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Dr.P.Ramachandran
Editor-in-Chief

Dr.S.Thangavelu
Executive Editor

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Journal Office and address for communications: Dr. P.Ramachandran, Editor-in-Chief, Indian Journal of Practical Pediatrics, 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India. Tel.No. : 044-28190032
E.mail : ijpp_iap@rediffmail.com

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PERINATOLOGY

CURRENT SCENARIO OF PERINATAL HEALTH IN INDIA

* **Kanya Mukhopadhyay**

Abstract: *India contributes to nearly 1/4th of global births as well as 1/4th of global neonatal deaths. Perinatal mortality and maternal mortality are also significantly high as compared to developed countries. With launch of several government programs, though infant mortality rate has come down significantly, the neonatal mortality has not shown any significant improvement. The low birth weight and its related complications contribute significantly to neonatal mortality in addition to sepsis and asphyxia. We are still quite far off from achieving millennium development goal 4. National Rural health mission is an ambitious project launched by government of India to improve antenatal and perinatal health and thereby reducing maternal and neonatal mortality in our country.*

Keywords: *Neonatal mortality, Perinatal mortality, maternal mortality, National Rural health mission*

In India 260 lakhs babies are born every year but nearly 9 lakhs die during the neonatal period. Out of these nearly 7 lakhs die within the first week after birth and a majority within the first 48 hours of life. Out of all global neonatal deaths (approx. 40 lakhs), 99% die in developing countries (average NMR 33 per 1000 live births) and 1% die in developed countries (average NMR 4 per 1000 live births). India contributes to 25% of global neonatal deaths. NMR is highly variable from state to state (from 10-11 in Goa and Kerala to upto 70 in Uttarpradesh, Madhya Pradesh and Chhattisgarh). Though IMR has decreased from 146 in 1951 to 50 per thousand as per sample registration survey 2009 (SRS 2009), NMR has been quite static and has reduced only marginally from 37 (SRS 2005) to 34 per 1000 live births (SRS 2009) and currently 31 per 1000 as per UNICEF reports. NMR contributes to about 2/3rd of IMR and nearly 1/2 of under 5 mortality.

Hence there is an urgent need for reduction of neonatal mortality which will impact infant mortality and under-5 mortality. The care of sick, preterm and low birth weight babies at various levels needs significant improvement to reduce neonatal mortality. Under Millennium Development Goal (MDG)-4, the IMR is targeted to be 30 and U5 MR to be 38 per 1000 live births and maternal mortality less than 100 per 100000 live births by 2015 which seems unlikely to be achieved. The National Rural Health Mission (NRHM) was launched in April 2005 with the objective of meeting the above outcomes by improving the reproductive and child health delivery system.

Perinatal health

Perinatal health is a very sensitive indicator of health status of the population.

The perinatal period commences at 22 completed weeks (154 days) of gestation and ends at seven completed days after birth.

The perinatal mortality rate is calculated as the sum of the number of stillbirths and early neonatal deaths divided by the number of pregnancies of seven or more months' duration.

Perinatal mortality rate =

$$\frac{(\text{still birth} + \text{early neonatal death})}{\text{Total birth (live birth + still birth)}} \times 1000$$

Exact data on perinatal mortality is difficult to obtain because of underreporting of stillbirths and infant deaths at the age 0-6 days. In India, as per National Family Health Survey 3 (NFHS 3) data, perinatal mortality was estimated to be 49 deaths per 1,000 pregnancies lasting seven or more months (including live births and stillbirths) during the period 2001-05.

Perinatal mortality is lowest (43-44) when the mother's age at delivery is 20-39 years. It is higher for mothers who are less than 20 years (67) and at ages 40-49 years (51). The interval between the previous pregnancy and the current pregnancy has a strong negative effect on perinatal mortality. The perinatal mortality rate is 71 when the interval is less than 15 months, but only 30-31 when the interval is 27 months or more. It is also high for first pregnancies

* Additional Professor,
Neonatal Unit,
Department of Pediatrics,
PGIMER, Chandigarh.

(66), for rural mothers, mothers with no education and less than 5 years of education, and mothers in the lowest wealth quintile.

Intrauterine death occurs either before onset of labor (antepartum death) or during labor (intrapartum death). Antepartum death could be due to pregnancy related complications or maternal diseases while intra partum deaths occur due to complications during labor.

Intrapartum stillbirths

The proportion of babies that die intrapartum is a very important indicator of quality of health delivery system. Intrapartum stillbirths are much higher in developing countries (24% to 37% of all stillbirths) whereas in developed countries it is about 10% of all still births. The risk of an intrapartum stillbirth is on an average 14 times greater in developing than in developed countries. In the least developed countries, the risk increases to at least 17 times more than in developed countries. Intrapartum deaths are largely avoidable through appropriate care during delivery.

Perinatal mortality is an important indicator of maternal care and of maternal health and nutrition; it reflects the quality of obstetric and pediatric care available. Most of the deaths occur in developing countries and stillbirths represent more than half of perinatal deaths. More than one-third of stillbirths take place intrapartum, i.e., during delivery, and are largely avoidable. The perinatal mortality rate is five times higher in developing than in developed regions: 10 per 1000 total births in developed regions; 50 per 1000 in developing regions and over 60 per 1000 in least developed countries.

PMR varies widely from state to state in India. Kerala (11), Goa and Sikkim have much lower level than Assam, Uttar Pradesh, Bihar, Jharkhand, Orissa, and Rajasthan which have high levels of perinatal mortality, Chhattisgarh having the highest (64).

As per NFHS3, 47 % of births in the five years preceding the survey were assisted by health personnel, including 35% by a doctor and 10% by an auxiliary nurse midwife, nurse, midwife, or lady health visitor. More than one-third of births (37%) were assisted by a traditional birth attendant and 16% were assisted by only friends, relatives, or other persons.

Neonatal deaths and stillbirths stem from poor maternal health, inadequate care during pregnancy, inappropriate management of complications during pregnancy and delivery, poor hygiene during delivery and the first critical

hours after birth and lack of newborn care. Antenatal coverage in our country varies from 20%-90% depending on the state. Several factors such as women's status in society, their nutritional status at the time of conception, early childbearing, too many closely spaced pregnancies and harmful practices, such as inadequate cord care, letting the baby stay wet and cold and various social taboos such as discarding colostrum and feeding milk other than breast milk and profound gender bias compromise neonatal health.

Neonatal mortality

Major causes of neonatal mortality are asphyxia (23%), sepsis (33%) and complications related to low birth weight and prematurity (27%). Low birth weight rate varies from 6% in developed countries to 30%-40% in developing countries. Maternal health and nutrition at conception are important determinants of weight at birth which affects neonatal health. Congenital malformation (1%-7%) is an uncommon cause of death though they occur more frequently in developing countries due to intrauterine infection or folate deficiency leading to neural tube defect or iodine deficiency leading to hypothyroidism.

Complications during birth, such as obstructed labor and fetal malpresentations, are common causes of perinatal death due to asphyxia and birth trauma in the absence of obstetric care. In developing countries asphyxia causes around seven deaths per 1000 births, whereas in developed countries this proportion is less than one death per 1000 births. Majority of deaths occur soon after birth, some just before birth.

Prolonged labor or prolonged rupture of membranes is the risk factor for early onset neonatal sepsis and 33% of newborn infants die because of this soon after birth. Though neonatal tetanus earlier was a major cause of death, it has now declined dramatically.

Early neonatal deaths are mostly due to complications during pregnancy or childbirth, preterm birth and malformations; late neonatal deaths are mostly due to infections acquired either at home or in hospital.

In our country another problem is of urban poor who live in slums and have poor access to proper health care (NMR is worse in urban poor than rural rich). The NMR of urban rich and poor are 28 and 49 whereas NMR of rural rich and poor is 37 and 57 respectively.

Prevention

1. Most of the neonatal deaths are preventable by appropriate management at home, in communities and health facilities but are often not provided adequately.

2. Inappropriate practices such as delayed initiation of breastfeeding, delayed clothing and early bathing, not seeking care at right time and applying harmful material on cord-stump and gender bias increase the risk of newborn deaths. Health facilities are often ill equipped to provide essential newborn care to all newborns and special newborn care to sick newborns. These have to be addressed.

- Home-based neonatal care (HBNC) operational guidelines have been in place and are being implemented through NRHM.

Maternal mortality

Globally, every year over 500,000 women die of pregnancy related causes and 99 percent of these deaths occur in developing countries. Nearly 67000 mothers die every year in India. The current Maternal Mortality Ratio (MMR) in India is 254 per 100,000 live births according to SRS Report for 2004-2006 which has come down from 301 as per SRS 2001-2003. Wide disparities exist across states in India. The MMR ranges from 95 in Kerala to 480 in Assam. MMR has a direct impact on infant mortality. Babies whose mothers die during the first 6 weeks of their lives are far more likely to die in the first two years of life than babies whose mothers survive.

Causes of maternal mortality

About half of all maternal deaths occur because of hemorrhage and sepsis. A large number of deaths are preventable through safe deliveries and adequate maternal care. More than half of all married women are anemic and one-third of them are malnourished (have a body mass index below normal).

Interventions to reduce maternal, perinatal and neonatal mortality

Maternal and child health has remained an integral part of the Family Welfare Programme of India since the time of the First and Second Five-Year Plans (1951-56 and 1956- 61) when the Government of India took steps to strengthen maternal and child health services. As part of the Minimum Needs Programme initiated during the Fifth Five-Year Plan (1974-79), maternal health, child health, and nutrition services were integrated with family planning services. In 1992-93, the Child Survival and Safe Motherhood Programme (CSSM) continued the process of integration by bringing together several key child survival interventions with safe motherhood and family planning activities (Ministry of Health and Family Welfare, 1992). In 1996, safe motherhood and child health services were

incorporated into the Reproductive and Child Health Programme (RCH). National Population Policy (NPP) adopted by the Government of India in 2000 reiterates the government's commitment to safe motherhood programme within the wider context of reproductive health (Ministry of Health and Family Welfare, 2000). For 2010, the goals were 80% institutional deliveries, 100% of deliveries be attended by trained personnel, and maternal mortality ratio should be reduced to a level below 100 per 100,000 live births.

To improve the availability of and access to quality health care, especially for those residing in rural areas, the poor, women and children, the government launched the NRHM in 2005 for the 2005-2012 period which is still continuing. One of the important goals of the NRHM is to provide access to improved health care at the household level through female Accredited Social Health Activists (ASHA), who act as an interface between the community and the public health system. The ASHA acts as a bridge between the ANM and the villagers, and she is accountable to Panchayat. She helps to promote referrals for universal immunization, escort services for RCH, construction of household toilets and other health care delivery programmes (Ministry of Health and Family Welfare, 2006).

Most of the earlier government programmes (ARI, Diarrheal diseases and immunization) have focused on infants and children which has brought down IMR significantly but not NMR as Maternal and Child Health Supplemental Programme and Postpartum Programme were not sufficient. Now these programmes are integrated into Reproductive and Child Health Programme which was launched in 1996. Department of Women and Child Development initiated the Integrated Child Development Services (ICDS) in 1976. Under the ICDS programme, anganwadi centres provide children with health, nutrition, and education services from birth to six years of age and nutritional and health services to pregnant women and breastfeeding mothers. UNICEF continues to support most of the government programmes in action and is working closely with NRHM for the programs such as Janani Suraksha Yojna (JSY) to encourage women to have institutional deliveries. Facility based neonatal care (FBNC) is being made available by creating special care nursery units (SNCU) across all districts of India. Another new programme which has been launched by Govt of India is Navjaat Shishu Suraksha Karyakram (NSSK) under NRHM in which basic resuscitation and newborn care are being provided and training module has been developed to train doctors, nurses and ANMs in low resource setting areas.

IMNCI

The Integrated Management of Neonatal and Childhood Illness (IMNCI) is the Indian adaptation of the WHO-UNICEF generic Integrated Management of Childhood Illness (IMCI) strategy and is the centerpiece of newborn and child health strategy under Reproductive Child Health II and National Rural health Mission. Aim of the strategy is to implement a comprehensive newborn and child health package at the household and the community level through medical officers, nurses and LHVs. However this excludes the skills required at facilities to manage new born and childhood illness. However, the health personnel and workers should possess optimum skills for managing newborn and children both at the community level as well as the facility level.

F-IMNCI is the integration of the facility-based care package with the IMNCI package, to empower the health personnel with the skills to manage new born and childhood illness at the community level as well as at the facility. It helps to build the capacities to handle referrals taking place from the community. Referrals include the most common childhood conditions responsible for over 70 % of all deaths in children under the age of 5 years in resource poor setting. The F-IMNCI training manual provides the optimum skills needed at the facilities by the medical officers and staff nurses. The introduction of F-IMNCI will help build capacities of the health personnel at facilities to address new born and childhood illness and thus help bridge the acute shortage of specialists.

Scenario in level II and level III hospitals in India

The scenario in level II and III hospitals in India is quite different from the total national picture. A much higher proportion of preterm and low birth weight babies get delivered in these setups when compared to the national average as per National neonatal perinatal data (NNPD) 2002-3. Currently there are about 50 accredited level II and III neonatal units in India where high tech care is provided to these babies. Causes of neonatal deaths are also different than national figures except sepsis which contributes a large majority of deaths. Other causes of death in these set ups are RDS, necrotizing enterocolitis and intraventricular hemorrhage. National Neonatology Forum (NNF) works in collaboration with various government agencies to impart training in resuscitation as well as to set up facility based neonatal care across India.

Strategies to improve mother and child health

National Rural health mission was initiated by Ministry of health and family welfare in 2005 with an aim to reduce maternal and infant mortality. Janani Suraksha Yojana (JSY) was launched with the main purpose to increase institutional deliveries so that skilled birth attendants are available and birth related mortality and morbidities can be avoided both for baby and mother. This has benefitted nearly 1 crore mothers annually. Though the institutional delivery has reached nearly 73% but still 27% women prefer to deliver at home as per coverage evaluation survey (CES) 2009 especially in rural areas. Reason for still preferring home delivery was high out of pocket expenses to avail the hospital facility.

These expenses were the following.

1. User charges for OPD, admissions, diagnostics tests, blood etc.
2. Purchase of medicine and consumables
3. In cases of caesarean section, extra expenditure
4. Transport from home to hospital, then in cases of referral to another hospital extra transport cost and also return to home

Hence to overcome this problem, Janani Shishu Suraksha Karyakram (JSSK) scheme was launched in June 2011 and under this scheme all charges related to delivery and newborn care upto 30 days of life are free including free pick up and drop back facility in all government hospitals. This scheme targets nearly 75 lakhs women who still deliver at home. All the 35 States/UTs have initiated implementation of this scheme.

JSSK Entitlements for pregnant women are as follows:

- Free and cashless delivery
- Free C-section
- Free drugs and consumables
- Free diagnostics
- Free provision of blood
- Free diet during stay in health institutions (Up to 3 days for normal delivery, 7 days for Caesarean sections)

- Free transport
 - Home to health institution
 - Between health institutions in case of referral
 - Drop back home after delivery
- Exemption from all kinds of user charges, including those for seeking hospital care up to 6 weeks post delivery (for post-natal complications)

JSSK Entitlements for sick neonates till 30 days after birth

- Free treatment at public health institutions
- Free drugs and consumables
- Free diagnostics
- Free provision of blood
- Free transport
 - Home to health institution
 - Between health institutions in case of referral
 - Drop back home after delivery
- Exemption from all kinds of user charges

Monitoring of this scheme is done at national level by National Health Systems Resource Centre (NHSRC) under guidance and support from Maternal Health division, Ministry of Health and Family Welfare, Government of India.

At the state level and district level, the state and district nodal officers monitor and follow up the progress in implementation of the scheme. In CMOs meeting at state level, the mission director and during MO meeting at district level, CMO reviews the progress of the scheme.

Role of UNICEF

UNICEF partners with the Government of India, state governments and communities, promote simple interventions which can significantly improve newborn survival.

UNICEF encourages home-based care of all newborns through its support to the Integrated Management of Neonatal and Childhood Illnesses (IMNCI) program. The program equips frontline workers with required skills and supplies. Following training on IMNCI, frontline workers (ASHAs and AWWs) visit newborns at their households three times in the first week of life. During the visits, workers assess the newborns, promote healthy practices, manage simple problems and refer those with serious illnesses.

UNICEF supports setting up and managing of Special Care Newborn Units (SCNUs) that provide state-of-the-art care for newborns in some of the least developed districts of the country.

To improve care of newborns at peripheral level, facility based newborn care has been launched by Govt of India in 2011. In this scheme, special newborn care units (SNCU), newborn stabilization units (NBSU) and newborn care corners (NBCC) at various health care levels are being established. All districts are supposed to develop such units and operational guidelines have been put in place along with extensive training of doctors and nurses. This intervention is expected to reduce neonatal mortality by 25%-30%.

The way forward

A large proportion of infant and under-five deaths occur soon after birth. Early neonatal mortality accounts for three out of four neonatal deaths. Early neonatal deaths can only be reduced through effective pregnancy, childbirth and postnatal care reaching all mothers and their babies which will consequently bring down infant mortality rate (IMR) and under 5 mortality rate. This will also reduce the large number of mostly invisible stillbirths. Mortality and morbidity in the perinatal and neonatal period are mainly caused by preventable and treatable conditions. Interventions that benefit mothers by reducing maternal deaths and complications, as well as special attention to the physiological needs of the newborn-baby-like resuscitation, immediate breast-feeding, warmth, hygiene (especially for delivery and cord care) and prevention, early detection and management of major diseases will improve survival and health of newborn infants. Facilities for safe and clean delivery, early detection and management of sexually transmitted diseases, adequate management of infections and complications during pregnancy and delivery should be available. Good maternal nutrition, prevention and management of anemia and high-quality antenatal care will reduce the incidence of complications and thereby improve chances of survival of the mother, the fetus and the newborn infant. The incidence of low birth weight, an important determinant of perinatal survival may take time to change substantially but universal access to care during pregnancy and childbirth and care of the newborn should be available immediately to improve health of mother and neonate.

Ethical and legal issues

With improvements in modern high technology there is a possibility of prolonging futile care in many circumstances. There are no formal guidelines in our country what to do in such situations.

These issues are relevant in the following cases

1. Gross congenital or potentially lethal malformations
2. Severe perinatal asphyxia
3. Extremely low weight and gestation
4. Severe grades of intracranial hemorrhage

While taking decisions on the above issues one should keep in mind the following:

- i. The value of human life
- ii. The principle of best interest
- iii. Withholding and withdrawing treatment and deliberate action to end life
- iv. Economic and social issues in our country
- v. Decision making by parents and clinicians – shared partnership.

Points to Remember

- *Millenium Development Goal 4 cannot be achieved without improving the reproductive and child health delivery system*
- *Perinatal health is a very sensitive indicator of health status of the population*

- *A large proportion of infant and under-five deaths occur soon after birth. Early neonatal mortality accounts for three out of four neonatal deaths. This can only be reduced through effective pregnancy, childbirth and postnatal care reaching all mothers and their babies.*
- *Most of the neonatal deaths are preventable by appropriate management at home, in communities and health facilities*

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CONGRATULATIONS

The honorary Doctor of Science (Honoris Causa) degree was conferred on Dr.A.Parthasarathy, Past National President, IAP & Founder Editor of IJPP, by the Governor of Tamilnadu & Chancellor, The Tamilnadu Dr M.G.R. Medical University during the 26th Annual Convocation held on 2nd September, 2014 in recognition of his significant contribution at the National and State level towards Preventive and Promotive Child Health, Immunization, Infectious Diseases, Polio Eradication, Community Pediatric Services and Pediatric Publications. It is also a matter of great pride that he is the first Pediatrician to get this honor in Tamilnadu.

NEWS AND NOTES

2nd International Congress on Micronutrient and Child Health (MCH-2014)

New Delhi, Date: November 3-7, 2014

Enquiries to:

Prof. Umesh Kapil

Email: mchws2014@gmail.com

Mobile: 09810609340

PERINATOLOGY

INTRAUTERINE FETAL MONITORING

* **Ruby Gupta**

** **Venkatesh Sampath**

Abstract: *Advances in obstetric and perinatal care combined with accessibility to health care have contributed to the decreased neonatal mortality (<10 deaths/1000 live-births) in developed nations. Neonatal and infant mortality continues to be very high in India. Intra-uterine fetal monitoring is a valuable tool to monitor fetal well-being and can help in preventing fetal demise and improving short-and long-term health outcomes for babies. This review outlines the different modalities available to monitor health of the fetus along with indications for their use and interpretation of findings.*

Keywords: *Intrauterine fetal monitoring, Invasive tests, Non-invasive tests.*

Intra-uterine fetal monitoring (IUFM) comprises a gamut of invasive and non-invasive tests that are available to monitor the health, activity and growth of the fetus during intrauterine life. IUFM encompasses fetal movement counts, ultrasound examination of major organ systems, Doppler ultrasound of the umbilical artery or other blood vessels, biophysical profile and the contraction stress test. Neonatal mortality (32 deaths/ 1000 live births) and infant mortality (47 deaths/1000 live-births) continue to be very high in India.¹ The goal of IUFM is to improve perinatal outcomes by detecting fetal growth restriction or hypoxia before the fetus has suffered long-lasting harm or even death and to decrease postnatal complications such as neonatal encephalopathy and cerebral palsy. While IUFM is indicated in every pregnancy, the frequency and timing of various tests employed need to be individualized based on maternal condition or obstetric complication. Interventions should consider the etiology, gestational age of fetus and risk of intra-uterine fetal demise.

* Assistant Professor in Pediatrics

** Associate Professor in Pediatrics,
Division of Neonatology,
Children's Hospital of Wisconsin,
Medical College of Wisconsin,
Wisconsin, USA.

Indications for surveillance

For low-risk pregnancies: Routine surveillance should include a first trimester ultrasound scan for gestational age assessment. Crown-rump length is the most accurate measure for dating in the first trimester.

A second trimester sonographic examination is performed at 18-20 weeks to screen for major congenital anomalies, cardiac defects, central nervous system defects and signs of aneuploidies. Additionally, this scan assesses placental location to rule out placenta previa, estimates amniotic fluid volume and examines for multiple gestation.

IUFM for complicated pregnancies: Comprehensive and continuous surveillance for high-risk pregnancies may be indicated for conditions listed in Table I. There is increased risk of perinatal mortality and morbidity in these pregnancies warranting a need for intense monitoring.

Table.I Maternal diseases and obstetrical conditions requiring comprehensive IUFM

Chronic medical conditions
Advanced maternal age (>40 yrs)
Thyroid disease
Severe cardiac disease
Renal disease
Systemic lupus erythematosus
Diabetes mellitus
Chronic hypertension
Coagulation disorders
Seizure disorder
Pregnancy related complications
Pregnancy-induced hypertension
Decreased fetal movements
Oligo- or polyhydramnios
Threatened preterm delivery
Intra-uterine growth retardation
Post-term pregnancy
Rh sensitization
Multiple pregnancy, if complicated (twin-twin transfusion)
Fetal anatomic abnormality

Fetal movement counts: Fetal activity starts as early as 7 weeks and becomes organized between 20 to 30 weeks and continues to mature until approximately 36 weeks. Awareness of fetal movement is a means for the mother to monitor her fetus without the need for a clinician or equipment. Mother's perception of fetal movement starts between 16-18 weeks. The presence of normal fetal movement suggests functional integrity of fetal regulatory systems. Normal maternal counts of fetal movements have large daily variations in normal pregnancies. The American College of Obstetricians and Gynecologists (ACOG) suggests counting distinct fetal movements on a daily basis after 28 weeks gestation.² The perception of 10 distinct movements in up to 2 hours is considered reassuring. The counting can be discontinued for that day after 10 movements.

Under the effect of hypoxia, decreased fetal movement can be a manifestation of a decompensated state, indicative of imminent injury or death. Poor perception of fetal activity may also be due to fetal sleep, decreased/increased amniotic fluid volume, fetal position (anterior position of the fetal spine) and anterior placenta. A woman presenting with decreased fetal movement needs a thorough evaluation to rule out fetal compromise and prevent imminent fetal death. It is recommended that pregnant women be given information prenatally about normal fetal activity and fetal movement counts. Women who monitor fetal movement counts and have concerns with decreased or absent fetal movements need immediate attention, should be examined and screened for fetal well-being within a few hours.

Ultrasound: Ultrasound estimation of fetal weight is the most reliable method for fetal growth monitoring in clinical practice. Measurement of head circumference, abdominal circumference, femur length and biparietal diameter are used to estimate fetal weight in different trimesters. In fetuses with growth retardation, serial growth measurements are used to assess change in fetal size over

time. A slower increase in various growth parameters over time is seen in infants who develop intra-uterine growth restriction when compared to fetuses with normal growth.

Doppler ultrasound: It is a non-invasive method for assessment of blood flow in fetal blood vessels performed in certain high-risk pregnancies to assess fetal health.

a) Umbilical artery flow: It assesses the resistance to perfusion of blood in the fetoplacental unit. Low impedance in the umbilical artery permits continuous forward flow throughout systole and diastole. Systolic to diastolic (S/D) ratio and pulsatility index (PI) are commonly used for quantitative assessment. With increasing placental vascular resistance, initially there is absent end-diastolic flow which progresses to reverse flow (Fig.1). This measurement is considered to be a useful adjunct in the management of pregnancies complicated by fetal-growth restriction (recommendation level B) and is done after 23 weeks gestation.³ Reversed flow is associated with 5-fold increase in fetal mortality.⁴ It might warrant immediate delivery but gestational age is also a major determinant of perinatal outcome. When IUGR is suspected, umbilical artery evaluation has been shown to significantly reduce induction of labor, C-sections and perinatal death without increasing the rate of unnecessary interventions.⁵ Routine doppler screening for the subsequent development of IUGR in a low-risk population is not recommended.

b) Middle cerebral artery flow. The middle cerebral arteries (MCA) are major branches of the circle of Willis and carry >80% of the cerebral circulation. In the hypoxic fetus, central redistribution of blood flow results in increased blood flow to the brain, known as brain sparing reflex. Doppler velocimetry of the MCA is useful for detection and management of fetal anemia of any cause (Fig.2).

The anemic fetus shunts blood preferentially to the brain to maintain adequate oxygenation. The peak MCA systolic velocity increases because of increased cardiac

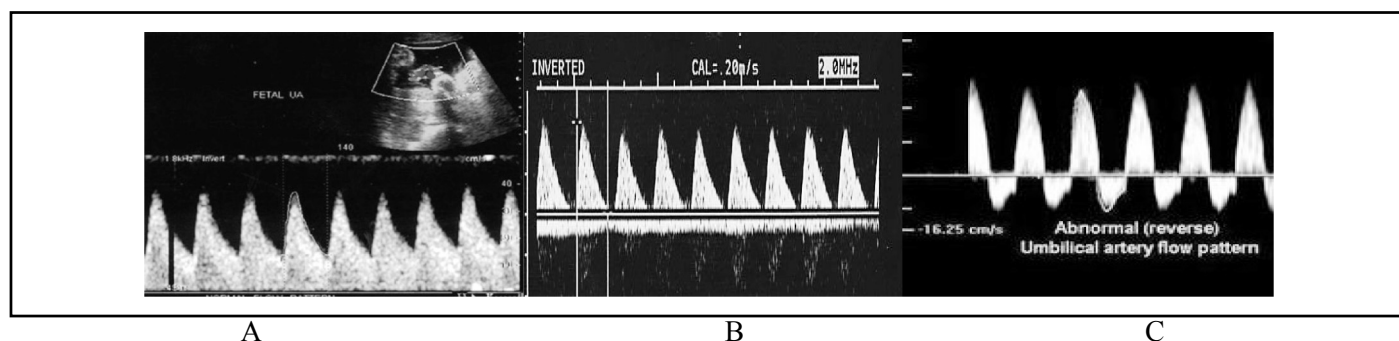


Fig.1. Umbilical artery waveform showing (A) normal, (B) absent, (C) reversed umbilical arterial flow during diastole.

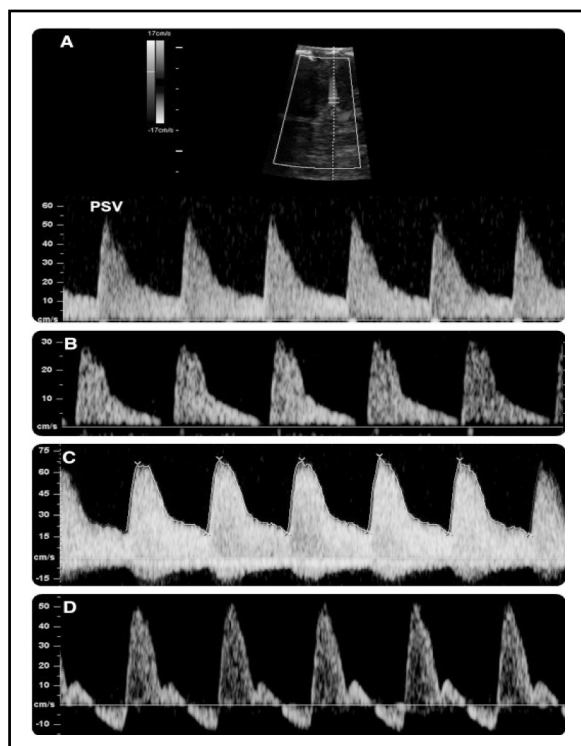


Fig.2.Middle cerebral artery (MCA) waveforms⁸ demonstrating (A); borderline, (B); normal, (C); abnormal, and (D); reversed blood flow in the MCA. Note - Peak systolic velocities (PSV) of <30cm/s in (B) when compared to >50cm/s in (A), (C) and (D).

output and decreased blood viscosity.⁶ In fetuses with Rh isoimmunization, use of MCA Doppler velocimetry is comparable to serial measurement of bilirubin by amniocentesis for estimating severity of disease and may be even better because it is non-invasive.⁷

c) Ductus venosus flow: Doppler ultrasound of fetal venous circulation reflects the physiologic status of the right ventricle. Doppler waveforms are biphasic in shape with two peaks followed by a nadir in late diastole with atrial contraction. Absent or reversed ductal flow is usually a late finding. It may represent myocardial impairment and is linked to increased perinatal mortality. It is a useful adjunct in monitoring fetal growth restriction, complicated twin gestation and fetal supra ventricular tachyarrhythmia.

d) Uterine artery Doppler flow: Abnormal resistance to flow in the uterine arteries can be a sign of inadequate placental trophoblast invasion and is a prelude to the development of pre-eclampsia, eclampsia and intrauterine growth restriction. Uterine artery doppler flow screening in the first trimester or early second trimester can predict

future risk of pre-eclampsia and premature birth with >80% sensitivity and 10% false-positive rate.⁹ However, its use for prediction of fetal growth restriction is still investigational.

Amniotic fluid volume: Amniotic fluid (AF) volume reflects a chronic measure of intrauterine environment. AF is the byproduct of fetal urination, gastrointestinal motility, tracheal efflux and amniotic membrane transfer to and from fetal and maternal water compartments. Adequate amniotic fluid requires normal perfusion of the fetal kidneys and lung. Decreased uteroplacental perfusion causes hypoxemia which can lead to redistribution of blood away from the kidneys, resulting in decreased urine output and subsequent oligohydramnios. Surrogate measures of AFV are the largest vertical pocket method (maximal vertical pocket-MVP) and the amniotic fluid index (AFI). A meta-analysis including 18 studies concluded that an AFI of <5.0 cm significantly increased the risk of either caesarean delivery for fetal distress or a low 5-minute Apgar score.¹⁰ Weekly testing is sufficient if AFI exceeds 8 cm, while twice weekly testing should apply to pregnancies in which AFI is below 5 cm. AFI needs to be used in conjunction with other tests for monitoring fetal well-being. However it cannot be used as the sole indicator of fetal well-being.

Non-stress test (NST): It is the most widely used, non-invasive test of fetal health. The fetal heart rate variability is controlled by the autonomic nervous system. There is temporary increase in heart rate in response to fetal movement. Current ACOG criteria typically consider an NST to be reactive if there are two accelerations exceeding 15 beats per minute amplitude and 15 seconds' duration in a 20-minute window for term pregnancies and 10 beats per minute amplitude and 10 seconds' duration for gestational ages below 32 weeks.¹¹ Under the effect of hypoxia there is decrease in acceleration as well as decrease in fetal heart rate variability. Non-reactivity may be associated with fetal sleep-like states and maternal use of central nervous system depressant drugs. NST has a low false-negative rate but high false positive rate for predicting fetal death within 1 week of a normal test. This means that while a normal NST test is reassuring of continued fetal well-being, an NST which is non-reassuring is not always predictive of a poor outcome. There is no consensus on the optimal frequency of testing. Usually it is done weekly in conjunction with other tests but frequent monitoring may be needed for non-reassuring NSTs or in complicated high risk pregnancies when the fetus is at significant risk of compromise.

Vibroacoustic NST: It is a variation of standard NST. A loud vibroacoustic signal over the maternal abdomen

produces fetal heart rate acceleration. It has been shown to reduce testing time and the incidence of false non-reactive NSTs in otherwise healthy fetuses.

Biophysical profile (BPP): BPP takes into account acute biophysical parameters like fetal tone, present or absent; fetal movement, present or absent; fetal breathing motion, present or absent for 30 sec; non-stress test, reactive or non-reactive; and a biophysical parameter like amniotic fluid volume, AFI more or less than 5. Each component can score either 2 for being present or 0 if not present. Score of 8 or greater is considered reassuring.¹² If the largest vertical amniotic fluid pocket is <2 cm, further evaluation is warranted, regardless of biophysical composite score. The BPP has a false-negative rate of 0.6/1000 and false positive rate of 50% for predicting intrauterine asphyxia or fetal death.¹³

Modified biophysical profile (MBPP): MBPP has become increasingly popular because of the labor-intensiveness of standard BPP. It is the combination of biweekly NST and amniotic fluid index. It takes only 10 minutes to perform. A study by Miller, et al. found that MBPP has low false-negative rate of 0.8/1000 for intrauterine fetal death within seven days of reassuring test.¹⁴ However, 60% of those delivered because of an abnormal antepartum test had no evidence of short-term or long-term fetal compromise. False-positive test results led to preterm delivery in 1.5% of those tested before term.¹⁴

Contraction stress test (CST): The CST was the first important intrauterine assessment test for uteroplacental function. It is performed with intravenous oxytocin until at least three moderate or strong contractions per 10 minutes generated. It provides a direct insight of placental and fetal reserve during uterine contractions. Use of CST as the primary means of fetal surveillance results in low incidence of unexpected fetal death within 7 days of a negative test result.¹⁵ This is not a very practical test because it is invasive and prolonged, adds to the stress if the fetus is already stressed, contraction strength cannot be regulated and there is a 30% false-positive rate.¹⁶ CST can also induce preterm labor and is contraindicated in previous caesarian section, twin gestation, and placenta previa.

Conclusions

Contemporary IUFM comprises serial, systematic fetal assessment during pregnancy aimed at identifying fetuses at risk of growth restriction or asphyxia with the aim of preventing fetal demise, and growth and developmental impairment. NST, BPP and MBPP are

non-invasive tests that are accurate in predicting fetal well-being but are not robust in accurately predicting fetal compromise or impending demise and may lead to unnecessary interventions. Addition of Doppler ultrasound improves the predictive accuracy of said tests and therefore reduces the risk of unnecessary premature deliveries and caesarean sections.

In order to decrease the infant and neonatal mortality in India, IUFM should be used early in high-risk pregnancies to identify and monitor fetal compromise and appropriate interventions performed to prevent fetal demise and improve perinatal outcomes. Commonly used tests for IUFM during each trimester been summarized in (Fig.3).

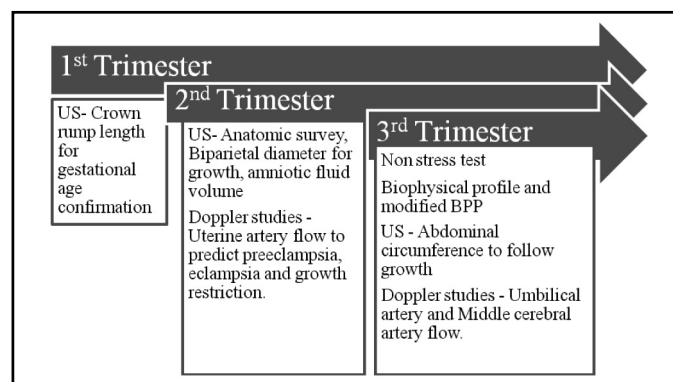


Fig.3. Widely used tests for IUFM classified by timing in pregnancy

Points to Remember

- Intrauterine fetal monitoring comprises of systematic, multi-modality fetal assessments done during pregnancy aimed at identifying fetal growth restriction and asphyxia with the goal of preventing fetal demise and improving perinatal outcome.*
- Surveillance of the fetus should be done for all pregnancies but should be frequent and intense in high-risk pregnancies.*
- Many of the tests done for intrauterine fetal monitoring are non-invasive, and while normal tests accurately predict good fetal health, an abnormal test does not necessarily result in an adverse outcome.*
- A combination of tests including biophysical profile and doppler velocimetry increase the sensitivity of diagnosing fetal compromise without greatly increasing false-positive errors and unnecessary interventions.*

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CLIPPINGS

Fetal manipulation for facilitating tests of fetal wellbeing

Manual fetal manipulation has been suggested to improve the efficiency of antepartum fetal heart rate testing. Objective of this review was to assess the merits or adverse effects of the use of manual fetal manipulation in conjunction with tests of fetal wellbeing.

Selection criteria: All published and unpublished randomised controlled trials assessing the use of fetal manipulation versus mock stimulation, no stimulation or other types of stimulation, used in conjunction with cardiotocography or other tests of fetal wellbeing.

Authors' conclusions: There is insufficient evidence to support the use of manual fetal manipulation during cardiotocography or other tests of fetal wellbeing. More studies of manual fetal manipulation that utilises standardised protocol should be encouraged.

Tan KH, Sabapathy A, Wei X. Fetal manipulation for facilitating tests of fetal wellbeing. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD003396. DOI: 10.1002/14651858.CD003396.pub2. Assessed as up to date: September 30, 2013.

PERINATOLOGY

ULTRASOUND GUIDED DIAGNOSTIC STUDIES IN PREGNANCY

* **Indrani S**

** **Suresh S**

Abstract: *Rapid advances in the field of ultrasound technology along with its increasing use have opened up a new era of ultrasonographic obstetrics. Better understanding of congenital disorders has led to a variety of diagnostic and therapeutic prenatal interventions under ultrasound guidance. In this article we have reviewed the diagnostic tests that are done during the antenatal period.*

Keywords: *Prenatal ultrasound, Diagnostic testing.*

Over the last few decades, rapid strides have been made in ultrasound technology. This has paved the way for increasing use of ultrasound in obstetric care. In the words of Prof. Yves Ville, “We have moved from an era of obstetric ultrasound to ultrasonographic obstetrics”.¹ Concurrent advances in genetics have shown the path towards better understanding of genetic disorders, opening the doors to prenatal diagnosis and fetal therapy, thus helping to provide answers and solutions to several fetal problems.

Prenatal interventions are always performed under continuous ultrasound guidance. Diagnostic or therapeutic interventions must be done by well trained personnel in an appropriate setting. A close knit team work comprising of a fetal medicine specialist, obstetrician, geneticist, neonatologist and perinatal pathologist is essential. A close liaison with laboratories which test prenatal samples is also vital as these samples have to be handled differently and the information sought from a sample like the chorionic villus or amniotic fluid may vary from fetus to fetus.

Indications for prenatal diagnostic testing would include

- Positive screening test for Down syndrome (First or second trimester)

- Advanced maternal age
- History of chromosomal abnormality or single gene disorder in a sibling
- Chromosomal translocation in one parent
- Structural anomaly detected on ultrasound
- Immune and non-immune hydrops
- Congenital infection
- Fetal growth disorders (secondary to aneuploidy, IEM)
- Positive non-invasive prenatal test (NIPT)

While seeking a prenatal diagnosis, it is imperative to sample the appropriate fetal tissue which depends on the nature of the problem, gestational age and the information sought. For example, chorionic villus sampling can be performed for identifying numerical chromosomal aberrations while structural aberrations and rearrangements are better assessed from amniotic fluid and fetal blood due to better banding. For molecular diagnosis, it is ideal to have chorionic villi as the DNA yield is better as compared with that obtained from amniotic fluid after several days of culturing. Fetal DNA can also be obtained directly from the fetal blood. Rapid aneuploidy testing (2–3 days) may be performed by Qualitative Fluorescence Polymerase Chain Reaction (QF-PCR) or Fluorescence In Situ Hybridization (FISH) for common aneuploidies. A newer technology BACs-on-Beads technology enables rapid detection of copy number changes in targeted genomic regions from a minute amount of DNA.²

A pre-procedure counselling explaining the risks, benefits and limitations of the procedure is mandatory.

Amniocentesis

Amniocentesis is performed in the second trimester after 15 weeks.^{3,4} During this period, the volume of amniotic fluid is about 200 mL and about 20 mL of fluid can be drawn safely. Attempts at early amniocentesis prior to 14 weeks have shown a high rate of complications like lung hypoplasia and limb deformities like talipes.

Amniocentesis is an out patient procedure. Under continuous ultrasound guidance and strict aseptic

* Associate Director,

** Director,

MediScan Systems,
Chennai.

precautions, a 22G spinal needle is introduced into a pool of amniotic fluid which is devoid of fetal parts. The amnion is pierced with a sharp "jab" of the needle to avoid tenting of the membrane.⁵ The first few mL of fluid is discarded to minimize the risk of maternal cell contamination and 20 mL of fluid withdrawn and transferred into a sterile tube. It is preferable to avoid the placenta but if the placenta is completely anterior, needle is inserted through the thinnest edge. Colour Doppler will help to avoid major subchorionic vessels. The amniotic fluid is usually colourless, or faint yellow. Dark red or dark brown colour indicates prior intra amniotic bleed. If the colour is bright red, it indicates fresh bleed which is usually from the placental edge. The fetal heart rate is documented post procedure. Non alloimmunised Rh negative women must be given 300 µg of Rh immunoglobulin at the end of the procedure.

