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Editorial

Knowledge and science is ever expanding. There has to be enhancement and upgrading of knowledge and therapy. As health of the fetus and neonate is interlinked with health of mother, the idea of journal on 'Maternal–Fetal and Neonatal Medicine' is conceptualized. It is my proud Privilege to release inaugural issue of the journal.

The term Eclampsia is derived from a Greek word, which means 'flashes of light'. Pre-eclampsia has been called the disease of theories, that begins in placenta and ends at maternal endothelium**. Dr. Gadappa** has described Eclampsia, clinical manifestation of severe pre-eclampsia, with Symptomatology. Author has highlighted clinical implications of Eclampsia with focus on monitoring and interventions of this dreaded clinical entity. William Hunter expressed his fear:

" There are but two things that have much effect on me at labour: Haemorrhage and convulsions."

Successful motherhood is the unique achievement in a woman's life. Though it is a natural phenomena, yet the way to achieve it may endanger the life of both mother as well as fetus. Focus of obstetrical care has changed from treating maternal and fetal diseases to predicting and preventing them. In preconceptional counseling for chronic medical disorders, I explore the opportunities to treat and control medical disorders before conception. This ensures that woman enters pregnancy with an optimum state of health which would be safe for herself and fetus.

Millennium Development Goal 4 [MDG4] is unlikely to be met, partly because of slow progress towards reducing Neonatal Mortality**. Dr. Omprakash Shukla** has emphasized that neonatal infections represent an important Cause of morbidity and mortality in neonatal period. Lethargy, poor feeding, fever or hypothermia are the most commonly observed features of Neonatal infections.

The journey through the birth canal is the first, but the most hazardous journey the individual takes. It is the responsibility of the obstetrician to make the journey safe. **Dr. Jayendra Gohil** captures Birth Asphyxia as a huge global problem with fresh stillbirth, neonatal death and longterm neuro development problems as its main serious outcomes. Anticipation is the key in preventing Birth Asphyxia. It is important to identify fetuses at risk of asphyxia and to closely monitor such high risk pregnancies. Appropriate interventions and prompt resuscitation will save many lives.

Childhood coughing is a common problem that can cause anxiety in parents. There are important differences from adult cough in terms of likely causes and management protocol. **Dr.Gautam Ghosh** has compiled clues in history, in case of chronic cough. Potentially serious lung disorders with chronic coughing are highlighted.

Encephalocele is one of the commonest neural tube defects**. Dr. (Mrs) Anjali Chitale,** in her case report on Encephalocele, shares her experiences at institution in rural set up with prevalence of patients from tribal region . Both maternal Diabetes Mellitus and obesity have been associated

with increase risk of Neural Tube Defects possibly due to sustained state of Hyperglycemia and/or Hyperinsulinemia. Additional studies should be done to explore the etiological heterogenecity of encephalocele using better marker of folate status and wide range of risk factors.

We are committed to disseminate recent information in the fast progressive world of obstetrics, Fetal medicine and Neonatology. Our contributors have enabled us to accomplish this. Contribution and comments from esteem readers will help in improvisation of the Journal.

I conclude the editorial, with Swami Vivekanand's inspiring message:

"Arise, Awake, stop not until your goal is achieved".

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Review Article

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Eclampsia: Preventable Obstetrical Tragedy

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Abstract

Eclampsia is the prominent cause of maternal and perinatal mortality and morbidity. Prevalence of Hypertensive disorders is more in developing countries in contrast to developed countries. Eclampsia, clinical manifestation of severe preeclampsia is discussed with symptomatology. Differential diagnosis of convulsions in pregnancy is reviewed. MgSO4 & Labetalol these two drugs are the backbone in the treatment of eclampsia and ramin boon in desguise. Various protocols for management of Eclampsia are evaluated

Keywords: Maternal mortality; Eclampsia; Convulsions; MGSO4; Edema.

Introduction

Hypertensive disorders are the most common medical complications of pregnancy, with reported incidence between 5% and 10%. [1] The incidence varies from country to country and even region to region of the same country. In contrast to developed countries, prevalence is more in developing countries particularly rural areas contributing significant cause for maternal mortality. Eclampsia, placental abruption, ascitis, hepatic infarction, hepatic rupture, intraabdominal bleeding, pulmonary oedema and acute renal failure are all severe clinical manifestations associated with preeclampsia that can result in maternal death. In the fifth century, Hippocrates noted that headaches, convulsions, and drowsiness were ominous signs associated with pregnancy. In 1619, Varandaeus coined the term *eclampsia* in a treatise on gynaecology.

In this article, we highlight clinical implications of Eclampsia. We focus on monitoring and interventions of this dreaded clinical entity.

Eclampsia, which is considered a complication of severe preeclampsia, is commonly defined as new onset of grand mal seizure activity and/or unexplained coma during pregnancy or postpartum in a woman with signs or symptoms of preeclampsia.

It typically occurs during or after the 20th week of gestation or in the postpartum period. However women in whom eclampsia develops exhibit a wide spectrum of signs ranging from severe hypertension, severe proteinuria and generalized edema to absent or minimal hypertension, no proteinuria and no edema.[2] Most cases of eclampsia present in the third trimester of pregnancy, with about 80% of eclamptic seizures occurring intrapartum or within the first 48 hours following delivery. Rare cases have been reported before 20 weeks' gestation or as late as 23days postpartum[3]. Although the incidence of eclampsia in the developed world has fallen steadily and now less than 1:3000 pregnancies[4],the incidence in some developing countries is as high as 1:1000 pregnancies.[5] Early admission and investigations, use of MgSO4,and timely delivery in women with severe hypertension have been shown to reduce the incidence of eclampsia.[6] The "eclampsia box" recommended by the eclampsia trial collaborative group could be of great

	Douglas & Redman (n=325)(%)	Katz *et al* (n=53)(%)	Chames *et al* (n=89)(%)
Headache	50	64	70
Visual changes	19	32	30
Rt.upper quadrant/epigastric pain	19	Not reported	12
At least one	59	Not reported	75

From Sibai BM : Diagnosis, differential diagnosis & management of eclampsia. Obstet Gynecol 105:402,2005.

advantage to under–resourced countries.[7] This includes MgSO4, it's antidote (Calcium gluconate) and necessary paraphernalia to administer the anticonvulsant.

Pathophysiology

The pathophysiology continues to be the subject of extensive investigation and speculation. Several theories and pathologic mechanisms have been implicated as possible etiologic factors but none of these has been proved conclusively. It is not clear whether the pathologic features in eclampsia are a cause or an effect of the convulsions.[2]

Diagnosis

The diagnosis of eclampsia is secure in the presence of generalized oedema, hypertension, proteinuria, and convulsions. However, women in whom eclampsia develops exhibit a wide spectrum of signs ranging from severe hypertension, severe proteinuria, and generalized oedema to absent or minimal hypertension, no proteinuria, and no edema.[2]
Symptoms of women with eclampsia

Several clinical symptoms are potentially helpful in establishing the diagnosis of eclampsia. These include headaches, blurred vision, photophobia, epigastric pain. In Author's experience (a series of study of Eclampsia patient, n=201, in 2004-2006, Headache (40%) was the most common warning symptom followed by nausea (25%), epigastric pain (20%).

Hypertension is considered the hallmark for the diagnosis of eclampsia. Hypertension can be severe in 20%-54% of cases or mild in 30-60% of cases. However, in 16% of cases hypertension may be absent. In addition, severe hypertension is more common in patients who develop antepartum eclampsia (58%) and in those who develop eclampsia at 32 weeks gestation or later (71%). Moreover, hypertension is absent in only 10% of women who develop eclampsia at or before 32 weeks of gestation.[3] The diagnosis of eclampsia is usually associated with proteinuria (at least 1+on dipstick). In a series of 399 women with eclampsia, subsequent proteinuria(>3+on diasick) was present in only 48% of the cases whereas proteinuria was absent in 14% of the cases. Several clinical signs and symptoms are potentially helpful in establishing the diagnosis of eclampsia.[3]

Although most cases of postpartum eclampsia occur within the first 48 hours, some cases can develop beyond 48 hours postpartum and have been reported as late as 23 days postpartum. In later cases , an extensive neurological evaluation may be needed to rule out the presence of other cerebral pathology. Cerebral imaging is not necessary for the diagnosis and management of most women with eclampsia. Cerebral

Time of Onset of Eclampsia in Relation to Delivery

	Douglas & Redman (n=383)(%)	Knight (n=214) (%)	Katz (n=53) (%)	Tufnell (n=82) (%)	Matter & Sibai (n=399) (%)	Chmes *et al* (n=89%)
Antepartum	38	96	53	45	53	67*
Intrapartum	18	41	36	12	19	-
Postpartum	4	75	11	26	28	33
<48hr	39		5	24	11	
>48hr	5		6	2	17	7
						26

*Includes antepartum and intrapartum cases

imaging is indicated for patients with focal neurological deficits or prolonged coma. In these patients, haemorrhage and other serious abnormalities requiring specific pharmacological treatment or surgery must be excluded. Cerebral imaging may also be helpful in patients who have an atypical presentation for eclampsia. Advances in MRI as well as cerebral vascular Doppler velocimetry, may aid our understanding regarding the pathogenesis and improving long-term outcome of this condition. In summary, cerebral imaging findings in eclampsia are similar to those found in patients with hypertensive encephalopathy. The classical findings are referred to as posterior reversible encephalopathy syndrome (PRES). Although patients with severe preeclampsia are at greater risk for seizures, 25% of patients have symptoms consistent with mild preeclampsia before the seizures.

Differential Diagnosis

The presenting symptoms, clinical findings and many of the laboratory findings may overlap with a number of medical and surgical conditions. Most common cause of convulsions developing in association with hypertension or proteinuria during pregnancy or immediately postpartum is eclampsia. An effort should be made to identify an accurate diagnosis given that management strategies may differ among these conditions.

Hypertensive encephalopathy, seizuredisorder, hypoglycemia, hyponatremia, TTP, Amniotic fluid embolism, CVAs, Haemorrhage, ruptured aneurism ,Arterial embolism, venous thrombosis, hypoxic ischemic encephalopathy, Agiomas, cerebral malaria, organophosphorus poisoning.

Maternal and perinatal Outcome could be attributed to 3 delays (delay in transport, delay in seeking t/t and delay in diagnosis).In addition, lack of resources and intensive care facilities may be responsible. Eclampsia is associated with a slightly increased risk for maternal death in developed countries (0% to 8%)[2],but the maternal mortality rate may be as high as 14% in developing countries.

Pregnancies complicated by eclampsia are also associated with increased rates of maternal morbidities such as abruption palcentae (7-10%), DIC (7-11%), Pulmonary edema (3-5%), ARF (5-9%), Aspiration pneumonia (2-3%) and cardiopulmonary arrest (2-5%). Rarely ARDS and cerebral haemorrhage may occur.[2] It is important to note that maternal complications are greatest among women who develop antepartum eclampsia, particularly remote from term.

There is high perinatal mortality in eclamptic pregnancies. The reported perinatal death rate is 5.6% - 11.8% high rates of perinatal mortality[2] are attributed to prematurity, abruption placentae and IUGR.

Management of Eclampsia

Eclamptic convulsions are life-threatening emergencies and require the proper treatment to decrease maternal morbidity and mortality. Principles of management include Control of convulsions, control of blood pressure and delivery. Delivery is the only definitive treatment for eclampsia.

Supportive Care

Emergency medical services personnel should secure an intravenous (IV) line with a large-bore catheter, along with cardiac monitoring, oxygen supplimentation and transportion of the patient in the left lateral decubitus position keeping airway petent.

After the seizure has ended, a 16- to 18-gauge IV line should be established for drawing specimens and administering fluids and medications. (Fluid management is critical in patients with eclampsia.) IV fluids should be limited to isotonic solutions to replace urine output plus about 700 mL/d to replace insensible losses.

Pharmacologic Considerations for Control and Prevention of Subsequent Convulsions

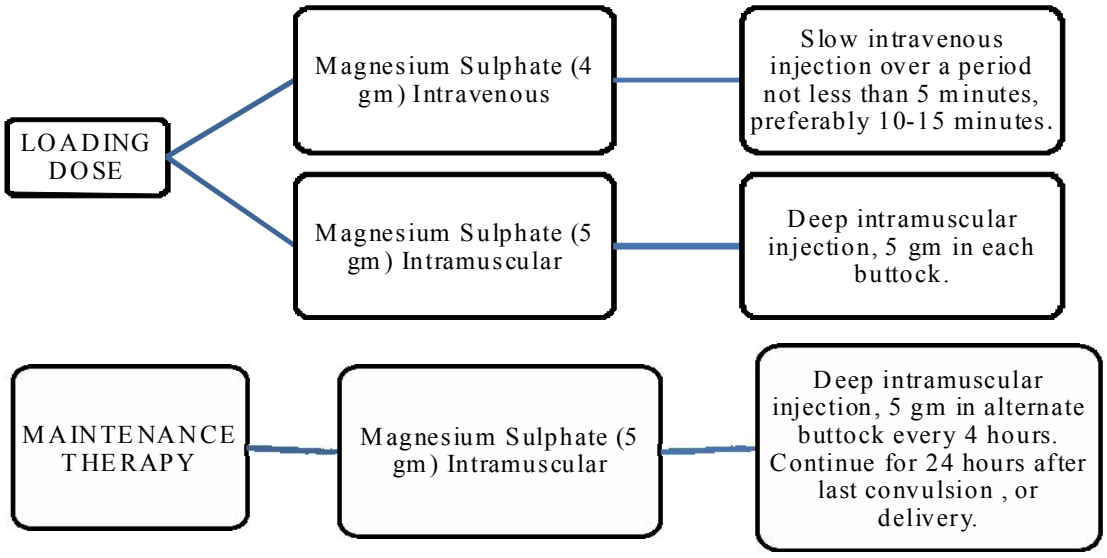
Pharmacotherapy goals are to reduce morbidity, prevent complications, and correct eclampsia. The drug of choice to treat and prevent eclampsia is Magnesium sulphate Familiarity with second-line medications phenytoin and diazepam/lorazepam is required for cases in which magnesium sulphate may be contraindicated (eg, myasthenia gravis) or ineffective.

Treatment Regimens for Magnesium Sulphate (MgSO4)

There were two separate regimens for giving MgSO4 and clinicians at each centre chose which they would use. Both regimens were based on current recommendations and reflected clinical practice in the collaborating centres. An initial intravenous loading dose was followed by 24 hours by either an I/V infusion or regular intramuscular regimen. This

Flow Chart for the Intravenous (I/V) Magnesium Sulphate Regimen

Pritchard & colleagues.



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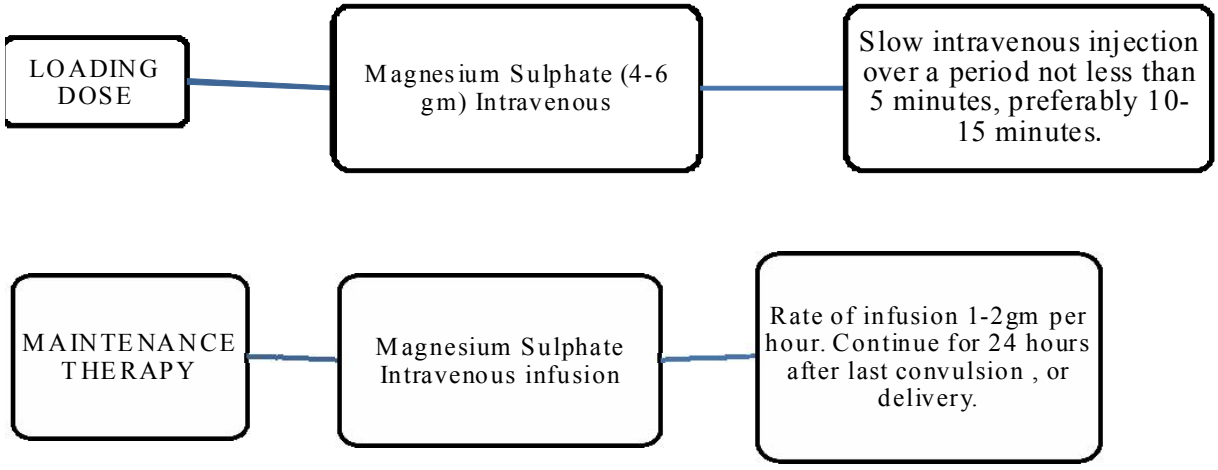

was administered as described by Pritchard & colleagues. A loading dose of 4 gm I/V (usually in 20%solution) over 5 minutes minimum, preferably 10-15 minutes was followed immediately by 5gm in a 50% solution as a deep I/M injection into the upper outer quadrant of each buttock. Maintenance therapy was a further 5 gm I/M every 4 hrs, continued for 24 hours after the last intravenous regimens. The intravenous regimen was as described by Zuspan"s. A loading dose of 4gm I/V was followed by an infusion of 1 gm/hour continued for 24 hours after the last fit. In most centres, the rate of infusion was controlled manually.

