Neonatal Hypoglycemia and an Overview of Glucose Homeostasis, Infant of Diabetic Mothers

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Incidence of Hypoglycemia among Term Births

- 1-5 per 1,000 births
- 8% in LGA
- 15% in SGA (IUGR)
- 30% in entire population of high risk infants

Glucose Biochemistry

A. Glucose Homeostasis in Utero
- Fetal Energy is in the form of glucose, lactate
- free fatty acids, ketones, surplus amino acids
- alanine
- Facilitated diffusion across the placenta
- Fetal blood glucose concentration is ~70% of maternal glucose value
- Maternal hyperglycemia leads to fetal hyperglycemia and pancreatic stimulation of fetal insulin production and secretion
Glucose Biochemistry and Homeostasis in Utero

- Insulin appears in the fetal pancreas and plasma at 12 weeks gestation
- Permissive in accumulation of hepatic glycogen stores

- High insulin: glucagon production and stores
  - increased glycogen synthesis and
  - suppression of glycogenolysis
  - suppresses lipolysis

Glucose Homeostasis in Utero

- Marked increase in glycogen synthesis during early and mid-gestation associated with increase in circulating concentrations of insulin and cortisol

- Fetal hormonal and metabolic milieu established a ready substrate supply that can be used during the metabolic transition from fetus to newborn

Birth presents an Energy Crisis for the Newborn

Change in Glucose Homeostasis at Birth

- At Delivery - rapid glycogenolysis (if there are glycogen stores)
- Adaptive response with a surge in plasma glucagon and a decrease in plasma insulin (high glucagon to insulin) which mobilizes glucose and fatty acids from glycogen and triglyceride deposits (brown fat)
- High glucagon: insulin induces synthesis of enzymes required for gluconeogenesis

- LOW BLOOD GLUCOSE VALUES ARE USUALLY NOT RELATED TO SIGNIFICANT METABOLIC DEFECTS RATHER A NORMAL PROCESS OF METABOLIC ADAPTATION TO EXTRAUTERINE LIFE.
Maintenance of Normal Hepatic Glucose in Newborn

- Adequate stores of glycogen and gluconeogenic precursors (fatty acids, glycerol, amino acids, and lactate) often not present in IUGR
- Appropriate concentration and activities of hepatic enzymes required for glycogenolysis and gluconeogenesis
- Normally functioning liver, adrenal axis & fetal pancreas

Definition of Hypoglycemia

- Definition of hypoglycemia is a population based statistical point estimate rather than a functional
- Value resulting in a low “cut off” value for the level of Glucose for a specific infant.
- Many problems with the statistical definition: preterm vs term, whole blood glucose vs plasma glucose, and time from birth

Defining a “Normal” Glucose and Hypoglycemia

- Clinical Approach-symptoms-irritability, jitteriness, lethargy, stupor, apnea/cyanotic episodes, poor feeding, hypothermia, hypotonia, tremors, seizures
- Epidemiological Approach-have been erroneously interpreted and used to define “cut off” points between hypo, eu, or hyperglycemia rather than recognizing that hypoglycemia reflects a continuum of biological abnormalities ranging from mild to severe
Defining “Normal” Glucose Levels or Hypoglycemia

- Approach based on acute metabolic, endocrine, and neurologic function—inadequate evidence because of few data sets in specific populations. It is also related to glucose delivery, not merely glucose level.
- Approach based on long-term neurologic/developmental outcome—datasets limits and lack of suitable euglycemic control population in these studies.
- Static versus Dynamic processes requires continuous glucose monitoring devices not intermitant “heel stick” or blood draw methods that may be associated with pain or events that can alter blood glucose levels.

Definition of Neonatal Hypoglycemia

- Cornblatt 2000 “The definition of clinically significant hypoglycemia remains one of the most confused and contentious issues in contemporary neonatology.” Pediatrics May 2000; 105(5): 1141-5.
- Inder, T. 2010 “3 important principles in relationship to hypoglycemia-mediated cerebral injury in the newborn” with first being “prolonged and severe hypoglycemia which would not relate to a single blood glucose level of < 45 mg/dL. The second principle related to the general cerebral vulnerability a pattern of injury. The third outlined that “mild hypoglycemia combined with mild hypoxia-ischemia resulted in cerebral injury, whereas either of the two conditions did not.”
- Hay et al 2010 “The experimental and human clinical data that blood glucoses <45 mg/dL cause injury is supported neither by clinical data in humans or animals.”

