DR. SUSHMA SHARMA

GDM & DM in Pregnancy

Walk the Talk

- Epidemiology
- Classification
- Pathogenesis of glucose intolerance
- Consequences –Maternal/Fetal
- Fetal Evaluation
- Screening
- Management

Prevalence of DM

- Incidence continues to rise
- Global prevalence-2010, 6.4% adult population - 171 million
- By 2030-7.8% - 438 million
- Varies from 10.2% in Western Pacific to 3.8% in African region - highest increase.
- 70% in low-& middle income countries.
- India is the world capital - 50.8 million, followed by China with 43.2 million.
- largest age group - 40-59 years.
- T2DM most common form with incidence of 85-95%

Increasing Prevalence of GDM

- Abnormal maternal glucose regulation occurs in 3-10% of pregnancies
- GDM accounts for 90% of cases of DM in pregnancy
- Overt - 35% type 1 DM, and 65% type 2 DM

- Not limited to western countries
- Increase is noted in India and China
- 3.8-20% in different part of India, more in urban – DIPSI
- Compared with white women the RR of GDM in Indian women is 11.3

Increase is attributable to:

- Sedentary lifestyles
- Changes in diet
- Immigration from high-risk populations
- Childhood and adolescent obesity

- *Women who were either SGA or LGA at birth are at ↑sed risk for GDM*

- **Interventions medical during preg - 17 alpha-hydroxyprogesterone caproate**

CLASSIFICATION

- **A. GESTATIONAL DIABETES: Glucose intolerance: 1 abnormal value on GTT or hgbA1c - 5.7 to 6.4%.** re-test in 4 weeks.
  - **A1 - Euglycemia achieved with diet and exercise.**
  - **A2 - Require medication to achieve euglycemia.**

- **PREEXISTING DIABETES**
  - **Type I. No endogenous insulin, ketosis prone**
  - **Type II. Late onset, associated with obesity, insulin resistant**

Pre-gestational Diabetes

- Diabetes that antedates pregnancy
- White's classification based on –
  - patient's condition before pregnancy
  - duration of diabetes
  - age of onset
  - complications

White's Classification

- A - Abnormal glucose tolerance test at any age or of any duration treated only by diet therapy
- B - Onset at age ≥20 yrs and duration of <10 yrs
- C - Onset at age 10 to 19 yrs or duration of 10 to 19 yrs
- D - Onset before 10 yrs of age, duration > 20 yrs, benign retinopathy, or hypertension (not preeclampsia)
  - D1 - Onset before age 10 yr
  - D2 - Duration over 20 yrs
  - D3 - Calcification of vessels of the leg (macrovascular disease)
  - D4 - Benign retinopathy (microvascular disease)
  - D4 - Hypertension (not preeclampsia)
- R - Proliferative retinopathy or vitreous hemorrhage
- F - Renal nephropathy with over 500 mg/d proteinuria
- RF - Criteria for both classes R and F
- G - Many pregnancy failures
- H - Evidence of arteriosclerotic heart disease
- T - Prior renal transplant

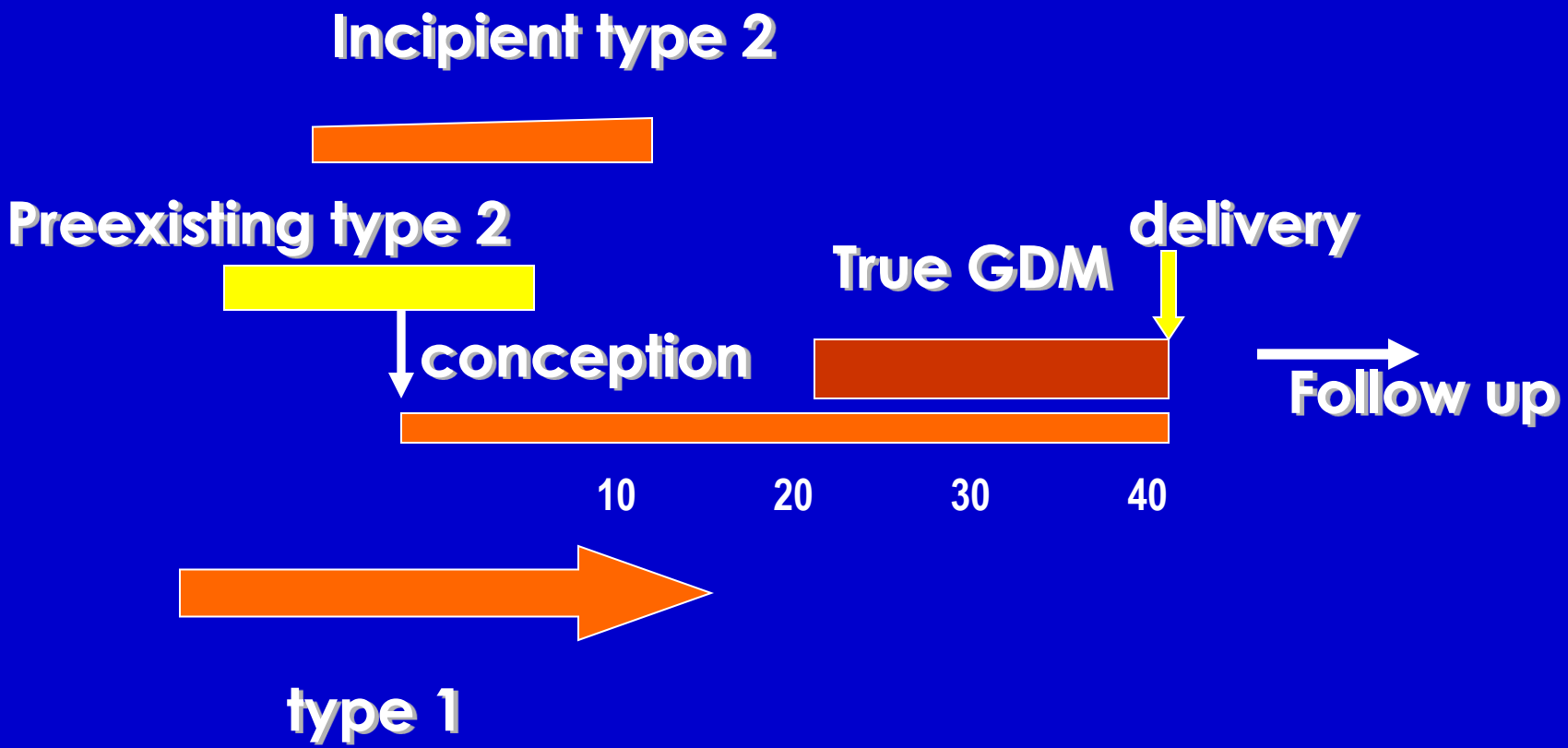
Impaired Glucose Tolerance / Isolated Abnormal Plasma Glucose

- Pre-diabetic state of dysglycemia, with insulin resistance & increased risk of CVS pathology, may precede type 2DM by many yrs, a risk factor for mortality
- Only one abnormal glucose value in 100 gram GTT
- Maternal and fetal morbidity increased
- Increased incidence of LSCS, pre-eclampsia and macrosomia
- Higher BG under ambulatory conditions
- Significant correlation with fetal macrosomia

Gestational Diabetes Mellitus

- *Defined as glucose intolerance with onset or first recognition during pregnancy.*
  - Many are denovo pregnancy induced
  - Some are type 2 (35-40%)
  - 10% have antibodies
- *Whether insulin or only diet modification is used for tx*
- *Persists or not after Delivery.*

D M


Incipient type 2
Preexisting type 2
delivery
True GDM
conception
Follow up
10
20
30
40
type 1

Maternal-fetal Metabolism in Normal Pregnancy

Fuel Metabolism in Pregnancy

- Goal is uninterrupted nutrient supply to fetus
- Metabolic goals of pregnancy are
  - In early pregnancy to develop anabolic stores to meet metabolic demands in late pregnancy
  - In late pregnancy to provide fuels for fetal growth and energy needs.

Metabolic Changes

Glucose Metabolism in Pregnancy

- Early pregnancy
  - E2/PRL stimulates b cells
  - Glucose tolerance is normal or slightly improved
  - Peripheral (muscle) sensitivity to insulin normal
  - Hepatic basal glucose production is normal
  - Due to peripheral glucose utilization – 10% fall in BG levels

- **Late pregnancy**
  - **Fetoplacental unit extracts glucose and amino acids, fat is used mainly for fuel metabolism**
  - **Insulin sensitivity decreases progressively up to 50-80% during the third trimester**
  - **variety of hormones secreted by the placenta, especially hPL and placental growth hormone variant, cortisol, PRL,E2 and Prog**

Early Pregnancy

Necessary to provide proper energy to conceptus

↓

Hormones associated such as HPL & cortisol

↓

↓se glucose levels

↓

Promote fat deposition & stimulate appetite

Rising serum levels of E & P

increased insulin production & secretion

Meal sets in motion a complex series of hormonal actions,

↓

Increase in blood glucose

↓

Sec. secretion of pancreatic insulin, glucagon, somatomedins, & adrenal catecholamines.

↓

These adjustments ensure that an ample, but not excessive, supply of glucose is available to mother & fetus.

- Hypoglycemia reaches a nadir by 12th week
- Average decrease 15 mg/dL
- Fasting values are normal by the 10th week, comparable ↓se in postprandial values
- Acts to protect the developing embryo from elevated glucose levels

Placental steroid & peptide hormones (eg, E, P, chorionic somatomammotropin) ↑se linearly throughout 2nd & 3rd trimesters.