Parentral MgSO4 therapy should be continued for at least 24 hours after delivery or for at least 24 hours after the last convulsion.

Recurrent Convulsions

In both the intramuscular and intravenous regimens, if convulsion recur after 30 minutes, a further 2-4 gm was given intravenously over 5 minutes and same dose schedule can be continued. There was no evidence from the Collaborative Trial [8] of any difference between the intramuscular and intravenous regimens in their effects on recurrent convulsions. However intramuscular injections are painful and are complicated by local abscess formation in 0.5% of cases. The intravenous route is therefore preferred. It is rational and sensible for clinicians to adopt the treatment regimens for MgSO4 used in the Collaborative Eclampsia Trial.[8] This has the considerable practical and economic advantage that serum monitoring is not required. Although some authors have advocated 2 gm/h for I/V maintenance therapy, this should not be considered for routine practice until it has been adequately evaluated in comparison to intravenous regimens described here. About 10% of women with eclampsia will have an additional seizure after receiving magnesium sulfate. Another 2 g bolus of magnesium may be given in these cases. For the rare patient who continues to have seizure activity while receiving adequate magnesium therapy, seizures may be treated with sodium amobarbital, 250 mg IV over 3-5 minutes. Alternatively, lorazepam (Ativan) 4 mg IV over 2-5 minutes (may repeat in 5-15 min to maximum of 8 mg in 12 hours) or diazepam (Valium), 5-10 mg IV slowly (may be repeated every 15 min up to 30 mg) can be used per protocol for status epilepticus. However, these drugs can be associated with prolonged neonatal neurologic depression

Magnesium Toxicity and Their Management

The following guidelines were provided for management of the potential complications of MgSO4:

- *Respiratory Arrest:* Stop magnesium therapy and give 1 gm calcium gluconate I/V as antidote for magnesium toxicity along with immediate intubatation and ventilatition. Ventilation should be continued until the resumption of normal spontaneous respiration.
- *Respiratory depression:* Stop magnesium therapy, give 1 gm calcium gluconate I/V along with oxygen mask and maintain airway.
- *Absent Patellar Reflexes:* In case of respiration is normal, further doses of MgSO4 to be withheld/deferred until the reflexes return and if respiration is depressed then manage as above. MgSO4 can be restarted if considered necessary once reflexes have returned but at a reduced dose unless there have been further convulsions.
- *Urine Output*-< 100 *ml in* 4 *h:* If there are no other signs of magnesium toxicity, the next I/M dose of MgSO4 to be reduced to 2.5 gm or the I/V infusion to 0.5 gm/h . Particular attention to be paid to fluid balance and blood loss.

Monitoring during Magnesium Sulphate (MgSO4) Therapy

MgSO4 has no sedative effect, so on recovering from the post ictal phase the

woman should be alert and oriented. However magnesium can depress neuromuscular transmission at the Myoneural Junction, causing muscular paralysis as serum levels increase. The rationale for clinical monitoring is that loss of the patellar reflex (knee jerk) precedes respiratory depression and respiratory arrest. Frequent monitoring of the patellar reflex and respiratory rate are therefore essential if complications of therapy are to be minimised. Also magnesium is cleared by the kidney. So if renal function is impaired, less magnesium will be required. The therapeutic serum level needed to prevent convulsions is generally believed to be between 2 and 4 mmol/L. Loss of patellar reflexes occurs above 5 mmol/L and respiratory depressions at levels above 6 mmol/L. In the Collaborative Trial [8] serum magnesium levels were not measured but data from Sibai *et al.*[9] would suggest that levels were consistently less than 2 mmol/L with this regime. So to measure the serum magnesium was not essential and was not observed in the trial and the protocol for monitoring would be predominantly, clinical and to be based on ensuring that respiration is not depressed, the patellar reflexes are present and renal function is adequate. These can be monitored hourly with recourse to serum levels if there is clinical concern or if further seizures occur.

Summary of Clinical Monitoring during Administration of MgSO4

Only to give the next I/M dose or only to continue the I/V infusion if

- Respiratory rate > 16/min,
- Urine output > 25 ml/h,
- Patellar reflexes are present.

The Collaborative Eclampsia Trial[8] provides compelling evidence that MgSO4 is superior to diazepam and phenytoin for the treatment of eclampsia. It is rational and sensible for clinicians to adopt the treatment regimens for MgSO4 used in the collaborative trial while prejudice may prevent obstetrician from evaluating magnesium but they can no longer justify not using it. It should be feasible to make it clearly and readily available for the care of all women regardless of where they live in countries until now magnesium sulphate has not been routinely used for eclampsia, there should be some regional or national strategy to ensure affordable and regular supplies.

Control of Hypertension: BP should be assessed with the goal of maintaining the systolic BP between 140 and 160 mm of Hg and diastolic BP between 90-105 mm of Hg is reasonable. This can be achieved by using Labetalol or Hydralazine. Diuretics are used only in the setting of pulmonary edema.Care must be taken not to decrease the BP too drastically; an excessive decrease can cause inadequate uteroplacental perfusion and fetal distress.

Maternal Monitoring: Depending on the clinical course, regularly check the patient's neurologic status for signs of increased intracranial pressure or bleeding (eg, funduscopic examination). Keep nothing by

Drug Treatment in Hypertensive Emergencies

Drug	Onset (min)	Peak action (min)	Duration (hr)	Dosage	Mechanism
Hydralazine	10-20	20-40	3-8	5-10mg IV bolus, repeated every 20 min if necessary	Direct dilatation of arterioles
Labetalol	1-2	10	6-16	20 mg IV bolus repeated every 10 min if necessary doubling the dose till 2220 mg	Alpha and beta blocker
Nifedipine	5-10	10-20	4-8	10 mg orally to be repeated after 30 min if necessary	Calcium channel blocker

mouth (including medications) until the patient is medically stabilized or delivered, because she is at risk for aspiration when post ictal and may have recurrent seizures Monitor fluid intake and urine output, maternal respiratory rate, and oxygenation, as indicated, and continuously monitor fetal status. Pulmonary arterial pressure monitoring is rarely indicated but may be helpful in patients who have evidence of pulmonary edema or oliguria/anuria. Once the seizure is controlled and the patient has regained consciousness, the patient's general medical condition should be assessed to identify any other causes for seizures. Induction of labor may be initiated when the patient is stable.

Fetal Monitoring: Fetal heart rate and uterine contractions should be continuously monitored. Fetal bradycardia is common following the eclamptic seizure and has been reported to last from 30 seconds to 9 minutes. The interval from the onset of the seizure to the fall in the fetal heart rate is typically 5 minutes or less. Transitory fetal tachycardia may occur following the bradycardia. Typically, emergent caesarean delivery is not indicated for this post seizure transient bradycardia; it spontaneously resolves.

Delivery (Antepartum or Intrapartum Eclampsia): Delivery is the treatment for eclampsia after the patient has been stabilized. No attempt should be made to deliver the infant either vaginally or by caesarean delivery until the acute phase of the seizure or coma has passed. The mode of delivery should be based on obstetric indications but should be chosen with awareness that vaginal delivery is preferable from a maternal standpoint. Adequate maternal pain relief for labor and delivery is vital and may be provided with either systemic opioids or epidural anaesthesia. In the absence of fetal malpresentation or fetal distress, oxytocin or prostaglandins may be initiated to induce labour. Cesarean delivery may be considered in patients with an unfavourable cervix and a gestational age of 30 weeks or less, as induction under these circumstances may result in a prolonged intrapartum course and is frequently unsuccessful in avoiding caesarean delivery, given the high rate of intrapartum complications. When emergent caesarean delivery is indicated, substantiating the absence of coagulopathy before the procedure is important. Irrespective of gestational age, a prolonged induction with clinically significant worsening of maternal cardiovascular, hematologic, renal, hepatic, and/or neural status is generally an indication for caesarean delivery when the anticipated delivery time is remote.

Surgical Therapy: Cesarean delivery may be necessary for obstetric indications or a deteriorating maternal condition. The patient should be stabilized with respect to seizures, oxygenation, and hemodynamic status before the initiation of cesarean delivery. BP should be controlled and coagulopathies monitored or corrected.

Anesthesia

An anaesthesiology consultation may be obtained. Early evaluation is recommended to assist with cardiopulmonary stabilization and to prepare for a possible operative delivery or endotracheal intubation.

For nonemergency caesarean delivery, epidural or combined techniques of regional anaesthesia are preferred. Regional anaesthesia is contraindicated in the presence of coagulopathy or severe thrombocytopenia (< 50,000 platelets/μL). General anaesthesia in women with eclampsia increases the risk of aspiration, and airway edema may make intubation difficult. It also can produce significant increases in systemic and cerebral pressures during intubation and extubation. The use of spinal anaesthesia requires caution because of the possibility of total sympathetic blockade, resulting in maternal hypotension and uteroplacental insufficiency.

Postpartum Outpatient Monitoring

Follow up 1-2 weeks after delivery to evaluate the patient for BP control and any residual deficits from the eclamptic seizure.

Patients with persistent hypertension past 12 weeks puerperium or neurologic changes may need medical referral. Although the incidence of eclampsia has declined in recent years, mainly due to the improvement of healthcare, serious adverse outcomes still exist five percent of patients with hypertension develop severe preeclampsia, and about 25% of women with eclampsia have hypertension in subsequent pregnancies. About 2% of women with eclampsia develop eclampsia with future pregnancies.[10]

Is Eclampsia Preventable?

Prevention of eclampsia reqires knowledge of it's etiology and pathophysiology and of the methods to predict patients at high risk for development of convulsions. However the pathogenesis of eclampsia is largly unknown. Prevention of eclampsia can be primary by preventing the development of preeclampsia or secondary by employing antihypertensive agents that prevents convulsions in women with established preeclampsia . Prevention can be tertiary by preventing subsequent convulsions in women with established eclampsia..Magnesium sulphate halves the risk of eclampsia, and probably reduces the risk of maternal death. There do not appear to be substantive harmful effects to mother or baby in the short term.[11] Magpie Trial follow up study collaborative Group [12] reported that the reduction in the risk of eclampsia following prophylaxis with magnesium sulphate was not associated with an excess of death or disability for the women after 2 years.

Subsequent Pregnancy Outcome

Women with a history of eclampsia are at increased risk for all forms of preeclampsia in subsequent pregnancies. In general, the rate of preeclampsia in subsequent pregnancies is about 25%,with subsequently higher rates if the onset of eclampsia was in the second trimester. The rate of recurrent eclampsia is 2%.[10]

Conclusion

Eclampsia is a common complication still associated with high level of maternal and perinatal mortality as well as morbidity. Eclampsia is an obstetrical emergency posing significant burden on heath care system. A systemic and well begun programme with a positive thinking will definitely show road to success to accept the challenges. ANC coverage should be strengthened to detect preclampsia, and prevent eclampsia. Management in the hospital should be optimized to prevent recurrent convulsions and complications after admission.

The "Eclampsia box" recommended by Eclampsia trail collaborative group could be of great advantage to under-resourced countries. This includes magnesium sulphate, it's antidote calcium gluconate,and the necessary paraphernalia to administer the anticonvulsant Prompt evaluation and aggressive management of patient with control and prevention of convulsions with MGSO4, control of Hypertension, termination of pregnancy with supportive care will definately reduce mortality and morbidity of this lifethreatening condition.

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Review Article

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Neonatal Infections

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Abstract

Neonatal infections represent an important cause of morbidity and mortality in neonatal period. NICU patients are at increased risk of neonatal infections because of poor intra-partum and postnatal infection-control practices and also having poor immune defence mechanism. Sepsis is characterized by lethargy, poor feeding, fever or hypothermia and various nonspecific features. Sepsis screen is useful for diagnosis. Blood culture is gold standard. Simple hand washing is a good effective measure to reduce sepsis.

Keywords: Neonatal infection; Hand washing; Sepsis screen.

"An infection acquired in hospital by a patient who was admitted for a reason other than that infection. An infection occurring in a patient in a hospital or other health care facility in whom the infection was not present or incubating at the time of admission. This also includes infections acquired in the hospital but appearing after discharge."[1]

Definition

A universally accepted definition of septicemia is not yet available. According to a working definition, it is a syndrome of Bacteremia with isolation of organisms from blood, CSF, urine or some other body fluid in the first four weeks of life.[2,3,4]

Classification

According to onset of symptoms of sepsis, neonatal septicemia can be divided into 2 main classes:

Early Onset Septicemia (EOS):

Early onset sepsis presents within first 72 hours of life. Source of infection is generally the maternal genital tract. Clinical manifestations include:

- Generalized sepsis
- Pneumonia
- Meningitis

90 % neonates are symptomatic by the first 24 hours of life. Western studies indicate that Group B streptococcus is the most common organism involved in EOS.[2]

Risk factors associated with EOS are as under:

1. Prematurity (< 37 weeks)
2. Low Birth Weight(LBW)(<2500gram)
3. Intrapartum fever in the mother (> 37.5° C)
4. Chorio-amnionitis (foul smelling liquor)
5. Prolonged Rupture Of Membrane(PROM) (> 24 hours)
6. Prolonged and difficult instrumental delivery
7. Perinatal asphyxia[2,3,5,6,7,8]

Late Onset Septicemia (LOS)

Late onset septicemia presents after 72 hours of age. It can be further divided into two distinct entities:

- Disease occurring in the otherwise healthy newborns in the community known as community acquired septicemia.
- Disease affecting premature or sick neonates in the neonatal intensive care unit (NICU) or Nursery who require to stay for other morbidities. This is often known as nosocomial sepsis or Hospital Acquired Infection (HAI) in newborn.

Risk Factors Associated with LOS in NICU

1. Prematurity
2. Low birth weight
3. Intravenous Cannulation, esp. central lines
4. Ryle's Tube insertion
5. Overcrowding in NICU & Nursery
6. Mechanical ventilation.[6,7,8,9,10]

Epidemiology

Incidence of neonatal septicemia in various studies is 1-4/1000; there is almost equal distribution of early and late onset cases. [11, 12]

- Sanghvi *et al*, found the incidence to be 5.6/1000 live birth and 3.87% of NICU admissions.[13]
- According to recent data from National Neonatal Perinatal Database (NNPD) 2002-03, incidence of neonatal sepsis has been reported to be 3.0% in intramural live births in tertiary care centers.[14]

Pathogenesis

Infection in the neonate may be acquired by one of the following routes:

1. In Utero (Congenital)

Intrauterine infections Mechanisms are as under:

a) Trans placental blood stream infection: Apparent or in apparent maternal bacteremia through maternal circulation is carried into intervillous space of placenta and into the fetal blood stream.

b) Ascending infection: PROM, prolonged labour causes infection of amniotic fluid and fetal infection.

The sequence of events in ascending infection is as under:

a. Colonization of birth canal,
b. Upward spread of organism leading to chorio-deciduitis,
c. Development of Chorio-amnionitis,
d. Inhalation and ingestion of contaminated amniotic fluid.

Babies infected in this way exhibit the highest mortality rate.

2. At the Time of Birth (Natal)

During birth, fetus comes into contact of bacteria from maternal vagina, perineum and skin and gets colonized. This may lead to EOS. Microorganisms acquired at the time of delivery colonize mucous membranes and proliferate locally before causing blood stream infection.

3. After Birth during the Neonatal Period (Postnatal)

This is the most important mode of transmission of infection for late onset sepsis(LOS). Infection may be acquired in the NICU/Nursery or in the community.[2,3,15]

In a hospitalized neonate, major portals of entry are:

1) *Umbilicus:* Devitalized umbilical cord tissue allows proliferation of microorganism. Use of umbilical vein catheters, umbilical cord blood sampling in the NICU promotes entry of microorganisms.[2,3]
2) *Trachea and Respiratory Tract:* Endotracheal intubation(ET) done during resuscitation as well as ET tube kept in situ for invasive mode of ventilation is an important portal for the entry of pathogens. Contamination of respiratory equipment especially with

Gram Negative (Gram -ve) organisms that thrive in moist environment such as Acinetobacter, pseudomonas and fusobacterium frequently lead to colonization of the respiratory tract. Aspiration of colonized gastric and oro-pharyngeal secretion around the endotracheal tube may also occur.[2,3]

3) *Site of Intravascular Catheter:* Intravascular devices commonly used in the NICU are peripheral intravenous catheters, peripherally inserted central catheters, surgically placed Central venous catheters and percutaneous arterial catheters.

The rate of catheters related blood stream infections is directly related to the number of days catheters are in place and inversely related to the gestational age and birth weight of the patients.

