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UPDATES IN PERINATAL PRACTICE

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President's Message

Dear Friends,
Warm Greetings!

I am extremely elated to see this issue on Updates in Perinatal Practice in ICOG campus. ICOG has always been in forefront for encouraging and disseminating knowledge, education and research in the field of Obstetrics and Gynaecology .

Perinatology is an area where the parameters of surveillance and intervention are of utmost importance not only to the mother, fetus and neonate directly but also to the family and society as a whole. Any serious catastrophe in the perinatal period can have widespread implications. The need to standardise management protocols in this area is immense and it requires a "team approach" usually as many stakeholders are involved . This edition of the newsletter is dedicated to the very enigmatic topic of "Perinatology" including an article on " simulation training in neonatal resuscitation "which is a practical, innovative solution to a situation that stumps even the most experienced Obstetricians.

My theme of this year is " Swastha Nari , Sukhi Nari" or "Healthy Woman, Happy Woman". This theme is supported by five pillars of Academics, Fellowship, Research, Advocacy and above all Social work. These newsletters and updates are a step towards fulfilling my theme of the year. With the motto of **"Badlaav"** I envisaged a year of academic and administrative endeavours furthering this cause of women's health (nari Swasthya) by changing traditional paradigms of care and venturing into new frontiers.

So friends, empower yourself with all the knowledge and practical tips in this field of perinatology.

I wish you all a Happy Reading !!

Dr Hrishikesh Pai
President - FOGSI 2022-2024

Chairperson's Message

Dear Friends,
Warm Greetings!

It brings me great pleasure to present to you all the issue of ICOG Campus on "Updates in Perinatol practice". My motto as chairperson of this esteemed college this year is to "Refresh, Research and Reform" so that we develop a holistic approach towards enhancing knowledge and skills of the ICOG members and fellows. This **RRR approach** will help them combat the challenges posed by complex clinical scenarios in day to day lives.

The thought process behind having an issue on a topic that includes the combined problems of mother and child health including delivery-period challenges as well as neonatal care issues. Perinatology envisages the entire realm of safe motherhood and healthy neonates. We have carefully handpicked the topics to cover the range of clinical possibilities and although it is not possible to cover each and every topic in a small newsletter – an attempt has definitely been made to provide an insight into the possible broad areas in perinatal care

Working together as a dynamic and cohesive team is the secret to providing holistic Perinatal care and I applaud the issue editor Dr Chinmayee Ratha for her efforts in preparing this issue of the ICOG campus emphasising the crucial role of interdisciplinary co ordination in current Perinatal practice. I hope the readers find this experience refreshing and worthwhile. I look forward to a very eventful year and invite your participation in all our academic activities
Happy Reading

Prof. Laxmi Srikhande
Chairperson - ICOG

Vice Chairperson's Message

Dear Friends,
Warm Greetings!

"Updates in perinatal practice" is a much awaited compendium of articles in Perinatology which itself is a composite science including the clinical aspects of Obstetrics, Fetal Medicine and Neonatology as a continuum of care.

The ICOG campus has always been looked upon as a popular theoretical refresher for challenging clinical topics for its readers and the present issue only attempts to live upto such expectations.

The topics have been selected very carefully along various aspects of perinatal care along with inputs from neonatologists as well which adds an extra dimension over and above our familiar Obstetric perspectives. Interdisciplinary care is evolving as an answer to the everchanging questions and challenges being thrown open by the developments in ObGyn, fetal medicine, neonatology, genetics and metabolomics – all of which have actually redefind contemporary perinatal care.

Hence I hope our audience finds this edition of the ICOG campus a very interesting reading experience. I congratulate ICOG chairperson Dr Laxmi Shrikhande for conceptualising the publication and Dr Chinmayee Ratha for perfect execution.

Dr. Parag Biniwale
Vice Chairperson - ICOG

Secretary's Message

Dear Friends,
Namaskar

It has been the aim of the ICOG to keep improving the status of women's health care in our country and we will continue to work in that direction.

I am happy that this edition of the ICOG Campus is concentrating on the Perinatal Practice updates. Perinatology is a very vital area of mother and child health and perinatal parameters are important indicators of a nation's health care status. As in every field of medicine, there are rapid strides in development happening in perinatology as well and hence a "Campus" addressing all these will be very useful to all clinicians. I am happy to see articles ranging from antenatal challenges to neonatal problems being addressed in this issue.

I congratulate Dr Chinmayee Ratha and her team along with all contributors for bring out the "Campus".

I wish the readers a great learning experience.

Happy Reading!

Dr. Ashok Kumar
Secretary - ICOG

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FROM the EDITOR's Desk

Dear Friends,
Warm Greetings!

At the outset I thank the chairperson ICOG Dr Laxmi Srikhande madam for this splendid opportunity of putting together an issue of the ICOG Campus on Updates in Perinatal practice. I particularly thank Dr AshokKumar, the dynamic secretary of ICOG for his constant support and solutions to our multiple querieswhich has helped bring this issue out in time, and Dr Parag Biniwale, Vice-chair ICOG who has been a guiding light through all our endeavours.

The journey of a fetus into the real world is one of the most arduous journeys filled with perils at every stage. However it has been well established that many pregnancy complications manifest in late pregnancy and approximately 0.3 to 0.4 percent of patients experience de novo severe maternal morbidity (SMM) after discharge, and this accounts for approximately 15 percent of SMM but almost two-thirds of the maternal deaths tend to occur in the postnatal period.

More than two-thirds of newborn deaths occur within the first week after birth, most occur in the first 24 hours of birth and both Obstetricians and Neonatologists need to be not only alert about this fact but also aware of various risk factors and prophylactic measures.

The emerging paradigm of inter disciplinary care in the perinatal period is extremely useful in ensuring healthy mothers and safe childbirths not only in preventing obstetric morbidity but more importantly ensuring "intact survival" and a power to overcome congenital problems.

In this issue of updates in perinatal practice we start with an insightful article that addresses the role of Fetalmedicine in Obstetrics . This highlights the importance of the fetal unit that eventually becomes an important determinant in "perinatal health" redefining the traditional Obstetric care to address the two different entities of the mother and the fetus as separate patients. We have articles on persistent clinical challenges like chorioamnionitis and the updates on techniques like fetal neuroprotection with magnesium sulfate which help improving perinatal outcomes.

Improving newborn outcomes by simulation training in neonatal resuscitation is a progressive step towards enhancing perinatal care and in this issue we have a special article on improving such training with futuristic concepts. In this era of new -age diagnosis screening in the neonatal period with metabolomics supported by genomics can go a long way in identifying the burden of genetic and metabolic diseases.

This changing paradigm in Perinatology has been highlighted in this issue of the ICOG Campus in sync with the President FOGSI Dr Hrishikesh Pai's philosophy of **"Badlaav"** – a positive change. The importance of the first 1000 days of human life is already established and with a proper outlook this crucial period can be converted into an avenue for better perinatal health – the pathway to that is "perinatal preparedness" !!

Happy reading.