↓

↑se insulin resistance

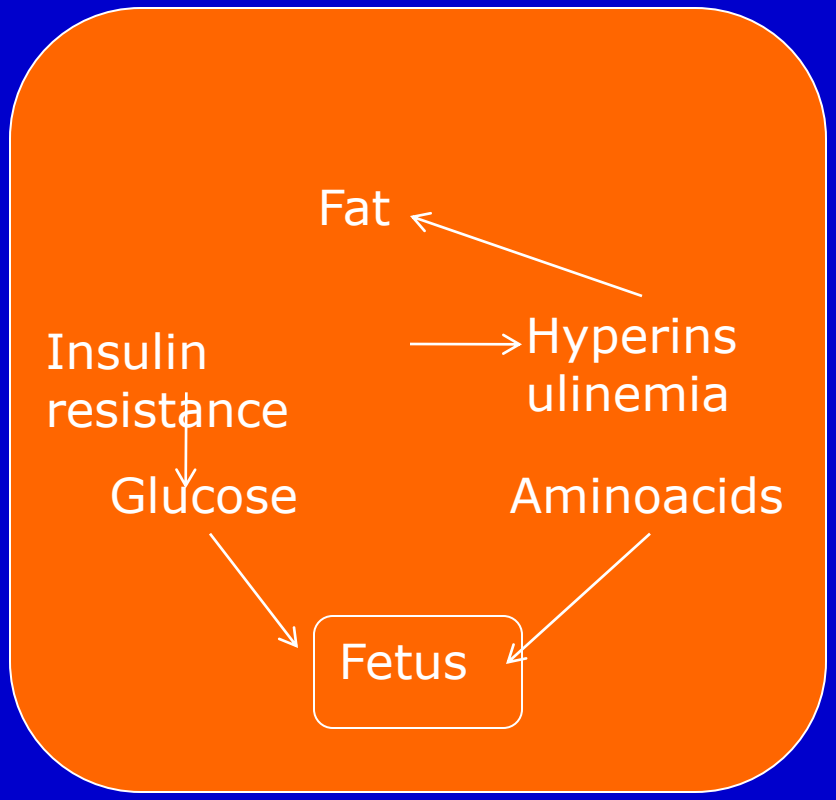
↓

↑sed insulin secretion.

- 24 hr mean insulin levels are 50% higher in 3rd trimester compared with nonpregnant state

Glucose Metabolism in Pregnancy

FASTING
accelerated starvation & esxaggerated ketosis (maternal hypoglycemia, hypoinsulinemia, hyperlipidemia,& hyperketonemia)



FED
hyperglycemia, hyperinsulinemia, hyperlipidemia, and reduced tissue sensitivity to insulin

In the Second Trimester

- Higher FPG & PPG level
- This facilitates placental transfer of glucose
- Glucose transfer is via a carrier-mediated active transport system that becomes saturated at 250 mg/dL
- Fetal glucose levels are 80% of maternal values

During a Healthy Pregnancy

- Mean bl sugar F ↓se progressively to low value of 74 ± 2.7 (SD) mg/dL
- Peak PP blood sugar rarely exceed 120 mg/dL
- When 2-hr PP glucose levels are maintained <120 mg/dL, app 20% of fetuses demonstrate macrosomia. If up to 160 mg/dL, macrosomia rates rise to 35%.

- Maternal amino acid levels are lowered by active placental transfer to the fetus.
- Fetal levels of amino acids are 2- to 3-fold higher than maternal levels, but not as high as levels within the placenta.
- Lipid metabolism - storage until midgestation; then, as fetal demands increase, there is enhanced mobilization (lipolysis).

Carbohydrate Metabolism up to 20 weeks

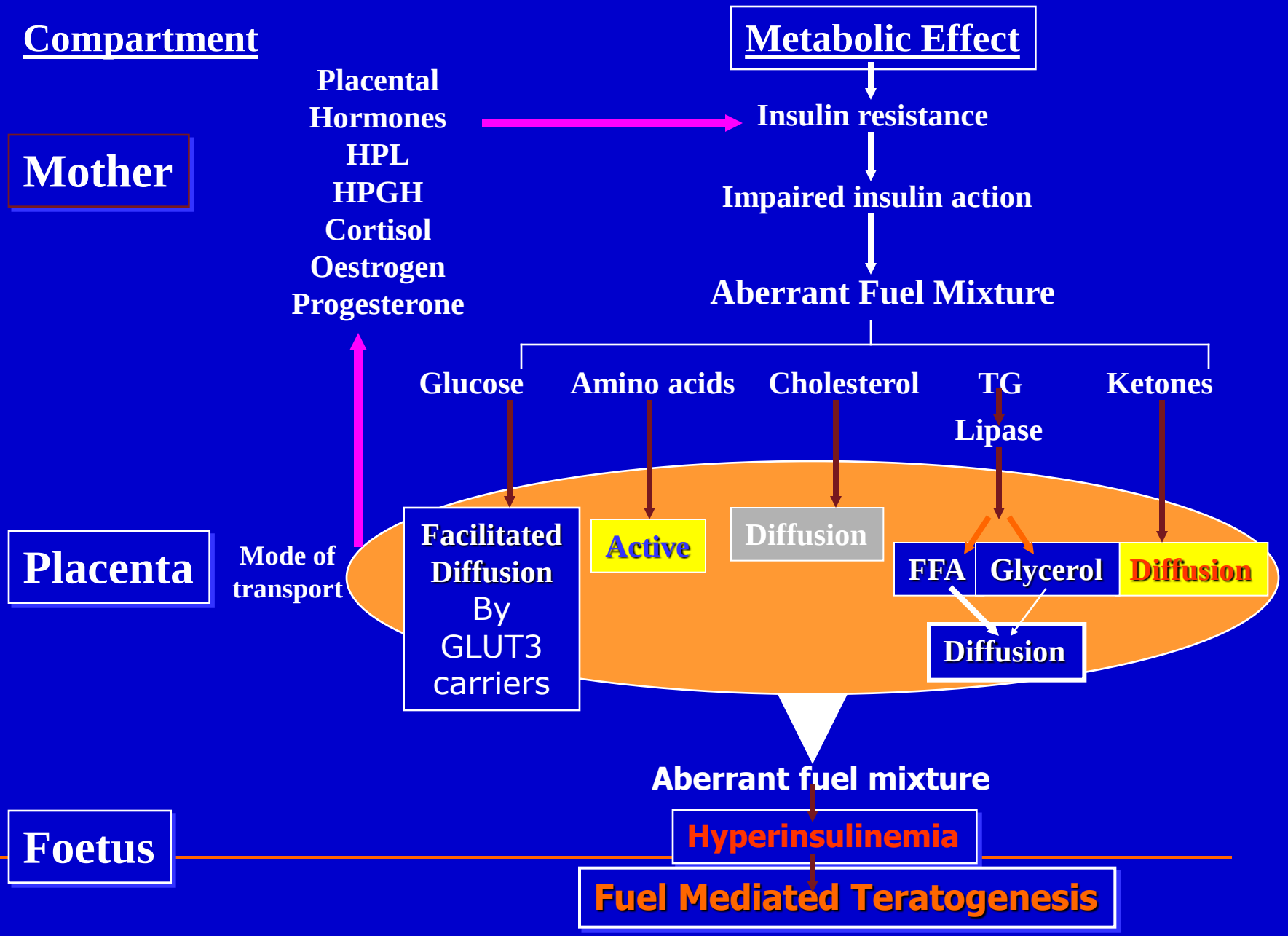
Hormonal alteration	Effect	Metabolic change
Estrogen and progesterone Beta –cell hyperplasia and increased insulin secretion	Tissue glycogen storage ↓sed hepatic glucose production ↑sed peripheral glucose utilization ↓sed fasting plasma glucose	Anabolic ↑sed due to sex steroids + Hyperinsulinemia

Carbohydrate Metabolism 20-40 weeks

Hormonal Alterations	Effects	Metabolic change
↑sed hCS ↑sed prolactin ↓sed bound and free cortisol	↓sed diabetogenic glucose tolerance Insulin resistance ↓sed hepatic glycogen stores ↑sed hepatic glucose production	Facilitated anabolism during feeding Accelerated starvation during fasting Ensure glucose and AA to fetus

GDM

- Precise mechanisms remain unknown
- Hallmark is ↑sed insulin resistance
- Inability to secrete sufficient insulin to compensate for the increased nutritional needs of gestation due to:
  - ↑sed adiposity of pregnancy,
  - ↑sed anti-insulin hormones, such as HPL, HPGH, prolactin, cortisol (potent), P & E (weak)
  - enzymes with insulinase activity
    - Oxytocinase, histaminase, alkaline phosphatase


Compartment
Metabolic Effect
Mother
Placental Hormones
HPL
HPGH
Cortisol
Oestrogen
Progesterone
Insulin resistance
Impaired insulin action
Aberrant Fuel Mixture
Glucose
Amino acids
Cholesterol
TG
Lipase
Ketones
Placenta
Mode of transport
Facilitated Diffusion By GLUT3 carriers
Active
Diffusion
FFA
Glycerol
Diffusion
Diffusion
Aberrant fuel mixture
Foetus
Hyperinsulinemia
Fuel Mediated Teratogenesis

Inflammatory Mediators in GDM

- Increase in inflammatory response
  - Increase in TNF-α
  - Increase in IL-6
- Decrease in anti-inflammatory response
  - Decrease in adiponectin
  - Decrease in IL-10
  - Pharmacological inhibition of inflammatory mediators – Salicylates,Thiazolidinediones

Changes in Maternal Metabolism in normal pregnancy

- ↓sed fasting plasma glucose level
- ↑sed PP plasma glucose level
- ↑sed F /PP plasma insulin levels
- β-cell hypertrophy & hyperplasia
- ↓sed insulin sensitivity
- Enhanced lipolysis

Perinatal Mortality, Morbidity & Birth Injury

If Maternal pancreatic insulin response is inadequate,

↓

Recurrent PP maternal hyperglycemic episodes.

↓

Fetal, hyperglycemia

↓

Accelerated growth exhibited by the fetus.

Macrosomia

↓

Conversion of excess glucose into fat causes depletion in fetal O_2 levels.

