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## NEONATOLOGY TODAY

### Editorial and Subscription Offices

16 Cove Rd, Ste. 200

Westerly, RI 02891 USA

[www.NeonatologyToday.net](http://www.NeonatologyToday.net)

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## Hypoglycemia and Hyperglycemia in Neonates

By Kaninghat Prasanth, MD, MRCPCH;  
Sachin Gupta, MD and Tsu F. Yeh, MD, PhD

It has been almost a century since hypoglycemia in newborn has been recognized as a problem. In spite of innumerable studies, management of hypoglycemia in newborn infants remains a challenge to healthcare providers. In more recent times, hyperglycemia has also been recognized as a problem.

The purpose of this paper is to review the physiology, pathophysiology, clinical signs and symptoms and evidence based management of hypoglycemia and hyperglycemia.

### Glucose Metabolism in the Fetus

#### Glucose metabolism in normal healthy fetus:

The normal healthy fetus receives a constant influx of glucose from the mother. This constant influx provides for basal fetal metabolism. The normal fetoplacental glucose utilization rate is 5 to 6 mg/kg/min. After 27 weeks gestation, this glucose influx also provides for conversion into glycogen, which is deposited mainly in the liver. The fetal glucose levels are maintained by transport of maternal glucose across the placenta along a concentration gradient by a facilitated, carrier-mediated diffusion<sup>1</sup>. Under normal circumstances, the source of fetal glucose is almost entirely derived from the maternal glucose pool<sup>1</sup>. There is a linear relationship between fetal and maternal glucose levels, with the fetal plasma glucose level being lower than that of the maternal plasma glucose. This linear relationship is maintained during maternal euglycemia, hypoglycemia or hyperglycemia<sup>1</sup>.

In a normal healthy fetus, endogenous glucose production is either absent or very negligible. The enzymes for gluconeogenesis are present by the 2-3 months gestation and occurs from lactate, pyruvate or alanine<sup>2</sup>.

The main role of fetal insulin is to ensure glucose is used for growth and storage. Fetal insulin is detected after 13 weeks gestation. The fetal pancreas can release insulin in response to glucose and amino acid by 20 week gestation<sup>3</sup>. In addition, maternal transfer of amino acids (mainly alanine) have also been shown as a potential source of energy.

#### Glucose metabolism in abnormal maternal and fetal states

When the supply of glucose to the fetus becomes low and prolonged, the fetus responds by initiating glycogenolysis and later gluconeogenesis. It is important to note that although the fetal glucose is mainly derived from the mother, this is not the only source of energy for the fetus<sup>4</sup>. The fetal brain can use ketones as alternative fuel, especially in situations of prolonged maternal fasting. However, there was one study which suggested that such fetuses whose mothers were ketotic in pregnancy, had developmental delay<sup>5</sup>. In the IUGR fetus, the chronic low glucose levels cause abnormal development of fetal pancreatic beta cells, both in number and in efficiency of insulin secretion. These fetuses also develop resistance to insulin increase hepatic gluconeogenesis. Thus an IUGR fetus can have hypoglycemia due to increased utilization of glucose and low storage or can have hyperglycemia due to increased glucose production due to insulin resistance<sup>6</sup>. In cases of maternal hyperglycemia as result of gestational or insulin-dependent diabetes, fetuses tend to up-regulate insulin secretion.

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## Glucose Metabolism in the Immediate Postnatal Period

### Normal full term infant

Maternal supply of glucose and nutrients ends with the clamping of the cord. The transition from intra-uterine to postnatal nutrition is initially a catabolic process. (Table 1)

Table 1
Events at birth at term normal infant
Decrease in insulin
Increase in glucagon
Increase in epinephrine
Increase in nor-epinephrine
Increase in cortisol

After birth, there is normal physiological fall in the blood glucose level, and it reaches a nadir by 1-2 hours of age. As a result of changes showed in the Table 1, the glucose levels then rise spontaneously to a steady level by 2-4 hours of age<sup>1</sup>. The rate of glucose production in a full term newborn during fasting is 4-6 mg/kg/min. The gradual fall of insulin levels and increase of glucagon, catecholamines and cortisol have the following effects:

1. Hepatic glycogenolysis.
2. Hepatic gluconeogenesis.
3. Lipolysis.
4. Betaoxidation of fatty acids to produce ketone bodies.

Among the catecholamines, epinephrine increases more than norepinephrine in response to hypoglycemia. Epinephrine initially increases hepatic glycogenolysis, followed by sustained increase in hepatic and renal gluconeogenesis.

### Preterm infants

In preterm infants, the hormonal response is reduced and there is a lower activity of gluconeogenic enzymes<sup>7</sup>. In addition there is reduced hepatic glycogen stores.

### Glucose metabolism in the newborn brain

Glucose is the primary metabolic fuel for the brain. During normoglycemia, 95% of the energy requirements are from glucose, 4% from lactate and less than 1% from ketone bodies (beta-hydroxybutyrate and acetoacetate)<sup>8</sup>. The central nervous system consumes about 30% of the total hepatic glucose output. Studies have shown that a linear relationship exists

between the size of the brain and hepatic glucose production<sup>9</sup>. The bigger the brain size, the more hepatic the glucose output. The mechanism by which the brain regulates hepatic glucose has yet to be elucidated<sup>9</sup>.

The uptake of glucose by the brain is via a carrier-mediated, facilitated diffusion. This process is not energy dependent. The uptake is mediated by a specific protein known as the glucose transporter (GLUT). GLUT 1 & 3 are the main cerebral glucose transporters. The various glucose transporter proteins are summarized in the Table 2.

The glucose taken up by the brain mainly serves three purposes<sup>8</sup>:

1. To be a source of energy for brain metabolism.
2. To provide storage as glycogen in the astrocytes to be used in periods of hypoglycemia.
3. To enter the pentose monophosphate shunt, and provide important substrates for nucleic acid synthesis.