Amniocentesis is a relatively safe procedure. Complications like amniotic fluid leakage, chorioamnionitis and significant fetomaternal hemorrhage are rare. Miscarriage can occur in about 0.5% of the cases and is marginally higher in twin pregnancies.⁶ Chronic amniotic fluid leakage, though rare, can cause oligohydramnios resulting in respiratory distress and talipes in the new born. However there is no statistical evidence to prove an association between amniocentesis and neurodevelopmental, respiratory and orthopedic disorders.

Special situations

Twin pregnancies

In dichorionic pregnancies, both the sacs must be sampled while in monochorionic pregnancies, sampling one sac will be sufficient as discordant karyotypes in monochorionic twins is rare.



Fig.1. Amniocentesis in dichorionic twins showing needle in one sac

Since the results will come at a later date, it is important to be able to identify the specific karyotype for each twin.

In twin pregnancies, sampling the two sacs with two separate needle insertions is ideal. The entire set including the needle has to be changed (Fig.1) before the other sac is sampled. This ensures that there will be no contamination of the samples. In the single needle technique, the needle is inserted into one sac and the other sac is entered through the membrane. After the needle enters the second sac, a few milliliters of amniotic fluid is discarded. The multi-needle technique does not appear to increase the risk of adverse outcome compared with single needle technique

Vertical transmission of infection

The risk of vertical transmission of maternal infection has been reported in various small studies. Guidelines from Society of Obstetricians and Gynecologists of Canada (SOGC) mention that the risk of fetal infection after amniocentesis for Hepatitis B and C is low but mentions that prior knowledge of the maternal status is useful in counselling for hepatitis B and even though hepatitis C has a low risk of transmission, the patients must be cautioned that this information is based only on a few studies.⁷ Most of the reports of increased vertical transmission rates in HIV have been from the pre zidovudine era. The rate of vertical HIV transmission from amniocentesis is low in women under treatment for HIV, and the residual risk may be related to the type of therapy. The risk appears to be lowest in women receiving Highly Active Anti Retroviral Therapy (HAART)⁸.

Chorionic villus sampling

A positive first trimester screening is the most common indication for performing chorionic villus sampling.⁹ It is also performed when molecular diagnosis is sought for a



Fig.2. Transabdominal CVS showing needle in the placenta

genetic disorder when a specific known mutation is to be identified. Chorionic villus sampling (CVS) is usually performed after 11 weeks when the crown-rump length (CRL) is >45mm. The transabdominal route (Fig.2) is preferred to the transcervical route. When the placenta is completely posterior, deferring the procedure by a week will help to access the placenta in most cases.

Transabdominal CVS^{10,11} is performed under local anesthesia and continuous ultrasound guidance using a 18G spinal needle. The needle is introduced parallel to the chorion frondosum into the substance of the placenta. A 10 mL syringe with 2 mL of culture media is then attached to the proximal end of the needle. Suction is applied and a gentle to and fro motion of the needle ensures aspiration of adequate villi into the medium in the syringe. The needle is withdrawn maintaining the suction. A minimum of 15–20 mg of tissue will be required for culture. If molecular studies are required then 40–50 mg will be needed.

Transcervical CVS is performed using a special cannula with a malleable obturator which is introduced through the cervical canal and is directed into the chorion by transabdominal ultrasound guidance by a second operator (Fig.3). The cannula is then withdrawn with continuous suction being maintained.

A double needle technique has also been used wherein a larger outer needle is first introduced into the uterus and a smaller gauge needle is passed through this needle to sample the villi. The advantage of this technique is that re-sampling can be done with ease if the sample is inadequate in the first pass. The transabdominal approach is easier and can be performed in the ultrasound room. Lower complication rates have been reported after transabdominal CVS.

It is mandatory for all Rh negative non-sensitized women undergoing CVS to receive anti-D immunoglobulin.



Fig.3. Transcervical CVS. Note needle in the posterior placenta

Contraindications to transabdominal route are rare and include extreme retroflexion, while contraindications for transcervical approach include active vaginal or cervical infection. Relative contraindications include vaginal bleeding within 2 weeks prior to the procedure, cervical polyps, lower segment fibroids that prevent passage of the catheter and markedly retroverted, retroflexed uterus.

Complications of CVS¹²

Fetal loss rates varying from 0.6%-5% have been reported after CVS. The loss rates reduce with operator expertise and increase with the number of attempts made to obtain a sample. Vaginal bleeding is more common after transcervical CVS than after transabdominal CVS. A subchorionic hematoma may form in about 4% of the cases which usually resolves spontaneously. The risk of fetomaternal hemorrhage is dependent on the amount of tissue aspirated.

Chorioamnionitis and premature rupture of membranes (PROM) are rare complications. CVS performed prior to 9 weeks may be associated with oromandibular limb hypogenesis syndrome and terminal transverse limb reduction deformities. These are believed to be caused by transient fetal hypoperfusion and vasospastic phenomena secondary to vascular disruption to the placental circulation. These have not been reported when CVS is done after 11 weeks.

CVS in multiple pregnancy¹³

CVS in multiple pregnancy is a challenge especially if both placentae are either anterior or posterior in dichorionic pregnancies. Care has to be taken to ensure that representative samples are taken from each placenta without contamination. In monochorionic pregnancies, a single sample is sufficient.

Confined placental mosaicism is a discrepancy between the chromosomal make up of the baby and the placenta. It is seen when trisomy is noted on a CVS sample but a normal karyotype on fetal sampling or amniocentesis and is noted in 1%-2% of ongoing pregnancies after CVS.

Fetal blood sampling

Daffos, et al were the first to use an ultrasound-guided percutaneous technique to enter the umbilical cord and draw a sample of fetal blood. Fetal blood sampling is performed when it is necessary to know the hematological status of the fetus, the most common being for assessing fetal anemia. However, at present fetal anemia can be diagnosed non-invasively by Doppler study of the fetal middle cerebral

artery (MCA). An MCA peak systolic velocity (PSV) of > 1.5 MoM is indicative of fetal anemia warranting an intrauterine transfusion.¹⁴ Fetal blood sampling can be done using a 22/20G spinal needle from the umbilical cord near the insertion to the placenta or the free loop (Fig.4a and 4b).^{15, 16} The two other sites from which a blood sample can be obtained are the intrahepatic portion of the umbilical vein (Fig.4c) and the heart.



Fig.4a. Fetal blood sampling through anterior placenta



Fig.4b. Fetal blood sampling from free loop of the cord



Fig.4c. Intrahepatic fetal blood sampling

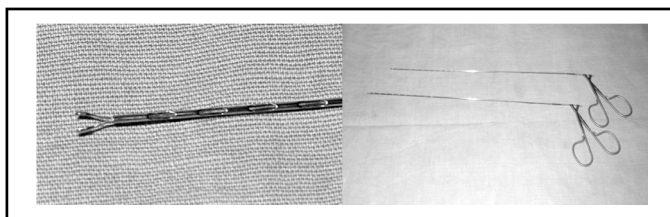


Fig.5a. Fetal skin biopsy forceps and zoomed view of the tip of fetal skin biopsy forceps.



Fig.5b. Ultrasound of Fetal skin biopsy. Note: forceps grasping skin of the fetal thigh.

Direct fetal cardiac sampling, is resorted to only in cases where there is no other route available and if the patient has opted for termination pregnancy for a lethal abnormality. After the fetal blood sample is obtained, the sample is checked for possible maternal cell contamination by a Kleihauer-Betke test especially when the sample is taken from the placental insertion site. If the sampling is done from the intrahepatic portion of the umbilical vein or fetal heart, the Kleihauer-Betke test is not necessary.

In skilled hands, the overall fetal loss rate is comparable to that of CVS and amniocentesis, ranging between 1%-2%. There appears to be no increased incidence of preterm labour or IUGR after a fetal blood sampling.

If the needle punctures the umbilical artery, bradycardia is noticed which usually reverts back to normal rate after the needle is withdrawn. Other complications include umbilical cord hematoma, bleed, abruptio placenta, IUD and infections.¹⁷⁻²¹

Fetal skin biopsy

Fetal skin biopsy is done to diagnose genodermatoses. Bullous diseases, keratinization diseases, pigment cell disorders and disorders of the epidermal appendages (ectodermal dysplasias) can be done by fetal skin biopsy.²² Samples of 16 to 22 weeks' gestation fetal skin obtained by ultrasound-guided biopsy are evaluated using morphologic

(light and electron microscopy) immunohistochemical and biochemical methods. It is performed when the diagnosis is firmly established in the index case. The advent of molecular diagnosis has significantly reduced the need for fetal skin biopsy in the recent years.

Fetal skin sampling is done between 16-22 weeks under ultrasound guidance using a special biopsy forceps (Fig.5a). Fetal analgesia using fentanyl and paralysis with intramuscular pancuronium is preferred. The site of sampling is usually the gluteal region and the thighs (Fig.5b). Usually 7-8 bits are taken from various sites. An electron microscopic study and light microscopy of the fetal skin is done to establish the diagnosis. The samples must be handled with care, stored and transported in the appropriate fashion.

As with any other prenatal invasive procedure there is a risk of miscarriage, amniotic fluid leakage and chorioamnionitis which is about 5% from fetoscopic biopsy.²² Since very few case series of ultrasound guided skin biopsy have been reported, it is difficult to quantify the risks of this procedure.

Points to Remember

- *Ultrasound guided sampling of amniotic fluid, chorionic villi and fetal blood can be done safely when indicated.*
- *The most common indication is for detection of aneuploidy after a positive screening test followed by molecular testing for genetic disorders.*
- *Fetal skin biopsy is performed for identification of genodermatoses.*
- *Pretest counselling and informed consent is mandatory and operator skill is essential to reduce fetal loss rates.*

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NEWS AND NOTES

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Bhagaban Thakur Chwmuhan, North Banamalipur,

Agartala, Tripura (W) 799 001, Mobile: 9436124052,

email: dr_sanjibdb@rediffmail.com

Dr. Parthasarathi Chakraborty, Conference Secretariat,

3 Mantri Bari Road, P.O. & P.S., Agartala,

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PERINATOLOGY

INTRAUTERINE GROWTH RESTRICTION: ANTENATAL DETECTION AND MANAGEMENT

***Lakshmi Shanmugasundaram**

Abstract: *Low birth weight is an important cause of perinatal mortality and morbidity. All fetuses with less than 10th centile growth do not have intrauterine growth restriction (IUGR). Some are constitutionally small, as determined by their parental background. Fetal biometry, doppler studies, liquor volume, fetal anatomy survey, fetal movement pattern, maternal health condition and gestation are the variables to be considered when monitoring or planning delivery for small-for-gestation babies. Risk factors, staging of fetal wellbeing, fetal biometry nomograms, management and morbidity (short term and long term) have been reviewed. Monitoring and delivery should ideally be carried out at a perinatal centre along with long term follow-up.*

Keywords: *Intrauterine growth restriction, Antenatal detection, Management.*

Intrauterine growth restriction (IUGR) is observed in about 23.8% of the newborns and approximately 30 million IUGR babies are delivered worldwide every year. Nearly 75% of all affected babies are born in Asia. The prevalence varies in India from 24.6% to 39%.¹ Clinical suspicion is paramount and ultrasound scan remains the gold standard for diagnosing fetal growth restriction. Low birth weight is one of the important causes of perinatal mortality and also impacts significantly the immediate and long-term outcomes. A small-for-gestational age fetus can be associated with several complications. The fetal complications of IUGR are listed in Table.I.

Table.I Fetal complications of IUGR

Antenatal	Chronic hypoxia, anomalies, stillbirth
Intrapartum	Operative deliveries, cardiotocography (CTG) abnormalities, perinatal hypoxia, stillbirth and meconium aspiration
Neonatal	Feeding difficulties, necrotizing enterocolitis, respiratory distress, hypoglycemia/electrolyte imbalance, hypothermia, anemia, infections and gestation related complications
Childhood and adulthood	70% non-anomalous newborns tend to have a normal catch-up growth and 30% newborns have failure to thrive, increased cerebral palsy risk. As adults-higher risk of coronary artery disease, hypertension, dyslipidemia & metabolic syndrome ²

Definition of intrauterine growth restriction

All fetuses, measuring <10th centile are not growth-restricted. IUGR is a process of pathological interference with the normal growth potential of the fetus. Parental race and body habitus, are the common reasons for a constitutionally small fetus or small for gestational age (SGA).

There is no universally accepted definition for IUGR. Various centile cut-offs are used world-wide, ranging from 3rd centile to 10th centile. Lower the centile, higher the probability of perinatal adverse outcomes. At our institute (IRM & WH), IUGR is defined as biometry/estimated fetal growth of <5th centile.

Ultrasound growth evaluation serially can show any or a combination of the following (Fig.1–4):

1. Slowing or static interval growth velocity
2. Abdominal circumference increase of <1cm over 2 weeks.
3. Biometry [biparietal diameter (BPD), head

* Senior Consultant Obstetrician and Gynecologist, Institute of Reproductive Medicine and Women's Health (IRM and WH), Madras Medical Mission, Chennai.

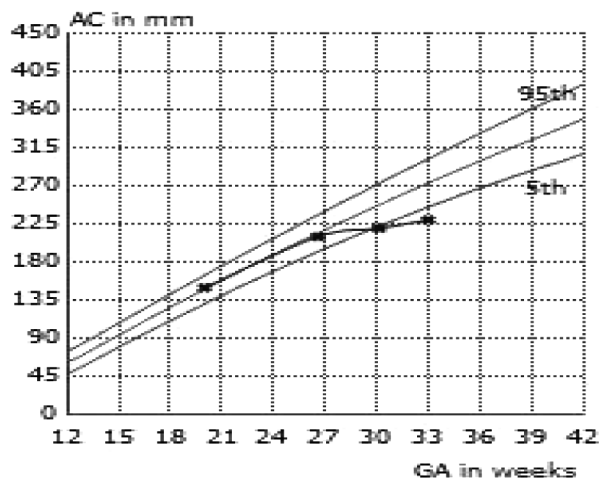


Fig.1. Abdominal circumference with slowing followed by static interval velocity

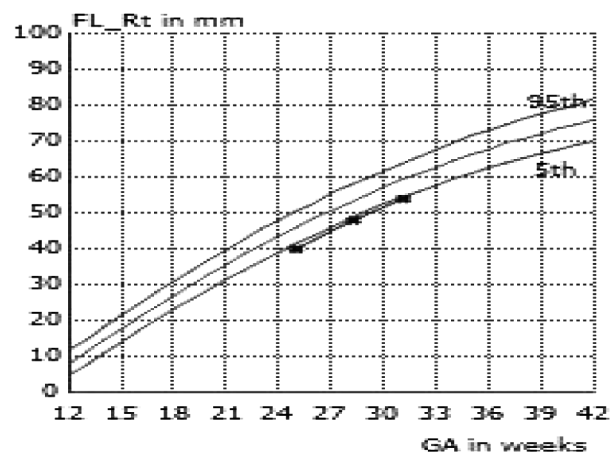


Fig.2. Interval growth of femur length along 5th centile

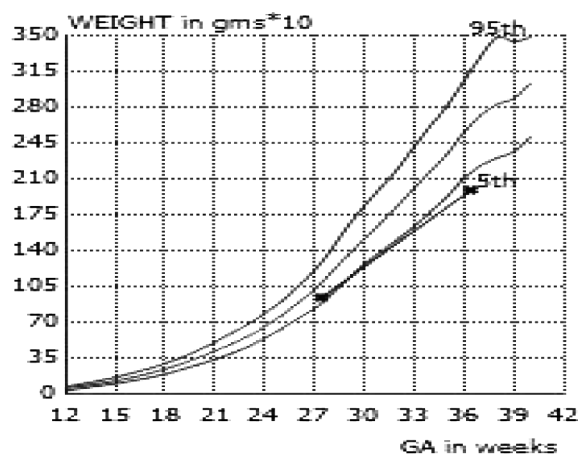


Fig.3. Slowing of interval growth from 5th centile to 2nd centile

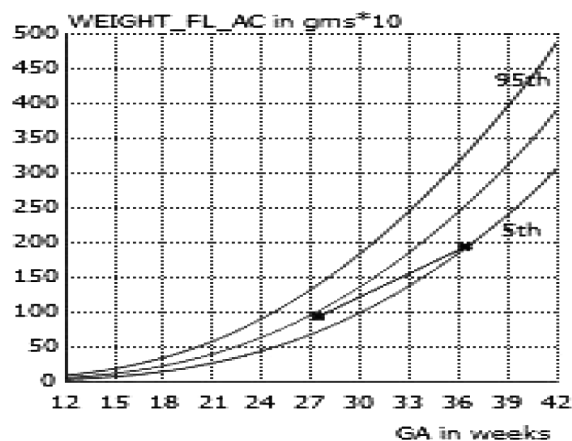


Fig.4. Slowing of interval growth from 50th centile to 5th centile

circumference (HC), abdominal circumference (AC), femur length (FL)] estimated fetal weight (EFW) <10th centile.

4. Reduction in liquor volume
5. Abnormal fetal arterial and venous Doppler

To assess interval growth, ideally a gap of 2–3 weeks, in between scans is required. Unlike IUGR, SGA fetuses tend to show satisfactory interval growth and do not develop Doppler abnormalities, but SGA babies can also develop neonatal and childhood complications.

Fundamentals for detecting IUGR

The very first step is accurate determination of gestational age, since the expected growth range and centiles vary with gestational age. Reliable menstrual history

can determine gestation with over 90% accuracy. However, a first trimester scan with optimal measurement (a trans-vaginal scan will be required until 7 weeks gestation) of fetal crown rump length is the most accurate tool for gestational age determination.³ Certain factors are high-risk for IUGR (Table.II). However, all through any pregnancy, vigilance and clinical assessment of fetal size is required.

Compared with primigravida a multipara with a previous appropriate for gestational age (AGA) fetus, is at a lower risk of IUGR. As pre-eclampsia is one of the common associations with IUGR, an elevated blood pressure should increase vigilance for IUGR and vice versa.

Abdominal palpation with symphysio-fundal height, from 26 weeks onwards, helps to identify women requiring

Table.II Risk factors for IUGR

Maternal risk factors	Fetal risk factors	Placental risk factors
Medical disorders: Hypertension, cardiac, renal and autoimmune disorders	Anomalies	Placental insufficiency
Medications like diuretics /substance abuse/tobacco	Fetal infections	Placental infarction
Past Obstetric history: Pre-eclampsia, small for gestational age fetus, abruption and intrauterine death	Chromosomal defects or genetic conditions	Cord abnormalities, velamentous insertion, 2-vessel cord
Current pregnancy: Low Body Mass Index, low first trimester PAPP-A, increased uterine artery resistance, fetal echogenic bowel pattern, recurrent bleeding and elevated BP	Multiple pregnancy	Placental abruption
Chronic infections: Malaria and HIV		

an ultrasound for fetal growth assesment. Symphysio-fundal height as a screening tool is useful, but has a wide range of accuracy of 40%–85%. Symphysio-fundal height of < 3cm for gestation requires an ultrasound for assessment of fetal growth. Symphysio-fundal height has less accuracy in multiple pregnancy fetus in transverse lie and obesity.

Detection rates of IUGR

Fetal growth by ultrasound scan, especially when assessing a very small or very large fetus, can over estimate or underestimate growth in 10% of pregnancies. Inaccuracy in detection is much higher in maternal obesity, fetal position not conducive for biometry measurements and oligohydramnios. Most studies agree that among the biometry measurements, abdominal circumference (AC) is relatively a more useful indicator of fetal growth. In low-risk populations detection of IUGR with AC has been reported to have sensitivity of 48%-64% and 31%-73% with estimated fetal weight (EFW). In high-risk populations, AC sensitivity of 73% - 95% for IUGR and 43% - 89% for EFW has been reported.⁴

In IUGR, ultrasound scan findings aid in timing of delivery. Hence, all obstetric sonologists/radiologists performing obstetric imaging must periodically audit the fetal growth findings to ensure that standards are met. At the authors' Institute, among 110 SGA fetuses between 2010 and 2013, ultrasound failed to identify SGA in 8 fetuses (7%).

Customised vs standard growth nomogram

Customized growth charts based on the pregnant mothers' racial background, body mass index and previous sibling birthweight have been extensively studied by Gardosi, et al.⁵ Compared with general population nomograms, the use of customised fetal weight centiles has been shown to improve the prediction of adverse perinatal outcomes including stillbirths, neonatal deaths, referral to higher level or special care unit or Apgar score <7 at 5 minutes and perinatal mortality.

Customized birthweight centile charts for 24 to 41 weeks gestation (1%-99%) can be accessed online electronically from the Reproductive Health Library.

The birth weight excel spreadsheet will allow adaptation to local populations mean birth weight.^{6,7} At the author's unit, antenatal growth centiles are calculated using Sonocare^R reporting software (provided by Media logic Solutions Private Limited) as shown in the above growth graph (Fig.1-4). The Sonocare^R charts are based on a large cohort of Indian pregnancies. At our unit, from 238 term low-risk singletons born at 40 weeks (2010-2013), the mean birth weight was calculated to be 3.20 kg (Fig.5). For twin gestation, mean birth weight at 37-38 weeks was 2.53 kg (Fig.6). Our units' singleton growth distribution correlated well with the Sonocare^R graphs, currently in use.

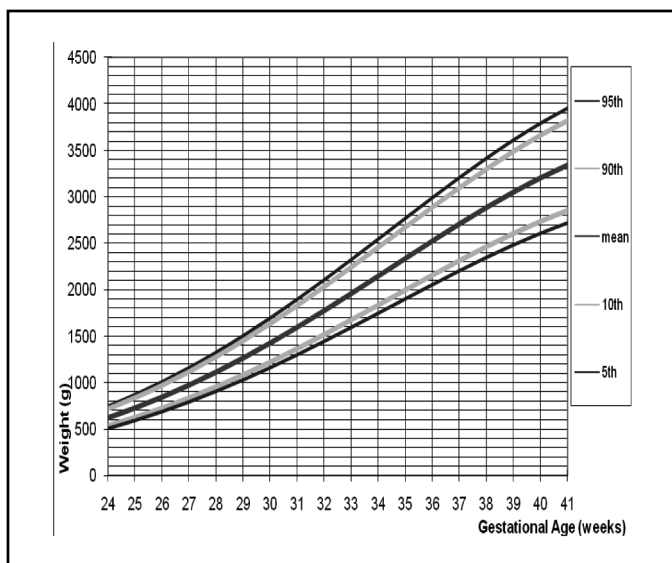


Fig.5. Singleton customized birth weight for IRM & WH (Adapted from the Reproductive Health Library⁷)

With multiple pregnancies, the Sonocare^R charts in current use, overestimates SGA, but carries the advantage of identifying those fetuses at increased risk for morbidity/mortality risk. 20 multiple pregnancy fetuses (out of the total 110 SGA), would not have been assessed to be <5th centile if customized twin centiles were to be applied, but four of them had perinatal problems. One fetus had antenatal Doppler abnormality, two showed mild developmental delay and one was a neonatal death (1.02 kg infant at 30 weeks with persistent low liquor volume from 23 weeks). Hence at our institute we continued use of Sonocare^R charts for both singleton and multiple pregnancies, rather than customized growth nomograms.

Fetal circulation

Blood with the highest concentration of oxygen and substrates enters the fetus via the umbilical vein.

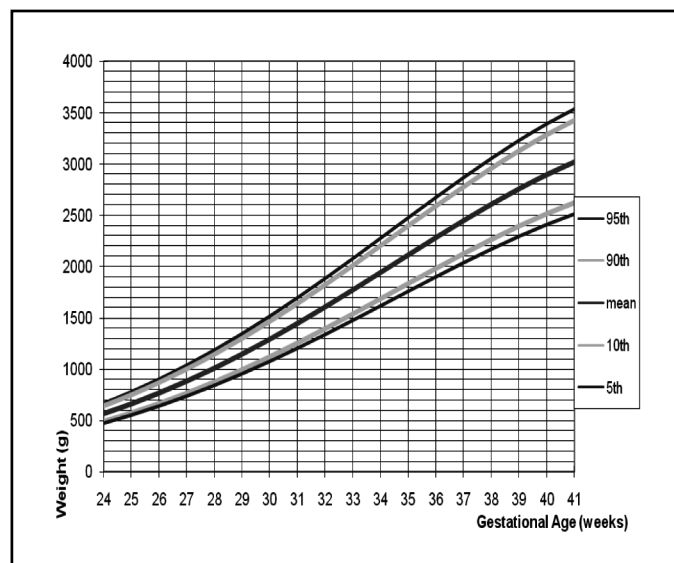


Fig.6. Twins customized birth weight graph for IRM&WH (Adapted from the Reproductive Health Library⁷)

The umbilical vein distributes 18%-25% of its oxygenated blood supply directly to the right atrium via the ductus venosus. The foramen ovale, due to its anatomical location, preferentially allows this oxygen-rich blood from the ductus venosus to reach the left ventricle, while the relatively less oxygenated blood enters the right ventricle. The oxygenated blood is then circulated, through pre-ductal aorta, to the myocardium and brain. In IUGR, normal Doppler flow patterns in the umbilical artery (UA), middle cerebral artery (MCA) and ductus venosus (DV), demonstrates that fetus has preserved its normal circulatory pattern (Fig.7).

Fetal Doppler patterns in IUGR

In IUGR, umbilical blood flow is significantly reduced, mainly due to changes in the placental vascular resistance. A decrease in the number of vessels in tertiary stem villi causes decreased flow through the UA and increased

Table.III Fetal Doppler Grading

	Stage of compromise	Stage of compensation	Stage of decompensation
Umbilical artery	Increased resistance	Absent end diastolic flow	Reversed end Diastolic flow
MCA		Increased diastolic flow	Normalisation of diastolic flow after redistribution flow pattern
DV			Increased Resistance and or Negative 'a' wave
Umbilical vein			Pulsatile flow

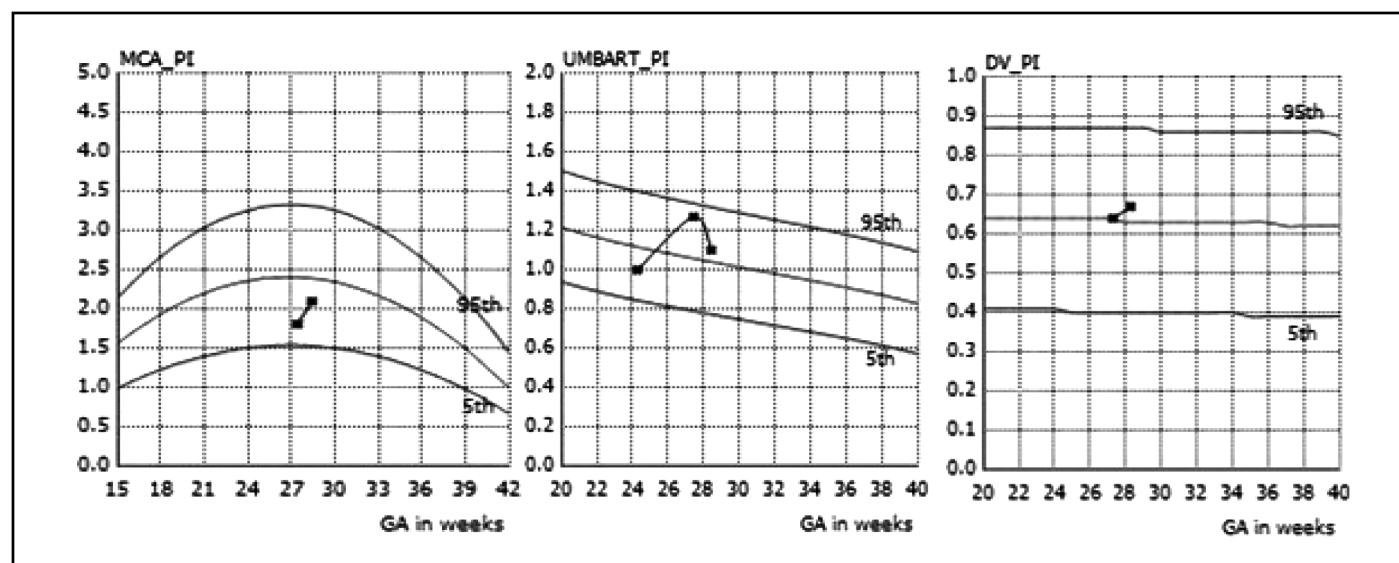


Fig.7. Normal umbilical artery, middle cerebral artery flow, ductus venosus

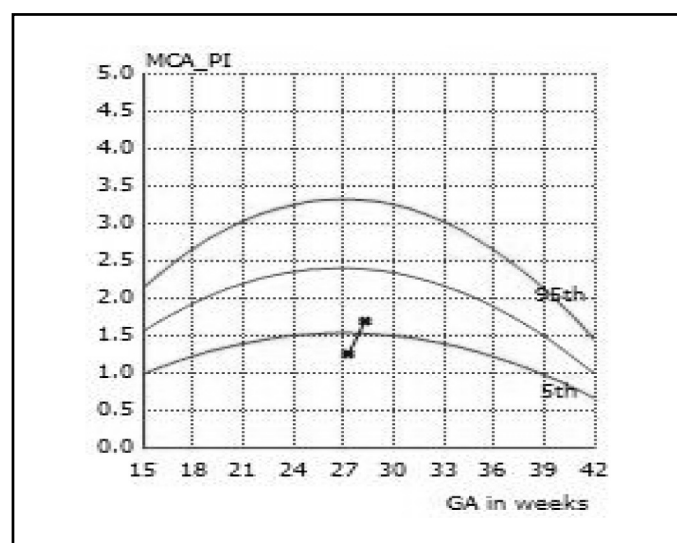


Fig.8. Stage of fetal decompensation- Normalization of MCA after redistribution

pulsatility index (PI) demonstrating placental insufficiency. When absent end diastolic flow (AEDF) is seen in UA, only 30% of placental perfusion tends to be functional.

Low MCA Doppler PI (<5% for gestation) and cerebro-umbilical ratio (C/U) of <1.08 are useful in predicting small-for-gestational age babies with adverse perinatal outcome⁸ but randomized trials are only available to support umbilical artery and ductus venosus flow study. In chronic fetal hypoxia, fetal circulation is redistributed to preserve circulation to vital organs, i.e., the heart, kidneys and brain. The resulting vasodilatation in the MCA is called 'brain-sparing effect' or 'redistribution pattern'- stage 1 doppler change suggestive of complicated IUGR. In stage

2 doppler changes of reversal of umbilical artery Doppler flow or increased ductus venosus PI is observed and this indicates a stage of fetal compromise. However, if hypoxia persists, the diastolic flow returns to the normal level 'normalization after redistribution', which is a terminal decompensation indicating high probability of fetal acidemia (Fig.8). Stage 3 doppler change suggestive of decompensated fetus.

Fetal Doppler monitoring schedule

Fetal Doppler monitoring in IUGR, especially in preterms, can help to prolong pregnancy until a stage of decompensation occurs.

Recommendations for monitoring that are based on current evidence⁹ suggest the following:

1. Normal UA, repeat surveillance every 14 days (grade B evidence). More frequent in case of severe SGA or associated medical complications like elevated blood pressure etc.
2. UA abnormal and delivery is not indicated, twice weekly biophysical profile and Doppler studies when end-diastolic velocities present or daily when AEDF/ REDF (reversed end diastolic flow).
3. MCA abnormal, delivery latest by 37 weeks gestation (grade C). Term SGA, with normal umbilical artery Doppler and abnormal middle cerebral artery Doppler (PI <5th centile) has moderate predictive value for acidosis at birth and should be used to time delivery (Grade C). Preterm MCA has limited accuracy.

In the early onset IUGR, timing of delivery can be tricky due to the need to avoid extreme prematurity, while

aiming to improve morbidity and to avoid mortality. For early onset IUGR, the TRUFFLE Study¹⁰ has demonstrated improving trend in perinatal mortality and morbidity - at 26 weeks gestation, 17% fetal and neonatal death occurred compared with 43% as reported in previous studies and at 30 weeks, mortality was <3%, in contrast to previous report of 17%.¹¹ This study has helped substantiate the role of ductus venosus Doppler and computerized CTG, but a full picture will emerge, when the two-year long term outcome for this study population is published. In IUGR, rate of progression and sequence of changes within the fetal circulation can be variable.¹² Study of aortic isthmus Doppler appears to demonstrate abnormality at an earlier stage of fetal compromise than ductus venosus and appears to have scope for use in future.

Medical interventions that improve IUGR outcome

Cochrane review on prophylactic dose of subcutaneous low molecular weight heparin¹³ has shown a statistically significant reduction in risk of perinatal mortality, preterm birth before 34 and 37 weeks' gestation, and infant birth weight below the 10th centile for gestational age. However, there is a lack of reliable information on infant health outcomes.

A low dose aspirin of 50-150 mg per day has been shown to reduce PIH in women and perinatal mortality in these fetuses with IUGR when started at <16 weeks in high risk women. The safety profile of low dose aspirin in pregnancy is well established.

L arginine supplementation has been tried in experimental animal models and human IUGR studies.

No conclusive benefit has been reported and possibility of harm with high dose protein supplements has also been studied. Hence there is no current evidence to support use of L arginine, outside a research setting.

In a small Indian study¹⁴, clinically overt vitamin A deficiency was observed in at least 24% mothers of IUGR and 10% in the control group. Due to wide variation, in nutritional status of Indian pregnant women, specific supplementation should be resorted to, only when there is proven deficiency and established therapeutic schedules.

Betamethasone, 12mg two doses intramuscular, 24 hours apart, prior to preterm delivery has a well established evidence base, in reducing neonatal morbidity in IUGR.

Points to Remember

- *Meticulous evaluation for an underlying cause is required when evaluating a small for gestation fetus.*
- *IUGR is associated with perinatal mortality and neuro-developmental delay, and still birth risk. Hence appropriate steps to periodically check fetal size clinically and confirmation by ultrasound is absolutely vital.*
- *In IUGR, UA and DV changes helps individualize care and timing of delivery before fetal decompensation occurs. There is a role for low dose aspirin and low molecular weight heparin to improve fetal outcome.*
- *IUGR scans should be done by a qualified sonologist, experienced in obstetric Dopplers. A secondary/tertiary centre referral should be considered. Presence of 24 hours monitoring facilities and obstetric, neonatal, anesthetic and nursing staff availability is important, especially in early onset IUGR.*
- *Long term follow-up of all SGA babies should incorporate neuro-developmental follow-up. This will enable us to understand the influence of all the monitoring parameters and intervention measures that can result in a good outcome.*

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CLIPPINGS

Speech and language therapy interventions for children with primary speech and language delay or disorder

It is thought that approximately 6% of children have speech and language difficulties of which the majority will not have any other significant developmental difficulties. Whilst most children's difficulties resolve, children whose difficulties persist into primary school may have long-term problems concerning literacy, socialisation, behaviour and school attainment.

Objectives: To examine the effectiveness of speech and language interventions for children with primary speech and language delay/disorder.

Selection criteria: The review considered randomised controlled trials of speech and language therapy interventions for children or adolescents with primary speech and language delay/disorder.

Authors' conclusions: The review shows that overall there is a positive effect of speech and language therapy interventions for children with expressive phonological and expressive vocabulary difficulties. The evidence for expressive syntax difficulties is more mixed, and there is a need for further research to investigate intervention for receptive language difficulties. There is a large degree of heterogeneity in the results, and the sources of this need to be investigated.

Law J, Garrett Z, Nye C. Speech and language therapy interventions for children with primary speech and language delay or disorder. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD004110. DOI: 10.1002/14651858.CD004110. Assessed as up to date: 9 May 2003.

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PERINATOLOGY

FETAL THERAPY: A REVIEW OF INVASIVE AND NON-INVASIVE THERAPIES

***Anuradha Dogiparthi**

****Tejo Pratap Oleti**

****Srinivas Murki**

Abstract: *Fetal therapy has significantly improved the outcomes of many medical and surgical disorders of the fetus in the recent past. Medical therapy for fetal thrombocytopenia, fetal goitre, arrhythmias and intrauterine infections including Human Immunodeficiency Virus (HIV) and appropriate use of antenatal steroids are mostly successful and safe to the fetus. Invasive therapies such as in-utero transfusions for Rh isoimmunisation and laser photocoagulation for twin to twin transfusion is almost routine in advanced centres. Stem cell and gene therapy for the management of many genetic, metabolic and blood disorders in the fetus/newborn are emerging. This review highlights many issues related to existing and newly developing invasive and non-invasive fetal therapies.*

Keywords: *Fetus, Invasive and non-invasive therapy, Fetal arrhythmias, Fetal thrombocytopenia, Perinatal HIV, Antenatal corticosteroids, Gene therapy.*

With improved fetal monitoring techniques such as three- and four-dimensional ultrasound, Doppler, laser photocoagulation, newer fetal surgical techniques, stem cell and gene therapy concepts, the scope for fetal therapy has improved dramatically in the last few decades. Fetal therapy can be broadly classified as a) transplacental therapy and b) invasive therapy. Medical management of fetal arrhythmias, goitre, congenital adrenal hyperplasia, thrombocytopenia, intrauterine infections and polyhydramnios constitute the main transplacental therapies (Table I), while fetal surgeries, thoraco-amniotic shunts, laser photocoagulation and intrauterine transfusions constitute the invasive therapies (Table II). Fetal stem cell and gene therapies are still experimental.

* Assistant Professor,
Kamineni Hospitals, Hyderabad.

** Consultant Neonatologist,
Fernandez Hospital, Hyderabad.

Trans-placental therapies

Fetal thrombocytopenia

These are non-invasive interventions to treat the fetus through administration of drug to the mother. Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is the most common reason for immune thrombocytopenia in fetus and newborn. FNAIT is caused by maternal sensitization to paternally derived antigen on fetal platelets mostly HPA-1a. This is the platelet equivalent of Rhesus disease, but unlike Rh isoimmunization, severe disease can occur even in the first pregnancy. The disease severity increases with subsequent pregnancies. The most dreaded complication of FNAIT is intracranial hemorrhage (ICH) which could occur in nearly 25% of affected fetuses.¹

Screening for FNAIT is performed on any fetus or newborn with unexplained thrombocytopenia or intracranial bleed. Antenatal management is possible only in subsequent pregnancies. In all affected fetuses and neonates, subsequent pregnancies need to be screened for fetal affection. If the mother is Human platelet alloantigen (HPA) negative, the father is to be screened. If the father is HPA negative, it is unnecessary to screen the fetus. If the father is homozygous positive, the fetus is considered to be affected. On the other hand if the father is heterozygous positive, the fetus needs to be screened for HPA antigen.

If the fetus is affected, antenatal therapy is divided into two risk strategies.¹

a) High risk: If fetal platelets are $< 20,000/\text{mm}^3$ or the previous sibling has had an ICH, the mother should be given weekly immunoglobulin at 1 g/kg and prednisolone 1mg/kg/day till delivery.

b) Low risk: If fetal platelets $> 20,000/\text{mm}^3$ with no ICH in previous affected sibling, IVIG should be given in a dose of 0.5 to 1g/kg/week till delivery.

The mechanism of action of IVIG is still not clear. The possible explanations are:

1. IVIG dilutes the transplacentally transferred IgG HPA antibodies.
2. IVIG blocks the Fc receptor on the placenta and decreases transfer to the fetus.

3. In the fetus IVIG blocks the Fc receptors on the macrophages and decreases the destruction of platelets.

Fetal arrhythmias

Supraventricular tachycardia (SVT), atrial flutter and second degree congenital heart block are the fetal arrhythmias that are amenable to transplacental therapy with anti-arrhythmic drugs. Fetal tachycardia is diagnosed when the HR >180/min. Differentiation of fetal tachyarrhythmia is possible by using M-mode and Doppler echocardiography. Simultaneous recording of the Doppler waveform at the superior vena cava and ascending aorta is an important tool in assessing the interval between atrial and ventricular contractions. The beginning of reverse flow at the SVC created by atrial contraction and the beginning of forward flow at the aorta created by ventricular contraction are interpreted as the beginning of P and QRS wave respectively by the electrocardiogram (ECG). Using Doppler waveform, the relation and time intervals of the atrial and ventricular contractions can be measured. Fetal SVT is defined by HR >180/min, 1:1 AV conduction and minimal beat-to-beat variability. In atrial flutter, the atrial rates are between 300 to 500 / min while the ventricular rates range from normal to >300bpm depending on the degree of AV block. Most cases of atrial flutter have a 2:1 AV block. Fetuses with higher ventricular rates tend to develop hydrops. Fetal bradycardia is defined as HR <100bpm. Isoimmune congenital heart block is the only form of bradyarrhythmia that is amenable to prenatal drug therapy.

Most cases of SVT and atrial flutter respond successfully to trans-placental administration of anti-arrhythmic drugs. Digoxin is the first line therapy for fetal tachyarrhythmia.² Sotalol, flecainide and amiodarone are used as second line anti-arrhythmic agents when digoxin fails to convert to sinus rhythm.

For fetuses with SVT and prolonged VA interval (time between ventricular stimulus and atrial stimulate following it) or hydrops, digoxin is rarely effective. Sotalol and flecainide have effective placental transfer and hence are preferred presence of fetal hydrops.³ Fetal intramuscular administration of digoxin with maternal administration of amiodarone is an alternative therapy for fetal hydrops and SVT.³

Beta stimulants and steroids have been reported to be effective transplacental treatments for fetal bradycardia. Beta stimulants such as ritodrine, terbutaline and salbutamol effectively increase fetal ventricular rate by approximately

10%–20% and reverse hydrops in some fetuses with AV block.³ Transplacental administration of steroids, such as dexamethasone and betamethasone, are effective for fetuses with AV block caused by anti-SSA antibody.⁴ Prenatal steroids work by two mechanisms. The first is a direct effect on the AV block. Administration of steroids in the early phase of AV block may revert it and normalize to sinus rhythm. The second mechanism involves improving the fetal myocarditis secondary to maternal antibodies. Maternal autoantibodies affect not only the AV node, but also fetal myocardium and can cause myocarditis. Transplacental administration of steroids is thought to be effective for treating myocarditis and may improve cardiac function of the fetus. This prenatal treatment of myocarditis is also thought to prevent postnatal cardiac dysfunction, such as endocardial fibroelastosis and late-onset dilated cardiomyopathy.