Dr Chinmayee Ratha
Issue Editor

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Impact of Fetal Medicine on Obstetrics

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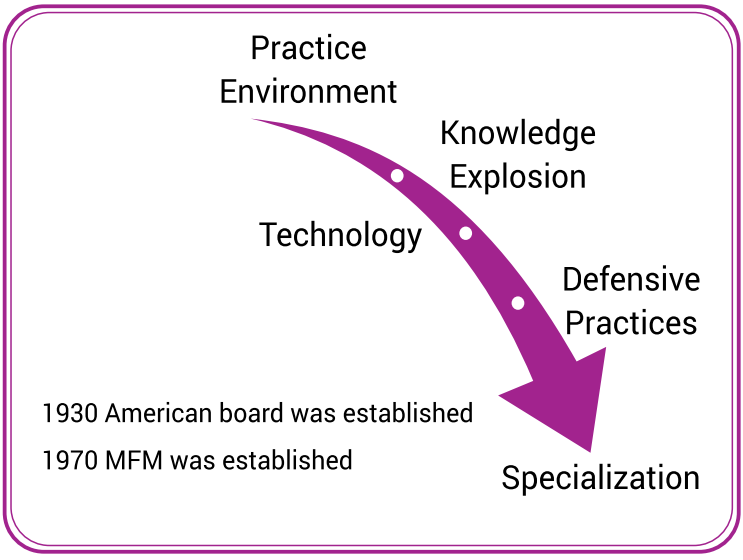
Obstetrics is that branch of medicine that deals with the care of women during pregnancy, childbirth and the recuperative period following delivery. Over the years the specialty has evolved from one where there were some observations and few procedures in labour to organised antenatal care which was developed to reduce maternal mortality. Initially all we could do was listen to the fetal heart but with the advent of ultrasound, we started to see the fetus. Over the past two decades, the major improvements in technology have made it possible not only to see but to evaluate, investigate and provide comprehensive care for the fetus. With these advances a sub specialty of OB/GYN called fetal medicine got established. Fetal medicine became that branch of medicine that deals with growth, development, care and treatment of the fetus and with environmental factors that might harm the fetus.

As fetal medicine expanded, the pregnant woman shifted, from one of prime focus. to a means of access to the fetus. Fetal medicine is a unique specialty where there is no direct access to the patient. The access is always through the mother and so sometimes there can be situations where the best interest of the mother and the foetus are in conflict. This also brings us to the issue of consent as the consent for testing and treating the “patient” is given by the parent. This is likely to become more relevant as complex foetal surgery and novel genetic therapy become more accessible.

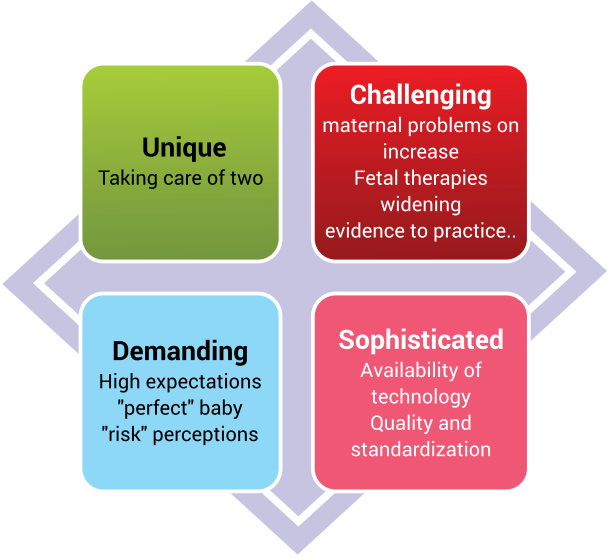
The obstetrician has the unique task of taking care of two people. Obstetrics is challenging as maternal problems are on the increase and fetal therapies are widening. It is a demanding specialty because there is high expectations from couples for the perfect baby. It is demanding also because of varying perceptions of risk which need to be communicated in. With the increasing availability of technology there is also the need to understand quality and standardisation of these sophisticated tests and treatment options. The advances in fetal medicine certainly impact

obstetric practice and the obstetrician needs to stay abreast and informed of current screening diagnostic and treatment possibilities to offer these where appropriate.

Fig 1 Practice environment changes over time



Where does that leave the OB?



The first area of impact of fetal medicine on obstetric practice is in fetal abnormalities. There has been a definite reduction in perinatal mortality and morbidity with the use of obstetric ultrasound. The detection rates are going up and there is earlier pick up of these up abnormalities as well. Here again it is important to emphasise that there is a difference between the pickup of an abnormality by doing an ultrasound and the interpretation and complete diagnosis of an ultrasound abnormality by fetal medicine specialist. For example, someone doing obstetric ultrasound could pick up a cyst in the posterior fossa and a cleft lip. However, the fetal medicine specialist would put it together and make a diagnosis of Palistair Hall Syndrome and counsel on the prognosis recurrence et cetera. With each anomaly detected, it is important to explain the scope of the problem, offer additional testing, gather appropriate opinions and help facilitate informed choice by the patient. This requires effective communication between the fetal medicine specialist and the obstetrician.

Sometimes the diagnosis and the path of counselling is not very clear. Here the dilemma of how much information to give to the patient, how much reassurance to offer and when follow up should be done can be more complex. This typically happens in scenarios such as borderline ventriculomegaly or an evolving anomaly where one cannot give complete reassurance. With increasing ability to image the foetus there are sometimes findings noted in the first trimester or early target scan, the significance of which is uncertain. Often the obstetrician may not completely clued in on the appropriate way to counsel the patient. In such situations if mixed messages are given the pregnancy is easily converted to a high anxiety state and sometimes inappropriate decision pregnancy termination is taken. It is therefore very important that there is a ongoing dialogue and communication between the obstetrician and the fetal medicine consultant

The second area of significant impact has been in the identification of fetal growth problems and reduction of stillbirth. The importance of dating pregnancy accurately and the ability to plot fetal growth on charts has helped us significantly in identifying both the growth restricted and my macrosomic fetus. Role of ultrasound and doppler is crucial to monitor growth restricted foetuses, identify those with hyperoxia and Time delivery before acidosis and neuronal injury set in. Our understanding of late Fetal growth restriction and timing of delivery to prevent late stillbirths has increased in the last few years. The

obstetrician needs to keep pace with changing under standing in this important area and build ability to monitor in keeping with advances in order to improve perinatal outcomes. While we are good at identifying the small baby, we are not that good at identifying the macrosomic fetus. In both situations, there is impact beyond immediate neonatal period which needs to be understood and follow up is important.

The third area of impact is in the way triage and risk stratification is now possible in the first trimester at the time of the 11 to 14 weeks scan. Here again it is important that the quality of the screening process is driven by the obstetrician understanding different principles of screening. If disjointed screening is done in centers without appropriate certifications and standardised processes, the outcome of the screening process could mean termination of a healthy pregnancy.

This first trimester screening has also helped us significantly address one of the most important causes of maternal mortality which is pre eclampsia. There is good evidence that we need to move from checklist risk stratification to composite risk scoring based on maternal history blood pressure biochemistry and uterine artery doppler. However, in order to realise its full potential and actually save lives, screening needs to be implemented across the country. This demands a scaling up of resources and trained personnel. Again, this is something that needs to be driven by obstetricians because we are the ones who are left struggling to manage the woman who seizes with high blood pressure or bleeds from DIC and severe pre-eclampsia.

There are some areas of fetal therapy where significant advances have been made to improve perinatal outcome. The management of Rhesus disease and complicated twin pregnancies are two such areas. Here The timing of referral makes all the difference to management and again it becomes the obstetrician's responsibility to guide in these situations. In other words even if we do not ourselves know how to handle, we must know when to refer where to refer and enough to give basic correct information to the couple and our care. The treatment done, it is also vital that there is coordinated follow up and good neonatal care to ensure that there is a healthy baby taken home after all the effort.

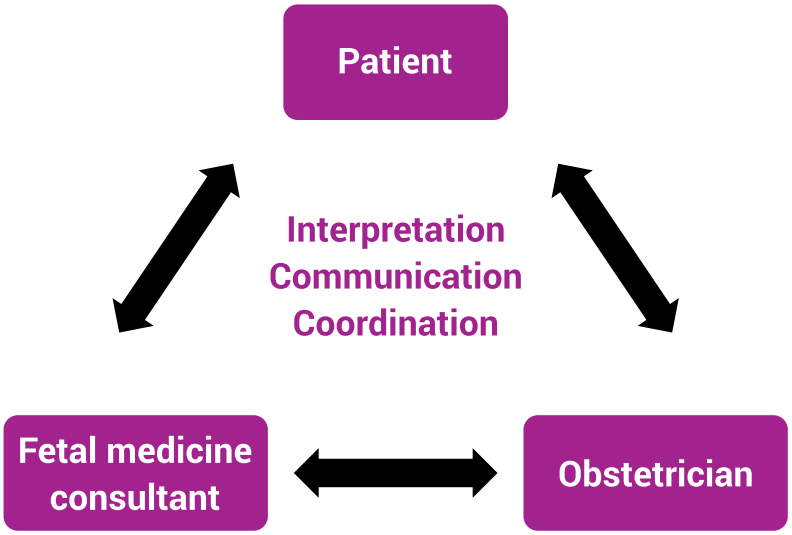
The other area where I feel personally that sub specialties like fetal medicine have impacted obstetrics is in the area of training. Fresh young graduates understandably are attracted to subspecialisation. They

believe that special skills are needed to know how to scan and treat the fetus or how to do laparoscopy surgery, they believe that everyone can deal with obstetrics and you don't have to have special skills to do it.