### Neuroprotective Mechanisms in Periods of Hypoglycemia

The most vulnerable period for hypoglycemic brain injury is during the transition from intra-uterine to postnatal nutrition. During this period of physiological fall in blood glucose, the brain adapts by various neuroprotective mechanisms. The immature brain is more tolerant of hypoglycemia than the mature brain<sup>9</sup>.

The main neuroprotective mechanisms are:

1. Circulatory changes.
2. Reduction of cerebral metabolism of glucose and use of alternate fuels.

**Circulatory changes:** The first physiological response of the newborn brain to hypoglycemia is to increase cerebral blood flow (CBF) to satisfy the metabolic needs. In periods of hypoglycemia, previously unperfused capillaries are utilized in an effort to maintain the delivery of glucose<sup>10</sup>. Cerebral blood flow in pre-term infants has been shown to increase by approximately 50% if the blood glucose was below a critical level of 30mg/dl, and cerebral blood flow continued to be high up to 30 minutes after the correction of hypoglycemia<sup>10,11</sup>.

**Alternate fuels:** During periods of hypoglycemia, the two most important alternate sources of fuel for the brain are lactate and ketone bodies<sup>8,9</sup>. The glycogen stored in the astrocytes may also contribute as well<sup>8</sup>. During suckling in the immediate post natal period, the concentration of ketone bodies increase and partially substitute glucose to sustain cerebral metabolism<sup>12</sup>.

### The Effects of Hypoglycemia on Brain

#### Biochemical Effects

**Acute effects** - The acute biochemical effects of hypoglycemia becomes evident only when increased CBF is no longer adequate to deliver the required amount of glucose to meet the metabolic needs of the brain<sup>8,9</sup>.

The main acute affects are:

1. An increase in glycogen mobilisation to increase availability of glucose.
2. A decrease in cerebral metabolic rate
3. An increase in lactate levels.
4. A decrease in amino acid levels and concomitant increase in ammonia.

Table 2		
Glucose Transporter	Primary site	Transport
GLUT 1	Ubiquitous, Erythrocyte, Brain	Glucose
GLUT 2	Liver, Pancreas, Intestine, Kidney	Glucose, Fructose
GLUT 3	Brain	Glucose
GLUT 4	Heart, Muscle, Brain, Adipose	Glucose
GLUT 5	Intestine, Testes, Kidney	Glucose, Fructose
GLUT 6	Brain, Spleen, Leucocyte	Glucose
GLUT 7	Unknown	Unknown
GLUT 8	Testes, Brain	Glucose
GLUT 9	Kidney, Liver	Unknown
GLUT 10	Liver, Pancreas	Glucose
GLUT 11	Heart, Muscle	Glucose, Fructose
GLUT 12	Heart, Muscle, Small intestine	Unknown

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*Late effects* - Continued decrease in glucose levels lead to neuronal death. The changes include:

1. A marked decrease in cerebral metabolic rate
2. An increase in extracellular glutamate
3. An increase in intracellular calcium
4. An increase in extra cellular potassium
5. A decrease in glutathione levels
6. An increase in free fatty acids

### **Pathological Effects of Hypoglycemia Brain Injury**

Hypoglycemia causes pathological evidence of neuronal injury in the following structures<sup>13</sup>:

- Cerebral cortex
- Hippocampus
- Basal ganglia
- Thalamus
- Brainstem
- Spinal cord

The neuronal necrosis observed were mostly nuclear pyknosis or chromatolysis. Ischemic neuronal injury was a rare feature<sup>13</sup>. Other pathological features include microcephaly, deep and wide sulci, atrophic gyri and periventricular leukomalacia. The only structure seemed to be spared is the cerebellum. Occipital lobe was most severely affected<sup>13</sup>. This predilection for occipital lobe is thought to be due to intensive axonal growth and synaptogenesis resulting in increased glucose demands during the newborn period<sup>14,15,16</sup>.

### **Neuro-Imaging in Hypoglycemia**

Current evidence suggests that hypoglycemic brain injury causes a specific pattern. Imaging studies, both CT and MRI reveal extensive cortical loss, most marked in the occipital region. The sensitivity of the occipital area to hypoglycemic injury may be explained as above<sup>15,16</sup>. The parietal cortex also seems to be more susceptible to hypoglycemic injury compared to other areas of the brain.

Table 3 lists the differences in brain injury between hypoglycemia and hypoxic ischemia.

<b>Table 3</b>	
<b>Differences in injury caused by hypoglycemia and hypoxic- ischaemia</b>	
<b>Hypoglycemic injury</b>	<b>Hypoxic- ischemic injury</b>
Superficial distribution of cortical damage - layers 2 & 3	Deeper cortical damage - layers 3,5,6
Pathology- acute degeneration of neurons and glial cells across cerebral cortex - mainly in occipital lobes.	Main involvement of bottom of cerebral sulci or in vascular 'water-shed' area.

## **Clinical Aspect of Hypoglycemia and Hyperglycemia**

### **Definition**

The plasma glucose level of less than 45mg/dl (2.5mmol/l) was originally first observed by Koh et al 22 yrs ago<sup>17</sup>. In their study of 17 subjects with ages ranging from 1 day to 12 yr old, they observed changes in the evoked potentials when the blood glucose were 45mg/dl (2.5 mmol/l).

Srinivasan et al suggested the following levels in term infants as hypoglycemia<sup>18</sup>:

- < 35 mg/dl, 0-3 hr.
- <40 mg/dl, 3-24 hr.
- < 45 mg/dl, > 24 hr.

More recently 'operational thresholds' have been suggested in managing hypoglycemia. This is discussed later in this paper<sup>19</sup>.