↓

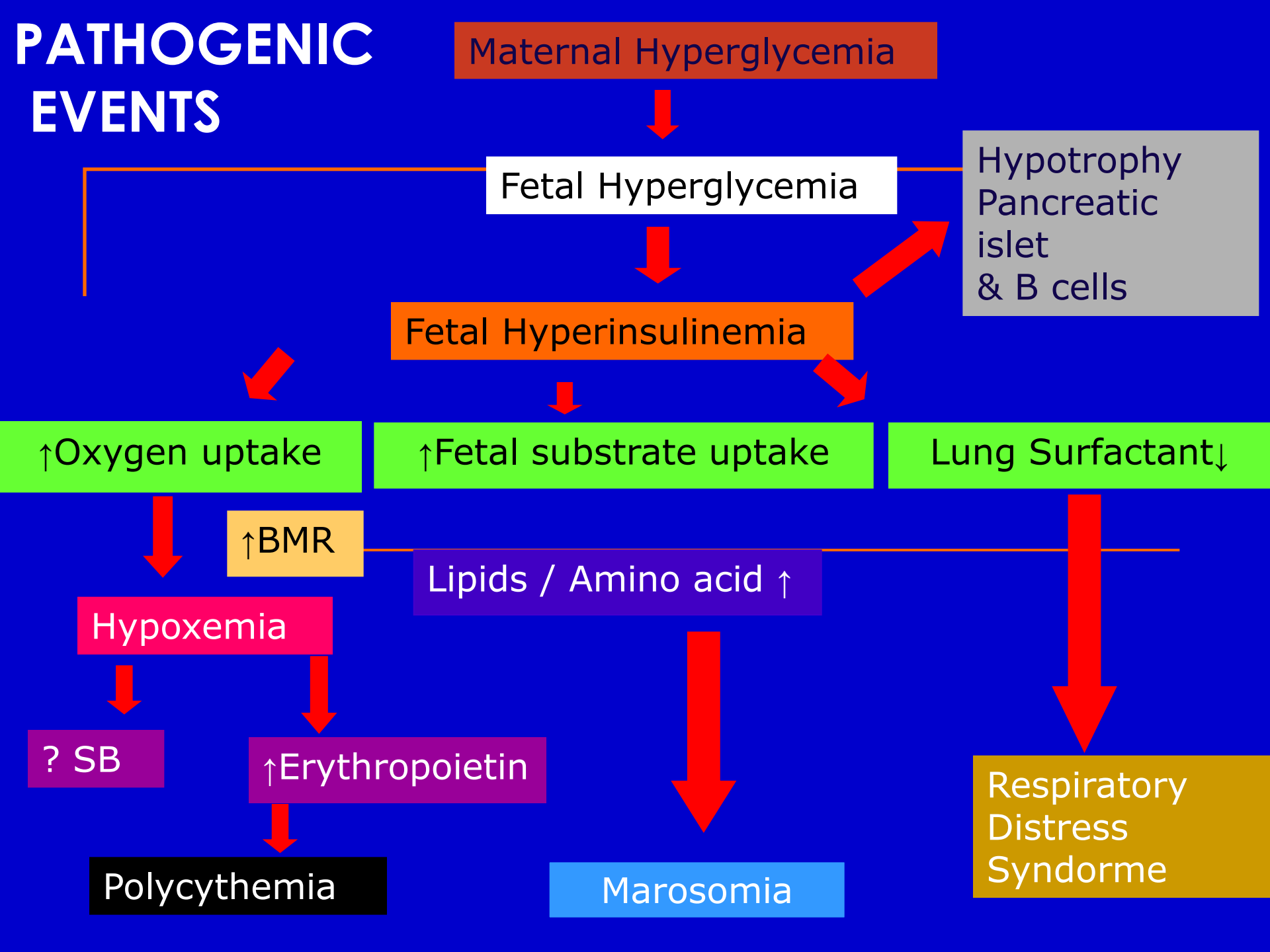
↑es in adrenal catecholamines,

↓

Hypertension, cardiac remodeling and hypertrophy, stimulation of erythropoietin, red blood cell hyperplasia, & ↑sed hematocrit. Polycythemia (hematocrit >65%)

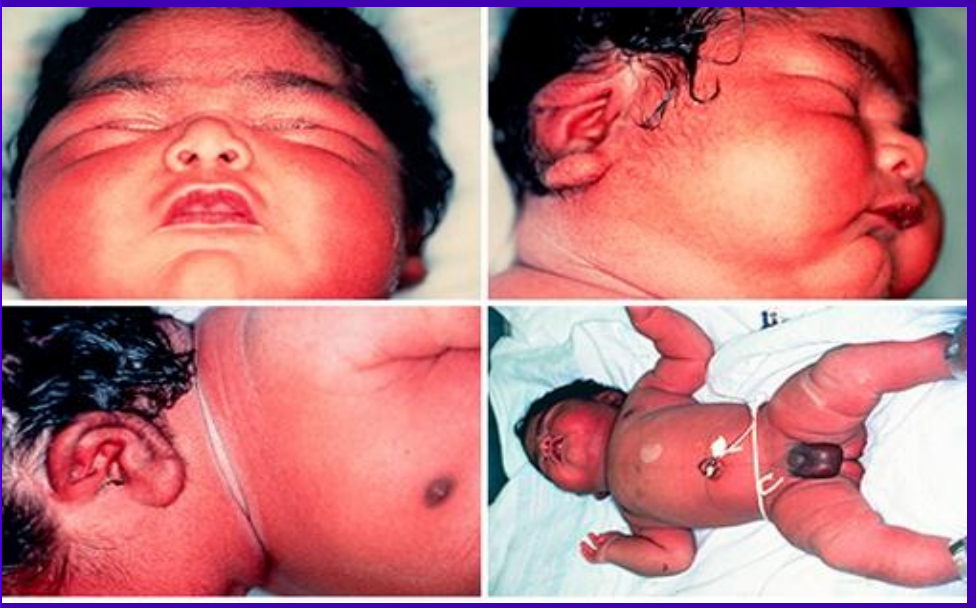
↓

Neonate vascular sludging, poor circulation, and postnatal hyperbilirubinemia.


PATHOGENIC EVENTS
Maternal Hyperglycemia
Fetal Hyperglycemia
Hypotrophy Pancreatic islet & B cells
Fetal Hyperinsulinemia
↑Oxygen uptake
↑Fetal substrate uptake
Lung Surfactant↓
↑BMR
Lipids / Amino acid ↑
Hypoxemia
? SB
↑Erythropoietin
Polycythemia
Marosomia
Respiratory Distress Syndorme

PEDERSEN THEORY

Maternal Diabetes → Glucose crosses placenta



Carbohydrate surplus of fetus

Increased secretion of insulin

Stimulation of protein, lipid & glycogen synthesis

Free amino acid

Stimulatory effect on development of B cells

Release Insulin like growth factor

MACROSOMIA

Perinatal Mortality in Diabetic Pregnancy

- ↓sed 30-fold since the discovery of insulin in 1922 & introduction of intensive obstetrical & infant care in 1970s.
- Double the risk of serious injury at birth
- Triple the likelihood of cesarean delivery and
- Quadruple the incidence of newborn intensive care unit (NICU) admission.

- Studies indicate that the risk of these morbidities is directly proportional to the degree of maternal hyperglycemia
- Congenital malformations, RDS, & extreme prematurity account for most perinatal deaths

Perinatal Mortality to Maternal Blood Glucose During Last Weeks of Pregnancy

Mean glucose level	Perinatal mortality
>150 mg% 100–150 mg% <100 mg%	24% 15% 4%

Perinatal Morbidity in Diabetic Pregnancy

Morbidity	Gestational Diabetes	Type 1 Diabetes	Type 2 Diabetes
Hyperbilirubinemia	29%	55%	44%
Hypoglycemia	9%	29%	24%
Respiratory distress	3%	8%	4%
Transient tachypnea	2%	3%	4%
Hypocalcemia	1%	4%	1%
Cardiomyopathy	1%	2%	1%
Polycythemia	1%	3%	3%

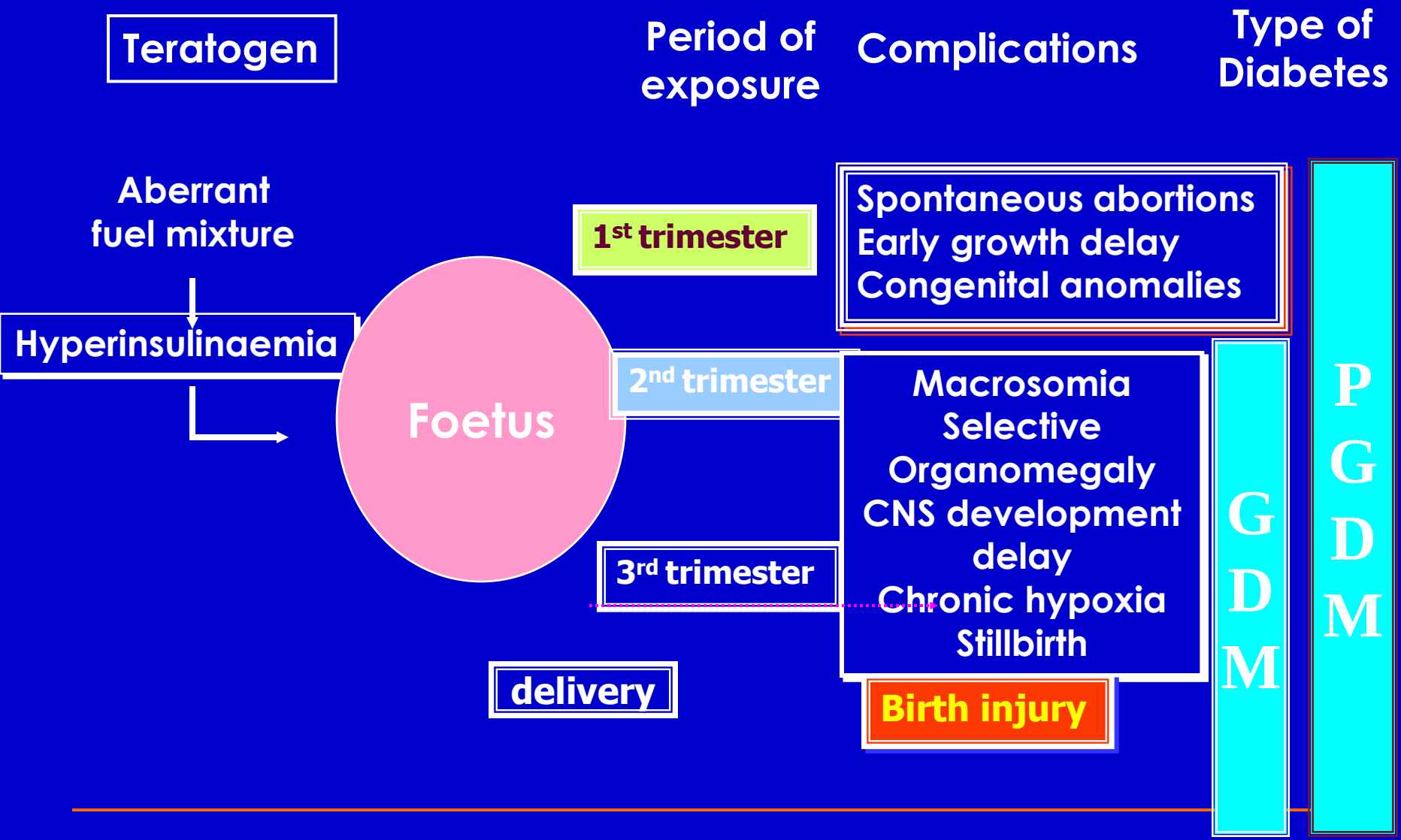
Adapted from California Department of Health Services, 1991