2011 AAP Hypoglycemia Guideline

Screening and Management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDMs/LGA Infants

<table>
<thead>
<tr>
<th>Birth to 4 hours of age</th>
<th>4 to 24 hours of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial feed within 1 hour</td>
<td>Continuous feeds q 2-3 hours</td>
</tr>
<tr>
<td>Screen glucose 30 minutes after 1st feed</td>
<td>Screen glucose prior to each feed</td>
</tr>
<tr>
<td>Initial screen &lt;25 mg/dL</td>
<td>Screen &lt;45 mg/dL</td>
</tr>
<tr>
<td>Feed and draw in 1 hour</td>
<td>Feed and check in 1 hour</td>
</tr>
<tr>
<td>&lt;25 mg/dL</td>
<td></td>
</tr>
<tr>
<td>25-42 mg/dL</td>
<td>&lt;35 mg/dL</td>
</tr>
<tr>
<td>Predicted glucose as needed</td>
<td>IV glucose as needed</td>
</tr>
<tr>
<td>35 - 45 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

Target glucose screen 245 mg/dL prior to routine feeds

- Glucose dose = 30-60 mg/kg/hour (max 12 mg/kg/hour) divided to achieve at 3-4 mg/kg/hour per min (50-100 ml/kg per day). Achieve glucose level at 45-50 mg/dL.

Symptoms of hypoglycemia include: irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, apnea, cyanosis, poor feeding.
Operational Thresholds

- **Indication for Interventions:**
  - Plasma Glucose concentrations <40 mg/dL in both preterm and term infant (in few hours after birth)
  - Serum Glucose <45 mg/dL if symptomatic will be treated as hypoglycemia
  - Less than 50-60 mg/dL after 24 hours

Confirmation of Screening Tests

- If a screening test (heel stick ChemStrip) reveals a low or threshold glucose level, obtain a STAT blood glucose (sent in a fluoride containing tube) for laboratory confirmation
- Whole blood glucose may be 10% lower than an ChemStrip glucose
- It is also critical that once a screening test documents that the screening glucose is >60 mg/dL, then this should be documented (basic metabolic profile).

Risk Factors for Hypoglycemia

- Changes in Maternal Metabolism: Intrapartum administration of glucose, drug treatment with terbutaline, propanolol, oral hypoglycemics, insulin, and diabetes during pregnancy
- Neonatal Issues: Perinatal hypoxia-ischemia, infection, hypothermia, hyperviscosity, hydrops fetalis, congenital cardiac malformations, IUGR, Hyperinsulinism, endocrine disorders, inborn errors of metabolism
Basic Mechanisms of Risk

- Limited Glycogen Stores
- Hyperinsulinism
- Diminished Glucose Production
- Limited Glucose Delivery

Limited Glycogen Stores and Supply

- Prematurity
- Perinatal stress/distress-especially HIE
- IUGR
- Disorders of Glycogen Metabolism
  - Glucose 6 phosphatase deficiency
  - Amylo-1,6 glucosidase deficiency
  - Phosphoenolpyruvate deficiency
- These limit either glycogen metabolism or glucose release resulting in excess glycogen stores, hepatomegaly, and hypoglycemia and are inherited primarily as autosomal recessive disorders

Hyperinsulinism

- Infants of Diabetic Mothers: Maternal hyperglycemia with fetal transfer of elevated maternal glucose levels to the fetus (~70%) causes fetal insulin secretion in excess
- Beckwith-Wiedemann Syndrome
- Erythroblastosis fetalis-hydrops
Hyperinsulinism

- Maternal Drug Effects of Neonatal Glucose Metabolism
- Chlorpromazine and benzothiazides
- Propanolol
- Beta-sympathomimetics (Terbutaline)
- Inappropriate intrapartum maternal glucose infusion
- Islet cell adenoma or Nesidioblastosis—primary abnormality of pancreatic beta-cell development resulting in sustained or persistent neonatal hyperinsulinism and hypoglycemia
- Beckwith-Wiedemann Syndrome

Others

- Hypothermia, Sepsis, increased work of breathing, HIE
- Normal glycogen stores but inadequate to meet increased energy demands
  - Cortisol and Growth Hormone Deficiencies
    - secondary to effects on hepatic glycogenolysis
    - and gluconeogenesis
  - Polycythemia
    - Direct result of increased glucose consumption by increased RBC mass and secondary to effects on intestinal adsorption of substrates

