

DIABETES IN PREGNANCY



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CLASSIFICATION

	Type 1 (insulin deficient)	Type 2 (insulin resistant)
HLA	Yes	none
subtypes	DR3, DR4	MODY
Genetic locus	Chromosome 6	unknown
Trigger	Virus	obesity
Inflammatory cells	Yes	no
Islet antibodies	yes	no
Seasonal trend	Fall/winter	none
Family hx.	uncommon	40%
Twin studies	20-50%	100%


CLASSIFICATION

	Type 1	Type 2
age	<30	>30
Autoimmune d	yes	no
habitus	Normal/wasted	obese
onset	Acute/subacute	slow
Glucagon	suppressible	resistant
Insulin status	Low-absent	Normal/high
coma	ketoacidosis	Hyperosmolar
therapy	insulin	Oral meds

Effect of long term intensified insulin treatment on development of microvascular complications of type 1 diabetes 7.5 years follow-up

Complications	Intensified(48)	Standard(54)	P value (OR)
Hb A1C	7.1	8.5	0.001
Retinopathy surgery	12(27%)	27(52%)	0.01(0.4)
Decreased visual acuity	6(14%)	18(35%)	0.02
Microalbuminuria (>200ug/min)	1(2%)	9(17%)	0.01(0.1)
Nephropathy(<GFR)	0	6(11%)	0.02
Peripheral neuropathy	2%	11%	0.01
Neuropathic foot ulcers	0	3	

Reichard et al NEJM 1993:329;304-309

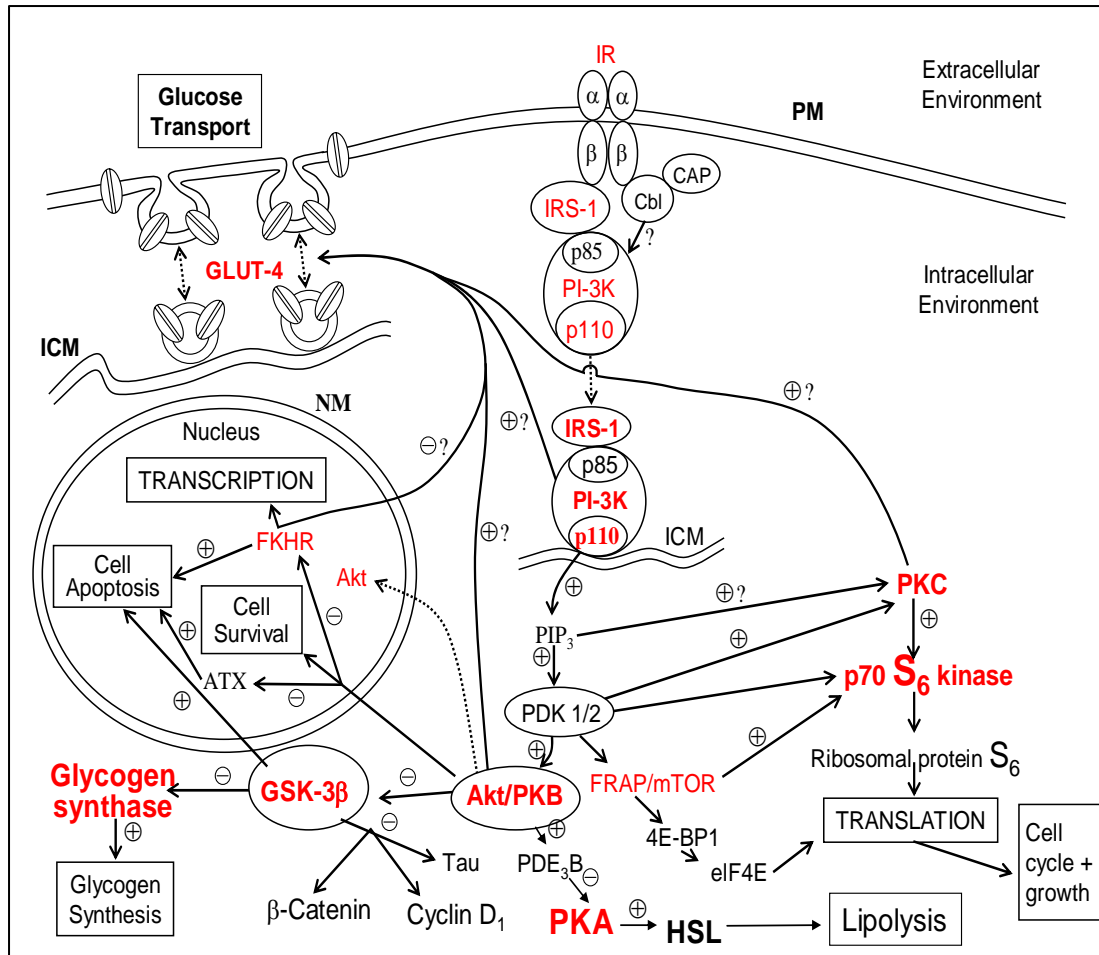


Metabolic syndrome

Major criteria

- **Insulin resistance**(hyperinsulinemia: glucose level)
- **Acanthosis nigricans**
- **Central obesity** (waist >40 in inches in XY, >35 inches in XX)
- **Hypertension** (BP $> 130/85$)
- **Dyslipidemia** (HDL <45 mg/dl in XX $< <35$ mg/dl XY, TGA >159 mg/dl)
- **Impaired glucose**(>110 mg/dl) or **type 2 diabetes**
- **Hyperuricemia**