Congenital adrenal hyperplasia (CAH)

More than 90% of CAH are caused by 21 hydroxylase deficiency and found in 1:10000 to 1:15000 live births. CAH is a genetic disorder with autosomal recessive inheritance. 21-hydroxylase is a microsomal cytochrome P450 enzyme that converts progesterone to deoxycorticosterone and 17 α hydroxyprogesterone to 11 deoxycortisol in the glomerulosa and fasciculate zones of the adrenal cortex respectively. The enzyme is the product of a gene (CYP21) located on the short arm of chromosome 6. The disease has two major consequences: cortisol deficiency and hyperproduction of adrenal androgens due to excess ACTH production. Cortisol deficiency presents after birth with salt wasting, vomiting, failure to thrive and acute metabolic crisis. Prenatal androgen excess leads to masculinization of female genitalia resulting in clitoromegaly, labial fusion, urogenital sinus and complete phallus in some fetuses. Excess ACTH results in hyperpigmentation of genitals, groins and axilla in both the sexes.

Prenatal diagnosis and treatment is often offered to a couple with a previously affected child. As soon as the pregnancy (≥ 8 weeks) is confirmed, the mother is started on dexamethasone 20 μ g/kg/day in 3 divided doses. Fetal sex is determined either with chorionic villus sampling or with amniocentesis. If the fetal sex is male, dexamethasone to the mother is stopped. If the fetal sex is female, DNA analysis is done to identify the mutation for CAH. If the female fetus is affected then treatment is continued till term, else treatment is terminated. Pre-natal dexamethasone prevents in utero virilization of CAH females and suppresses the adrenal hypertrophy.

Table.I Non-invasive fetal therapy

Disease	Fetal manifestations	Fetal/Neonatal Features	Fetal therapy
Alloimmune thrombocytopenia	Intracranial bleed Low platelets	Intracranial bleed, Low platelets	IVIG 0.5 to 1g/kg/week; Prednisolone 1mg/kg/day
Fetal tachyarrhythmia	HR >180/min Hydrops	CCF, Hydrops, Tachycardia	Digoxin (0.25mg/dose, thrice daily oral or 2mg loading followed by 0.5mg 12 hourly IV), Flecainide (100mg twice or thrice daily-Oral), Amiodarone (800-2400mg once daily-Oral), Sotalol (80-160mg twice daily-Oral)
Fetal bradycardia	HR<100/min Hydrops	Bradycardia, Congestive heart failure, Positive Ro and La Antibodies	Dexamethasone 4mg once daily for 6 weeks Salbutamol 16 mg thrice daily
Congenital adrenal hyperplasia	Virilisation of female external genitalia	Virilization of female external genitalia, Failure to thrive, Vomiting, Hyponatremia, Hyperkalemia, Hyperpigmentation	Dexamethasone 20µg/kg/day in 3 divided doses starting at 6 to 8 weeks in all at risk pregnancies and continue till term only if the fetus is female after 14 weeks.
Toxoplasmosis	PCR DNA positive Hepatosplenomegaly Hydrops	Rash, Thrombocytopenia, Hepatosplenomegaly, Chorioretinitis, Intracranial calcifications, Seizures, IUGR, Mental retardation	At risk fetus : Spiramycin 9×10 ⁶ units/day. Affected Fetus : Pyrimethamine: 100mg loading follow with 25 to 50mg once daily. Sulphadiazine: 1 g four times a day. Folinic Acid: 7.5mg per day
HIV	Nil	Not common	3 drug antiretroviral therapy (AZT+3TC+NVC or AZT+3TC+EFV) or 3 drug antiretroviral prophylaxis (AZT+3TC+LPV/r or AZT+3TC+ABC or AZT+3TC+EFV)
Methylmalonic acidemia	Nil	Normal at birth, Encephalopathy, Seizures, Acidosis	B12 therapy to the mother
Multiple carboxylase deficiency (biotin responsive)	Nil	Rashes, Diarrhoea, Liver dysfunction, Metabolic acidosis	Biotin to the mother
Maternal PKU	Nil	Microcephaly	Phenylalanine restricted diet

Disease	Fetal manifestations	Fetal/Neonatal Features	Fetal therapy
CCAM	Cystic lesion or mass in the thorax Shift of mediastinum	Cystic lesions in the thorax, Respiratory distress, Asymmetry in chest signs Hydrops fetalis	Betamethasone 12mg intramuscular 2 doses at 24 hours apart, Fetal Surgery
Neural tube defects	Swelling over the spine Hydrocephalus Lemon and banana Sign	Cystic mass over spine Lower limb paralysis Bladder and bowel dysfunction Arnold Chiari malformation	Folic Acid 0.4mg to all pregnant mothers prior to conception Folic Acid 4mg to all at risk pregnant Mothers starting 1 month prior to conception and till 3 months after conception
Congenital cardiac diseases like severe aortic and mitral stenosis	In some cases present with hydrops	Features of shock in early part of life	Balloon valvuloplasty
Antenatal Steroids	Nil	Decreased mortality, Decreased RDS, Airleak, Decreased IVH	To all preterm deliveries expected between 24 to 34 weeks of gestation Betamethasone 12 mg 24 hours apart for 2 doses Dexamethasone 6 mg 12 hourly for 4 doses
Intrauterine growth restriction	Abdominal girth Oligohydramnios	Small for gestation Increased skin folds Polycythemia Hypoglycemia PPHN Pulmonary hemorrhage Increased Infections Increased mortality	Balanced protein and energy supplementation specially for malnourished mothers Malarial chemoprophylaxis in malaria endemic areas

Dexamethasone is chosen for its ability to cross the placental barrier and its long half-life. Prenatal treatment must be done under careful, centralized and ideally long term medical supervision.⁵

Metabolic disorders

Inborn errors of metabolism include a wide range of diseases which include errors in metabolism of different substrates in the body. The clinical manifestations range from failure to thrive to severe encephalopathy leading to life threatening problems. Most of them occur due to single gene disorders, which can be diagnosed through CVS sampling.

Few of these disorders can be treated with dietary modification and vitamin supplementation in the early part of life. Definitive treatment is not available for many of

these disorders. Some of these disorders have their effects on developing fetus in utero.

Diseases like multiple carboxylase deficiency and methylmalonic acidemia caused due to deficiency of co-factors useful for their metabolism can be managed with their supplementation to pregnant mother. See Table.1 for their manifestations and treatment.

Fetal goiter

Large goiter in the fetus is an uncommon but potentially serious complication of the treatment of hyperthyroidism in pregnant mother with propylthiouracil or of maternal Graves disease. It could also occur due to fetal dyshormonogenesis or iodine deficiency or iodine excess. The cause of goitre in fetus need to be determined by fetal blood sampling. An enlarging goitre is a potential risk for the fetus, as it

Table.II Invasive fetal therapies

Disease	Fetal manifestations	Fetal/Neonatal features	Therapy
Twin to twin transfusion	Oligohydramnios Polydramnios Monochorionic twins Interconnecting vessels	Weight difference >25%, Hb difference >5g/dl	Laser photocoagulation
Fetal goiter	Mass	Airway obstruction, Difficult intubation	Levothyroxine Intra-amniotic 250 µg weekly
Rh isoimmunization	Hepato splenomegaly Hydrops Increased MCA blood flow	Anemia, Early jaundice, Hepatosplenomegaly, Hydrops, DCT positive	Intrauterine transfusion
Hydrops with arrhythmia	HR>180/min Hydrops	HR>180/min, Hydrops, ECG abnormality	Intramuscular digoxin Sotalol Flecainide
Posterior urethral valve	Bilateral hydronephrosis Distended and thickened bladder, Key hole appearance, Oligohydramnios	Bilateral, hydronephrosis, Distended and thickened bladder, Key hole appearance, Poor urinary stream	Vesicoamniotic shunt
CCAM	Cystic changes Mediastinal shift Polyhydramnios	Respiratory distress, Mediastinal shift, Hydrops, Cystic changes on the CXR	Open surgery
Pleural effusion	Mediastinal shift	Respiratory distress, Unilateral lung opacity, Decreased air entry	Aspiration Pleuroperitoneal shunt
Neck masses			Fetal surgery (EXIT procedure)
Sacroccygeal tumor			Fetal surgery
Congenital diaphragmatic hernia	Absent stomach bubble Polyhydramnios Mediastinal shift Lung-head ratio	Respiratory distress, Mediastinal shift, Scaphoid abdomen, Bowel in the chest	PLUG therapy
Ovarian cysts	Cystic intra-abdominal mass	Abdominal cystic mass	Aspiration of cystic contents

would obstruct the esophagus and trachea leading to fetal asphyxia, dystocia because of fetal neck hyperextension and polyhydramnios.

Prenatal treatment of fetal hypothyroidism requires direct administration of thyroid hormone to the fetus, because placenta is relatively impermeable to thyroxine and triiodothyronine in the maternal blood. Fetal therapy is possible with intravenous, intramuscular and intra-amniotic injection of levo thyroxine. Intravenous and intramuscular injections to the fetus are technically difficult; require frequent injections and poses risk of fetal injury and bleeding. Weekly intra-amniotic injections of thyroxine 250µg from the time of diagnosis till delivery regress the fetal goitre and may also have beneficial effects on the fetal brain.^{6,7}

Congenital cystic adenomatoid malformations (CCAM)

CCAM is a benign multi cystic mass of non-functioning pulmonary tissue that is usually restricted to one lobe of the lung. It is a discrete intra pulmonary mass containing cysts varying from < 1mm to >10 mm in size. Majority of CCAMs derive their blood supply from pulmonary artery. CCAM histologically is characterized by an overgrowth of terminal respiratory bronchioles that form cysts of various sizes and lack normal alveoli. A single course of prenatal betamethasone (12 mg intramuscular 24 hours apart) is effective in decreasing the size of CCAM and in resolution of hydrops in majority of microcystic/solid CCAMs.⁸ This therapy is most useful when CCAM volume to head (CVR) ratio is >1.6 or in the presence of hydrops. Betamethasone may down-regulate the abnormal gene expression or accelerate the lung maturation in the CCAM lung tissue.

Intrauterine infection

Maternal infection with toxoplasmosis and human immunodeficiency virus (HIV) are the viral infections in which treatment to the mother will prevent fetal infection or sequelae to the fetus.

Toxoplasma infection to the mother may occur through ingestion of infected, undercooked meat or contaminated food or water. Transmission to the fetus almost solely occurs when the primary infection occurs during pregnancy. Fetal infection would result in hearing or visual loss, mental and psychomotor retardation, seizures, hematological abnormalities, hepatosplenomegaly or death. The frequency of vertical transmission increases with gestational age. However, the severity of infection is more when affected early in gestation. Although it is ideal to screen all pregnant women for toxoplasmosis, it is usually recommended only

in symptomatic women or in women at risk. Serological tests and PCR are used to diagnose toxoplasmosis in pregnant women. Serological screening for IgG and IgM antibodies should be done as early in gestation as possible. If the serological tests are positive, then further tests are ordered to determine whether the infection was acquired recently or in the distant past. A negative IgG and IgM rules out toxoplasma infection. Positive IgM with negative IgG requires repeat testing at 1 to 3 weeks. If the repeat IgG is positive then it suggests recent infection. If IgG and IgM are both positive, further tests include IgA, IgE and Avidity test to determine the time of infection. Positive IgA, IgE and low avidity indicate recent infection. If mother is confirmed to be infected during pregnancy, fetal affection is confirmed with amniotic fluid PCR and ultrasound.

Toxoplasma infection during pregnancy without affected fetus should be treated with spiramycin. If the fetus is affected, the mother needs to be treated with pyrimethamine, sulphadiazine and folinic acid till delivery. Spiramycin would prevent maternofetal transmission; pyrimethamine with sulphadiazine and folinic acid would treat the fetal infection.⁹

Perinatal HIV

Nearly 1 million women in India are living with Human Immunodeficiency Virus infection. Nearly 4 per 1000 pregnant women are HIV positive in our country. Untreated, nearly 40% is at the risk of perinatal transmission (in utero, perinatal, postnatal) of HIV infection from the mother to the fetus/newborn. With prenatal diagnosis and prophylaxis during the perinatal period, perinatal HIV transmission is preventable in all but 2% or less. Without antiretroviral drugs during pregnancy, risk of transmission from mother to fetus is 1 in 4. Nearly 80% of this transmission occurs peripartum. Maternal HIV-1 RNA levels, CD4 lymphocyte count, presence of co-infections such as Hepatitis C, cytomegalovirus, bacterial vaginosis and maternal ARV prophylaxis, vaginal delivery, length of rupture of membranes, invasive procedures and prematurity increase chances of mother to child transmission of HIV.

HIV screening is universal in all pregnant women at the time of pregnancy registration with an option to refuse screening. In women at risk and in those whose status is unknown, third trimester or pre-delivery screening is recommended. If the mother meets the criteria for treatment, potent combination therapy (Anti-retroviral therapy) is the standard of care. All HIV infected pregnant women with CD4 cell count <350cells/mm³, irrespective of WHO clinical staging; and for all HIV infected pregnant women in WHO clinical stage 3 or 4, irrespective of CD4

cell count should be on antiretroviral therapy. The preferred first line ART regimen should include an AZT+3TC backbone (AZT+3TC+NVC or AZT+3TC+EFV). If mother does not require treatment for her health, 3 drug combination with anti-retroviral regimen is recommended for perinatal prophylaxis (AZT+3TC+LPV/r or AZT+3TC+ABC or AZT+3TC+EFV). If maternal CD4 count is high and HIV RNA levels are low, consider delay in prophylaxis till end of 1st trimester. Zidovudine monotherapy for prophylaxis is not recommended but may be considered if viral load is <1000 copies /mL.¹⁰

Intrauterine growth restriction

In a meta-analysis, providing pregnant females with balanced protein energy supplementation resulted in a significant reduction of 31% in the risk of small for gestational age infants [Relative risk (RR) with 95% confidence interval (CI) = 0.69(0.56 to 0.85)]. Pooled results for mean birth weight showed that balanced protein supplemented group gained more weight compared to control [Mean difference 59.89 g, 95 % CI 33.09-86.68]. This effect was more pronounced in malnourished women compared to adequately nourished women.¹¹ Effective prevention of malaria in pregnant women in malaria-endemic settings may reduce the likelihood of LBW by 5%-14%, and may reduce the amount of preventable LBW by more than 30%.

There is little evidence that other maternal antenatal treatment enhances fetal growth in growth restricted fetuses.¹² Numerous approaches have been tried in small randomized trials, including nutritional supplementation, maternal oxygen therapy and interventions to improve blood flow to the placenta, such as plasma volume expansion, low dose aspirin, heparin, bed rest and beta-mimetics, calcium channel blockers or sildenafil. None have consistently been shown to be of value. Antihypertensive therapy of hypertensive mothers does not improve fetal growth.

Antenatal steroids

Since the observation made by Liggins et al., the antenatal steroids have played major role in decreasing the mortality and morbidity of the premature neonates.¹³ The steroids act by both genomic and non-genomic pathways. These pathways will help in the maturation of different structural changes and physiological pathways. The major role has been attributed to lung maturation by increasing the production of surfactant from type II pneumocytes and improving the gas exchange by maturation of type I pneumocytes.

Drugs available: Commonly used drugs are dexamethasone and betamethasone. In case of non-availability of these two, hydrocortisone can be used. Hydrocortisone is least preferred as it is rapidly metabolized by placental enzymes.

Dosage and schedule: Complete course consists of

- Inj.Betamethasone: two doses given as 12 mg intramuscularly 24 hourly
- Inj.Dexamethasone: 4 doses given as 6 mg intravenously 12 hourly

Indication: To be given to all mothers with gestational age between 24 to 34 weeks who are at risk of anticipated preterm delivery in the next seven days. Maximum benefit has been shown to occur 24 hours after the completion of course of antenatal steroids.

Benefits: Cochrane systematic review¹⁴ has shown that there is reduction in the incidence of respiratory distress syndrome by 34% [RR with 95% CI = 0.66 (0.59-0.73), 21 studies, 4038 infants], reduction in moderate to severe RDS [RR, with 95% CI= 0.55 (0.43-0.71), 6 studies, 1686 infants], intra ventricular hemorrhage (IVH) [RR with 95% CI = 0.54 (0.43-0.69); 13 studies, 2872 infants] necrotizing enterocolitis (NEC) [RR with 95% CI = 0.46, (0.29-0.74); 8 studies, 1675 infants], mortality [RR with 95% CI= 0.69 (0.58-0.81) 18 studies, 3956 infants], systemic infection in the first 48 hours of life [RR with 95% CI = 0.56 (0.38-0.85); 5 studies, 1319 infants]

There was also a trend towards decreased incidence of patent ductus arteriosus (PDA) and other morbidities. These benefits also were present when the steroids were used in extremely premature neonates (22- 23 weeks of gestation).¹⁵

Dexamethasone has been shown to be more efficacious than betamethasone in reducing overall incidence of IVH¹⁶ However same benefit was not significant when only severe IVH was taken into account. Betamethasone is preferred over dexamethasone because of lesser number of doses and side effects.

There is no consensus for usage of repeat doses of corticosteroids when pregnancy was prolonged beyond seven days. However, recent systematic review done in 2011, showed that there is reduction in the incidence of hyaline membrane disease and composite outcome in the neonatal period. But there is no evidence of improvement in the long term neurodevelopmental outcomes.¹⁷

Use beyond 34 weeks of gestation: Given the lack of strong evidence for the use of antenatal steroids beyond 34 weeks, National Institutes of Health (NIH) Consensus Development Conference on the Effect of Glucocorticoids for Fetal Maturation on Perinatal Outcomes and Royal College of Obstetricians and Gynecologists stated that administration of antenatal corticosteroids after 34 weeks can be considered if there is evidence of pulmonary immaturity. This consensus was based on ASTECS trial.^{18,19}

Side effects

Mother : Antenatal corticosteroids are not shown to increase the incidence of puerperial sepsis or chorioamnionitis.

Infants and children : Evidence shows that there is no potential harmful effects on hypothalamic-pituitary axis (HPA) or increase in the incidence of infections in the neonatal period.

Contraindications: Documented evidence of clinical chorio-amnionitis in the pregnant mother.

Invasive fetal therapies

In-utero transfusions (IUT)

In utero isoimmunization in a Rh positive fetus is the commonest indication for in utero transfusion. Rh negative women who deliver Rh positive babies or had a Rh positive abortus or fetal death or exposed to Rh positive blood are at risk of producing anti-Rh antibodies. The antibodies produced in mother are transferred to the developing fetus and cause hemolysis of its red blood cells. The severity of disease ranges from neonatal hyperbilirubinemia to severe hydrops. The disease severity increases in subsequent pregnancies.

All the pregnant women who come for antenatal checkups are screened for Rh status at their first antenatal visit. All the Rh negative women should be screened for anti-Rh antibodies in their serum using indirect Coombs test (ICT). If the pregnant woman screened is positive with ICT, then the fetus should be screened for the presence of Rh isommunization i.e anemia and hemolysis. Both invasive and non-invasive methods are available for screening of fetus at risk of anemia. Invasive methods include direct measurement of hematocrit (Hct) by drawing fetal blood during cordocentesis and indirectly by presence of bilirubin in amniotic fluid which can be measured at optical density (OD) - 450 by using spectrophotometry.²⁰ The severity of anemia can also be measured indirectly by looking at the peak systolic velocity (PSV) of middle cerebral

artery with doppler-ultrasonography.^{21,22} PSV of MCA increases with increasing anemia secondary to hyperdynamic fetal circulation. Nomograms are available for all the methods.

The affected fetus can be managed with intrauterine transfusion (IUT). The less popular methods are intra peritoneal transfusion and antenatal intravenous immunoglobulin administration.²³⁻²⁵ IUT can be done after the fetus attains period of viability. IUT can be done by using umbilical vessels, hepatic vein or rarely intracardiac. Umbilical vessels are the preferred ones among all. Umbilical vein is preferred over artery because of fewer complications. Complications of IUT include fetal bradycardia and cardiac failure, umbilical cord hematoma, chorioamnionitis and preterm labor.

The steps in intrauterine transfusion are described in Box 1.

Intrauterine transfusion may also be used for the treatment of fetal anemia due to other blood group incompatibility and parvo-viral infection.

Laser photocoagulation

Twin to twin transfusion syndrome (TTTS) affects 10%-15% of monochorionic diamniotic gestations. This results in oligohydramnios in the donor fetus and polyhydramnios in the recipient twin. Progression to severe TTTS manifests in the donor twin by abnormal doppler wave form abnormality in the umbilical artery. Progression also results in maladaptive changes in the recipient twin with cardio myopathy, abnormal ductus venosus wave form patterns and hydrops. Fetoscopic laser photocoagulation is the primary therapeutic modality for TTTS between 18 to 26 weeks of gestation.²⁷ Laser photocoagulation involves conscious sedation or local anesthesia to the mother, percutaneous fetoscopy and selective ablation of the anastomotic vessels in the inter twin membrane. Complications of these procedures may include premature rupture of membranes, chorioamniotic membrane separation, preterm labor and preterm delivery. Fetoscopic laser photocoagulation is also used for the treatment of twin reversed arterial perfusion (TRAP).

Fetal surgeries

Improved fetal imaging, maternal and fetal anesthesia, instrumentation and techniques have resulted in better outcome of fetuses with complex developmental malformations. Although fetal surgery was meant to prevent fetal death, recent trends suggest improved functional outcome and decreased long term morbidity. Fetal surgery

Box.1. Steps in intrauterine transfusion

1. Maternal sedation and antibiotics
2. Antenatal steroids if ≥ 26 weeks of gestation
3. Localize the placenta by ultrasonography
4. Identify the umbilical vessels near to placenta
5. Abdomen should be prepared by using appropriate anti-septic solutions according to the unit protocol
6. Local anesthetics to be injected at the site of puncture on abdomen
7. Introduce the lumbar puncture needle (20G) into umbilical vessel
8. Paralyze the fetus with pancuronium with adequate dosage
9. The path of the needle to be guided by ultrasonography
10. Take the blood from the vessel for grouping and hematocrit estimation
11. Then slowly push the 'O' negative packed RBC matched with mother
12. Blood should be O negative, Cytomegalovirus irradiated
13. Various formulas* are available for the volume of blood to be given
14. Target the Hct around 40
15. The volume transfused to be low if the disease severity more, as the fetus can go into decompensating heart failure
16. Monitor fetal heart rate and vital parameters of pregnant mother throughout the procedure
17. Take fetal blood after the procedure for measuring post-procedure Hct⁶
18. Monitor the mother after procedure for the complications like onset of labor, hemorrhage and infection
19. Give prophylactic antibiotics according to the unit protocol
20. Repeat the procedure every 2 weeks
21. Deliver if ≥ 34 weeks

* Mandelbrot's formula²⁶ Amount (mL) to be transfused = $\frac{\text{Hct (final)} - \text{Hct (present)}}{\text{Hct (transfused blood)}} \times \text{EFW} \times 150$

EFW = Estimated fetal weight

is often recommended for giant neck masses, congenital lung masses, sacrococcygeal teratomas, severe forms of congenital diaphragmatic (CDH) hernia and myelo meningocele. Fetal surgery is categorized to open maternal fetal surgery and ex-utero intra partum treatment (EXIT).

Thoracoamniotic shunt, ventriculo amniotic shunt and vesico amniotic shunts are the most popular fetal surgical procedures. Thoraco-amniotic shunt is offered in pregnancies complicated by hydrops secondary to the presence of a large or multiple communicating macrocyts in CCAM or bronchopulmonary sequestration related pleural effusions. Shunt decreases the CCAM mass volume by 50 to 80%. Vesico amniotic shunt is offered to fetuses with lower urinary tract obstructions (PUV or urethral atresias) complicated with oligohydramnios. This procedure may improve the prenatal survival but the long term effects on the kidney and overall outcome are not well documented. Ventriculo- amniotic shunt may be recommended for a rapidly progressing hydrocephalus in a fetus with isolated aqueductal stenosis.

EXIT therapy can be used to secure airway, vascular catheters and also for performing surgeries. It needs team effort involving obstetricians, anesthetists, pediatric surgeons and neonatologists. After the delivery of head and shoulders of the fetus, the uterine relaxation is maintained for continued functioning of placental function. The procedures will be completed during this window period (till placenta function deteriorates). The fetus will be monitored with pulse oximetry and cardiac monitors by placing appropriate probes.^{28,29} This therapy is used in conditions like severe airway compromise caused due to large neck masses and congenital high airway obstruction (CHOAS) and also in conditions which don't respond to initial resuscitation like CDH, pulmonary agenesis and cardiac lesions.

Stem cell and gene therapy

Although prenatal stem cell and gene therapy await clinical application, they offer tremendous potential for cure of many genetic disorders.³⁰ Normal development of fetus offers unique biological advantages for the engraftment of hematopoietic stem cells (HSC) and efficient gene transfer that are not present after birth.

Full potential for postnatal bone marrow transplant for many hematological and genetic disorders is limited by critical shortage of immunologically compatible donor cells, inability to control recipient and donor immune response and requirement for recipient myeloablation. In utero hematopoietic stem cell therapy is an attractive option to overcome these postnatal limitations.

Before population of the bone marrow and before thymic processing of self-antigen, the fetus is receptive for engraftment of foreign HSC without rejection and need for myeloablation. In the human fetus, the window of opportunity is before 14 weeks of gestation; i.e before release of differentiated T cells into the circulation and while the marrow is just beginning to develop sites for hematopoiesis. This window may extend in immunodeficiency states where T cell development is abnormal. During the window period, presentation of foreign antigen would result in clonal deletion of reactive T cells during negative phase of thymic processing. There would be no requirement for HLA matching. Transplanted HSC cells would not be rejected and the need for myeloablation is eliminated. The mother's uterus is the most ideal sterile environment which eliminates the need for 2 to 4 months isolation required for BMT. Also prenatal therapy would preclude the postnatal clinical manifestations of disease avoiding recurrent infections, multiple transfusions, growth delay and other complications of toxic drugs used for post natal BMT. Sickle cell disease, thalassemias, severe combined immunodeficiency, lysosomal storage disorders, Gauchers disease and Maroteaux-Lamy syndrome are some of the candidate diseases that are ideal for prenatal stem cell therapy.³¹

In genetic diseases which are not amenable to stem cell therapy, correction of genetic abnormality of the stem cell in situ may be an useful option. If safe and effective methods for gene transfer can be developed, a large number of diseases would be amenable to in-utero gene therapy. The goal of gene therapy is to deliver genetic material to cells for therapeutic benefit. Many obstacles of postnatal gene therapy can be overcome with fetal gene therapy. The advantages of fetal gene therapy are the following.

1. Prevention of disease before onset of irreversible organ damage
2. Stem cells and progenitor cells exist at high frequency and are exposed within various tissue compartments. Prior to the distribution of these cells within organs or tissue compartments, a window of opportunity exists when they are accessible for gene transfer. Transgenes can be targeted to these expanding cell populations, which will be inaccessible later in life.
3. Immunogenic vectors and transgenes can take advantage of the immature immune system of the fetus. Immunologic tolerance not only ensures long-term, stable transduction, but should also make postnatal treatment with the same vector and transgene possible

4. Small size of the fetus enables high vector to cell ratio with a limited amount of vector.

Cystic fibrosis, Crigler-Najjar disease, Pompe's disease, Leber's congenital amaurosis, MPS VII and Duchene muscular dystrophy are the genetic disorders that may be amenable to fetal gene therapy.

Points to Remember

- *Immunoglobulins and prednisolone are successfully used in the management of fetal thrombocytopenia.*
- *Beta stimulants and steroids form effective transplacental treatments for fetal bradycardia.*
- *Most cases of SVT and atrial flutter respond successfully to transplacental administration of antiarrhythmic drugs. Digoxin is the first line therapy for fetal tachyarrhythmia.*
- *Prenatal treatment for congenital adrenal hyperplasia with antenatal dexamethasone must be done under careful, centralized and ideally long term medical supervision.*
- *Prenatal treatment of fetal hypothyroidism requires direct intra-amniotic administration of thyroid hormone.*
- *In-utero infection with toxoplasmosis and perinatal transmission of HIV is preventable.*
- *Antenatal steroids to mothers with expected preterm delivery between 24 weeks to 34 weeks of gestation is highly effective in improving survival and overall outcome of preterm infants.*
- *Intrauterine transfusion should be used for the treatment of severe fetal anemia either due to blood group incompatibility or parvoviral infection.*
- *Fetoscopic laser photocoagulation is an ideal therapy for twin transfusion.*
- *Fetal surgeries, gene and stem cell therapies are very promising invasive interventions.*

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PERINATOLOGY

PRE AND PERIPARTUM INTERVENTION IN FETAL HYPOXIA

***Shyamala J**

Abstract: *Antepartum and intrapartum fetal surveillance are essential to prevent fetal death and to identify the hypoxic fetus before irreversible damage to vital organs can occur. Fetal surveillance methods rely on fetal biophysical parameters sensitive to hypoxemia and acidemia, such as heart rate and movement, besides blood flow in the fetal-placental circulation. An overview of umbilical artery Doppler, electronic fetal monitoring and fetal blood sampling is presented along with a brief discussion on interpretation and interventions.*

Keywords: *Fetal hypoxia, Intrapartum surveillance, Antepartum surveillance, Fetal resuscitation*

Normal fetal oxygenation

The human fetus develops in a profoundly hypoxic environment described by Sir Joseph Barcroft as 'Everest in utero', comparable to that endured by an adult on the summit of Mount Everest. He postulated that to survive the hypoxic uterine environment (~22–32 mmHg) the fetus must make several adaptations comparable to those seen in climbers ascending the great Himalayan peaks.^{1,2} The following adaptations permit the fetus to achieve a level of O₂ consumption similar to that in extra uterine life: (i) high fetal cardiac output, (ii) central shunting that allows the fetal ventricles to work largely in parallel rather than in series and permits umbilical vein blood to bypass the fetal liver via the ductus venosus-through the foramen ovale to the left heart for preferential distribution to the brain and myocardium, (iii) high fetal hemoglobin concentrations and (iv) leftward shift of O₂ dissociation curve of fetal erythrocytes because of high O₂ affinity.³

Causes of fetal hypoxia

Intrauterine hypoxia is associated with a variety of maternal, placental, and fetal conditions which may manifest

differently and have different outcomes. Kingdom and Kaufmann⁴ classify hypoxic pregnancy conditions into 3 subtypes:

- (a) Preplacental hypoxia, where both the mother and her fetus will be hypoxic. Main causes are a hypoxic environment (high-altitude) and pre-existing maternal cardiovascular diseases such as cyanotic heart disease, heart failure or pulmonary hypertension, maternal anemia, infections and chronic inflammation.
- (b) Uteroplacental hypoxia, where maternal oxygenation is normal but utero-placental circulation is impaired as in pregnancies complicated by IUGR, gestational hypertension and pre-eclampsia.
- (c) Postplacental hypoxia, where only the fetus is hypoxic, due to diminished uterine artery flow (i.e., mechanical compression, rupture), progressive fetal cardiac failure (i.e., complete congenital heart block, complex congenital heart malformations), or due to important genetic anomalies.

Fetal response to hypoxemia - Physiologic basis for antenatal surveillance

The biophysical response to hypoxia may be classified, as acute and chronic according to the temporal relation to the insult. Changes seen at the time of insult and for some time after are termed acute fetal response. This includes loss of fetal breathing movement, tone, gross body movements, heart rate variability and reactivity. Hypoxia causes decrease in both baseline variability and accelerations in response to movement. As hypoxia worsens, the fetus has intermittent episodes of bradycardia. There is a reflex redistribution of the fetal cardiac output towards vital organs like brain, heart and adrenals and away from non-vital organs like lungs and kidneys. If these mechanisms are inadequate for maintaining oxygen supply for essential metabolic needs, anaerobic metabolism will result, with accumulation of lactic acid. This results in acidemia and metabolic acidosis in the fetal compartment. Progressive metabolic acidosis causes a failure of protective adaptations.³ The degree and manifestation of clinical signs depends on the severity and chronicity of hypoxia. Prolonged hypoxia leads to decreased perfusion of kidneys and lungs causing decreased urine and lung fluid production and finally oligohydramnios - termed chronic response.⁵

* Consultant Neonatologist,
Apollo Children's Hospitals,
Chennai.

The methods commonly used for antenatal fetal surveillance rely on fetal biophysical parameters that are sensitive to hypoxemia and acidemia, such as heart rate and movement. The fetal heart rate (FHR) is normally controlled by the fetal central nervous system (CNS) and mediated by sympathetic or parasympathetic nerve impulses originating in the fetal brainstem. The presence of intermittent FHR accelerations associated with fetal movement is believed to be an indicator of an intact fetal autonomic nervous system.⁶

Antepartum fetal surveillance

Based on evidence from randomized controlled trials, various techniques are used for antepartum surveillance of fetus like fetal movement assessment, non-stress test (NST), biophysical profile (BPP), amniotic fluid volume, modified biophysical profile (MBPP), contraction stress test (CST) and Doppler velocimetry. These have already been discussed elsewhere in this issue. Umbilical artery Doppler is briefly discussed here because of its clinical importance.

Umbilical artery Doppler

Although most of the currently used antepartum fetal monitoring tests, such as the non-stress test (NST) and biophysical profile (BPP), have demonstrated significant diagnostic efficacy, only umbilical artery Doppler ultrasound has shown clinical effectiveness in improving the perinatal outcome, especially in pregnancies complicated with fetal growth restriction (FGR).⁷

Doppler velocimetry of the umbilical artery assesses the resistance to blood perfusion of the fetoplacental unit (Fig. 1A) and is the most important factor in management of IUGR fetuses. Due to increased resistance in placental circulation in IUGR of placental origin, blood velocity waveform changes in the umbilical artery usually occur early. The degree of waveform abnormality is correlated with severity of outcome. There is a progressive decrease in end-diastolic flow in the umbilical artery Doppler waveform until absent flow (Fig. 1B) and then reversed (Fig. 1C) flow during diastole occur. Absent and reversed end-diastolic flows are associated with high risk of intrauterine demise.

Appropriate timing of delivery is at present, the only available therapy in IUGR and prevents further worsening of the underlying hypoxia that may lead to irreversible damage to fetal organs or even fetal death. Findings of serial Doppler velocimetry may facilitate the sometimes very difficult timing of delivery.

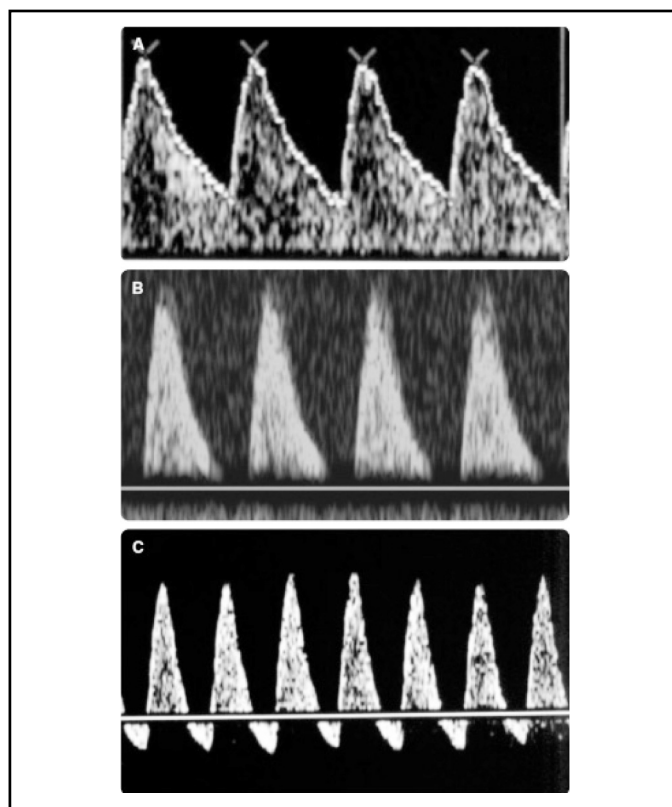


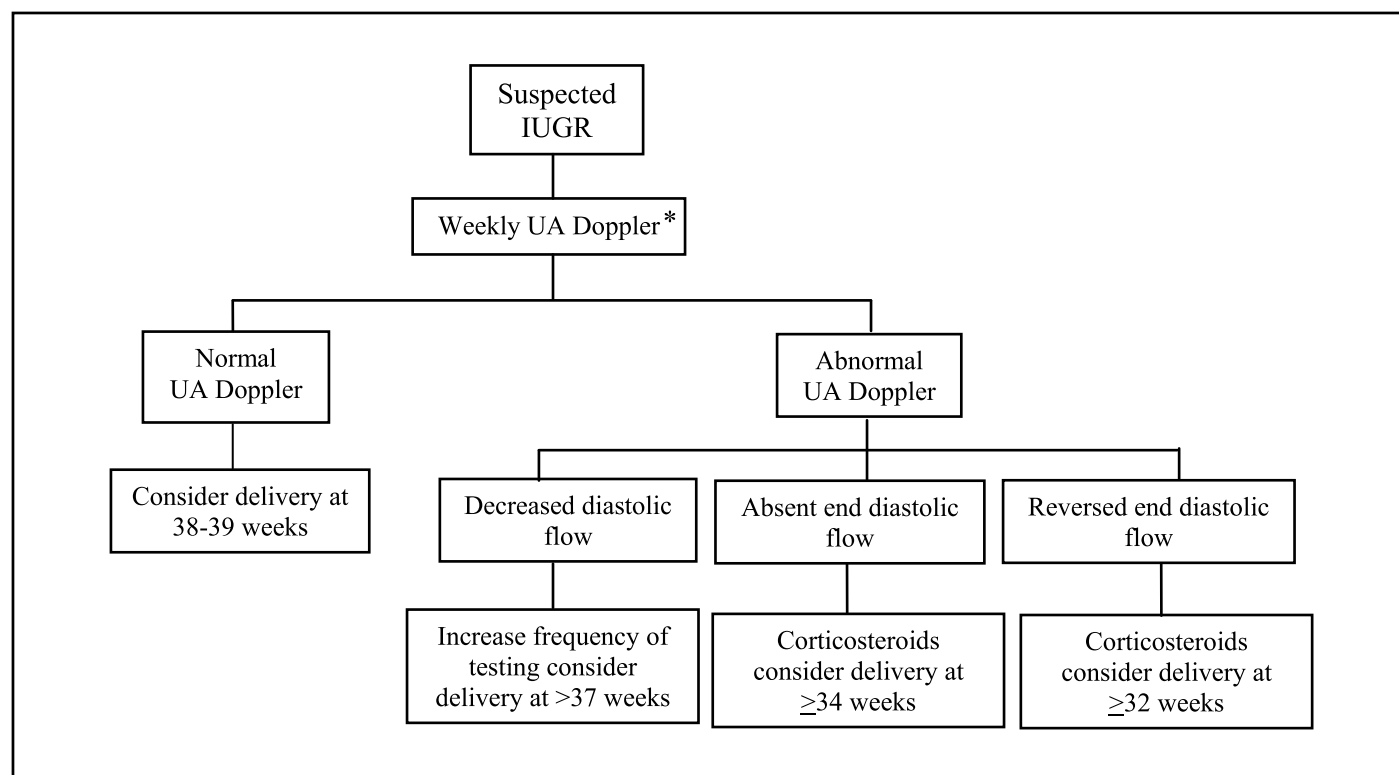
Fig. 1A. Examples of umbilical artery doppler flow waveforms

Fig. 1B. Absent flow

Fig. 1C. Reversed end-diastolic doppler flow in umbilical artery.⁸

The Society for Maternal Fetal Medicine (SMFM) recently published a clinical guideline as pertains to Doppler assessment in intrauterine growth restriction (IUGR).⁸ Once IUGR is suspected, umbilical artery Doppler studies should be performed usually every 1-2 weeks to assess for deterioration; if normal, they can be extended to less frequent intervals. The recommendations are:

- i) Antenatal corticosteroids should be administered if absent or reversed end-diastolic flow is noted <34 weeks in a pregnancy with suspected IUGR.
- ii) As long as fetal surveillance remains reassuring, women with suspected IUGR and absent umbilical artery end-diastolic flow may be managed expectantly until delivery at ≥ 34 weeks.
- (iii) As long as fetal surveillance remains reassuring, women with suspected IUGR and reversed umbilical artery end-diastolic flow may be managed expectantly until delivery at 32 weeks. (Fig. 2) However, the lower limit for



IUGR, intrauterine growth restriction; UA, uterine artery.

* - In conjunction with antepartum testing.

Fig.2. Algorithm for clinical use of Doppler ultrasound in management of suspected IUGR.⁸

delivery depends on consensus between obstetricians and neonatologists involved in caring for the preterm neonate and facilities available in that center.

Antepartum interventions based on fetal surveillance

The primary goal of fetal surveillance is to prevent fetal death while also trying to identify the compromised fetus before irreversible hypoxic damage to vital organs occurs. Antepartum surveillance can significantly reduce the risk of antepartum death. There are several well-recognized maternal conditions like hypertension, diabetes mellitus, chronic renal disease and pregnancy-associated conditions like IUGR, preterm premature rupture of membranes that increase risk for intrauterine fetal death. Such patients are appropriate for antenatal surveillance.⁹

Various evaluations can be performed in the event of reduced fetal movements reported by mother—NST, CST, BPP, modified BPP. All tests are associated with a false-positive rate and should be interpreted within the clinical context presented by the patient. A non-reactive NST or abnormal modified BPP should be followed by additional testing (CST or BPP). A positive CST increases concern

for hypoxemia induced acidosis. Usually a non-reactive NST and positive CST is an indication for delivery. A BPP score of 6 is considered equivocal and should prompt delivery in the term fetus. In the preterm fetus, repeat evaluation should be performed in 24 hours and corticosteroid administration can be considered in the interim for gestation less than 34 weeks.¹⁰ Continued equivocal testing should result in delivery or continued surveillance. BPP score of 4 usually indicates the need for delivery. BPP score of less than 4 should prompt expeditious delivery. Delivery of the fetus with an abnormal test result can be attempted via induction of labor in the absence of obstetric contraindications (placenta previa, classical uterine incision, etc). Saline amnioinfusion may be beneficial in the presence of oligohydramnios and an amniotic fluid index of less than 5 cm. Titration to an index of greater than 8 cm may reduce the incidence of meconium-stained fluid, variable decelerations, end-stage bradycardia, fetal distress and acute fetal acidosis.