Clinical Presentation of Hypoglycemia

- No signs or symptoms the “asymptomatic infant”
- Jitteriness
- Lethargy
- Apathy
- Tachypnea
- Bradycardia
- Apnea
- Cyanosis
- Seizures
- Irritability
Initial Approach to Determine Etiology

- Is there presence of a risk factor?
- Plot Growth Parameters (SGA, AGA, LGA)
- Consider sepsis for infants without risk factors
- If more than one week consider hyperinsulinemia, endocrine disorder or inborn error of metabolism

When do you “Screen” at risk infants?

- In any symptomatic infant screen immediately
- If asymptomatic, but at high risk, including IDM, possibly sepsis, premature, <1500 gm Birth Weight, SGA, LGA screen at 30 minutes after birth
- If Screen is positive, send whole blood for stat Glucose determination
- False Positives: Hematocrit <35%, contamination
- With isopropyl alcohol,
- False Negatives: Hematocrit >55%, Glucose values that are very low or very high (<20 and >200 mg/dL)
- False results if done at <18 degrees C or >35 degrees C.

Management Principles

- To normalize blood glucose concentrations as quickly as possible and to avoid further episodes of hypoglycemia by providing adequate substrate until normal glucose homeostasis can be maintained.
- Term, asymptomatic, mild hypoglycemia-enteral feedings-adequate amounts of maternal breast milk or standard infant formula to provide carbohydrate in the form of lactose plus protein and fats which are metabolized more slowly
- Blood increase by 30 mg/dL within the first hours after feeding a standard formula with 30-60 ml of feeding
Management Principles

- Infants whose blood glucose levels become normal following an enteral feeding should continue to have glucose monitoring before each feeding for 12-24 hours.
- When enteral feeding is considered a failure if within 30-60 minutes of a feeding the blood glucose level is again in the hypoglycemic range, begin IV glucose therapy OR if the infant becomes symptomatic.
- Prompt IV glucose therapy should avoid repeated episodes of hypoglycemia.
- May need to provide urgent 2 ml/kg of D10W IV to stabilize glucose level urgently.

Management Principles

- IV Glucose Therapy—Any symptomatic infant or any infant unable or unwilling to tolerate enteral feedings.
- Those infants in whom the disturbance in glucose homeostasis is severe or is expected to last more than an hour.
- IV Therapy: Initial bolus of D10W 2 ml/kg followed by glucose infusion that continuously provides 5-8 mg/kg/min of glucose.
- Blood Glucose checked after 30 minutes and repeated every 1-2 hours.
- If subsequent glucose values falls, bolus should be repeated an infusion rate increased 10-15% up to 12-15 mg/kg/minute—need to place a central line UVC or PICC line is needed.

Management Principles

- IV Glucose Therapy—maintain IV glucose therapy and continue to feed infant especially carbohydrates such as lactose and glucose.
- When can an infant be weaned from IV Glucose Therapy? Decrease glucose infusion by 10-15% each time the infant’s blood glucose is >60 mg/dL.
- Failure to tolerate IV glucose indicates further evaluation.
Management Principles

- Reduce energy needs: Place infant in thermo-neutral environment, avoid cold stress, avoid acidosis
- Monitor every 30 minutes until the glucose level is stable
- Consider sepsis if no other risk factors
- Avoid iatrogenic hyperinsulinism from umbilical arterial catheter glucose infusion close to pancreatic artery and rebound hypoglycemia following rapid IV bolus of hypertonic glucose
- Frequent boluses of D10W will induce an insulin surge and rebound hypoglycemia – try not to use more than 2 boluses of D10W

Management Principles

- If hypoglycemia is prolonged or recurrent or requires >12 mg/kg/minute to maintain euglycemia then consider conditions that are associated with hyperinsulinism syndromes, defects in carbohydrate, amino acid, or fatty acid metabolism
- Recurrent or persistent hypoglycemia poses the greatest risk for seizures and severe neurodevelopmental delays.