Glucose transport and insulin signaling

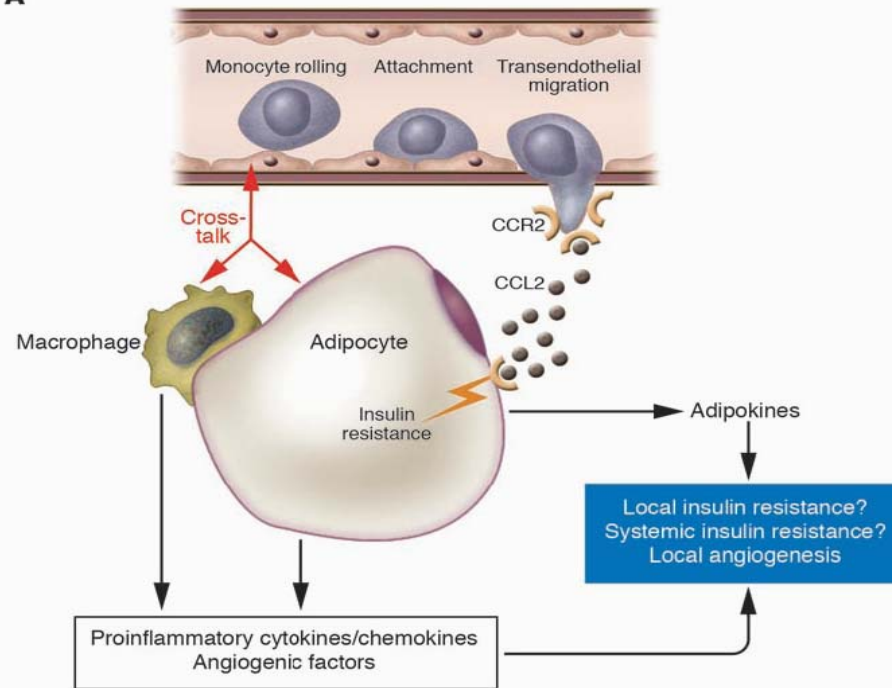




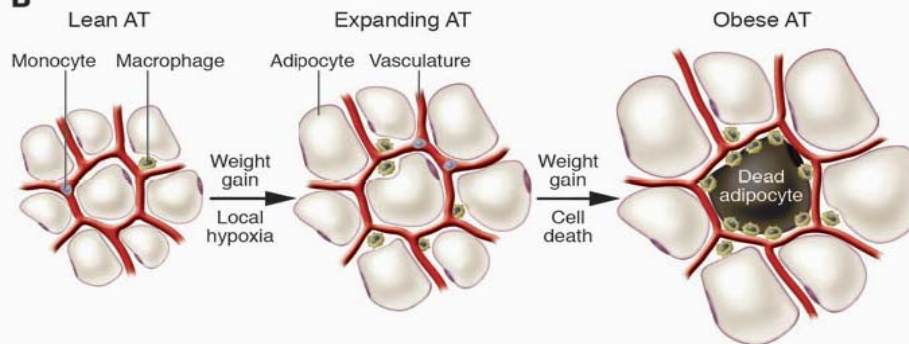
Type 2 diabetes (DM2)

- **Maybe a maladaptation to acute-phase response to injury resulting in low-grade chronic systemic inflammation in non-pregnant population**
- **Adipose tissue produce cytokines which cause insulin resistance and adiponectin which improves insulin sensitivity.**

A



B





Adipose tissue hormones

- **TNF alpha**
- **Interleukin-6:**
- **Resistin: increases insulin resistance**
- **Adiponectin: endogenous insulin sensitizer**
- **Leptin: increased in obesity**



Insulin signaling pathways

- The **PI-3 kinase cascade**: may be main pathway in glucose transport & glycogen synthesis.
- **Akt** seems to play role in regulating the antilipolytic effect of insulin, by phosphorylating and activating phosphodiesterase-3B (PDE3B), a cAMP-degrading enzyme
- Akt activation also affects other signaling pathways, i.e **GSK-3/glycogen synthase**, the FKHR , & p70 S6 kinase/translational control cascades



The MAPK signaling pathways:

- **Help determine the fate of a cell in the decision to remain quiescent, differentiate, proliferate or undergo apoptosis**
- **Stimulation by insulin (or other growth factors), the Erk1/2 cascade is sequentially activated**