Often, clinical situations unrelated to fetal well-being can temporarily affect the interpretation of surveillance techniques. Several maternal behaviors like tobacco and alcohol use¹¹ and serious maternal medical

conditions like diabetic ketoacidosis and acute asthma exacerbation often result in non-reassuring fetal surveillance. Rather than delivering the infant, stabilizing maternal status will result in improved fetal status, avoiding unnecessary preterm birth.

Resuscitative efforts are used in the antepartum period so that pregnancy can be safely prolonged. In an acute, short-lived event such as deceleration on NST, techniques like maternal repositioning, intravenous fluid bolus and oxygen administration can be used accompanied by continued monitoring. Antenatal corticosteroid administration for worsening fetal status is beneficial. Techniques for fetal resuscitation though advisable for common reversible indications, are not effective in chronic conditions like a growth restricted fetus in a mother with worsening hypertensive disease. Here, frequent testing with prompt recognition of worsening status is indicated to determine need for delivery.⁹

Intrapartum fetal surveillance

The process of labor and delivery is metabolically stressful which most healthy fetuses are able to tolerate with no adverse effect. Rarely, this process places the fetus in jeopardy of long-term neurologic damage or death as a result of profound hypoxemia and metabolic acidosis. Hence monitoring the health of the fetus during labor has become a key component of modern maternity care. Intrapartum fetal surveillance is done using electronic fetal monitoring, fetal blood sampling, fetal pulse oximetry, vibroacoustic stimulation of the fetus and ST analysis (STAN) of the fetal ECG.

Electronic fetal monitoring

This was developed in the 1960s by Edward Hon, along with Roberto Caldeyro-Barcia in Uruguay. It involves the placement of two transducers on the abdomen of a pregnant woman, one to record the fetal heart rate using ultrasound and the other to monitor the contractions of the uterus. The cardiotocograph record is then assessed by the obstetric medical team. The use of intrapartum electronic fetal monitoring (EFM) has steadily increased over the last 25 years and is currently considered the gold standard. FHR is normally controlled by the fetal CNS which in turn, is sensitive to hypoxia.

Interpretation of fetal heart rate patterns

A complete description of the EFM tracing includes uterine contractions, baseline fetal heart rate, baseline variability, presence of accelerations, periodic or episodic

decelerations, and changes or trends of the fetal heart rate pattern over time.¹² When EFM is used intrapartum, it should be reviewed frequently (Fig. 3).

The utility of EFM has been limited by the subjective nature of its interpretation. The 2008 National Institutes of Child Health and Human Development (NICHD) workshop dealing with standardization of nomenclature for intrapartum electronic fetal monitoring, jointly sponsored by NICHD, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal medicine, proposed certain criteria. The system selected by the workshop is one that is evidence-based, simple and applicable to clinical practice.^{12,13,14} Common terminology used when interpreting the EFM is summarized as per guidelines in Table I.^{12,15} Graphic representation of CTG is shown in Figs.3-7.

FHR tracing patterns provide information on the current acid-base status of the fetus and cannot predict the development of cerebral palsy. The 2008 NICHD workshop simplified categorization and interpretation of FHR tracings into a three-tier system as Category I, II and III.^{12, 15}

A category I tracing is predictive of normal fetal acid-base status, and routine obstetric care is continued.

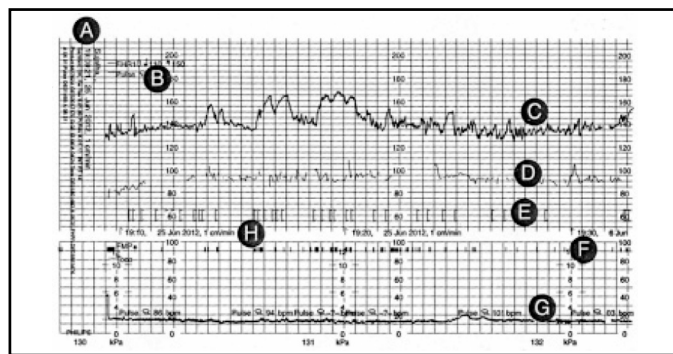


Fig.3. The Components of a CTG trace²⁰

- A- Patient identification details, machine self-test
- B- The traces, FHR 1 denotes first Doppler probe, Pulse – maternal pulsations, DFHR – direct FHR scalp electrode
- C- FHR trace
- D- Maternal pulsations trace through the tocograph probe
- E- Maternal perceptions of fetal movements denoted with event marker
- F- Fetal movement perceived by the CTG machine
- G- Uterine activity trace
- H- Date, time and paper speed

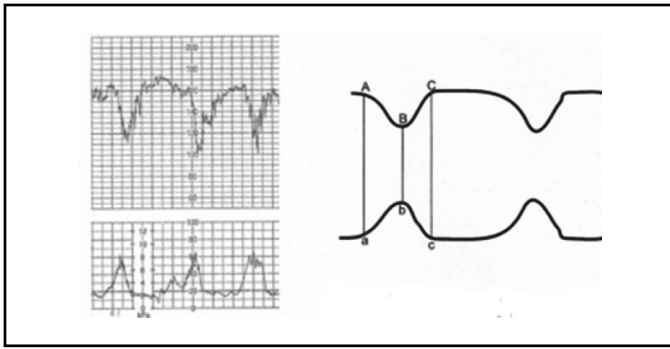


Fig.4. Early decelerations–Schematic representation.²¹ [They are a mirror image of contraction. Beginning (A), nadir (B) and recovery (C) of the FHR coincides with the beginning (a), peak (b) and the end (c) of contraction]. This is reassuring and not associated with fetal compromise. Occurs due to central vagal stimulation caused by altered cerebral blood flow

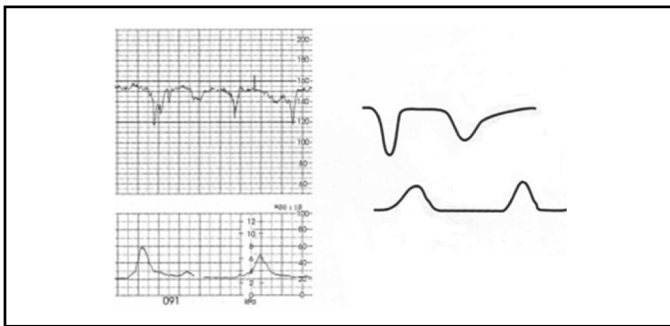


Fig.5. Variable decelerations – Schematic representation.²¹ There is no association between the decelerations with any specific phase of uterine contractions

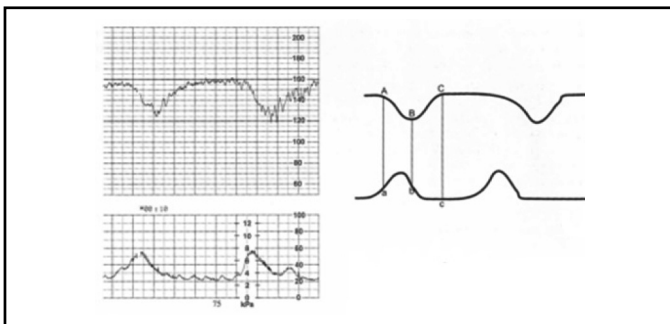


Fig.6. Late decelerations–Schematic representation.²¹ [The beginning (A), nadir (B), and the end of the deceleration (C) coincides with the ascending part of the contraction (a), after the peak of the contraction (b) and after the end of the contraction (c)] Reflect stress associated with uterine contractions.

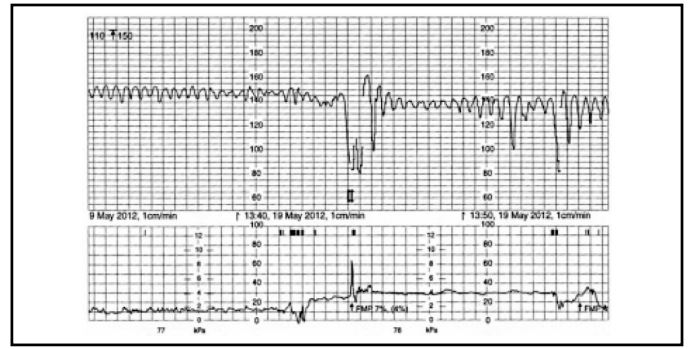


Fig.7. Sinusoidal pattern²⁰

Pattern representative of fetal hypoxia due to fetal anemia and associated with high perinatal morbidity and mortality.

(Regular oscillation of the baseline resembling a sine wave with 3-5 cycles per minute and an amplitude of 5-15 bpm above and below the baseline, lasting at least ten minutes with loss of baseline variability).

A category II tracing predicts that the fetal acid-base homeostatic system may be compromised. A category III tracing is predictive of fetal acidosis and requires prompt intervention, including intrauterine resuscitative measures which are directed at the underlying cause (Table II). An algorithm for the management of category II FHR patterns that reflects a synthesis of available evidence and current scientific thought is presented in a recent article for further reference.¹⁶

A recent Cochrane database review of 12 randomized controlled trials (more than 37,000 women) drew the following conclusions: “EFM has resulted in an increase in the rate of cesarean and operative vaginal deliveries but no decrease in perinatal mortality, neonatal seizures, or the risk of cerebral palsy.^{17,18} Additionally, a frequently cited study of EFM and the prediction of cerebral palsy shows that the positive predictive value of a non-reassuring fetal heart rate tracing to predict cerebral palsy was 0.14%, with a false-positive predictive rate exceeding 99%.¹⁹

Thus CTGs have a high degree of sensitivity but a low level of specificity which means that they are very good at identifying the fetuses that are well but are poor at recognizing those that are unwell. The positive predictive value of CTG for adverse outcome is low and the negative predictive value high. The increased intervention rates associated with EFM can be reduced with the use of fetal blood sampling which can be performed as an adjunct to an equivocal or abnormal CTG.¹⁸

Table.I Definition of terms to describe fetal heart tracings.^{12,15}

Baseline - Mean fetal heart rate observed in a 10-min period

- Normal: 110-160 bpm
- Fetal bradycardia: < 110 bpm
- Fetal tachycardia: > 160 bpm

Baseline variability - Measure of the amplitude (peak-to-trough) in beats per minute of momentary heart rate deflections from baseline observed in a 10-min period.

- Absent (undetectable amplitude), minimal (<5 bpm), moderate (6-25 bpm), marked (>25 bpm)

Accelerations- Abrupt increase from baseline

- ≥ 15 bpm increase, peaking in <30s
- Duration: ≥ 15 s and <2 min

Decelerations

Early - Gradual decrease (≥ 30 s from baseline to nadir) and return to baseline

- Coincident with uterine contraction

Variable - Abrupt decrease (<30 s from baseline to nadir) of > 15 bpm, lasting 15s – 2min

- +/- Coincident with uterine contraction

Late - Gradual decrease (≥ 30 s from baseline to nadir) and return to baseline

- Onset: After beginning of contraction
- Nadir: After peak of contraction
- Recovery: After resolution of contraction

Prolonged deceleration - Duration of 2-10 min

Intermittent deceleration - Decelerations with fewer than one-half of uterine contractions in a 20-min period.

Recurrent deceleration - Decelerations with more than one-half of uterine contractions in a 20-min period

Fetal blood sampling

Ominous fetal heart patterns may be noted on CTG in 50% of cases monitored during labor but only a small percentage of these are actually hypoxic. Hence, a diagnostic test is necessary, to distinguish between CTG abnormalities caused by vagal, harmless reflexes in the fetus

and those that are hypoxic in origin and therefore, potentially harmful. Fetal blood sampling (FBS) was introduced by Saling in 1962.²² Inadequate oxygen supply may lead to the development of acidosis (low pH levels) and increased lactate in the blood. After the amniotic membranes have ruptured and the cervix dilated to around 3 cm, it is possible to measure pH or lactate levels in a sample of blood taken from the baby's scalp. Interpretation of results: Normal pH: 7.25 - 7.35, Borderline pH: 7.20 - 7.25, Abnormal pH < 7.20. Scalp pH monitoring has disappeared largely from use because of its technical difficulty and unreliability²³

Scalp blood lactate

In animal studies with induced hypoxia, lactate seems to be an earlier marker than pH in the hypoxic process. It has been found to better predict morbidity like low Apgar scores at 5 minutes and hypoxic ischemic encephalopathy (HIE) when compared to low pH or metabolic acidemia.²⁴ A much smaller amount of blood is needed for the lactate test than to measure pH. A fetus with a scalp blood lactate concentration of > 4.8 mEq/L is at risk of acidosis and should be ideally delivered within 20–30 minutes. A recent Cochrane review identified two studies of 3348 mother baby pairs that compared lactate and pH testing in labor. Lactate testing was more likely to be successfully achieved than pH testing.²⁵

Contraindications to FBS include evidence of serious, sustained fetal compromise (where delivery should be immediate), fetal bleeding disorders, face or brow presentation and maternal infections like HIV, Hepatitis B, etc. FBS is not generally recommended in pregnancies less than 34 weeks of gestation.

Intrapartum resuscitation (Table-II)

The mainstay of techniques for fetal resuscitation include maternal repositioning, oxygen administration, discontinuation of induction agents, tocolysis and even amnioinfusion.²⁶ (Table.II) The ultimate resuscitation effort would be delivery, accomplished either via operative vaginal delivery or cesarean section.

Continuous electronic FHR monitoring is the primary diagnostic tool used to detect the compromised fetus in labor. Specific management depends on the category of fetal tracing. Category I tracings can be managed with close observation. Category II or III tracings require resuscitative measures depending on the characterization of the heart rate abnormality. Recurrent FHR decelerations always prompt further evaluation. Specific treatment such as decreasing or discontinuing oxytocin or use of tocolytics may be warranted.

Table II. Intrauterine resuscitative techniques⁹

Technique	FHR abnormality	Objective
Maternal repositioning	Bradycardia, prolonged deceleration, minimal variability	Restore blood flow and oxygenation
IV fluid bolus	Recurrent late decelerations, bradycardia, prolonged deceleration, minimal variability	Relieve hypotension, increase blood flow
Sympathomimetic drug administration	Bradycardia, prolonged deceleration, minimal variability	Relieve hypotension, increase blood flow
Oxygen administration	Minimal variability, late decelerations	Promote oxygenation
Amnioinfusion	Recurrent variable decelerations	Alleviate cord compression
Decrease/discontinue oxytocin; administer tocolytic	Tachysystole with category II or III tracing	Decrease contractions
Cervical examination	Bradycardia, prolonged deceleration	Identify cord prolapse or rapid cervical change

Resuscitative measures or interventions specifically address the abnormal FHR. Several non-surgical interventions can be used. Even though there is no conclusive evidence that oxygen administration to the mother improves fetal oxygenation, a common technique is to administer oxygen via face mask when the FHR has characteristics suggestive of hypoxia (late decelerations). Repositioning the patient to the lateral recumbent position is another technique. This type of positioning allows for the least amount of blood flow to other muscles and maximizes cardiac return and output. Increasing hydration by intravenous fluid administration potentially maximizes intravascular volume and uterine perfusion. Decreasing or discontinuing oxytocin allows for more time between contractions, and therefore more time to perfuse the placenta and deliver oxygen. Administering tocolytics can be used in the patient having excessive spontaneous contractions and associated non-reassuring FHR.²⁷

Category III tracings are abnormal and place the fetus at increased risk for fetal acidemia.¹² They are associated with increased risk for encephalopathy, cerebral palsy and neonatal acidosis. They have poor predictive value for overall abnormal neurologic outcome. The same resuscitative measures are used [i.e, positioning, fluid bolus, tocolysis if tachysystole (More than 5 uterine contractions in a 10-min period) is noted, amnioinfusion].²⁶ Expedient delivery must be achieved if they do not resolve. In general, a 30-min decision to incision time is used while planning delivery.²⁸

This can be accomplished via operative vaginal delivery (vacuum or forceps assisted) if appropriate or a cesarean section. In labor complicated by meconium stained liquor with normal FHR pattern, where it is decided to allow labor to continue, amnioinfusion can be considered as a preventive measure.

A word of caution is that current intrapartum monitoring tools like CTG, fetal blood sampling and ST-segment analysis (STAN) detect fetal asphyxia or injury operating via the hypoxia-ischemia pathway. They are relatively insensitive when non-hypoxia/ischemia or inflammatory pathways cause fetal injury as in maternal fever, chorioamnionitis, underlying diabetes or fetal stroke.²⁹

Conclusion

Electronic FHR monitoring was expected to reduce the number of cases of intrapartum asphyxia leading to death, neurologic damage, or cerebral palsy. Though intrapartum deaths have decreased significantly and cesarean deliveries have gone up, the rates of cerebral palsy have remained steady for the past 30 years. Studies from multiple centers around the world have shown that, at most, only 10%–20% of cases of cerebral palsy in term infants are related to intrapartum hypoxia. Majority of mental handicap is not caused by intrapartum events³⁰ which is also the conclusion of a 1985 report by the U.S National Institutes of Health.³¹ Many of the causes of newborn

encephalopathy start before birth.³² CTG is a non-specific method and depends heavily on subjective interpretation. Only with the addition of non-subjective information like STAN, will the risk decrease.³³ Studies are ongoing.

Various antepartum and intrapartum monitoring tools are available for fetal surveillance. Limitations of these tools should be borne in mind when interventions are planned based on the findings. Prompt assessment can identify the fetus in need of delivery or further evaluation. Judicious use of resuscitative techniques can help reduce perinatal hypoxia without contributing to morbidity. Further research is needed to develop new monitoring techniques and resuscitative therapies.

Points to Remember

- *Umbilical artery Doppler ultrasound has shown clinical effectiveness in improving the perinatal outcome, especially in pregnancies complicated with fetal growth restriction .*
- *Intrapartum fetal surveillance is done using electronic fetal monitoring, fetal blood sampling, vibroacoustic stimulation of the fetus and ST analysis of the fetal ECG. Limitations of monitoring tests should be kept in mind.*
- *Fetal heart monitoring in labor is the gold standard among the current monitoring techniques and has largely eliminated intrapartum fetal death but interpretation is subjective. More objective monitoring techniques are required to eliminate observer bias.*
- *A number of resuscitative therapies like maternal positioning, O₂ therapy, saline infusion, amnioinfusion and discontinuing oxytocin are available to resuscitate the potentially compromised fetus, although the ultimate technique is delivery.*

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CLIPPINGS

Powered/electric toothbrushes compared to manual toothbrushes for maintaining oral health Updated

Removing dental plaque may play a key role maintaining oral health. There is conflicting evidence for the relative merits of manual and powered toothbrushing in achieving this. This is an update of a Cochrane review first published in 2003, and previously updated in 2005.

Objectives was to compare manual and powered toothbrushes in everyday use, by people of any age, in relation to the removal of plaque, the health of the gingivae, staining and calculus, dependability, adverse effects and cost.

Selection criteria: Randomised controlled trials of at least four weeks of unsupervised powered toothbrushing versus manual toothbrushing for oral health in children and adults

Authors' conclusions: Powered toothbrushes reduce plaque and gingivitis more than manual tooth brushing in the short and long term. The clinical importance of these findings remains unclear. Observation of methodological guidelines and greater standardisation of design would benefit both future trials and meta-analyses. Cost, reliability and side effects were inconsistently reported. Any reported side effects were localised and only temporary.

Yaacob M, Worthington HV, Deacon SA, Deery C, Walmsley A, Robinson PG, Glennly A. Powered versus manual toothbrushing for oral health. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD002281. DOI: 10.1002/14651858.CD002281.pub3

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PERINATOLOGY

PRE AND PERINATAL INFECTIONS

* **Swarnarekha Bhat**

Abstract: *Infections occurring during pregnancy can affect the fetus and neonate in many ways. It could result in abortion, cause malformations or present in the neonatal period as intra uterine infections. There are many infections: bacterial, viral and protozoal infections which can result in intrauterine infections. Recognition of these conditions both during pregnancy and in the neonatal period is important as some conditions are treatable. Emphasis is also needed on preventing infections from occurring during pregnancy by adolescent immunization for infections like rubella and varicella.*

Keywords: *Intrauterine infections, Prenatal infections.*

Infections occurring during pregnancy can affect the fetus and newborn. These infections can be caused by bacteria, viruses or, in rare cases, parasites and are transmitted directly from the mother to an embryo, fetus or baby during pregnancy or childbirth. Infection can also be transmitted to the baby during lactation. The first described intrauterine infection was congenital rubella syndrome. Subsequently infections due to toxoplasma, syphilis, cytomegalovirus and hepatitis were given the ToRCHES terminology

The original ToRCHES group of infections has now expanded to TORCHES CLAP¹

The scope of this article will include an overview of perinatal infections - highlighting the general concepts, followed by specific infections. HIV will not be included in this review. The following aspects will be discussed: modes of transmission, effect on fetus and newborn, clinical manifestations, diagnosis, treatment, prevention and prognosis.

Infections	
To	Toxoplasma
R	Rubella
C	CMV
H	Herpes simplex, Hepatitis
E	Enteroviruses
S	Syphilis
C	Chicken pox
L	Lyme disease
A	AIDS
P	Parvovirus

General concepts^{1,2,3}

Infections during pregnancy

The TORCHES CLAP group of infections can be symptomatic or asymptomatic and picked up during routine screening. If diagnosed, not all infections can be treated. The infections that can be treated include toxoplasma, syphilis, herpes and HIV. Treatment during first trimester poses a special problem as use of medications may not be safe. In this context the best way to prevent intrauterine infections is to protect women of reproductive age group. Immunization can be given to prevent Rubella, Hepatitis B, Varicella and screening can be done for HIV, Hepatitis B and C, Toxoplasmosis, CMV.

Infections during pregnancy can result in fetal or neonatal infection and transmission can occur through any of the following routes:

Antepartum (Intrauterine): Transplacental or ascending from the genital tract

Intrapartum: Contact with infected blood, body secretions during birth

Postpartum: Breast feeding or by direct contact

* Senior Consultant,
Neonatology and Pediatrics,
Mazumdar Shaw Medical Centre,
Narayana Health, Bangalore.

Pregnancy outcome following infections can be any one of the following depending on the timing of infection.

1. Early pregnancy loss
2. Still birth
3. Preterm
4. IUGR
5. Congenital anomalies
6. Congenital infection
7. Neonatal death
8. Cerebral palsy, neurologic sequelae
9. Behavioural problems

Early pregnancy loss is typical of toxoplasmosis. Teratogenic effect is seen commonly with CMV, rubella, chicken pox infections. Coxsackie B3 and B4 infections can cause congenital heart disease. Parvovirus infection causes hydrops fetalis.

Clinical manifestations of intrauterine infections include: growth restriction, hepatosplenomegaly, jaundice, pneumonia, encephalitis, microcephaly, intracranial calcification, eye and ear involvement (Table.I).

Diagnosis is usually based on serology or identifying the organism through PCR in blood, CSF or urine. Treatment is possible for some infections. But since sequelae is likely

to occur, long term follow up and multidisciplinary care is required in children suspected to have intrauterine infections. Protection prior to conception plays an important role in prevention of IU infections. Diagnosis during pregnancy is possible, but treatment will be possible only in some conditions like syphilis, toxoplasmosis.

Epidemiology of intrauterine infections in India^{4,5,6}

There are no epidemiological studies giving the prevalence of these infections, however data from ophthalmic units have shown that intrauterine infections particularly CMV and rubella account for 17.8% and 8.4 % respectively among children with congenital cataract. Among children suspected to have intrauterine infections 2.8% had rubella IgM positivity and 12.5 % had CMV positivity. Other studies have reported that CRS accounts for 10%-15% of pediatric cataract and 1 to 15% of all children suspected to have IU infections have CRS.³ With improved coverage of MMR vaccine rubella infections may be on the decline. Toxoplasmosis and syphilis are much less frequently seen, but anecdotal reports of newer infections are now being seen frequently.

Cytomegalovirus (CMV)^{7,8}

Cytomegalovirus is an ubiquitous virus spread through interpersonal contact. In India 80%-90% of adults are seropositive. Infection during pregnancy can affect the fetus and neonate by transplacental, intrapartum route or during

Table.I Clinical manifestations of intrauterine infections¹

Disease	Abortion	Congenital anomalies	Still birth	IUGR	Preterm birth	Neonatal death	Postnatal disease	Deafness	Ocular problems	Neurologic sequelae
Toxoplasma	+		+	+					+	+
Rubella	±	+	+	+						
Cytomegalovirus				+	+	+	+	+	+	+
Herpes						+	+		+	+
Hepatitis B,C							+			
Enterovirus		±	+							
Syphilis	+	+	+	+	+	+	+	+		+
Chicken pox		+	±	+	+	+	+		+	+
Lyme disease			+	+	±					
AIDS				±			+			
Parvovirus	+		+							
Malaria			+	+	+					

breast feeding. Risk of transmission can be as high as 30%-40% during primary infection and is reduced to 1-3% during re infection. 11% to 12% of all infected neonates are symptomatic. Among symptomatic neonates 60% to 80% may have sequelae. This is decreased to 8% to 15% in asymptomatic neonates. The most common sequelae is hearing loss.

Clinical manifestations: Like all other IU infections it causes immediate and long term effects. Sequelae include sensorineural deafness, visual problems, cerebral palsy and seizures.

Clinical feature	Frequency
Petechiae	76 %
CNS	68 %
Jaundice	67 %
Hepatosplenomegaly	60 %
SGA	50 %
Sequelae	40% - 60 %

Diagnosis can be confirmed by IgM antibodies, urinary or salivary PCR or PP65 antigen.

Treatment: Antiviral therapy should be started if there is CNS involvement or serious end organ disease, like hepatitis, pneumonia. Ganciclovir 6mg/kg/day IV for 6 weeks or oral Valganciclovir 16mg/kg/day for 6 weeks is the treatment.

Herpes⁹

HSV 1 and 2 both can be transmitted perinatally, but risk of transmission of HSV 2 is higher. Transmission occurs mostly during intrapartum period - upto 85%, in utero and postnatal transmission accounts for 5% and 10% respectively. Risk of transmission is higher in primigravida, during vaginal delivery, if membranes have ruptured and if maternal antibodies have not developed. Clinical manifestations of neonatal HSV infection typically fall into three categories

Categories of HSV infection in neonates

SEM	Skin, eye and mouth involvement	45 %	No mortality or sequelae
CNS	Encephalitis like presentation	30 %	Sequelae upto 30 %
Disseminated	Multisystem involvement	25 %	Mortality high: up to 30%

First trimester infection results in microcephaly, microphthalmia, choreoretinitis and intracranial calcification.

Diagnosis can be confirmed by IgM antibodies and CSF or blood HSV DNA PCR. Fetal infection can be diagnosed by amniotic fluid PCR.

Symptomatic neonates should be treated with IV Acyclovir: 60mg/kg/day for 14 days if there is only SEM involvement and 21 days for CNS and disseminated Herpes. There is some data to suggest that continuing oral acyclovir at 300 mg/m²/ day for 6 months may be beneficial.

Treatment with acyclovir has made a big difference to both immediate and long term outcome. Pretreatment era 50% to 80 % of neonates would die and 50% to 70% of survivors would have sequelae, post treatment mortality has reduced to 4% to 30% and sequelae to 27% to 60 %

Toxoplasmosis^{10,11,12,13}

Toxoplasma infection in pregnancy is usually asymptomatic. 10% may present with fever, and lymphadenopathy. If infection occurs in the first trimester, abortions can occur or the fetus may be affected resulting in congenital toxoplasmosis. If toxoplasmosis is suspected during pregnancy, diagnosis can be confirmed by amniotic fluid PCR > 18 weeks of gestation. Pregnant women who acquire the infection can be treated with spiramycin. If the fetus is affected, sulfadiazine pyrimethamine combination can be used after the first trimester to prevent transmission from mother to fetus in first trimester.

Global burden of congenital toxoplasmosis is 1.5 per 1000 live births per year as per WHO. Transmission risk is highest near term gestation and can be as high as 80% but clinical manifestations are more likely to occur when fetus is affected in the first or second trimester. Clinical manifestation of toxoplasmosis is similar to other intrauterine infections, except that both hydrocephalus and microcephaly can occur, cataract is less common but other ocular manifestations such as choreoretinitis, optic atrophy and retinal detachment can occur.

Diagnostic tests for congenital toxoplasmosis include:

- IgG antibody by the Sabin Feldman dye test (DT) positive in neonatal period and at 12 months
- IgM immunosorbent agglutination assay: 3 to 12
- IgA antibody test by ELISA > 1
- PCR positive in amniotic fluid, blood, CSF, urine.
- Combination of IgM and IgA increases sensitivity to 93%

Treatment of symptomatic neonates:

Pyrimethamine	2mg/kg/day	2 months
	1mg/kg/day	2 to 6 months
	1mg/kg/day. 3/week	6 to 12 months
Sulfadiazine	100mg/kg/day	12 months
Folinic acid	10mg. 3/week	12 months

Congenital Rubella Syndrome^{5,6, 14,15}**Epidemiology**

Global estimates of congenital rubella syndrome prior to introduction of Rubella vaccine varied from 0.8 to 4/1000 live births. This has reduced to 0.1 to 0.2/1000 live births in the post-vaccination era and is likely to be eliminated in many of the developed countries

In India, there is no epidemiologic data, but a recent literature review⁵ suggests that CRS is a significant problem. CRS accounts for 10% to 15 % of childhood cataract, among children suspected to have intrauterine infections. CRS accounts for 1% to 28 % of cases and among children with mental sub normality CRS accounts for 7.6% to 13 % of children. This study also shows that 10% to 30% of adolescent girls are susceptible to getting rubella infection. The seronegativity of women in the child bearing age has been reported to be 10% to 15%.

Rubella during pregnancy can be asymptomatic or symptomatic, typical manifestations being fever, posterior cervical lymphadenopathy with rash and arthritis. The diagnosis can be confirmed by IgM antibody or PCR. If diagnosis is confirmed, there is no specific treatment. Parents need to be counseled regarding risk of transmission and effect on the fetus and newborn.

The risk of transmission is maximum in the first trimester when teratogenicity is likely to occur. Risk of transmission is as high as 90 % in the first 11 weeks and reduces to 50% between 11 and 12 weeks gestation. Transmission is unlikely to occur after 17 weeks. Clinical manifestations specific to CRS include: congenital heart disease, ocular manifestations, hearing loss and microcephaly, mental retardation as originally described by Gregg. Other manifestations are similar to other intra uterine infections: neonatal hepatitis like presentation, encephalitis, pneumonia, thrombocytopenia and typical ocular manifestations - cataract, microphthalmia, microcornea, chorioretinitis. The most common cardiac lesions include pulmonary artery hypoplasia, PDA, VSD and ASD.

Diagnosis can be confirmed by IgM antibody and PCR. Excretion in the urine is likely to occur for up to 6 months. There is no specific treatment and prevention is the best strategy.

Strategies in prevention of rubella

The recommendation in India would be to club rubella prevention with measles prevention. A universal combined vaccine strategy would be ideal: giving a two dose schedule to both boys and girls. In India this can be administered as MMR vaccine at 12 to 15 months and at 4 to 6 years. Till such time a universal coverage can be achieved - the option would be catch up immunization of boys and girls between 1 and 10 years.

Congenital syphilis¹⁶

Over the years with routine testing and treatment of syphilis during pregnancy the incidence of congenital syphilis is on the decline. However awareness of this condition is important as treatment is possible. Syphilis during pregnancy typically results in mid-trimester abortions or if infection occurs towards term, intrauterine death can occur. Diagnosis during pregnancy is based on serology. If mother is VDRL positive she must be treated with penicillin.

Table.II Sequelae following intrauterine infections¹⁸

	Overall	Developmental delay	Hearing	Vision	Epilepsy
CMV	47%	66%	67%	3%	6%
Herpes	37%	94%	2%	47%	23%
Rubella	89%	6%	80%	27%	
Toxoplasmosis	21%	26%	-	82%	11%

Typical manifestations of congenital syphilis include: periostitis, snuffles, skin lesions, hepatosplenomegaly, jaundice and nephrotic syndrome. Diagnosis is confirmed by non treponemal or treponemal tests. Treatment is crystalline penicillin IV 50,000 units /kg/day for 10 to 14 days.

Chicken pox¹

Varicella zoster infection during pregnancy can cause teratogenicity during early pregnancy and low birth weight. Incidence of congenital varicella syndrome is 0.2% in the first 12 weeks and 2% between 13 to 20 weeks. In addition to the teratogenic effect VZV infection during term pregnancy can cause neonatal chicken pox.

The congenital malformations associated with VZV infection in the first 20 weeks of pregnancy include cicatricial skin lesions, microphthalmia, cataract, choreoretinitis, hypoplastic limb, seizures, microcephaly and low birth weight.

If a neonate develops chicken pox in the first 10 days of birth it is likely to be due to perinatal infection. The chances that a neonate will get chicken pox is highest if the pregnant woman has chicken pox within four days of delivery, chances of infection is negligible if chicken pox occurs more than four days prior to delivery as maternally transmitted antibodies will protect the neonate. Neonatal chicken pox should be treated with acyclovir.

Parvovirus¹⁷

Parvovirus B19 is a single-stranded DNA virus causing typically erythema infectiosum in children and adults or fever associated with joint pains and or a transient aplastic crisis.

The characteristic rash has been described as slapped cheek appearance of the face followed by rash on the abdomen and limbs. Transmission is by person to person spread through fomites and less by aerosol route. Many adults and children may be asymptomatic

If parvovirus infection occurs during pregnancy, the fetus can be affected due to transplacental transmission. Transmission rates can be as high as 25% to 50%. Manifestations include fetal death particularly if infection occurs in the first 20 weeks of pregnancy and non-immune hydrops. Studies have shown that fetal death can occur in 9% and hydrops in 3% to 4%, if parvovirus infection occurs during pregnancy. If infection occurs during second and third trimesters, manifestations include anemia, hydrops, myocarditis and cardiac failure. Doppler velocimetry of the MCA is useful to detect severity of anemia. There is no

specific treatment or preventive method, if hydrops is detected in utero blood transfusion can be attempted to correct anemia

Malaria¹

Among plasmodia infections occurring during pregnancy, P falciparum and P vivax infections are more frequently associated with fetal and neonatal problems. Parasitemia is higher during pregnancy and nearly 45% of primigravida pregnant women having malaria are found to have placental infection. If untreated, fetal perinatal loss can be as high as 60% to 70%. The incidence of low birth weight neonates among pregnant women with malaria can be as high as 44% if there is placental infection.

Congenital malaria: Malaria in the neonatal period is believed to be of congenital origin if parasitemia occurs in the first 7 days after birth. Incidence of congenital malaria is 0.3%. The incidence is low possibly due to transplacental transfer of malaria IgG antibodies. Manifestations include fever, splenomegaly, anemia, jaundice and a sepsis-like presentation.

Prevention: It is advised that all pregnant women in endemic areas are protected against mosquito bites. Role of chemoprophylaxis is controversial. Data suggests that providing weekly chloroquine prophylaxis to pregnant women in malaria endemic areas reduces low birth weight and maternal anemia

Points to Remember

- *The original ToRCHES group of infections has now been expanded to TORCHES CLAP including few more organisms.*
- *Diagnosis is usually based on serology or identifying the organism through PCR in blood, CSF or urine. Treatment is possible for some infections.*
- *With better antenatal care and intrapartum care problems such as asphyxia may come down, long term neurosequelae due to intrauterine infections will become a common problem unless preventive measures are instituted.*
- *The presentation of intrauterine infections is varied and is a differential diagnosis for children with hepatitis, neurologic abnormality or seizures.*
- *Since treatment may not be possible always, preventive measures should be instituted whenever possible.*

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CLIPPINGS

Heated, humidified air for the common cold

Heated, humidified air has long been used by sufferers of the common cold. The theoretical basis is that steam may help congested mucus drain better and heat may destroy the cold virus as it does in vitro.

Objective was to assess the effects of inhaling heated water vapour (steam) in the treatment of the common cold by comparing symptoms, viral shedding and nasal resistance.

Selection criteria: Randomised controlled trials (RCTs) using heated water vapour in participants with the common cold or participants with experimentally induced common cold.

Authors' conclusions: Steam inhalation has not shown any consistent benefits in the treatment of the common cold, hence is not recommended in the routine treatment of common cold symptoms until more double-blind, randomised trials with a standardised treatment modality are conducted.

Singh M, Singh M. Heated, humidified air for the common cold. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD001728. DOI: 10.1002/14651858.CD001728.pub5. Assessed as up to date: 12 March 2013.

PERINATOLOGY

RECENT ADVANCES IN THE MANAGEMENT OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY

***Abiramalatha T**
****Niranjan Thomas**

Abstract: Hypoxic ischemic encephalopathy (HIE) is an important cause of neonatal mortality and morbidity. Brain injury in HIE involves a cascade of neurochemical mechanisms that occurs in two phases. Till recently, management of HIE consisted of only supportive care. Animal studies and clinical research have progressed our understanding of the pathophysiology of HIE, leading to discovery of novel neuroprotective strategies. Therapeutic hypothermia is the standard of care in developed countries but is yet to become routine clinical practice in India. New treatment options like erythropoietin, xenon, magnesium sulphate and melatonin are still in an experimental stage. In this article we discuss the recent advances in supportive care, therapeutic hypothermia and other neuroprotective strategies for infants with HIE.

Keywords: Hypoxic ischemic encephalopathy, Treatment, Neuroprotection, Therapeutic hypothermia

Hypoxic ischemic encephalopathy (HIE) is a clinical condition characterized by altered sensorium, abnormalities of muscle tone, posture and reflexes and difficulty in initiating and sustaining respiratory effort at birth resulting from a hypoxic ischemic insult. According to Western data the incidence of HIE is 1.5 per 1000 live births.¹ As per National Neonatal-Perinatal Data Base², the incidence in India is 14 per 1000 live births with birth asphyxia causing 30% of neonatal and 50% of perinatal deaths. Among the neonates with HIE, 10-15% will die, 10-15% will develop cerebral palsy and upto 40% will develop other disabilities.

Pathophysiology

There are 2 phases of brain injury following asphyxia. The phase of primary energy failure starts immediately after the asphyxia insult, hypoxia-ischemia leads to anaerobic metabolism and exhaustion of ATP. This leads to failure of Na/K ATPase membrane pump and loss of normal ionic homeostasis, resulting in neuronal membrane depolarization and release of neurotransmitters such as glutamate. The subsequent elevation in intracellular calcium concentrations triggers a number of destructive pathways. Activation of proteases, lipases and nitric oxide synthetase results in free radical injury and apoptotic cell death (Fig.1).

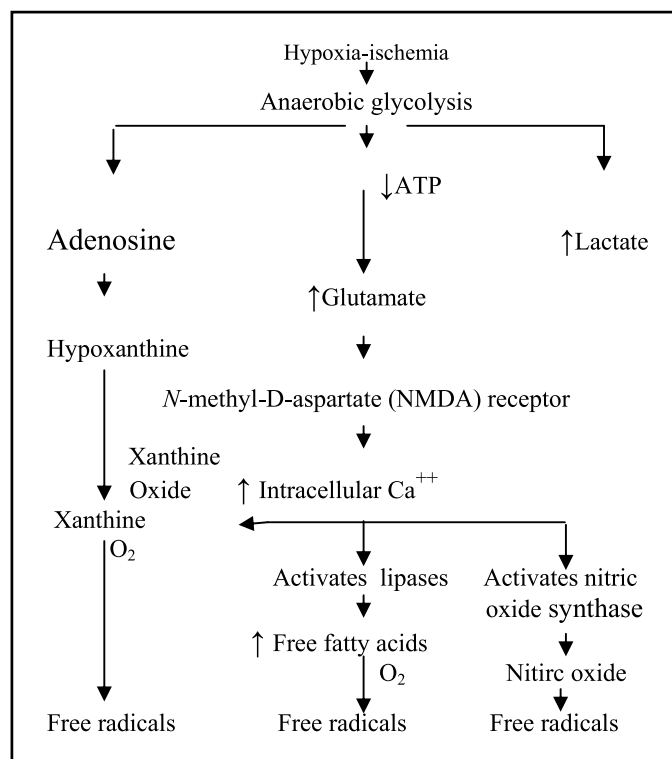


Fig.1. Potential pathways for brain injury after hypoxia-ischemia

When cerebral circulation and oxygenation are re-established after resuscitation, cellular energy metabolism is restored, ATP levels return to baseline, glutamate is cleared and lactate levels improve. The initial reperfusion phase is followed by a latent phase. During this time, there may be

* Senior Registrar

** Professor & Head,
Department of Neonatology,
Christian Medical College,
Vellore.

complete recovery or secondary energy failure may subsequently develop. The secondary energy failure phase occurs 6–15 hours after the initial insult, reaches its nadir by 24–48 hours and may continue for days to weeks. During this phase, a second cascade of brain injury occurs as a result of accumulation of excitatory neurotransmitters, oxidative injury, apoptosis and activation of inflammation. The latent resolution phase corresponds to a therapeutic window of approximately six hours. Initiation of therapies in the therapeutic window has been successful in reducing brain damage.

Supportive management (Box.1)

Standard intensive care is critical in the management of infants with HIE. Management of multi-organ dysfunction, maintenance of acid-base, hemodynamic and electrolyte balance and control of seizures would help in preventing further damage to the injured brain and improving the neurodevelopmental outcome.

Box 1. Supportive management of babies with HIE

Delivery room

Resuscitation beginning with room air $\pm$ supplemental oxygen if needed

Temperature

Avoid hyperthermia

Oxygenation and ventilation

Maintain PaO₂ and PaCO₂ in normal range

Perfusion

Promptly treat hypotension/ Avoid hypertension

Fluid and electrolytes

Initial fluid restriction/ Monitor daily weight and sodium

Maintain blood glucose in normal range

Prompt correction of coagulopathy and bleeding

Treatment of seizures

Delivery room management: In the past, the recommendation was to initiate resuscitation of the depressed neonate with 100% oxygen. Current guidelines recommend beginning resuscitation with room air and increasing FiO₂ using blended oxygen based on defined preductal saturation targets³. If blended oxygen is not available, resuscitation should be initiated with room air. If the baby has bradycardia (HR <60 per minute) after

90 seconds of resuscitation, oxygen concentration should then be increased to 100% until recovery of a normal heart rate.