More extensive evaluations

- Assay for insulin, C-peptide, cortisol, growth hormone, beta-hydroxybutyrate, lactate, free fatty acids, T4, TSH
- Urine for reducing substances, ketones, urine organic acids
- Familial hyperinsulinemic syndrome–gene analysis
Adjuctive Therapies

- Corticosteroids >> decrease peripheral glucose utilization with dose of hydrocortisone 5-15 mg/kg/day or prednisone 2 mg/kg/day
- Glucagon >> stimulates glycogenolysis with a dose of 30 mcg/kg if insulin level is normal or up to 300 mcg if insulin level increased
- Diazoxide >> inhibits insulin secretion in doses of 15 mg/kg/day (usually given q8hr)
- Somatostatin (octreotide) >> inhibits insulin and growth hormone release in doses of 5-10 mcg/kg every 6-8 hr (injection only)

Consequences of Hypoglycemia

- Selective Neuronal necrosis in multiple brain regions including the superficial cortex, dentate gyrus, hippocampus and caudate and putamen
- In preterm infants predisposes to IVH
- Impaired cognitive and motor function
- Imaging studies in term infants and selected preterm infants

Neuropathology in Hypoglycemia

- Acute Changes: In severe hypoglycemia neonatal brain pathology reveals: neuronal injury in cerebral cortex, hippocampus, basal ganglia, thalamus, brainstem, and spinal cord
- Neuronal necrosis occurred when coexists with ischemic injury, and periventricular leukomalacia in some cases
- Chronic Changes: microcephaly, diffuse neuronal loss in cortex, increase in astrocytes and microglia, calcifications in the necrotic zones, sparing of cerebellum
- Anderson, JM, Milner, RDG, Strich, SJ. J. Neurol
- Bankder, B. Dev. Med Child Neurol 1967
- All very old studies!
Symptomatic hypoglycemia is associated with parieto-occipital white matter abnormalities, as well as, abnormal signals in the deep gray matter structures of the thalamus and basal ganglia. Yager, JY. Hypoglycemic Injury to the immature brain. Clinics in Perinatology 2002

MRI: Bilateral occipital lobe and parenchymal tissue loss, thinning of the posterior parietal occipital areas, generalized thinning of cerebral cortex

Spar HA, Lewine, JD, Orrison, W.W. AJNR 1994

18 term infants with symptomatic hypoglycemia
39% showed MRI and US abnormalities
4 showed patchy hyperintense lesions on MRI in occipital periventricular white matter or thalamus
3 of 4 infants on repeat MRI no lesions

35 infants, no HIE, mean glucose 20 mg/dL.
White matter abnormalities in 94%, 40% with basal ganglia/thalamic lesions, 30% with white matter hemorrhag, 11% with abnormal posterior limb of the internal capsule
65% with neurodevelopment impairments at 18 months
This is a widely quoted study and used in medical-legal testimony
Images from Burns, C. Pediatrics 2008

Neuroimaging Tam et al Pediatrics 2008

- 25 neonates diffuse weighted MRI at 6 days
- Restricted diffusion in the occipital lobes was found in 50% in term infant but not in preterm infants
- Cortical visual deficits were significant proportion of infants with recurrent hypoglycemia and correlated to low apparent diffusion coefficient values in the mesial occipital poles with long term visual problems

Neuroimaging Studies Alkalay et al Clin Peds 2005

- 23 cases with occipital lobe lesions found in 82% with visual involvement with glucose ranges from 7-26 mg/dL within the first 48 hours of birth
- Occipital lobe involvement 82%
- Dilatation of lateral ventricles 41%
- Parietal lobe involvement 29%
- Presenting Symptoms
  - Seizures 70%
  - Major Seuelae Mother and Psychomotor delay 65%,
  - Visual impairment 41%, Microcephaly 35%
52 infants all with glucose levels < 46 mg/dL
- 3.72 fold increased odds ratio in corticospinal tract injury
- 4.82 fold increased odds in worsened neuromotor score (P<.038) and a 15 point lower cognition and language score on the BSID (P<.01) at 12 months

Multicenter study of 661 preterm infants <1850 g with outcomes at 18 months
- Reduced mental and psychomotor developmental scores were found to be related to increasing number of days with glucose levels of <47 mg/dL.
- Relative risk for neurodevelopmental impairment was 3.5 times greater in infants with blood glucose <47 mg/dL for >5 days.

