# Introduction

Amniotic fluid is the physical buffer and barrier to the outside world, along with providing fetal nutritional requirements and playing a significant role in fetal gut maturation and development. The human fetus swallows over 200 mL of amniotic fluid per kilogram of weight each day and such swallowing is essential for normal small bowel development ***(Lima-Rogel et al., 2004).***

It was originally thought that the volume of amniotic fluid being swallowed was what helped the growth, development, and maturation of the intestinal tract ***(Mortensen, 2011).*** Numerous research studies using a simulated amniotic fluid solution, found that the growth factors in the amniotic fluid are actually responsible for the growth, development, and maturation of the intestinal tract ***(Calhoun et al., 2000).***

These growth factors specific to amniotic fluid include recombinant human erythropoietin (rhEPO) and recombinant human granulocyte colony stimulating factor (rhG-CSF). This experimental solution has the electrolyte composition of amniotic fluid and contains albumin, rhEPO and rhG-CSF. These factors are stable in this solution ***(Calhoun et al., 2000)***.

The ingested G-CSF and EPO are highly protected from digestion in the neonatal intestine and remain biologically active. They bind to specific receptors that are expressed on the surface

of fetal villous enterocytes ***(Calhoun and Christensen, 2000)***. The ingested growth factors are not absorbed into the blood but have a topical antiapoptotic action on enterocytes ***(Juul and Christensen, 2003).***

The swallowing of the amniotic fluid stops abruptly when infants are born prematurely. Optimizing enteral nutrition in preterm neonates is not easy because of the common occurrence of feeding intolerance due to gastro-intestinal hypomotility and the risk of NEC. It is not uncommon to take several days or even weeks to establish full enteral feeds in high risk preterm neonates ***(Patole et al., 2005)***.

Disuse atrophy of the small bowel mucosa following several days of enteral fasting is one factor that can contribute to, or delay recovery from, feeding intolerance among preterm infants ***(Hernandez et al., 1999)***.

Human milk feeding is the only currently accepted modality for NEC prevention. This finding may be related to the presence of growth factors in human milk ***(Yurdakök, 2008)***.

Before feedings are started in these infants, small trophic feedings are helpful in reducing feeding intolerance. Unfortunately the amount of G-CSF and EPO provided by trophic feedings are extremely small, when compared to the amounts received in utero from swallowing amniotic fluid ***(Smith, 2011).***

# Aim of the Work

TO test the validity of a hypothesis suggesting that feeding intolerance and necrotizing enterocolitis could be prevented in very low birth weight neonates by early administration of a simulated amniotic fluid solution given enterally.

# Prematurity

## I-DEFINITION

Premature infants are live born infants delivered before completed 37 weeks from the first day of the last menstrual period ***(Stoll and Kliegman, 2004)***. Low birth weight infants (LBW) are infants weighing 2500 gm or less at birth, may be caused by a short gestation (prematurity), intra-uterine growth retardation (IUGR) or both ***(Beherman et al., 2000)***. Very-low-birth-weight (VLBW) infants are those who weigh less than 1500 gm at birth, while extremely low birth weight (ELBW) are infants who weigh less than 1000 gm at birth ***(Cockburn, 2000)***.

## II-INCIDENCE

In developing countries, approximately 70% of LBW infants have IUGR, while in developed countries 30 % of LBW infants have IUGR. Infants with IUGR have greater morbidity and mortality than appropriate for gestational age ***(Beherman et al., 2000).***

In 2000, 7.6% of live born neonates in USA weighed less than 2.500g; the rate of blacks was almost twice that for whites. The incidence of LBW is getting higher because of increased number of premature infants ***(Barbara et al., 2004)***.The estimated percentage of LBW varied from 5-10% for Egypt ***(Mansour et al., 2002)***.

## III-ETIOLOGY

***Premature and/or LBW delivery is associated with the following conditions according to Lee (2008):***

1. Low socioeconomic status, whether measured by family income, educational level, residency, social class, or occupation.
2. African-American women's rate of very premature (<32weeks' gestation) delivery is almost three times that of Caucasian women.
3. Women under age 16 or over 35 are more likely to deliver premature LBW infants.
4. Maternal activity requiring long periods of standing or substantial amounts of physical stress may be associated with IUGR and prematurity.
5. Acute or chronic maternal illness is associated with early delivery whether spontaneous or, not infrequently, induced.
6. Multiple- gestation births frequently occur prematurely (57% of twins and 93% of triplets).
7. Prior poor birth outcome is the strongest predictor of poor birth outcome. A preterm first birth is the best predictor of preterm second birth.
8. Obstetric factors such as uterine malformation, uterine trauma, placenta previa, abruptio placentae, hypertensive disorders, preterm cervical shortening or "incompetent"

previous cervical surgery, premature rupture of membranes, and amnionitis also contribute to prematurity.