Ventilation and oxygenation: Hypoxemia disturbs cerebral autoregulation resulting in pressure-passive circulation, increasing the risk of ischemia with only moderate decreases in arterial blood pressure. Hypoxia also causes increased white matter injury due to the limited vasodilatory capacity in neonatal cerebral white matter. Hyperoxia increases neuronal injury by causing cerebral vasoconstriction and increasing oxidative stress. Hypercarbia impairs cerebral autoregulation, causes cerebral vasodilatation and intracranial hemorrhage, and worsens neuronal intracellular acidosis. Hypocarbica causes cerebral vasoconstriction and accentuates ischemic injury. In a study adjusting for the severity of birth asphyxia⁴, during the first 20–120 minutes of life, peak PaO₂ values exceeding 200 mmHg was significantly associated with adverse outcomes (OR with 95% CI = 3.85; 1.67–8.88) and trough PaCO₂ values of 20 mmHg or lower also was significantly associated with adverse outcomes (OR with 95% CI = 2.34; 1.02–5.37). Hence oxygen supplementation and ventilation should be rigorously controlled maintaining PaO₂ between 60–100 mm of Hg and PaCO₂ between 30–55 mm of Hg.

Cardiac dysfunction: Hypoxia induced cardiac injury may manifest as decreased ventricular function, abnormalities of rate and rhythm, tricuspid regurgitation and hypotension. Avoidance of hypotension is especially important because of the pressure passive cerebral circulation. On the other hand, hypertension may cause cerebral overperfusion and intracranial hemorrhage. Mean arterial pressure should be maintained ≥ 40 mm of Hg. If echocardiographic assessment indicates adequate cardiac contractility but evidence of hypovolemia, normal saline bolus (10–20 mL/kg) can be considered or blood transfusion may be given if hematocrit is < 30. Inotropes can be started if echocardiographic assessment indicates poor contractility or if BP is low despite volume replacement.

Fluid and electrolytes: Infants with HIE often develop fluid overload state presenting clinically with edema, decreased urine output and hyponatremia. This may be due to renal failure resulting from acute tubular necrosis, syndrome of inappropriate anti-diuretic hormone release (SIADH) or the fluid boluses given during resuscitation. Management is by fluid restriction with daily monitoring of weight and serum sodium levels. Electrolyte disturbances like hypocalcemia and hypomagnesemia are common and should be managed appropriately

Control of blood glucose levels: Both hypoglycemia and hyperglycemia accentuate neuronal injury, hence blood glucose should be monitored closely and maintained in the normal range.

Coagulopathy and other organ injury: Disseminated intravascular coagulation and bleeding manifestations may occur and must be treated promptly with transfusion of blood components. Renal dysfunction due to acute tubular necrosis is common but is usually transient and resolves over the first week of life. Liver damage manifests as elevated liver enzymes and may exacerbate coagulation problems. Excessive early enteral feeding may facilitate the occurrence of necrotizing enterocolitis, because the gut may be injured by hypoxic-ischemic damage.

Treatment of seizures: Seizures are associated with a markedly accelerated cerebral metabolic rate which may lead to a rapid fall in brain glucose, an increase in lactate and a decrease in ATP. In addition, seizures are associated frequently with hypoventilation and apnea with consequent hypoxemia and hypercarbia, both of which aggravate neuronal damage. Experimental evidence suggests that repetitive seizures disturb brain growth and development as well as increase the risk of subsequent epilepsy. Phenobarbitone is the most commonly used first-line anticonvulsant and phenytoin as the second choice. Both the drugs together is effective in suppressing only just more than fifty percent of the seizures. Other drugs used are benzodiazepines and lignocaine. Newer anticonvulsants like topiramate and levetiracetam are less well studied. Continuous EEG studies show that a considerable electrographic seizure burden often remains after anticonvulsant treatment due to electro-clinical dissociation. Whether treating all electrographic seizures is necessary, is still unclear.

Neuroprotective treatment strategies: Animal studies and clinical research have resulted in considerable progress in understanding the cascade of neurochemical events that mediate brain damage after a hypoxic-ischemic insult and have helped identify new treatment strategies, principle of which is therapeutic hypothermia.

Therapeutic hypothermia: Therapeutic hypothermia is a neuroprotective intervention that can reduce the severity of the secondary reperfusion brain injury associated with HIE if begun during the latent resolution phase. Hypothermia acts at various levels of the cascade of neuronal injury. It reduces cerebral metabolism and energy utilization, attenuates excitotoxic injury, inhibits apoptosis, suppresses free radical production and inhibits the inflammatory cascade. A recent Cochrane meta-analysis has shown that therapeutic hypothermia resulted in a

significant reduction in mortality or major neurodevelopmental disability at 18 months of age [RR with 95% CI = 0.75, 0.68 to 0.83].⁵ It was shown that cooling reduces mortality without increasing major disability in survivors and the benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects.⁵

Eligibility criteria (Box.2): Babies who benefit maximally from cooling are those with moderate encephalopathy. The inclusion criteria are given in (Box.2) and babies should fulfill the criteria A, B and C before being cooled.

Box 2. Eligibility criteria for therapeutic hypothermia

A. Both

- ≥36 weeks / ≥ 1800 grams
- < 6 hours of age

B. Any one

- APGAR score @ 10 minutes <5
- ABG(cord/1 hour postnatal) pH <7, Base Deficit >- 16
- Need for prolonged resuscitation/IPPV for ≥ 10 minutes

C. Moderate to severe encephalopathy on modified Sarnat or Thompson score **OR any seizures**

Cooling should be initiated within the therapeutic window period of 6 hours. The earlier cooling is commenced, the better the outcome. This is particularly critical since the therapeutic window is substantially reduced with increasing severity of injury. The core temperature should be maintained at 33.5° C (33 - 34° C) for 72 hours and after this the baby should be re-warmed slowly at a rate of 0.2-0.5° C/hour. Rapid re-warming may cause hypotension, hypoglycemia and hyperkalemia.

Methods and Equipment: Induced hypothermia can be achieved via selective head cooling (SHC) with mild systemic hypothermia or whole body cooling (WBC), both of which have been shown to be neuroprotective. However, whole body cooling is easier to practice and in a porcine model, SHC resulted in larger observed temperature gradients, resulting in warmer deeper structures and a cooler brain periphery, whereas whole-body cooling was associated with more homogeneous cooling. Although WBC may theoretically cause more systemic complications, there were no major short-term consequences to either method of cooling.

There are standard equipments available, the Olympic Cool Cap for SHC and Tecotherm, Criticool and Blanketrol Cincinnati Sub-zero System for Whole Body Cooling. However as these equipments are expensive, low-cost cooling methods using cool gel/ice packs, cooling fans, water bottles, phase-changing material and cooling pots have been described and studies from India have documented feasibility in cooling babies with low cost methods.⁶ These low-cost cooling systems are associated with greater variability in temperature compared to servo-controlled systems. Such large fluctuations in temperature may adversely affect the neuroprotection and these methods should be used with caution only in an intensive care setting.

Complications: Though there are many possible complications of induced hypothermia, data from the randomized controlled trials have shown therapeutic hypothermia to be safe. Only sinus bradycardia and thrombocytopenia were statistically more common in the hypothermia group, both of which were however clinically not significant.⁵ Our experience is similar except that some of the babies had coagulopathy and hyperglycemia, which have not been reported from the western trials.⁶

Other neuroprotective strategies: Though therapeutic hypothermia improves neurodevelopmental outcome, it is insufficient by itself. Many (40%-50%) infants treated with hypothermia still die or have significant neurological disability.⁷ Hence, there is an urgent need to develop additional treatment strategies.

Xenon: Xenon is a noble gas used in anesthesia. It is a potent N-methyl-D-aspartate (NMDA) antagonist and it has additional mechanisms of action such as inhibition of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate receptors, reduction of neurotransmitter release and inhibition of apoptosis. Xenon has been shown to be neuroprotective in animal models of HIE and is synergistic with hypothermia. Human trials are ongoing which try to evaluate the effect of xenon in neonatal HIE (NCT01545271, NCT00934700). The major disadvantage would be that it is very expensive and requires special ventilators for administration.

Erythropoietin (Epo): Epo is a hematopoietic growth factor, produced locally in the brain. It is neuroprotective especially against hypoxic-ischemic neuronal injury and enhances neurogenesis. It is also anti-inflammatory and anti-apoptotic. High dose Epo (5000 U/kg) has been found to reduce the infarct size in neonatal stroke, but there were concerns regarding safety. A recent randomized prospective study reported that repeated, low dose (300 or 500 U/kg every other day) Epo was safe and resulted in improved

neurological outcome at 18 months of age in patients with moderate HIE.⁸ Routine use of Epo in HIE awaits further research.

N-Acetyl Cysteine: N-Acetyl cysteine (NAC) is a free radical scavenger, restores intracellular glutathione levels, attenuates reperfusion injury and decreases inflammation and nitric oxide production. Adding NAC therapy to systemic hypothermia reduced brain volume loss after neonatal rodent HI, with increased myelin expression and improved reflexes. In a clinical trial, NAC was shown to decrease the incidence of periventricular leukomalacia by 39% in preterm infants.⁹ Human trials of NAC in HIE are awaited.

Melatonin: Melatonin is a potent free radical scavenger as well as an indirect antioxidant. It easily crosses the blood-brain barrier and is safe in children. Animal studies have shown melatonin to be neuro protective in HIE and is synergistic with hypothermia. Human trials are awaited.

Anticonvulsants: Prophylactic phenobarbitone before cooling has been shown to be ineffective in decreasing the incidence of HIE or in reducing mortality in babies with birth asphyxia.¹⁰

Topiramate modulates AMPA/kainate and GABA-A activated ion channels as well as voltage-activated Na⁺ and Ca⁺⁺ channels. These effects may make it a potential neuroprotectant, acting by reducing excitatory amino acid release and calcium overload in the ischemic cells and by increasing the seizure threshold. A pilot study is ongoing to explore the possible therapeutic role of topiramate in combination with moderate hypothermia (NeoNATI trial).

Levetiracetam regulates AMPA and NMDA receptor-mediated excitatory synaptic transmission and reduces glutamate release especially in the hippocampus. In contrast to several traditional antiepileptics such as phenobarbitone and phenytoin, levetiracetam does not induce cell death by apoptosis in the developing brain. However, the use of levetiracetam in human neonates has not yet been formally evaluated and experience is still limited.

Allopurinol: Allopurinol inhibits xanthine oxidase which is the primary source of superoxide radical. It also scavenges other oxygen free radicals. It has been shown to decrease reperfusion injury and brain damage in animal models of HIE. However a recent Cochrane meta-analysis could not find significant improvement in neurodevelopmental outcome in babies treated with allopurinol due to insufficient data, hence more trials are needed.¹¹

Magnesium sulphate (MgSO₄): Magnesium is a naturally occurring NMDA receptor antagonist. It also

decreases levels of inflammatory cytokines, decreases platelet aggregation and is essential for glutathione synthesis. Postnatal MgSO_4 treatment was shown to improve short-term neurologic outcome at discharge in term infants with perinatal asphyxia.¹² A multicentric trial is ongoing to assess the efficacy of MgSO_4 along with cooling in the management of term and near term babies with HIE (NCT01646619).

Other neuroprotective strategies under consideration

Drugs: Indomethacin, bumetanide, memantine, sodium cromoglycate, minocycline, pomegranate polyphenols, 2-iminobiotin, necrostatin.

Growth factors: Nerve growth factor, insulin-like growth factor- 1, brain derived neurotrophic factor

Cord blood Stem cells therapy: Animal studies support the idea that cord blood stem cells have a neuroprotective effect in neonatal HIE. These effects have been attributed to immunomodulation, activation of endogenous stem cells, release of growth factors and anti-apoptotic mechanisms. One registered clinical study is investigating the role of autologous cord-blood transplantation in HIE (NCT00593242).

Biomarkers

Clinical parameters: Based on the clinical staging of encephalopathy by Sarnat, stage 1 encephalopathy has 98%-100% normal neurological outcome and <1% mortality while stage 2 has 20%-37% and stage 3 has almost 100% mortality or morbidity. The widely used APGAR score and cord/1st hour blood gas acid-base parameters show a rather broad, imprecise relationship with HIE. Infants at either extremes are correctly identified with reasonable precision (i.e. none versus severe HIE), but not the intermediate group. In a retrospective cohort study¹³, the 3 most significant predictors were shown to be chest compressions for > 1 minute, onset of respiration after 20 minutes of life and base deficit >16mmol/ L in cord gas. The risk of severe adverse outcome was 64% with any 1 predictor, 76% with any 2 predictors and 93% with all of the 3 predictors present.

Sero-markers: S100B, neuron-specific enolase, activin A, adrenomedullin, and interleukin (IL)-1 β , and IL-6 are some of the bio-markers being evaluated for predicting the severity of HIE and neurodevelopmental outcome. There are several limitations in using these sero markers, as they are produced by multiple body tissues and hence are not specific for brain and HIE. There are very, few long term follow-up studies

so far to assess their neurodevelopmental predictive value and, most studies were based on samples taken after 24 hours-too late to decide therapeutic options. Further, while they distinguish between no or mild injury and severe injury, they are not very useful in predicting outcome in moderate encephalopathy. Hence their use awaits further trials.

MRI and MRS: In a nested sub-study from the TOBY trial, the presence of abnormal signal intensity in the posterior limb of the internal capsule, moderate or severe basal ganglia or thalami signal abnormalities and severe white matter abnormalities in MRI were strongly predictive of subsequent serious neurological abnormalities.¹⁴ Deep gray matter Lactate/N-acetyl aspartate (Lac/NAA) was shown to be the most accurate quantitative MR biomarker for prediction of neurodevelopmental outcome after HIE with a sensitivity of 82% and specificity of 95% and the results were not influenced by the age at scanning during the first 30 days after birth.¹⁵

Electrophysiological markers: In a recent systematic review analyzing the value of various prognostic tests in HIE, amplitude-integrated EEG (aEEG) was shown to be the most promising with a sensitivity of 93 and specificity of 90.¹⁶ Both the severity of the abnormality in the aEEG and the speed of recovery are of prognostic significance. Severely abnormal aEEG patterns (Burst suppression, low voltage or isoelectric trace) persisting for more than 48-72 hours are predictive of adverse neurodevelopmental outcome. Spontaneous recovery of severely abnormal aEEG patterns is not uncommon, the sooner the abnormalities on aEEG disappear, the better the prognosis. Normal voltage patterns up to 48 hours of life are predictive of normal neurologic outcomes.

A good neurodevelopmental outcome was predicted by the onset of sleep wake cycle (SWC) in aEEG before 36 hours in 82% of infants with HIE.¹⁷ Never achieving SWC always predicts poor outcome.

Therapeutic hypothermia changes the predictive value of aEEG. Normalisation of an infant's aEEG in an infant who recovers takes 24 hours if not cooled, whereas it may take 48 hours in an infant who is cooled.¹⁸

Other electrophysiological studies like visual evoked potentials (VEP), brainstem evoked auditory response (BERA) and sensory evoked potentials (SEP) also have prognostic value in HIE but are yet to be used widely.

Near infrared spectroscopy (NIRS): NIRS is a bedside and non-invasive technique that can be used to monitor cerebral oxygenation status in HIE, is still a research tool under evaluation.

Points to Remember

- *HIE is a common cause of neonatal mortality and morbidity.*
- *Adequate intensive care and supportive measures will improve neurodevelopmental outcome.*
- *Therapeutic hypothermia has become the standard of care in developed countries, but is yet to become a routine clinical practice in India.*
- *Other novel neuroprotective therapies are under investigations.*
- *Apart from clinical parameters, EEG and MRI are of great value in assessing the severity of HIE and predicting the long-term neurodevelopmental outcome.*

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PERINATOLOGY

EARLY ONSET NEONATAL SEPSIS- WHAT IS NEW?

***Aparna Chandrasekaran**

Abstract: *With improved obstetric care and intrapartum antibiotic management, developed countries have achieved considerable reduction in mortality and morbidities due to early onset sepsis (EOS). However, the problem poses a significant burden to the health care system in the developing world. The identification of a neonate at risk for EOS is based on a constellation of perinatal risk factors and clinical signs along with laboratory abnormalities. Diagnostic tests lack sufficient positive as well as negative predictive value in EOS. Blood culture remains the gold standard in diagnosis. Treatment of asymptomatic at risk infants requires consideration of gestational age, presence of clinical chorioamnionitis, additive value of other perinatal risk factors and ability to observe the neonate meticulously.*

Keywords: *Early onset sepsis, Neonatal sepsis, Chorioamnionitis*

With improved obstetric care and intrapartum antibiotic management, developed countries have achieved considerable reduction in early onset sepsis (EOS)-related mortality and morbidities, although the incidence of death as well as antimicrobial resistance is still dangerously high in India. The identification of a neonate at risk for EOS is based on a constellation of perinatal risk factors and clinical signs along with laboratory abnormalities. Diagnostic tests lack sufficient positive as well as negative predictive value in EOS. Blood culture remains the gold standard in diagnosis. Treatment of asymptomatic at-risk infants requires consideration of gestational age, presence of clinical chorioamnionitis, additive value of other perinatal risk factors and ability to observe the neonate meticulously.

National Institute of Child Health and Human Development (NICHD) defines neonatal early onset sepsis

(EOS) as the onset of signs of infection within 3 days of life.¹ The time frame before which sepsis is recognised as 'early onset' is variable from 24 hours to 7 days.² Essentially, the definitions try to delineate a cut-off point beyond which the origin of infections is usually nosocomial (late onset sepsis), rather than intrapartum (early onset sepsis). However, the distinction blurs out in developing countries where neonates are at risk of acquiring environmental pathogens from the facility or community soon after birth due to unhygienic practices.³

Incidence of EOS has declined in the developed nations following improved obstetric management and evidence-based intrapartum antimicrobial therapy. The incidence of EOS has declined from 3-4 cases/1000 live births to 0.8-1/1000 live births in the post GBS prophylaxis era.⁴ Nevertheless, preterm very low birth weight neonates (VLBW) are at ten times greater risk of mortality (30%) from EOS compared to term neonates (2%-3%), in addition to morbidities such as chronic lung disease, white matter damage and neurodevelopmental impairment.⁵

This article attempts to capture newer understanding in the pathogenesis of EOS and their clinical implications.

Defects in neonatal immune defence mechanisms

Neonatal immunity is deficient at multiple steps. Invading pathogens first come into contact with the antigen presenting cells (APCs) like the monocytes, macrophages and Langerhans cells of skin. However, neonatal APCs have defective expression of major histocompatibility complex II (MHC II) and co-stimulatory molecules, resulting in reduced presentation to CD₄⁺ cells. Further, neonates exhibit a skewed response to stimulation by pathogens, marked by predominance of Th2 polarizing anti-inflammatory cytokines such as interleukin IL-10 rather than the usual Th1 polarizing cytokine response such as tumour necrosis factor TNF α , IL-12 and interferon. This deficient pathogen recognition and activation of immune system is being targeted with toll-like receptor agonists (TLR 8 agonists) in vitro.⁵

Neonates, particularly extremely low birth weight (ELBW) neonates, exhibit quantitative as well as qualitative

* Junior Consultant,
Neonatology,
CHILDS Trust Hospital,
Chennai.

defects in neutrophil and mast cell function during multiple steps - recruitment, rolling, diapedesis and microbicidal respiratory burst activity, which increase the risk of infection. In addition, defects in non-cellular immune mechanisms like mannose binding lectin (MBL) stimulated alternate complement pathway, cytokines, acute phase reactants and transplacentally acquired immunoglobulins also contribute variably to the susceptibility to infection.⁵

Chorioamnionitis – Emerging insights into the maternal microbiome

The foetus is optimally placed in sterile amniotic fluid. Infection of the membranes and/or placenta (chorioamnionitis) usually follows ascending infection in the setting of prolonged rupture of membranes (common with *Ureaplasma* and *Mycoplasma* species), and rarely, haematogenous spread (*Listeria monocytogenes*) or iatrogenic (following amniocentesis) (Fig. 1).⁶

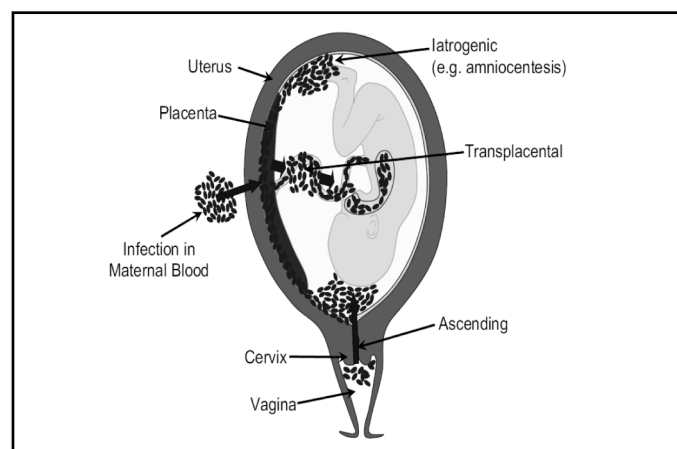


Fig.1. Routes of spread of intra-amniotic infection⁶

In term pregnancies, less than 1% of amniotic fluid cultures are positive¹ whereas, microbial invasion of amniotic fluid is demonstrable in 32% of spontaneous preterm births and 75% in cases of preterm premature rupture of membranes (PPROM).⁷ Almost 80% of deliveries below 30 weeks gestation are associated with clinical or histological chorioamnionitis.⁶

Infection is usually polymicrobial, the commonest being *Ureaplasma urealyticum* (45%) and *Mycoplasma hominis* (30%), often implicated in non-gonococcal urethritis in men and female genital infections. Although once considered non-virulent, these fastidious bacteria are now being linked with infertility, stillbirths and pregnancy losses.⁶ Despite being commonly positive in neonatal cord blood, this

organism is surprisingly not linked with neonatal early onset sepsis.⁸ Other common organisms include *Gardnerella vaginalis* (25%), *Bacteroides* (30%), Group B *Streptococcus* (15%) and *Escherichia coli* (8%).⁶

The pathogenesis of maternal and foetal response in chorioamnionitis is elucidated in (Fig.2). The common pathogens and their variable clinical profile are shown in (Fig.3).

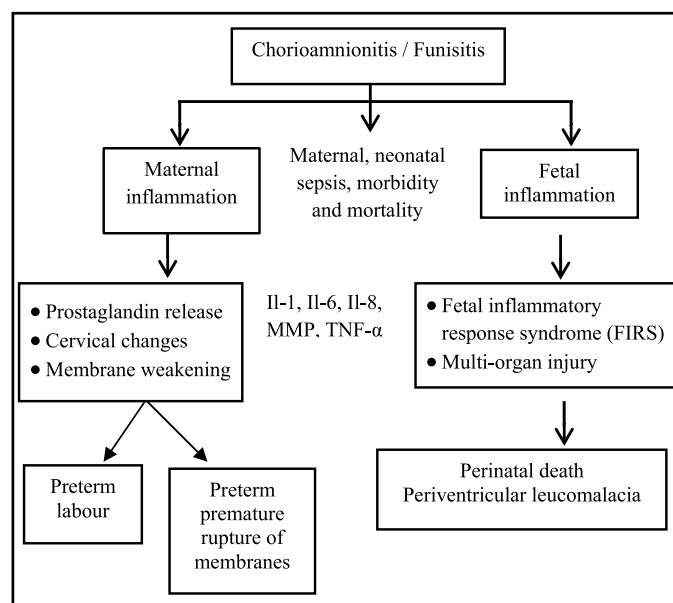


Fig.2. Pathogenesis of maternal and fetal effects of chorioamnionitis⁶

(IL- Interleukin, MMP- Matrix metalloproteinase, TNF a- Tumour necrosis factor alpha).

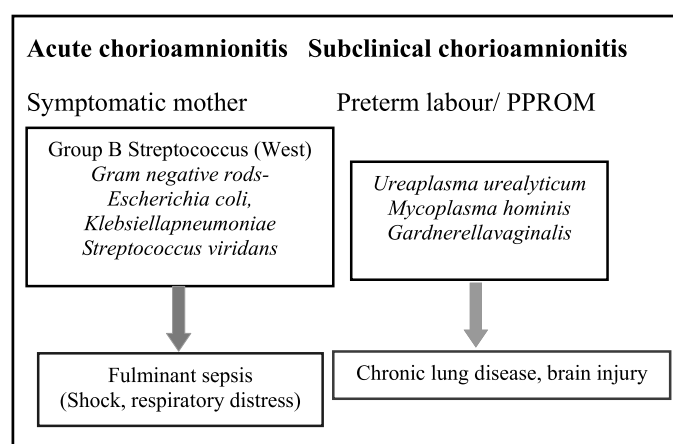


Fig.3. Microbes responsible for chorioamnionitis and the morbidities associated

The chief clinical signs of chorioamnionitis include maternal fever greater than 100.4°F (present in 95%-100% cases), maternal (>100/min) and foetal (>160/min)

tachycardia (in 80% and 70% cases, respectively) and foul smelling liquor (4%-25% cases).⁶

Risk Factors for early onset sepsis

Western and Indian data have demonstrated common risk factors for EOS. In a systematic review by Benitz, the risk factors associated early onset Group B Streptococcal sepsis were identified (Table I).⁹

Table.I Risk factors for early onset GBS sepsis in developed nations⁹

Risk Factor	Odds ratio (95% CI)
Birth weight < 2500 grams	7.37 (4.48-12.1)
Gestation < 37 weeks	5.80 (2.15-15.7)
PROM > 18 hours	7.28 (4.42-12.0)
Preterm premature rupture of membranes	5.2 (2.4-11.6)
Maternal intrapartum fever > 37.5deg C	4.05 (2.17-7.56)
Chorioamnionitis	6.43 (2.32-17.80)
Maternal vaginal swab positivity for GBS at delivery	204 (100-419)

PROM – Prolonged rupture of membranes; GBS – Group B streptococcus; CI- Confidence interval.

Previously, a number of Indian studies have recognized the following risk factors for EOS: birth asphyxia, unclean vaginal examinations, foul smelling liquor, labour >24 hours, prolonged rupture of membranes >24 hours, birth weight <2 kg, prematurity, maternal fever, gastric polymorphs >20/high power field and meconium stained liquor.^{10,11} But most of these studies were small, failed to perform multivariate analysis, allotted weights to individual factors arbitrarily and ignored the use of intrapartum antibiotics.

In a recent study from Chandigarh, 13 risk factors were evaluated among 601 asymptomatic neonates born at or before 34 weeks, of which 6 risk factors were independently predictive of development of EOS - intrapartum per vaginal examinations ≥ 3 times, clinical chorioamnionitis, birth weight <1.5 kg, male gender, not received intrapartum antibiotics and gestation ≤ 30 weeks. (Table II) Each of these items were scored 2, 3 or 6, depending on their odds ratio for development of EOS and neonates with total score ≥ 6 were initiated on antibiotics after sending a blood culture, while neonates with

Table.II Risk factors for early onset sepsis in India (N=602)¹²

Risk factor	Odds ratio	95% CI	Score allotted
Birth weight < 1500 grams	2.8	1.5-5.1	3
Gestation < 30 weeks	2.0	1.1-3.5	2
Per vaginal exams ≥ 3	9.5	3.0-30.5	6
Intrapartum antibiotics not received	2.1	1.0-4.1	2
Male gender	2.7	1.6-4.7	3
Clinical chorioamnionitis	8.8	1.8-43.2	6

EOS- early onset sepsis, CI- Confidence interval; (Decimals rounded off to 1 digit).

score below 6 were observed carefully for signs of sepsis. It is interesting to note that absence of maternal intrapartum antibiotic prophylaxis was identified as a significant risk factor in this Indian study for the first time.¹²

Obstetric management and prevention of chorioamnionitis

Management of clinically proven chorioamnionitis with broad spectrum antibiotics - ampicillin (6 hourly) and gentamycin (8 to 24 hourly) reduces the incidence of neonatal sepsis by 80%.¹³ Intravenous clindamycin is sometimes added for anaerobic cover and provides modest action against *M hominis*. However, Ureaplasma, the commonest pathogen causing chorioamnionitis remains unaffected by the above regimen, yet neonatal EOS with Ureaplasma species is hardly reported to be a clinical problem.⁶ There are currently no trials supporting the addition of macrolides in the background of maternal chorioamnionitis.

The Centres for Disease control (CDC) recommends intrapartum GBS prophylaxis to be started in any parturient with

1. GBS positive antenatal cultures or molecular test at admission (except in caesarean section without labour or membrane rupture)

2. Unknown maternal colonization status with gestation <37 weeks, rupture of membranes >18 hours, or temperature >100.4°F (>38°C)
3. GBS bacteriuria during current pregnancy
4. Previous infant with invasive GBS disease¹⁴

Expectant management of PPRM is associated with chorioamnionitis in 70% cases. Two large multicentre studies, ORACLE Children Studies (OCS) – I and II, evaluated the use of erythromycin and/or amoxicillin-clavulanate (co-amoxiclav) in pregnant women by use of a factorial randomized design. The first group (ORACLE 1 trial) consisted of 4826 women with preterm premature rupture of membranes (PPROM) and the second group (ORACLE 2 trial) consisted women with spontaneous preterm labour (SPL). The composite outcome of chronic lung disease or ultrasound diagnosed brain injury, need for surfactant and requirement of oxygen in the first week were lesser with use of erythromycin, while co-amoxiclav use was associated with increase in necrotising enterocolitis (3.8% vs 2.4%, $p=0.004$) in ORACLE I. (ORACLE). There was no significant benefit or harm with either antibiotic in ORACLE II.^{15,16}

Despite these short term benefits, use of erythromycin was not associated with any long term neurological benefits at 7 years follow up in ORACLE I, rather resulted in a greater risk of functional impairment, when compared to no erythromycin (OR 1.18; 1.02-1.37) in ORACLE II. This finding was limited by the loss to follow up rate of nearly 30% and telephonic interview based maternal report of functional status. The disadvantage being caused by failure of oral antibiotics to eradicate infection, continued exposure of foetus to low grade infection, inflammation secondary to non-infectious aetiology and direct drug toxicity could not be ruled out.¹⁷

Evaluation and management of a neonate with suspected EOS

Diagnosis of EOS

EOS presents with a wide spectrum of signs such as lethargy, irritability, apnea, respiratory distress, temperature instability, fever or hypothermia and shock, leading commonly to over diagnosis as well as under diagnosis.

The WHO young infants study identified 7 simple clinical signs - history of difficulty in feeding, convulsions, movement only when stimulated, respiratory rate of 60 breaths per minute, severe chest in drawing, temperature of 37.5°C or more or below 35.5°C, to have reasonable sensitivity (85%) and specificity (75%) in identifying neonates with severe illness in the first 6 days of life.¹⁸

Blood culture

Blood culture remains the gold standard in diagnosing neonatal sepsis. The inoculated sample should be of appropriate volume in order to optimize detection rates. Use of optimal volume of inoculum increases the chances of detection of bacteremia by two times. This is true in neonates where low grade bacteremia is (≤ 4 Colony Forming Units [CFU]/mL), seen in 25% cases.¹ Currently, there is no role for urine or body surface cultures in a neonate with suspected EOS.

Septic screen panels

The positive predictive value of the sepsis screen panels in neonates is poor (<30%); however, negative predictive accuracy has been high (>99%) in clinical studies (Table. III).

In EOS, sepsis screen panels consisting C-reactive protein and neutrophil indices have been shown to have

Table.III Sepsis screen panels in evaluating neonates with suspected sepsis¹⁹

Author/ year	Parameters	Sensitivity/ specificity	LR ⁺ /LR ⁻
Philip 1980	Any 2 + ve of: ITR>0.2, WBC<5000, CRP >8 mg/L, ESR >15 mm/1 st hr, Haptoglobin >25 mg/dL	93/ 88	7.8/0.08
Gerdes 1987	Any 2 + ve of: WBC <5000/mm ³ , ITR >0.2, and CRP > 1 mg/dL	100/83	5.9/0

WBC: white blood cell count; ITR- Immature to total neutrophil ratio; ESR- erythrocyte sedimentation rate; CRP- C-reactive protein; LR⁺- Likelihood ratio of positive test, LR⁻-Likelihood ratio of negative test

poor sensitivity in the first 24 hours of life when compared to those performed beyond that period.¹ The addition of procalcitonin and IL-6 to screen panels increases the diagnostic yield.

Microbial infection induces the calcitonin gene-related peptide (CALC1) gene in all tissues of the body, leading to an ubiquitous rise in procalcitonin (PCT), a 116-aminoacid peptide. PCT concentrations increase within 2 hours of an infectious episode, peak at 12 hours, and normalize within 2 to 3 days. In contrast, CRP can be detected in the plasma after 12 hours and reaches a plateau after 20–72 hours. A physiological increase in procalcitonin during the first 24 hours and elevation in hypoxemia, respiratory distress and myocardial compromise can cause confusion in interpretation, although the degree of elevation in sepsis is far greater and correlates well with mortality.²⁰

Lumbar puncture

Cerebrospinal fluid (CSF) examination in EOS is reserved for neonates with signs of sepsis who can safely undergo the procedure, neonates with a positive blood

culture, neonates likely to be bacteremic (on the basis of laboratory data), and not responding to antimicrobial therapy in the expected manner.¹ It is avoided in the asymptomatic neonate who is “at risk” of EOS.

Treatment of EOS

Whom to treat

The critically sick neonate with features of sepsis should be evaluated and initiated on broad spectrum antibiotics irrespective of the risk factors without waiting for the results of laboratory screen for sepsis. The greatest clinical challenge lies in distinguishing neonates with early signs of sepsis from neonates with non-infectious conditions (e.g., Transient tachypnoea of newborn). In relatively mature infants with no risk factors for sepsis who improve within the first 6hrs (this cut-off is empirical), it may be reasonable to withhold antibiotics.

Well-appearing, ‘at-risk’ infants should not be treated more than 48 hours if the blood culture is negative and the infant remains well. Suggested algorithms for management of EOS are given in (Fig.4).

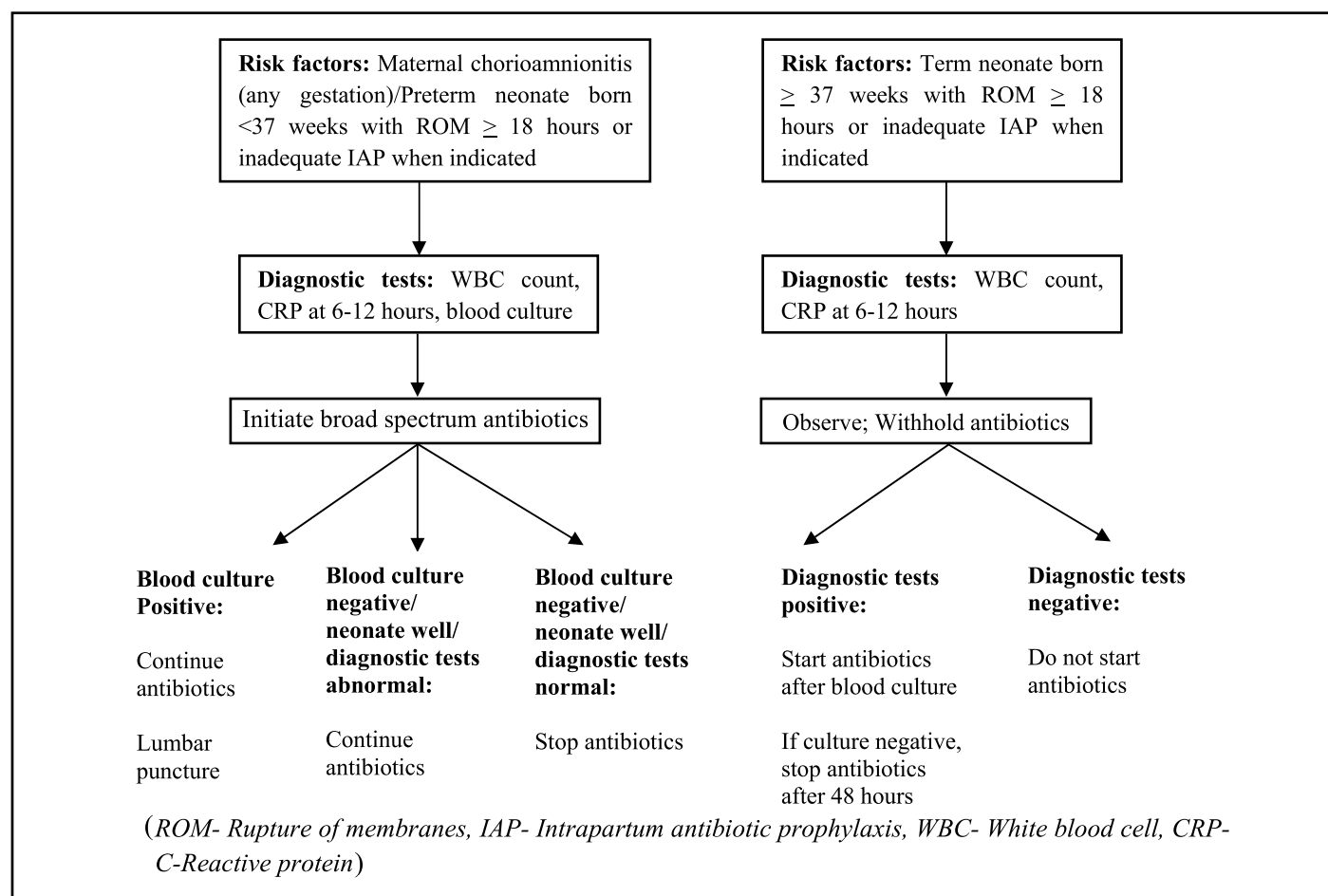


Fig.4. Algorithms for managing asymptomatic neonates with suspected EOS¹

What to start

The optimal treatment of neonates with EOS relies on intravenous broad spectrum antibiotics depending upon the antibiotic sensitivity pattern of organisms commonly grown in the unit. Usually penicillin (ampicillin) and aminoglycoside are used.¹ If there is any obvious evidence of staphylococcal infection, cloxacillin or vancomycin (if neonate is critically ill) may be added. However, Indian data suggests that 80% of organisms causing early onset gram negative sepsis are resistant to ampicillin, third generation cephalosporins and gentamicin, indicating that multi organ resistance is a major problem. Alternative regimens include quinolones (ciprofloxacin)/ piperacillin-tazobactam and amikacin.²¹

Further directions

Biomarkers

Role of novel biomarkers including cytokines (IL-1 β , IL 6, IL 8, IL 10 and IL-18), acute phase reactants (CRP, procalcitonin, serum amyloid A [SAA]), cell surface markers (E selectin, P selectin, CD11b, CD64 and CD69), receptor (IL 2 soluble receptor) and enzymes (neutrophil elastase and urokinase plasminogen activator) is being increasingly studied.⁵

Proteomics

New proteomic approaches are being studied with the advent of specific inflammatory markers such as calgranulins and defensins in the identification of chorioamnionitis, intra-amniotic infection and EOS, and in better understanding of the immune mechanisms in sepsis.²²

Molecular methods

Molecular methods such as amplification techniques using polymerase chain reaction (PCR) followed by downstream applications such as sequencing or microarray/probe hybridization are becoming more commonly available. A meta analysis of 23 studies which evaluated the diagnostic utility of molecular techniques versus conventional tests in sepsis found mean sensitivity of 0.90 (95% CI: 0.78–0.95) and specificity of 0.96 (95% CI: 0.94–0.97), with real-time PCR and broad-range PCR performing better than other techniques.²³

Points to Remember

- *Early onset sepsis (EOS) is a major cause of morbidity and mortality especially among very low birth weight neonates*

- *Multiple deficiencies in innate and acquired immunity, cellular and non-cellular, underlie the predisposition to sepsis*
- *The common organisms causing chorioamnionitis are Ureaplasma, M hominis, anaerobes, Group B Streptococcus (GBS) and aerobic gram negative bacteria (E coli)*
- *Management of clinically proven chorioamnionitis with broad spectrum antibiotics - ampicillin (6 hourly) and gentamycin (8- to 24-hourly) occasionally with clindamycin reduces the incidence of neonatal sepsis by 80%*
- *Administration of oral erythromycin to mothers on expectant management of PPRM has been associated with better short term respiratory outcomes and prolongation of pregnancy, although the long term effects are debatable due to continued exposure of fetus to on-going inflammation*
- *In EOS, sepsis screen panels consisting C-reactive protein and neutrophil indices have been shown to have poor sensitivity in the first 24 hours of life. Addition of procalcitonin and IL-6 may improve sensitivity*
- *Blood culture using 1 ml blood drawn in a pediatric blood culture bottle remains the gold standard for diagnosis. Cultures of body surfaces, urine or gastric aspirate have no value*
- *Well-appearing, 'at-risk' infants should not be treated more than 48 hours if the blood culture is negative and the infant remains well.*

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Tel: +91-80-46466346/25634123/22065834. Email: nbc@stjohns.in

PERINATOLOGY

SAFETY ISSUES FOR DRUGS IN PREGNANCY AND LACTATION - MINI READY RECKONER

***Ratnakumari TL**

As described by various citations, every woman in the general population has a 3-5% risk of having a child with a birth defect or mental retardation. Unlike in developing world birth defects are the leading cause of infant mortality in the developed countries like United States due to reduction of many of the other preventable causes.

A well developed neonate without any malformation is a gift from above and when it is not, then one has the onerous duty of evaluating the probable cause for such defects. Most of the intrauterine infections can be benign and only few of the drugs taken can have some teratogenic effect. Only 10% of congenitally presented malformations are due to teratogens.

The time of exposure at risk is usually the first 60 days' gestation, that is during organogenesis. Specific agents produce predictable lesions most of the time, depending on the dose or threshold effect. In many circumstances, the same agent and dose may not consistently produce the same change in structure or function of an organ or system. Genetically mediated changes by some enzymes can be responsible for certain malformations and hence changes which occur in utero on organogenesis are not the same for all individuals. It is a well known fact that thermolabile mutation of 5, 10-methylene tetrahydrofolate reductase may be one of the enzymes well documented to be responsible for neural tube or other birth defects.

Hence, the practicing obstetricians and pediatricians / neonatologists should be aware of the teratogenic potential of any drug or medication, which the mother may have to consume. It is only prudent to consider at which stage of pregnancy such a medication is taken and how much.