Fetal Consequences

First Trimester	Second Trimester	Third Trimester
-Malformations -Growth Restriction -Fetal Wastage	-Hypertrophic cardiomyopathy -Polyhydramnios -Erythraemia -Placental Insufficiency -Preeclampsia -Fetal loss -Low IQ	-Hypoglycemia -Hypocalcemia -Hyperbilirubinemia -Respiratory distress syndrome -Macrosomia -Hypomangnesmia -Intrauterine Death

Mechanism of Teratogenesis

- Disruption of normal functioning of the yolk sac
- Diffusion of intracellular myoinositol with resultant disruption of AA/PG metabolism
- Oxidative metabolism and generation of free oxygen radicals
- Glucose induced mutations in embryonic DNA


Teratogen
Period of exposure
Complications
Type of Diabetes
Aberrant fuel mixture
Hyperinsulinaemia
Foetus
1st trimester
Spontaneous abortions
Early growth delay
Congenital anomalies
2nd trimester
Macrosomia
Selective Organomegaly
CNS development delay
Chronic hypoxia
Stillbirth
3rd trimester
delivery
Birth injury
GDM
PGDM

Malformations in infants of Diabetic Mothers, No Risk in GDM

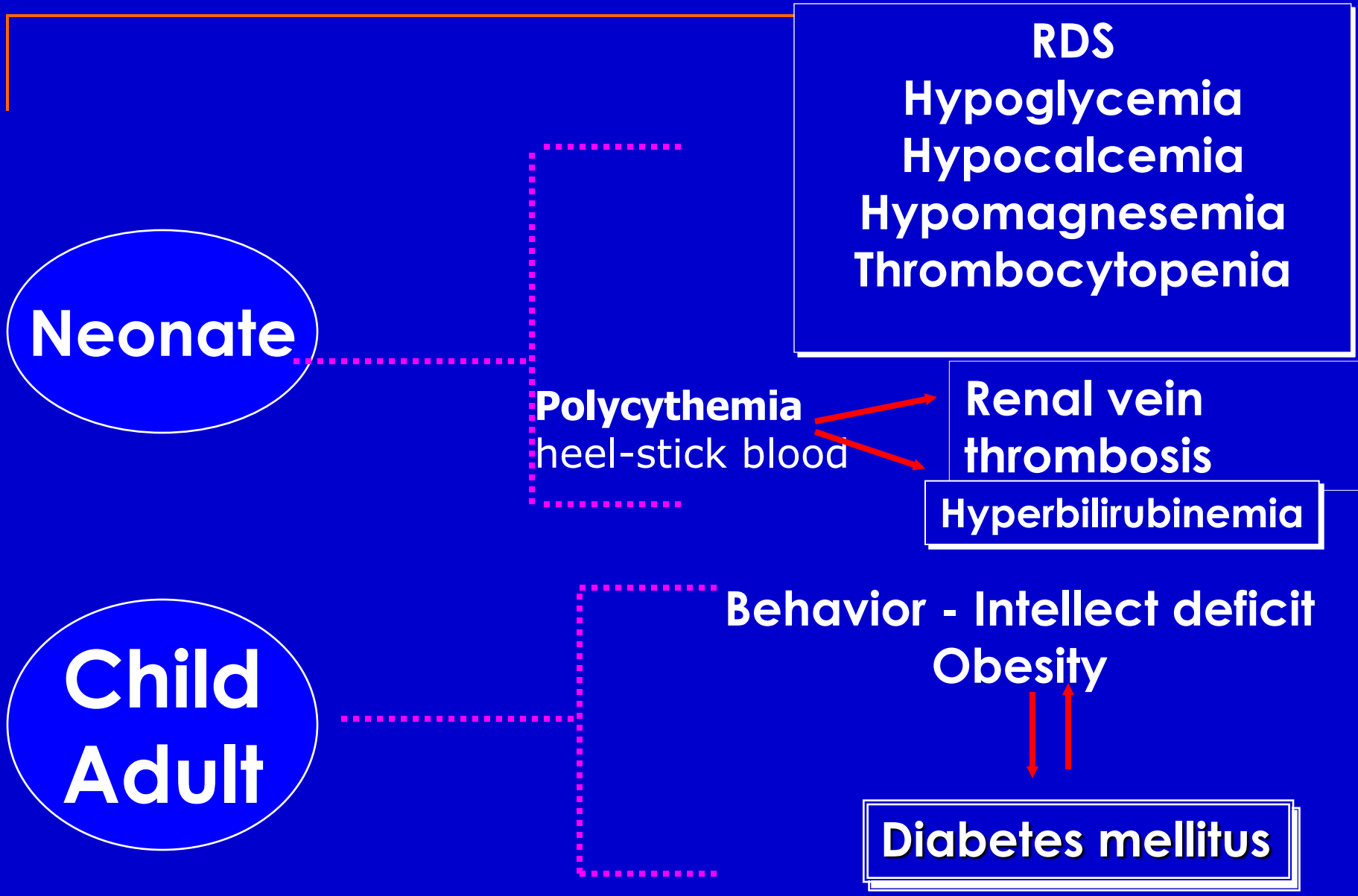
Anomaly	Onset
Caudal regression	3 wks
Spina bifida	6 wks
Anencephaly	4 wks
Myelocele	4 wks
Hydrocephalus	5 wks
Dextrocardia	4 wks
Conus arteriosus defects	5 wks
VSD	6 wks
Renal agenesis/hypoplasia	6 wks

Birth Injury

- With strict glycemic control, the birth injury rate only slightly higher than controls (3.2 vs. 2.5%).
- Shoulder dystocia – 2 to 4 fold higher
- Brachial plexus trauma
- Facial nerve injury and
- Cephalohematoma

Neonatal Complications

- Hypoglycemia
- Hypocalcemia
- RDS
- Polycythemia
- Hyperbilirubinemia
- Macrosomia
- Inheritance of Diabetes
- Metabolic syndrome later in life
- Cardiovascular risk factors in offspring


RDS
Hypoglycemia
Hypocalcemia
Hypomagnesemia
Thrombocytopenia
Neonate
Polycythemia
heel-stick blood
Renal vein thrombosis
Hyperbilirubinemia
Child
Adult
Behavior - Intellect deficit
Obesity
Diabetes mellitus

Maternal Complications

- Worsening retinopathy – 10% new DR, 20% mild NPDR and 55% mod-severe NPDR progresses
- Worsening proteinuria. GFR decline depends on preconception creatinine and proteinuria
- Hypertension and Cardiovascular disease
- Neuropathy – No worsening (gastroparesis, nausea, orthostatic dizziness can be worsened)
- Infection

- Hypoglycemia
- Diabetic Ketoacidosis
- Diabetic gastropathy
- Cesarean delivery: 56 %
- Preterm delivery: 42 %
- Preeclampsia: 18 %
- 50% lifetime risk in developing Type II DM in GDM
- Recurrence risk of GDM is 30-50%

Management

- Risk approach
- Screening
- Confirmation of diagnosis
- Fetal evaluation
- Maternal monitoring
- Diabetic emergencies
- Medical nutrition therapy
- Insulin

American Diabetes Association Recommendations 2010

Risk Approach

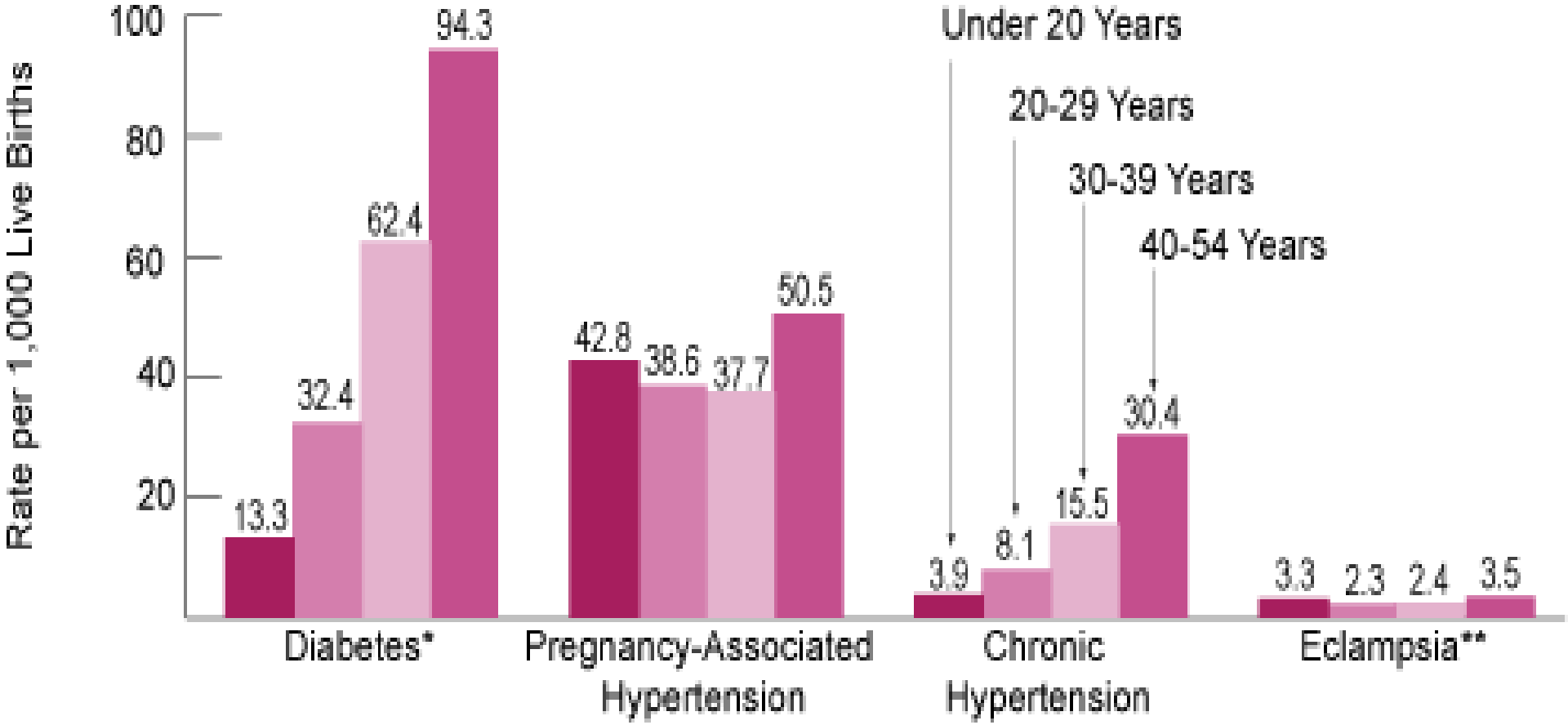
Very High risk	Low risk
Severe obesity GDM during a previous pregnancy Delivery of an LGA infant Presence of glycosuria Diagnosis of PCO syndrome Strong family H/O type 2 diabetes	Age < 25 years Wt normal before pregnancy Member of an ethnic group with a low prevalence of diabetes No known diabetes in 1st degree relatives No H/O of abnormal glucose tolerance No H/O of poor obstetric outcome

Other Risk Factors

- Prior malformed or stillborn infant
- Glycosuria, Hydramnios, Congenital anomalies, Recurrent moniliasis or Hypertension in current pregnancy

Selected Maternal Morbidities and Risk Factors in Pregnancy, by Maternal Age, 2006

Source II.21, II.24: Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System



*Includes gestational and chronic diabetes. **Eclampsia is characterized by seizures and generally follows preeclampsia, which is marked by high blood pressure, weight gain, and protein in the urine.