Any time there is a seizure in a pregnant mom, a maternal collapse, unexpected bleeding or a baby that needs safe lift out, the obstetrician is in the centre of it all. These are complicated and emotionally charged situations and we do need special skills to manage these. While it is important that subspecialities develop, we cannot imagine a world without the obstetrician.

Another impact of FM

In this area of sub-specialisation & advancing technology, we need to keep abreast and develop strong teams with the Subspecialist. Just as the relationship between the mother and the foetus is symbiotic, the relationship between the obstetrician and the fetal medicine specialist is also special and Symbiotic. Strong well informed and communicating teams will enable us to ensure the supervision of the well-being of the mother and the baby, of providing appropriate choices to the couple and helping them make informed choices while respecting their privacy and choice.



"Team work makes the Dream work"

Antenatal administration of magnesium sulphate for fetal neuroprotection: Evidence and recommendations

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Preterm birth (before 37 completed weeks of gestation) is a leading cause of neonatal mortality and morbidity. An estimated 15 million babies are born preterm every year and about 1 million children die each year due to complications of preterm birth [1]. The 10 countries with the greatest number of preterm births are [2]:

i. India: 3 519 100
ii. China: 1 172 300
iii. Nigeria: 773 600
iv. Pakistan: 748 100
v. Indonesia: 675 700
vi. United States of America: 517 400
vii. Bangladesh: 424 100
viii. Philippines: 348 900
ix. Democratic Republic of the Congo: 341 400
x. Brazil: 279 300

Preterm birth before 32 weeks of gestation constitutes 25% of all preterm births and is associated with higher neonatal morbidity and mortality and adverse long-term outcomes for the child [3]. The World Health Organization classifies sub-categories of preterm birth, based on gestational age [4]:

i. Extremely preterm (less than 28 weeks)
ii. Very preterm (28 to 32 weeks)
iii. Moderate to late preterm (32 to 37 weeks)

Progressive improvement in neonatal care over the years leads to better survival of preterm babies, but neurological impairment remains a concern. Cerebral palsy is a leading cause of neurological impairment, with prematurity and low birth weight being its commonest associated

risk factors. Primary prevention of preterm birth by some interventions like smoking cessation, progesterone support and cervical encerclagemay help to avoid or delay preterm birth in some women. But in situations where preterm birth is inevitable, some measures help to improve neonatal outcome like antenatal steroids, antibiotics in preterm pre-labour rupture of membranes and magnesium sulphate to prevent future neurological impairment of the child. Interventions for the newborn baby like thermal care, feeding support, kangaroo mother care, safe oxygen use are also advocated. Cerebral palsy (CP) resultsin permanent disorders of development of movement and posture and is caused by an insult to the fetal or infant brain. The prevalence of CP is 2 to 2.5 per 1000 live births and its risk is highest at earlier gestational ages [5, 6].Compared with infants born at term, infants born preterm have a CP risk that is 3-fold higher at 34 to 36 weeks,8-14 fold higher at 30 to 33 weeks, 46-fold higher at 28 to 30 weeks and 30-80 foldhigher at <28 weeks of gestation [6].

Magnesium Sulphate for fetal neuroprotection

Antenatal administration of magnesium sulphate may reduce the risk of CP and an individual participant data meta-analysis has shown it toreduce the incidence of CP as well as thecombined risk of fetal or infant death, regardless of the reason for preterm birth [7]. Although the effectiveness of magnesium sulphate for prevention and treatment of eclampsia is proven, there is less understanding of its mechanism of neuroprotection. Magnesium acts in many intracellular processes, causes cerebral vasodilation, reduction in inflammatory cytokines and/or oxygen free radicals, and/or inhibition of calcium influx into cells. Various mechanisms have been proposed for the neuro-protective role of magnesium sulphate:

- Non-competitive NMDA (n-methyl-d-aspartate) receptor antagonistto prevent calcium –induced excitatory injury[8]
- Reduces extracellular glutamate under ischaemic conditions which reduces excitatory injury
- Magnesium limits calcium influx through voltage-gated channels, which may reduce the activation of apoptosis
- Anti-inflammatoryaction reduces oxidative stress by reducing production of pro-inflammatory cytokines like interleukin-6 and tumor necrosis factor-α

Indications for giving magnesium sulphate for neuroprotection of fetus and neonate

Women at gestational age from the period of viability (usually taken as 24 weeks of gestation) to 30 weeks [9] or ≤ 31+6 weeks [10] or ≤ 33+6 weeks [6] who are at risk of imminent preterm birth i.e. within the next 24 hours.

- women in active labour (cervical dilatation ≥4cms)
- planned preterm birth for obstetric or maternal indication

The upper limit of gestation for neuroprotection is not well studied. Costantine et al in a meta-analysis have compared the gestation of <32-34 weeks (5235 fetuses) with <30 weeks (3107 fetuses) and found that in utero exposure to magnesium sulfate reduced the outcome of death or cerebral palsy similarly in both gestational age groups [11]. However, the number needed to prevent one case of cerebral palsy in <32-34 weeks group was 56 women whereas in <30 weeks, it was 46 women [11].An ongoing trial (MAGENTA) in which upper cut-off of gestation for magnesium sulphate eligibility between 30 to 34 weeks is being studied; results are awaited [12].

Doseof magnesium sulphate for neuroprotection

Different doseschedules of magnesium sulphate for neuroprotection have been tried in various studies, however the route of administration was intravenous only. A word of caution is to discontinue magnesium sulphate if delivery is not imminent and definitely not give beyond the stipulated duration of 12 or 24 hours or a maximum of 24 hours of therapy.

Dosage schedule of magnesium sulphate foneuroprotection
4 gm IV over 20 minutes followed by 1g /hour until delivery or for 24 hours, whichever comes first [6]
Single dose 4 gm IV over 30 minutes [13]
6 gm IV over 20-30 minutes, followed by infusion of 2 gm/hour for 12 hours [14]

For planned birth
There are no clear differences between the above regimens in neonatal

outcome.The maternal adverse effects are dose dependent, so aloading dose of 4 gm IV and maintenance dose of 1 gm/hour seems to be moreacceptable. There is insufficient evidence to support the role of repeat treatment if patient goes out of the labor [6]. There was no difference in the composite outcome of cerebral palsy or death among re treatment (RR 0.90; 95% CI 0.73-1.1) and no re-treatment group (RR 0.91, 95%CI 0.74-1.13) [10].