Immunology

The newborn has a well-developedand functional immune system with certain limitations. During first 8-12 weeks of intrauterine life, fetus is immunologically incompetent. There are maturational deficiencies in complement activity, immunoglobulin content and defective phagocytic response causing defective inflammatory response in the newborn.[15,16]

Humoral Immune Response

Immunoglobulins: Immunoglobulins are a heterogeneous group of proteins detectable in plasma and body fluids and on the surface of B lymphocytes. The five known classes of immunoglobulins are IgG, Igram, IgA, IgE and IgD. [16,17]

Passive Transfer: Immunoglobulins of the IgA class are passively transferred to the fetus from the mother beginning at approximately 20 weeks of gestation. The full term infant has a complete repertoire of maternal IgG antibodies. Transplacentally acquired IgG protects the neonate against bacterial and viral infections.

Active Antibody Production: At 12 weeks, G-lymphocytes are seen in the fetal liver. They produce immunoglobulins. Sequence of appearance of immunoglobulins is Igram followed by IgGand IgA. Presence of elevated concentrations of Igram is suggestive of intrauterine infection.Igram is the most important immunoglobulin type in neonatal host defenses. Adult concentrations of IgA are not achieved until approximately 10 year of age. IgA is almost undetectable in cord blood. Colostrum derived secretory IgA may provide a source of IgA found in both the gastrointestinal tract and other secretions of the newborn infant.

The role of IgD and IgE in immunogenicity is not very well defined.

Passive Transfer

Immunoglobulins of the IgG class are passively transferred to the fetus from the mother beginning at third month of gestation.

The Igram, IgA, IgD and IgE do not cross placental barrier and are absent at birth. IgG offers protection against gram positive bacteria.

Active Antibody Production

At 12 weeks, B-lymphocytes are seen in the fetal liver. They produce immunoglobulins. Sequence of appearance of immunoglobulins is Igram followed by IgG and IgA. At birth newborns have only a small amount of actively produced immunoglobulin.

Humoral Mediators

There is no passive transplacental transfer of complement. The levels of complement proteins increase rapidly after birth reaching adult values by 3 to 6 months of age.

Due to deficiency of complement at birth, opsonic activity is markedly deficient especially towards gram negative organisms.

Cellular Immune Response

The various phagocytes, macrophages (neutrophils, eosinophil) and macrophages, (histiocytes, monocytes, RE cells) are functionally active by the end of first trimester.

Functional Differences between Fetal and Adult Lymphocytes

Fetal T-cells produce less IFN-r than adult T-cells, B-lymphocytes have weaker ability to induce immunoglobulin synthesis. Other limitation of fetal lymphocytes included less mitogen induced proliferation, presence of different proportions of helper and regulatory cell surface marker.

Polymorphonuclear Neutrophils

Neonatal Polymorphonuclear neutrophils (PMNs) are present at early stages of gestation but their functional capacities are different from those of adult PMNS. There is lack of neutrophils precursors in bone marrow aspirates of infected neonates.

Systemic bacterial infections in newborns are commonly associated with profound neutropenia.

Polymorphonuclear leucocytes in the new born have deficient chemotaxis and deficient phagocytic activity thus producing ineffective inflammatory response.

Preterm babies have lower levels of IgG and various components of complement system. Neonates with IUGR suffer from poor cell mediated immune response. Hence these two groups of neonates are susceptible to infection.

Clinical Feature

The spectrum of symptoms in LOS ranges from a mild increase in apnea to fulminant sepsis.

The earliest signs of sepsis may be subtle or may be a part of variability in the course of the infant.

Lethargy, poor feeding, fever or hypothermia are the most commonly reserved features in various studies.[2,3,4,5, 15,16,17,18,19,20,21]

Non Specific Features

1) Lethargy
2) Poor feeding / Feed intolerance
3) Tachycardia
4) Respiratory Distress
5) Poor perfusion, prolonged Capillary Refilling Time(CRT)
6) Hypothermia
7) Fever
8) Jaundice
9) Pallor
10) Sclerema
11) Hypoglycemia

Specific Features Related to Various Systems

Respiratory (R/S)

- Tachypnea
- Distress
- Apnea
- Grunting

Cardio Vascular System (CVS)

- Tachycardia
- Poor perfusion
- Shock
- Hypotension

Central Nervous System (CNS)

- Lethargy
- Irritability
- Neck Retraction
- Abnormal Moro's reflex
- Bulging fontanelle

- Convulsions
- Abnormal / shrill cry

Gastro Intenstinal System (GI)

- Vomiting
- Diarrhea
- GI bleed
- Abdominal distension
- Hepato-splenomegaly
- Necrotizing enterocolitis

Hepatic System

- Hepato-splenomegaly
- Hyperbilirubinemia

Hematology

- Bleeding
- Petechiae

Different etiological agents cause similar clinical picture, hence differentiation based on clinical features is not possible.

Associated Illnesses

According to report of NNPD 2003 and other studies meningitis and pneumonia are commonly associated with sepsis. Pneumonia is seen in around 50% of cases of septicemia[15,19] especially along with EOS. Meningitis is seen in one third of cases of LOS.

Superficial infections like conjunctivitis, pyoderma, and abscesses are seen in association with Gram Positive(Gram +ve) organisms.

Superficial Infection

1) Pyoderma: In various studies incidence is found to be 1-2% in extramural babies and 0.3% in intramural babies.[14]

It is generally associated with sepsis by Coagulase Negative Staphylococcus, Staphylococcus aureus and Streptococcus pyogenes.[2,3]

2) Conjunctivitis: The incidence of conjunctivitis too is more in extramural (3-4.5%) as compared to intramural babies (0.9%). Organisms associated with conjunctivitis include Chlamydia trachomatis, Gram Positive (Gram +ve) cocci. Purulent conjunctivitis should be suspected to be caused by gonococci. [2,3,14]

Conjunctivitis usually responds to topical application of Tetracycline, 1.0% or Erythromycin, Ciplox or Tobramycin eye drops. For gonococcal conjunctivitis, crystalline penicillin is the drug of choice.[3]

3) Umbilical Sepsis: Incidence is between 0.2-2.1percent, greater in extramural babies. Predisposing factors are unclean delivery and cord tie, application of unhygienic substance to cord in the community.[15]

In hospital deliveries, umbilical catheterization is a common predisposing factor.

4) Thrush: Incidence is 0.3-1.3%. In the community use of feeding bottles, contaminated nipples, passage through infected birth canal are predisposing factors.

Prolonged antibiotic usage in NICU contributes to fungal colonization. Thrush is characterized by discrete white patches or spots over the buccal mucosa and gums, sometimes extending to the posterior pharyngeal wall. Perineal moniliasis and monilial diarrhea may be associated.

The baby presents with difficulty in sucking and swallowing. Oral applications of 0.5% gentian violet or Nystatin or Ketoconazole mouth washes are effective.[2,14]

Systemic Infection

1. Pneumonia

In a neonate with respiratory distress, pneumonia is diagnosed in the presence of a positive blood culture if any two of the following are present: (According to NNPD definition).[15]

a. Predisposing factors
b. Maternal fever, PROM, foul smelling liquor.
c. Clinical picture suggestive of pneumonia
d. X-Ray picture suggestive of pneumonia
e. Positive septic screen.

Organisms commonly associated with pneumonia are Group B streptococcus especially in western studies. Other organisms are Staphylococcusaureus, Streptococci and Gram -ve organisms like Klebsiella pneumonia. [14,19]

2. Meningitis

About one - third of neonates with LOS have coexistent meningitis. [15] Evidence of meningeal irritation is generally absent in neonates. Common signs observed are:

- Irritability/lethargy
- Convulsions
- Bulging fontanelle
- Neck retraction

Mortality of neonatal meningitis in developing countries is around 33-48%.[6]

A multicenter WHO study in developing countries found that organisms in meningitis are mainly Gram –ve such as Klebsiella, E coli, Pseudomonas and Salmonella.[2,6] After 1 week to 90 days, streptococcus pneumonia becomes very common. Among Gram +ve organisms, Staph aureus and CONS are common causative organisms.

In developed countries GBS (36%) Serratia (31%) and Listeria (5-10%) account for majority of cases[2,6]. Ideally meningitis should be suspected in all cases of LOS and a lumbar puncture should be done.[20]

The above CSF values suggest meningitis,

Cerebrospinal Fluid (CSF) Chemistry[2]

	TERM NEWBORN	PRETERM NEWBORN
TC	0-32	0-29
DC	61% PMNC	57% PMNC
PROTIEN	20-170 mg%	65-150 mg%
GLUCOSE	34-119 mg%	24-63 mg%

Culture and sensitivity is confirmatory.

Other deep infections found in conjunction with LOS with lesser incidence are as follow.

3. Arthritis/Osteomyelitis

It occurs through hematogenous seeding or direct extension from overlying skin following venipuncture or skin abscess. Staphylococcusaureus & Neisseria gonorrhea. Hip, Knee, and wrist are commonly involved in septic arthritis while Osteomyelitis may affect any bone.[3]

4. Urinary Tract Infections

It incidence is reported to range between 0.1-1% and more common in preterm and male babies.[3]

5. Necrotizing Enterocolitis (NEC)

There is marked abdominal distention, bilious vomiting and passage of blood and mucous per rectum. The bowel sound is absent or diminished with evidence of peritonitis and free air under diaphragram with obliteration of hepatic dullness in terminal stages.[3]

Microbiology of LOS

According to studies done in developed countries nearly half of the cases of LOS are caused by Coagulase negative staphylococci (CONS). In the NICHD study, 22% of cases occurred by other Gram +ve organisms (GBS, Staph. aureus, Enterococcus), 18% by Gram – ve organisms (E coli, Klebsiella, Pseudomonas, Enterobacter, Serratia) and 12% by fungal species (Candida albicans and Candida parapsilosis).[20]

However, in studies from developing countries like India, the Klebsiella species was the most common organism isolated and followed by Staph. Aureus, E. coli and Pseudomonas.[20]

According to NNPD, data in 2002-2003 extramural as were as intramural neonates,

Klebsiella and Staphylococcus were the most prominent isolates.[14]

Laboratory Investigations

Definitive diagnosis of septicemia is by isolation of etiologic agent from the blood,CSF, urine or other body fluids. However, result of these investigations is available only after a few days.

When there is suspicion of sepsis, it is reasonable to draw a CBC, rapid diagnostic tests and blood culture. If results of CBC are abnormal or the neonate worsens clinically, empirical antibiotic therapy should be started.[2,3,15,19,20]

Investigations Helpful in the Diagnosis and Management of LOS …

Sepsis Screen

All newborn suspected sepsis should have septic screen to corroborate the diagnosis of sepsis. The components of septic screen are following.[15,18,20]

1. Total leukocyte count: <5000/cumm
2. Absolute neutrophil count: as per Monroe chart
3. Immature/total neutrophil count: >0.2
4. Micro ESR: >15 mm in 1st hour
5. C-reactive protein: >1 mg/dl

Leucocytes Counts

a) *Total Leucocytes Counts (TLC):* At birth it is 18,000/mm^3. At 1st week of life it falls to around 12,000. In septicemia, TC may be deceased, increased or remains normal. Leucopoenia (TC< 5.000) is considered a sensitive indicator of sepsis.[15,18,21]

b) *Differential Leucocytes Count (DLC):* There is a neutrophilic predominance at birth which decreases rapidly in the 1st few days of life. After the 1st week lymphocytes were predominate. The relative predominance of neutrophils or lymphocytes has not been reported to suggest septicemia.[15,18,21]

c) *Absolute Neutrophil Count (ANC):* The lower limit of ANC is 1800 / mm^3, rise to 7200/ mm^3 at 12 hours of age and declines and persists at 1800/mm^3 after 72 hours of age. The stable value between 1800-5400 remains throughout the neonatal period. In sepsis, either neutropenia or neutrophilia may be found.[15,18,21]

d) *Band Cells:* Band cell is animmature neutrophil in which the width of the narrowest part of the nucleus is less than half of the widest part. Presence of increased number of band cells is considered the most sensitive indicator of sepsis. Band cell to total neutrophils ratio of >20% or absolute band cell count (ABC)> 500 suggest inflammation.[19]

Platelet Count

Normal platelet count in a new born is 150,000 - 400,000/mm^3. Thrombocytopenia commonly accompanies systemic infections in neonate. Late onset thrombocytopenia (48hours) is almost always associated with sepsis or necrotizing enterocolitis.[19]

Serum C - Reactive Protein (S.CRP)

It is an acute phase reactant. It is raised in various conditions like infections, trauma or infraction, malignancy, collagen vascular disease. In neonates, rise in Sepsis. CRP is usually associated with septicemia CRP > 1 mg/dl is considered a positive screen for probable sepsis. Quantitative essay, rising value and fall after therapy is an important parameter for detection of sepsis.[19,21]

Micro ESR

Positive value for sepsis screen > 15 mm/1st hour. [21]

These parameters were also found to be useful in the differentiation between viral and bacterial infection in infants.[3]

Other tests indicative of morbidities present along with sepsis are:

1) *Packed Cell Volume (PCV):* To maintain normal range of PCV is impotent dueto ensure adequate tissue oxygenation during intensive care periods and also after intensive careto treat clinically significant symptomatic anaemia.[20,22]
2) *Blood Sugar Estimation:* Babies born prematurely or smaller than average, or to mothers with diabetes, are tested for hypoglycemia at birth.Hypoglycemia means that you have glucose< 45mg%. Glucose is a vital source of fuel for the brain, and a lack of it will negatively affect brain growth and function.

Hyperglycemia seen in low birth weight and premature infants is usually a transient phenomenon. The various risk factors are low birth weight, stress factors, sepsis, asphyxia, respiratory distress syndrome and high glucose infusion rate (>6 mg/kg/min).[23]

Isolation of Organisms from Body

1. Blood Culture: It is the definitive diagnostic test for neonatal septicemia to isolate the organism causing the illness. It also helps in determining the use of specific antibiotics and the duration of treatment.

However results of blood culture are available only after 48-72 hours and antibiotic use cannot be deferred until then. In about 40% of highly suspected cases blood culture might be sterile.

It is now possible to detect bacterial growth within 12-24 hours by using improved bacteriological techniques such as BACTEC and BACT/ALERT blood culture system.

These advanced techniques can detect bacteria at a concentration of 1-2 colony forming unit/ ml. [2,3,21]

2) CSF Culture: The incidence of meningitis in neonatal sepsis has varied from 0.3-3%invarious studies[15,21].

The clinical features of septicemia and meningitis often overlap; it is quite possible to have meningitis along with septicemia without any specific symptomatology.

This justifies the extra precaution of performing Lumbar puncture (LP) in neonates suspected to have sepsis.

In EOS, lumbarpuncture is indicated in the presence of a positive blood culture or if the clinical picture is consistent with septicemia. It is not indicated if antibiotics have been started solely due to the presence of risk factors.

In situations of late onset sepsis,Lumbar puncture (LP) should be done in all infants prior to starting antibiotics. Lumbar puncture could be postponed in a critically sick neonate.

It should be performed once the patient condition is stabilized.[2,3,19]

3) Urine Culture: In early onset sepsis, urine cultures have a low yield and are not indicated. Urinecultures obtained by suprapubic puncture or bladder catheterization have been recommended in allcases of LOS.

Since the procedures are painful and the yield is often poor, we do not recommend aroutineurine culture in neonates with sepsis.

However, neonates at risk for fungal sepsis and very low birth weight infants with poor weight gain should have a urine examination done to excludeurinary tract infection (UTI).[3,19]

UTI may be diagnosed in the presence of one of the following:

- Supra-pubic aspiration specimen, greater than 1,000 colony-forming units per mL;
- catheter specimen, greater than 10,000 colony-forming units per mL;
- clean-catch, midstream specimen, 100,000 colony-forming units per mL Or greater.[24]

4) Pus Swab Culture: From umbilical, conjunctiva or ear discharge from pustule or abscess.

5) Buffy Coat Smear Examination: It is a useful test for early diagnosis of neonatal bacteremia. Blood collected from peripheral vein in EDTA bulb is centrifuged at 2500 RPM

for 15 minutes, supernatant plasma is aspirated with a pipette and two smears are prepared from the buffy layer below.

It is stained with methylene blue which helps in easy detection of organism and other stained with gram stain which helps in knowing the type of organism.

6) Procalcitonin: The adjunctive tests, including measurements of Procalcitonin (PCT) levels have been studied for their ability to predict sepsis in neonates with clinical symptoms of infection.. The positive predictive values of IL-6,IL-8 and PCT were higher than of CRP.[25]

Radiological Investigations

X ray chest and abdomen: A chest x-ray should be considered in the presence of respiratory distress Orapnea.