PRENATAL MANAGEMENT

Screening Tests for GDM

Best method still controversial

When to Screen

- At initial prenatal visit –
  - Populations with a high prevalence of type 2 DM
  - High-risk groups
- 75-g OGTT after overnight fast at 24-28 wks
- 32^{nd} -34^{th} week or later if necessary

75 gms OGTT

- Fasting - no caloric intake for at least 8-14 hrs
- Casual (random) - any time of day without regard to time since last meal
- 3 days prior, pt. should consume over 150 grams of carbohydrate / day with her usual physical activity
- 75 grams glucose consumed with 250-300 ml of water over 5 minutes
- Finger stick glucose / urine testing should not be used
- Venous glucose levels are recommended

ADA - 100G OGTT

- Adopted for diagnosis of GDM
- Based on Carpenter and Coustan Criteria
- BI is collected in fasting & at 1, 2 & 3 hrs after an oral load of 100 gm glucose

100gm OGTT	Venous Plasma
Fasting	> 95 mg/dl
1 hr	> 180
2 hr	> 155
3hr	> 140

- Two or more values must met/exceeded to diagnose GDM

ADA.Gestational diabetes mellitus .Diabetes Care 2004

Criteria of Diagnosis

- ADA recommendations
- WHO criteria
- Urine Glucose
- Spot Test
- HbA1C, Serum fructosamine

- **Diagnosis OGTT**

3 H	
Fasting	5.3
1h	10.6
2h	9.2
3h	8.1

2H	
Fasting	5.3
1h	10.6
2h	8.9

- **2 or more values greater than or equal to above cutoffs diagnostic of GDM**
- **single abnormal value indicates CHO intolerance**

ADA Guidelines 2011

- First Prenatal Visit – Measure FPG or random (casual), A1C on all or only high-risk women
- If FPG is <5.1 mmol/L (92 mg/dL), test at 24 to 28 wks with 75-g OGTT after over night fast
- All diagnosed with GDM or overt DM should undergo postpartum glucose testing.

When	Diagnosis	Test	Cut-off for diagnosis
1st prenatal visit	Overt DM	FPG	126 mg/dL (7.0 mmol/L)
		HbA1C	≥ 6.5%
		Random[a]	200 mg/dL (11.1 mmol/L)
24-28 weeks	GDM	FPG	92 mg/dL (5.1 mmol/L)
		75g OGTT-1 hr	180 mg/dL (10.0 mmol/L)
		75g OGTT-2 hr	153 mg/dL (8.5 mmol/L)

WHO 75G OGTT

- Plasma glucose (mg%)
- Fasting 126
- 2 hours 140

- One step procedure
- Simple, economic and feasible
- Causes least disturbance in pregnant woman's routine activities
- Serves dual purpose of screening and diagnosis
- Predicts adverse pregnancy outcome

Diabet Med.1998

Spot Test (DIPSI)

- Venous sample for screening
- Values of fasting - 85 mg/dl
- Non-fasting – 120 mg/dl
- If values higher than cut-off, OGTT recommended

Whom and When to Screen? Indian Scenario - The DIPSI Guidelines

- 75 gm GCT with single PG at 2 hrs
  - ≥ 140 mg/dL is GDM
  - ≥ 120 mg/dL is DGGT
- Universal screening
- First trimester, if negative at 24 – 28 wks and then at 32 – 34 weeks

Glycosylated Hb

- Not suitable for screening
- Useful in pre-gestational DM to know retrospective blood glucose control
- Useful in monitoring the control but not for daily Mx

Serum Fructosamine

- Not a useful screening test
- To assess the short term control during last 2 weeks

Patients with Preexisting Diabetes (Type 1 or Type II; Class B-T)

Type 1 Diabetes

- Rarely diagnosed during pregnancy, usually diagnosed during childhood
- Often present with unexpected coma in pregnancy.

Type 2 Diabetes

- It can be difficult to distinguish GDM from type 2 DM that preceded pregnancy but was unrecognized, or whose onset occurred during pregnancy

Pre-diabetes

- Pre-diabetes have impaired fasting glucose (IFG) - FBS100 to125 mg/dL or impaired glucose tolerance (IGT) – 140 to199 mg/dL after a 2-h OGTT or both.
- If identified before pregnancy are extremely high risk of developing GDM.
- Should receive early (first-trimester) diabetic screening.
- Not meaningful in prenatal management, unless exceed the plasma glucose limits for diagnosing GDM

- Normal prenatal laboratory tests
- Additional test's for patients with DM OR GDM

First visit

- Hgb A1C
- Collect 24 hr urine (protein, creatinine clearance, creatinine)
- CVS status - ECG and echocardiogram
- Eye exam
- Bl urea nitrogen, serum creatinine,
- TSH, and free thyroxine levels
- Whites Class D-T need eye exam and renal evaluation each trimester
- capillary blood sugar 4-7 times daily

2nd Trimester Laboratory Testing

- Spot urine protein-to-creatinine study in women with elevated value in first trimester
- MSAFP
- HbA1C
- Capillary blood sugar 4-7 times daily

If Preeclampsia is suggested

- 24-hr urine collection
- BI urea nitrogen & serum creatinine
- Liver function tests
- Uric acid
- CBC

Ultrasound

- Dating scan at 8 – 12 wks
- Nuchal translucency 11-14 wks
- Targeted scan including fetal echo at 18-20 wks
- Growth scan at 26 wks and every 4 wks thereafter
- NST + AFI twice wkly starting at 32 wks; 28 - wks if poorly controlled or class D- T.

Gestational Diabetes

- A1 (Diet controlled)
  - Targeted scan at 16-18 wks (no fetal echo)
  - Fasting & 2 hr PPG
  - Growth scan at 34-36 wks
- A2 (not controlled with diet alone)
  - Targeted scan at 16-18 wks (no fetal echo)
  - Fasting & 2 hr PPG
  - Growth scan every 4 wks after insulin or oral medication started (but no earlier than 26 wks)
  - Twice wkly antenatal testing at 28 - 32 wks

Fetal Evaluation

Procedure	Low risk	High risk
Fetal kick counts	28	28
USG for fetal growth	28 & 37 weeks	Monthly
NST	In GDM 36weeks Semiweekly	28-34 weeks, Semiweekly
FHS/BPP/Doppler	36 weeks, weekly	27 weeks-1-3/week
Amniocentesis For lung maturity	-	35 - 38 wks

Prepregnancy Management of Preexisting Diabetes

Nutritional & metabolic intervention must be initiated well before pregnancy begins, because birth defects occur during the critical 3-6 wks after conception.

Goals for Therapy

- To maintain glucose levels as near to normal as possible before conception, throughout the pregnancy, during labor and in postpartum period so as to reduce complications

- Managed through a team comprised of an obstetrician, diabetes physician, a diabetes educator, dietitian, midwife and Pediatrician

- **Insulin regimen should:**
  - **Result in a smooth glucose profile throughout the day, with no hypoglycemic reactions bet meals or at night.**
  - **HbA1C is (< 6.5%) at least 3 months before conception**
- **1.0 mg/day of folic acid for at least 3 months before conception to minimize the risk of neural tube defects in the fetus.**

- Ensure no transmissible diseases: HBsAg, HIV, rubella
- Try and achieve normal body weight: diet/exercise
- Stop drugs : oral hypoglycemic drugs, ACE inhibitors, beta blockers

MANAGEMENT ISSUES

Interdisciplinary team effort

- Patient education
- Medical Nutrition therapy
- Glycemic monitoring: SMBG and targets
- Pharmacological therapy
- Fetal monitoring: ultrasound
- Planning on delivery

Tx Targets - Controversial

Glucose level

Fasting - 90-99 mg/dL (5.0–5.5 mmol/L)
1- hr PP - < 140 mg/dL (7.8 mmol/L)
2- hr PP - < 120-127 mg/dL (6.7–7.1 mmol/L)

Glycemic Targets

- ACOG
  - F venous plasma ≤ 95 mg/dl
  - 1 hr PP ≤ 140 mg/dl
  - 2 hr PP ≤ 120 mg/dl
  - Pre-meal ≤ 100 mg/dl
  - A1C ≤ 6%
- ADA
  - Premeal 80-110
  - 2 hr PP not >155

These are venous plasma targets, not glucometer targets

Medical Nutrition Therapy

- Goals
  - Achieve normoglycemia
  - Prevent ketosis
  - Provide adequate weight gain
  - Contribute to fetal well-being
- Nutritional plan
  - Calorie allotment
  - Calorie distribution
  - CH2O intake

Calorie Allotment

- 30 kcal/kg current wt/day who are BMI 22 to 25.
- 24 kcal/kg current wt/day in overweight (BMI 26 to 29).
- 12 to 15 kcal/kg current wt/day for morbidly obese (BMI >30).
- 40 kcal/kg current wt/day who are less than BMI 22.

Weight Status	Recommended Caloric Intake If pregravid weight is:	Recommended Weight Gain
Within desirable range	30 Kcal/Kg/day/ present weight	25-30 lbs./11-16 kg.
120-150% desirable range	24 kcal/kg/day current weight	15-lbs./7 kg.
>150% desirable range	12-18 kcal/kg/day present weight	15 lbs./7kg
<90% desirable range	36-40 kcal/kg/day or 30-kcal/kg present weight	28-35 lbs./13-21 kg.

