalled for clinical evaluation and serum testing (algorithm 1), which occurs around one week of age. If a second test is done, the results should be interpreted using a lower TSH cutoff (typically >10 mIU/L after one week of age).

b. Thyroid ultrasound and radionuclide uptake and scan. Either 99m-pertechnetate or iodine-123 can be used. The 99m-pertechnetate scan is more readily available and allows a good scan picture, but because it is not organified, there is no measure of uptake. Iodine-123 must be specially ordered due to its short half-life, but it will provide both a scan and a measure of uptake. Iodine – 123 scan is less readily available.

c. Ultrasound of thyroid gland should be done once congenital hypothyroidism (CH) is biochemically confirmed. Scintigraphy can be done either before or with in seven days of starting levothyroxine (till time TSH is elevated).

Please note that imaging should never be the reason to delay the initiation of therapy in CH.



Algorithm for screening and diagnosis of congenital hypothyroidism (2)

d. Thyroid hypoplasia

Interpretation of scan - A large gland in a normal location typically is seen with one of the enzymatic defects. A positive perchlorate discharge test is compatible with an organification defect. Decreased uptake on scan associated with a normally located thyroid gland on ultrasound suggests the possibility of a loss-of-function TSH receptor gene mutation or maternally transmitted TSH receptor-blocking antibodies.

e. The initial levothyroxine dose is 10-15 µg/kg,

given as a single dose, as a crushed tablet in expressed breastmilk. The first follow-up including thyroid function tests (FT4/T4) should be done 2 wk after starting treatment by which time normalization of FT4/T4 is expected. If the levels are low for age, a slight increase in the dose is required. On the other hand, the dose should not be decreased if a single value of T4 is found above the normal range. The next test, after 1 month, should include both T4/FT4 and TSH; normalization of TSH is expected by this time. The sample for thyroid function is taken before (or minimum 4 h after) ingestion of LT4.

f. Follow-up is done every 2 months in early infancy till 6 months of age, every 3 months during age 6 mo to 3 y and every 3–6 mo thereafter, till growth and pubertal development is completed. Any dose change is followed by a biochemical evaluation after 4 weeks. Hearing test and clinical evaluation for other congenital malformations must be performed for all babies with CH. Babies with the possibility of transient CH should be re-evaluated at the age of 3 y, for permanence of CH and the need for lifelong therapy.

g. Criteria for initiating treatment (2)

-Low T4 (<100 nmol/L or 8 µg/dL) or low FT4 (<12 pmol/L or <1.1 ng/dL) irrespective of TSH

-Mild low T4 (<128 nmol/L or 10 µg/dL) or low FT4 (<15 pmol/L or 1.17 ng/dL) in the presence of elevated venous TSH >20 mIU/L if age is <2 wk and >10 mIU/L if age is >2 wk

-Normal T4/FT4 with persistently elevated TSH > 10 mIU/L at age > 3 wk

h. For preterm babies, screening for CH may be done at 2, 6 and 10 weeks of age using TSH and Free T4. This is because these babies will often have delayed rise of TSH due to immaturity of HPT axis.

Answer 3.

a. We shall start screening for MBD at 4 weeks of age, using Serum Calcium, Phosphorus and alkaline phosphatase (ALP). Combination of deceased serum phosphate levels <5.6mg/dl (<1.8mmol/L) and increased ALP levels >900 IU in preterm infants <33wks indicates low bone mineral density and has a sensitivity of 100% and specificity of 70% for diagnosing MBD (3,4).

b. Risk factors for MBD in this baby (apart from extreme prematurity and ELBW):

Delayed initiation of enteral feeds

Suspect NEC

Bone active medications- Diuretics and steroids

c. PTH, TRP (tubular reabsorption of phosphate), Vitamin D levels, serum calcium levels, Xray as needed.

d. High PTH with low PO4, high ALP and low TRP (normal TRP 85-95%) suggest primarily calcium deficient state. In this primarily calcium deficient state, mainstay of treatment will be calcium supplementation (40 to 100 mg/kg/day) in 2 to 4 divided doses. This would normalize elevated PTH, thus reversing resultant bone resorption and hypophosphatemia. Along with this, we would supplement Vit D 800-1000 IU/day.