An abdominal x-ray is indicated in the presence of abdominal signs and/or Suspicion of necrotizing enterocolitis (NEC). [19]

Treatment

Antimicrobial Therapy

There cannot be single recommendations for the antibiotic regimen for neonatal sepsis in all settings. The choice of antibiotics depends on the prevailing flora responsible for sepsis in the given unit and their antimicrobial sensitivity.[21]

Adjunctive Therapy

Intravenous Immunoglobulin

Multiple studies have been conducted to study role of IVIG. Immunoglobulins administered intravenously in high doses contains intact antibody molecules and maintain normal biologic activities at the Fc fragment such as compliment activation, opsonic activity, binding to cell surface receptors. Several studies have been carried out to evaluate the efficacy to IgG for the prophylaxis of infection in high risk infants with variable results.

The common finding of their studies was: no significant immediate or late side effects have been reported. IVIG dosage most commonly used in these studies was 0.5-0.8 g/kg/d to a maximum of 2-2.5g/kg/d total dosage.

Therefore meta-analyses suggested that treatment with IVIG was of unequivocal benefit in preventing death in neonates with sepsis; the survival rate could be improved two to six fold when IVIG was added to standard therapies in septicemic infants.

A meta-analysis of 19 trials revealed that use of IVIG decreases LOS by 3-4%. However, IVIG was not associated with a decrease in mortality or other serious outcomes.[26,27]

Granulocyte Colony Stimulating Factor

G-CSF has been shown to resolve preeclampsia associated neutropenia, and may decrease the rate of LOS in this population of neonates.

CSFs comprise a family of glycoproteins whose physiological role involves proliferative

Guidelines for initial combination thearapy[21]

	1st line	2nd line
Community-acquired (resistant strain unlikely)	Penicillin or Ampicillin and Gentamicin	Cefotax and other aminoglycoside (as per C/S report)
Hospital-acquired (Some strains are likely to be resistant)	Ampicillin or Cloxacillin, Gentamicin or Amikacin	Add Cefotaxime (as per C/S report)
Hospital-acquired sepsis. (Most strains are likely to be resistant)	Cefotaxime or Piperacillin-Tazobactam or Ciprofloxacin or Amikacin	Same (Avoid Cipro)

changes on early stem cell precursors and late progenitor cell and functional activation of mature peripheral blood cells.

Treatment with CSFs is associated with an increase in absolute neutrophil, eosinophil, monocyte, lymphocyte, and platelet counts and decreased mortality in critically ill septic neutropenic neonates and results suggest that CSF may be effective in the treatment of neonatal sepsis with neutropenia.[28]

Exchange Transfusion

Mechanisms of exchange transfusion are:

1) Improved oxygen carrying capacity of blood.
2) Increased opsonic and granulocyte activity.
3) Removal of bacteria, endotoxins and inflammatory mediators.

Problems with Exchange Transfusion

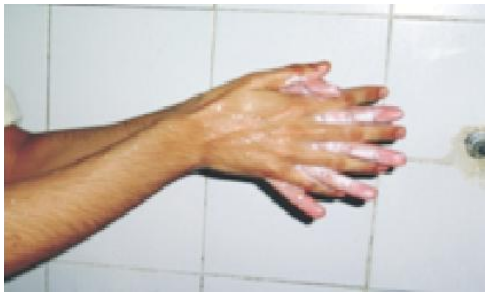
1) Technical difficulties especially after falling of umbilical cord
2) Increased risk of infection transmission
3) Increased risk of graft versus host disease
4) Production of leucocyte and platelet antibodies.
5) Increased RBC deformability and its consequent increased destruction. Current status of exchange transfusion in neonatal sepsis can be only considered experimental. Its use can be considered are in septic neonates with Sclerema or unresponsive DIC, as an adjunct to antibiotic and other supportive care.[2,3]

Prevention of Hospital Acquired Infection in NICU

Reducing Person-to-Person Transmission

- *Hand Decontamination:* Specific hand disinfectants: alcoholic rubs with antiseptic and emollient gels which can be applied to physically clean hands.
- There must be written policies and

Figure 1



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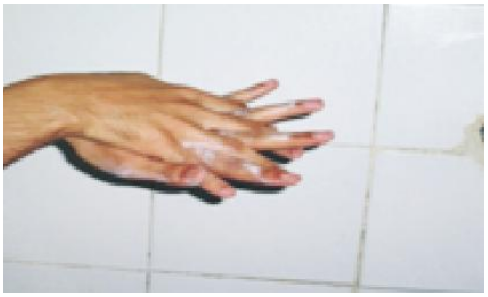

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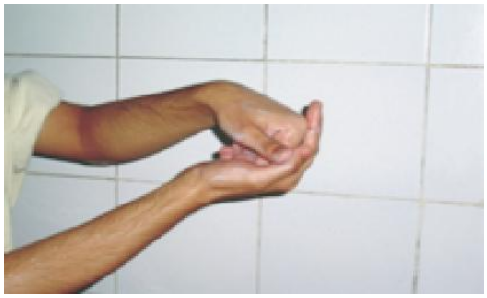

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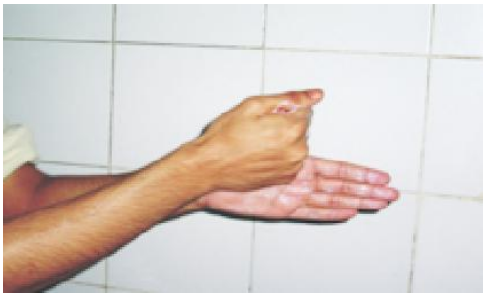

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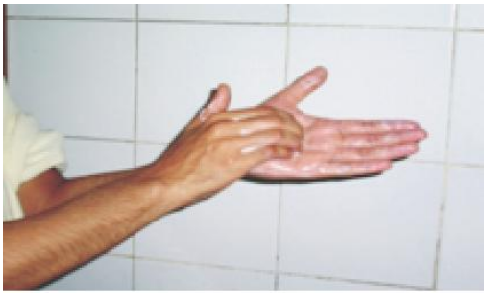
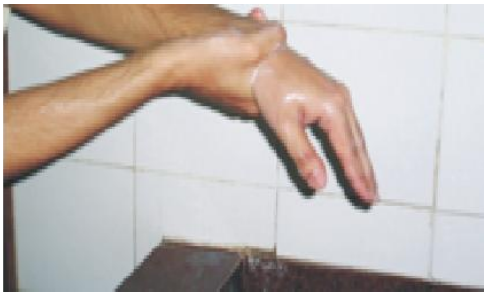


Figure 6



procedures for hand washing.[29,30]

Hand Washing-Simple and Effective for Prevention of Nosocomial Sepsis:[21]

Six Steps are:-

1. Palm and fingers
2. Finger & knuckles
3. Finger tips
4. Back of hands
5. Thumbs
6. Wrists and forearms

Wash hands for 2 complete minutes before entering NICU& before any procedure wash hands for atleast 20 seconds before and after touching the baby.

Personal Hygiene

- All staff must maintain good personal hygiene.
- Nails must be clean and kept short.
- Hair must be worn short or pinned up.
- Beard and moustaches must be kept trimmed short and clean.

Cleaning of the Hospital Environment

- Routine cleaning is necessary to ensure a hospital environment which is visibly clean, and free from dust and soil.
- Ninety per cent of microorganisms are present within "visible dirt", and the purpose of routine cleaning is to eliminate this dirt.
- Neither soap nor detergents have antimicrobial activity, and the cleaning process depends essentially on mechanical action.
- There must be policies specifying the frequency of cleaning and cleaning agents used for walls, floors, windows, beds, curtains, screens, fixtures, furniture, baths and toilets, and all reused medical devices.

Disinfection of Patient Equipment

MEA

Measures to Prevent Sepsis

- Disinfection removes microorganisms without complete sterilization to prevent transmission of organisms between patients.
- It must be high level of sporicidal, virucidal, fungicidal and bactericidal activity.

Sterilization

- Sterilization is the destruction of all microorganisms. Operationally this is defined as a decrease in the microbial load by 10^{-6} Sterilization can be achieved by either physical or chemical means.

Ethylene Oxide and Formaldehyde, Acetic Acid.

- Well Designed NICU[3]
- Prevention of overcrowding
- Space 120-180 square feet per bed.
- Sinks within 20ft. of each bed.
- Commonly used equipment close to bed side.
- Isolation of infected new born.

Recommendation is that anyone who enters in the nursery must take off bangles, wrist-watches, rings etc. Soap and water should be applied from tips of fingers to the elbow.

Practices to Prevent Entry of Microbes into the Nursery Environment:[2,3,30]

1) *Restricted Entry*
   a. Family member should be allowed after procedure of hand washing and gowning.
   b. Segregating infected babies into separate facility.
   c. Staff having fever, rhinorrhea, respiratory infection, pyoderma, intestinal infections and conjunctivitis should not be allowed in nursery.
2) *Use of Gowns/Mask/Slippers:* of doubtful value
3) *Air Changes:* Air conditioners should provide 12 air changes in the nursery per hour.
4) *Decontamination of equipment like*
   a. Incubators
   b. Ventilators
   c. Resuscitation bags
   d. laryngoscopes.
5) Good housekeeping practices.
6) Use of disposable items in plenty
7) Laminar flow systems should be used to prepare fluid reconstitute drugs and to make TPN solutions
8) Prohibiting use of stock solutions
9) Prevention of spread of infection through fomites:
   a. Files
   b. Stethoscopes
   c. Thermometers
   d. Measuring tapes
10) Use of separate equipment for each baby
11) Safe injection practices

Prevention of IV Line Related Infection [34,35]

- Intravenous (IV) fluids to be used judiciously and when absolutely necessary. Discourage over use of antibiotics.
- IV line insertion under strict aseptic precautions.
- Reducing the time IV line is in place.
- A recent study suggests that removal of central venous line promptly after identification of positive culture results in fewer complications.

Establishment of Early Enteral Feeds[2]

Concept of Minimal Enteral Nutrition (MEN)

MEN or trophic feeds are feedings that are delivered in very small volumes (< 10 ml/kg Id) for induction of gut maturity.

Benefits of MEN include:

1) Improved levels of gut hormones
2) Less feed intolerance.
3) Earlier progression to full enteral feeds
4) Improved weight gain
5) Improved calcium and phosphorus retention
6) Fewer days on parenteral nutrition early colostrum could be used as MEN. Early enteral feeds in VLBW infants may have the greatest effect on reducing LOS by reducing exposure to hyper alimentations and decreases use of central catheters. A retrospect cohort study of 212 VLBW infants from a single center revealed lower rates of LOS in infants receiving breast milk (20%) versus infants receiving formula (47%).

Antibiotic Restriction

The following points should be considered before starting antibiotics:

1) Need to start antibiotics: A precise clinical diagnosis of sepsis should be established before starting antibiotics. It should be based upon sign, symptoms, and laboratory tests.
2) Choice of antibiotics and right combination: It depends on the following:
   a. Most probable etiologic agent: It can be decided on the basis of prevailing organism at that time in the nursery and community.
   b. Bacterial isolates from culture
   c. Sensitivity pattern of organism isolated. (2,3,18,19, 32, 33, 34, 35)

Reserve Drugs

- Ceftriaxone
- Aztreonam and Imipenem
- Vancomycin (for Methicillin Resistant Staph Aureus)
- Linezolid, Polymyxin-B, etc.

Complication of over use of broad spectrum antibiotics in neonatal ICU has been emergence of resistant strains of organisms and fungal growth. [2,18,19]

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Original Article

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Preconceptional Care for Chronic Medical Conditions

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Abstract

The goal of this article is to pay tribute to the Fetus who develops maternal bonding in intrauterine life. This bonding is healthier, secure and strengthened if preconception care is rendered to mother. Medical ethics demand that fetus is a patient, fetus has rights. Several of the medical conditions , personal behaviors, psychosocial risks and environmental exposures associated with negative outcomes can be identified and modified before conception through clinical interventions. For certain conditions , opportunities for preventive interventions occur only before conception. Preconceptional Care for chronic medical conditions is discussed.

Keywords: Preconceptional care; Fetus medical conditions; Interventions.

Introduction

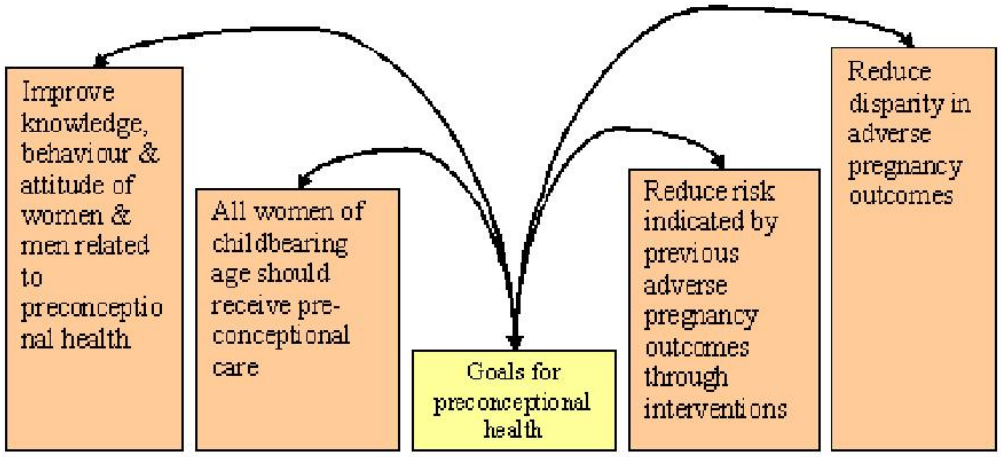
Successful motherhood is the unique achievement in a woman's life. Though it is a natural phenomenon, yet the way to achieve it may endanger the life of both mother as well as the fetus. Preconception, conception, pregnancy, birth and childbearing are in continuum. Earlier events affect the present and future. Therefore good antenatal care begins before pregnancy. Focus of obstetrical care has changed, from treating maternal and fetal diseases to predicting and preventing them.

Preconception care involves screening for conditions which may impact fertility, fetal development or mother's ability to adopt to pregnancy. Preconception care is a set of interventions that aim to identify and modify biomedical, behavioral and social risks of woman's health or pregnancy outcome through prevention and management.

Preconception care focuses on the potential medical genetic, gynaecological and psychosocial problems of a couple before conception. Preconception care leads to better pregnancy outcome because preconception care interferes before the critical period of organogenesis. Usually prenatal counseling takes place after this critical period. In addition, with the application of preconception care there is a shift from acute care to counseling based preventive care, which might make preconception care cost effective. Several of the medical conditions, personal behaviors, psychosocial risks and environmental exposures associated with negative pregnancy outcomes can be identified and modified before conception through clinical interventions.

It is beyond the scope of this article to review all the conditions and factors amenable to preconception care . These will be highlighted in the next review series. In this article we explore the common medical conditions that are associated with adverse pregnancy outcomes for women and their offsprings .We also focuss the degree to which specific preconception interventions and treatment can impact the effects of the condition on birth outcomes. Because avoiding, delaying or achieving optimum timing of a pregnancy is often an important component of Preconception care of women with medical

Figure 1: Goal of Preconceptional Health



conditions.We explore several interventions that, if implemented before pregnancy; can improve pregnancy outcomes for women and infants.

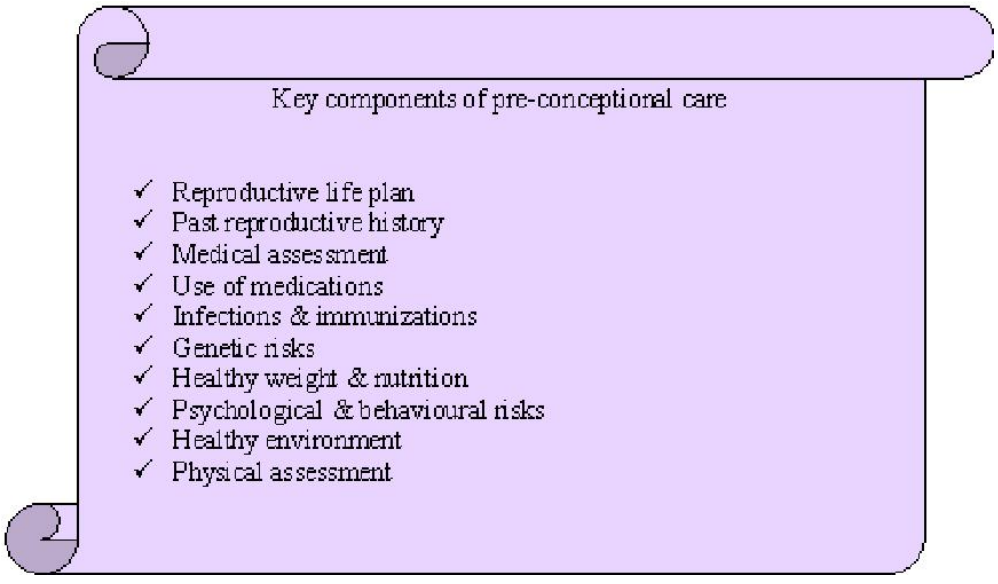
Strategies for Preconceptional Counseling

- Risk identification, reduction and elimination
- Health promotion
- Interventions or modifications to achieve optimal outcome
- Treatment and/or referral
- Ongoing education, counseling and support.