Fetal and maternal monitoring during magnesium sulphate infusion

The Pulse, respiratory rate, blood pressure and urine output of the women to be monitored in a similar manner as recommended for women with pre-eclampsia or eclampsia. The fetal heart rate has to be monitored carefully and delivery should never be delayed for magnesium sulphate when urgent delivery is indicated for either maternal or fetal indication. After starting magnesium sulphate for neuroprotection, tocolytics should be discontinued. There is a risk of neuromuscular blockage with concomitant use of magnesium sulphate and nifedipine or other calcium channel but literature failed to demonstrate this except few case reports. That is why; there is no contraindication to use magnesium sulphate when patient is on nifedipine [6].Previously, it was said that the neonatologist should be informed before hand as there is a possibility of altered neurological examination of neonate (hypotonia or apnoea), but new evidence suggests that the need for neonatal resuscitation is not increased [6,15]

Recommendations and literature for antenatal magnesium sulphate therapy for fetal neuroprotection :

Evidence for antenatal magnesium sulphate therapy for neuroprotection has been summarized in :

Table 1. Recommendations of the WHO

Table 2. SOGC are summarized

Table 1: Review of literature about the use of antenatal magnesium suphate for fetal neuroprotection

Name/Year	Year	Number of Cases	Gestation	Conclusion
Levitonet al[16]	1988	272		Preterm infants born to women with pre eclampsia had a lower incidence of adverse CNS outcome (3.1% ,1/32) as compared to babies born to women without pre eclampsia (23%, 55 /240)
Van de Boret al[17]	1987	484	<32 weeks	Infants of mothers with preeclampsia had a significantly lower risk of developing periventricular or intraventricular haemorrhage (PIVH); OR: 0.5; CI: 0.3 -0.9).
Case-control study: California cerebral palsy project[18]	1995	192		Fewer cases of cerebral palsy with antenatal magnesium sulphate
Cochrane review [15]	2008	6145 Five Trials		Antenatal magnesium sulphate given to women at risk of preterm birth substantially reduced the risk of cerebral palsy in their child (RR: 0.68; 95% CI 0.54 to 0.87). Significant reduction in rate of substantial gross motor dysfunction (RR 0.61; 95% CI 0.44 to 0.85; four trials; 5980 infants). No statistically significant effect on paediatric mortality (RR 1.04; 95% CI 0.92 to 1.17; five trials; 6145 infants), or on other neurological impairments or disabilities in first few years of life The neuroprotective role for antenatal magnesium sulphate therapy given to women at risk of preterm birth for the preterm fetus is now established.

				The number of women needed to be treated to benefit one baby by avoiding cerebral palsy is 63 (95% confidence interval 43 to 155).
RCT MASP Trial (Magnesium suphate for pre term birth) 2011-2019 [19][20]	2020	680	<32 weeks	The children were followed up at a corrected age of 18 months or older with a review of their medical charts and with the Ages and Stages Questionnaire. The crude rates of moderate to severe cerebral palsy in the $MgSO_4$ group and the placebo group were 2.0% and 3.3%, respectively. The adjusted odds of moderate to severe cerebral palsy were lower in the $MgSO_4$ group than in the placebo group (odds ratio 0.61; 95% CI 0.23-1.65).
Meta-analysis & trial sequential analysis [21]	2020	5917 (Six Trials)	<32 weeks	MgSO4intervention in women at imminent risk for preterm birth decreased the offspring's cerebral palsy risk (meta-analysis RR 0.68, 95% Ci0. 54-0.85; TSA RR 0.69, 95% CI 0.48–0.97)
Ongoing Trials (Results awaited)				
MAGENTA trail [12]	Determining the upper cut off for the gestation age for neuroprotection			

Table 2:Recommendations on the use of antenatal magnesium sulphate to reduce cerebral palsy in the neonates of women with imminent preterm birth

	2015 (WHO) [10]	2019 (SOGC) [6]
Gestational age	Imminent pre term birth before 32 weeks	Imminent pre term birth up to 33 +6 weeks
Dose	Insufficient evidence to recommend one specific dosing regimen: 4 gm IV followed by 1 gm per hour maintenance dose	4 gram intra venous loading dose, over 30 minute with or without 1 gram per hour maintenance infusion until birth

	OR 6 gm IV followed by 2 gm per hour maintenance dose OR 4 gm IV single dose	
Maximum duration	24 hours or until delivery	24 hours or until delivery
Type of gestation	Singleton or multiple gestation	Singleton or multiple gestation

Conclusion

The available literature and a recent metanalysis with a trial sequential analysis have provided a conclusive evidencethat theantenatal magnesium suphate decreases the risk of cerebral palsy in the neonates of women with imminent preterm birth from the period of viability (usually taken as 24 weeks of gestation) to≤ 31+6 weeks [10] or ≤ 33+6 weeks of gestation [6, 21]. The Royal College of Obstetricians and Gynaecologists (RCOG) and the American College of Obstetricians and Gynecologists (ACOG) also support the use of magnesium suphate for neuroprotection [22, 23]. There is lack of international consensus regarding the upper range of gestational age for neuroprotection as the frequency of cerebral palsy is lesser with increasing gestational age. The results of ongoing MAGENTA trial will add more information to this aspect [12].

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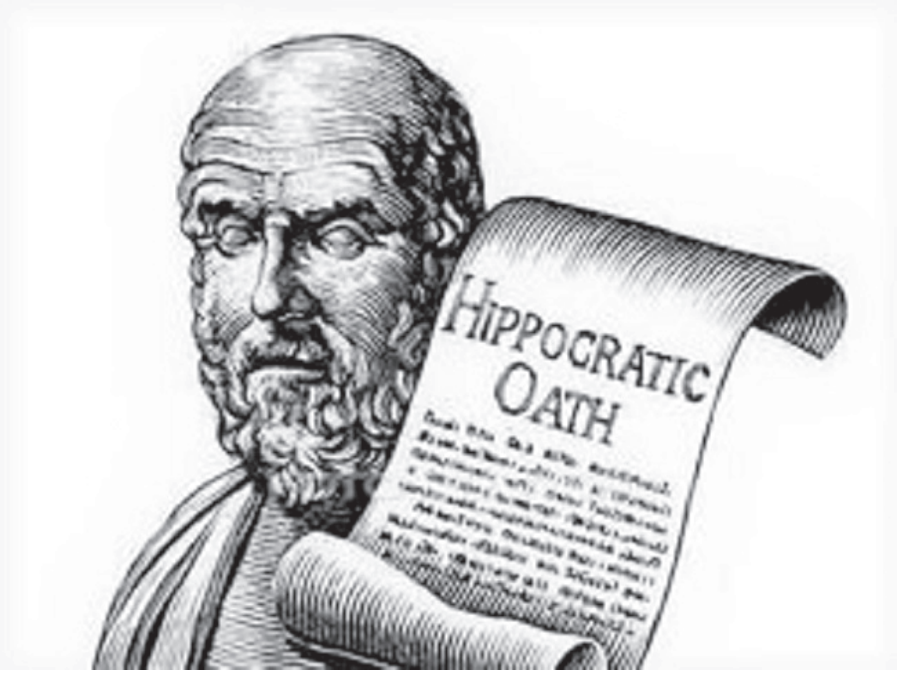

Chorioamnionitis

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Chorioamnionitis in clinical practice has been extensively used to signify infection or inflammation of the of the membranes and placenta which can negatively affect health of the mother and the fetus/neonate by causing morbidity and rarely mortality. Long term neuro developmental delay may also be seen in many children. For the purpose of clinical management a new term " Triple I – Intrauterine infection and/or inflammation" has been proposed by the national institute of child health and human development expert panel and ACOG (1) and the term chorioamnionitis is reserved for pathological purposes.

It occurs in 1- 5% of term pregnancies(2) and in preterm deliveries the frequency of clinical and subclinical is approximately 25% (3).
The principal pathogens are E coli, anaerobic gram positive cocci; GBS and genital mycoplasma amongst others.

Adequate diagnosis and management of Chorioamnionitis is important as it induces delivery by triggering maternal inflammatory response (4,5) apart from increasing the risk of infection and rarely sepsis both in the mother and neonate. Bacterial infection induces uterine contractions via the medium of endotoxins and exotoxins leading to prostaglandin release, injury to membranes and ripening of cervix. Hence timely intervention to predict and prevent and manage it is important. It may present with clinical signs and laboratory evidence but the majority of time the infection is subclinical. (1, 4, 5-7).Because of the mother's immune response, incidence of confirmed Chorioamnionits is less than for histologic evidence of the same.