Phosphate supplementation in this condition will result in binding to ionized calcium, therefore causing a further increase in PTH and in fact exacerbation of MBDP.

e. Current recommendations (ESPGHAN 2010):
Calcium 120-140 mg/kg/day
Phosphorus 60-90 mg/ kg/day
Vit D 800-1000 IU/day

Calcium phosphorus supplementation/ fortification is continued until 40 weeks postmenstrual age. Vit D is continued till 1 year

of age. Babies with MBD would need fortification for a longer duration, till phosphate normalizes and ALP touches baseline.

Answer 4.

a. Hypocalcemia, hypomagnesemia

b. We will give a bolus dose of 2 mL/kg 10% calcium gluconate diluted 1:1 with 5% dextrose over 10 minutes under cardiac monitoring. This is followed by maintenance calcium at 80 mg/kg/day of elemental calcium (8 mL/kg/day of 10% calcium gluconate; 1 mL=9.4 mg of elemental calcium) for 48 hours. This may be tapered to 50% dose if calcium levels normalize for another 24 hours and then discontinued.

c. Magnesium levels to be done. Magnesium level <1.5mg/dl is suggestive of hypomagnesemia.

Correction of associated hypomagnesemia: Give 50% magnesium sulfate solution (500 mg/ml or 4 mEq/mL)—50 mg/kg or 0.1 ml/kg/per dose every 12 hours, through IM or IV route. IV dose should be preferable in NICU and given over 2 hrs.

d. Other complications:

Systemic: Macrosomia, birth trauma, RDS, Renal vein thrombosis, small left colon syndrome, Asymmetric septal hypertrophy, poor feeding

Metabolic: Hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia, hyperbilirubinemia

Long-term: Metabolic syndrome, obesity, Diabetes

e. Timing of delivery (ACOG): For women with GDM that is controlled with diet and exercise, delivery should not be before 39 weeks of gestation, unless indicated otherwise. In such women, expectant management up to 40 6/7 weeks is generally appropriate. For women with GDM that is well controlled by medications, delivery is recommended at 39 0/7 to 39 6/7 weeks of gestation.

f. Screening at 4–12 weeks postpartum is recommended for all women who had GDM to identify women with diabetes, impaired fasting glucose levels, or impaired glucose tolerance. They should be referred for preventive or medical therapy. The ADA and ACOG recommend repeat testing every 1–3 years for women who had a pregnancy affected by GDM and normal postpartum screening test results.

Answer 5.

a. Hypercalcemia

b. Causes: Iatrogenic/ Improper medications/ imbalance of calcium intake

Hypervitaminosis D/ Vitamin D intoxication

Hyperparathyroidism

Familial hypocalciuric hypercalcemia

William's syndrome

Sub cutaneous fat necrosis

c. Vitamin D and Calcium supplementation (if being given) – we should check the dose and preparation.

d. PTH levels, serum phosphorus, ALP, Vitamin D levels

Renal function tests

USG KUB to look for nephrocalcinosis

e. Baby has Hypervitaminosis D/ Vitamin D intoxication due to inappropriately high Vitamin D ingestion over 1 month.

Treatment: Saline bolus (10-20 ml/kg), Furosemide (1 mg/kg/dose 8th hrly), Glucocorticoids (Hydrocortisone/ Methylprednisolone (4 mg/kg/day) followed by oral prednisolone (1mg/kg/day). Calcitonin (8 IU/kg/day) and Pamidronate (0.5 mg/kg/day infusion) may be given in refractory hypercalcemia.