Long-term study of 13 children with neonatal hypoglycemia of <27 mg/dL compared to 15 children without neonatal hypoglycemia
- Assessments done at an average of 7.75 years of age showed: Significantly more difficulties in a screening test for minimal brain dysfunction, more hyperactivity, impulsiveness, and inattentiveness, lower developmental scores compared to controls.
Hypoglycemia is a Medical Legal Issue

- Google Neonatal Hypoglycemia and you will find more advertisements for Malpractice Attorneys than meaningful scientific articles.
- It is critical that the operational definition of hypoglycemia be followed without strict adherence to “the numbers.” Put the numbers in clinical context.
- Document times when hypoglycemia detected and when resolved and actions taken to correct hypoglycemia.

Conclusions

- Disturbance of glucose homeostasis that result in hypoglycemia is a common occurrence, with an imperfect definition—but with definite AAP guidelines for treatment.
- Long term neurodevelopment impact is well documented.
- Multiple causations and extensive evaluation may be needed.

Diminished Glucose Production

- IUGR-decreased glycogen stores and impaired gluconeogenesis due to elevated of glyconeogenic precursors (alanine) in the blood and defects in phosphoenolpyruvate carboxylase activity (rate limiting enzyme for gluconeogenesis).
- Inborn Errors of Methbolism-aminoacidopathies (amino acids involved in gluconeogenesis).
- Familial hyperinsulinemia more frequent than recognized.
- Neonatal “diabetes” is often associated with two gene defects affecting insulin release and is more common than previously thought.
Infant of the Diabetic Mother

First described: 1880
Insulin isolated in 1921
Maternal mortality decreased from 50 to 9%
Stillbirths decreased from >20% to 2% in the 1980s
Congenital malformations remain high

Infants of Diabetic Mothers

- IDM: "The infants are remarkable not only because, like fetal versions of Shadrach, Meshach, and Abednego, they emerge at least alive from within the fiery furnace of diabetes mellitus, but because they resemble one another so closely that they might well be twins. Unlike one another so closely that they might well be sired. They are phlegmatic, plump, liberally coated with vernix caseosa, full-faced and plethoric. The umbilical cord and the placenta share in the gigantism. During their first two minutes extra-uterine there lie on their backs, bloated and flushed, their legs flexed and abducted, their lightly closed hands on each side of the head, the abdomen prominent and their respiration sighing. They convey a distinct impression of having had much of food and fluid pressed on them by an insistent hostess that they desire only peace so they may recover from their excesses." Farquhar 1959

WHAT IS MATERNAL DIABETES?

- AMERICAN DIABETES ASSOCIATION: 2010
- HbA1C = 6.5% (normal HbA1C = 5.7-5.9)
- FAST PLASMA GLUCOSE GREATER THAN 126 MG/DL, FASTING IS DEFINED AS NO CALORIC INTAKE FOR AT LEAST 8 HOURS
- A 2-HOUR PLASMA GLUCOSE LEVEL >200 MG/DL DURING A 75GM ORAL GLUCOSE CHALLENGE
- A RANDOM PLASMA GLUCOSE LEVEL OF <200 MG/DL IN A MOTHER WITH CLASSIC SYMPTOMS OF HYPERGLYCEMIA
Impact of Gestation DM on Perinatal Mortality

<table>
<thead>
<tr>
<th>Method</th>
<th>GDM Cases</th>
<th>Non-GDM Cases</th>
<th>p-value</th>
<th>Rate %</th>
<th>CI %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacLachlan 2007</td>
<td>1 106</td>
<td>11 4514</td>
<td>2.7%</td>
<td>95.0-20.8%</td>
<td>7.9%</td>
</tr>
<tr>
<td>MACOS 2005</td>
<td>12 38</td>
<td>101 4114</td>
<td>1.4%</td>
<td>85-2.24%</td>
<td>62.2%</td>
</tr>
<tr>
<td>Total</td>
<td>13 494</td>
<td>114 4913</td>
<td>1.5%</td>
<td>96.6-2.22%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Diabetic Embryopathy and Fetopathy

- In the first trimester from the time of conception maternal hyperglycemic can cause diabetic embryopathy resulting in major birth defects and in spontaneous abortions
- Diabetic fetopathy occurs in the second and third trimesters resulting in fetal hyperinsulinemia and macrosomia.