Chronic Medical Disorders

Because 40 to 50 % of pregnancies are unintended, family physician should consider the potential for pregnancy when writing each prescription.[1] All women of reproductive age, including those with disabilities should receive counseling about the potential effects of any medication they use on pregnancy related outcomes and about options to alter dosage or switch to safer medication prior to

Figure 2: Key Components of Preconceptional Care



conception. Consultation with a maternal & fetal medicine specialist may be beneficial in these circumstances.

Diabetes Mellitus

- Use contraception until excellent glucose control is achieved
- self—monitoring and balancing food intake, exercise and insulin
- Transition to insulin (type 2 diabetes) & pump
- Giving specific goals: Fasting glucose 60 to 100 mg per dL (3.3 to 5.6 mmol per L) & Two-hour postprandial glucose 100 to 120 mg per dL (5.6 to 6.7 mmol per L), HbAIC (glycosylated hemoglobin)within normal range.
- Identify, evaluate and treat: Hypertension, Nephropathy, Retinopathy, Thyroid disease, Hyperlipidemia
- Counseling on risks of pregnancy, requirement for increased visits and close monitoring.
- Relative contraindications to pregnancy: Blood urea nitrogen greater than 30 mg per dL(10.7 mmol per L), Creatinine clearance less than 30mL per minute (0.5 mL per second), Coronary artery disease.[2]

Women with glycosylated hemoglobin [HbAIC] levels higher than 8.4% have shown to have a 32% rate of spontaneous abortion and a sevenfold increased risk of severe fetal anomalies compared with women who have good diabetes control.[2] Intensive diabetic management starting before conception decreases the risk of abortions and congenital anomalies apart from decreasing the complications of pregnancy. Insulin has long been the drug of choice for women with type 1 and type 2 diabetes mellitus during pregnancy. Promising results have been shown by Research on use of glyburide in patients with gestational diabetes over oral agents in women with preexisting diabetes.[2] The incidence of neural tube defects has been reduced by consumption of folate daily beginning of at least one month before conception and may also reduce the incidence

of other malformations such as orofacial clefting, limb deficiencies, cardiac defects, urinary tract defects and omphalocele.[3] Increased folate intake is required for women with a history of medical conditions such as epilepsy or diabetes mellitus or a previous gestation with a neural tube defect.

Hypertension

Chronic hypertension can lead to uncomplicated pregnancy or result in lethal conditions like preeclampsia, renal insufficiency and fetal growth retardation. Review during pregnancy is required as angiotensin converting enzyme inhibitors, angiotensin[2] receptor antagonist and thiazide are associated with congenital defects if used in the first and second trimesters of pregnancy.[2] Among beta blockers, atenolo, especially when started early in pregnancy, has been associated with fetal growth restriction. Methyldopa and calcium channel blockers are commonly used during pregnancy. Patients should be evaluated for end organ damage such as retinopathy, renal disease and Left Ventricular Hypertrophy Hence fundoscopy, ECG, Echocardiography should be performed in all patients as and when necessary.

Cardiac Disease

Planning pregnancy in patients with preexisting cardiac disease should be a multi-Disciplinary exercise. The Obstetrician and Cardiologist are ideally consulted at preconceptional stage.

Preconceptional assessment should be aimed at:

- Arriving at the precise diagnosis of cardiac lesion
- Assessment of functional status
- Preconceptional care screening for maternal diseases , which are likely to

adversely impact cardiac status e.g. anaemia.

- Review of cardiac medications with an intention to discontinue or modify drugs that are harmful.
- The risk of Congenital Heart Disease in child

PCC is very important in women with artificial valves on oral anticoagulants .Most of the congenital legions and Mitral Stenosis are better corrected surgically before the woman embarks upon a pregnancy.

Contraindications for Pregnancy (WHO)[4]

- Eisenmenger Syndrome
- Primary Pulmonary Hypertention
- Uncorrected Severe Coarctation
- Marfan's Syndrome
- Severe Mitral Stenosis with complications
- Severe Symptomatic Aortic Stenosis
- Previous Postpartum Cardiomyopathy

Psychiatric Conditions

Mentally ill women are in special need of preconception interventions. Planning for pregnancy is of particular importance in women with schizophrenia because pregnancy is a time of physical and emotional vulnerability during which psychosocial, hormonal and lifestyle changes impinge on mental health. Psychosis during pregnancy is of great concern as it can lead to fetal distress, denial of pregnancy, failure to participate in prenatal care, and/or failure to recognize the signs of labor. Neonatal complications such as fetal anomalies, placental abnormalities, preterm delivery, low birth weight, intrauterine growth retardation, and fetal and infant demise.[5] Untreated schizophrenia during pregnancy places the woman at high risk of postpartum depression, with an increased probability of suicide and infanticide. Possibly, pregnancy for a woman with schizophrenia should be planned so as to coincide with a time of emotional wellbeing, when the woman feels well and able to handle the psychological and physiological demands of pregnancy and parenthood. It is recommended that women with mental illness be in remission for at least one year prior to considering pregnancy. Such women should be identified, properly diagnosed and treated prior to conception

Thyroid Disease

Thyroid disease is the second most common endocrine disease affecting women of reproductive age.[6] Hypothyroidism, particularly during first trimester, is associated with intellectual impairment of the offspring as well as pregnancy complications including Hypertention and preeclampsia, placental abruption, anemia, preterm birth ,low birth weight and fetal death. All women with symptoms of Hypothyroidism should be screened for thyroid Disease and if hypothyroid, they should be adequately replaced. Women being treated for hypothyroidism will require increased doses of Thyroxine early and throughout pregnancy. Treatment of Thyroid conditions improve outcome. For women with Hyperthyroidism who are pregnant, the medication of choice is Propylthiouracil. Regarding Preconceptional care, euthyroidism should be achieved before conception. It is customary to avoid pregnancy for first 6 months after radioactive Iodine Treatment.[6]

Phenylketonuria

Women with Phenylketonuria should maintain low Phenylalaline diets before conception. Elevated Phenylalaline levels result in mental retardation, microcephaly, delayed speech, seizures, and behavioural abnormalities. Fetus exposed to maternal Phenylalaline levels of 20 mg/dl has 73 % chance of microcephaly and 12% chance of Congenital Heart Disease.[6]

Asthma

For 30% of women with asthma, the severity of the disease worsens during pregnancy. In patients with severe or poorly controlled asthma prior to pregnancy, disease may worsen during pregnancy. Uncontrolled asthma during pregnancy can result in serious complications for both the mother and fetus. Maternal complications include preeclampsia and Hyperemesis Gravidarum. Fetal complications include stillbirth and infant death, neonatal hypoxia, IUGR, premature birth and low birth weight. Maternal use of oral corticosteroids has been associated with reduced birthweight, increased risk of preeclampsia and increased risk of oral clefts (first–trimester use). The preferred steroid is Budesonide because this is the only inhaled corticosteroid with FDA category B.[6]

Subsequent pregnancies tend to follow a course similar to the first pregnancy in any given event. Preconceptional care for asthmatics includes counseling woman regarding medication, use of peak flowmeter , inhalers and vaccination for influenza.

Chronic Renal Disease

Women with moderate to severe renal disease before pregnancy are at risk for developing worsening renal function during pregnancy. Maternal morbidity associated with chronic renal disease include development of Preeclampsia & anemia. Adverse pregnancy outcomes include preterm delivery, IUGR, increased fetal loss and stillbirth.[6]

The potential impact of chronic renal disease is dependant on:

- The degree of serum creatinine elevation > 1.4 mg/dl
- Creatinine clearance rate <30ml/minute
- BUN > 100mg/dl
- Proteinuria 3 gram/24 hours
- Renal legions of membranoproliferative & focal glomerulonephritis.

Women in Preconceptional period should be advised to plan a pregnancy when renal function is normal or near normal to avoid worsening of the disease and reduced risk to the fetus.

Autoimmune Disease

Seventy percent of those with autoimmune disorders are women in reproductive age group.[7] Associated maternal risks include disease flares ,Hypertension and related complications. The risk to the fetus includes abortion, pregnancy loss, IUGR, Foetal Cardiac Arrythmia and death. The Preconceptional period is the ideal time to counsel patients about these risks and advice them to plan pregnancy during a disease free period.[7]

Anaemia

Iron deficiency is the most common nutritional deficiency world wide & is a most common cause of Anaemia in pregnancy.[8] Potential fetal complications secondary to anaemia include prematurity & IUGR. Anaemia exposes the women to various maternal complications like cardiac failure, uterine inertia, post partum Haemorrhage, puerperal sepsis. Centre for Disease Control & prevention recommends 18 mg/day for women & 27 mg/day for all pregnant women. Centre for Disease Control & prevention guidelines issued during 1998 state that for girl aged 12-18 years and non pregnant women of childbearing age, iron status screening should occur every 5 years during routine examination .Annual iron screening should be conducted for a woman with existing risk factors for iron deficiency. If Anaemia is confirmed with a second test, a trial of oral iron is warranted.[8]

Thromboembolism

A personal or family history of venous thromboembolism demands testing for thrombophilia before pregnancy as a history

of a deep venous thrombosis have a 7-12% risk of recurrence during pregnancy.[2] Heparin is indicated for prophylaxis and should be started as early in pregnancy as possible. Switching from warfarin to heparin before conception is advised because warfarin is teratogenic.[2]

Epilepsy

Epilepsy in pregnancy treated with anticonvulsants is associated with an overall two-to three-fold increased risk of congenital malformation compared to the general population. The two types of congenital anomaly commonly associated with maternal epilepsy are absolute risk of 1.8% for congenital heart disease and 1.7% for facial clefts [1]. Maternal epilepsy may affect fetal and child health through the effects of seizures during pregnancy or through the genetic background associated with epilepsy.[2]

Polytherapy increases the risk of congenital anomalies , so does a genetic predisposition to decrease enzymatic action of epoxide hydrolase in the foetus. Preconceptional strategies to reduce the risk are monotherapy , switching over to drugs that are least teratogenic ,discontinuation of medication if a woman had no seizure in the past 2 years, has a normal neurological evaluation and EEG and supplementation with folic acid.

Thalassemia

The progress in molecular genetics to analyze the genotype of a single cell, together with advances in assisted reproduction techniques, has paved the way for developing preimplantation and preconceptional diagnosis. These techniques are nowadays widely available, including countries where β-thalassemia is prevalent such as Cyprus. Preconceptional diagnosis is based on the analysis of the first polar body of unfertilized eggs followed by analysis of the second polar bodies after fertilization, which is performed to avoid misdiagnosis resulting from recombination during the first meiosis. Diagnosis is obtained by multiple nested PCR analysis to detect the mutations as well as polymorphic alleles at the β-globin. Then HLA typing of the embryo to select a nonaffected fetus HLA compatible with a previous affected sibling is done. The most important challenge for the future is the organization of national preventive programs in populations in which thalassemias are prevalent such as the Middle East, the Indian subcontinent and the Far East.[9]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most common rheumatic disease that complicates pregnancies.[6] Fortunately, the disease remits in approximately 70-80% of patients during pregnancy, probably because of the normal shift to a less inflammatory state and human leukocyte antigen mismatch between the mother and fetus. However, 20-30% of patients will continue to have active or worsening disease during pregnancy. Active RA may increase the risk of low birthweight and corticosteroid use may increase the risk of fetal growth restriction and preterm premature rupture of membranes. Approximately 90% of patients flare in the postpartum period, usually within the first 3 months. The flare may be caused by decreased progesterone and cortisol, increased prolactin. Presently it is unclear whether breast-feeding might exacerbate postpartum flare. No treatment is curative for RA; however, several therapies modify the disease or result in the control of symptoms associated with RA. NSAIDs should be discontinued by 27 weeks gestation to avoid premature closure of ductus arteriosus. NSAIDs are compatible with breast-feeding, although there is potential risk of jaundice and kernicterus. Corticosteroids may be used, but breast-feeding should occur 4 hours after the last dosing. Hydroxychloroquine and sulfasalazine should be used cautiously, and azathioprine, cyclosporine, cyclophosphamide, methotrexate, and chlorambucil should be avoided. Patients should be advised of the natural history of the

disease during pregnancy and the likelihood of flare during pregnancy. Also, patients should be counseled about the extremely teratogenic effects of methotrexate and leflunomide and the need to discontinue these medications prior to pregnancy.[6]

Barriers to the Implementation of Preconception Care

Delivery of preconception care depends upon practitioners as understanding the barriers of preconception enables implementing the preconception care that allows more appropriate targeting of quality improvement interventions. Pregnancy is a window of opportunity for promoting positive health behaviors as it is a time when women do not practice unhealthy habits.[2] While women realize the importance of optimizing their health before pregnancy, many studies have shown that women of reproductive age demonstrate low levels of knowledge and behavior related to preconception Care.[3] The barriers were primarily related to four domains:

(1) beliefs about capabilities;

(2) motivations and goals;

(3) environmental context and resources and

(4) memory, attention and decision making.

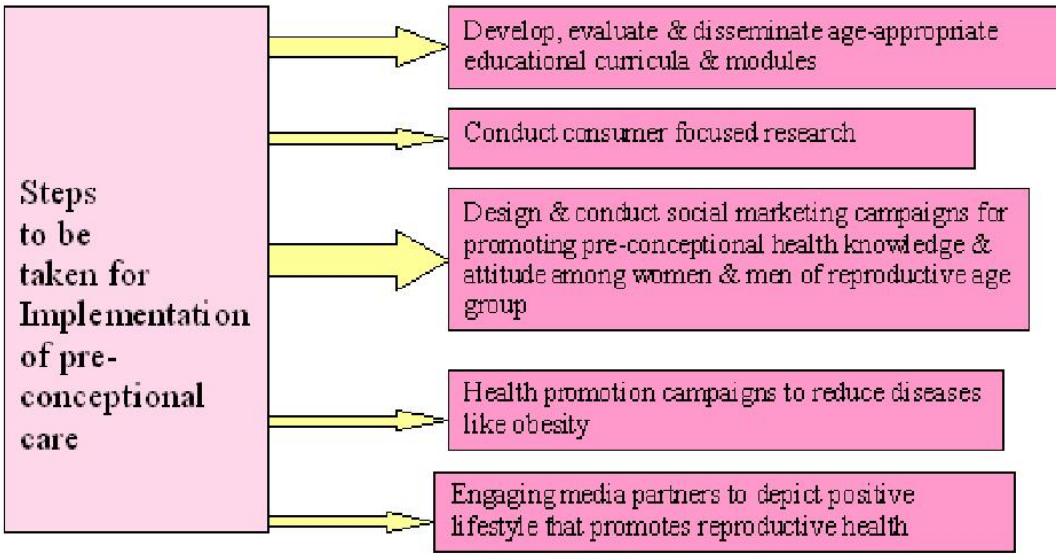
Study has identified some of the barriers and enablers to the delivery and uptake of Preconceptional care guidelines. The biggest barrier identified is the time constraints faced by practitioners in a standard consultation. Other barriers to the delivery of Preconceptional care were the lack of women presenting at the preconception stage. Other barriers are competing preventive care issues, the availability and access to practitioners who deliver Preconceptional care, the cost associated with extending consultations to include Preconceptional care and the lack of resources for assisting in the delivery of preconception care guidelines.

Based on such barriers the Preconceptional care guidelines should include the availability of Preconceptional care checklists as well as patient brochures, handouts and waiting room posters which outline the benefits and availability of Preconceptional care consultations. The availability of a checklist may prove useful for practitioners as it will ensure that all aspects of the Preconceptional care are discussed with patients, even when time is limited. There is also the potential for Preconceptional care to be delivered by a practice nurse or for a risk screen to be undertaken online by patients prior to a consultation.

Dealing with Preconceptional care in an "opportunistic" way is problematic because non-attendees and those who are most in need may inadvertently be denied access to Preconceptional care. Women's awareness is required along with attending for antenatal care at the preconception stage.