### **Glucose Monitoring**

Accurate testing of the levels in the newborn is crucial to the diagnoses and management of hypo or hyperglycemia. The type of sample and the method of analysis are critical in interpreting values. Glucose levels in plasma are 13-18% higher than in whole blood and arterial samples will have 10-15% higher glucose levels than venous samples<sup>20</sup>. Whole blood with a higher hematocrit has a lower glucose level than whole blood with a lower hematocrit. Because the rate of in-vitro glycolysis is high in neonatal red blood cells, blood samples should be stored on ice or cells separated immediately to prevent falsely low values. Blood glucose values of a blood sample at room temperature drops at the rate of 15-20mg/dl/hr<sup>21</sup>.

The choice of method of measurement of blood or plasma glucose level depends on efficiency and accuracy. Rapid measurement of whole blood glucose is accomplished by glucose oxidase -peroxidase chromogen test strips. The method is hemotocrit dependent. It is important to have any abnormal result (either low or high) confirmed by standard laboratory methods. The

laboratory analysers use different enzymes to measure glucose and are not affected by metabolites or hematocrit levels.

### **Causes of Hypoglycemia - A**

#### **Clinico-pathologic Classification (Table 4)**

Causes of hypoglycemia can be classified as:

1. Transient Asymptomatic Hypoglycemia
2. Hypoglycemia due to a specific etiology:
  - Inadequate supply of glucose
  - Increased utilization of glucose
  - Unknown mechanism
  - Inborn errors of metabolism or hormonal deficiencies
  - Latrogenic factors

### **Symptoms of Hypoglycemia**

In 1935 Whipple et al described, what is now known as Whipple triad, for the diagnosis of hypoglycemia - presence of characteristic clinical symptoms, confirmation on low plasma glucose level during the clinical symptoms and resolution of clinical symptoms once plasma glucose is normalized.

The main symptoms of hypoglycemia are jitteriness, poor feeding, hypotonia, lethargy, weak cry and seizures.

### **Diagnostic Evaluation of Infants with Hypoglycemia**

The majority of cases of hypoglycemia are seen in infants with low reserve to cope with the immediate periods of fasting or with transient hyper-insulinism, such as infant whose mothers are diabetic. They readily respond to enteral or parenteral supplementation of glucose.

However, occasionally hypoglycemia may be a sign of metabolic or hormonal disorders. The hypoglycemia occurring in such infants is usually severe, refractory or persistent and more likely to have associated clinical features.

Investigations of the cause of hypoglycemia are warranted if the following factors are present:

- A family history of previous infant death or developmental delay
- Persistent or recurrent hypoglycemia
- Symptomatic hypoglycemia in healthy looking term infant with growth appropriate for age
- Hypoglycemia with seizures or altering states of consciousness
- Hypoglycemia requiring glucose delivery of more than 10 mg/kg/min



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- Hypoglycemia-associated dysmorphic features or other abnormal clinical features (eg. micropenis, exomphalos)

The pertinent investigations and probable conditions are summarized in Table 5. It is important to obtain the samples at the time of hypoglycemia episodes.

### Management of Hypoglycemia

Management of hypoglycemia is based on individual patient taking into account the physiologic maturity and pathological influences on the patient. In 2000, Cornblath et al suggested operational thresholds in treatment of hypoglycemia based on 5 broad classification<sup>19</sup>:

1. The Term Infant: Healthy term infants born after a normal pregnancy and delivery do not need monitoring of blood glucose. Blood glucose should be measured only if they have clinical manifestations or any new risk of metabolic imbalances emerge.
2. The Infant with signs of hypoglycemia: If any infant show signs of hypoglycemia, treatment should be commenced to maintain plasma glucose above 45mg/dl.
3. Infants with risk factors for compromised metabolic adaptation: Glucose monitoring should be initiated soon after birth, within 2 to 3 hours after birth and before feeding. This should also be done at

point when there is abnormal clinical signs. If the plasma glucose is less than 36mg/dl, close monitoring is recommended with interventions if the plasma glucose remains below this level, if the level does not increase after a feed, or if abnormal clinical signs develop. If the glucose level is below 25mg/dl, intravenous glucose infusion should be given and glucose levels maintained above 45mg/dl. They recommend maintaining plasma glucose level above 60mg/dl in cases of persistent hypoglycemia.

4. Preterm infants: There is no evidence to suggest any lower plasma glucose value for preterm infants.
5. Infants on Parenteral Nutrition: The recommendation is to keep plasma glucose above 45mg/dl. These infants have higher levels of insulin and no significant lipolysis or ketogenesis.

Once the decision to intervene has been taken, the various treatment options are:

1. Continued enteral feed.
2. Intravenous infusion of dextrose- initially a bolus of 200 mg/kg of dextrose, followed by a constant infusion of 8 mg/kg/min. the concentration used is 10% dextrose. This infusion is increased by 2 mg/kg/min, if hypoglycemia persists. Continuous glucose infusion must be started after giving a minibolus to prevent rebound hypoglycemia. Treatment by multiple miniboluses without continuous infusion