Molecular Mechanisms of CNS and perhaps other Diabetic Embryopathy Defects

- A failure in closure of the neural folds during the early stage of embryogenesis
- Apoptosis in the neuroepithelium of the neural tube is a hallmark of maternal diabetes induced neural tube defects
- Caspase-8 (inducer of apoptosis or marker thereof) is an essential factor in hyperglycemia induced embryonic malformations
- Caspase-8 induces apoptosis through directly cleaving effector caspases or stimulating mitochondria
- Inhibition of Caspase (in mouse model) decreased rate of Neurotube disorders
- Folic Acid is critical for providing sufficient methyl groups to resist hypomethylation of chromosomal histones
- Folic Acid supplementation prior to conception has been shown to reduce NTD
Diabetic Embryopathy

- The risk of isolated and multiple congenital anomalies is highest in infants of mothers with pregestational diabetes Adjust OR 8.62 (5.27-14.1)
- Infants born of mothers with gestational diabetes Adjusted OR 1.5 (1.13-2.0)
- Specific Cardiovascular anomalies occur 2-9% of diabetic pregnancies: Transposition of the Great Arteries, Double Outlet Right Ventricle, VSD, Truncus Arteriosus, Tricuspid Atresia and PDA

Causes of Diabetic Embryopathy

- Periconceptional hyperglycemia is key in the pathogenesis of Diabetic Embryopathy
- Hyperglycemia leads to inhibition of the myoinositol uptake that is essential for embryonic development during gastrulation and neural tube stages of embryogenesis.
- Myoinositol deficiency causes perturbations in the phosphoinositide system that lead to abnormalities in the arachidonic acid-prostaglandin pathways
- Folic acid insufficiency contributes to NTD

and anomalies is associated with Hemoglobin A1c

- HbA1c is a normal minor hemoglobin that differs from HbA by the addition of glucose to the amino-terminal valine of the beta chain. Glycosylation of hemoglobin occurs during circulation of the red cell and depends on the average concentration of glucose to which the red cell is being exposed during its life cycle.
- Measurement of HbA1c levels provides an index of chronic glucose elevation.
- Thus maternal hyperglycemia results in elevated HbA1c.
### Distribution of HbA1c at the first prenatal visit and frequency of congenital anomalies

- HbA1c 4.6-7.0 (nl) 7.7-8.5 8.7-9.9 10.0-10.5 >10.5
- Cong An.% 1.89 1.69 6.25 9.1 25

- Major anomalies in infants and initial HbA1c (indicating periconceptional diabetic control)
- Sacral Agensis  HbA1c 11.5; VSD 7-9.6; Holoprosencephaly 12.8, Endocardial Cushion Defects 10, THUS PERICONCEPTIONAL HBA1C MONITORING IS VERY CRUCIAL – PLAN THE PREGNANCY!!!

### Maternal HbA1c and Risk for Congenital Anomalies — Guerin et al 2007  1977 pregnancies

![Graph showing maternal HbA1c and risk for congenital anomalies]

- Anencephaly and spina bifida occur 13-20 times more frequently among IDMs compared to non-DM mothers
- Flexion contractures of the limbs, vertebral anomalies, cleft palate, and intestinal anomalies
- Major of cases of neonatal small left colon in IDMs
- Caudal Regression-syndrome consists of structural defects of the caudal region, including incomplete development of the sacrum, and lumbar vertebrae.
Malformations Associated with Pre-existing Diabetes

- CNS-open neural tube defects, holoprosencephaly, absence of corpus callosum, Arnold-Chiari anomaly, schizencephaly, microcephaly, agenesis of olfactory tracts, hydrocephaly
- CV-TGA, VSD, ASD, TOF, Coarctation, Hypoplastic LV
- GI-pyloric stenosis, duodenal atresia, microcolon, anorectal atresia, omphalo-enteric fistula, hernias
- MS-Caudal agenesis, craniosynostosis, costovertebral anomalies, limb reduction, joint contractions
- Cleft Palate, Microtia, Ear dysplasia

Caudal Regression Usually Associated with HbA1c>12%

### Diabetes......Obesity
Birth Defects, Congenital Anomalies

- Associated with Macroscopic Obesity
  - Nuchal fold defect
  - Micrognathia
  - Skin defects
  - Bowel anomalies
  - Multiple congenital anomalies

- GI Small Left Colon Syndrome
- Bowel atresia
  - Bowel obstruction (feeding difficulties)
  - Diabetic Embryopathy – Cardiac anomalies