Imparting Preconceptional Care

Consideration must also be given to the views of women on the barriers and enablers to the delivery and uptake of Preconceptional care. Understanding the views of both women and practitioner consultant. Research is necessary to determine which of the target should be prioritized for intervention.. Understanding the views of both women and General Practitioner as well as the theoretical basis for changing their behavior will be essential when designing effective implementation strategies for improving the delivery and uptake of Preconceptional care. These strategies may also need to consider the role practice nurses and other health professionals may have in facilitating better uptake of Preconceptional care , especially among high-risk patients who should be actively targeted. Promotional materials and letters of invitations from General Practitioner advising patients of the availability of and the need for preconception care could also be used to increase the uptake of Preconceptional care. Given the potential for evidence-based Preconceptional care to reduce maternal and neonatal morbidity and mortality, it is essential



that effective strategies are put in place to deliver evidence based Preconceptional care guidelines.

Discussion

Preconceptional care is not a conceptual debate but a primary approach used to address various health issues and emerging national challenges. A healthy baby and a healthy mother are valued hopes and dreams of families and cultural heritage across the world.

Advances in medical Therapeutices have made more pregnancies possible in women with preexisting medical conditions. In some conditions, medical care and interventions prior to conception can have a tremendous impact on pregnancy outcome.

Preconceptional care in medical conditions must be a multidisciplinary team. Preconceptional care allows;

- Decision to allow or avoid pregnancy
- Influences on timing of conception
- Optimizes women's health and medical conditions before conception.

Preconception care should be tailored to meet the needs of the individual woman. Because preconception care needs to be provided across the lifespan and not during only one visit, certain recommendations will be more relevant to women at different life stages and with varying levels of risk. Health promotion, risk screening, and interventions are different for a young woman who has never experienced pregnancy than for a woman aged 35 years who has had three children. Women with chronic diseases, pregnancy complications, might need more intensive interventions. Such variations also place constraints on how interventions can and should be integrated.

Health promotion and disease prevention should be integrated into a continuum of care throughout the lifecycle of woman. With an integrated continuum approach to health, rather than series of episodic events, higher levels of women's wellness will be achieved.

Striving for Preconceptional care would benefit mother, child and society, while moving towards that goal, work within existing systems to provide Preconceptional to all women, especially those at elevated risk. It

has potential for impact on pregnancy outcomes and women's health.

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Review Article

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Birth Asphyxia

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Abstract

Birth asphyxia is an important cause of acute neurologic injury, occurring in 2 to 3 cases per 1000 term live births in developed countries, with a higher incidence in less developed countries. Birth asphyxia related neonatal mortality and morbidity including long-term neuro-developmental sequele was seen in 25%-60% of survivors. It is estimated that around 23% perinatal deaths are due to birth asphyxia, with a large proportion of stillbirths. Asphyxia should not be confused with hypoxic ischemic encephalopathy (HIE) or cerebral palsy (CP) since not all asphyxiated neonates develop HIE or CP and there are other causes for the same. In this article there is description of definitions, aetiologies, pathophysiology, clinical features, basic and recent investigations, older and newer treatment of birth asphyxia.

Although there is no specific treatment for birth asphyxia only supportive treatment (fluid and electrolytes balance, oxygenation and ventilation etc.) to prevent the complications and primary preventive measures (electronic fetal heart monitoring, training to birth attendants, home based newborn care) are helpful.

In the developed world, for the HIE, hypothermia has been the only treatment that has worked somewhat (8 -18%). The preferred cooling is whole body with a heart-lung bypass or ECMO; since that is rarely available, external whole body or external head cooling is the next best option. Prevention of reperfusion injury by early (within 6 hours) antioxidant therapy seems to hold the promise for future and should be studied.

Key words:Birth Asphyxia; HIE; Hypoxic- Ischemic Encephalopathy; Neonatal Encephalopathy; Neonatal Depression.

Introduction

Birth asphyxia is a major cause of neonatal deaths, especially in rural India and in urban places where birth attendants trained in resuscitation are not available immediately. It also results into severe neurological long term morbidity; hardly any specific treatment is available. Perinataly asphyxiated newborns born in absence of trained manpower results in higher number of stillbirths. Prevention of the primary events and complications seem to be the best strategy at present.

Definition of birth asphyxia designed for use in hospital based settings require evaluation of umbilical cord p^H, Apgar scores, neurologic clinical status, and markers of multisystem organ function[1] and are not feasible for community settings.[2] The majority of neonatal deaths occur in the home without medical supervision; community-based definitions must rely on data gathered from verbal autopsy methods and use more general symptom- and sign-based algorithms. For example, the National Neonatology Forum of India has defined birth asphyxia as "gasping and ineffective breathing or lack of breathing at 1 minute after birth."[3] Such sign-based

definitions are not, however, implemented consistently, and varying study-specific definitions may affect estimation of the proportion of neonatal deaths attributed to birth asphyxia.

Regarding the definition according to American College of Obstetricians and Gynaecologists and the American Academy of Paediatrics, a neonate is labelled to be asphyxiated if the following conditions are fulfilled: (1) Umbilical cord arterial $p^H < 7$; (2) Apgar score of 0 to 3 for longer than 5 minutes; (3) Neurological manifestations (e.g., seizures, coma, or hypotonia); and (4) Multisystem organ dysfunction, e.g., cardiovascular, gastrointestinal, haematological, pulmonary, or renal system.[4]

Outcome of birth asphyxia depends on Apgar score at 5 minutes, heart rate at 90 seconds, time to first breath, duration of resuscitation, arterial blood gases and acid – base status at 10, and 30 minutes of age.[5] It is measured as short term (early) and long-term outcome. The early outcome is either death/or presence of hypoxic ischemic encephalopathy (HIE) grade I, II or III, according to Sarnat staging.[6]

Perinatal asphyxia refers to a condition during the first and second stage of labour in which impaired gas exchange leads to fetal hypoxemia and hypercarbia. It is identified by fetal acidosis as measured in umbilical arterial blood.[7]

Perinatal Hypoxia, Ischemia, and Asphyxia

These pathophyslogical terms describe respectively, lack of oxygen, blood flow, and gas exchanges to the fetus or newborn. These terms should be reserved for circumstances when there are rigorous prenatal, perinatal, and postnatal data to support their use.[7]

Perinatal/Neonatal depression is the preferred clinical descriptive term (over Birth Asphyxia by ACOG, but not in vogue) that pertains to the condition of the infant on physical examination in immediate postnatal period (i.e., in the first hour after birth). The clinical features of infants with these conditions include depressed mental status, muscle hypotonia and possibly disturbance in spontaneous respiration and cardiovascular function. These terms make no association with the prenatal or later postnatal condition (i.e., beyond the first hour) condition, physical exam, laboratory tests, imaging studies or electroencephalograms. After the first hour or so life, neonatal encephalopathy is the preferred descriptive terms for infants with abnormal mental status and associated findings.[7]

Neonatal encephalopathy is a clinical and not an etiologic term that describes an abnormal neurobehavioral state consists of decreased level of consciousness and usually the other signs of brain stem and/or motor dysfunction. It does not imply a specific aetiology, nor does it imply irreversible neurological injury as it may be caused by such reversible conditions as maternal medications or hypoglycemia.[7]

Hypoxic ischemic encephalopathy is a term that encephalopathy as described above with objective data to support a hypoxic ischemic mechanism as the underlying cause for the encephalopathy.[7]

Hypoxic ischemic brain injury refers to neuropathology attributable to hypoxia and/or as ischemia as evidence by biochemical (such as creatine kinase brain bound [CK-BB] ,elecrtophyiologic (EEG), neuoroimaging (head ultrasonography), MRI, CT or pathological (post-mortem) abnormalities.[7]

Neonatal Encephalopathy or Neonatal Neurological Syndrome[8]

- term infant <7 days at onset
- depressed consciousness level
- abdominal tone and power
- feeding difficulty
- seizure

Incidence

Birth asphyxia is an important cause of acute neurologic injury, occurring in 2 to 3 cases per 1000 term live births in developed countries, with a higher incidence in less developed countries. Birth asphyxia related neonatal mortality and morbidity including long-term neuro-developmental disorders was seen in 25%-60% of survivors.[9]

It is estimated that around 23% neonatal deaths are due to birth asphyxia, with a large proportion of stillbirths. Though the improved obstetric care has reduced the incidence of birth asphyxia in developed countries, but in developing countries, still have a higher rate, ranging from 4.6 per 1000.[10]

According to the World Health Organization (WHO), incidence of birth asphyxia is around 3% that is from 130 million newborns each year globally, around four million develop birth asphyxia, and from asphyxiated babies around 1.2 million die and the same number develop severe consequences, such as epilepsy, cerebral palsy, and developmental delay.[11]

Etiology[7]

In the term newborns may be due to impaired gas exchange across the placenta that leads to inadequate oxygen provision and removal of carbon dioxide and hydrogen to fetus. It can also occur due to secondary causes in postpartum period due to pulmonary, cardiovascular and neurological abnormality.

Etiologies of asphyxia may be multiple such as: maternal factors like hypertension, hypotension, chorioamnionitis, hypoxia from pulmonary cardiac disorders, diabetes, vascular disease, cocaine, alcohol abuse. Placental factors, uterine rupture, umbilical cord problems, foetal factors and neonatal factors are also playing an important role.

Pathophysiology[12]

Pathophysiology of hypoxic ischemic encephalopathy includes ischemia superimposed on hypoxia, which is required for injury. The injury then evolves over hours to days after the insult. Enhanced neuronal excitability with clinical seizures, abnormal EEG and encephalopathy are integral component of the cascade. Specific structures and tissues are vulnerable to injury.

Glutamate toxicity is considered to be the most important part of the pathophysiology of HIE. The Fas ligand and mitochondrial involvement are very vital. When there is lack of energy after HIE, glutamate which is generally reabsorbed from the synaptic area does not get absorbed. That in turn leads to stimulation of two glutamate receptors: the NMDA receptor and AMPA receptor. It causes injury to mitochondria. The anti-apoptotic inducing factor is generated which causes DNA fragmentation and apoptosis.

Neurotransmitted excitotoxicity happens through glutamate which in turn stimulates NMDA, AMPA and Kainate receptors. Inflammatory cytokines release like IL-1, IL-6, IL-8, tumour necrosis factor and lipopolysaccharide which can cause direct injury. Oxidative stress causes synthesis of nitric oxide and peroxynitrites. A study found that apoptosis inducing factors are responsible for cell death in men or in male child, caspases are responsible for cell death in female newborns. The cells die but they take different pathways for male and female fetuses.

The thalamus, putamen, globuspallidus, and subthalamic nucleus are vulnerable regions in the brain. These are the phases of cerebral injury over time. Secondary injury occurs between three to ten days because of failure of oxidative mechanisms, seizures, cytotoxins, swelling and excitotoxins which finally causes cell death.

Hypothermia is acting as a broad inhibitory actions on harmful cellular processes induced by HIE. People have postulated that hypothermia decreases lose of organic phosphates, slows the rates of metabolites consumption and lactic acid accumulation and reduces oxygen consumption, Reduction in astrocytosis and TNF-a, IL-6 level leading

to a reduction in neuronal loss.

The Reperfusion Period: The cascade of deleterious events that lead to cell death after insults that result in oxygen deprivation and energy failure occur primarily following termination of the insult. This is initiated by energy depletion, accumulation of extra cellular excitatory amino acids, increase in cytosolic calcium and generation of *free radicals*. This delayed death of neurons following termination of the insult has a bearing on the possibility that intervention, before the reperfusion injury period, would only, be beneficial.

Clinical Features

Neonatal Encephalopathy Grading[13]

Mild

- alternate level of consciousness-periods of lethargy, irritability and hyper alertness, no normal sleep cycle
- The infants are jittery, feed poorly
- Cranial nerves examination – normal
- Muscle tone may be increased and deep tendon reflexes are frequently increased.
- Primitive reflexes are normal exception Moro's which may be increased
- No seizures.
- Autonomic signs (Pupillary dilation and tachycardia)

Moderate - more lethargic, poor feeding, hypotonia, clonus is usually present gag reflex usually depressed, spontaneous myoclonus or extra pyramidal dysfunction. Pupils are constricted, may have bradycardia. Seizures frequently occur in 24 hours.

Severe - infant is comatose and flaccid with absent reflexes. pupils are often fixed or sluggishly reactive doll's eye reflex is absent. May have bradycardia and frequently has apnoea and hypotension.

Following etiologies should be excluded (with corresponding clinical features)

Persistent stiff baby syndrome with encephalopathy due to glycine abnormality or organic acidemia (3-methylchrotonyl CoA carboxylase def.)

- Hepatomegaly suggests tyrosenemia, heamosederosis and occasional mitochondrial disorder.
- Hiccup: Non ketotic hypergylcinemia
- Urine (smell): Maple syrup urine disease,Isovaleric acidemia

Multiorgan Dysfunction:[7]

Kidney: proximal tubule commonly affected leads to acute tubular necrosis with oliguria.

Cardiac: mainly caused by transient myocardial infarction. Absence of sinus arrhythmia (variability in the heart rate with respiration) is a sign of poor prognosis.

Gastrointestinal: increased risk of bowel ischemia and necrotizing enterocolitis.

Haematological: disseminated intravascular coagulation

Liver: inadequate glycogen stores with resultant hypoglycemia, altered metabolism, or elimation of drugs.

Pulmonary: PPHN, haemorrhage, pulmonary oedema.

Investigation[7]

Laboratory evaluation of asphyxia

Cardiac Evaluation

1. Cardiac troponin I and cardiac troponin T may be elevated (normal values are troponin I=0 to 28±0.42 µg/l troponin T=0 to 0.097µg/l).Elevation of CK-MB fraction >5 to 10% may indicate myocardial injury.

Neurological markers CK-BB may be

increased in asphyxiated newborns within 12 hours of the insult but has not been correlated with long term neuro developmental outcome.

Renal evaluation BUN and creatinine may be elevated in perinatal asphyxia. Typically elevation is noted 2-4 days after the insult. Urine levels of β2 micro globulin have been used as indicator of proximal tubular necrosis (although not routinely used), renal sonography abnormality correlate with occurrence of oliguria.

Brain Imaging

Cranial USG: is normal in 50% cases, non specific cerebral oedema, and ventricular lesion best seen.Slit like ventrical is not very specific; is present in normal new born also.Basal ganglia and thalamic echo:If hemorrhagic necrosis persist>7 days there is poor prognosis.

Doppler: anterior cerebral artery blood flow if RI<0.55 (resistive index) than poor prognosis.

If Basal ganglia and thalamus are affected then severe cognitive behaviour

White matter affected then severe cognitive behaviour

If brain stem affected then feeding problem

Cerebral Cortex: mild cognitive disorder

EEG: Spike and Waves

- IBI (inter burst interval) :on day 7 > 20 seconds, low voltage (flat)-poor prognosis .
- Diffuse cortico-thalamic necrosis has discontinuity, birth suppressive low voltage and isoelectric patterns.
- PVL (periventricular leukomalacia) - excessive sharp waves, positive vertex or rolandic.

Amplitude Integrated aEEG: reflects HIE insult. It should be done in first 6 hours (5-10mv reactive) if <5 or >10mv is abnormal. aEEG has been used to evaluate the background pattern particularly when rapid assessment is needed for determination of treatment with therapeutic hypothermia.

Computed Tomography (CT)

May be use to detect cerebral oedema or hemorrhage and eventually HI brain injury. CT is only indicated if imaging urgently needed to determine clinical treatment and neither ultrasound nor MRI is available on an emergency basis.

Magnetic Resonances Imagine (MRI)

Conventional T1, T2 weighted images are the best modality for determining the severity and extent of HI brain injury. These sequences are best for detection of brain injury after 7 – 10days.

1. Diffusion weighted imaging (DWI): can show abnormalities within hours of an HI insult that may be useful in diagnoses of neonatal HIE and an early indicated of possible brain injury.
2. Proton magnetic resonance spectroscopy (MRS): measures the relative concentrations of various metabolites in tissue.
3. Susceptibility weighted imaging may be useful for detection of haemorrhage or hemorrhagic injury.
4. MR angiography or venography may occasionally be useful if there is suspicion of vascular anomalies thromboembolic disease or sinus venous thrombosis resulting in HI brain injury.

Visual evoked potential or somato sensory potential should be done in 6 hours.

Near infrared spectroscopy (NIRS) is a direct measure of cerebral blood flow and it should be done within 48 hour. It is a research tool only.

Neonatal and early Infantile deterioration:- MSUD, Methylmelonic acidemia, Propionic acidemia, Isovolemic acidemia, Multi carboxylase deficiency, Urea cycle disorder, Non ketotic hyperglycenimia.

Many of the procedures are not possible because of critical condition of patient and not availability of bedside instruments.