Table 4

Pathology	At Risk Group	Mechanism
Inadequate supply of glucose	<ol style="list-style-type: none"> <li>1. Maternal beta-blocker administration</li> <li>2. Preterm infants</li> <li>3. IUGR/ SGA</li> <li>4. Metabolic disease</li> <li>5. Sepsis</li> <li>6. Perinatal stress</li> <li>7. Hypothermia</li> </ol>	<p>Suppressed catecholamine response</p> <p>Low storage of glycogen Inadequate responses of hormone and enzyme Feeding intolerance</p> <p>Low storage of glycogen Inadequate responses of hormone and enzyme Feeding intolerance</p> <p>Defects of enzymes of gluconeogenesis, glycogenolysis or fatty acid oxidation</p> <p>Feeding intolerance Inadequate hormone or enzyme response Hypoxia, acidosis and alteration in blood pressure stimulate catecholamine release in utero. Hypoxia accelerates glucose use by increasing the rate of anaerobic glycolysis</p> <p>Increased use of glucose by tissue. Stimulation of catecholamines, thereby depleting glycogen reserves</p>
Increased utilization of glucose	<ol style="list-style-type: none"> <li>1. Infant of Diabetic mother</li> <li>2. Maternal use of chlorpropamide or benzothiazide</li> <li>3. Exchange Transfusion</li> <li>4. Beckwith - Wiedemann Syndrome</li> <li>5. Islet cell adenoma/Nesidioblastosis</li> <li>6. Malposition of umbilical artery catheter tip (between T10- L2)</li> </ol>	<p>Hyperinsulinism</p> <p>Hyperinsulinism - Direct stimulation of fetal beta cells</p> <p>Hyperinsulinism - Stimulation of insulin secretion by glucose in stored erythrocytes</p> <p>Hyperinsulinism</p> <p>Hyperinsulinism</p> <p>Hyperinsulinism - Glucose flow into celiac axis stimulating insulin secretion</p>
Unknown mechanism	<ol style="list-style-type: none"> <li>1. Congenital hypopituitarism</li> <li>2. Polycythemia - Hyperviscosity Syndrome</li> <li>3. Rhesus hemolytic disease</li> <li>4. Trisomy 13 mosaicism</li> <li>5. Congenital adrenal hyperplasia</li> </ol>	<p>Possibly by growth hormone deficiency</p> <p>Possibly by decrease in plasma volume due to polycythemia leading to reduced availability of glucose</p> <p>Possibly by Hyperinsulinism - Reduced glutathione released from hemolysed red cell stimulate Insulin secretion</p>

**Table 5**

Sample	Test	Suggestive condition
Blood	Glucose	Confirm hypo/hyperglycemia
Increased utilization of glucose	Hematocrit	Polycythemia
	Serum electrolytes	
	Arterial Blood gas	Acidosis
	Liver function tests	
	Insulin and C-peptide	Hyperinsulinism
	Cortisol	Adrenal disorders
	Growth hormone	Hypopituitarism
	Lactate	Acidosis in various metabolic disorders
	Ketone bodies	Disorders of fatty acid metabolism
	Pyruvate	
	Alanine	
	Free fatty acids	Disorders of fatty acid metabolism
	Ammonia	Urea cycle defects
	Serum amino acids	Disorders of amino acid metabolism
	Total and free carnitine levels	
	Gal - 1 - Put	
Urine	Ketones	
	Organic acids	Disorders of fatty acid metabolism
	Reducing substances	
Ophthalmic evaluation	cataract	Metabolic disorders
Cranial ultrasound/MRI		

Brand et al<sup>22</sup> conducted a retrospective study to evaluate the effects of transient hypoglycemia in the first day of life. Their study group were healthy large for gestational age (LGA) infants born to non-diabetic mothers. Blood glucose measurements were done at 1, 3 and 5 hours of age. Their definition of hypoglycemia was blood glucose less than 2.2 mmol/L (40mg/dl) in the first hour of life and blood glucose less than 2.5 mmol/l (46mg/dl) subsequently. These infants were tested using the Denver Developmental Scale, non-verbal intelligence test, and the child behaviour check list. This study suggested that transient mild hypoglycemia (1.5-2 mmol/L) in healthy term LGA infants does not appear to be harmful to psychomotor development at age of 4 years.

Duvanel et al<sup>23</sup> conducted a prospective study involving small-for-gestational-age (SGA) preterm infants. They compared infants with blood glucose levels less than 2.6 mmol/l to a similar group who maintained normoglycemic. Any infant with less than 2 mmol/l was treated with intravenous 10% dextrose at the rate of 5 to 9 mg/kg/minute. They conducted neurodevelopmental and neurological examinations from 6, 12 and 18 months of corrected gestational age. Further psychometric tests were performed at 3.5 and 6 years of age.

Their study concluded that:

1. The incidence of hypoglycemia in SGA preterm infants was 73%, more common than previously thought.
2. Head circumference at 12, 18 months and at 5 years was significantly reduced in infants who had repetitive hypoglycemia. (6 episodes or more).
3. Psychometric tests at 6, 12 and 18 months were similar between infants with repetitive hypoglycemia (6 episodes or more) and the control group. However, perceptible performance scale and motricity index were decreased in repetitive hypoglycemia group at 3.5 years of age.
4. Infants with recurrent moderate hypoglycemia (blood glucose between 0.6 to 1.6 mmol/L) had lower neurodevelopmental scores than the group with a single unique severe episode of hypoglycemia at 3.5 and 5 years of age.

Lucas et al conducted a multicentric study involving 661 preterm infants (weighing less than 1850g). The authors determined that the plasma glucose levels every six hours for the first 48 to 72 hours of age<sup>24</sup>. They concluded that:

1. The incidence of hypoglycemia below 1.6 mmol/l occurred in 28% of the infants.
2. Moderate hypoglycemia (less than 2.6 mmol/L) occurred in 67% of infants.
3. Plasma glucose below 2.6 mmol/l resulted in reduction of motor and mental development scores at 18 months.
4. The deficit increased with the number of days of hypoglycemia.

is not recommended. Glucose infusion can be increased to 12-14mg/kg/min, after which further increases may produce fluid overload, venous thrombosis. Any dextrose infusion having a concentration of more than 10% should be given through a central access eg. UVC, PCVC. Once normoglycemia is achieved glucose infusion should be decreased gradually by 2mg/kg/min, while increasing enteral feeds.