For the diagnosis of clinical Chorioamnionitis, there should be evidence of maternal fever, leucocytosis and maternal – fetal tachycardia with uterine tenderness and foul vaginal discharge. The subclinical infection is not accompanied by fever and is defined by inflammation of chorion

hence routine use of antibiotics is to be discouraged according to some authors if apart from fever no other features are seen. But once Chorioamnionitis is confirmed CDC recommends antibiotic coverage to reduce both maternal, fetal and neonatal complications (1)

REFER to algorithm changed here

COMPLICATIONS – maternal complications include increased risk of Caesarean section, endomyometritis, wound infection, pelvic abscess and PPH(13).

Fetal and neonatal complications – Fetal exposure to infection may lead to fetal death, neonatal sepsis. The fetal response to infection FIRS aggravates the complications. (14) .The neonatal outcome in turn is also adversely affected due to risk of Bronchopulmonary dysplasia, Necrotising Enterocolitis, Interventricular hemorrhage, PDA, and Neonatal sepsis (15).

MANAGEMENT – Chorioamnionitis is an acute condition needing proactive treatment and management because both mother and fetus may be severely affected and complications may set in(2).

AS Obstetricians if there is evidence of frank rupture of membranes (ROM) it is better to start antibiotic coverage, because the clinical signs and _laboratory data used to diagnose chorioamnionitis have poor predictive value and may appear or be actually absent.(16-18) Caesarean section is only advised for obstetric indication and time to delivery under antibiotic coverage does not affect morbidity.

GUIDELINES for ANTIBIOTICS

Once maternal chorioamnionitis is diagnosed, CDC recommends full sepsis workup and introduction of antibiotics for wellbeing of both mother and fetus (19). Evidence form RCTs has also shown that immediate broad spectrum antibiotic coverage reduces maternal and fetal complications.

IV Ampicillin 6 hourly, gentamicin 8 – 24 hourly till delivery occurs is the typical regime and Clindamycin and Metronidazole may be added if Caesarean is performed for anaerobic coverage; caesarean is performed only for obstetric indications.

MATERNAL MANAGEMENT – Counselling of both the mother and her family is very important in any scenario as it better for clinical management and from medicolegal perspective too; Specially when the fetus /neonate is away from term. The perinatal outcome of neonate is inversely proportional to the gestational age at which delivery occurs or has to be expedited if there is evidence of confirmed chorioamnionitis. The NICU and Neonatologist have to be informed well in advance and team counselling of the family by the Obstetrician and Neonatologist should be done.

- **START** antibiotics and supportive treatment with fluids, antipyretics. This is particularly important as fetal acidosis in the setting of fever increases incidence of neonatal encephalopathy (20). Antipyretics also reduce fetal tachycardia thereby reducing tendency of Caesarean for non reassuring fetal status.(14)

- **ADMISSION AND TRANSFER TO UNIT WITH NICU** – At whatever gestational age delivery occurs, it is better to shift the baby to NICU to watch out for neonatal sepsis.

- **WHETHER EXPECTANT MANAGEMENT OR TO EXPEDITE DELIVERY** – In confirmed "Triple I" if delivery is not imminent it is best to facilitate early delivery under antibiotic coverage . From maternal perspective vaginal route is preferred. From Neonatal outlook it is better that baby delivers by Caesarean section. But Caesarean is only done obviously for Obstetric indications. In mothers with only maternal fever & suspected "Triple I", decision of MgSO4 & tocolysis and encirclage may have to be taken.

- **STEROIDS** – Dexamethasone is preferred.

- **MgSO4** – In extreme preterm scenario, Neuroprotection provided by Magnesium sulphate is invaluable(21)

- **CONCLUSION** – "Prevention is the best cure" , this adage lends itself to the present scenario of Chorioamnionitis or "Triple I". Majority of the times, PROM near or away from term has a cause and effect relation with Chorioamnionitis and viceversa. Management of PROM hence also becomes very crucial for us and all other causes of Intrauterine inflammation and or Infection should be looked into and managed

and amnion and vice versa. Sometimes isolated maternal fever may be there without other signs of infection. At the same time, maternal signs may not always be present and evidence of inflammation or infection may not always accompany one another(1). Due to the low specificity of symptoms , other causes of fever and symptoms if any should always be ruled out(8) .

Subclinical chorioamnionitis is asymptomatic and is defined by inflammation of the membranes and plaecenta which is more common than clinical chorioamnionitis (4,5). Amniotic fluid culture has been recommended by some studies to prove infection of the membranes to confirm diagnosis of chorioamnionitis . Many studies have shown higher positive culture of amniotic fluid in women at early gestational age(9) and high levels of IL – 6 in cord blood in preterm compared with term newborns born after amniotic cavity invasion by microbes (10). But amniocentesis for amniotic fluid culture is still not recommended routinely and remains for research and study purposes.

RISK FACTORS FOR CHORIOAMNIONITIS – (2)

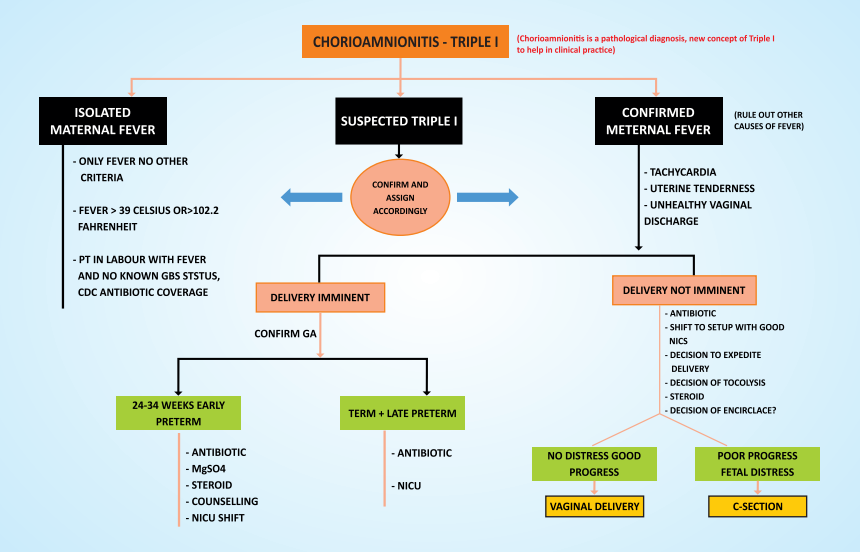
- Rupture of membranes – If prolonged ROM in any situation persists for more than 24 hours and it can increase the risk of neonatal infection (sepsis) because of chorioamnionitis.
- Prolonged labour
- Nulliparity
- Multiple vaginal examination
- Immunocompromised patients
- Pre-existing genital tract infection

Microorganisms causing chorioamnionitis – it is mostly polymicrobial infection and over 65% of positive amniotic fluid cultures involve two or more organisms, common among these are Ureaplasma and Mycoplasma (11,12).

DIAGNOSIS – CHORIOAMNIONITIS / TRIPLE I

Clinically if the mother has fever (>39 degree Celsius or >102.2 Fahrenheit), tachycardia (>100/min for mother &>160/min for fetus), leucocytosis (>15,000), uterine tenderness and there is foul smelling vaginal discharge it is taken as evidence of Chorioamnionitis . For research purposes confirmation by amniotic fluid culture can be done (under study) . But maternal fever may be due to other causes too and

aggressively. To prevent both maternal and fetal/neonatal morbidity which leads to long term clinical complications it is important that we be proactive and follow protocols while managing such patients and form good team with Neonatologist to provide best results .



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Teaching New-born Resuscitation Using Simulation

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Introduction:

It is estimated that 10% of new-borns need some intervention in the delivery room to establish spontaneous respirations and approximately 1% need more extensive resuscitations. In Indiatwenty percent of neonatal deaths are due to birth asphyxia. Therefore, it is essential that all the health care providers who attend deliveries should be trained in neonatal resuscitation. AAP's (American Academy of Paediatrics) Neonatal Resuscitation Programme(NRP) is widely taught in India. However, many health care providers who care for new-borns are not trained in formal NRP. It is also shown that there are deficiencies in psychomotor skills as well as lack of adherence to the recommended NRP flow diagram steps in actual resuscitations even among those who were trained in formal NRP.The gap between the expected standards and the practice can be minimised by regular rehearsals of simulated scenarios of resuscitation.