The Food and Drug Administration classifies drugs into five pregnancy risk categories: Category A suggests no risk based on evidence from controlled human trials.

Category B suggests either no risk shown in animal studies but no adequate studies in humans or some risk in animal studies that are not confirmed by human studies.

Category C is either definite risk shown in animal studies but no adequate human studies or no available data for animals or humans.

Category D includes drugs with some risk but with a benefit that may exceed that risk for the treated life threatening conditions, such as streptomycin for tuberculosis.

Category X is for drugs that are contraindicated in pregnancy on the basis of animal and human evidence and whose risk exceeds the benefits.

Drugs are discussed under the following categories:

1. Known teratogens (Table I)
2. Agents acting on pregnant women that may adversely affect the newborn infant (Table II)
3. Drugs in lactation (Table III)

Drugs and lactation

Drugs are classified for breastfeeding safety under the following heads

1. Compatible with breastfeeding
2. Avoid if possible. Monitor infant for side-effects. May inhibit lactation
3. Avoid
4. No data available

Some additional considerations

The safety of certain drugs also depends on the age of the infant. Premature babies and infants less than 1 month of age have a different capacity to absorb and excrete drugs than older infants. Thus, in general, extra caution is needed for these infants.

* Professor of Pediatrics,
PGIMSR,
Chennai.

Table.I Some known teratogens

• Radiation Atomic weapons, radioiodine, therapeutic radiation • Infections CMV, HSV I & II, parvovirus B-19, rubella, syphilis, toxoplasmosis, varicella, Venezuelan equine encephalitis virus • Maternal systemic issues Alcoholism Amniocentesis, early (before 70 days of post conception) Chorionic villus sampling (before 60 days of post conception) Cretinism, endemic Diabetes Folic acid deficiency Hyperthermia Myasthenia gravis Phenyl ketonuria Rheumatic disease Sjogren's syndrome Virilizing tumors Systemic lupus erythematosus • Drugs and Environmental Chemicals ACE inhibitors Aminopterin Androgenic hormones Busulfan Cigarette smoking Cocaine Coumarin anticoagulants Cyclophosphamide Diethyl stilbestrol Etretinate Fluconazole (high doses) Iodides Isotretinoin - Accutane Lithium Mercury, organic Methimazole	Methotrexate Methylene blue (via intraamniotic injection) Misoprostol Penicillamine Phenytoin Tetracyclines Thalidomide Toluene (abuse) Trimethadione Valproic acid • Possible teratogens Alcohol (Binge drinking) Carbamazepine Colchicine Disulfiram Ergotamine Glucocorticoids Lead Primidone Streptomycin Vitamin A (high doses) Zidovudine (AZT) Zinc deficiency • Unlikely teratogens Anesthetics Aspartame Aspirin Bendectin® (antinauseant) Electromagnetic waves Hydroxy progesterone LSD Marijuana Medroxy progesterone Metronidazole Oral contraceptives Progesterone Rubella vaccine Spermicides Video display terminals Ultrasound
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Table.II Agents acting on pregnant women that may adversely affect the newborn infant

Acebutolol-IUGR, hypotension, bradycardia
Acetazolamide-metabolic acidosis
Amiodarone-bradycardia, hypothyroidism
Anesthetic agents (volatile)-CNS depression
Adrenal corticosteroids-adrenocortical failure (rare)
Ammonium chloride-acidosis (clinically inapparent)
Aspirin-neonatal bleeding, prolonged gestation
Atenolol-IUGR, hypoglycemia
Baclofen-withdrawal
Bromides-rash, CNS depression, IUGR
Captopril, enalapril-transient anuric renal failure, oligohydramnios
Caudal-paracervical anesthesia with mepivacaine (accidental introduction of anesthetic into scalp of baby)-bradypnea, apnea, bradycardia, convulsions
Cholinergic agents (edrophonium, pyridostigmine)-transient muscle weakness
CNS depressants (narcotics, barbiturates, benzodiazepines) during labor-CNS depression, hypotonia
Cephalothin-positive direct Coombs test reaction
Dexamethasone-periventricular leukomalacia
Fluoxetine and other SSRIs-transient neonatal withdrawal, hypertonicity, minor anomalies
Haloperidol-withdrawal
Hexamethonium bromide-paralytic ileus
Ibuprofen-oligohydramnios, pulmonary hypertension
Imipramine-withdrawal
Indomethacin-oliguria, oligohydramnios, intestinal perforation, pulmonary hypertension
Intravenous fluids during labor (e.g.salt-free solutions)-electrolyte disturbances, hyponatremia, hypoglycemiaIodide (radioactive)-goiter
Iodides-goiter
Lead-reduced intellectual function
Magnesium sulfate-respiratory depression, meconium plug, hypotonia
Methimazole-goiter, hypothyroidism
Morphine and its derivatives (addiction)-withdrawal symptoms (poor feeding, vomiting, diarrhea, restlessness, yawning and stretching, dyspnea and cyanosis, fever and sweating, pallor, tremors, convulsions)
Naphthalene-hemolytic anemic (in G6PD-deficient infants)
Nitrofurantoin-hemolytic anemia (in G6PD-deficient infants)
Oxytocin-hyperbilirubinemia, hyponatremia
Phenobarbital-bleeding diathesis (vitamin K deficiency), possible long-term reduction in IQ, sedation
Primaquine-hemolytic anemia (in G6PD-deficient infants)
Propranolol-hypoglycemia, bradycardia, apnea
Propylthiouracil-goiter, hypothyroidism
Pyridoxine-seizures
Sulfonamides-interfere with protein binding of bilirubin; kericterus at low levels of serum bilirubin, hemolysis with G6PD deficiency
Sulfonylurea agents-refractory hypoglycemia
Sympathomimetic (tocolytic β -agonist) agents-tachycardia
Thiazides-neonatal thrombocytopenia (rare)

CNS, central nervous system; G6PD, glucose-6-phosphate dehydrogenase; IUGR, intrauterine growth restriction; SSRI, selective serotonin reuptake inhibitor.

Table.III Drug safety during breast feeding (Individual drugs / groups)

Drug	Compatible / Safe	Compatible / Monitor for side effect in infants	Avoid if possible
1. Antipyretics, analgesics Paracetamol Acetylsalicylic acid, ibuprofen	Safe for short courses		
2. Opioid analgesics Codeine, morphine, Pethidine	Safe for occasional doses	For repeated doses (apnea, bradycardia, cyanosis)	
3. Antihistamines Chlorpheniramine: Cetirizine	Compatible with breastfeeding in occasional doses.	Though not harmful, advised to avoid	May inhibit lactation
4. Antidotes Charcoal, Aceetyl Cysteine, Desferoxamine, Methionine, Naloxone, penicillamine, Sodium calcium edetate, Sodium thiosulphate, Dimercaprol, Methylene blue	Compatible		
5. Antiepileptics Diazepam Phenytoin Phenobarbitone Valproic acid Carbamazepine Clonazepam Levetiracetam	Compatible for single dose	Repeat doses: monitor for drowsiness Monitor infant for methemoglobinemia Monitor for drowsiness, poor suckling and poor weight gain Monitor for jaundice	Small quantity secreted in milk.manufacturer advice-Avoid
6. Antifilarial DEC, Ivermectin	No data available		
7. Antibacterials Chloramphenicol Ciprofloxacin Doxycycline Metronidazole Nalidixic acid	No data available	Monitor for jaundice, marrow depression Monitor for staining of infant's teeth	Avoid if possible Avoid if possible, animal data carcinogenic Avoid if possible, animal data carcinogenic Avoid if possible, in preterm and <1 mo old and G6PD def infants.SE hemolysis and jaundice

Drug	Compatible / Safe	Compatible / Monitor for side effect in infants	Avoid if possible
Gentamycin Penicillins (Amoxicillin, ampicillin, benzathine penicillin, benzyl penicillin, cloxacillin, phenoxymethyl penicillin, Procaine penicillin) Amoxicillin – clavulanic acid, Ceftriaxone, ceftazidime Nitrofurantoin Cotrimoxazole Clindamycin Vancomycin	Generally safe Trace amounts in breast milk Safe for term infant	Monitor for oral thrush, diarrhea Monitor for allergy in infant Restricted indications Monitor if preterm infant for hemolysis, jaundice Avoid if possible. Monitor for diarrhea, bloody stools Avoid if possible. Monitor for diarrhea, bloody stools	Avoid if possible if PT, < 1 mo old & in G6PD deficient infants
8. Antileprosy drugs: Dapsone Clofazamine	Safe for term infants	Monitor if preterm infant for hemolysis, jaundice May cause reversible skin discoloration	Avoid in infant with G6 PD deficiency
9. Antituberculosis drugs* Isoniazid, ethambutol, pyrazinamide, rifampicin Streptomycin	Compatible Compatible	Monitor infant for jaundice Monitor for thrush and diarrhea	
10. Antifungal drugs Amphotericin B, griseofulvin, Flucytosine Fluconazole, nystatin	No data available Compatible		
11. Antiviral drugs Acyclovir Antiretroviral drugs** Nivirapine, Zidovudine Lamivudine	Compatible Short term effects minimal. But long term effects are serious but rare.		Avoid
12. Antiamebic drugs Diloxanide Metronidazole	No data available		Avoid if possible

Drug	Compatible / Safe	Compatible / Monitor for side effect in infants	Avoid if possible
13. Antimalarial drugs Chloroquin, quinine, primaquin, Sulphadoxin+Pyrimethamine Mefloquin Proguanil	Compatible Compatible	Monitor especially if Preterm or < 1 mo old.	Avoid in G6PD def infant Avoid
14. Antianemia drugs Ferrous salts, folic acid, hydroxyl cobalamine, iron dextran	Compatible		
15. Drugs affecting coagulation. Desmopressin, heparin, phytomenadione, protamine sulphate, warfarin	Compatible		
16. Drugs used in hypertension or heart failure Atenolol Captopril, hydrochlorthiazide, methyldopa, digoxin, dopamine. Antiarrhythmic drugs Procainamide Isoprenaline	Compatible Compatible No data available	Avoid if possible, in preterm and < 1 mo old. Monitor for hypotension, bradycardia, cyanosis	Avoid if possible
17. Antithrombotic drugs, Lipid lowering agents Statins Aspirin	Compatible	Rather safe decide individually	
18. Dermatology (topical) drugs. Antifungal, anti infective, antipruritic, anti-inflammatory, scabicide, UV blocking agents	Compatible		
19. Diuretics Amiloride, frusemide, hydrochlorthiazide			Avoid if possible. May inhibit lactation
20. Antacids, antiemetics, laxative-Senna Aluminium hydroxide, magnesium hydroxide	Compatible		
21. Hormones and synthetic substitutes Steroids: Prednisolone Hydrocortisone, dexamethasone (No data for prolonged use)	Compatible Compatible for short term use		

Drug	Compatible / Safe	Compatible / Monitor for side effect in infants	Avoid if possible
Testosterone Contraceptives: ethinylestradiol+ levonorgestrel ethinylestradiol+ norethisterone Insulin Glibenclamide Metformin Levothyroxine, propyl thiouracil Potassium Iodide	Compatible Compatible Compatible No data available Compatible	Monitor the infant for hypoglycaemia Avoid if possible. Monitor for hypothyroidism	Avoid breastfeeding Safe from 6 weeks postpartum
22. All sera and immunoglobulins Anti D (human), antitetanus (human), Diphtheria antitoxin (human) Rabies immunoglobulin Antivenom	Compatible No data available		
23. Vaccines Diphtheria, Pertussis, tetanus, polio, measles, hepatitis β , Influenza, meningococcal, mumps, rabies (inactivated), rubella, typhoid, yellow fever	Compatible		
24. Oxytocics Ergometrine Oxytocin	Compatible in single dose	Avoid repeated doses if possible. Ergometrine may inhibit lactation	Oxytocin may cause physiological dependence of the oxytocin reflex in the mother
25. Psychotherapeutic drugs: Chlorpromazine, haloperidol, fluphenazine Amitriptyline Lithium carbonate Clomipramine		Avoid if possible. Monitor the infant for drowsiness Compatible up to 150 mg/day Avoid if possible. Monitor restlessness or weakness in baby. Monitor lithium levels in mother's blood Compatible	
26. Drugs acting on respiratory tract: Salbutamol, theophylline, epinephrine, beclomethasone Ipratropium, Dextromethorphan	Compatible No data available		

Drug	Compatible / Safe	Compatible / Monitor for side effect in infants	Avoid if possible
27. Vitamins Ascorbic acid Ergocalciferol Iodine Thiamine, pyridoxine, nicotinamide, retinol, riboflavin, calcium gluconate	Compatible in usual doses. Compatible in usual doses. Compatible in usual doses. Compatible	In large doses are used, monitor (haemolysis and jaundice), especially in preterm In pharmacological doses check serum calcium in infant Monitor for hypothyroidism	
28. Radiocontrast media Amidotrizoate, barium sulphate, iopanoic acid, propylidone, meglumineiotroxate	Compatible		
29. Disinfectants and antiseptics Chlorhexidine, ethanol, glutaraldehyde	Compatible		
30. All general anaesthetics Ether, halothane, ketamine, nitrous oxide, thiopental	Compatible		
31. All local anaesthetics Bupivacaine, lidocaine Ephedrine	Compatible Compatible	Monitor infant	
32. Preoperative medication Atropine, Chloral hydrate, Diazepam, Morphine, Promethazine	Compatible	Monitor infant	

* A woman who is breastfeeding and has TB should receive a full course of anti-TB chemotherapy. Appropriate chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby. All the anti-TB drugs are compatible with breastfeeding and a woman taking them can safely continue to breastfeed her baby. The mother and baby should stay together and the baby should continue to breastfeed in the normal way. The baby should receive isoniazid prophylaxis and BCG immunization.

** Drugs for the treatment of human immunodeficiency virus (HIV) infection include nucleoside reverse

transcriptase inhibitors, non -nucleoside reverse transcriptase inhibitors and protease inhibitors. The drugs zidovudine and nevirapine have been shown to reduce or prevent mother-to-child transmission of HIV. This is the only indication for which they are included here. Single drug use with zidovudine, except in pregnancy, is now regarded as obsolete, because of the development of resistance. Triple therapy is beyond the budgets of most national drug programmes and therefore HIV/AIDS treatment policies must be decided at country or institutional level.

Table.IV General guidelines for drugs during breast feeding

Anticancer drugs (anti metabolites); Radioactive substances (stop breastfeeding temporarily)	Breastfeeding contraindicated
Continue breastfeeding	
Selected psychiatric drugs and anticonvulsants (see individual drug)	Side-effects possible. Monitor baby for drowsiness.
Chloramphenicol, tetracyclines, metronidazole, quinolone antibiotics (e.g. ciprofloxacin)	Use alternative drug if possible
Sulfonamides, dapsone, sulfamethoxazole+trimethoprim (cotrimoxazole) sulfadoxine+pyrimethamine	Monitor baby for jaundice
Estrogens, including estrogen-containing contraceptives, thiazide diuretics, ergometrine	Use alternative drug (may inhibit lactation)
Most commonly used drugs: Analgesics and antipyretics: Short courses of paracetamol, acetylsalicylic acid, ibuprofen; occasional doses of morphine and pethidine. Antibiotics: Ampicillin, amoxicillin, cloxacillin and other penicillins, erythromycin Antituberculosis drugs, anti-leprosy drugs (see dapsone above). Antimalarials (except mefloquine, sulfadoxine + pyrimethamine), anthelmintics, antifungals. Bronchodilators (e.g. Salbutamol), corticosteroids, antihistamines, antacids, drugs for diabetes, most anti-hypertensives, digoxin Nutritional supplements of iodine, iron, vitamins.	Safe in usual dosage. Monitor baby

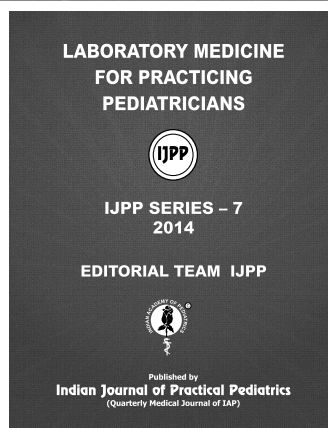
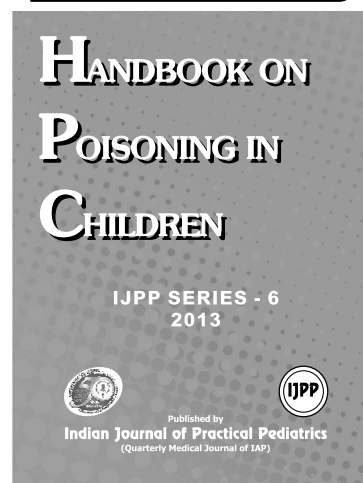
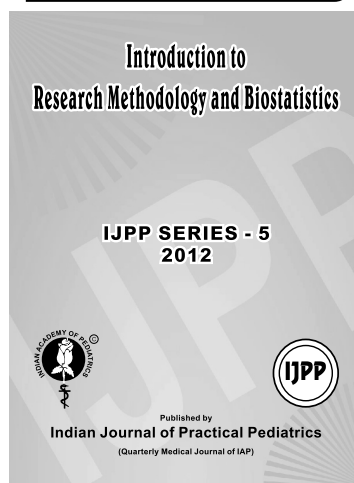
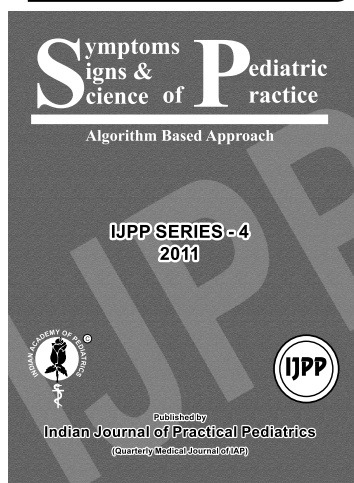
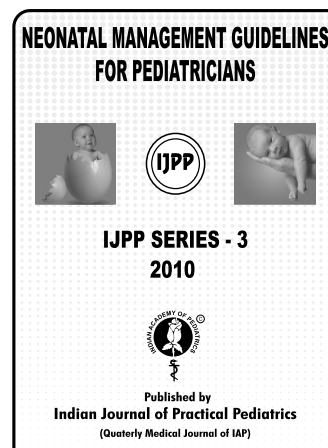
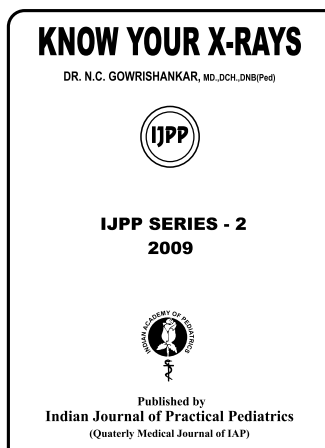
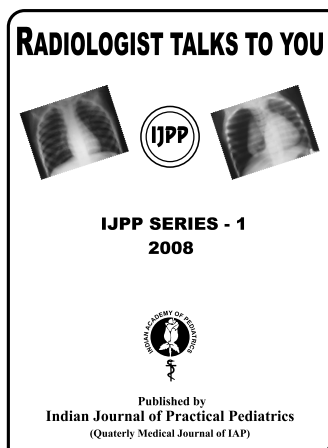
All drug formulations should have a printed (Table IV) guidelines for the specific drug and specific directive if any should be printed within the wrapper / carton for the drug as mandated by law.

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RATIONAL ANTIBIOTIC THERAPY

ANTIBIOTIC STEWARDSHIP – LAST CHANCE TO SAVE HUMAN RACE!

* **Amdekar YK**

‘Stewardship’ means an ethic that embodies responsible planning and management of resources. In simple words, it means guardian or keeper of house. So the term can be applied to every field.

‘Antibiotic stewardship’ refers to coordinated interventions designed to improve and monitor appropriate use of antibiotics in terms of selection, dose and duration of therapy and route of administration. It seeks to achieve optimal clinical outcome, minimise toxicity and adverse reactions, reduce cost of therapy and limit development of drug resistance. Knowing societal need for antibiotics and their diminishing effectiveness, there is a need for antibiotic stewardship.

Every doctor is aware of rational antibiotic therapy and the dire consequences, if not followed. However knowledge-practice gap exists. Knowledge translation is not simply an exercise of transmission of facts converted into clinical decision-making. Besides facts, skills and practical wisdom decide final outcome. So, CMEs would not work.

We need to study genesis of antibiotic misuse. Primarily it is lack of confidence coupled with lack of time. Confidence can be built by interactive sessions on day-to-day problems faced by practitioners. We have been conducting STEER programs that are intended to Sensitise doctors to Think Enabling Excellence and Rationality. Lack of time is merely an excuse and it is said that most busy persons are never short of time as they manage time well. Poor documentation and lack of communication skills enhance irrationality. While there is no legal mandate for rational antibiotic use, it is moral responsibility of every doctor. But, sadly, left to individuals, most doctors will not change.

We need motivation to change – intrinsic or extrinsic. Intrinsic motivation is driven by joy of achieving excellence and it has to come from within. Can we motivate doctors by sensitising them through regular column in our journals – “irrational prescription – is it yours?” Extrinsic motivation has to be forced by legal pressure or demand from empowered society. Can a law be enacted that pharmacist is not allowed to dispense antibiotic unless prescription is accompanied with provisional diagnosis that justifies antibiotic? It is time we motivate lay persons to demand their rights of rational therapy. Can we get sponsors to spread the messages of rational drug therapy in print and electronic media instead of sponsoring entertainment in conferences? Rational antibiotic use is possible in an institution that should have antibiotic policy based on local epidemiology and it should be available for local practicing doctors. Barring essential antibiotics for general use, other antibiotics should have restricted use, only allowed if two doctors together justify its need.

This is the last chance as time is running out. We need to act together and now!

Sample prescription

10 month old healthy infant presented with high fever, cold and cough for 2 days. Doctor prescribed drugs as follows.

Amoxycillin-clavulanic acid 5 mL twice a day for 3 days
Mefenamic acid 2.5 mL thrice a day for 3 days
Antihistamine 2.5 mL thrice a day for 3 days
Cough mixture 2.5 mL thrice a day X 3 days

2 days later, fever subsided, cold and cough continued but infant developed loose stools

Doctor changed the prescription as follows :

Stop Amoxy-clav and mefenamic acid
Ofloxacin + metronidazole 2.5 mL thrice a day for 3 days
Continue antihistamine and cough mixture

Comments

History suggests acute viral respiratory infection and so antibiotic at this juncture is not justified. Paracetamol is

* Medical Director,
B.J. Wadia Children's Hospital,
Mumbai.

the drug of choice and should be administered only on SOS basis to treat discomfort caused by fever and not necessary to bring down temperature to normal. As rhinorrhea and cough are self-limiting symptoms antihistamine and cough mixtures are not indicated. At the best one can try to make the infant comfortable by non-pharmacological methods such as hydration, upright position, proper ventilation in the room and saline nasal drops in case of blocked nose. Safe home remedies may be tried such as honey, ginger and lemon in lukewarm water after 6 months of age as recommended by IMNCI also.

Antibiotic is justified only in dysentery and cholera. Obviously, it was not necessary in this infant. Moreover, combination of ofloxacin and metronidazole is irrational. Loose stools in this infant may be drug induced or part of viral infection and does not need any drugs. All that is required is to monitor hydration status by adequate liquids.

Anyway infant got well. Did such prescription cause any harm? Antibiotic may result in side effects – as probably happened in this infant and repeated use may lead to antibiotic resistance. Besides it involves unnecessary cost.

CLIPPINGS

Non surgical therapy for anal fissure.

Because of the disability associated with surgery for anal fissure and the risk of incontinence, medical alternatives for surgery have been sought. Most recently, pharmacologic methods that relax the anal smooth muscle, to accomplish reversibly what occurs in surgery, have been used to obtain fissure healing.

Objectives was to assess the efficacy and morbidity of various medical therapies for anal fissure.

Selection criteria: Studies in which participants were randomized to a non-surgical therapy for anal fissure. Comparison groups may include an operative procedure, an alternate medical therapy or placebo. Chronic fissure, acute fissure and fissure in children are included in the review. Atypical fissures associated with inflammatory bowel disease or cancer or anal infection are excluded

Authors' conclusions: Medical therapy for chronic anal fissure, currently consisting of topical glyceryl trinitrate, botulinum toxin injection or the topical calcium channel blockers nifedipine or diltiazem in acute and chronic fissure and fissure in children may be applied with a chance of cure that is marginally better than placebo. For chronic fissure in adults all medical therapies are far less effective than surgery. A few of the newer agents investigated show promise based only upon single studies (clove oil, sildenafil and a "healer cream") but lack comparison to more established medications.

Nelson RL, Thomas K, Morgan J, Jones A. Non surgical therapy for anal fissure. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD003431. DOI: 10.1002/14651858.CD003431.pub3.

Assessed as up to date: 12 September 2011.

NEWS AND NOTES

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GENERAL ARTICLE

NON-TENDER LYMPHADENOPATHY - HOW FAR TO INVESTIGATE AND TREAT?

* **Agrawal S**

Abstract: *Examining the lymph nodes is an important aspect of the general physical examination of both well and ill children and adolescents. The challenge for the general pediatrician is to learn how to distinguish pathologic from non-pathologic lymph nodes and to develop a rational approach to the evaluation of lymphadenopathy. Because of its association with malignancy, lymphadenopathy can be a major source of parental anxiety. Therefore, it is crucial to know when to provide reassurance and to recognize when concern is sufficient to warrant extensive workup.*

Keywords: *Lymphadenopathy, Evaluation, Children.*

Lymph nodes are normal structures and certain lymph nodes may be palpable in a healthy child, particularly the younger ones. Different studies have revealed variable prevalence of cervical lymphadenopathy from 38% to 45% in one study¹ to 90% in another study². Conversely, the presence of abnormally enlarged lymph nodes ('lymphadenopathy') can be a clue to a serious underlying systemic disease, and the differential diagnosis of lymphadenopathy can be broad.

Tender v/s non-tender lymphadenopathy

Tender lymphadenopathy is most frequently caused by infection, especially if there is associated erythema, warmth, induration or fluctuation. Occasionally, malignancy can cause node tenderness because of hemorrhage in the node and subsequent stretching of the capsule. Common causes of tender enlargement of lymph nodes are acute suppurative lymphadenopathy, pediculosis of scalp, Kawasaki disease and very rarely, necrotizing lymphadenopathy (Kikuchi-Fujimoto disease).

What is abnormal?

Although defining 'normal' and 'abnormal' in terms of size can be challenging, a rule of thumb is as follows - the size of normal lymph nodes in the axillary and cervical regions are up to 1 cm and in the inguinal regions up to 1.5 cm. As mentioned, the size limits differ somewhat with age and generally are less stringent in young children than in adolescents and adults, presumably because of the frequent antigenic exposure in early childhood to common childhood illnesses and the gradual acquisition of antibodies and immunity. Risk of underlying malignancy increases with increasing size of the lymph node, with 2 cm in diameter seeming to be an important threshold for cervical nodes in children.

Acute lymphadenopathy is the presence of nodes with up to 2 weeks duration, subacute up to 2-6 weeks duration and chronic is considered in any lymphadenopathy that does not resolve by 6 weeks.³

Besides the size and duration, the site of lymphadenopathy is also important. Axillary and inguinal lymph nodes are generally not associated with high likelihood of disease, and in contrast a palpable supraclavicular gland should bring malignancy in to the differential diagnosis.

Clinical approach to lymphadenopathy

When confronted with a child having abnormal lymph nodes, various factors need to be considered to arrive at a reasonable diagnosis. The important ones to be considered are: 1) age of the child 2) location of the lymph nodes 3) nature of the lymph nodes 4) whether enlargement is localized or generalized 5) duration and 6) whether systemic involvement is present or not.

In 2006 Yaris, et al. performed a retrospective review of 126 patients with the aim to identify clinical and laboratory findings that aided diagnosis during evaluation of lymphadenopathy. They pointed out that history and physical exam with the help of laboratory findings helped in making a diagnosis in 61.2% of cases.⁴ Age of the patient is important because normal size of various lymph nodes changes with age, as do the diagnosis that should be entertained. Lymph nodes generally are not palpable in the

* Director and DNB Co-ordinator,
Ekta Institute of Child Health,
Raipur.

newborn, though occipital glands are an occasional exception. Over a period of time and with antigenic exposure, the volume of lymph node tissue increases making them palpable.

The differential diagnosis also varies with the age. Some congenital lesions when present as neck mass will come in the reckoning. (Table I) Lymphomas are extremely rare below 3 years of age. Hodgkin lymphoma is an important cause of lymphadenopathy in adolescents and adults. Upper respiratory tract infections, otitis and conjunctivitis frequently lead to a nearly chronic reactive cervical lymphadenopathy in the preschool and early school age groups. Size of the lymph nodes is also important and has been alluded to in the discussion on definition of abnormal.

Table.I Differential diagnosis of neck mass in an infant

Thyroglossal duct cyst	Moves with tongue protrusion and is midline.
Dermoid cyst	Midline and often has calcifications on plain films
Branchial cleft cyst	Smooth and fluctuant along sternocleidomastoid border
Laryngocele	Enlarges with Valsalva maneuver
Hemangioma	Mass presents after birth, rapidly grows, becomes static and is red or bluish in color
Cystic hygroma	Transilluminates and is compressible
Sternocleidomastoid tumor	Presents with torticollis
Cervical ribs	Hard and immobile, may be bilateral

Location of lymphnode

As outlined in Table II, one must look at the drainage area of the enlarged nodes to elucidate the cause. Examples of this association include anterior cervical lymphadenopathy related to pharyngitis. A palpable lymph node in the supraclavicular fossa should prompt a thorough evaluation for a cause, with malignancy high in the differential diagnosis and the threshold to carry out an

Table.II Drainage area of common lymph node groups

Lymph node group	Region drained by lymph nodes
Occipital	Posterior scalp
Postauricular	Temporal and parietal scalp
Preauricular	Anterior and temporal scalp, anterior ear canal and pinna, conjunctiva
Parotid	Forehead and temporal scalp, midface, external ear canal, middle ear, gums, parotid gland
Submandibular	Cheek, nose, lips, tongue, submandibular salivary gland, buccal mucosa
Submental	Lower lip, floor of mouth
Superficial cervical	Lower larynx, lower ear canal, parotid
Deep cervical	Tonsils, adenoids, posterior scalp and neck, tongue, larynx, thyroid, palate, nose, esophagus, paranasal sinuses
Supraclavicular	Right side: mediastinum, lungs; Left side: abdomen
Deltopectoral	Arm
Axillary	Arm, breast, thorax, neck
Epitrochlear	Medial arm below elbow
Inguinal	Lower extremity, genitalia, buttocks, abdominal wall below umbilicus
Popliteal	Lower leg

excisional biopsy should be really low. Inguinal and axillary lymph nodes are less likely to be associated with a disease.

Localized versus generalized lymphadenopathy

It is useful to classify lymphadenopathy as either generalized, where two or more nodal groups or sites are involved, or localized to a single area.

Localized lymphadenopathy is a more common presenting observed in a primary care practice than generalized lymphadenopathy, with cervical lymph nodes being involved most commonly, followed by inguinal nodes. Localized adenopathy can occur from infection of the node itself (lymphadenitis) or from an infection in its drainage area. Supraclavicular and posterior cervical nodes in adults carry much higher risk of being malignant than anterior cervical.⁵

The major causes of non-infectious generalized lymphadenopathy are medications, malignancy and autoimmune disease. A thorough clinical examination for systemic involvement should be done with special emphasis on skin rash, joint and pulmonary involvement and hepatosplenomegaly.

The most common drugs associated with lymphadenopathy are penicillin, cephalosporin, sulfonamide, carbamezapine, phenytoin, isoniazid and pyrimethamine.

Infections which are commonly associated with generalized lymphadenopathy are viral giving rise to reactive enlargement of the nodes. Infectious mononucleosis, toxoplasmosis, tuberculosis and HIV are common infective causes.

The most common childhood cancer is acute leukemia, in which generalized lymphadenopathy can be a prominent feature. The adenopathy usually is non-tender and may be bulky and grow rapidly. Other physical findings may include pallor, bruising or petechiae and hepatosplenomegaly. Lymphomas can present with either generalized or localized lymphadenopathy; solid tumors such as neuroblastoma or rhabdomyosarcoma may involve the regional lymph nodes during its spread if undetected and untreated.

Autoimmune diseases such as systemic lupus erythematosus, juvenile idiopathic arthritis and dermatomyositis can cause generalized lymphadenopathy. In these settings, nodes are usually non-tender and discrete and range in size from 0.5 cm to a few centimeters in the cervical, axillary and inguinal regions.

Duration of the lymphadenopathy

The duration of adenopathy gives a clue to the probable causation many a times. Acute adenopathy most commonly is viral. Suppurative lymphadenitis lends itself easily to be picked up exhibiting signs of inflammation.

Subacute and chronic lymphadenopathy is likely to be tuberculous, both typical and atypical. Toxoplasmosis and EBV infections also may persist for a long time. Malignancy and autoimmune disorders also enter the list of differentials.

In 1995 Margalith, et al looked at the most common causes of subacute lymphadenitis and showed that atypical mycobacteria, bacteria causing cat scratch disease and toxoplasmosis, are the most common causative organisms found. To a lesser extent EBV and CMV are also implicated at times.⁶

More indolent causes of lymphadenitis include *Bartonella henselae* (cat-scratch disease), *Mycobacterium tuberculosis* and atypical mycobacteria. With these infections, fluctuant lymph nodes may develop over weeks to months and tenderness and signs of inflammation frequently are absent. The atypical mycobacterial infection generally is acquired from contact with the environment (eg, soil and water) rather than by person-to-person spread, as in tuberculosis. Atypical mycobacterial infection is one of the common causes of subacute lymphadenopathy. The most commonly involved species include *M. avium-intracellulare*, *M. haemophilum* and *M. scrofulaceum*. These infections develop over weeks to months and untreated cases usually will develop sinus tracts and cutaneous drainage for up to 12 months.

A study by Zeharia, et al in 2008 was performed retrospectively on 92 children diagnosed with atypical mycobacterial lymphadenopathy.⁷ Most of the children were less than 4 years old, with positive Mantoux, lymphadenopathy greater than 3cm in size, mainly unifocal in nature, involving submandibular, cervical or preauricular region and purulent drainage for 3-8 weeks. *M. avium-intracellulare* and *M. haemophilum* were the predominant atypical mycobacteria in that series of children.

RNTCP has suggested an algorithm for approach to a case suspected to have tuberculous lymphadenopathy (Fig.1).

Evaluation

In majority of cases, the history and physical examination usually reveal the cause of lymphadenopathy. In a case of localized cervical lymphadenopathy if clinical suspicion of malignancy is very low, a 3-4 week period of observation is required if the basic investigations are negative. When bacterial lymphadenitis is suspected, empiric treatment with antibiotics such as a first- or second-generation cephalosporin should be initiated. If there is no response to oral antibiotics, a tuberculin skin test should be done as part of the evaluation for both typical and atypical mycobacteria.

When worrisome features suggest a serious underlying disease, laboratory tests, imaging and biopsy may be indicated. Depending on the symptomatology and clinical

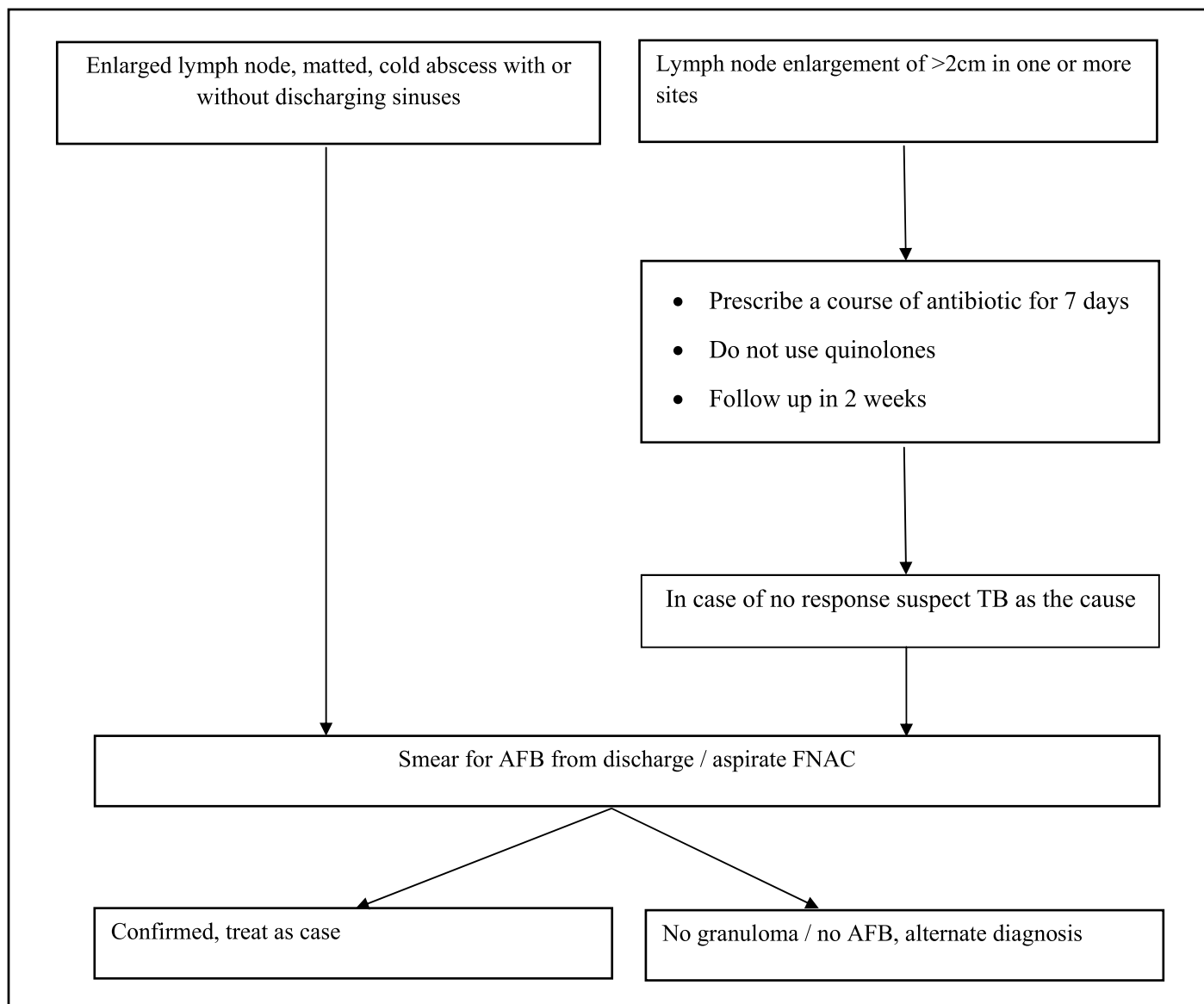


Fig.1. Algorithm for suspected tuberculous lymphadenopathy by RNCTP

(a negative Mantoux test does not exclude tuberculosis as the cause of lymphadenopathy)

features laboratory tests including a CBC, erythrocyte sedimentation rate (ESR), lactate dehydrogenase concentration (which can be a marker for hematologic malignancy), tuberculin skin test, monospot and specific serologic tests for infectious agents need to be done. A chest radiograph also can be very helpful to look for mediastinal or hilar adenopathy and should be done as part of workup in the basic investigations before referral for invasive tests. Any symptoms referable to the chest (cough, dyspnea, orthopnea, chest pain) also should prompt a chest radiograph.

The role of biopsy

Fine needle aspiration (FNA) is by far the least invasive form of biopsy and with the help of ultrasound it becomes

easier to biopsy the area of choice. The problem with FNAC is that it is not as reliable in children as it is in adults and therefore only a positive biopsy is trustworthy.⁸ Chau, et al in 2003 looked at 289 fine needle aspirations out of 550 patients that were referred to a lymphadenopathy clinic in Great Britain. They found that of those 289 biopsies, there was 97% specificity but only 49% sensitivity. Also they showed a false negative rate of 45% and of those false negatives 83% of the cases were lymphomas.⁹ Thus, fine-needle aspiration often is inadequate to diagnose lymphoma because tissue is minimal, there is no architectural detail and lymphomas such as Hodgkin disease may have only occasional malignant cells in a background of normal lymphocytes. When biopsy is indicated, an open, excision biopsy is optimal. The largest and most abnormal node should

be biopsied; in general, inguinal and axillary lymph nodes are less likely to be diagnostic. The highest yield is obtained with a supraclavicular or lower cervical chain node. Excisional biopsy is the treatment of choice for cervical lymphadenopathy caused by atypical mycobacteria.

Role of imaging

Imaging can include CXR, CT, MRI, ultrasound, ECHO (if Kawasaki disease is under consideration). CT and ultrasound can all be used to evaluate for abscess formation and to follow the progress of an abscess after it forms. However ultrasound is probably the better choice to decrease the amount of radiation and can be an excellent tool for repeated examinations.

Ultrasonography: In 2005 Ahuja, et al¹⁰ described the use of ultrasound to differentiate reactive from malignant lymphadenopathy. Reactive lymphadenopathy had the following characteristics with size less than 1 cm, oval shape with short:long ratio less than 0.5, normal hilar vascularity, a low resistive index with high blood flow when using doppler technology. Malignant lymphadenopathy had the following characteristics being greater than 1cm, round with a short:long ratio greater than 0.5 necrotic centre, no echogenic hilum, a high resistive index with low blood flow, and the ability to identify extracapsular spread.

Using these parameters they found a sensitivity of 95% and a specificity of 83% in differentiating reactive from malignant lymph nodes.

The shape of the cervical nodes was assessed by L/S (long axis to short axis) ratio. An L/S ratio <2 indicated a round node, whereas an L/S ratio >2 indicated an oval or elongated node. An abnormal lymph node with a L/S ratio <2 (or a short:long ratio greater than 0.5) was considered a useful test for malignancy.¹¹

Summary

Palpable lymph nodes are common in children and may be a normal finding or a sign of serious disease. Because parents frequently are concerned about lymphadenopathy, the role of primary care practitioner is to provide reassurance when appropriate and carry out a systematic evaluation when warranted.