3. Hydrocortisone - If the plasma glucose levels are not above 40mg/dl or if hypoglycemia recurs after intravenous glucose infusion of 12mg/kg/min, then hydrocortisone 10mg/kg/day in 2 divided doses given, IV, IM or orally. Hydrocortisone acts by the following mechanisms: reduces peripheral glucose utilization, increases the effects of exogenous glucagon and enhances gluconeogenesis. Hydrocortisone is continued for around 72 hours after stopping intravenous fluids.
4. Epinephrine - If hypoglycemia does not respond to the above-mentioned measures, then a trial of epinephrine is suggested. Initially, a subcutaneous injection is given, followed by intravenous infusion. Epinephrine acts by mobilizing stored fuels by glycogenolysis, gluconeogenesis, lipolysis, augmentation of glucagon action and suppression of insulin secretion. Hence epinephrine is particularly useful in infants with hyperinsulinism.

5. Glucagon - This is hardly used except if the infant has glucagon deficiency. There may be a use in diagnosing cases of hepatic glycogen storage disorders.
6. Diazoxide - This is a non-diuretic thiazide which inhibits pancreatic insulin secretion, hence often effective in infants with hyperinsulinism.
7. Human growth hormone - this is effective in infants with hypoglycemia secondary to growth hormone deficiency.
8. Somatostatin- this is mainly confined to pre-operative control in infants with suspected beta cell nesidioblastosis - adenoma spectrum.
9. Pancreatectomy - In cases of beta cell nesidioblastosis- adenoma spectrum, partial or full pancreatectomy may be effective if medical therapy fails.

### Neonatal Hypoglycemia and Neurodevelopment

All the controversies about hypoglycemia and its treatment aim at minimizing the final outcome -- neurodevelopmental disability. Several studies have tried to establish a 'safe' level of blood glucose above which there is no risk of neurodevelopmental disability. Although all of these studies have contributed to our understanding of hypoglycemia and long-term neuro-developmental disability, only a few are discussed here.

## Conclusion

In spite of the numerous studies, the extent of neuro-developmental impairment caused by hypoglycemia is still uncertain and many questions remain to be answered<sup>43</sup>.

## Hyperglycemia

The degree of prematurity plays a central role in incidence of hyperglycemia. Hyperglycemia is most commonly seen in preterm infants less than 30 week gestation, and in their first day of life<sup>25</sup>. There was a highly significant trend toward an increasing risk of hyperglycemia with decreasing body weight, such that the risk of hyperglycemia among infants weighing less than 1,000 g was 18 times greater than the risk among infants weighing more than 2,000 g<sup>25</sup>.

## Definition of Hyperglycemia

As with hypoglycemia, the threshold value of blood glucose used to diagnose hyperglycemia is variable.

The physiological threshold of blood glucose is above 125 mg/dl (7 mmol/L); the rationale being that the blood glucose levels in utero and in term infants rarely have blood glucose above 7 mmol/L.

Functional or interventional threshold - Most neonatologists would consider intervention when the blood glucose is above 180mg/dl (10 mmol/L).

## Possible Causes and Pathophysiological Effects of Hyperglycemia

### Causes of Hyperglycemia

1. **Prematurity** - prematurity predisposes to hyperglycemia by various mechanisms. The 'insulin' secreted by premature infants is actually a range of proinsulin polypeptides with the majority of the 'insulin' having only a tenth of the biological activity of mature insulin<sup>25</sup>. The tissues of preterm infants are also relatively resistant to insulin.
2. **Sepsis and Stress** - Hyperglycemia may be the first sign of infection. Infants experiencing stress as a result of sepsis or surgery have increased levels of catecholamines which causes hyperglycemia. Hyperglycemia is also seen in infants with an episode intracerebral bleed, because of the lower glucose consumption occurring during this bleeding episode.
3. **Parenteral Infusion** - Glucose delivery in excess of 10mg/kg/min especially in preterm infants are likely to cause high blood glucose levels.
4. **Medications** - Steroids, inotropes, theophylline all have been shown to increase blood glucose levels.
5. **Factitious** - Occasionally spurious levels are seen if venous samples are drawn when a glucose infusion is being run from down the vein, as it is also the case when a sample is taken from arterial line running dextrose infusion.
6. **Transient or Permanent Diabetes Mellitus.**

### Pathophysiological effects of hyperglycemia

Hyperglycemia will lead to osmotic diuresis, cause changes in osmolality of the plasma, which in turn lead to effects such as electrolyte disturbances, dehydration and intraventricular bleed. Plasma osmolality increases by 1 mosmol/L for each 18 mg/dL increase in plasma glucose concentration<sup>25</sup>. Osmotic diuresis is more likely at blood glucose levels above 360 mg/dl<sup>25</sup>. Hey et al suggested that even at 2% glucosuria, the additional osmolal load is extremely unlikely to cause osmotic diuresis<sup>25</sup>.

## Potential Adverse Effects of Hyperglycemia

Over the years various workers have recognized the deleterious effects of hyperglycemia. Hyperglycemia may be associated with higher mortality, higher incidence of IVH, infection, NEC, ROP, fungal infection and poor neurodevelopment outcome<sup>29-36</sup>.

## Management of Hyperglycemia

Although there is no definite value, most neonatologists would consider intervention at values of 180-200 mg/dl. The management of hyperglycemia is essentially maintaining a fine balance between providing enough glucose for growth of the infant and preventing the deleterious effects of hyperglycemia. Equally important is the recognition that hyperglycemia may be the first sign of sepsis. The salient features of management are:

1. **Investigating and treating underlying conditions** - Sepsis, stress, pain, hypoxia and medications are all known to induce hyperglycemia and it is prudent to correct them quickly.
2. **Optimizing nutrition** - Starting enteral feeds if possible, however, small the amount improves glycemic control. Also there may be a benefit by increasing amino acid infusion in the parenteral nutrition.
3. **Optimizing glucose delivery** - A stable infant needs about 6 mg/kg/min of glucose. An additional 2 mg/kg/min is needed if the infant is unwell. A glucose infusion above 12 mg/kg/min is counter-productive and is unnecessary.
4. **Insulin therapy** - Persistent hyperglycemia, in spite of the above measures, warrants treatment with insulin. We routinely start a dose of 0.05U/kg/hr, and monitor blood glucose every 2 hours. As evident from the NIRTURE study<sup>26</sup>, there is little clinical benefit in prophylactic early insulin therapy along with glucose infusion.