Dietary Therapy

- Avoid single large meals with large % of simple CHOs
- 6 feedings/day, with 3 major & 3 snacks

MNT

- Carbohydrates 35 – 45 %
- Protein 20 – 2 5 %
- Fats 35 – 40 %

- CHO intolerance is greatest after breakfast & may improve with splitting in two halves of equal portion & consuming at 2 hour gap
- Peaking of plasma glucose is high with breakfast (Dawn phenomenon) than with lunch and dinner, insulin secretion is higher with breakfast than with lunch or dinner

- CHOs no more than 50% of the diet, Include Complex CHOs & cellulose, such as whole grain breads and legumes.
- Do not skip meals and snacks
- Non caloric sweeteners may be used in moderation.
- Folate supplementation

Calorie and Carbohydrate Distribution

- Breakfast - 10-15% of total calories. *Limit carbohydrate initially to 15-45 Grams.
- 1 Snack - 5-10% of total calories. *
- Lunch - 20-30 % of total calories
- 2 Snack - 5-10% of total calories. *
- Supper - 30-40 %
- 3 Snack 5-10 % of total calories. *

*Protein added to early low-carbohydrate breakfast and snacks is helpful in reducing hunger

Artificial Sweeteners and Caffeine:

- Avoid saccharin as it crosses the placenta.
- Aspartame (contraindicated with phenalketonuria), acesulfame-K and sucralose are allowed in limited amounts. Artificial sweeteners containing CHO counted as part of total CHO
- Caffeine is allowed in moderation. <300 mg/day is allowed to limit potential harm to the fetus

Exercise

- ACOG recommends – 30 min/day of moderate exercise like walking, stationary bicycling, low impact aerobics and swimming
- Begin with 5 – 10 min of warm up period involving stretching exercises
- In sedentary women, exercise HR should not exceed 140 bpm
- Before exercise all pts should undergo medical evaluation and educated about the benefits and risk of exercise
- Exercising lower maternal glucose conc in GDM

Exercise

Absolute Contraindication

- Preterm Labor
- PROM
- Incompetent Cervix
- Persistent 2nd or 3rd trimester bleeding
- IUGR
- Placenta Previa beyond 26 week
- PIH

MEDICATION

INSULIN

ORAL DRUGS

Monitoring BG

- At least 4 times (SMBG)
  - Fasting and 3 one hr postprandial
- Pre vs. postprandial monitoring
  - Better glycemic control (HbA1c value 6.5 vs. 8.1 %)
  - ↓ incidence of LGA infants (12 vs. 42 %)
  - ↓rate of CS delivery for CPD (12 vs. 36 %)

Monitoring BG

- Home monitoring
  - Maintain log book
  - Use a memory meter
  - Calibrate the glucometer frequently
- HbA1C
  - Ancillary test for feedback to the pt
  - Lower values when compared to non-pregnant state – lower BG – measured every 2-4 weeks
  - Target < 5.1%

When to Start Insulin Therapy in GDM

Fastinga	Postprandial	Reference
105[b]	None	Metzger
>95	2 h> 120	Langer et al.
>100	1 h > 130	Ramus and Kitzmiller
>90	1 h> 120	Jovanovic–Peterson

a – Glucose concentrations (mg/dl) measured in finger–stick wholeblood samples unless designated otherwise.
b – Venous plasma sample.

Why Insulin?

Gold standard because of its-

- safety and efficacy
- it can not cross placenta because large mol wt (6000Da)
- NPH insulin is the only basal insulin that has been adequately studied in pregnancy

Insulin Analogue

- Produced by recombinant DNA methods.
- Effective and efficacious
- lispro & aspart is as efficacious as regular insulin for improving glucose control well studied
- No studies evaluating the use of glulisine

- Aspart, Lispro: category B
- Regular insulin: category B
- Glargine, Detemir: category C

Short Acting Analogs

- Plasma insulin level reached earlier & greater
- Better control of PP plasma glucose
- Less risk of post prandial hypoglycemia
- Gold standard of mealtime insulin replacement in adults

Safety of Insulin Glargine

- Has 2 molecules of arginine to the C-terminal of the beta chain & the replacement of aspartic acid with glycine in position A21,
- Category C
- Half-life (24 hrs)
- Risk - ↑ed affinity for IGF, lead to ↑ed fetal growth & other mitogenic effects
- Erika Pollex,2011 Systematic Review & Meta-analysis – no ↑ adverse fetal outcomes

Insulin Mixtures

- Biphasic human insulin: Premix insulin: mixtures of intermediate and short-acting acting insulin
  - NPH/Regular (70%/30%) or (50%/50%)

- Premix insulin analog:

  - Lispro Protamine/Lispro (50%/50%)
  - Lispro Protamine/Lispro (75%/25%)
  - Aspart Protamine/Aspart (70%/30%)

- Regimen and timing of insulin injections different from non-pregnant state because as pregnancy progress:
  - ↑sing fetal demand for glucose
  - Progressive lowering of maternal F & PPBG
  - ↑ses the risk of symptomatic hypoglycemia

- Thus short-acting insulin doses to control postprandial glucose surges within the target band only exacerbates the tendency to interprandial hypoglycemia.

Insulin Dosage

- If MNT fails to achieve control in 2 wks, insulin may be initiated
- Increase Dosage as Pregnancy Advances
- In a morbidly obese woman, insulin ↑sed to 1.5 to 2. u/kg to overcome the combined insulin resistance of pregnancy and obesity

Calculation of Insulin Dosing

- Total daily dose (TDD):
  - Wt in kg ✘ k
  - K = 0.6-0.7u/kg/day during first trimester
- 0.7-0.8 u/kg/day during 2nd trimester
- 0.9-1u/kg /day during 3rd trimester
- 50% of TDD by long acting insulin before breakfast (8am), before supper (4pm) & midnight
- 50% of TDD by rapid acting before breakfast (8am), lunch & before supper (4pm)

Insulin Therapy

- Start with Premix insulin 30/70 of any brand
- Total insulin dose/day can be divided as 2/3 in morning and 1/3 in evening
- Starting dose: 4 units before breakfast
- Every 4th day increase 2 units until 10 units
- If FPG remains > 90 mg/dl – 6 units before breakfast & 4 units before dinner
- Review with blood sugar test, adjust dose further

- Initially if post breakfast plasma glucose is high - Start Premix 50/50
- If 2 hr PG > 200 mg/dl at diagnosis, a starting dose of 8u of premixed insulin could be administered straightaway before breakfast and the dose has to be titrated on follow-up.

If insulin requirement drops, placental insufficiency or fetal jeopardy has to be suspected (may also be due to ↑sed utilization of maternal glucose by the supercharged beta cell mass of the macrosomic fetus.

Insulin Pump Therapy

- An insulin pump is a computerized mechanical device about size of a pager.
- Pumps rapid or short-acting insulin through a length of tubing to a small catheter or needle that is inserted into the fat layer under the skin.
- Insulin is pumped continually at a preprogrammed *basal* rate, and the pump wearer programs in a *bolus* amount of insulin at meals and snacks based on the amount of carbohydrate in the food to be eaten.
- Safely and successfully used in Type 2 & GDM, commonly in Type 1 diabetes.

Insulin Pump

- Allows insulin release close to physiologic
- Use short acting insulin
- 50-60% of total dose is basal rate
- 40-50% given as boluses
- Potential complications
  - Pump failure
  - Infection
  - Increased risk of DKA if above happens

OHA in Pregnancy

Primary Mechanism of OHA in Type II DM

Class of Drug	↑ Pancreatic Insulin Secretion	↓Hepatic Glucose Production	↑Pheripheral Glucose Utilization	↓Gut CHO Absorption
Sulfonylureas/ Meglitinides	+			
Biguanides	+	+	+	
Thiazolidinediones		+	+	
άGlucosidase inhibitors				+

- Tolbutamide and chlorpropamide 1st generation sulfonylureas
  - Cross placenta. Fetal hperinsulinemia. Prolonged fetal hypoglycemia

- Glibenclamide/Glyburide 2nd generation sulfonylureas
  - Category C
  - Act by releasing insulin from Bcells
  - Well absorbed independent with food intake
  - Metabolised in liver
  - Peak conc. – 2-3hrs, half life – 7-10hrs
  - do not significantly cross placenta.
  - Fetal conc no more than 1% to 2% of maternal conc.

- Observational studies – no excess anomalies or hypoglycemia
- Only RCT – 404 women. Glib vs insulin. No difference
- Intial dose 2.5mgm, can ↑sed upto 20, not more than 7.5mgm in single dose, 30-60min before food
- Adverse effect 3.2-4.1%

- Metformin (Biguanides)
  - Category B
  - Safe and effective after 1st trimester
  - Improves insulin sensitivity, inhibit glucogenesis, ↑Glucose uptake by muscle & adipose tissue, ↓intestinal absorption
  - Metabolized by CYP Pathway
  - Half life 6hrs
  - Starting dose 500-1000mgm, max - 2500
  - Vs. insulin – no serious adverse effects
  - No studies vs. glibenclamide
  - Crosses placenta 10-16%– not teratogenic in rat models
  - Adverse effect – 2 – 63%

- Acarbose (άGlucosidase inhibitors)
  - Two prelim studies
- Thiazolidinediones
  - Not studied
- Tolbutamide diffused across the placenta most freely, followed by chlorpropamide, then glipizide, with glyburide crossing the least.

GDM

- A1 Diabetes (Gestational)
  - No medication
  - If AC > 70 percentile at 28 wks - prophylactic insulin.
- A2 Diabetes (Gestational)
  - Glyburide
    - Usual starting dose is 2.5mg BID
    - If not controlled ↑se dose in increments of 2.5mg to 5mg each wk to achieve control
    - Maximum 20mg/day
  - Not controlled at max dose will require insulin

Type II or A2 Not Controlled by Glyburide

- Insulin (Humalog and NPH)
- Current body wt in kg x (.2-1.0 units) = Total daily dose (TDD)
- TDD is only a starting point. Insulin should be adjusted PRN to control blood glucose.
- Use Lispro to cover meals, NPH to cover overnight

- Lispro should be taken 15 minutes before or immediately after each meal
- Units of Lispro
  - TDD x .25 pre-breakfast
  - TDD x .25 pre - lunch
  - TDD x .25 pre – dinner
  - TDD x .25 NPH at bedtime
- Give NPH at bedtime to cover morning fasting.
- NPH dose must be adjusted based on FBG

Type I DM

- Insulin (Humalog and Lantus)
- Current body wt in kg x (.6 to 1.0 units) =TDD
- TDD x .5 = basal dose of Lantus (give either HS or in am)
- Do not mix with other insulin
- Determine pre-meal insulin using rule of 1500
- Pre-meal correction
  - 1500/TDD = mg/dl that 1u of insulin will ↓se BG
  - Insulin/CHO Ratio (1500/TDD) x .33 = grams of CHO covered by 1 unit of insulin

GDM/ Type 2 DM

PPBG 120-180 mg/dl, FBG 95-140 mg/dl, HbA1c >6.5%

2.5 mg in morning,
↑ by 2.5 mg 1st wk
Add 5 mg in evening
↑5 mg in morning,
↑5 mg in evening
Max 20mg

Glyburide

Combination therapy

Insulin

2/3 in morning (1:2 short: NPH)
1/3 in evening (1:1 short: NPH,
super regular, bed time NPH)

ADA 2011

WHEN TO DELIVER AND HOW TO DELIVER

WHEN TO DELIVER

- Class A1
  - Labor spontaneously or induce 40-42 weeks, *Cochrane review-"little evidence to support elective induction at 38wks*
- Class A2 -C (good control with nl antepartum testing)
  - Induce at 39 – 40 weeks
- Class D - T or class A2 - C with poor control
  - Deliver at 37-38 weeks

Mode of Delivery

- Vaginal route – preferred
- Indications of C.S.