Answer 6

a. We will do following tests in the baby

Cord blood TRAb (TSH receptor antibody)

Free T4 and TSH between day 3-5

Yes, this baby is still at risk of developing hyperthyroidism. Mothers with Grave's disease (GD) have TRAb. The treatment of Grave's disease consists of antithyroid drugs, radioactive iodine ablation or surgical thyroidectomy. None of these treatments target TRAb. Hence, even if the mother has been adequately treated for hyperthyroidism in the past, she may still have TRAb, which may persist lifelong though the risk decreases with time. The TRAb are of two types. They can inhibit the production of thyroxine or stimulate the production of thyroxine. The TRAb belong to the immunoglobulin class G (IgG) and can easily cross the placenta and produce hyperthyroidism in the foetus and the neonate.

b. Baby has hyperthyroidism. Drugs for treatment:

Methimazole (0.2 -0.5 mg/kg/day in 2 divided doses)

Propranolol (2 mg/kg/day in 2-4 divided doses)

In severe hyperthyroidism, Lugol's solution (0.05 ml/ 1 drop 3 times a day) may be used to block release of thyroxine immediately. First dose should be given 1 hour after Methimazole. Additional therapy for severe cases may include prednisolone (1 to 2 mg/kg/day)

c. In mothers with Grave' disease or a past history of same, TRAb testing should be done at 18–20 weeks. A maternal TRAb value of at least 5 index units predicted neonatal thyrotoxicosis with a sensitivity of 100%, specificity of 76.0%, positive predictive value of 40.0%, and negative predictive value of 100%. Maternal FT4 levels should be maintained in the upper range of normal in the pregnancy.

d. Propylthiouracil (PTU) is used in the first trimester, followed by Methimazole (MMI). Antithyroid drugs should be given at low doses such that FHR is kept around 140/min. Beta blockers may be used in severe cases.

Adverse effects: PTU is hepatotoxic whereas MMI has teratogenic potential.

e. Methimazole is the drug of choice for treatment of hyperthyroidism in lactating women.

Answer 7.

a. Neonatal hyperglycaemia is defined as whole blood glucose level higher than 125 mg/dl or plasma glucose values higher than 145 mg/dl.

Common causes of neonatal hyperglycaemia:

Iatrogenic, Sepsis, Ingestion of hyperosmolar formula, Drugs (Steroids, caffeine, phenytoin) Hypoxia, Surgical procedures, Neonatal Diabetes Mellitus (transient or permanent).

b. Treatment: We will decrease the GIR to 4 mg/kg/min. If high sugar values persist and reach the treatment threshold, we shall start insulin 0.05 to 0.1 unit/kg over 15 minutes, every 4 to 6 hours as needed. Monitor glucose every 30 min to 1 hour. If glucose remains > 200 mg/dl even after 3 doses, initiate insulin infusion 0.05 to 0.2 unit/kg/hour. Monitor strictly for hypoglycaemia and hypokalaemia.

Operational thresholds at which treatment should be initiated for neonatal hyperglycaemia:

- Any blood glucose measurement of 360 mg/dl

- Persistent blood glucose values 270 mg/dl

- Persistent blood glucose values > 216 mg/dl with glycosuria 3+ on urinary dipstick testing. (Cloherty and Stark's Manual of Neonatal Care, South Asian Edition, Chapter 24, Page 333)

c. Diagnosis of NDM (Neonatal diabetes mellitus): NDM is persisting hyperglycaemia lasting more than 2 weeks presenting before 6 months of age, requiring insulin to maintain euglycemia.