9. Fetal conditions such as non reassuring testing, IUGR, or severe hydrops may require preterm delivery.
10. Inadvertent early delivery because of incorrect estimation of gestational age is now rare.

## IV-ASSESSMENT OF GESTATIONAL AGE

***Antenatal Assessment:***

There are several ways to estimate gestational age. The maternal history is reliable provided the first day of the last menstrual period. Otherwise the measurements made by ultrasonography scan taken before 20 weeks of gestation ***(Ballard et al., 1991).***

***Postnatal assessment using modified Ballard Score:***

Gestation can also be assessed from the physical characteristics of the skin, external genitalia, ears, breasts, and from neuromuscular behavior *(using the Ballard Score).* At the end of the examination the total score determines the gestational maturity in weeks, (Figure 1) ***(Ballard et al., 1991).***

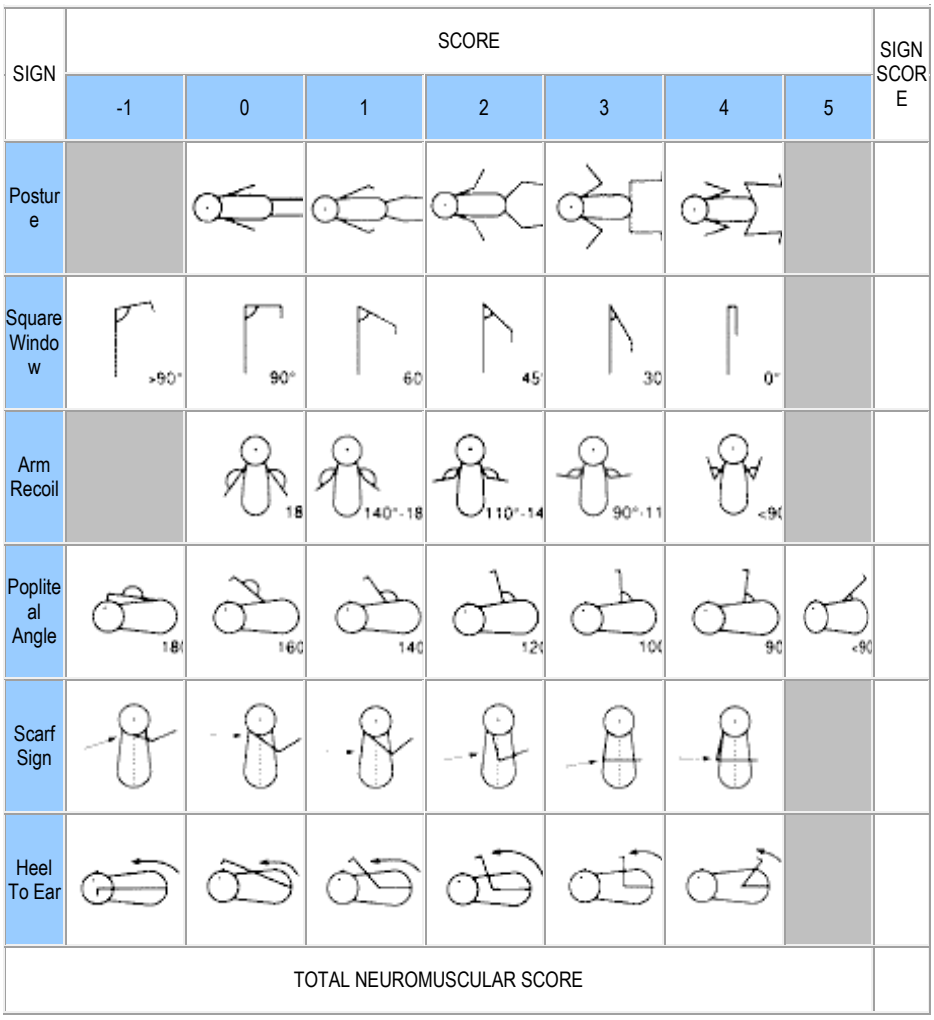


**Figure (1):** Gestational age assessment using Ballard Scoring system (Ballard et al 1991).

| SIGN | SCORE | | | | | | | SIGN SCORE |
|---|---|---|---|---|---|---|---|---|
| | -1 | 0 | 1 | 2 | 3 | 4 | 5 | |
| Skin | Sticky, friable, transparent | gelatinous, red, translucent | smooth pink, visible veins | superficial peeling and/or rash, few veins | cracking, pale areas, rare veins | parchment, deep cracking, no vessels | leathery, cracked, wrinkled | |
| Lanugo | None | sparse | abundant | thinning | bald areas | mostly bald | | |
| Plantar Surface | heel-toe 40-50mm: -1 <40mm: -2 | >50 mm no crease | faint red marks | anterior transverse crease only | creases ant. 2/3 | creases over entire sole | | |
| Breast | Imperceptible | barely perceptable | flat areola no bud | stippled areola 1-2 mm bud | raised areola 3-4 mm bud | full areola 5-10 mm bud | | |
| Eye / Ear | lids fused loosely: -1 tightly: -2 | lids open pinna flat stays folded | sl. curved pinna; soft; slow recoil | well-curved pinna; soft but ready recoil | formed and firm instant recoil | thick cartilage ear stiff | | |
| Genitals (Male) | scrotum flat, smooth | scrotum empty, faint rugae | testes in upper canal, rare rugae | testes descending, few rugae | testes down, good rugae | testes pendulous, deep rugae | | |
| Genitals (Female) | clitoris prominent and labia flat | prominent clitoris and small labia minora | prominent clitoris and enlarging minora | majora and minora equally prominent | majora large, minora small | majora cover clitoris and minora | | |
| TOTAL PHYSICAL MATURITY SCORE | | | | | | | | |

**(Cont.) Figure (1):**Gestational age assessment using Ballard Scoring system

| WEEKS | TOTAL SCORE (NEUROMUSCULAR + PHYSICAL) |
|---|---|
| 20 | -10 |
| 22 | -5 |