Points to Remember

- *The history and physical examination frequently can elucidate the cause of the lymphadenopathy.*

- *Infectious diseases are the most common underlying cause and antibiotics are indicated if there is lymphadenitis.*
- *Generalized lymphadenopathy is less common than localized lymphadenopathy and occurs in the setting of systemic disease.*
- *Supraclavicular location, size greater than 2 cm in a cervical lymph node, a hard, firm, or matted consistency of an enlarged lymph node, lack of associated infectious symptoms, lack of improvement over a 4-week period and accompanying constitutional symptoms should lead to additional evaluation and possible biopsy.*

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GENERAL ARTICLE

DISRUPTIVE BEHAVIOR DISORDERS IN ADOLESCENTS - MANAGEMENT

* **Pemde HK**

** **Agrawal G**

Abstract: *Disruptive behaviors in isolation are common during adolescence. When they become repetitive and form a pattern they are termed as 'Disruptive Behavior Disorder (DBD)'. Pediatricians are likely to encounter such children and adolescents in general practice. Features of DBD can be recognized quite early and even before adolescence. Such children should undergo detailed evaluation as early therapeutic interventions may prevent escalation of disruptive behaviors into disorder. This article describes features, diagnosis, and treatment of DBD and will enable the readers to provide shared-care (with mental health professionals) to adolescents with DBD.*

Keywords: *Disruptive behavior disorders, Adolescents, Management.*

Adolescence is a phase of changes and the changes occur not only in body but also in behavior. Adolescents' behavior develops from 'childlike' to 'adult-like' through behaviors known as 'being an adolescent'. The latter varies from family to family and from culture to culture and certain behaviors like risk taking, thrill seeking, limit testing, challenging rules and questioning authority are considered normal. But when it becomes a fixed pattern, repetitive and influences the routine functioning of adolescent and/or the family and other close contacts, then it represents a trajectory towards disruptive behaviors. Such behaviors are often harmful to self and to others in family and society and hence need evaluation and treatment.

This article describes diagnosis and treatment of 'disruptive behavior disorders (DBD)' i.e., oppositional defiant disorder (ODD) and conduct disorder (CD).

Development of disruptive behaviors

In every society certain behaviors are acceptable and some behaviors are unacceptable as determined by societal norms or by law. Context defines behavior and it is important to understand ecological and systemic approach to study the disruptive behaviors in adolescents. These behaviors affect others more than the self and hence categorized as 'externalizing (acting out) behaviors'.

Externalizing behavior problems

These refers to a constellation of behaviors characterized by non-compliance, aggression, destructiveness, attention problems, impulsivity, hyperactivity and delinquent type of behaviors. 'Conduct problems [conduct disorder (CD), antisocial behaviors, oppositional defiant disorder (ODD)]' and 'hyperactivity (attention deficit hyperactive disorders - ADHD)' are two main categories of externalizing disorders. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-TR) includes ODD, CD, antisocial personality disorder (ASPD) and disruptive behavior disorders not otherwise specified under DBD. These behaviors represent a trajectory from ODD in childhood, CD in adolescence and ASPD in adult life. However, various interventions can break or modify this trajectory. These individuals are known to have high levels of past traumatic experiences. Early recognition of these features and appropriate interactions can help these adolescents in avoiding the ill consequences of such behaviors and deviate from potential maladaptive patterns.

Diagnosis of DBD

Certain features (Table I) suggest the presence of DBD. The features of DBD could be gauged early in life (Table II) and such children and adolescents should be subjected to detailed history and evaluation.

Eliciting history

After establishing a good rapport with adolescent and family, history can be elicited using the following questions. The history given by the informant should be given more importance for DBD. 'YES' or 'NO' answers should be avoided and answers must be pursued to the fullest. History

* Professor

** Senior Research Professor,
Center for Adolescent Health,
Lady Hardinge Medical College,
New Delhi.

Table.I Features often associated with DBD

Child's behavior
Oppositional
Aggressive
Stealing
Vandalism
Family
Large size
Ineffective discipline
Parental style
Parental rejection
Neglect
Schooling
Deviant role models
Poor scholastic performance
Outcome
Truancy

about most serious accidents or injuries, regardless of whether a negative response was given, especially about cars, bicycles, falls from high places, blows to heads, headache, dizziness and blackout should be probed.

Detailed history about scars on face, arms, legs and body should also be asked.

- 1) Do you get frequently punished for doing wrong things?
- 2) Have you ever bullied or threatened anybody?

- 3) Have you ever got into physical fight with others?
- 4) Have you ever injured anyone with bat, knife or broken bottle or any similar objects?
- 5) Have you ever been in trouble with the law?
- 6) Have you ever stayed away from home because you were angry?
- 7) Do you enjoy setting fire or enjoy playing with fire?
- 8) Have you ever had sex with someone much younger or older than you? This can be asked to the parent / situational assessment to be done by the pediatrician. This history is important and relevant even in Indian context.
- 9) Have you ever missed school without permission from teachers or parents?
- 10) Do you face difficulty in understanding school subjects?

These questions can be the entry points for detailed history. The parents, teachers and other significant adolescents or adults in the immediate environment of the 'adolescent under evaluation' should also be included in the history taking as the children suffering from DBD may not actually realize the wrongdoings and may describe all these as 'normal' or may not reveal the truth.

Please, remember that a detailed physical and neurological examination is important to find any physical co-morbid condition.

Certain tools/scales can be used in the evaluation of an adolescent for DBD.

1) Child Behavior Checklist (CBCL)¹

The CBCL is one of the most comprehensively studied of the child and adolescent rating scales available. It is designed to be completed by an independent rater, usually the parent. It can be used for the age range 4-16 years and

Table.II Early indicators of DBD

5 Years	8 Years	11 Years	14 Years	17 Years
a) Oppositional and defiant	a) Gets into fights	a) Hard to control	a) Stealing and truancy	a) Career offender
b) Blamed by parents	b) Rejected by peers	b) Poor school achievements	b) Deviant peer group	b) Unemployed
c) Disliked by siblings	c) Low self-esteem	c) Blames others	c) Anti-social attitude	c) Drug misuse

Table.III ICD10 and DSM-IV-TR Criteria for ODD

ICD criteria of ODD	DSM criteria of ODD
• ODD is not separately defined in ICD	• Deliberate behavior of defiance • Arrogance with an intent to annoy • Highly irritable with temper outbursts • Vindictive with no remorse for own actions • Blaming people and resentfulness • All the above behavior should compromise academic, social and occupational functioning

provides information about a child's social functioning and behaviors. Eight subscales could be derived from the CBCL and each provides a measure of a unique but not totally independent category (aggression behavior, anxious

depressed, attention problems, delinquent problems, social problems, somatic complaints, thought problems and withdrawal). Detailed description is out of scope of this article.

2) Conner Scale²

This will yield a number of useful domains including conduct problems, learning problems, psychosomatic problems, impulsiveness, hyperactivity and anxiety.

Diagnosing DBD

DSM-IV-TR and WHO-ICD10 provide diagnostic criteria for ODD and CD (Table.III & IV)^{3,4}. In DSM-IV-TR, ODD is classified as a separate disorder and not as a subtype of conduct disorder.

Treatment

Pediatricians are likely to manage any adolescent with ODD and CD and it is important to be familiar with various modalities of treatment so that the family could be counseled and a shared care could be continued.

Individual and family therapy are most useful in treating ODD. Parents are educated about behavioral management techniques and parenting approaches. Interpersonal and cognitive behavioral psychotherapy are beneficial for children and adolescents. These treatment modalities help adolescents understand their own behaviors, their responses

Table.IV ICD10 and DSM-IV-TR Criteria for CD

ICD criteria for CD	DSM criteria for CD
• Fighting too much	• Overpowering animals and people, either by aggression, threat, fighting or intimidation
• Misbehaving or hurting persons or animals too much	• Forcing sexual activity with persons or animals
• Absconding from house and school without permission	• Cruelty towards animals or persons
• Manipulative behavior	• Involvement with the law for theft of possession weapons, purse snatching, fire setting, running away from school / home etc
• Frequent temper outburst	
• Disobedience and defiance so much so that it disturbs social, school and occupational functioning	• The disturbance in behavior should impair social, academic or occupational functioning
• It has to be persistent for not less than six months	

to situations, and the effects of their behaviors on others in their environment.

Treatment of ODD⁵

Family Intervention: In this there is a direct training of the parent in child management skills and careful assessment of family interactions.

Behavior therapy: It emphasizes teaching parents how to alter their behavior to discourage the child’s oppositional behavior and encourage appropriate behavior. It also focuses on selectively reinforcing and praising appropriate behavior and ignoring undesired behavior.

Individual psychotherapy: The child is helped to learn new strategies to develop a mastery and success in social situations with peers and families. Effort is targeted in restoring child’s self esteem so that he indulges less in provocative behavior.

Treatment of CD⁶

The following models have been found useful: Parent management training (PMT), Problem solving skills training (PSST) and Multi-systemic therapy (MST).

1. Parent management training (PMT)⁷: It aims to improve parenting skills. It addresses the parenting practices identified in research as contributing to conduct problems. It covers promoting play and positive relationship, praise and rewards for sociable behaviors, clear rules and clear commands, consistent and calm consequences for unwanted behaviors and reorganizing the child’s day to prevent trouble.

2. Problem solving skills training (PSST)⁸: It is a cognitive approach and includes anger management and child interpersonal skills, schemes for sorting difficulties at school e.g., learning disabilities and other class room behaviors, deviant peer group reduction and placing youth with CD in groups with well-functioning youth, etc.

3. Multi systemic therapy (MST)⁹: This differs from traditional family therapy in various regards. (i) Treatment is delivered in the situation where the patient lives e.g. at home.(ii) The therapist has a low case load (4-6 families) and the team is available round the clock. (iii) The therapist is responsible for ensuring that appointments are kept and making change happen. (iv) Regular written feedback on progress towards goal from multiple sources is gathered by the therapist and acted upon. (v) There is a manual for therapeutic approach and adherence is checked weekly by the supervisor.

4. Sociotherapy¹⁰: It is re-emerging as a treatment of DBD. It is a social science and form of social work that involves the study of groups of people, its constituent individuals and their behaviors, using learned information in case and care management towards holistic life enrichment or improvement of social and life conditions. Socio therapy has been used in the treatment and education of adolescents at Kanner Academy and Community Schools in Sarasota, Florida, USA¹¹. In these settings the working definition of sociotherapy is the practice of promoting healthy growth and living by facilitating therapeutic communities, personal relationships and positive peer culture. It is better known as the relationship therapy.

Pharmacotherapy

Co-morbidity in DBD should be looked for and should also be treated simultaneously. Some of the following drugs may be needed according to the indications.

- 1) Anti-depressants like fluoxetine, paroxetine, fluvoxamine, sertraline can be used for depression.
- 2) For mania or mixed affective episode anti-epileptics or lithium can be used.
- 3) For hyperactivity/impulsivity stimulant drugs like methylphenidate, dexamphetamine and imipramine are given.

Situations requiring referral to psychiatrist or psychotherapists are listed in Table V.

Table.V When to refer to a psychiatrist or a psychotherapist

1) When the treating physician is unable to make an effective working relationship with the parent or the adolescent
2) When adolescent engages in risky or illegal activities (substance abuse, reckless driving)
3) When adolescent is severely depressed or hasn’t responded to standard anti-depressant therapy
4) When adolescent has suicidal tendency
5) When adolescent has lost touch with reality (feature of psychosis)

Prognosis

Different set of circumstances play a role in how an individual shapes up.

The study by Laub and Simpson¹² on delinquent boys to age 70 showed how the individual can be steered away

from antisocial path. The prognosis of CD is varied, usually due to learning problems; they drop out of school and hence have poor vocational qualification. They have low social economic status due to low income and in turn get more exposed to alcohol and drug abuse, with few friends and limited involvement with relatives. Episodes of deliberate self-harming behavior also occur commonly. Many of them develop into 'anti social personality disorder'.

Points to Remember

- *Occasional disruptive behaviors if repeated in a pattern that negatively affects others may then be a 'disruptive behavior disorder'.*
- *Early recognition and appropriate interventions are likely to help in effectively dealing with these behaviors and prevent their escalation into a disorder.*
- *Pediatricians can play a very important role by not avoiding the complaints of parents about such behaviors. Pediatricians can coordinate with various professionals like psychiatrists, counselors and social workers to extend appropriate care to these children and adolescents, and their families.*

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NEWS AND NOTES

3rd Kawasaki Disease Summit and 12th National Conference of Pediatric Rheumatology Society Chandigarh, October 31 - November 2, 2014

Enquiries to:

Dr. Anju Gupta

Secretary, IAP Rheumatology Group

Email: anjupgi@gmail.com

Website: <https://sites.google.com/site/prhescon>

DRUG PROFILE

DRUGS FOR CHILDHOOD CONSTIPATION

***Jeesson C Unni**

Abstract: *Childhood constipation is a common problem in office practice. The therapy comprises of parental education, toilet retraining, dietary modification and drug therapy. An initial complete bowel evaluation with the help of enema or oral polyethylene glycol (PEG) followed by maintenance dose of laxative in correct dose as a long term therapy is found to be effective. A minimum period of 2 to 3 months maintenance treatment is essential before planning tapering and stoppage of drug. Though the response is good in majority of children, a sizable proportion also relapses.*

Keywords: *Constipation, Children, Disimpaction, Enema, Polyethylene glycol, Laxative.*

Constipation is a common problem for which children are seen in the out-patient department. Almost 5% of pediatric office visits and 25% of child referrals to gastroenterologists are for constipation.¹ Recurrent abdominal pain and encopresis may be the presenting symptom and fecal impaction causes one of the most excruciating forms of abdominal pain in children. Thus the relief a child gets on disimpaction is gratifying. It is therefore important to recognize chronic constipation and understand its therapy. It is important to rule out organic and endocrine causes, especially in the newborn period.

Definition: Chronic constipation is defined as the delay in defecation of 2 weeks duration or more sufficient to cause significant distress to the child.² Functional constipation accounts for 85%–95% of chronic constipation.^{2,3,4} We will deal with management of functional constipation in this article.

Management

The 4 steps of management include

a) Educating parents regarding the need for early therapy and long-term maintenance, need for the child to forget the

pain of defecation (and that the time taken for this fear to subside is directly proportional to the duration and severity of the problem and may take longer if the child has developed a fissure-in-ano in the process)

b) Advice on behavioural therapy including toilet 're-training'- cajoling and playfully engaging the child to ensure that they regularly relax while sitting on a comfortable potty for around 5 min after every major meal even if there is no result for a few months; maintaining a record (without the child realizing that the event is being closely monitored) of stool frequency; intensity of discomfort/pain; frequency of soiling, if present; laxative use (generic name of laxative used, compliance, taste and in what form it is accepted, response to each dose as and when tapered); and effect of positive reinforcement (reward system employed, if any) of child's willful acceptance of daily medication, expected duration of potty-sitting. Parents need to be aware that constant use of diapers hampers toilet training and that they need to always keep the child's underwear clean.

c) Diet that softens stool include an increase in fluid intake, high fiber diet-ideally age in years + 5gm (apple with peel, tomato with its skin, a bowl of oats daily, fruits, vegetables, whole grains, whole pulses and beans). Avoid fine wheat flour (maida) and maida products like noodles, parotta, vermicilli, chocolates, cakes, ice-cream, cocoa and a predominantly milk diet. However, it is difficult to coax children to take the quantity of high fiber containing food products required to soften stools.

d) Pharmacotherapy (Table I): Should go hand in hand with all the above mentioned strategies. The success of drug therapy lies in identifying the correct dose of laxative in each child that would produce the desired effect. Pharmacotherapy includes clearing the large amount of accumulated feces that would be blocking the rectum (disimpaction) followed by maintenance therapy and then gradual tapering while monitoring stool frequency and consistency.⁵ The aim is to prevent a build-up of hard stools recurring again. Long-term therapy is required (for many months and tapered gradually) till the child forgets the pain associated with defecation. The enlarged and distended rectum needs to gradually get back to a normal size so as to function properly again. Constipation is then unlikely to recur.

* Editor-in-Chief
IAP Drug Formulary,
Cochin.

Table I. Laxatives – mechanism of action, dose and side effects

Drug name	Mechanism of action	Onset of action	Recommended dose	Adverse effects/precautions/disadvantages	Advantages
Glycerin	Osmotic laxative	15-30 min	Rectal: <1 yr 1gm, 1-12 yr 2gm; 12-18 yr 4 gm after moistening as single dose.	N/A	
Magnesium hydroxide	Osmotic laxative		Oral: <3 yr: 0.5 mL/kg/dose 3-12 yr: 5-10 ml bedtime 12-18 yr: 25-30 mL/day	Risk of hypermagnesemia, hypophosphatemia or secondary hypocalcemia if overdose and/or renal dysfunction; chalky taste	Effective; inexpensive
Polyethylene glycol 3350	Osmotic laxative	1-3 days	Oral: 1 sachet or 1 heap tablespoon once daily - mixed with a liquid Fecal impaction: 25mL/kg/hr upto 1000mL/hr until clear/thick liquid stool or 1-1.5gm/kg/ day over 4hrs/day for 3 days	Expensive; requires preparation	Effective; flavorless; odorless
Lactulose	Osmotic laxative		Oral: initial dose <1 yr 5mL, 1-5 yr 10mL, 5-10 yr 20mL, >12 yr 30mL in 2 divided doses. Then adjust according to response (Usual dose 1-3 mL/kg/day in divided doses)	Abdominal cramping; flatulence	Effective
Lactitol	Osmotic laxative		Administer oral once daily along with evening meals - the dose may also be given in the morning if that is more convenient. Constipation: 2-6yr age - 10mL; > 6yr 10-15mL	Colicky abdominal pain. Other rare side effects include abdominal discomfort, nausea, dyspepsia, epigastric pain, urgency of defecation, borborygmi or anal pruritis and vomiting.	Effective
Sorbitol	Hyperosmotic laxative	Oral: 6.4-8.48 h	Oral: 2-11 yr: 2 mL/kg (as 70% solution) ≥12 yr: 30-150 mL (as 70% solution) OR 1-3 mL/kg/day in 2 divided doses Rectal enema: 2-11 yr: 30-60 mL (as 25%-30% solution) ≥12 yr: 120 mL (as 25%-30% solution)	Flatulence; abdominal cramping	Effective
Bisacodyl	Stimulant laxative	Oral: 6-10 h Rectal: 15-60 min	Orally < 3-10 yr 5 mg, > 10 yr 5-10 mg daily bedtime (max 15-20 mg). Rectal suppositories < 10 yr 5 mg, > 10 yr 5-10 mg daily once in the morning	Abdominal cramping; diarrhea; hypokalemia; cathartic color [†] ; not recommended for impaction; not indicated for long-term use	
Sodium picosulphate	Stimulant	10-14 h	2-5yr 2.5mL, 5-19yr 2.5-5mL, >10yr 5-15mL as single dose at bedtime	mild abdominal discomfort	
Senna	Stimulant laxative	Oral: 6-24 h Rectal: 0.5-2 h	Oral tabs 6-12yr 1-2 tabs, 12-18yr 2-4tabs. Liquid < 2yr 0.5mg/kg 2-6yr 2.5-5mL, 6-12yr 5-10mL, 12-18 yr 10- 20mL.	Abdominal cramping; idiosyncratic hepatitis; melanosis coli [‡] ; not recommended for impaction; not indicated for long-term use	Gentle
Liquid paraffin	Lubricant laxative	6-8 h	Oral 3-12 yr 0.5-1mL/kg and 12 -18yr 10-30ml once daily	Aspiration/lipoid pneumonia; anal leakage; poor palatability	Inexpensive
Docusate	Surfactant laxative	12-72 h	< 3yr 10-40mg/24hr in 1-4 divided doses, 3-6 yr 20-60 mg/24hr in 1-4 divided doses, 6-12 yr 40-150 mg/24hr, > 12 yr 50-400 mg/24hr	Anal or rectal burning and pain, diarrhoea, rash,	

Disimpaction - Complete bowel evacuation is absolutely essential when initiating therapy as otherwise there would be a deterioration of continence if regular maintenance dose of laxatives alone were to be introduced.⁶ Enemas and Polyethylene glycol (PEG) were equally effective in treating fecal impaction in children⁶ but one recent Randomized Controlled Trial (RCT) suggested that enema may be superior to PEG for immediate relief of symptoms.⁷ Oral PEG, being less invasive, is preferred as rectal administration is a painful procedure⁸ if not done with care; and children who are already having painful stooling find this route unacceptable and persistence with rectal administration only increases the fear of rectal passage of any substance.

If enemas are used, the phosphate enema is preferable to glycerin or saline enemas.⁵ If a mineral oil enema is used, it should be administered 1 to 3 hours prior to a phosphate or saline solution enema. The mineral oil enema softens and lubricates the stool and primes it for evacuation by the hypertonic enemas that would directly stimulate colonic contraction.⁹ Preschoolers and older children will require an adult-sized enema to relieve impaction; and one to three enemas may be required within a 12- to 24-hour period.

Dose of PEG with or without electrolytes for disimpaction is 25mL/kg/hr up to 1000mL/hr until clear/thick liquid stool is passed to indicate that all colonic content has been evacuated. It may also be given at 1-1.5gm/kg/day over 4 hrs/day for 3 days. Compliance to these regimens is poor as palatability and volumes to be administered are problem issues in children; so much so that in small children it needs to be administered via a nasogastric tube.

Maintenance: This phase must aim at achieving a regular daily stool pattern of one to two soft stools; a mushy consistency indicates complete evacuation of the bowel and this involves all the earlier mentioned steps along with pharmacotherapy and may need to be sustained for months. Though laxatives have been extensively used in children there are very few randomized control trials of their use in chronic constipation. A Cochrane review suggested PEG to be most effective; other laxatives-milk of magnesia, liquid paraffin and lactulose also have some effect.¹⁰ Therefore, the choice of laxative depends on the ability of the family to obtain the medication, along with the cost, taste, ease of administration and personal preference. Once the 'correct dose' (dose that achieves target stooling pattern as mentioned earlier) is identified that dose must be maintained for at least 2–3 months before tapering off. Stimulant laxatives like senna, sodium picosulfate and

bisacodyl are not recommended during maintenance because of possibility of developing dependence. However, they may be used intermittently for 1–3 days as necessary in refractory cases; but they are absolutely contraindicated in infants.

Tapering off of laxative dose: After target bowel habits are achieved and sustained for a few months, the dose of laxatives should be gradually tapered off.⁵ Relapses are common and therefore tapering must be individualized and if there are indications of relapse on the lower dose the dose should be again increased and a stimulant laxative may be added for a few days. High fibre diet must be ensured while the child is being weaned off laxatives.

Results of therapy: Unless constipation is picked up early and a wholesome therapy started immediately, the results in young babies are poor because they resist medication and are often not given the prescribed dose of medication regularly due to parental concerns of continuous medications. Reviews suggest a 60% response to therapy.¹¹ Relapses are common in 53% of children after 1 year of therapy and at 5 years 50% continue to suffer from constipation.¹²

Points to Remember

- *Constipation is a common problem in pediatrics and it requires prompt attention, education, and acute and long-term management to avoid physical and emotional complications.*
- *A multi-disciplinary approach is needed and long-term follow-up is essential.*
- *Each child would require separate approach and therapy need to be fine tuned during these follow-up visits.*

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CLIPPINGS

Routine ultrasound in late pregnancy (after 24 weeks' gestation)

Diagnostic ultrasound is used selectively in late pregnancy where there are specific clinical indications. However, the value of routine late pregnancy ultrasound screening in unselected populations is controversial. The rationale for such screening would be the detection of clinical conditions which place the fetus or mother at high risk, which would not necessarily have been detected by other means such as clinical examination, and for which subsequent management would improve perinatal outcome.

Objectives was to assess the effects on obstetric practice and pregnancy outcome of routine late pregnancy ultrasound, defined as greater than 24 weeks' gestation, in women with either unselected or low-risk pregnancies.

Selection criteria: All acceptably controlled trials of routine ultrasound in late pregnancy (defined as after 24 weeks).

Authors' conclusions: Based on existing evidence, routine late pregnancy ultrasound in low-risk or unselected populations does not confer benefit on mother or baby. It may be associated with a small increase in caesarean section rates. There is a lack of data about the potential psychological effects of routine ultrasound in late pregnancy, and limited data about its effects on both short- and long-term neonatal and childhood outcome. Placental grading in the third trimester may be valuable, but whether reported results are reproducible remains to be seen, and future research of late pregnancy ultrasound should include evaluation of placental textural assessment.

Bricker L, Neilson JP, Dowswell T. Routine ultrasound in late pregnancy (after 24 weeks' gestation). Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD001451. DOI: 10.1002/14651858.CD001451.pub3. Assessed as up to date: 28 May 2008.

DERMATOLOGY

SKIN CARE FOR NEWBORN

* **Madhu R**

Abstract: *Skin is the largest organ in the human body and has important functions such as fluid homeostasis, thermoregulation and protection against invasion of microorganisms absorption of noxious substances and physical trauma. The skin of a term neonate is thinner than the adult skin and that of a preterm baby is thinner than the skin of a term baby. The skin of a newborn undergoes structural and functional modifications from the first few days of life almost up to the first year of life. Hence care of newborn skin requires special attention. Skin care comprises of cleansing and maintenance of protective functions of the skin. Cleansers used in adults should not be used in neonates as they disturb the skin barrier, acid mantle and increase the pH of the skin. Maintenance of the barrier function is vital to the neonate, for barrier disruption results in increased transepidermal water loss (TEWL), thermal dysregulation, increased percutaneous absorption of noxious substances and trauma. An ideal cleanser for a newborn should be mild, fragrance free and should not disturb the acid mantle and barrier function of the skin. Touch therapy plays an important role in the growth and development of a neonate. Massage offers multiple physiological and psychological benefits to the baby. Babies massaged with oil showed reduced stress behaviour and lesser cortisol levels than those given massage without oil.*

Keywords: *Newborn, Preterm, Skin barrier, Cleanser, Massage.*

Skin care for newborn

Skin is the largest organ in the human body, with varied important functions such as protective barrier function, thermoregulation, UV protection, repair and regeneration of wounds, protection against invasion of microbes and external antigens, synthesis of essential nutrients,

mechanical, immunological, sensory autonomic functions and sociosexual communication.¹ Skin of a neonate or an infant is not a miniature of the adult's skin. The skin of a newborn baby is 40% to 60% thinner than the adult skin. Stratum corneum of a preterm baby is thinner than that of a term baby. The ratio of body surface area to weight of a term neonate is up to five times and that of a preterm baby is seven times that of an adult.² The skin of a newborn baby undergoes both structural and functional modifications starting from the first few days of life up to almost the first year to adapt to the transition from the in utero wet world to the extra uterine dry environment.³ In comparison to the skin of the adult, newborn baby's skin is less hydrated and there is reduced amount of Natural Moisturization Factor (NMF).⁴ At birth, the mean pH of the skin surface of a newborn is 6.4, unlike the adult skin acidic pH which ranges from 5 to 5.5. The maturation of acid mantle of the epidermis of a neonate occurs over the first four days and the pH becomes 4.95.⁵ Alkaline pH predisposes to diaper dermatitis and favors the colonization of *Staphylococcus aureus* and *Candida albicans*. On the other hand, acidic pH has a bactericidal effect and plays an important role in defense against infection. Use of alkaline soaps and detergents which may shift the pH to alkaline range increases the vulnerability to cutaneous infection and may also augment fluid loss.⁴ The structural and functional immaturity of the skin of a preterm baby results in increased transepidermal water loss (TEWL), susceptibility to mechanical trauma, microbial invasion and percutaneous absorption of toxins. In this background, it becomes imperative to provide optimum care for the skin of a newborn which in turn will help to reduce the morbidity associated with immature skin barrier.⁶ Skin care encompasses cleansing and maintenance of skin health. It is essential to recapitulate our knowledge about cleansers, before we deal with the skin care of preterm and term babies.

Cleansers

Cleansing is the process of removal of dirt, sebum, microorganisms, exfoliated corneum cells and oil in cosmetic products from the skin surface by a complex interaction between the skin barrier, dirt, body secretions and a surfactant. Cleansing with only water results in the removal

* Senior Assistant Professor,
Department of Dermatology (Mycology),
Madras Medical College,
Chennai.

of water soluble dirt but not the fat soluble particles. Cleansers are surface- active substances that emulsify the fat soluble particles and convert them into water soluble matter which can be washed off in water. Use of cleansers dates way back to 2000 BC, with the mention about soap making found in the Sumerian clay tablets. Galen, a Greek physician in the 2nd century and Gabiribne Hayyan in the 8th century have written about soap as a cleanser. The first wrapped soap bar was developed by the English in 1884.^{7,8} Today, 130 years later, a wide variety of soaps, special soaps and liquid cleansers have flooded the market.

Cleansers are composed of surfactants (to emulsify the debris), moisturizers (to hydrate the skin and maintain the skin barrier), binders (to stabilize the formulation), lather enhancers (found in some products), fillers (generally used to harden bar soaps and cleansers), preservatives, fragrance and colour.⁹ Among these, surfactants are the major constituents and they act by reducing the surface tension between water and air with an end result of cleansing the skin of fat soluble impurities. Surfactants may be ionic, non-ionic and silicone containing surfactants. Ionic surfactants are in turn classified as anionic (negatively charged), cationic (positively charged) and amphoteric (both positive and negatively charged). Anionic surfactants have the highest foaming ability and are very aggressive towards the skin barrier (e.g. sodium tallowate, sodium lauryl sulphate). Amphoteric surfactants have low foaming ability and are aggressive towards the skin barrier. (e.g. Disodium lauroamphodiacetate, cocoamidopropyl betaine). Non-ionic surfactants have the lowest foaming ability and are very less aggressive towards the skin barrier. Aggressiveness of anionic surfactants may be reduced by mixing with amphoteric or non-ionic surfactants.¹⁰ Adverse effects such as dryness and skin irritation occur based on the type and amount of surfactant present in the cleanser.⁸

Cleansers, whether formulated as bars or liquids have been basically classified into three categories namely true soaps, syndet bars and combars. Soaps are fatty acid salts derived from animal fat (Tallow) or vegetable fat processed with lye (sodium or potassium hydroxide) by saponification. True soaps are composed of long chain fatty acid-alkali salts with a pH between 9 and 10.^{11,12} This high alkaline nature causes dissolution of lipids from the skin surface, disruption of stratum corneum barrier and acid mantle and raises the skin pH.³ Soap precipitates in hard water, producing insoluble calcium or magnesium salts that prevent foam formation.¹³ Use of soaps may result in after-wash tightness, dryness and irritation of the skin manifested by

erythema associated with itching.⁸ Special additives added to the soaps have resulted in the various subsets of soaps such as superfatted soaps, transparent soaps and medicated/antibacterial soaps. While superfatted soaps contain increased oil and fat such as paraffin, mineral oil, triglycerides and lanolin with a fat ratio up to 10%, transparent soaps contain glycerine and sucrose. These soaps will help to minimize the dryness of the skin. Antibacterial soaps contain antibacterial agents such as triclosan, triclocarban etc. Triclosan which is the most common ingredient in these soaps reduces the skin biofilm bacteria count by blocking the lipid synthesis in the bacterial cell wall.^{11,12}

Harsh effects of the soaps on the skin resulted in the development of syndets or synthetic detergents which are synthetically derived organic quaternary ammonium compounds or polymerized or sulfonated fatty acids. These are composed of synthetic detergents and fillers that contain less than 10% soap with a pH of 5.5-7. Syndets unlike soaps are not manufactured by saponification. Syndets maintain the neutral pH and are less likely to produce adverse effects like dryness and irritation of the skin. Common synthetic detergents in bar type cleansers are sodium cocoate, sodium isethionate, sodium coccoyl isethionate, sodium palmitate and sodium tallowate. Combars are composed of alkaline soaps to which surface active agents with a pH of 9 to 10 have been added. They are milder cleansers than true soaps. But when compared to syndets, combars are better cleansers.¹²

Cleanser variants

Soapless cleansers are lotions that are primarily composed of either glycerin or propylene glycol and cetyl/steryl alcohols. They are hygroscopic and lubricating in nature and can be wiped off without using water.

Liquid cleansers with appropriate blend of anionic, non-ionic and amphoteric surfactants are available. They are milder in nature and do not disrupt the skin barrier or acid mantle. They are more hygienic than the wash bars.

Ideal cleanser

An ideal skin cleanser is one that has minimal interaction with the skin and yet removes all the unwanted materials from the skin surface of the baby. It should be mild and not affect the skin barrier or the acid mantle of the skin surface of the baby. It should definitely not cause any skin or eye irritation and must be fragrance-free. A liquid cleanser is preferred to soap, as it is more hygienic and easily spreadable.¹⁰

Shampoo

Most shampoos are soapless and are made of sulfonated oil. They consist of principal surfactants for detergent and foaming power, secondary surfactants to improve and condition the hair and additives to complete the formulation and special effects. Other basic ingredients include thickeners, opacifiers, sequestering agents, pH adjusters and preservatives. As shampoo contains a large component of water, preservatives are a must. Formaldehyde is the most common preservative used in shampoos. Additives such as colour and fragrance may cause allergic reactions. Baby shampoo ideally should be fragrance-free and should not cause eye irritation. Detergents that are commonly used in the shampoo include anionic detergents like lauryl/laureth sulfates, sarcosines, sulfosuccinates; cationic detergents such as amino esters, long chain amino acids; amphoterics like imidazoliniums, sultaines, betaines and non-ionic detergents like polyoxyethylene fatty alcohols/sorbitol esters. Shampoos with amphoteric surfactant and acidic or neutral pH are ideal for baby hair. Medicated shampoos with ketoconazole, zinc pyrithione, tar, salicylic acid etc. are available.^{14, 15}

Care of newborn skin

General principles to be adopted in the care of skin of a newborn baby are gentle cleansing, maintenance of hydration and moisturization, prevention of friction and maceration in the body folds and protection from irritants.

Vernix caseosa

The term, 'Vernix caseosa' first appeared in 1846 in the Dunglison dictionary of Medical Sciences. 'Vernix' means 'to varnish' and 'caseous' means 'cheesy'. Vernix caseosa is a naturally occurring, complex, lipid-rich substance coating the skin surface of the fetus in the last trimester of pregnancy, produced in part by fetal sebaceous glands and keratinocytes.¹⁶ It is a chalky white mixture of shed epithelial cells, sebum and sometimes lanugo hair. Vernix is composed mainly of water (81%), lipids (cholesterol esters, wax esters, squalene, cholesterol, triglycerides, free fatty acids, phospholipids – 9%) and proteins (10%). It has a complex structure similar to stratum corneum but lacks the lipid lamellae and is more plastic due to the absence of intercorneal desmosomal connections. Preterm babies tend to have very little vernix compared to the term babies, while the post term babies may not have vernix. Vernix is highly beneficial to the fetus and the newborn. It is a natural cleanser and moisturizer with anti-infective, antioxidant and wound healing properties. It facilitates the development of

acid mantle and supports the normal bacterial colonization.^{10,17} WHO recommends that immediately after birth, the baby is placed on the mother's abdomen or on a warm, clean, dry surface and then the whole body and hair is wiped with a dry, warm cloth.¹⁸ With due regard given to the various functions of the vernix, WHO guidelines for newborn care and guidelines from North Trent Neonatal Network recommend that it should not be removed.^{18,19} Vernix is to be removed while giving the first bath 6 hours after birth.¹⁸ European guidelines recommend wiping or washing vernix with water immediately after delivery according to the local cultural preferences.²⁰

The first bath

There are different schools of thought as to when the first bath can be given. The first bath can be given to a full term well baby, once the baby is hemodynamically stable. WHO guidelines for newborn care recommends initial bath, 6 hours after birth.^{6,18} In practice, bath is usually given to a term healthy baby weighing more than 2.5 Kg, 2 - 6 hours after birth.²¹ In term, IUGR babies, only sponge bath is to be given until the baby's weight is 2.5 kg. Some international guidelines recommend delaying of first bath to second or third day, to assist skin maturation.¹⁰ European guidelines leaves the timing of first bath to local cultural preferences. If the first bath is to be given by health workers, it is recommended that they wear gloves.²⁰ Some studies have advocated the initial bath after fall of the umbilical cord. It has shown that bathing makes the babies calmer and quieter than washing with cloth or sponge.³ Bathing, by virtue of the tactile stimulation, provides a pleasurable experience for the baby and promotes the bonding between the baby and the parent or the care giver.

Bath should always be given in a warm room. The temperature of bath water should not exceed 37°C.¹³ Studies have shown that bathing in water with appropriate temperature results in less heat loss and keeps the babies comfortable.³ Before placing the baby in the bath, parents or caregiver should mix the water to ensure even temperature and check, prior to wearing gloves, if done by health care provider. While giving a tub bath, depth of the water should be 5 cm up to the hip of the baby. As bath tub and bath toys are potential sources of infection, they must always be disinfected before bath.²⁰ Bath duration should not exceed 5 minutes. During bath, the superficial layers of the skin become well hydrated and thick with a corresponding reduction in the cell cohesion. The over hydrated skin is more fragile with a decreased threshold for injury. This explains why the bath duration should be short.¹³

Routine bathing

Routine bathing of newborns and infants does not cause any harm. European guidelines recommend bathing babies 2–3 times per week until the baby is crawling or as often required by the local culture.²⁰ North Trent Neonatal Network guidelines advocate a bath frequency of 2–3 times per week if necessary.¹⁹ This bath frequency does not suit the climatic conditions in India, where daily bath will be more preferable.¹⁰ However, during winter and in the hilly regions, babies may be bathed twice or thrice a week.

After bathing, baby should be immediately dried from head to foot, following which baby is to be wrapped in a dry, warm towel and placed next to the mother. This is of high significance especially when the baby is bathed during the first hour of life, in order to prevent hypothermia.

Cleansers

Braun, et al showed that the acid mantle was disturbed by alkaline soaps and not syndets. In another study, Braun et al observed that the reduction in lipid content by washing with syndets was comparable with the use of tap water (37%:52%), whereas lipid loss was 93% after washing with soap. Recovery of the lipid content could be observed over time, but was not complete 120 min after washing. Gfatter et al concluded that dissolution of lipids from the skin surface was more pronounced with alkaline soap than with detergent. Changes in the lipid composition of the stratum corneum may reduce the skin barrier function. Noviello et al examined the daily use of a bath product in infants in the age group from 0-52 weeks and observed that the regular use of syndets during the first weeks of life resulted in a faster decrease of skin surface pH. It was also found that washing with alkaline soap but not with mild cleansers increases the surface pH.³ Even temporary increases in skin pH may be expected to disrupt biochemical processes of desquamation, lipid synthesis and NMF generation.²² Galzote and colleagues reported that washing routines with water alone or using a mild baby wash proved clinically equivalent with regard to changes in skin hydration, skin surface pH, and TEWL.³

All the above mentioned studies point against the use of alkaline soaps during the neonatal period. European guidelines recommend the use of liquid cleansers instead of using only water.²⁰ A mild liquid cleanser with acidic or neutral pH i.e. with an appropriate blend of ionic, non-ionic and amphoteric surfactants, which will not affect skin barrier function or acid mantle will be ideal to be used in the neonates and infants.¹⁰ Syndets and mild soaps may be used in infants. In case of cost constraint, minimal use

of mild soap for the flexures may be advised. Minimal use of cleanser is to be encouraged.

Care of napkin area

Diaper area is exposed to excessive hydration, occlusion, friction and maceration. Fecal ureases catalyze the breakdown of urea to ammonia, which increases the pH of the skin surface. This increase in pH contributes to the activity of fecal enzymes, proteases, ureases and lipases which are highly irritant to the skin. Water and wash cloth are the gold standards for cleansing the nappy area. Mother should be advised to use only cloth napkins which should be changed frequently. It is most important to keep the area dry. Moistened cloths or cotton balls soaked in lukewarm water can be used to clean the area after defecation. Creams containing zinc oxide and petrolatum based preparation help to maintain the skin barrier function.²³ Cloth napkins are to be washed with a mild detergent in warm water and dried in good sunlight. Use of antiseptics and wipes with fragrance are to be avoided.

Care of the umbilical cord

The umbilicus cord should be kept dry and clean. Cleaning with lukewarm water will suffice. Cord should be kept exposed to air.

Care of scalp

Cradle cap or seborrheic dermatitis of the scalp can sometimes be worrisome to the mother. Mineral oil can be applied to the crusts and removed after 2-3 hours. Baby shampoos are useful in the removal of crusts and scales. Baby shampoos should be free from fragrance. The pH of the baby shampoos should be close to that of tears and should not cause irritation to the eyes. Baby's first hair wash is to be given after the cord falls. Hair wash may be given every third day or as and when required.

Use of baby powders

Powders are not to be used in neonates. Powders applied in the flexures will result in occlusion of the sweat glands and cause miliaria. Mothers have the habit of applying powder using puffs which may result in accidental inhalation. Mothers should be advised to smear the powder on the hands and then gently apply on the baby's skin.

Care of skin of preterm baby

Skin of a preterm baby is thinner than that of a term baby. Stratum corneum which plays an important role in the barrier function develops only in the third trimester.

Maturation to transepidermal water loss (TEWL) occurs by 34 weeks. As a result, preterm babies have immature barrier function which results in increased TEWL, increased skin permeability, impaired thermoregulation, increased percutaneous absorption and susceptibility to trauma. However there is acceleration of permeability barrier maturation following birth, as a result of which most preterm babies have competent barriers by 2 to 3 weeks postnatal age. But, in preterm babies born at 22 to 25 weeks, it takes about 8 weeks to mature. Acid mantle develops over 2–8 weeks after birth.

Gentle and minimal handling of the preterm babies is to be practiced. Hand hygiene measures are to be followed strictly before handling these babies, as they are more prone for developing infections. Sponge bath with water is to be given until the baby weighs 2.5 kg, after which baby may be given regular baths with mild skin cleanser. Position of the baby is to be frequently changed. Micropore adhesives may be used to secure IV cannulas. They may be removed gently with warm water soaked gauze piece. Use of isopropyl alcohol is discouraged. Transcutaneous oxygen monitor electrodes should not be left in place for more than an hour without surveillance. Gentle application of emollients will help to reduce the dryness and maintain the barrier function.²⁴ Emollients decrease the risk for invasive infections in preterm infants by preventing access to deeper tissues and the bloodstream through skin portals of entry.