Suspect NDM	- Growth restriction, polyuria, dehydration, failure to thrive - Glucose 200–250 mg/dL or more than few days (no alternative cause) - Glucose >300 mg/dL regardless of the time course - Need for insulin before 6–12 months of age
First-line tests	Urine ketones, serum glucose, C peptide, and insulin levels, pancreatic ultrasound, thyroid function tests, hepatic and renal functions, ophthalmological evaluation
Second-tier test	Glutamate decarboxylase, zinc transporter-8, insulin, and islet antigen-2 autoantibodies, IgE levels, X-rays spine, and limbs
Genetic analysis	For all NDM
(IgE: immunoglobulin E; NDM: neonatal diabetes mellitus)	

d. Etiology of NDM:
Transient NDM: Genetic defect in 6q24, ABCC8, KCNJ11
Permanent NDM: Genetic defect in KCNJ11, ABCC8, GCK, INS genes
Syndromic causes: IPE syndrome, Wolcott-Rallison syndrome, GLIS3
Treatment options for NDM: Sulfonylureas, Insulin

e. IPEX syndrome (Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

Genetic defect in FOXP3-IPEX.

Answer 8.

a. Congenital adrenal hyperplasia (CAH) and Difference or disorders of sex development (DSD)

b. Investigations:

1. Adrenocortical profile: Serum 17-OHP, cortisol, 11-deoxycortisol, 17-OH pregnenolone, dihydroepiandrostenedione (DHEA) and androstenedione should be measured. Apart from 17-OH pregnenolone, the rest of the tests are available on the LC-MS/MS platform. (5)
2. Karyotype/ FISH
3. USG pelvis
4. Genetic confirmation of diagnosis by clinical exome sequencing can be offered

c. CAH due to 21-OH deficiency and 46 XX DSD.

Emergency management of adrenal crisis consists of management of shock with normal saline boluses followed by 1.5-2 times maintenance fluids in form of 5%Dextrose with NS, correction of hypoglycemia and electrolyte disturbances and initiation of hydrocortisone replacement therapy (100 mg/m^2/ day in four divided doses) after acquiring samples for confirmation of diagnosis.

Maintenance therapy consists of hydrocortisone 10-15 mg/m^2/day in 3 divided doses, Fludrocortisone 0.1-0.2 mg/day and salt supplementation in doses of 1-2.5 g per day, divided with feeds. This can be done by adding a pinch of common salt each time in expressed breast milk/ feeds. Hydrocortisone and fludrocortisone are given lifelong. The normal family pot diet usually suffices for the sodium requirement after infancy and salt supplementation is usually required in the first year of life only.

d. Factors to be considered while taking decisions on the sex of rearing are underlying diagnosis, genital appearance, internal anatomy, likely gender identity, future fertility, the feasibility of surgical correction, and psychosocial factors. The sex of rearing in a 46 XX DSD neonate with CAH is best assigned as female due to likely female gender identity, preserved fertility, and the possibility of surgical correction.

e. All children with CAH should be monitored for steroid excess clinically. Physical examination should look for hyperpigmentation, cushingoid features, growth, body fat distribution, pigmented striae, and blood pressure for hypertension. Lab monitoring on follow-up should be done as below. Parents should be clearly instructed to increase the dose of hydrocortisone in stress such as febrile illness and gastroenteritis.

Table: Monitoring of children with Classical Congenital Adrenal Hyperplasia

Age, frequency	Investigations
First 3 months, monthly	Serum electrolytes, baseline 17-hydroxyprogesterone recorded
3-12 months, 3 monthly	Serum electrolytes, Serum 17 (OH) P, Serum androstenedione, total testosterone, ACTH Plasma renin activity
12-30 months, 4 monthly	Skeletal age assessment annually after 24 months of age Serum electrolytes, Serum 17 (OH) P, Serum androstenedione, total testosterone, ACTH Plasma renin activity

f. Prenatal dexamethasone administration to a pregnant woman with a prior CAH affected child for prevention of virilization of a female fetus should be considered only experimental and offered after a complete discussion with the family about possible maternal adverse effects, variable genital outcome and unknown long-term side effects of dexamethasone therapy. As of now, the use of prenatal steroids is not recommended and may be started only after a detailed discussion with the family (6)

g. Early genital surgery during infancy or early childhood is recommended for severely virilized (≥ Prader stage 3) female babies. Corrective genital surgery includes vaginoplasty, clitoroplasty and labial surgery. Most children need a staged repair.