| 24 | 0 |
| 26 | 5 |
| 28 | 10 |
| 30 | 15 |
| 32 | 20 |
| 34 | 25 |
| 36 | 30 |
| 38 | 35 |
| 40 | 40 |
| 42 | 45 |
| 44 | 50 |

**(cont.) Figure (1):**Gestational age assessment using Ballard Scoring system (Ballard et al 1991).

## V-COMPLICATIONS

Preterm delivery is a major cause of perinatal mortality and morbidity, (Table 1). Respiratory distress syndrome (RDS), persistent pulmonary hypertension, intracranial hemorrhage, as well as necrotizing enterocolitis are due to the difficulty of extra uterine adaptation due to immaturity of organ systems ***(Hohlagschwandtner et al., 2001; Watts and Saigal, 2006).***

**Table (1):** Neonatal problems associated with premature infants

| |
|---|
| **Respiratory**<br>▪ Respiratory distress syndrome (Hyaline membrane disease)<br>▪ Bronchopulmonary dysplasia<br>▪ Pneumothorax, pneumomediastinum, interstitial emphysema<br>▪ Congenital pneumonia<br>▪ Pulmonary hypoplasia<br>▪ Pulmonary haemorrhage<br>▪ Apnea |
| **Cardiovascular**<br>▪ Patent ductus arteriosus<br>▪ Hypotension<br>▪ Hypertension<br>▪ Bradycardia (with apnea)<br>▪ Congenital malformation |
| **Haematologic**<br>▪ Anemia (early or late onset)<br>▪ Hyperbilirubinemia-indirect<br>▪ Subcutaneous, organ (liver, adrenal) haemorrhage<br>▪ Disseminated intravascular coagulopathy<br>▪ Vitamin K deficiency.<br>▪ Hydrops - immune or nonimmune |
| **Gastrointestinal**<br>▪ Poor gastrointestinal function - poor motility<br>▪ Necrotizing enterocolitis<br>▪ Hyperbilirubinemia direct and indirect<br>▪ Congenital anomalies producing polyhydraminos<br>▪ Spontaneous gastrointestinal isolated perforation |
| **Metabolic- endocrinal**<br>▪ Hypocalcemia<br>▪ Hypoglycemia<br>▪ Hyperglycemia<br>▪ Late metabolic acidosis<br>▪ Hypothermia<br>▪ Euthyroid but low - thyroxin status |
| **Central nervous system**<br>▪ Intraventricular haemorrhage<br>▪ Periventricular leukomalacia<br>▪ Hypoxic ischemic encephalopathy<br>▪ Seizures<br>▪ Retinopathy of prematurity<br>▪ Deafness<br>▪ Hypotonia<br>▪ Congenital malformation<br>▪ Kernictrus (bilirubin encephalopathy)<br>▪ Drugs (narcotic withdrawal) |

***(Stoll and Kleigman, 2004)***

## VI-MANAGEMENT

### A-Prevention of premature labor:

The therapeutic interventions implemented in the setting of preterm labor have the following purposes: (1) to prevent premature onset of contractions and labor, (2) to control contractions when they do occur and delay the time from onset of contractions to the actual time of delivery, and (3) to optimize fetal status and maturation prior to preterm delivery.

Programs attempting to decrease the rate of preterm delivery have traditionally used two main approaches:

(1) Education and surveillance programs.