Why Simulation is the right tool to teach Neonatal Resuscitation?

Health care providers attending deliveries can feel very stressful when new-borns require more than routine care. The care teams must know the proper steps of neonatal resuscitation, be able to perform the technical procedures, and work effectively as a team. Simulated exercises provide the safe learning environment for the learners to improve their skills and team behaviour. Therefore, simulation is an ideal educational methodology to teach neonatal resuscitation. Very rightly, NRP has officially added simulation into its courses in 2010.

What is the Evidence ?

A metanalysis by Mileder et al revealed thatsimulation-based neonatal and infant resuscitation teaching can improve cognitive, technical and behavioural skills of the learners during neonatal resuscitation. A study from India showed that simulation training had a positive impact on the quality of key skills in simulated and live resuscitations. Simulation can help refine team responsibilities, and identify latent safety threats. Multidisciplinary crisis resource management training may result in a significant decrease in clinical error rate. By reducing the incidence of medical errors and potentially improving patient safety, teamwork and communication training might ultimately be one of the greatest benefits of simulation based teaching of neonatal resuscitation. However there arelack of studies focussing on patient outcomes.

How to teach ?

The learning objectives to teach neonatal resuscitation include clinical knowledge, psychomotor skills and behavioural skills.

Clinical knowledge – Teaching clinical knowledge can be achieved by short interactive lectures, recorded sessions or providing standard guidelines neonatal resuscitation to the learners. One may also consider designing electronic interactive modules to improve learners' knowledge. Displaying charts of NRP algorithm near the resuscitator aids to remind the learners the key steps of resuscitation. Providing study material in local languages with pictorial description can further e.g. flow charts used in Helping Babies Breath training program.

NRP Algorithm Chart near Resuscitation Area

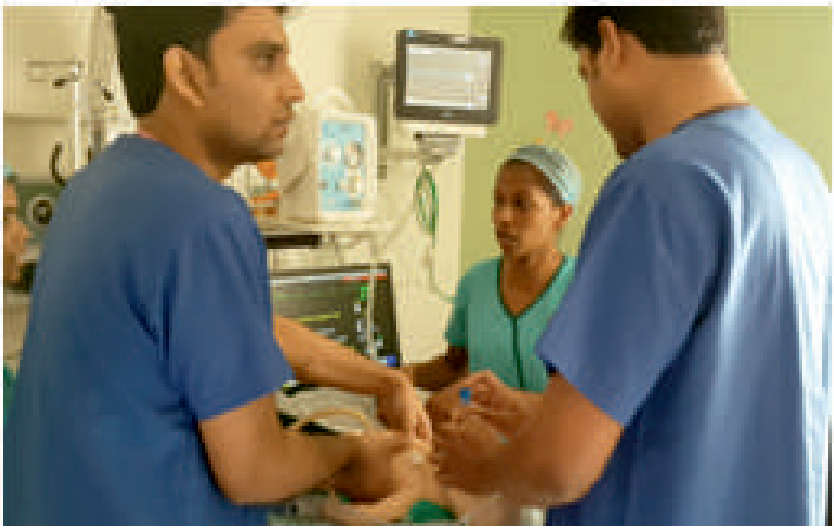
Improving Practical Skills –The key practical skills in neonatal resuscitation are opening the airway, positive pressure ventilation and chest compression.

One way to teach practical skills is Rapid Cycle Deliberate Practice (RCDP). The facilitator stop the participants at any time when error occurs to correct it. The session is paused and restarted several times until the participants learn the skill. RCDP allow the learners multiple opportunities to "do it right", applying the concepts of over learning and automatization, creating muscle memory for the "right way.

Teaching Practical Skill of Bag and Mask Ventilation using Rapid Cycle Deliberate Practice (RCDP)

However, once the learner has demonstrated these cognitive and psychomotor skills, it is key that they also learn to function effectively within a team during a resuscitation.

Team Workand Behavioural Skills – Full immersion simulation scenarios are used to teach team work and behavioural skills. Behavioural skills training have been correlated with improved NRP compliance and overall quality of care in the delivery room.



Full Immersion Simulation Scenario of Neonatal Resuscitation

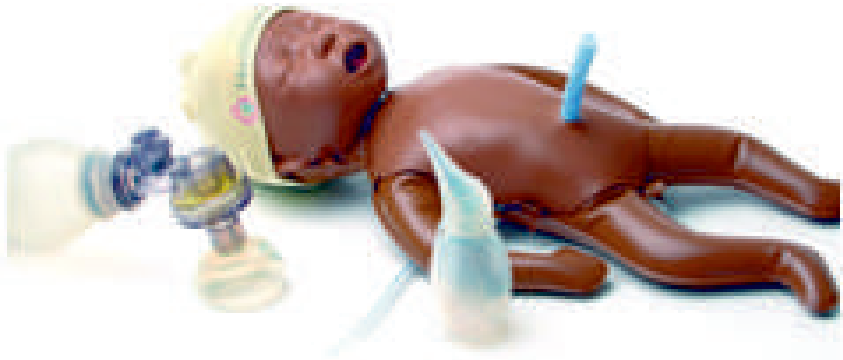
Where to teach ?

Full immersion scenarios can be done in the same clinical area e.g labour ward and obstetric operating theatre, or education centre or dedicated simulation centre. The advantages of the doing in-situ simulation, in the same clinical area where the clinical teams work are, it can improve the environmental fidelity and it can also identify any system issues i.e. latent safety threats. Disadvantages of in-situ simulation are – it can affect the routine clinical care. Some of the simulation equipment can be used in the real situations by mistake, therefore it is important to label all the simulation equipment and drugs clearly stating that they are for simulation use only.

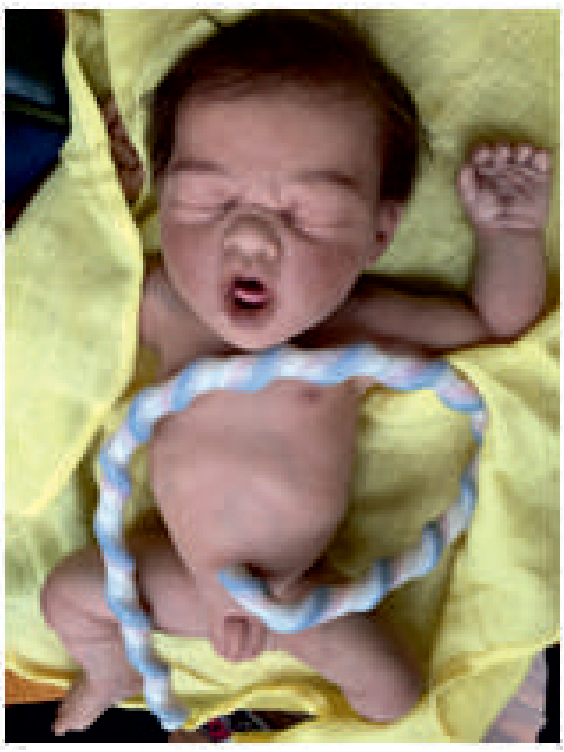
Which mannequins to use ?

The low technology mannequins or task trainers are sufficient to teach the psychomotor skills e.g.Intubation head; to teach emergency UVC, one may use real umbilical cords collected from the labour ward. For full immersion scenarios high technology mannequins add to the fidelity, however they are expensive. High technology mannequins are not compulsory. One can improve the fidelity with other means like using a monitor screen and real time equipment etc. A high-technology simulator

is likely to be of added benefit when used in a thoughtful manner alongside the other aspects of effective simulation as noted previously, but is not essential.