Prevention of Complication

Neuroprotective strategies for hypoxic ischemic encephalopathy are

- Decreased cerebral metabolic rate caused by hypothermia
- Block NMDA receptor channel caused by magnesium sulphate
- Decreased glutamate release by adenosine
- Inhibition of voltage sensitive calcium channels by calcium channel blockers.
- Decreased free radical reactions by allopurinol, vitamin C, E and superoxide dismutase.
- Prevention of free radical formation- indomethacin, iron chelators, allopurinol, and caspase inhibitors.[12]

Human Error Most Common Cause of Birth Asphyxia: poor fetal monitoring in 50% of cases, Norwegian study shows: "In most compensated cases, poor fetal monitoring led to an inadequate supply of oxygen to the infant," concludes Dr. Andresen. "Training for midwives and obstetricians, along with high-quality audits, could help to reduce claims for compensation after birth asphyxia."[14]

*Genetic Abnormalities may Cause Cerebral Palsy, a Study Suggests***:** "there is a widespread misconception that most cases of cp are caused by difficult delivery leading to birth asphyxia," said andres moreno de luca, M.D., research scientist at the Genomic Medicine Institute, Geisinger Health System, and lead author of the paper. "What we're finding is a growing body of evidence that suggests mutations in multiple genes are responsible for CP. in fact; we suspect these genetic abnormalities may also be the cause of some difficult births to begin with."[15]

Effect of Training Traditional Birth Attendants on Neonatal Mortality (Lufwanyama Neonatal Survival Project): a Randomised Controlled Study. Training traditional birth attendants to manage common perinatal conditions significantly reduced neonatal mortality in a rural African setting. This approach has high potential to be applied to similar settings with dispersed rural populations.[16]

Effect of Home-based Neonatal Care and Management of Sepsis on Neonatal Mortality: Field Trial in Rural India: Abhay Bang and colleagues chose 39 intervention and 47 control villages in the Gadchiroli district in India, collected baseline data for 2 years (1993-95), and then introduced neonatal care in the intervention villages (1995-98). Village health workers trained in neonatal care made home visits and managed birth asphyxia, premature birth or low birth weight, hypothermia, and breast-feeding problems. They diagnosed and treated neonatal sepsis. Assistance by trained traditional birth attendants, health education, and fortnightly supervisory visits were also provided. Other workers recorded all births and deaths in the intervention and the control area (1993-98) to estimate mortality rates.[3]

Findings: Population characteristics in the intervention and control areas, and the baseline mortality rates (1993-95) were similar. Baseline (1993-95) neonatal mortality rate in the intervention and the control areas was 62 and 58 per 1000 live births, respectively. In the third year of intervention 93% of neonates received home-based care. Neonatal, infant, and perinatal mortality rates in the intervention area (net percentage reduction) compared with the control area, were 25.5 (62.2%), 38.8 (45.7%), and 47.8 (71.0%), respectively ($p<0.001$). Case fatality in neonatal sepsis declined from 16.6% (163 cases) before treatment, to 2.8% (71 cases) after treatment by village health workers ($p<0.01$). Home-based neonatal care cost US$5.3 per neonate, and in 1997-98 such care averted one death (fetal or neonatal) per 18 neonates cared for.

Home-based neonatal care, including management of sepsis is acceptable, feasible, and reduced neonatal and infant mortality by nearly 50% among our malnourished, illiterate, rural study population. This approach could

reduce neonatal mortality substantially in developing countries.[3]

Electronic Fetal Heart Rate Monitoring Decreases Neonatal Mortality and Reduces the Event of Birth Asphyxia.[17] The results showed that in 2004, 89% of singleton pregnancies had EFM. EFM was associated with significantly lower infant mortality (adjusted RR 0.75; 95% CI 0.69, 0.81); this was mainly driven by the lower risk of early neonatal mortality (adjusted RR 0.50; 95% CI 0.44, 0.57) associated with EFM. In low-risk pregnancies, EFM was associated with decreased risk for low (< 4) 5 min Apgar scores (RR 0.54; 95% CI 0.49, 0.51), whereas in high risk pregnancies EFM was also associated with decreased risk of neonatal seizures (adjusted RR 0.65; 95% CI 0.46, 0.94).

The study demonstrates that the use of EFM decreased early neonatal mortality by 53%.

Treatment[7]

No specific treatment; only supportive measures:

1. *Ventilation:* CO_2 should be maintaining in normal range. Hypercapnia can cause cerebral acidosis and cerebral vasodilatation. This may lead to more flow to uninjured areas and relative ischemia to injured areas (Steal phenomenon). Excessive hypocapnia leads to low cerebral blood flow.

2. *Oxygenation:* Hypoxemia treated with supplement O_2 and/or ventilation. Hyperoxia may cause decrease CBF or exacerbate free radical damage. Keeping target oxygen to optimum lower levels

3. *Temparature:* Hyperthermia should always be avoided. In full-term babies the warmer may be kept switched off.

4. *Perfusion:* Cardiovascular stability and mean systemic arterial BP are important to maintain cerebral perfusion pressure.

5. *Maintain Physiological Metabolic State:* Hypoglycemia and hypocalcemia should be managed because hypocalcemia can compromise cardiac contractility and may cause seizures.

6. *Judicious Fluid Management*

SIADH (Syndrome of Inappropriate Anti-Diuretic Hormone) is often seen on 3rd or 4th day of life. Fluid restriction may aid in minimizing cerebral oedema found in SIADH, although the effect of fluid restriction on long term outcome in newborns that are not in renal failure is not known.

7. *Seizure control:*

Anticonvulsant

Phenobarbital is drug of choice, loading dose is 20 mg/kg IV. If seizure continues additional loading dose of 5-10 mg/kg may be given.

Maintenance dose is 3-5 mg/kg/day. The side effect of Phenobarbital may lead to respiratory depression and death in non ventilated newborns.

Phenytoin may be added if seizures are not controlled, loading dose of 15 to 20 mg/kg to maintenance dose of 4 to 8 mg/kg/day.

Fosphenytoin is used in place of phenytoin.

Benzodiazepines are used as third line drugs as lorazepam.

Levetiracetam have been recently use due to easy availability, efficacy and safety.

Long term anticonvulsant treatment can be weaned when the clinical exam and EEG indicate that the newborn is no longer having seizure. Other target organ injury is managed accordingly.

8. Antibiotics: Birth asphyxia is a risk factor for sepsis therefore antibiotics are used by majority of Indian centres. The evidence for this in full-term babies is not strong enough to justify starting antibiotics when this is the only risk factor present. The deaths and morbidity per se are not caused by sepsis. So changing antibiotics, because patient's condition has worsened, will not improve the outcome. One should strictly follow culture reports for choice of antibiotics. If sepsis prevention protocols are strictly followed then antibiotics are not to be started unless cultures are positive for bacteria. The condition birth asphyxia per se, or patient

on assisted ventilation in itself, should never be an indication. If majority babies of birth asphyxia are found to be culture positive sepsis then aseptic precautions need to be reviewed.

Neuroprotective Strategies

- Agents tested in animals with no data in human newborns include antagonists of excitotoxic neurotransmitter receptors as NMDA receptor blockade, free radical scavengers such as allopurinol, superoxide dismutase, vitamin E, calcium channel blocker ($MgSO_4$), cyclooxygenes inhibitors such as indomethacin, benzodiazepine receptor stimulation such as midazolam, and enhancers of protein synthesis such as dexamethasone.
- Hypothermia and anti-oxidants seem to show some promise.

There are new agents such as xenon and erythropoietin that have undergone preliminary phase 1 trials but there are no data supporting the use of these agents except for therapeutic hypothermia for neuro-protection.

Therapeutic Hypothermia

Decrease the risk of brain injury in newborns exposed to perinatal hypoxia. Both total body and head pulling have been shown to be safe and effective. Criteria (inclusion) for total body cooling to newborns at risk for HIE.

- Gestational age ≥ 36 weeks and birth weight ≥ 2000gm.
- Evidence of fetal distress.
- Evidence of neonatal distress.
- Evidence of neonatal encephalopathy by physical exam.
- Abnormal aEEG (amplitude integrated EEG) with minimum 20 min recording.

Criteria (exclusion) for total body cooling to newborns at risk for HIE.

- Inability to initiate cooling by 6hrs of age.
- Presence of lethal chromosomal anomalies (trisomy 13 or 18).
- Presence of severe congenital anomalies (complex cyanotic CHD, major CNS malformation).
- Symptomatic systemic bacterial or congenital viral infection.
- Bleeding diathesis (platelet < 50000).
- Major Intra cranial haemorrhage.

Cooling should be started before 6hrs of age. The target temperature goal during cooling is 33.5 C (33-34) with acceptable range (32.5-34.5).

Safety monitoring of newborns is must during 72hrs of therapeutic hypothermia and re-warming temperature. At the end of 72hrs of induced hypothermia the newborn is re-warmed at the rate of 0.5C every 2 hrs until reach to 36.5C.

In the developed world hypothermia has been the only treatment that has worked somewhat for HIE. It has been shown by four major studies- NICHD neonatal network study showed 18%, cool cap study showed 11% improvement TOBY which was done in UK and Europe showed 8% improvement and ICE study which was done in Australia mainly showed 15% improvement. This means only one in ten babies would benefit. In addition the high cost of machine (Rs. 20 to 60 lacs) is beyond the reach of many. The preferred cooling is whole body with a heart-lung bypass or ECMO; since that is rarely available, external whole body or external head cooling is the next best option.

Prognosis[7]

Increased risk of death or severe disability-hypoglycaemia, if glucose <2.2mmol/L in the first 30 minutes, or increase by 18-fold for death or disability, increased peripheral neutrophil counts in first 96 hours, high percentage nucleated RBC/WBC, high lactate in cord blood.[18]

The presence of seizures increases the newborn risk of developing CP 40 to 70 times,

if occurring during first 48 hours. Early onset and difficult to control seizure has poor prognosis.

According to Severity of HIE

Mild: good prognosis (98- 100% normal neurological outcomes and <1% mortality).

Moderate: not sure (20 – 37% die or abnormal neuro-developmental outcome).

Severe: poor prognosis (severe neurological outcome or death).

Traditional signs of recovery-eg Apgar scores, early establishment of suck feeds, visual responsiveness, head growth- have low sensitivity/specificity for predicting neurodisability.

If no neurological abnormality in two weeks of birth it suggests normal development.

Follow-up:

All the neonates with the moderate and severe asphyxia, especially those with stage II and III HIE staging should be followed in the High risk clinic; they should have a complete neurological assessment and intervention if needed during the follow up. A formal psychometric assessment at 18 months should be performed in all these babies. Follow-up also should include vision and hearing assessment, for vision, ROP, deafness, and pulmonary assessment and chest physiotherapy when appropriate especially in preterms.

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Original Article

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Evaluation of a Child with Chronic Cough

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Abstract

Childhood coughing is a common problem that can cause anxiety in parents. Chronic cough in children is generally defined as a cough lasting longer than eight weeks. Cough is a nonspecific reaction to irritation anywhere from the pharynx to the lungs. Common causes are hyperactive airway disease (Asthma), allergic rhinosinusitis , infections (TB, pertussis, Chlamydia), environmental irritants and psycogenic habit cough. A detailed history with relevant clinical examination will solve the majority of the problem. A very few may need targeted investigations. Management is addressed to specific causes. Symptomatic therapy e.g honey or demulcents (after counseling care givers) may reduce nonspecific cough to a great extent.

Keywords: Chronic cough; Cough syrups; Airway disease.

Definition

Cough in children may arise from causes anywhere along the airway, from the nose to the alveoli. Cough is a nonspecific reaction to irritation anywhere from the pharynx to the lungs. Childhood coughing is a common problem that can cause anxiety in parents. There are important differences from adult cough in terms of likely causes and management guidelines.[1,2]

Chronic cough in children is generally defined as a cough lasting longer than eight weeks. This timeframe is used because most simple infective causes of cough will resolve in 3-4 weeks, and the eight-week definition identifies those who may need further investigations.[2]

The timeframe between acute and chronic cough (3-8 weeks) is sometimes called 'subacute cough' or 'prolonged acute cough' (eg a slowly resolving post-viral cough). If a cough is starting to resolve after three weeks, further time may be allowed before investigating further. However, if the cough is not improving by the third week or is increasing in severity, earlier investigations may be indicated[3].

A recurrent cough without a cold is taken as repeated (>2/ year) cough episodes apart from those associated with head colds that each last more than 7–14 days. If the periods of resolution are short, recurrent cough will be difficult to distinguish from persistent chronic cough.[1,3,4]

Figure I: Profile of Cough in Children[1,5]

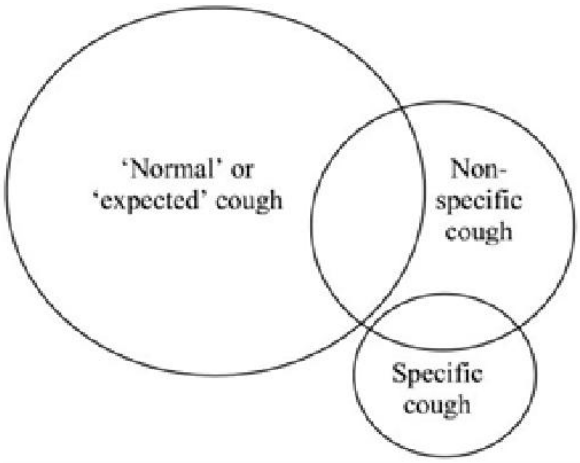

Table I: Causes of Chronic Cough[5,6,7]

Most common causes	Less common causes	Rare causes
Allergic rhinitis	Infection - Sinusitis, Chlamydia, Tuberculosis, Pertussis	Foreign body in the airway
Viral upper respiratory infection	Irritants - May be secondary to stimuli such as smoke	Abnormal mechanical clearance - Immotile ciliary syndrome, CF
Reactive airway disease (Asthma)	Habitual/Functional - Resolves completely during sleep	Immune deficiency states- Hypogammaglobulinemia/HIV
		Congenital abnormalities - TEF, GOR, vascular ring

Table II: Causes of Cough according to Age[6,7]

Infant	Underlying diseases - TEF, GOR
Young children	Viral infection HRAD (hyperreactive airway disease
Older children	Tuberculosis Sinusitis
Adolescents	Irritants – Smoke Habitual / Functional

Treatment of Chronic Cough

Recommendations[1,8]

a) An attempt should be made to remove children with chronic cough from exposure to aeroirritants such as environmental tobacco smoke.

b) *Treatments:* cough with a specific diagnosis : Evidence-based guidelines and review articles exist for treatments of the following specific disorders associated with cough and should be referred to: asthma; cystic fibrosis; immune deficiencies; primary ciliary dyskinesia; tuberculosis.

c) Children with protracted bacterial bronchitis should first have other underlying conditions excluded and sputum cultured before this diagnosis is made. A trial treatment of physiotherapy and a prolonged course (eg, 4–6 weeks) of appropriate antibiotics may be tried.

d) *Treatments:* non-specific isolated cough in an otherwise well child : Parental reassurance is required and usually the cough eventually subsides with the passage of time. If the impact of the cough is mild and there are no diagnostic pointers in an otherwise well child, a period of observation with no diagnostic tests or treatments should be considered.

e) In otherwise well children with non-specific isolated coughing with no specific disease pointers, empirical trials of anti-asthma, anti-allergic rhinitis or antigastro-oesophageal reflux therapy are unlikely to be beneficial and are generally not recommended.

f) *Asthma Therapy:* anti-asthma therapy has not been shown to be effective for children with non-specific persistent isolated cough (either not effective or insufficient evidence). Two RCTs have compared inhaled corticosteroids (beclomethasone, fluticasone) with placebo for treating children with isolated non-specific cough. A small beneficial effect was observed only for the study using very high dose fluticasone but the author advises caution regarding the potential for side effects. If a trial of anti-asthma therapy is used to diagnose problem coughing as being caused by asthma, the treatment should be effectively delivered in adequate doses and clearcut outcomes recorded. A definite period of time should be set (eg, 8–12 weeks) after which the trial of anti-asthma

Table III: Clues in History[1,7,9,10]