(2) Uterine activity monitoring.

***(Ramsey and Goldenberg, 2006)***.

***General measures to reduce preterm labour:***

1. Bed Rest
2. Hydration or Sedation
3. Progesterone treatment
4. Cerclage
5. Pessaries
6. Tocolytics

***Specific Measures:***

1. B- Sympathomimetic Agents
2. Magnesium Sulphate

3. Prostaglandin Synthetase Inhibitors
4. Calcium Channel Blockers
5. Oxytocin Antagonists
6. Nitric Oxide Donars.

***(Ramsey and Goldenberg, 2006)***.

**B- Active management:**

**1-Immediate postnatal management:**

**a- Delivery:**

Once preterm delivery is established, it is vital to move the patient to the intensive care area of labor ward and warn the appropriate medical and nursing staff of impending delivery ***(Lorenz et al., 2001).***

Narcotic analgesia is best avoided because it influences the control of respiration and temperature regulation in newborn. Epidural anesthesia or Entonox by inhalation is preferred ***(Ritchie, 1999).***

Cesarean section has been advocated for fetus presenting by the breech and weight between 500-1500 gm. If vaginal delivery is chosen, the best results are achieved when the obstetrician and pediatrician are well prepared and the mother is cooperative. At the end of second stage, delivery is expected by generous episiotomies and gentle fundal pressure, since forcing the head rapidly through a tight vaginal ring causes

intracranial damage ***(Hohlagschwandtner et al., 2001).***

**b. Assessment of baby at the first and five minutes:**

After delivery, decision should be made, whether placental transfusion will be permitted or not. The infant's blood volume will increase by 25% if cord clamping is delayed 30-60 seconds. This increase will raise blood pressure and oxygen carrying capacity. However excessive transfusion can lead to symptomatic plethora and hyperbilirubinemia. This increase in blood volume has a beneficial effect on RDS and that is why a 45 seconds delay in cord clamping has been advised, except for the growth retarded or distressed infant who has already had excess red blood cells in utero ***(Rennie and Roberton, 1999).***

The baby should be assessed by using Apgar score to see if further resuscitation is needed. Resuscitation of VLBW infants must be done with minimal handling to avoid trauma with maintenance of body heat. An incubator with a temperature of 35°C to 38°C or a powerful radiant heater is necessary ***(American Academy of Pediatrics, 2004).***

**2- Neonatal management:**

**a- Thermoregulation:**

Heat loss in the preterm infant is accelerated because of a large ratio of surface area to body mass and reduced insulation of subcutaneous tissue. Furthermore, water loss

through the skin is accelerated because of immaturity of the skin and inability of the skin blood vessels to vasoconstrict in response to cold. For these reasons, the thermal environment of the preterm infant must be carefully regulated ***(Bernstein et al., 1998).***

The infant should be kept in a neutral thermal environment which allows him to maintain a stable core body temperature with minimal heat production through oxygen consumption ***(Chatson, 2004).***

The baby's temperature should be measured on admission and then 6 hourly for 48 hours using low reading mercury rectal thermometer. Daily temperature measurements are adequate thereafter. The aim should be to keep the baby's temperature in the range of 36-37°C and certainly above 35°C ***(Rennie and Roberton, 1999).***

**b- Monitoring the high-risk infant:**

At a minimum, equipment to monitor heart, respiration and blood pressure should be available. The ideal monitoring equipment has memory capabilities to assess episodes of apnea and bradycardia. Oxygen saturation can be correlated with arterial oxygen tension ($PaO_2$) as needed ***(Di-Fiore et al., 2001).***

Arterial blood gases, electrolytes, glucose, calcium, bilirubin and other chemistries must be measured in small volumes of blood ***(De Klerk and De Klerk, 2001).***

**c- Fluid and electrolyte therapy:**

In most circumstances, the majority of fluid requirement up to 200 ml/kg/day in the first week of life in VLBW infants is determined by insensible losses and urine losses. The rate of water loss is a function of gestational age (body weight), environment (losses are greater under a radiant warmer than in an isolette), and the use of phototherapy ***(Ambalavanan, 2002).***

Electrolyte requirements are minimal for the initial 24-48 hours until there is excretion in the urine. Basal requirements are as follows:

- Sodium 3 mEq/Kg/day
- Potassium 2 mEq/Kg/day
- Chloride 2-3 mEq/Kg/day
- Bicarbonate 2-3 mEq/Kg/day

Sodium and bicarbonate losses in the urine are frequently excessive in infants of gestational age less than 30 weeks ***(Rennie and Roberton, 1999).***

Initial fluid management after birth is determined by the infant's size. Infants weighing more than 1000 gm should start at 80-100 ml/Kg/d of 10% dextrose in water ($D_{10}W$),