Low Technology Newborn Mannequin



MediumTechnology Newborn Mannequin

Conclusion:

The gap between the expected standards and the practice in neonatal resuscitation can be minimised by regular rehearsals of simulated scenarios of resuscitation. Therefore, simulation basedteaching seems to be ideal methodology to teach neonatal resuscitation. It showed to improve cognitive, technical and behavioural skills of the learners during neonatal resuscitation.

Further Reading:

- Vail et al. The power of practice: simulation training improving the quality of neonatal resuscitation skills in Bihar, India, BMC Pediatrics (2018) 18:291

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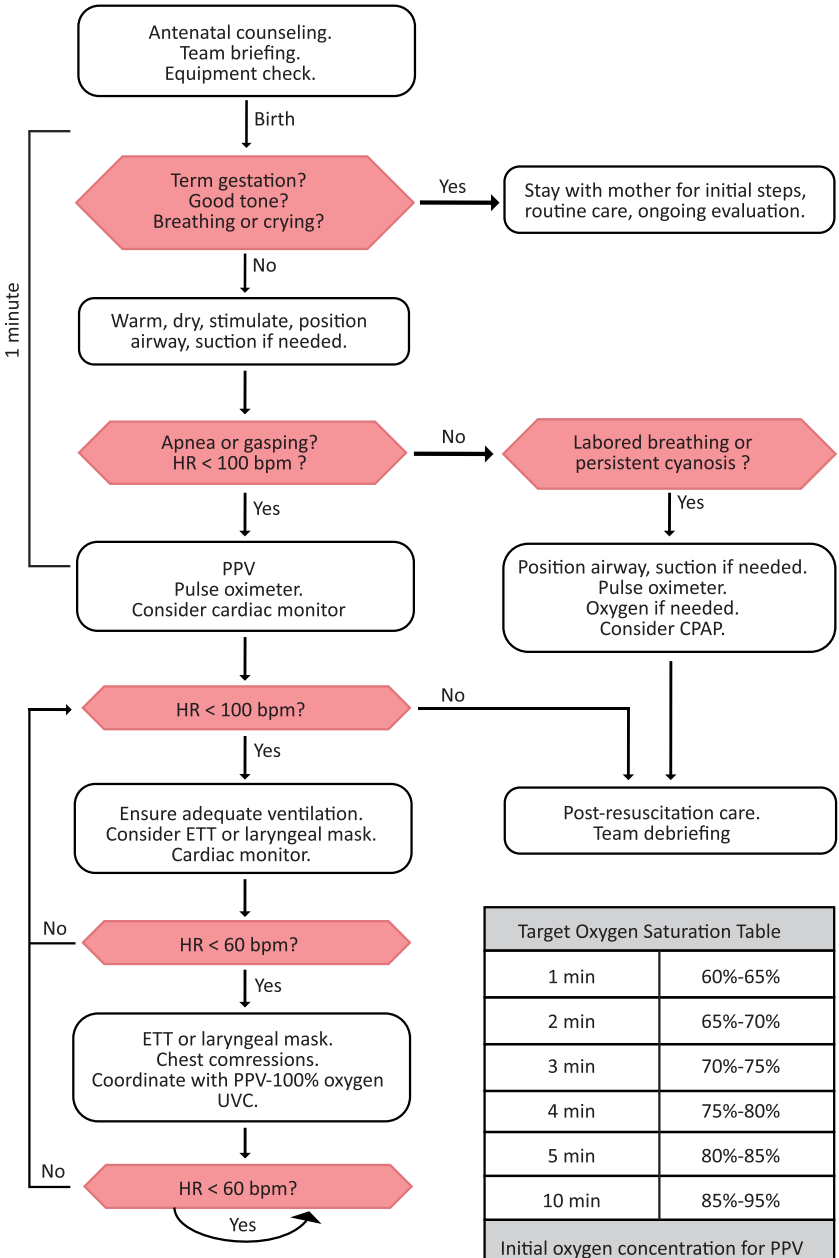
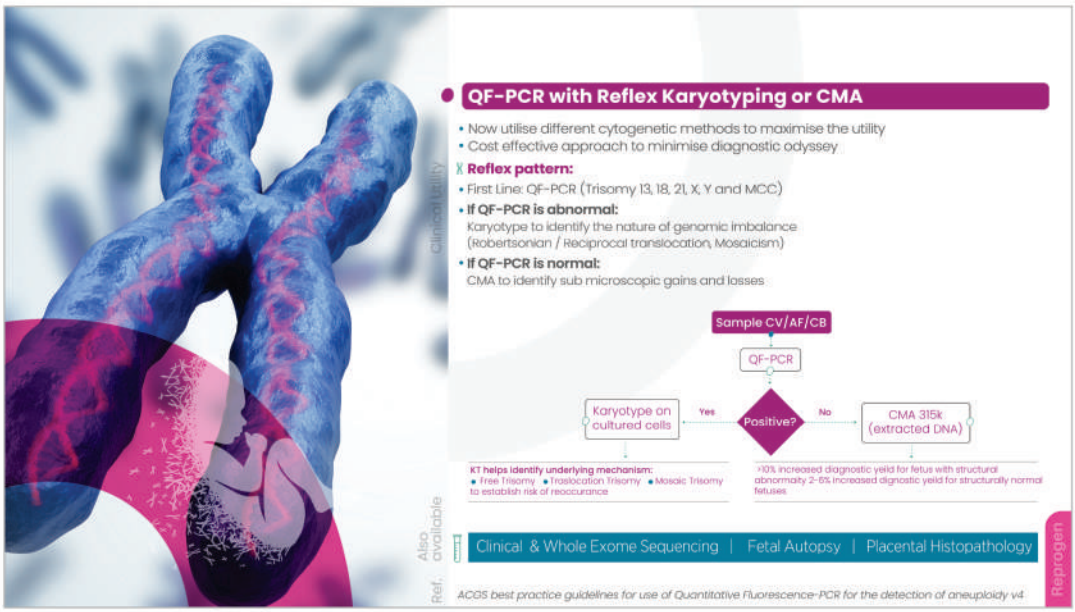
Neonatal Resuscitation program®8th Edition Algorithm



Target Oxygen Saturation Table	
1 min	60%-65%
2 min	65%-70%
3 min	70%-75%
4 min	75%-80%
5 min	80%-85%
10 min	85%-95%
Initial oxygen concentration for PPV	
> 35 weeks GA	21% oxygen
< 35 weeks GA	21%-30% oxygen

QFPCR with Reflex Karyotyping or Chromosomal Microarray (CMA)

QFPCR performed for aneuploidy of chromosomes X, Y, 13, 18, and 21 along with MCC as the first line test. If QFPCR results are normal, sample will be reflexed to genomic chromosomal microarray. If QFPCR results are abnormal, sample will be reflexed to chromosome analysis by Karyotype.



Comprehensive Newborn Screening An Emerging-Paradigm in Perinatal Care

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Introduction:

Newborn Screening (NBS)is a set of laboratory evaluation used to screen newborns for genetic and metabolic disorders within 42 to 78 hours of birth. Early detection of these conditions enables interventions to be provided very early in the life of a newborn when they can make a significant impact on health outcomes and even help to prevent severe, irreversible disability to start a healthy life.Newborn Screening (NBS) is a government-run healthcare programme that was created with the goal of achieving cost-effective early diagnosis of treatable disorders, where timely intervention is critical to improving long-term outcomes [1]. NBS programme not only screen the neonates but the process involves parental education, appropriate follow up after diagnostic screening, disease management and if required, continued evaluation [2].

History:

Newborn screening beganwhen scientist Dr. Robert Guthrie developed a blood test based on bacterial inhibition assay that could detect the metabolic condition, phenylketonuria (PKU) shortly after birth [3]. Pilot studies were then conducted to identify pre-symptomatic newborns with PKU. Soon after the success of PKUidentification in newborns, assays were developed to screen for other inborn metabolic errors, such as maple syrup urine disease and homocystinuria. Over the following years, enzymatic activity assay was developed to screen for galactosemia [4],

biotinidase deficiency and radioimmunoassay to screen for congenital hypothyroidism [5], and congenital adrenal hyperplasia.In 1990s, with the introduction of Tandem mass spectroscopy, revolutionary development occurred in NBS as the technique allowed the simultaneous measurement of multiple analytes in an NBS bloodspot [6]. This has ultimately resulted in reduction of cost and turnaround time for testing allowing NBS to be expanded to the format that is now used in many countries.