  -EFW->4.5 Kg [ACOG]

  -H/O shoulder Dystocia, previous stillbirth

  -other obstetric indications
- EFW - 4 - 4.5Kg - Role of CS controversial

Labor and Delivery

- INDUCTION
  - usual medication (insulin or glyburide) at bedtime
  - Eat nothing after midnight
  - Do not take morning medication
  - In morning, check BG and start insulin drip
- SPONTANEOUS LABOR
  - Check BG
  - Ask about last insulin or oral medication
  - Start insulin drip

Scheduled C-Section

- Usual medication (insulin or glyburide) at bedtime
- Eat nothing after midnight
- Do not take morning medication
- Check blood glucose
- Perform CS within 2 hrs
- If unable to perform surgery immediately or pt in poor control, start insulin drip, Perform CS after 4-6 hrs euglycemia.

Intrapartum Management

- Strict asepsis
- Restrict number of PV examinations
- Electronic fetal heart rate monitoring
- Partogram
- Obstetrician to be well versed with the Mx of SHOULDER DYSTOCIA
- Call Paediatrician

Insulin During Labor

- Tight control of maternal glycaemia is essential throughout labor.
- In labor no extra insulin is required because labor is a form of exercise
- Monitor BS- 1 hourly
- Target BS-70-100 mg/dl
- Monitor urine sugar & ketone 2-4 hourly

Plasma Glucose and Insulin IV Fluid

PLASMA GLUCOSE At time of onset of labour	*INSULIN / IV FLUIDS*
< 70 mg/dl	5% GNS - 100 ml/hr
90-120 mg/dl	NS - 100 ml/hr
120-140 mg/dl	NS -100 ml/hr *plus4 units of Reg. insulin added with IV fluid*
140-180 mg/dl	NS - 100 ml/hr *plus6 units of Reg. insulin added with IV fluid*
>180 mg/dl	NS - 100 ml/hr *plus8 units of Reg. insulin added with IV fluid*

Drip rate: 16 to 20 drops per minute. Maternal Capillary blood glucose to be checked by glucometer every 1 hour and drip rate adjusted.

CPG Guidelines

Insulin by Sliding Scale During Labor

Low Dose Protocol

- For type 1 DM and GDM on insulin receiving <40 U/day antenatally

Blood Glucose(mmol/l)	Novo Rapid/Humalog s/c
0-5	Nil
5.1-7.0	2 units
7.1-10.0	4 units
10.1-13.0	6 units
>13	8 units

High Dose Protocol

- For type II and GDM on insulin receiving >40/antenatally

Blood Glucose(mmol/l)	Novorapid/Humalog
0-5	Nil
5.1-7.0	4 units
7.1-10.0	6 units
10.1-13.0	8 units
>13	10 units

Postpartum Care

- Maintain hydration
- Insulin infusion is discontinued
- GDM on diet-no monitoring
- GDM on insulin /Pre-gestational DM-

  -Monitor BS 2-4 hourly

  -Honeymoon period[24-48 hrs]- no insulin/very low doses of insulin is needed.

Postpartum Care Continued

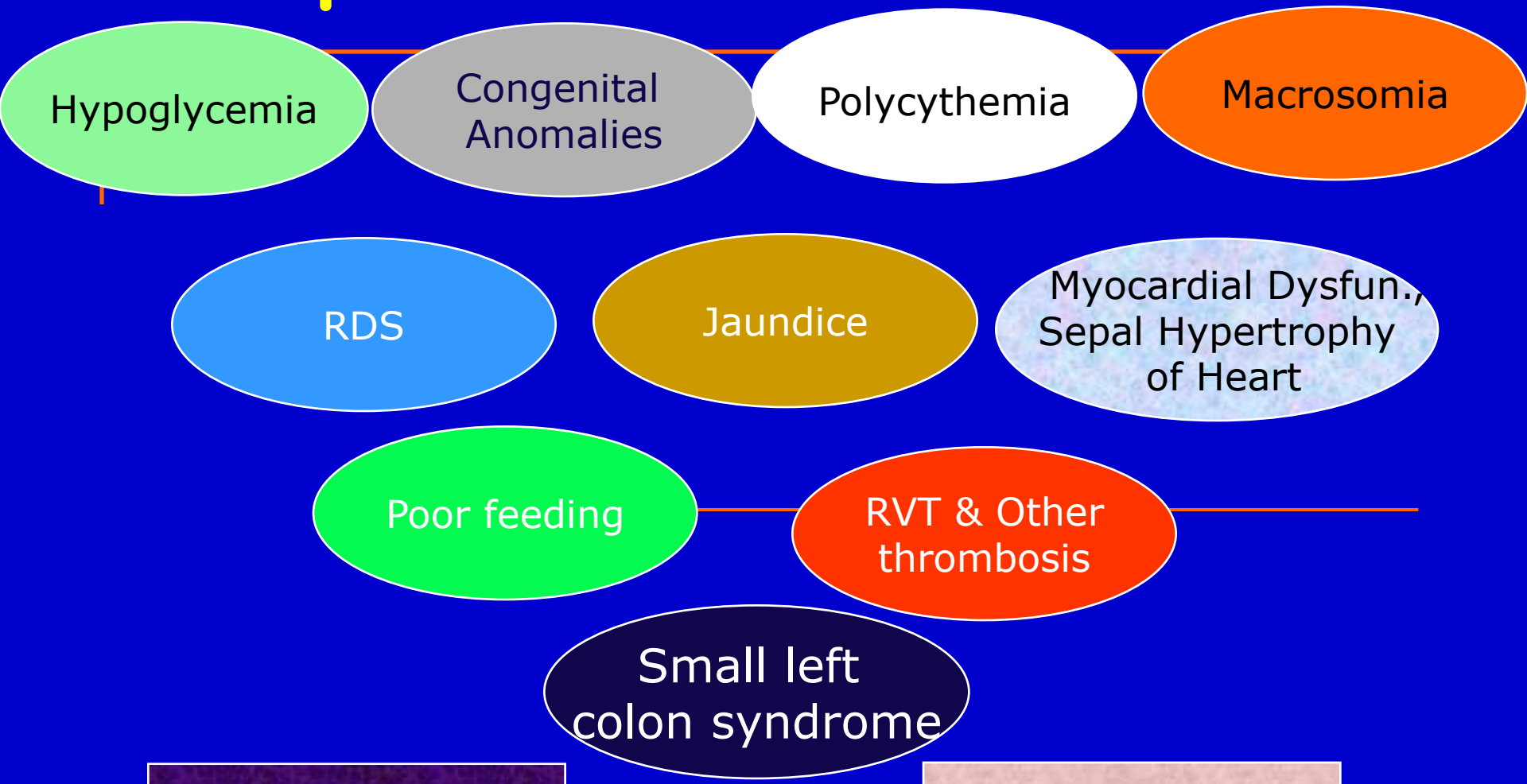
- Type 1 DM-restart insulin [0.5-0.6U/Kg] on day 2-5 post delivery.
- Breast feeding: helps in weight loss.
  - Insulin, tolbutamide compatible.
  - Chlropropamide secreted small amounts
  - Glyburide and glipizide not secreted
  - Metformin secreted - no adverse effects

- Check BG before discharge
- Lifestyle modification: exercise, weight reduction & healthy diet
- 75 OGTT at 6-12 wks postpartum: classify patients into normal/impaired glucose tolerance and diabetes
- If normal reassess at 3 yrs interval
- Counseling for future pregnancies

Mx of Preterm Labor

- Avoid Beta mimetic drugs
- Tocolytics of choice
  - Nifedipine
  - Magnesium Sulphate
- Cortecosteroids
  - can be used
  - Intensive BS monitoring for 5-7 days
  - Dose of insulin to be increased

Anticipation & Initial Assessment



Principle of Management of Neonate

- Before Delivery
  - L:S Ratio
  - Saturated SPC Content
  - Screening for major congenital anomalies
- After Delivery
  - APGAR
  - Exam of Placenta
  - Cord Blood – Glucose, pH, Hematocrit, Calcium, S.Bil
  - NEONATAL CARE