Answer 9.

a. Hypopituitarism (Midline defects, hypoglycemia, persistent jaundice)

Hypocortisolism due to ACTH deficiency, central hypothyroidism, central hypogonadism due to LH/FSH deficiency, growth hormone deficiency, prolactin and vasopressin deficiency.

b. We shall start first with hydrocortisone supplementation and correction of cortisol levels, followed by levothyroxine supplementation. Cortisol deficiency should always be treated before thyroid hormone replacement (if there is an associated deficiency) to prevent adrenal crisis.

c. Corpus callosum agenesis, septo optic dysplasia, holoprosencephaly.

d. Random GH levels <7 ng/mL in the first week of life, in association with other pituitary hormone deficiency, can be used to diagnose neonatal growth hormone deficiency. There is no role of GH stimulation test in newborns.

e. All neonates born at term gestation, have a higher level of gonadotropins, starting at around 4–6 weeks till 6 months in males and 2 years in females (mini puberty). The ideal time to evaluate is around 4 to 6 weeks. In males (14 days to 6 months), LH levels <0.8 IU/L and total testosterone <30 ng/dL can be taken as an indicator of central hypogonadism whereas in females (14 days to 2 years), a serum level of FSH <1.0 IU/L is diagnostic of hypogonadotropic hypogonadism (HH).

Answer 10.

a. **In an apparent female baby**

Clitoromegaly >1 cm

Presence of inguinal hernia

Posterior labial fusion

In an apparent male baby

Bilateral non-palpable gonads

Phallus length <2.5 cm (micropenis)

Hypospadias associated with separation of scrotal sacs (bifid scrotum) or an undescended testis (not isolated hypospadias)

Penoscrotal hypospadias (severe hypospadias)

b. The external masculinizing score (EMS) is used to classify the degree of under masculinization 46 XY DSD infants. It is based on the size of the phallus, position of the urethral meatus, presence of gonads, and degree of scrotal fusion, each carrying scores from 0 to 3 to give a total score of 12. Lower scores indicate a more severe form of under- virilization and an EMS <9–10 indicates a need for further evaluation.

c. Detailed antenatal history including maternal drug use (antiandrogens, danazol, progesterone, and spironolactone). History of maternal virilization in the antenatal period (aromatase deficiency and luteoma of pregnancy). Detailed family chart and pedigree for any consanguinity, family history of DSD, sibling deaths, and infertility.

d. As this baby has a palpable gonad, this baby is likely to have 46 XY DSD. The presence of palpable gonad points to the presence of testis and Y chromosome material.

e. Causes of 46 XY DSD:
Androgen insensivity
– Partial
– Complete

5 alpha reductase deficiency

Testosterone biosynthetic defects

– 17 Beta HSD deficiency

– 3Beta HSD

– 17 alpha-hydroxylase/ 17,20 lyase deficiency

– Congenital lipoid adrenal hyperplasia

Leydig cell hypoplasia

Drugs

Persistent Mullerian Duct Syndrome

Complete/ partial gonadal dysgenesis.

f. Karyotype, USG pelvis, genitogram and cystourethrogram while planning surgery. Biochemical and hormonal evaluation is as follows:

Adrenal hormones (after 48 hours):

17OHP

Cortisol

Adrenal steroid profile (in CAH)

Electrolytes and blood sugar

Gonadotropins: LH and FSH (after 1 week) *

Androgens (after 1 week) *

Androstenedione

Testosterone

DHT

AMH

Inhibin B

*After beginning of minipuberty (preferably after 2 weeks)

(AMH: anti-Müllerian hormone; CAH: congenital adrenal hyperplasia; DHT: dihydroxytestosterone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; 17OHP: 17OH-progesterone)

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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.

You can contact us at following email addresses:

info@nnfdelhi.org

drgupta.naveen@gmail.com

Please call or Whats App at 9811758133