The Wilson and Jungner Principles

In response to the growing interest in expanding NBS, the World Health Organization (WHO) sponsored a meeting in 1968, which resulted in the publication of the Wilson and Jungner guidelines[7].This set of guidelines proposed ten principles to guide the development and implementation of a screening test and provided basis for the development of future NBS programme.
WHO Wilson–Jungner criteria for appraising the validity of a screening programme[8]

Knowledge of the disease

- The condition must be a significant health issue
- There must be a distinguishable latent or early symptomatic stage.
- ·The natural history of the condition, including its progression from latent to declared disease, must be thoroughly understood.

Knowledge of the test

- A suitable test or examination should be available.
- The population should accept the test.
- Case finding should be a continuous process rather than a one-time event.

Treatment for the disease

- There should be an accepted treatment for patients with recognised disease.
- Diagnostic and treatment facilities should be available
- There should be an agreed policy concerning whom to treat as patients

Cost considerations

- Costs of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole

Challenges in conventional NBS:

Conventional NBS primarily detects levels of amino acids, acyl carnitines, and biochemical markers that indicate congenital disorders. However it is associated with certain limitations [9].

- Conventional NBS screens for only few common congenital disorders.
- The majority of the newborn screening panelsare based on biochemical testing where metabolites or enzymatic activities are evaluated. These parameters are often influenced by multiple factors leading to false positive screening.
- Some disorders do not manifest evident symptoms during the regular NBS time window (e.g. hearing loss) or the existing screening methods/ biomarkers are not sufficiently sensitive and specific (e.g. urea cycle defects); therefore, these disorders could not be detected readily by conventional NBS methods.
- A positive NBS screening requires genetic confirmation, which increases the cost burden.

Next Generation Sequencing (NGS) in NBS

With the advancement in the technology the cost of genome sequencing is rapidly decreasing. Disease diagnosis at the genetic level could be a great supplemental technology for conventional screening, especially for the disorders which do not result in significant alterations of the metabolitesor the disorders for which biochemical markers are not available such as severe combined immune deficiency (SCID), spinal muscular atrophy (SMA) and congenital hearing loss.

Today, NGS is used as a first-tier diagnostic test for detecting genetic variants in critically ill neonates or neonates in the NICU suspected of having an inborn metabolic disorders (IMDs). Recent studies revealed that the application of NGS for confirmation of diagnosed IMDs has significantly reduced the number of false positive cases [10].Additionally, for some disorders the different genetic variants are associated with mild to severe phenotypes therefore in such cases genetic level information will be beneficial for the management. Introduction of NGS in NBS not only helps in the early identification of the condition before its onset and its management but also gives insights into whether the baby is a carrier for the condition which can be valuable information in the long term.

Two approaches can be used for a comprehensive NBS using NGS (i) Whole Exome Sequencing (WES), (ii) targeted gene sequencing. WES targets entire exonic region of the DNA. Although, this approach has the potential to analyze large number of disorders (both treatable and untreatable), it is also associated with certain limitations as WES is not only expensive but also creates unnecessary negative emotions and anxiety in parents. This approach also deviates from the core goals of NBS programs. Whereas in targeted gene sequencing, WHO Wilson–Jungner criteria can be used for panel designing and therefore can be used for mass screening.

Targeted Newborn Genetic Screening Panel:

Considering the advantages of gene sequencing in NBS, we at GreenarrayGenomic Research and Solutions have developed a custom NGS-based short newborn genetic screening panel to screen the most prevalent congenital genetic disorders. This panel is designed to screen 47 genes associated with 35 congenital disorders for which treatment is possible. The Indian academy of pediatrics criteria was used for the selection of disorders to be screened. We screened a total of 300 newborn

samples, 157 females and 143 males. Pathogenic variants were detected in 101 of the samples. Out of the 86 carriers, 11 were homozygous and 4 were hemizygous 167 samples tested negative for NBS since no pathogenic variants were identified. VOUS variants were identified in 32 samples. We have also analyzed the common variants in Indian cohorts. 12 common benign and common pathogenic variants were identified, with MTHFR c.1286A>C and BTD c.1270G>C being the most common benign and pathogenic variants respectively.

The cases presented below will demonstrate how the comprehensive new born genetic approach aidedperinatal care.

Case 1

A healthy baby was born to a normal, non-consanguineous couple with no known genetic history. The couple opted for newborn genetic screening for their baby as a routine screening. Newborn Genetic screening revealed a pathogenic homozygous mutation in the GJB2 gene (W24X, c.71 G>A). This gene provides instructions for making a protein called gap junction beta 2, more commonly known as connexin 26. This protein is found in the cells throughout the body, including the inner ear. Because of its presence in the inner ear, especially in the snail-shaped structure called the cochlea, this is an important gene associated with non-syndromic hearing loss. The c.71G>A (p. W24X) mutation in GJB2 gene is a nonsense mutation consisting of a G-to-A transition at position 71, resulting in a trp24-to-ter substitution (24 amino acids instead of 226 amino acid). This mutation is associated with autosomal recessive non-syndromic sensorineural hearing loss.

Clinical management for hearing loss was immediately started (before the age of 6 months) which has been shown to improve auditory development, expressive and receptive language outcomes, and quality of life.

Case 2

A healthy baby was born to a normal, non-consanguineous couple; with an elder sibling with 2 episodes of seizures (after 1yr) and mild developmental delay. So, the couple opted for newborn screening for the second newborn baby. Newborn Genetic Screening detected a homozygous pathogenic variant in ACADM gene (c.130C>T, Gln44Ter)

associated with reduced activity of medium-chain acyl-CoA dehydrogenase (MCAD). This condition can have a disease onset within 1 to 3 years of age and shows varying penetrance. Therefore the condition might get missed in conventional NBS window frame. If not detected in time, this can lead to developmental issues or, in severe cases, failure to thrive. The identified variant was also confirmed using Sanger sequencing. After this finding the 3years old sibling of this baby was also tested for this variant which revealed similar homozygous pathogenic variant. In this case newborn genetic screening helped in early identification of disease before the onset of symptoms

Case 3

A healthy baby boy was born to a normal, non-consanguineous couple with no known family history. The couple opted for conventional Newborn screening panel after 48 hours and was tested negative [screened for 8 metabolic conditions along with Congenital Adrenal Hyperpalasia (CAH)]. After one month the baby was presented with failure to thrive and vomiting; suspected with malnutrition and severe dehydration. At the age of 2.5 months further medical examination revealed that he has developed hyponatremia (112 mmol/L) and metabolic acidosis and the 17OHP level was extremely high (> 900 nmol/L). Based on these observations the baby was diagnosed with Salt Wasting-CAH.Doctor referred for genetic test to confirm the cause. The test result revealed two pathogenic mutations in the CYP21A2 gene p. [Ile172Asn;Val358Ile]. This is an autosomal recessive condition onset of which can be at any age. In this case the baby boy was misdiagnosed to be negative by conventional NBS for CAH at birth as the baby had no symptoms at birth and this screening method cannot provide with predisposition information.

Conclusion:

Comprehensive newborn screening using NGS approachmarks an important paradigm shift in order to improve rates of diagnosis, understanding disease prognosis, and developing new therapies. Newborn Genetic Screening embraces the same principles of predictability, prevention, and personalization as conventional NBS in order to enable timely intervention, management, and treatment of childhood-onset or inherited conditions in a baby. Every newborn deserves a healthy start and with the increasing use of information technology, it is more likely that Newborn Genetic Screening will become

the front line of information provision in population-based screening programs.

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