## Neonatal Diabetes Mellitus

Neonatal diabetes mellitus is a very rare but well recognized condition having an incidence of 1 in 400,00- 500,000 newborns<sup>27</sup>.

Neonatal Diabetes Mellitus (NDM) is defined as persistent hyperglycemia occurring in the first month of life, lasting for at least 2 weeks, and requiring insulin. Some have suggested the age of onset be extended to the first 6 months of age and the condition to be renamed as 'Congenital Diabetes Mellitus.'

### Clinical Features

The majority of infants with NDM have IUGR, not surprisingly given the role fetal insulin has on fetal growth. The clinical features are hyperglycemia, IUGR/ SGA, failure to thrive, dehydration, ketoacidosis and coma.

Therapy with insulin corrects the hyperglycemia and results in catch-up growth. No dysmorphic features have been associated with NDM, and it is not possible to differentiate between Transient NDM and Permanent NDM clinically<sup>26</sup>.

1. **Transient Neonatal Diabetes Mellitus (TNDM)**<sup>26</sup> - Fifty to sixty percent of NDM are transient. The insulin dependence resolves in 3-4 months of age in majority of cases. The following mutations have been observed in TNDM:
  - Gene mutation on chromosome (6-70%)
  - ABCC8 mutation (13%)
  - KCNJ11 mutation (10%)

Infants with TNMD have a risk of relapsing into a permanent diabetic state around adolescence or adulthood.

2. **Permanent Neonatal Diabetes Mellitus (PNMD)**<sup>26</sup> - 40-50%. As the name suggests, the hallmark of PNMD is hyperglycemia without resolution of insulin dependence. Multiple gene defects have been associated with this condition with about 50% of cases linked to potassium channel mutation.

## Treatment of Neonatal Diabetes Mellitus

Prompt correction of dehydration and electrolyte imbalances, insulin therapy and high calorie diet are the mainstay of treatment. Depending on the gene mutation, a few of these cases may also be treated by sulphonyl ureas. However these are best left to specialized centers who are experienced in managing such patients. Given the complex nature of gene mutations and inheritance, all families must be offered genetic counseling.

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## NT

*Kaninghat Prasanth, MD, MRCPCB  
Division of Neonatology  
Department of Pediatrics  
John H. Stroger Jr. Hospital of Cook  
County, Chicago  
Chicago, IL USA*

*Sachin Gupta, MD  
Division of Neonatology  
Department of Pediatrics  
John H. Stroger Jr. Hospital of Cook  
County, Chicago  
Chicago, IL USA*

## Corresponding Author

*T.F. Yeh, MD, PhD  
Division of Neonatology  
Department of Pediatrics  
John H. Stroger Jr. Hospital of Cook  
County  
1902 W. Harrison St.  
Chicago, IL 60612 USA*

and

*China Medical University  
91 Hsieh Shih St.  
Taichung, Taiwan  
or  
Taipei Medical University  
Wu-Shin St. Taipei, Taiwan*

*tsufuhy@yahoo.com*

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# 'CAN' Syndrome (Cord-Around-the-Neck Syndrome)

By Morarji Peesay, MD; Nitin Mehta, MBBS

To date, I do not think anyone has coined the term "CAN Syndrome." Many of us are very well-acquainted with the term "Cord-Around-the-Neck," but have not yet thought of it as an actual syndrome. The CAN Syndrome is a complex syndrome which is similar to the act of one being strangulated at varying intensities. We as neonatologists are well aware of the signs and symptoms associated with CAN, and manage it routinely in the NICU. I think it deserves attention to heighten its awareness, since it is such a commonly encountered condition.

To those who practice obstetrics, it seems that this delicate thread (the umbilical cord) all too often becomes wrapped around the newborn's neck. Much like a hangman's noose, the nuchal cord is often blamed for problems that are encountered during delivery, and is sometimes cited as a major cause of fetal distress and perinatal mortality. The actual significance that a nuchal cord has on the outcome of an infant is controversial.

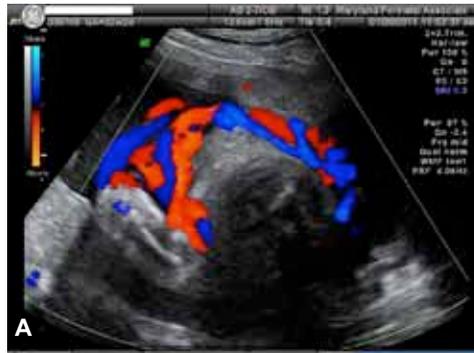
So, could the nuchal cord really affect the outcome of delivery and have long-term effects on the infant?

As neonatologists, we have encountered CAN scenarios multiple times. These infants look pale, dusky, hypovolemic, and most often need some resuscitation (we frequently admit them in NICU for fluid resuscitation). The basic work-up of these infants has shown that they are mildly acidotic and anemic. They may also have mild respiratory distress manifested by minimal retraction, grunting, and flaring. Those infants who have the cord-around-the-neck may also have petechiae above the cord entanglement, usually seen on the face and neck and upper part of chest. They may also be somewhat obtunded and have a stupor with a low tone. They are slow to feed and may also have feeding difficulties transiently.

All these features suggest to me that these infants may go into transient encephalopathy which may lead to long-term complications that we do not know.