Question	Examples	Diagnosis
How did the cough start?	Very acute onset	Retained inhaled foreign body
	Head cold	Post viral Cough
When did the cough start	Neonatal onset (especially if in first few days of life)	Aspiration Congenital malformation Cystic fibrosis Primary cilial dyskinesia Lung infection in utero
What is the quality of the cough	Productive (''moist or wet'')	Chronic suppurative lung disease (bronchiectasis) eg, cystic fibrosis
	Paroxysmal spasmodic cough with or without an inspiratory "whoop" and vomit	Pertussis or pertussis-like illness
	Haemoptysis	Cystic fibrosis Other bronchiectasis Retained inhaled foreign body Tuberculosis Tumour Pulmonary haemosiderosis Pulmonary arteriovenous malformation
	''Bizarre honking cough'' in a child exhibiting ''la belle indifference'' to the cough and which increases with attention	Psychogenic cough
	Dry repetitive cough, disappears with sleep	Habit cough
	Brassy, barking or "seal-like"	Tracheal or glottic cause (eg, tracheomalacia and/or bronchomalacia)
	Cough producing casts of the airways	Persistent bacterial bronchitis
	Staccato	Chlamydia in infants
	Copius sputum / purulent	Suppurative Lung Disease
Is the cough relentlessly progressive?		Inhaled foreign body Lobar collapse Tuberculosis Rapidly expanding intrathoracic lesion
Is the cough an isolated symptom	Isolated cough (otherwise well) / recent school entry / family contact + / parental smoking	Non-specific isolated cough Recurrent viral bronchitis Psychogenic cough
	Associated wheezing present	Asthma Retained inhaled foreign body Recurrent pulmonary aspiration Airways compression or tracheobronchomalacia Bronchiolitis obliterans or interstitial lung disease Neonatal chronic lung disease Cardiac disease with either congestive heart failure or large left to right shunts
	Associated ill health, recurrent pneumonia or pulmonary infiltrates	Cystic fibrosis Immune deficiencies Primary cilial disorders Recurrent pulmonary aspiration Retained inhaled foreign body Tuberculosis Persistent bacterial bronchitis Anatomical disorder
	Associated shortness of breath and restrictive lung defect	Interstitial lung disease
What triggers the cough?	Exercise, cold air, early morning	Asthma
	Lying down	Postnasal drip, gastro-oesophageal reflux disease
	Feeding	Recurrent pulmonary aspiration

Table IV: Clues in Physical Examionation [9,10,11]

Physical Examination	*Suggestive Diagnosis*
Failure to thrive	Chronic systemic illness
Halitosis in the absence of periodontitis	Sinusitis, bronchiectasis
Increased respiratory rate with retractions	Pneumonia
Clubbing	Chronic lung disease including bronchiectasis
Signs of atopy, eczema wheezing	Asthma
Subconjunctival hemorrhage	Pertussis
Oral thrush	HIV infection
Stridor, croupy cough	Upper airway obstruction
Coarse crepitation	Bronchiectasis

Table V: Potentially Serious Lung Disorders with Chronic Coughing[1,10,12]

Condition	Investigations
Cystic fibrosis	Sweat test, nasal potential difference, assessment of pancreatic function, genotyping
Immune deficiencies	Differential white cell counts, immunoglobulin levels and subsets, functional antibody responses and lymphocyte subset analysis
Primary ciliary disorders	Screening FnNO, saccharine test, cilial ultrastructure and function, culture of ciliated epithelium
Protracted bacterial bronchitis	Chest radiography, sputum for culture, exclusion of other causes in this table. Response to 4–6 weeks antibiotic and physiotherapy / HRCT scan
Recurrent pulmonary aspiration: Laryngeal cleft or 'H' type tracheo-oesophageal fistula Post-TOF repair with swallowing incoordination Neuromuscular or neurodevelopmental disorder GOR, hiatal hernia	Barium swallow, videofluoroscopy, 24 h p^H studies, milk isotope scan, fat-laden macrophage index* on bronchalveolar lavage if bronchoscopy indicated. Oesophagoscopy with biopsy may be indicated. NB. There is little evidence that GOR alone is a cause of cough in otherwise healthy children
Retained inhaled foreign body	Chest radiography and HRCT scan may show focal lung disease Rigid bronchoscopy is both diagnostic and therapeutic and is almost always indicated if the history is suggestive of inhaled retained foreign body
Tuberculosis	Chest radiography, Mantoux, early morning gastric aspirates and gamma interferon tests
Anatomical disorder (eg, bronchomalacia) or lung malformation (eg, cystic congenital thoracic malformation)	Bronchoscopy and CT scan
Interstitial lung disease	Spirometry (restrictive defect), chest radiography and HRCT scan, lung biopsy

FnNO, fractional nasal nitric oxide; HRCT, high-resolution CT; TOF, tracheooesophageal fistula; GOR, gastro-oesophageal reflux

Table VI: Patterns, Causes and Potential Investigations of Chronic or Frequently Recurrent Cough in Otherwise Healthy Children[1,8,12]

Etiology	Pattern	Cause	Potential investigation
Frequently recurring viral bronchitis	Episodic, frequent in winter, associated with"head colds'', may occur ''back-to-back''	Viral infections Crowded living conditions, ETS and attendance in child care nursery	None Chest radiography Examine during a period when symptom free
Postviral cough	Troublesome cough (day and night) following a respiratory infection and slowly resolving over next 2–3 months	Viral respiratory infections, Chlamydia and Mycoplasma infections	chest radiography, serology Consider trial of asthma therapy (some mild asthmatics have prolonged recovery from each viral infection)
Pertussis and pertussis-like illness	Troublesome spasmodic cough after initial respiratory infection which slowly resolves over 3–6 months. Vomiting clear tenacious mucus. Older child may complain of difficulty catching breath	Bordetella pertussis, parapertussis, adenovirus, influenza, parainfluenza	Chest radiograph, positive serology or culture may be helpful in reducing requirements for further investigation
Cough variant asthma ??	Isolated cough (no wheezing) due to asthma. Confidence in diagnosis increased when strong atopic background present and cough responds rapidly to anti-asthma medication but relapses when stopped	Asthma	None, chest radiograph. Is airways obstruction present and reversible? BHR or BDR tests, Is there eosinophillic inflammation? Induced sputum, allergy tests, FeNO, response to asthma medication
Allergic rhinitis, postnasal drip and sinusitis – cough likely due to concomitant tracheobronchial inflammation	Not fully accepted as a cause of cough. Cough when ''head hits the pillow'' or constant throat clearing by day. May have transverse nasal crease of ''allergic salute	Causes of allergic rhinitis	ENT examination, often no investigations needed Chest radiography, allergy tests Response to antirhinitis treatment within 2 weeks / CT scan of sinuses
Psychogenic cough	Usually an older child/adolescent (1) Tic-like "habit cough'' persisting after head cold or during times of stress (2) Bizarre disruptive honking cough with child exhibiting ''la belle indifference". Cough goes away with concentration or sleep	Underlying stress Bizarre honking cough usually serving a purpose with some secondary gain	It is important to do investigations to assure the doctor and parent that no major disease is being missed. However, it is important not to keep performing futile investigations that may reinforce the underlying problem

ETS, exposure to environmental tobacco smoke; FeNO, fractional exhaled nitric oxide concentration; BDR, bronchodilator responsiveness; BHR, bronchial hyperreactivity

medication should be stopped.

g) Postnasal drip and rhinosinusitis therapy : In children with a throat clearing type of cough and signs of allergic rhinitis, allergen avoidance and a trial of therapy is indicated. Allergen avoidance, oral antihistamines and intranasal corticosteroids are the cornerstones of management.

h) Empirical gastro-oesophageal reflux therapy is not indicated for non-specific cough in children.

i) In arriving at a diagnosis of psychogenic or habit cough, the physician should first be sure that organic causes are unlikely and that the suggestive features are present. Suggestive features of non-organic coughing include:

   i) bizarre honking disruptive coughing;

   ii) cough that obviously increases with attention and decreases with involvement and concentration in some activity or sleep;

   iii) child exhibits ''la belle indifference'' to the disruptive coughing.

Habit or ''tic''-like coughs are generally less disruptive.

Psychotherapy such as behaviour modification regimes may be helpful in treating psychogenic coughing

Summary of Management[5,9]

Group I

- Hyperreactive airway disease – Bronchodilators / ICS
- Persistent cough following viral URI - symptomatics/ Honey
- Irritant dry cough- Avoid exposure to smoke
- Habitual cough- resolves completely during sleep

Group II

- Sinusitis- Amoxicillin/Macrolides
- Chlamydia pneumonia- Macrolides
- Tuberculosis- Mantoux/X-ray chest/ contact history - ATT
- Pertussis- Treat with Macrolides

Group III

- Foreign body obstruction in the airway
- Abnormal mechanical clearance
- Immuno-deficiency states
- Congenital abnormalities

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Encephalocele: Our Experience

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Abstract

Introduction:Encephalocele is one of the commonest neural tube defects, with the frequency of approximately 1–4 : 1000 births. We conducted a study of epidemiology of encephalocele, at our institution in rural set-up , to know the role of antenatal checkups (folic acid supplementation and prenatal sonography) of mother, in decreasing the incidence of encephalocele in rural and tribal population.

Aims & Objectives:To study the role of antenatal checkups of mother, on the incidence of encephalocele in rural and tribal population.

Materials & Methods:The study has been conducted at A.C.P.M Medical College, Dhule for a period of five years from 1998 to 2003.The study consists of twenty three patients of encephalocele. Age of presentation was observed. All the patients underwent routine investigations and sonography. They all were surgically managed. Progress of the patients was followed up. All the data was collected, tabulated and analysed.

Result:None of the patients' mother has received preconceptional counselling and antenatal care. Therefore none of them received folic acid supplementation, during pregnancy or prior to it. Consequently, sonographic detection of encephalocele was missed.Hence, we would like to postulate, that lack of antenatal checkups, has resulted in increased incidence of encephalocele in tribal population.

Conclusion:Improvement in antenatal checkups (folic acid supplementation and prenatal sonography) of mother has resulted in decreasing incidence of enceohalocele in rural and tribal population.

Keywords:Encephalocele; Antenatal;Folic acid supplementation;Prenatal sonography.

Introduction

Encephalocele is one of the commonest neural tube defects, with the frequency of approximately 1–4: 1000 births. Encephalocele may be of congenital, spontaneous, and traumatic origin.[1,2,3,4,5] It is seen more commonly in females. We conducted a study of epidemiology of encephalocele at our institution in rural set-up where most of the patients are from tribal region. This case series included neonates with encephalocele for 5 years. Social factors are responsible for the increase in number of male patients presenting at our hospital for treatment.

Material & Methods

The study protocol was approved by ethics committee and informed consent of guardians was taken. We did a study of the epidemiology of encephalocele for five years from 1998 to 2003.

23 patients were treated for encephalocele during this period. Age of presentation was observed.

At birth – two patients

Within a month – 15 patients

After one month – six patients

No patient was diagnosed with encephalocele antenataly. All the patients underwent routine investigations and sonography. They all were surgically managed. Progress of the patients was followed up. All the data was collected, tabulated and analysed.

Table 1: Distribution of Incidence of Encephalocele

Year	No. of cases presented at our OPD	%
1998-1999	17	74
2000-2001	5	22
2002-2003	1	4

Table 2: Time of presentation/detection

Age of presentation	No. of cases presented at our OPD	%
ANC	0	0
At birth	2	9
Within a month	15	65
After one month	6	26

Table 3: Sex distribution

Sex	No. of patients	%
Male	23	100
Female	0	0

Table 4: Antenatal Checkup done

ANC	No. of patients	%
Done	0	0
Not done	23	100

Obervation

Discussion

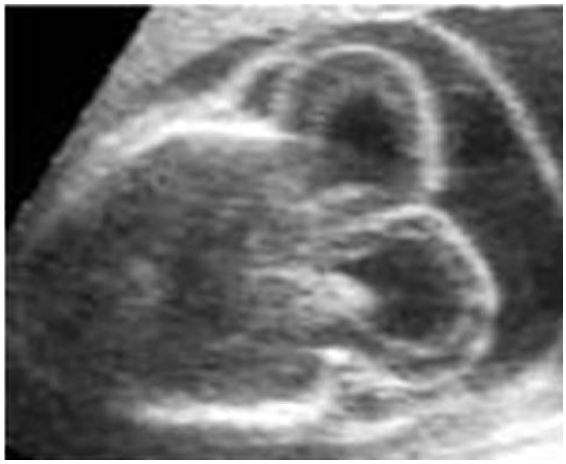
Encephalocele is one end of spectrum of open NTD. It is a spherical fluid filled structure beyond calvarian confines. Earliest can be diagnosed at 13 weeks, by USG, according to literature, pathophysiology of encephalocele is failure of surface ectoderm to separate from neuroectoderm early in embryonic development. It is mesodermal defect in calvaria and duramater resulting in herniation of CSF, brain tissue and meninges through defect. Common site is occipital area in 75% of cases.

The incidence of neural tube defects have been reduced by consumption of folate daily, beginning of at least one month before conception.[6] Increase folate intake is required in previous gestation with a neural tube defect. So preconceptional intervention and anomaly scan at second trimester play major role in prevention of this malformation.

None of the patients' mother has received preconceptional counselling and antenatal care. Therefore none of them received folic acid supplementation during pregnancy or prior to it. Consequently, sonographic detection of encephalocele was missed.

Hence, we would like to postulate that lack of antenatal checkup (folic acid supplementation and prenatal sonography) resulted in increased incidence of encephalocele in tribal population. It seems that social factors might be responsible for decrease in number of female patients with encephalocele presented for treatment in our

Encephalocele



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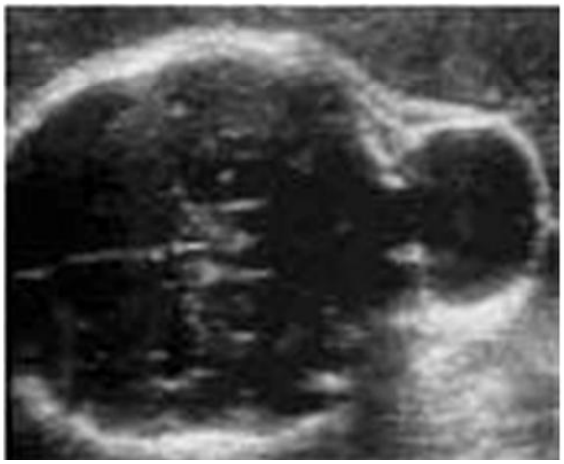

institution.

Conclusion

Improvement in antenatal checkups (folic acid supplementation and prenatal sonography) of mother has resulted in decreasing incidence of enceohalocele in rural and tribal population.

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The second page should carry the full title of the manuscript and an abstract (of no more than 150 words for case reports, brief reports and 250 words for original articles). The abstract should be structured and state the Context (Background), Aims, Settings and Design, Methods and Material, Statistical analysis used, Results and Conclusions. Below the abstract should provide 3 to 10 keywords.

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State the background of the study and purpose of thestudy and summarize the rationale for the study or observation.

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The methods section should include only information that was available at the time the plan or protocol for the study was written such as study approach, design, type of sample, sample size, sampling technique, setting of the study, description of data collection tools and methods; all information obtained during the conduct of the study belongs in the Results section.

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Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Extra or supplementary materials and technical details can be placed in an appendix where it will be accessible but will not interrupt the flow of the text; alternatively, it can be published only in the electronic version of the journal.

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Include summary of key findings (primary outcome measures, secondary outcome measures, results as they relate to a prior hypothesis); Strengths and limitations of the study (study question, study design, data collection, analysis and interpretation); Interpretation and implications in the context of the totality of evidence (is there a systematic review to refer to, if not, could one be reasonably done here and now?, what this study adds to the available evidence, effects on patient care and health policy, possible mechanisms); Controversies raised by this study; and Future research directions (for this particular research collaboration, underlying mechanisms, clinical research). Do not repeat in detail data or other material given in the Introduction or the Results section.

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Standard journal article

[1] Flink H, Tegelberg Å, Thörn M, Lagerlöf F. Effect of oral iron supplementation on unstimulated salivary flow rate: A randomized, double-blind, placebo-controlled trial. J Oral Pathol Med 2006;35:540-7.

[2] Twetman S, Axelsson S, Dahlgren H, Holm AK, Källestål C, Lagerlöf F, et al. Caries-preventive effect of fluoride toothpaste: A systematic review. Acta Odontol Scand 2003;61:347-55.

Article in supplement or special issue

[3] Fleischer W, Reimer K. Povidone iodine antisepsis. State of the art. Dermatology 1997;195 Suppl 2:3-9.

Corporate (collective) author

[4] American Academy of Periodontology. Sonic and ultrasonic scalers in periodontics. J Periodontol 2000;71:1792-801.

Unpublished article

[5] Garoushi S, Lassila LV, Tezvergil A, Vallittu PK. Static and fatigue compression test for particulate filler composite resin with fiber-reinforced composite substructure. Dent Mater 2006.

Personal author(s)

[6] Hosmer D, Lemeshow S. Applied logistic regression, 2nd edn. New York: Wiley-Interscience; 2000.

Chapter in book

[7] Nauntofte B, Tenovuo J, Lagerlöf F. Secretion and composition of saliva. In: Fejerskov O, Kidd EAM, editors. Dental caries: The disease and its clinical management. Oxford: Blackwell Munksgaard; 2003. p. 7-27.

No author given

[8] World Health Organization. Oral health surveys - basic methods, 4th edn. Geneva: World Health Organization; 1997.

Reference from electronic media

[9] National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/theme_health/HSQ 20.pdf (accessed Jan 24, 2005): 7-18. Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.

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