Emollients

The word emollient is derived from the Latin verb 'mollire,' to soften.²⁵ Emollients are lipid containing substances that soften the skin and prevent transepidermal water loss. They help in the restoration of skin barrier and thus retard further damage. Various emollients that are available are hydrocarbon oils (petrolatum, mineral oil, paraffin, squalene), fatty acids (lanolin acid, stearic acid), fatty alcohol (lanolin alcohol, cetyl alcohol) etc.¹¹ Regular use of emollients is indicated in preterm babies, IUGR and post-term babies. Emollients augment skin barrier function and reduce the incidence of systemic infections in preterm babies. Emollients may be used in term healthy babies with cleanser induced dryness.

Touch therapy Massage

Tiffany Field founded the Touch Research Institute at the University of Miami, School of Medicine, the first center in the World solely devoted to the study of touch and its application in science and medicine in 1992. Touch is considered absolutely essential for the growth and development of a neonate. Lack of appropriate touch results in poor growth of the infant, delayed attachment to parent

and psychological disturbances.²⁶ Systematic application of touch is termed as massage. Massage promotes circulation, suppleness and relaxation of the different areas of the body and tones up the muscles. Massage results in promotion of mother-infant bonding - the one to one, focused, uninterrupted time sharing touch, eye contact, body smells, body sounds and voice.

Benefits of massage

Massage increases activity of the vagus nerve which may lead to an increase in food absorption hormones such as insulin. Massage results in increased weight gain by increasing insulin and insulin like growth factor-1 (IGF-1), the latter has an important role in growth promotion by stimulating cell growth and multiplication and inhibiting apoptosis.²⁷ Greater bone mineralization and more optimal behavioral and motor responses were observed in infants given massage compared to controls.^{28,29,30} In a study by Tiffany et al, tactile/kinesthetic stimulation was given to 20 preterm neonates during transitional ("grower") nursery care and was observed that these babies were more active and alert, and had 47% greater weight gain. They showed better performance on the Brazelton scale than the control infants in terms of mature habituation, orientation, motor and range of state behaviours. Massage given to the preterm babies helped to reduce the duration of hospital stay and the health care cost.²⁹

Oil massage

Oil massage of infants has been traditionally practiced in countries like India and Bangladesh. Choice of the oil is very important so that there are no untoward effects. Oil enhances skin barrier function, acts as a source of warmth and nutrition and increases weight gain. Infants showed reduced stress behaviour and lower cortisol levels following massage with oil versus massage without oil.³¹ Very low birth weight preterm neonates given oil massage showed better weight gain. Coconut oil, sunflower oil, mineral oil and synthetic oil are being used for massage. Studies have shown mustard oil to cause irritant and allergic contact dermatitis.³² A study by Danby et al observed that while sunflower oil enhances the skin barrier function, olive oil caused erythema and disruption of skin barrier function.³³ Care should be taken to avoid miliaria and oil folliculitis, while using vegetable oils for massage during summer. Oil massage should be given before bath during summer and after bath during winter.

Who? When? Where? How?

Massage is ideally given by the mother/father/grandparents or caregiver. Massage may be started after the tenth day of life in a well baby. Massage is to be given

when the baby is alert and active, preferably 1-2 hours after feed. A full body massage will take 15 to 30 minutes. Massage is to be done in a warm room. Mother should have cut the nails and removed the rings and watch. Strokes should be gentle and firm and not jerky. These gentle strokes given from head to foot will result in tactile and kinesthetic stimulation. As the baby may not lie still, one should work with and not against the movements. Comfortable signs of a baby enjoying massage are happy vocal sounds (eg cooing), easy breathing pattern, bright-eyed look, ability to focus and take in surroundings comfortably and enjoying stretching, sucking, clasping own hands or feet.

Conclusion

Proper skin care of a term neonate or preterm will help to reduce the morbidity associated with immature barrier function. Gentle handling of preterm babies with preventive measures such as avoidance of antiseptics should be practiced. Liquid cleansers and syndets are preferred to soaps in the neonatal period. Emollients help to improve the texture of skin and maintain the skin barrier. Massage, especially oil massage has a positive impact on the growth and development of the baby. Hence every parent should be encouraged to give massage to their babies.

Points to Remember

- *Immediately after bath, baby should be wiped dry with a warm cloth. Vernix caseosa is not to be removed.*
- *First bath is to be given 6 hours after birth to a term well baby weighing > 2.5 kg.*
- *Term/ small for date/ IUGR/ preterm babies to be give sponge bath until weight becomes 2.5 kg, after which regular bath may be given.*
- *Daily bath is preferable. In hilly regions and during winter, frequency may be thrice weekly.*
- *Bath should be given in a warm room. Duration should not more than 5 minutes*
- *Bathing with a mild cleanser is superior to cleaning with cloth/sponging.*
- *Syndets are preferred to soaps. Soaps with alkaline pH are best avoided during neonatal period.*
- *In case of cost constraint, minimal use of mild soap for the flexures may be advised.*
- *Gentle and minimal handling of preterm babies with strict adherence to hand hygiene measures.*
- *Umbilical cord is to be kept clean and dry.*

- *The nappy area is to be kept dry with frequent change of diapers; cloth nappies are preferable; moistened cloth is to be used to cleanse the area; emollients and barrier creams are useful.*
- *Shampoos with acidic or neutral pH are ideal for baby's hair. Should be fragrance free.*
- *Massage especially oil massage should be encouraged, so as to reap the multiple benefits of massage of the baby.*

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Organizing Secretary

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SURGERY

ANTENATAL DETECTION OF GI TRACT ANOMALIES AND MANAGEMENT

* **Pavai Arunachalam**

Abstract: *A short review of the antenatal ultrasound diagnosis of gastrointestinal tract anomalies including abdominal wall defects has been done. The plan of management based on the defect is discussed.*

Keywords: *Antenatal ultrasound, Intestinal atresia, Abdominal wall defects.*

During early embryogenesis, intestinal growth is faster than the growth of the abdominal cavity. There will be a focal abdominal mass at the insertion of umbilicus due to physiological hernia of the bowel. The physiological hernia occurs at the 6th post-conception week and returns by the twelfth week. The presence of a hernia beyond the twelfth week, the size of the mass more than 7 mm and presence of liver in the hernial sac are considered abnormal.

Abdominal wall defects

Foetus with antenatally detected abdominal wall defects should be delivered at a tertiary care center. If delivered elsewhere, baby should be transferred with NG tube in situ, appropriate and adequate IV fluids and antibiotics. The defect should be covered by cling wrap before transport to prevent infection, fluid loss and compromise to the bowel.

The congenital abdominal wall defects include exomphalos, gastroschisis, Cantrell's pentalogy (supraumbilical exomphalos, lower sternal defect, pericardial defect, cardiac anomaly and diaphragmatic defect), cloacal exstrophy (infra umbilical exomphalos, exstrophy of the bladder and imperforate anus), OEIS syndrome (omphalocele, exstrophy, imperforate anus and spinal anomalies) and body stalk anomaly.

Gastroschisis is the herniation of the bowel through a defect to the right of the umbilical cord. It is characterized

by evisceration of bowel to the right of a normal umbilical cord without any covering membrane (Fig.1). This occurs due to an in-utero vascular accident. It occurs in young mothers especially with substance abuse. It can be differentiated from exomphalos by the absence of a sac and free floating bowel. It is difficult to differentiate it from a ruptured exomphalos. Associated syndromes are not common. Sonographically it can be diagnosed by the presence of free floating bowel to the right of a normal cord insertion. In addition, stomach is not in the left hypochondrium and contents are usually small bowel. The maternal serum alpha protein (MSAFP) is 9.42 MoM.¹



Fig.1. Gastroschisis – bowel which is thickened and lying outside the abdominal wall due to a defect to the right of the umbilical cord

Management: Antenatally close follow up for fetal distress should be done by looking out for increasing bowel dilatation, oligohydraminos or polyhydraminos and alteration in the MCA/UA (middle cerebral artery/umbilical artery) flow. When there is intrauterine growth retardation (IUGR) the MCA becomes low resistance and UA becomes high resistance.² Presence of fetal distress or increasing bowel dilatation (indicating volvulus) is an indication for early delivery. Associated bowel atresias are not uncommon.

Baby should be delivered at a tertiary care center. The role of caesarean section is debatable. If delivered elsewhere, bowel should be decompressed by NG tube,

* Professor and HOD,
Department of Pediatric Surgery,
PSG Hospital,
Coimbatore.

started on IV fluids and antibiotics. The extruded bowel should be covered by a sterile plastic sheet and nursed in lateral position during transfer in order to prevent ischemia to bowel due to strangulation. The baby should be taken up for surgery as early as possible. Bianchi's repair can be done wherein the baby is sedated and reduction of the bowel can be done in the newborn intensive care unit and the defect closed by strapping the cord across the defect.³

Bowel is edematous due to exposure to the amniotic fluid and will need TPN due to prolonged ileus. Associated bowel atresias have to be noted and repair done. In the presence of edematous bowel a silo can be created and delayed closure can be performed.

Exomphalos is the herniation of the bowel into the base of the umbilical cord. It is covered by a membrane comprising of peritoneum, Wharton's jelly and amnion. It can be an isolated one or present as a part of syndrome such as Trisomy 13, Trisomy 18, Cantrell's pentalogy, Beckwith Wiedemann syndrome, Turner's syndrome and triploidy. It is classified into major or minor depending on the size of the defect (<5cm is minor and > 5cm is major).



Fig.2. Exomphalos - antenatal ultrasound - bowel lying outside the abdominal wall covered by a membrane

Antenatal diagnosis: The persistence of the fetal herniation beyond 12 weeks is diagnostic of exomphalos (Fig.2). The cord inserts at the summit of the mass and is covered by a membrane (Fig.3). The contents of the omphalocele should be noted. The size of the defect, the presence of liver and associated defects are prognostic indicators. It can be detected by ultrasound from the twelfth week of life. There may be polyhydramnios. Elevated Maternal serum AFP (MSAFP) may be present and the median value for MSAFP¹ is 4.18 MoM. Acetylcholinesterase may also be increased.⁴



Fig.3. Exomphalos minor with membrane covering the bowel

Management: The diagnosis of exomphalos or increased level of MSAFP warrants further investigation. A detailed ultrasound including fetal ECHO should be done and screening should be done for other structural anomalies (cardiac in 40%) and chromosomal anomalies such as Trisomy 13, 18 and Triploidy and 45XO.⁵ Mortality is high in the presence of structural and chromosomal anomalies. Small size and presence of only small bowel should elicit a strong suspicion of chromosomal abnormality. Amniocentesis should be done to rule out chromosomal abnormality. Good prognosis is present if there is no other abnormality. Large omphaloceles have a prolonged post operative period due to difficulty in closure of the large defect.

Delivery should be done at a tertiary care center. Indication for elective caesarean section is controversial and can be done after explaining the prognosis. Large exomphalos with liver is a risk for fetal liver damage during normal delivery.

Post-delivery management: After delivery, the neonate has to be screened for other anomalies. Baby should be kept nil by mouth, started on IV fluids, injection Vitamin K and antibiotics. Nasogastric tube should be inserted for decompressing the stomach. X-ray abdomen should be taken to rule out associated diaphragmatic defects. Blood should be cross matched. If diagnosed after birth and has to be transported, then the exomphalos should be covered by sterile non-sticking gauze or cling wrap to prevent adherence to the sac. The sac should be supported to prevent bowel compromise and may have to be placed in a lateral position. If the baby is non-syndromic with a small defect, primary closure can be performed. If primary closure can be achieved, baby may need post operative ventilation if the intra abdominal pressure is high. The presence of a large defect, herniation of liver and associated anomalies may be an indication for conservative

management. This can be achieved either by a silo and then closure or by induction epithelization using silver sulphadiazine. Conservative management is followed by prolonged total parenteral nutrition (TPN) and prolonged hospital stay. This has to be followed by surgical repair. Though uncommon, presence of associated bowel atresia should be looked for at the time of repair.

Pentology of Cantrell

The prognosis depends on the severity but is usually fatal if diagnosed by the antenatal ultrasound⁶(Fig.4).



Fig.4. Cantrell's pentology

Bladder exstrophy: A defect of the lower abdominal wall and anterior wall of the bladder results in exstrophy of the bladder with epispadias. The bladder is opened out in the suprapubic region and there is epispadias with pubic diastasis. In the antenatal ultrasound, the absence of bladder even after 10-15 minutes (rule out other causes of anuria) should elicit a suspicion of this anomaly. The presence of a soft tissue mass on the lower anterior abdominal wall with low insertion of umbilical cord and umbilical arteries on either side of abdominal wall mass is diagnostic. The MSAFP may be elevated.

Management: Amniocentesis and counseling should be done. Fetal karyotyping should be done for Trisomy 13 and 21. If diagnosed after delivery, the newborn should be transferred covering a sterile dressing over the exposed mucosa. Primary closure within 48 hours is ideal as the presence of maternal hormone relaxin prevents pubic diastasis. In the presence of associated anomalies or other co-morbidity surgery can be done at a later date.

Cloacal exstrophy or vesico-intestinal fissure: When the exstrophy of bowel occurs along with bladder exstrophy. It is diagnosed by the presence of bowel mass between hemi-bladder with an exomphalos on the top.

Associated anomalies are common. If the cloacal membrane is intact, it may appear as a cystic pelvic mass.

Management: After counseling the parents, termination may be offered if diagnosed earlier than 20 weeks. After delivery baby should be transferred as surgery will be required in the immediate postnatal period. A sterile dressing should be applied and baby should be started on NG aspiration and IV fluids. Closure of the bowel and creation of colostomy is done. The bladder exstrophy is closed at a later date. Multiple surgeries have to be performed and the child will need bowel and bladder management. The presence of cloacal exstrophy in a male is a surgical challenge and there are few reports of conversion to female gender due to poor results.

OEIS syndrome (Omphalocele, exstrophy, imperforate anus and spinal deformities): Prenatal counseling and termination may be offered as complex reconstructive surgery is required.⁷

Body stalk anomaly should be suspected when there is a large thoraco-abdominal defect with absent umbilical cord and spinal and bony defects. (Figs.5,6) This can be easily identified. The vessels run directly from the placenta to the fetus and the mass of bowel and liver can be seen anterior or lateral to the abdominal wall.⁸ Severe kypho-scoliosis is a typical presentation. Severe oligohydramnios can prevent adequate visualization and fetal MRI should be done. MSAFP will be elevated. It can be diagnosed in the first trimester visualization and fetal MRI should be done. The MSAFP will be elevated. It can be diagnosed in the first trimester and termination can be offered for this lethal defect. There are no known chromosomal abnormalities.

Principles in antenatal imaging of bowel atresia

Abdominal circumference is one of the important



Fig.5. U/S showing body stalk anomaly



Fig.6. Fetus showing body stalk anomaly - Absent umbilical cord with abdominal wall defect

criteria for diagnosing IUGR. Stomach is seen by 11 weeks and the abdominal wall should be seen on either side of the cord. The kidneys and bladder should be noted. Small bowel is normally seen in the 2nd and third trimester and the normal size is less than 7 mm. Colon is seen in the third trimester and the normal size is less than 18 mm.

Bowel echogenecity: Should be diagnosed only with a 5 MHz transducer as higher resolution gives rise to false positive results. Normal bowel is more echogenic than liver and less than bone, which is graded as follows:

Grade 0 – Less than liver

Grade I = Normal More than liver and less than bone

Grade II = As that of bone

Grade III = More than bone

Grade II and III are abnormal. This can be focal or diffuse. Focal is more likely to be pathological.

Grade II and III should be investigated. The fetus should be karyotyped for trisomy 21, screening should be done for cystic fibrosis, cytomegalovirus infection should be ruled out and serial ultrasound should be done to watch for IUGR.

Atresia

Esophageal atresia (EA) with distal tracheo-esophageal fistula (TEF) is the most common type of EA with TEF. Esophageal atresia may be sporadic or may be associated with syndromes such as Trisomy 13, 18 and can recur in families. Associated anomalies can occur in 50-80%. The presence of small stomach, polyhydramnios intra-uterine growth retardation and pouch sign (filling of

upper esophagus during swallowing) is diagnostic in an antenatal ultrasound. It may be a part of VACTERL association and detailed ultrasound screening has to be done including fetal ECHO.

Management: The baby should be delivered in a tertiary care centre. Presence of drooling of saliva with respiratory distress is suggestive and can be diagnosed by passing a 10Fr feeding tube through the oral cavity. X-ray of the chest and abdomen AP and lateral should be taken. Suctioning should be done every fifteen minutes (with Replogle tube if available) to prevent aspiration. The presence of gas in the abdomen is diagnostic of distal fistula. Other associated atresia such as duodenal atresia should be ruled out. baby should be placed in a head up position to prevent reflux of gastric contents into the trachea in the presence of a fistula. The baby should be screened for associated cardiac and renal anomalies by ECHO and renal ultrasound. In the presence of esophageal atresia with duodenal atresia, Trisomy 21 should be ruled out by karyotyping. The presence of upper pouch fistula can be ruled out by either bronchoscopy or a small amount of water soluble contrast instilled into the upper pouch fistula.

Intubation should be done only in the presence of aspiration pneumonitis or if ventilation is essential and the tube should be positioned beyond the fistula. Right thoracotomy, division of fistula and esophago-esophageal anastomosis should be performed. In the presence of multiple anomalies or the gap is too long to be bridged, staged procedure can be performed. Elective ventilation with the head flexed should be done post operatively. Post operatively oral suction should be done as it takes a few days for the upper pouch to function and propel the saliva distally. The baby can be fed through the feeding tube and oral contrast is done on the fifth post operative day. If there is no leak, the feeding tube can be removed and the baby can be fed orally.

Duodenal atresia

Failure of recanalization of duodenum can give rise to duodenal atresia (complete obstruction) or duodenal stenosis (incomplete obstruction). This can be seen as early as the twelfth week but usually diagnosed only by the seventh month. More than 50% have associated congenital anomalies and there is a 30% association with Trisomy 21.⁹ It can be diagnosed by double bubble appearance and the continuity between the stomach and duodenum should be ascertained by antenatal ultrasound. Maternal polyhydramnios may be present and 50% may be associated with preterm labor and low birth weight.

After delivery, the baby has to be stabilized before surgery. Nasogastric aspiration has to be done and the aspirate is bilious due to obstruction at the level of ampulla. It may be non-bilious if the obstruction is above the ampulla. In the presence of duodenal obstruction, it is imperative to rule out malrotation either by a contrast study or by ultrasound. The orientation of the mesenteric vessels is abnormal with 'whirlpool sign' in the presence of volvulus with malrotation. Laparotomy and duodeno-duodenostomy is done. If malrotation is suspected early laparotomy has to be done. There may be prolonged ileus after surgery and total parenteral nutrition has to be started. Long term prognosis is good.

Jejunal and ileal atresia

This occurs due to vascular compromise or may be a part of cystic fibrosis. Normal bowel is less than seven mm in diameter. Presence of dilatation with hyper peristalsis is suggestive of jejunal/ileal atresia. Fetal MRI may be more diagnostic of atresia.¹⁰ The prognostic factors are the presence of ascites, peritoneal calcification and pseudo cyst. Long term outcome depends on the presence of short gut and association with cystic fibrosis. Observation should be done antenatally for polyhydramnios, intra uterine growth retardation. Fetal ascites or increasing dilatation may be indication for early delivery. A genetic basis has been established for type III (b) and type IV of atresia and cystic fibrosis. Associated anomalies are rare.

After delivery, baby should be stabilized prior to surgery. A rectal wash may reveal a meconium or mucus plug. Contrast enema will show an unused colon. Laparotomy, resection and anastomosis is the treatment of choice. Early surgery has to be done in the presence of ascites or abdominal distension as it is a sign of complicated atresia. TPN has to be given as there will be prolonged ileus. Type III (b) and IV may be associated with short bowel and will need long term follow up.

Meconium peritonitis / pseudocyst

This usually occurs with cystic fibrosis but may occur when there is in-utero vascular accident followed by atresia and in-utero perforation. The presence of ascites, calcifications and dilated bowel is diagnostic of meconium peritonitis. Cystic fibrosis should be ruled out.

A diagnosis of volvulus should be done when there is a dilated non-peristaltic bowel and early delivery may have to be done. This may be a cause for fetal demise.

Management: Counseling should be done regarding the

requirement of surgery in the immediate post-natal period and should be delivered in a tertiary care center. The mother should be observed for polyhydramnios. Rectal wash should be done followed by a contrast enema. Filling of colon with filling defects and reflux of contrast into the small bowel is diagnostic and may be therapeutic. A suspicion of complicated meconium ileus should be entertained in the presence of abdominal distension or abdominal wall edema. If there is a suspicion of complication, contrast should not be done and early surgery should be performed.

All intestinal atresias delivered elsewhere should be transported with IV fluids, NG tube and antibiotics as early surgery decreases the morbidity.

Imperforate anus

This condition is usually not detected by antenatal ultrasound. A strong suspicion should be entertained in the presence of VACTERL anomalies. The rectum size should be measured and a U or V shaped bowel in the pelvis suggests imperforate anus.

After delivery, the baby has to be screened for VACTERL anomalies. In the presence of a small speck of meconium in the perineum, anoplasty needs to be carried out. If the examination of perineum is not suggestive of low anomaly, naso-gastric aspiration should be done after 6 hours. After 24 hours a prone trans lateral film should be taken to find the position of the rectum. A colostomy will be done in the presence of a high or an intermediate anomaly.

The recto-vestibular fistula is the most common anomaly in the female and probing should be done. Simple dilatation is sufficient and then anal transposition can be done at a later date. The presence of a single opening in the female is suggestive of cloaca and urgent ultrasound has to be done as they may have associated vaginal and urethral obstruction.

All structural anomalies of the GIT are ideally delivered in a place where they can be counseled and operated as transport causes delay, hypothermia and metabolic acidosis. Proper counseling after antenatal detection of structural anomaly goes a long way in decreasing the morbidity and mortality of the condition.

Points to Remember

Abdominal wall defects:

- ***Physiological hernia occurs at the sixth post-conception week and returns by the twelfth week.***

- *Presence of bowel outside the peritoneal cavity is diagnostic*
- *In exomphalos the bowel is covered by a membrane and in gastroschisis it is free floating*
- *Chromosomal anomalies are associated with exomphalos and hence karyotyping should be done and atresias are common with gastroschisis*
- *Early surgery and primary closure whenever possible*
- *May need post op ventilation and total parenteral nutrition for ileus or short bowel*

Intestinal atresia:

- *Presence of polyhydramnios is an indication for detailed ultrasound looking for gastrointestinal atresia.*
- *Esophageal atresia and imperforate anus may be associated with VACTERL anomaly.*
- *In the presence of duodenal atresia, Trisomy 21 and malrotation should be ruled out.*
- *Prognostic factors are the presence of ascites, peritoneal calcification and pseudocyst with atresia.*

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NEWS AND NOTES

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Enquiries to:

Larry Madoff

Email: IMED@isid.org

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Dr. Ashok Rai

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RADIOLOGY

SKELETAL MATURATION IN THE PEDIATRIC AGE GROUP

***Vijayalakshmi G**
****Natarajan B**

Children grow and develop at different rates. All major characteristics of development appear to be genetically determined. Mechanical influences such as moulding by muscular activity also influence bone growth. After birth and till adolescence, before all the epiphyses are fused, increased activity augments growth in both length and girth. The reduced limb bone growth seen in paralysis, for example, poliomyelitis implies that muscle activity is necessary for proper skeletal development. Metabolic influences such as the availability of calcium, phosphorus, vitamin A, C and D, pituitary, thyroid, parathyroid, adrenal and gonadal hormones are all essential for skeletal form and dimensions. Therefore, genetic, metabolic and mechanical factors account for the size and proportion of the body.

Disturbances in any of these factors result in recognized pathologies; however, it is often difficult to distinguish pathological from normal variation which has quite a wide range over the whole population. E.g., between the extremes of dwarfism and gigantism much variation in height occurs. Therefore, bone age is more reliable as an indicator of development. The two methods used to assess bone age accurately are the Greulich and Pyle method and the Tanner-Whitehouse technique. The Greulich and Pyle method consists of matching the X-ray of the child's hand with the atlas that consists of hand X-rays of children of various age groups. The children are divided and grouped into three month intervals up to one year, then six monthly intervals up to 5 years and then annually up to 12 years.

The Tanner Whitehouse method is based on the concept of 'maturity indicators' since each bone develops to a reasonably constant final shape after going through a series of recognizable states. Each bone is classified into

eight or nine stages to which scores are attached. For the same stage boys and girls have different scores. There are three separate maturity scoring systems. The carpal score concerns the seven carpals. The radius, ulna and short finger bone (RUS) score defines the score for the thirteen bones comprising the radius, ulna and short finger bones (1, 3 and 5 fingers) and the TW 20 bone score combines the carpal and RUS scores. Maturity scores are plotted against chronological age from which centile standard curves have been constructed. The bone age of a given child is the age at which the 50th centile corresponds to the score of the child. Individual centres appear and grow from tiny nodules to their final size. Since it is not possible to memorize all the standards, perusal of the atlas and tables are necessary. There is an online service (boneXpert[®]) for a fee in pounds that assesses age on submission of X-rays.

There are other atlases for age estimation. The Gilsanz and Ratib Atlas is a digital compilation of ideal sex and age specific images of the development of hand bones. There is also a bone age application for usage in iphones and ipads.

Bone age determination and assessment of development status is part of medical examination for many clinical conditions. For a quick assessment pediatricians and radiologists still use the age-old method of assessing skeletal age from appearance of ossification centres. Forensic medicine specialists also rely on this. So now we will see how to assess skeletal age using this method and by making use of a limited number of specific X-rays. Further evaluation can be carried out by the other methods.

At birth an X-ray of both knees can be taken to see epiphyses (lower femoral and upper tibial) which should be present in a full term baby. This is often useful to rule out hypothyroidism. The X-ray shown in Fig. 1 is that of a three-month-old baby with hypothyroidism. The epiphyses at the knee are not seen. Both hands and wrists can be taken for children of all ages. The capitate and hamate can be present at birth but can be delayed up to 3 to 6 months. For children aged 3 years and more, both knees lateral and for 5 years and more the elbow AP and lateral are taken. Knees can be excluded in children more than 6 years or if elbow centres are developing normally. The upper femoral epiphysis can be noted for 10 months to 1 year. Accelerated skeletal

* Professor,
Department of Radiology,
ICH & HC, Chennai.

** Asst. Professor,
Department of Radiology,
ICH & HC, Chennai.

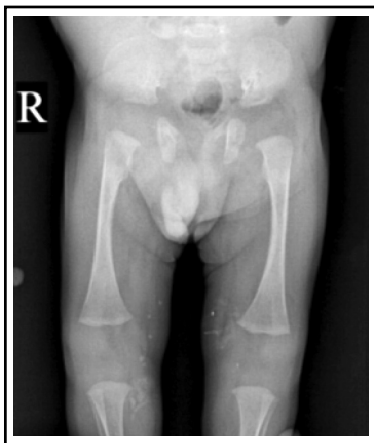


Fig.1. Hypothyroidism. The knee epiphyses have not appeared in this 3-month-old child

maturation is seen in a three month old child (Fig.2). The upper femoral epiphysis has appeared.

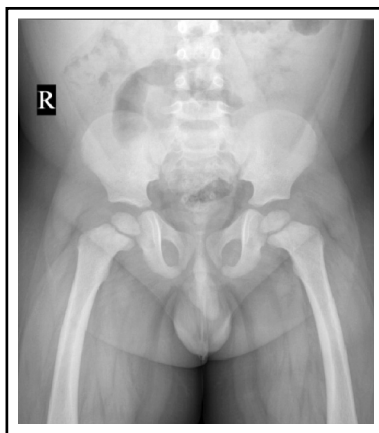


Fig.2. Advanced skeletal maturation in a 3-month-old. The upper femoral epiphysis is seen.

In the hands, all the centres of the 3rd and 4th fingers are present by the age of 2 years 3 months. The 5th middle phalanx and the proximal phalanx of the 2nd finger can appear at the same time but the other phalanges can be delayed up to 3 years 9 months with a wide range that makes it unsuitable for practical use. However the values seen in children coming to ICH & HC, Chennai, are close to the Greulich and Pyle atlas. The 1st metacarpal shows great constancy and can be used as a marker for 2 years 6 month to 3 years, though it can appear by the age of 2 years in girls. The 2nd metacarpal appears a little earlier than the other metacarpals (1 year 9 months)

We have found that the patella is a useful indicator for 4 years. Variability is minimal and there is no difference between boys and girls. It bridges the gap between hand and elbow centres.

The distal radius can be timed to one and half to two years. The X-ray shown in Fig.3 is the same 3 month old child as in Fig.2. The distal radius centre has appeared. The distal ulna and ulnar styloid show a wide range of appearance and need not be used in routine practice. The radial head is timed to 6 to 7 years and the medial epicondyle at 8 years. The olecranon is seen at 10 to 11 years though it can sometimes appear by 8 years 6 months. The lateral epicondyle earlier seen at 14 (study in ICH 1990-95) is nowadays seen by 11 years 6 months (study in ICH 2005-10) due to advanced puberty.

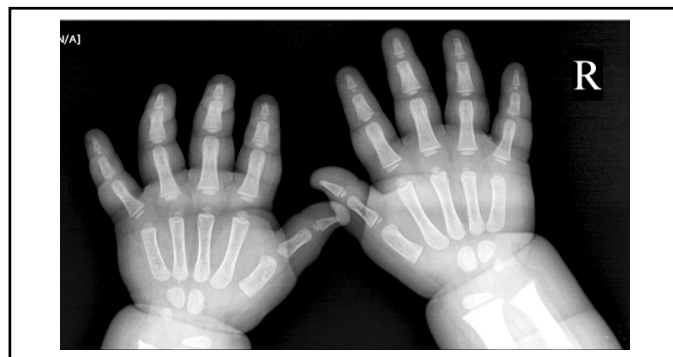


Fig.3. Same child as in Fig 2. The distal radius (1y 6 m) is seen.

The carpal bones show such great variation that they are eliminated from age estimation, but the pisiform is quite constant at 10 years 6 months for girls and a year later for boys.

For older children the triradiate cartilage which fuses by 15 years and the the iliac crest which appears at 16 years and fuses by 19 can be used.

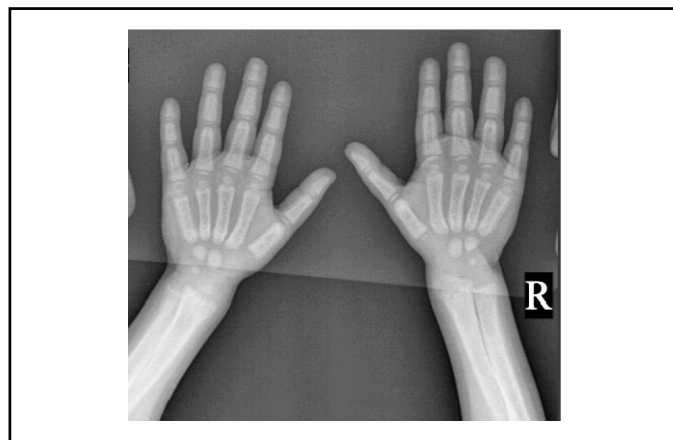


Fig.4. Renal rickets. Features of rickets are seen with a delayed bone age of 2 years

The above facts can be used to assess bone age in the evaluation of any child with growth retardation, advanced or delayed puberty. Delayed skeletal maturation seen along

with widened physes is a feature of renal rickets. The X-ray shown in Fig.4 belongs to a seven year old girl in chronic renal failure. The 1st metacarpal centre is seen as a speck, just beginning to appear. Bone age is just 2

years. Normal skeletal maturation is seen in familial short stature while it is delayed in constitutional growth delay. Bone age is also used to monitor children on growth hormone or GnRH analogs.

CLIPPINGS

Topical anti-inflammatory agents for seborrhoeic dermatitis of the face or scalp

Seborrhoeic dermatitis is a chronic inflammatory skin disorder affecting primarily the skin of the scalp, face, chest, and intertriginous areas, causing scaling and redness of the skin. Current treatment options include antifungal, anti-inflammatory, and keratolytic agents, as well as phototherapy.

Objectives was to assess the effects of topical pharmacological interventions with established anti-inflammatory action for seborrhoeic dermatitis occurring in adolescents and adults.

Selection criteria: We included RCTs in adults or adolescents (> 16 years) with diagnosed seborrhoeic dermatitis of the scalp or face, comparing topical anti-inflammatory treatments (steroids, calcineurin inhibitors, and lithium salts) with other treatments.

Authors' conclusions: Topical steroids are an effective treatment for seborrhoeic dermatitis of the face and scalp in adolescents and adults, with no differences between mild and strong steroids in the short-term. There is some evidence of the benefit of topical calcineurin inhibitor or lithium salt treatment. Treatment with azoles seems as effective as steroids concerning short-term total clearance, but in other outcomes, strong steroids were more effective. Calcineurin inhibitor and azole treatment appeared comparable. Lithium salts were more effective than azoles in producing total clearance.

Steroids are similarly effective to calcineurin inhibitors but with less adverse effects. Most of the included studies were small and short, lasting four weeks or less. Future trials should be appropriately blinded; include more than 200 to 300 participants; and compare steroids to calcineurin inhibitors or lithium salts, and calcineurin inhibitors to azoles or lithium salts. The follow-up time should be at least one year, and quality of life should be addressed. There is also a need for the development of well-validated outcome measures.

Kastarinen H, Oksanen T, Okokon EO, Kiviniemi VV, Airola K, Jyrkkä J, Oravilahti T, Rannanheimo PK, Verbeek JH. Topical anti-inflammatory agents for seborrhoeic dermatitis of the face or scalp. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD009446. DOI: 10.1002/14651858.CD009446.pub2. Assessed as up to date: 18 September 2013.

NEWS AND NOTES

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Enquiries to: Dr. Rajesh Maaheshwari (Jeswani)

Email: raj_masoom001@yahoo.com

CASE STUDY

RECTUS SHEATH HEMATOMA PRESENTING AS ACUTE ABDOMEN - A CASE REPORT

***Anurag S**
****Minhas A**
****Vidit G**
*****Anjani K**

Abstract: Rectus sheath hematoma is a rare entity in hemophilia. It is an uncommon cause of pain abdomen. It can occur either spontaneously or after trauma. It may be misdiagnosed as acute abdomen, inflammatory disease or any tumour of the abdomen. We report a case of rectus sheath hematoma in a 5 yr old hemophilic male presenting with abdominal pain.

Keywords: Hemophilia A, Rectus sheath hematoma, Factor VIII therapy.

Acute abdominal pain in a patient with hemophilia may have many origins, such as gastrointestinal tract bleeding, hematomas (spontaneous or trauma induced), pseudotumors, iliopsoas bleed or retroperitoneal bleeding. Rectus sheath hematoma is an uncommon and often clinically misdiagnosed cause of abdominal pain. It is the result of bleeding into the rectus sheath from damage to the superior or inferior epigastric arteries or their branches or from a direct tear of the rectus muscle.¹ While usually a self-limiting entity, rectus sheath hematoma can cause hypovolemic shock following sufficient expansion, with associated mortality.

The following report highlights a case of rectus sheath hematoma in a hemophilia child who presented with acute abdomen.

Case report

A 5-year-old male child presented with complaint of acute onset pain abdomen of two days' duration after returning from school. The pain was severe in nature, localized just below umbilicus, non-radiating and worsened with activity. The parents did not give any clear history of trauma. Also, there was no history of vomiting, constipation, excessive coughing or strenuous exercise.

On examination, the child appeared pale and there was a palpable abdominal lump. The lump was approximately 3-4 cm in diameter, located just below the umbilicus, had a boggy feeling and the margins were not well circumscribed. It became more prominent when the child was made to get up from lying down position and this gave a suspicion of pathology in the abdominal wall. Investigations revealed normocytic normochromic anemia with hemoglobin of 5.8gm/dL, normal total leucocyte count and normal platelet count (1.8 lacs/cmm). Coagulation profile showed deranged APTT (66.24secs) with a normal prothrombin time. Bleeding time was normal but clotting time was deranged.

On further probing, we found a family history of hemophilia A in a maternal uncle. So, Factor VIII levels of the child were ordered and they were found to be marginally reduced (47%). This could be the reason that the child remained undiagnosed till 5 years of age and never had any complication of hemophilia like recurrent bleeding episodes or arthropathy. USG abdomen revealed presence of infraumbilical hematoma of $1.7 \times 0.93 \times 1.65$ cm size and 1.44 ml volume in anterior abdominal wall (Fig.1).



Fig.1. Hematoma rectus sheath

* Professor,
** Senior Registrar
*** Registrar,
Department of Pediatrics,
Umaid Hospital,
Regional Institute for Mother and Child Health,
Dr.S.N. Medical College,
Jodhpur, Rajasthan.

The child was given bed rest, intravenous fluids, Factor VIII therapy, blood transfusion and oral analgesics. He responded well to the above management and was discharged after 7 days. On follow-up after 15 days, the size of hematoma reduced to $1.53 \times 0.62 \times 0.66$ cm and volume reduced to 0.33 ml (Fig.2).

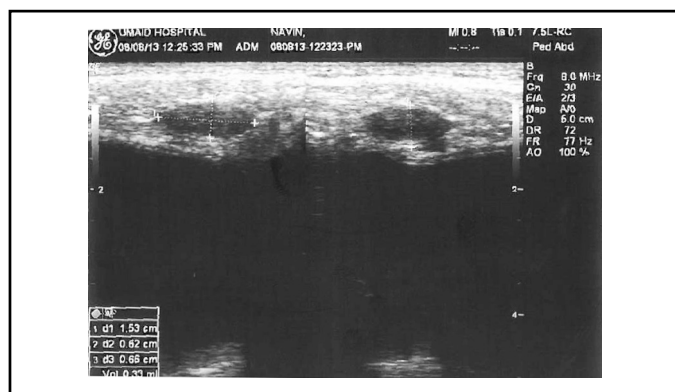


Fig.2 Resolving hematoma

Discussion

Rectus sheath hematoma is a well known but rare cause of pain abdomen. Studies have shown that bleeding rarely occurs spontaneously with mild hemophilia. More than 90% cases of bleeding in mild hemophiliacs, in different studies, have been shown to occur following trauma.² In such cases, soft tissue bleeding is more common than intra-articular bleeds. In our case, although the parents of the child were not giving a clear history of trauma, it is quite possible that child might have sustained an injury while playing in the school. This can be attributed to the fact that the child started complaining of an excruciating abdominal pain just after returning from school.

Rectus sheath hematoma commonly occurs in the lower quadrants of the abdominal wall and almost never crosses the midline.^{3,4,5} Hematoma below the linea semicircularis causes an indirect irritation of peritoneum due to weak posterior rectus sheath in this region leading to misdiagnoses as acute abdomen.^{3,4} The usual signs and symptoms on presentation are crampy abdominal pain, palpable abdominal lump, anaemia, nausea, vomiting, fever, tachycardia, peritoneal irritation and abdominal distension.⁶ It can be differentiated from intra-abdominal pathologies with the help of Carnett sign and Fothergill sign.⁴ Fothergill sign is positive when the rectus sheath hematoma becomes palpable when the patient tenses his rectus muscle by touching his chest with his chin. Carnett sign is exacerbation of pain and tenderness over the hematoma, due to contraction of rectus muscle, when patient is made to sit halfway up in a supine position. Both signs were positive in our child.

USG, CT and MRI are widely used diagnostic modalities. Ultrasound is usually the initial investigation. It has a high sensitivity rate and is time and cost effective. Classical ultrasonographic appearances range from sonolucent (early stage) to sonodense (late stage) appearance with time from initial injury. Computed Tomography (CT) is considered a more sensitive investigation and is useful in cases of inconclusive ultrasound. Magnetic Resonance Imaging is less commonly employed but is as sensitive as CT.⁵ Conservative treatment method should be preferred in hemodynamically stable patients and those with non-expanding hematoma.⁷ In our case, conservative treatment was sufficient. Factor VIII therapy was given to manage the underlying cause. In cases where conservative treatment fails, surgical approach can be preferred but mortality is high.

To conclude, hemophilia should be considered as a potential differential while investigating a case of intra abdominal bleed/hematoma. Rectus sheath hematoma in hemophilia is a rare entity and very few cases have been reported in literature. Early diagnosis is helpful in successful conservative management and in avoiding unnecessary surgical interventions and its complications.

Points to Remember

- *Rectus sheath hematoma should be thought of and ruled out in a hemophilia child presenting with acute abdominal pain.*

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LETTER TO THE EDITOR

With reference to the article on the WHO Multicentre Growth Charts in the journal.¹ The application of WHO growth standards for the under-5 age group and growth references for 5-18 years has been discussed. As we know the construction of growth references for the age group of 5-18 years has been derived from the NCHS 1977 data using the BCPE (Box-Cox power exponential) method and the new WHO 2007 references are primarily statistical adjustments of it, and no new data has been added. This was made so that the curves fitted smoothly with the 2006 MGRS under 5 centiles.²

However, it is important to understand that the WHO charts depict growth of American children in 1977 and are probably not appropriate for use in a developing country like India. It is important that when references and not standards are used, up to date country specific data is used. Hence it would be more logical and appropriate to use the most recently described 2009 Indian references by Khadilkar, et al.³ They best represent the current growth trend prevailing in our country. If we use WHO 2007 references we will over diagnosing stunting especially during pubertal years as the pubertal growth spurt is attenuated in Indian children. The prescriptive 2012 BMI charts by the same author use the Asian cut-offs of 23 and 28 for diagnosing overweight and obesity in Indian children, which is again probably more relevant to use.⁴ Thus, the use of contemporary nationally representative growth charts is the need of the hour.

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Dr. Meghna Chawla

Assistant Professor, Pediatrics

SKN Medical College and General Hospital

Pune.

REPLY

The views expressed by the author in the letter are sometimes expressed, and are not unreasonable. However, if India is to have its statistics available for international comparison, a unified international standard is recommended.

Dr. Anuradha Bose

Professor of Pediatrics

Christian Medical College

Vellore.

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