To-date, and to my knowledge, there are no EEG findings in these infants. There are no studies assessing the neurological status of these infants or their Sarnat scoring. Long-term effects of oxygen deprivation, acidosis, and hypovolemia secondary to CAN are unknown.

I define the CAN Syndrome as a cluster of cardio-respiratory and neurological signs and



A - Fetal scan showing Doppler flow of umbilical cord around the neck; B, D and E - 3D image of fetal scan showing CAN; C and E - Fetal scan showing CAN in 3D. Photos as courtesy Maryland Perinatal Associates.

symptoms that occur secondary to the initial wrapping of the cord around the neck.

The cluster of symptomatology includes: pallor (anemia), duskiness, hypovolemia, acidosis, mild respiratory distress, petechiae on the face, neck and upper chest, stupor, hypotonic, feeding difficulties.

It is a transient phenomenon, but may have long-term effects in the infant. These could be related to the prolonged strangling of the tight cord-around-the-neck.

There may be long-term effects related to prolonged and tight cord round the neck keeping in mind that it is similar to strangulation of young newborn.

Recognizing this as a syndrome has several advantages:

1. It will heighten the awareness of such a cluster of signs and symptoms related to CAN.
2. It allows us to focus on the long-term neurological aspects of prognosis, and prognosticate better after further studies.
3. it might bring better diagnostic modality and management in the future.
4. It will bring recognition to the infants inadvertently subjected to CAN.

Twenty-five percent of pregnant women present with nuchal cords, and the majority of them don't have significant problems related to it. Despite the good prognosis in most of the cases, some studies demonstrate that the

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***“I define the CAN Syndrome as a cluster of cardio-respiratory and neurological signs and symptoms that occur secondary to the initial wrapping of the cord around the neck.”***

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presence of a nuchal cord is associated with variable fetal heart rate deceleration, decreased fetal movement, umbilical arterial metabolic acidemia, neonatal anemia, and, in extreme situations, intrauterine fetal demise. Antenatally, a nuchal cord can sometimes be detected by ultrasonography, but no action is required by the obstetrician. In no study was it possible to distinguish between a loose and a tight cord on ultrasound. According to Larson, nuchal entanglement increases from 6% at 20 weeks of gestation to 30% at, and around 40 to 42 weeks.

The most common fetal effects of nuchal cords are fetal heart rate decelerations during labor or a change in fetal behavior prenatally.

The presence of two or more loops is estimated to affect between 2-8% of all pregnancies. Obstetricians routinely check for nuchal cords as they deliver the baby. If they feel it, they can slip the cord over the baby's head. Sometimes, if the cord is tightly wrapped, it is clamped and cut before the shoulders are delivered. However, recent studies show that there is little reason to check for a cord, because cutting it cuts off the oxygen that the placenta is supplying and outcomes are better if the baby is delivered. The cord, then, is no longer compressed after the birth, and will continue to provide oxygen for a few more minutes. This is only possible if the delivery is rapid. The cord may become coiled around various parts of the body of the fetus, usually around the neck. Some suggest that Nuchal cord is caused by movement of the fetus through a loop of cord. Nuchal cord has been associated with labor induction and augmentation, prolonged second stage of labor, and fetal heart rate abnormalities. Nuchal cords very rarely cause fetal demise, and are not an

intrinsic reason for intervention. The importance of nuchal cord vis a vis the management of third trimester pregnancy and labor has been debated for many years.

Studies were unable to demonstrate any association between nuchal cords and maternal age, race, parity, pre-pregnancy weight, or weight gain. Infant sex was not significantly associated with nuchal cords, either.

The average umbilical cord length is 50 to 58 cm, with longest reported cord measuring 175 cm. The length of the umbilical cord predisposes an infant to a nuchal cord. Longer cords tend to become looped around the neck. Nuchal coiling can occur in shorter cords, however, in which case the cord tends to be more tightly wrapped around the infant's neck.

In 1995, Larson had studied the intrapartum complications associated with multiple nuchal cord entanglement. He concluded that the group with four or more loops involved had significantly lower birth weight, more episodes of severe variable and late decelerations, meconium, and a higher incidence of operative delivery. However, if signs of fetal discomfort -- such as decreased fetal movement or persistent fetal heart variable decelerations, or even signs of fetal distress like repeated late decelerations -- are present, operative intervention is recommended.

Although the presence of a single nuchal cord does not require changes in the management of the pregnancy, does the prenatal detection of multiple loops alter the management?

*Does CAN Syndrome have long-term effects? Does releasing tight cord around the neck prior to delivery of the infant minimize short-term or long-term effects?*

Although some authors seem to suggest that those newborns delivered with four or more nuchal loops around the neck are at a higher risk to develop complications. Does tight cord around matter for long-term neurological sequel rather than multiple loops around the neck? A long-term follow-up of these infants may shed some light.

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NT

#### Corresponding Author



Morarji Peesay, MD, FAAP  
Neonatal Attending  
Georgetown University Hospital  
3800 Reservoir Rd. NW  
Washington, DC 20007 USA  
Tel: 301.774.8758; Fax: 301.774.2425  
peesay@yahoo.com



Nitin Mehta, MBBS  
Georgetown University Hospital  
3800 Reservoir Road, NW  
Main Hospital Building  
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# Global Neonatology Today: A Monthly Column: Commentary Concerning the Millennium Development Goals: Pros and Cons

By Dharmapuri Vidyasagar, MD, FAAP, FCCM

Despite the world-wide acceptance of the Millennium Development Goals, and their target dates and the indicators, there is no lack of debate on the pros and cons of the concept and the implementation process of MDGs by 2015.

The supporters believe that the Millennium Development Goals (MDGs) are indeed important for the progress of the people around the world. The critics believe that the goals for global development are too narrow. Here are the important points in favor and against the concept of MDGs.