Central nervous system

- Neural tube defects
  - Microcephaly
  - Hydrocephaly
  - Holoprosencephaly
Diabetic Fetopathy
- LGA >90% in birthweight, length and head circum
- Polycythemia (increased increase in erythropoietin)
- Increased catecholamine
- Increased size (both hyperplasia and hypertrophy) of insulin sensitive tissues (Liver, Muscle, Cardiac Muscle, and Subcutaneous Fat). Accumulation of fat in the truncal areas.
- Diabetic Cardiomyopathy-ventricular and LF outflow muscular hypertrophy

Incidence of Shoulder Dystocia in LGA and Macrosomic Infant of Non-Diabetic and Diabetic Mothers Ca 1992
- Of 175,886 Vaginal deliveries >3.5 kg incidence of 6,238 (3%) of Shoulder Dystocia
- BW                    Non Diabetic         Diabetic
- 4.9-4.25                5.2%                      12.2%
- 4.25-4.5                9.1%                      16.7%
- 4.4-4.75                14.3%                      27.3%
- 4.75-5.0                21.1%                      34.8%
- Shoulder dystocia increased the use of Vacuum or Forceps by 35-45%

IDM Maladapation to Exauterine Life
- Prematurity 36% (14% < 34 weeks; 22% between 34-37%)
- Respiratory Distress 34%
- Hyperbilirubinemia 25%
- Polycythemia 5%

47% of IDM require NICU Admission for the above disorders and/or hypoglycemia management
Metabolic Maladaptation

- Hypoglycemia—22% of IDM have glucose levels <40mg%, and these infants often require Glucose Infusion Rates >10 mg/kg/min
- Hypocalcemia—30% with serum concentration <1.8 mMol/L or iCa < 0.8 mMol/L
- Hypomagnesemia—40% within first 3 days
- Polycythemia and hyperviscosity—17%
- Hyperbilirubinemia—11-29% of IDMs
- Diabetic Cardiomyopathy—thickening of intraventricular septum and obstructed LV outflow tract

PERINATAL MORBIDITY IN DIABETIC PREGNANCY

<table>
<thead>
<tr>
<th>MORBIDITY</th>
<th>GEST DM</th>
<th>TYPE I DM</th>
<th>TYPE II DM</th>
</tr>
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<tbody>
<tr>
<td>Hyperbilirubinemia</td>
<td>29%</td>
<td>35%</td>
<td>44%</td>
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<tr>
<td>Hypoglycemia</td>
<td>9%</td>
<td>29%</td>
<td>24%</td>
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<tr>
<td>Resp Distress</td>
<td>3%</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>TTNB</td>
<td>2%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>1%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

- From California Dept of Health 2001
- Others that must be considered are renal vein thrombosis, neonatal small colon

Periconceptional Care is Critical

- Clinical Practice Guideline—Mothers with DM require pre-conceptual counseling, pre-conception and first trimester folic acid supplementation, and glucose control
- Pregnancy in women with diabetes should be planned. Good contraceptive advise and pre-pregnancy counseling are essential. Euglycemia should be maintained before and during pregnancy.

All women with diabetes should have counseling regarding intake of Folic Acid 4-5 mg per day pre-conceptually and in the first 12 weeks of pregnancy.
Neonatal Consultation is Critical

- Ideally a third trimester fetal echocardiogram to predict neonatal cardiac disease—help mom and us be prepared
- Explain risks of fetal embryopathy—many detected by by fetal ultrasonography and potential interventions
- Explain common perinatal maladaptations—50% require NICU admission, IV glucose, other metabolic issue management.
- Risk for RDS especially in late preterm infants and risk of TTN at term—delayed pulmonary surfactant maturation
- Predict feeding issues related to GI functional obstruction and delayed feeding in most IDM infants

We Can Do Better!

- We need to reach young women with DM/Obesity education prior to pregnancy
- We must focus on communities that get late prenatal care
- We must inform women about the benefits of Folic Acid—for example the Hispanic Community does not consume FA fortified foods similar to other populations—need to fortify corn meal and beans, or culturally related foodstuffs

Team Work and Problem Anticipatioin

- “The care of the IDM by a knowledgeable team of healthcare providers should begin at birth with close evaluation, monitoring, and treatment of the newborn infant in a timely and experienced manner.” Houchange D. Modanlou, M.D. 2012