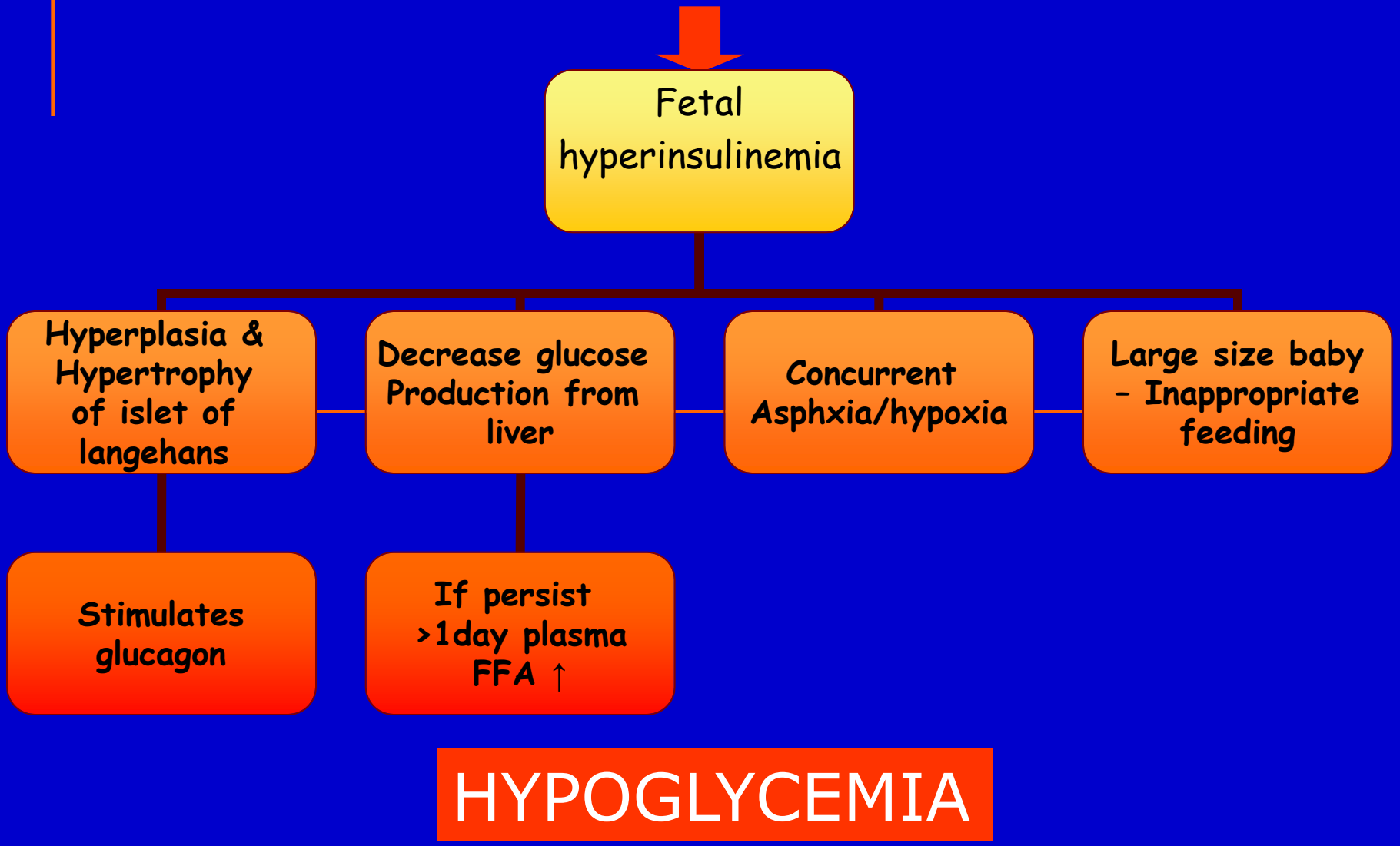
- Hypoglycemia a major concern:
  - 50 % of macrosomic infants
  - 5–15 % optimally controlled GDM

- ↑sed risk : bl glucose during labor & delivery > 90 mg/dl

Anticipate and treat hypoglycemia

Hypoglycemia

Placental transfer of glucose & other nutrition



HYPOGLYCEMIA

Management of Neonate

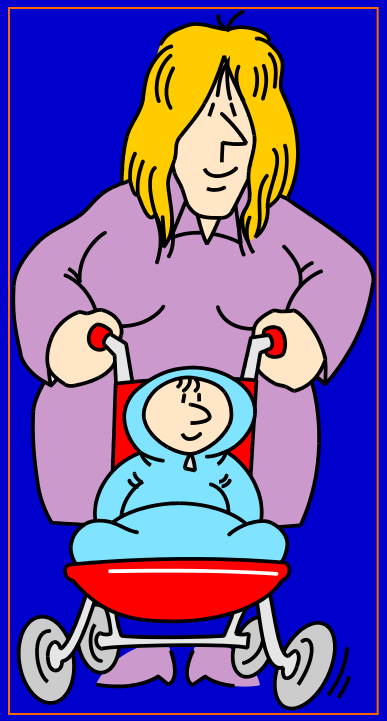
- Hypoglycemia <40 mg/dl
- Encourage early breast feeding
- If symptomatic give a bolus of 2- 4 ml/kg, IV 10% dextrose
- Check after 30 minutes, start feeds
- IV dextrose : 6-8 mg/kg/min infusion
- Check for calcium, if seizure/irritability/RDS
- Examine infant for other congenital abnormalities

Contraception

- Low dose EP can be used
- Progestin only pills shown to ↑se risk of T2DM in GDM
- IUCD – not ↑sed PID

Future Risks - Mother

- At least 6 wks post delivery, GDM - ≥ 90% normoglycemic
- Recurrence of GDM – 30-60%
  - Older
  - Multipara
  - Weight gain inter-pregnancy
  - Higher infant BW in index pregnancy
- IGT and T2DM
  - 20% IGT postpartum
  - 3.7% @ 6m , 4.9% @ 15m and 18.9% @ 9 y



Diabetic Ketoacidosis in Pregnancy

- Acute medical emergency
- Fetal loss rates >50%
- Maternal mortality rates < 1%
- Most commonly with pre-gestational, poorly controlled insulin dependent diabetes or in newly diagnosed insulin dependent diabetes.
- Provoked by stress such as infection, surgery, or labor

Pathophysiology of DKA

- Results from relative or absolute lack of circulating insulin and/or an excess of counter regulatory hormones.

Decreasing insulin/glucagon ratio interrupts normal production & disposal of glucose

↓

hyperglycemia and ketosis

↓

yields b-hydroxybutyrate & acetoacetate which decrease pH, ↑ respiratory rate & compensatory respiratory alkalosis

↓

metabolic buffering system is depressed.

Signs and Symptoms of DKA:

- Malaise
- Headache
- Dry mouth
- Weight loss
- Dehydration
- Nausea/Vomiting
- Polyuria/polydypsia
- Shortness of breath
- Abdominal pain
- Mental status changes

Diagnosis of DKA:

- CBC, serum electrolytes, BUN, creatinine, glucose, arterial blood gases, bicarbonate, urinalysis, lactate, serum ketones
- Blood sugar: DKA can occur with BG > 200 mg/dl in pregnancy
- Serum ketonemia: +ve, given in dilutional titer
- Acidosis: arterial pH less than 7.35
- Electrolytes + Anion Gap: Defined as Na-(CL+HCO3) >12. reduction in HCO3 is proportional to ↑ keto acids conc. & anion gap = decrease in HCO3

Treatment of DKA

- Goals of therapy
  - Re-hydration
  - Correction of acidemia
  - Normalization of serum glucose
  - Restoration of electrolyte homeostasis
  - Elimination of the underlying cause

Management Guideline

- Make a clear diagnosis (Blood gas; blood sugar; anion gap; serum ketones)
- Admit medical intensive care unit
- Frequent monitoring of maternal BP, HR, pulse oximetry & continuous EFM (based on gestational age)
- Hourly intake & output
- Other labs as indicated - liver function test, chest x-ray, sepsis work-up & cultures

Fluid Replacement

- **Goal - correct of total fluid deficit over 12-24 hrs. range bet 6-8 liters.**
- **Initial fluid (0.9 NS only)**
- **Over first hour: 1 liter**
- **Over next 2 hours: 500 ml/hr**
- **Over next 4-6 hours: 250 ml/hr to replace Na deficit, to correct hypotension, & ↑ urine output (if low)**
- **After BP & urine output stabilize - 0.45 NS at 250-500 cc/hr & then ↓se infusion rate**

- When blood sugar >250 ml/dl,
  - add 5% Dextrose to IV fluids (D5 .45 NS) at 150-250 ml/hr to prevent cerebral edema caused by rapid ↓ in glucose.
  - Insulin infusion should be continued to keep serum glucose bet 150 - 200 mg/dL until metabolic control is achieved.
- Avoid lactate-containing solution as this will aggravate acidosis.

Insulin Therapy in DKA

- Initial dose - regular insulin 0.4 units/kg IV bolus
- Begin insulin drip with regular insulin at 5-10 units/hr
- Blood sugar is monitored 1 hourly
- Double insulin infusion rate if BG not ↓sed by 25% in 2 hours.
- As BG>250 mg/dl & 5% D5 to fluids (D5 .45 NS).
- ↓ infusion to 1-2 units/hr as BG <150 mg/dl
- When the patient is eating, switch to long-acting insulin.

Potassium Replacement

- Loss usually 5-10 meq/kg.
- As acidosis corrected, K^+ re-enter cell & serum K^+ ↓.
- If initial K^+ is normal or low,
  - replace immediately with 10 meq/hr.
  - Or add KCl (40 meq/L) to each liter of replacement fluid (rate of 150-250 ml/hr), will give app 5-10 meq/hr replacement.
- K^+ dose should be ↓ed by 50% if pt remains oliguric.
- If initial K^+ is high, begin replacement at 10 meq/hr after adequate urinary output is established.

- Replacement K^+ conc never be >40 meq/hr.
- Monitor K^+ levels 2-4 hourly during tx.
- Oral K^+ given for 1 week after acute DKA to correct the total body deficit.

Correction of Acidosis

- Most cases will correct with above tx.
- HCO_3^- rarely needed & should only be used if pH is <7.10;
- Rapid correction with HCO_3^- cause iatrogenic metabolic alkalosis & paradoxical fall in CSF pH. This causes a worsening of cerebral acidosis & ↑se obtunded mental status.

Broad spectrum antibiotics should be initiated pending results of sepsis work-up and cultures, if indicated.

Fetal Considerations

- With >24 weeks, live fetus, monitored continuously for fetal heart rate.
- Fetuses exposed to maternal acidosis may have ↓sed variability and late decelerations. Ominous patterns correct themselves with correction of maternal metabolic disturbance.
- Maternal O2 therapy useful in non-reassuring FHS.
- Delivery of compromised fetus should be undertaken ONLY after mother metabolically stable.
- Avoid betamimetics & corticosteroids while DKA is being controlled.

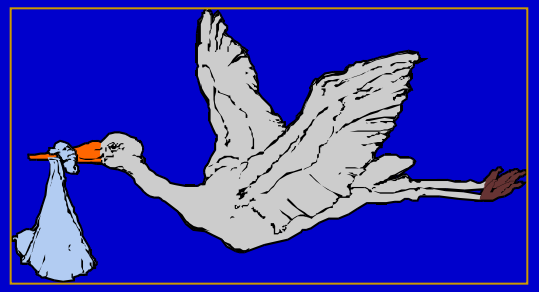
Take Home Message

- Common problem in India
- Early diagnosis in pre-gestational & gestational period is must
- Tight glycemic targets for optimal maternal and fetal outcome
- Diet, exercise, education, & insulin are mainstay
- Insulin analogs lyspro & aspart are also safe
- Glyburide & metformin are effective alternative
- Long term follow up of mother & baby is essential

- **Role of the Obstetrician**
  - preconception counseling
  - attention to maternal glucose control
- **Role of the Pediatrician**
  - Understand the fetal metabolic consequences of maternal diabetes
  - Anticipate and treat complications

Women and Diabetes

- Diabetes no longer means
  - Abstinence
  - Amenorrhea
  - Inability to conceive
  - Inability to deliver healthy children
  - Death during pregnancy



- With all continuous advancements in research

We hope for the pt to become

Diabetic free

in near future.


Thank
You