## THE PROS

1. MDGs, even though somewhat narrowed to eight major goals, MDGs motivate governments to work toward improving and achieving targets.
2. Secondly, whether the countries reach the set Goals or not by 2015, they would have stimulated leadership towards the betterment of their countries.
3. The above two points lay the foundation for countries lacking large banks of thinkers and policy makers.
4. The MDGs have also increased the awareness of the public regarding their fundamental rights regarding health, education, and rights of women and children, which are important for the economic growth of the country.
5. The MDGs have highlighted the available opportunities, and ways to improve lives of individuals and the community in which they live.
6. The MDGs will be a success, so long as some progress is made towards the goals. It is the poorer countries that have the most progress to make towards the goals; thus any progress they make is inspiring.
7. It is important, therefore, that the success or failure of the Goals should not be judged simply by whether the goals are achieved by the year 2015, as long as progress has and is being made.
8. The target of 2015 gives a motivation. No target, no aim; no aim, no motivation, hence no progress.

In spite of the wide acceptance of MDGs and worldwide activity towards achieving the targets, there are critics.

## THE CONS

1. The critics feel both that the MDGs are too narrow and, hence, the implementation is too narrow as well.
2. MDGs only focus only on economic, social and cultural rights, and not the corresponding civil and political rights.

3. Even within economic, social, and cultural rights, opponents further criticize the Goals because they do not include targets for expanding people's participation in government, increasing employment opportunities, reproductive health care rights, and institutional governance reforms.
4. Similarly, critics disapprove of the narrow indicators used to measure progress towards the Goals. These critics do not consider indicators such as school enrollment gaps to be a meaningful measurement of human development progress.
5. The underlying concern is that just because countries may lack a certain number of telephones or statistically have an equal number of boy and girl students enrolled in school, does not necessarily mean that the Millennium Development Goal that the indicators relate to is being met (or that a country is falling short).

In my view, MDGs #4 and #5, regarding school enrollment and the equality of educational opportunities for boys and girls, and access to telephones, is too important to ignore. First, harnessing the brains of future citizens is critical to nation-building; closing school enrollment and equality gaps should, therefore, be considered a priority. The number of telephones on its face value may not sound like a rather significant achievement; however, telephones have been a significant and noticeable contribution to growth of human development.

In response, supporters of the MDGs respond that the MDG indicators cannot be taken out of context, viewing the indicators not as ends in themselves, but rather as benchmarks of progress towards the broader goal to which they relate.

6. Other commentators criticize the very concept of having global goals and criticize the MDGs in particular for being too idealistic and setting the stage for disappointment. *Without aiming high you will remain where you are forever.*
7. Here, the concern is that countries that fail to meet the Goals by 2015, or that do not make sufficient progress towards that end, will be stigmatized as failures, resulting in further political separation between rich and poor countries. *Indeed, not so these countries would need more help, cajoling or other plans from global leadership.*
8. The critics are also concerned that, while the Goals may be attainable at the global level, it may be impractical to expect all regions and countries to reach the various indicators and targets. *This is but to be expected and normal; nothing wrong.*
9. Some countries have objected to the vast influence that donors have over how countries approach the implementation of the MDGs. Many communities feel that local officials have been undermined by the agendas of donors and UN agencies, instead of allowing communities to take their own approach to reaching the MDGs. *These are genuine concerns.*



## The Barth Syndrome Foundation

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info@barthsyndrome.org

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10. Many countries have expressed concern about the practice of relying on statistics to evaluate country and region progress. While statistics may be useful in measuring global progress overall, averages can be misleading since progress typically varies even within a single country. These critics note that statistical averages have a tendency to lead to unwarranted conclusions not based on real observations. *I agree, however, averages are only for comparison. Countries should make self-assessment and self-evaluations.*
11. The MDGs will only be successful in open, participatory political cultures. *This is very true, and underlies all the MDGs.*

It is important to recognize that the Goals must be supported by political will if they are to succeed. Both the people and governments, at both the national and local levels, must feel that the MDGs are their own goals, and not just those of the international community. People and local governments must work together in the decision-making process for the Goals to have a higher likelihood of success.

Despite the various pros and cons of the Millennium Development Goals, one thing is clear – the international community has taken them seriously, and it is still hopeful that the Goals will be met in the next five years.

It is clear that MDG #8 is fundamental to the success of implementing all other MDGs. The Minister from Uruguay emphasized the need for complying with MDG #8 by all member states as he spoke to a high-level plenary meeting of the UN General Assembly on the Millennium Development Goals (MDGs).

"Compliance with development goal number eight is essential for achieving the other millennium development goals, since commitment to development must be a collective commitment," of states of the globe. He said that though his country has been doing its part in working toward the MDGs, such cooperation between countries is very helpful in facilitating development progress."

"International trade, technology transfer, affordable access to medicines, an endur-

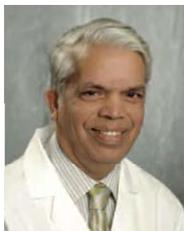
***“Despite the various pros and cons of the Millennium Development Goals, one thing is clear – the international community has taken them seriously, and it is still hopeful that the Goals will be met in the next five years.”***

ing solution to the problems of external debt and compliance with the commitments to ODA (official development assistance), just to mention a few of the goals established in this framework, are fundamental in the efforts carried out at all levels in order to achieve development," Lemes said.

The world's rich countries agreed to give 0.7% of their gross national income as official international development aid, annually. However, only five European countries, namely Norway, Sweden, Luxembourg, the Netherlands and Denmark, have carried out their pledges.

There is much more to be done, and ***“The Clock is Ticking!”***

NT



*Dharmapuri Vidyasagar, MD, FAAP, FCCM  
University of Illinois at Chicago  
Professor Emeritus Pediatrics  
Division of Neonatology  
Phone: +1.312.996.4185  
Fax: +1.312.413.7901  
dvsagarmd@yahoo.com*

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