Glycogen synthase (GSK3)

- In adipose tissue, as in muscle, insulin promotes the storage of glucose by accelerating the rate of glucose transport into the cell and the activity of glycogen synthase (GS), the rate-limiting enzyme in glycogen synthesis; and by inactivating glycogen phosphorylase.
- Defects in GS activity and glycogen deposition are early events in the development of insulin resistance.
- GSK-3, a serine/threonine kinase, phosphorylates and deactivates GS. GSK3 impairs insulin signaling, by increasing serine phosphorylation of IRS-1, and possibly directly reducing IR tyrosine autophosphorylation
- In adipocytes, insulin decreases GSK-3 activity by ~50%, and contributes to the insulin regulation of glycogen synthesis .



Glucose transporter (GLUT)-4:

- **The cell membrane is a lipid bilayer that is impermeable to carbohydrates. In order for glucose to enter a cell it requires a transporter molecule. Only GLUT-4 seems to require insulin to transport glucose in muscle and adipose cells. In response to insulin, the rate at which intracellular vesicles containing GLUT-4 translocate to the plasma membrane from intracellular storage pools increases, essentially incorporating GLUT-4 to the cell membrane and increasing the rate of glucose transport into the cells.**



Diabetogenic stress of pregnancy

- **Human Placental Lactogen**
- **Free Cortisol**
- **Estrogen**
- **Progesterone**
- **Progressive maternal insulin resistance resulting increased insulin production**



New Paradigm

- **Kiwan et al longitudinally showed that TNF-a was the most significant predictor of insulin sensitivity pregnancy even after adjusting for fat mass with no correlation of insulin sensitivity with reproductive hormones and cortisol and suggested that a TNF-a is new paradigm to explain GDM.**



TNF-alpha mechanism

- **lipoprotein lipase**
- **decrease insulin receptor signaling by reducing tyrosine kinase activity**
- **inducing serine phosphorylation of insulin receptor substrate -1 which inhibits IRS-1**
- **Decreases glucose transport by decreasing GLUT 4 gene expression**
- **Decrease adiponectin production**



Dr. Priscilla White (1900-1989)

GESTATIONAL DIABETES CLASSIFICATION

CLASS	FBS	2HPPBS	THERAPY
A1	< 95 mg/dl	<120 mg/dl	diet
A2	>95 mg/dl	>120 mg/dl	insulin

White Classification

CLASS	Onset age yr	Duration yr	Vascular d
B	≥ 20	< 10	none
C	10-19	10-19	none
D	< 10	≥ 20	Benign Retinopathy
F	any	any	nephropathy
R	any	any	Proliferative Retinopathy
H	any	any	Heart disease
T	any	any	Renal transplant

Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in Netherlands

Outcome	Type 1 DM (n=314)	National (n= 196981)	RR
Preeclampsia	12.7%	1.05%	12.1
Prematurity	32.2%	7.1%	4.5
Cesarean section	44.3%	12%	3.7
Maternal mortality	0.6%	0.01%	60
Birth defects	8.8%	2.6%	3.4
Perinatal mortality	2.8%	0.8%	3.5
Macrosomia	45.1%	10%	4.5
Hypoglycemia :1st trimester 3rd trimester	41% 17%	84% were planned with good glycemc control HbA1c<7 in 75% & folic use in 70%	
Mean duration of diabetes	17 years		

Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in Netherlands

Outcome	Type 1 DM(n=324 infants)
Overall neonatal morbidity	80.2%
Shoulder dystocia	14%
Clavicle fracture	2%
Erbs palsy	1%
Neonatal hypoglycemia	64%
Hyberbilirubinemia	25%
Respiratory disorders	15%
Respiratory distress	5%
Hypertrophic cardiomyopathy	5%
Apgar score <7 at 5 minutes	5%



Poor pregnancy outcome in women with type 2 diabetes. Clausen et al Diabetes Care 28:323-328,2005

Perinatal mortality (4/61;6.7%) in type 2 diabetes was increased 4- & 9 fold respectively compared to type 1 diabetes (n=240) and background population despite **similar glycemic controls** in both type 1& 2 diabetics and the rate of **birth defects** was more than doubled but not significantly. Type 2 diabetics from **1996-2001** had worse perinatal mortality/birth defects compared to type 2 diabetics from 1982-1990.



Effect of treatment of Gestational diabetes on pregnancy outcome. Crowther et al. NEJM 2005,352:2477-86.

- **Prospective trial randomized women between 24-34 weeks who had gestational diabetes to receive dietary advice, glucose monitoring and insulin therapy (intervention group) or routine care. Primary outcome was serious perinatal complications defined as death, shoulder dystocia, bone fracture or nerve palsy.**
- **Conclusion: Treatment of gestational diabetes reduces serious perinatal morbidity and may also improve woman's health related quality of life.**

Effect of treatment of Gestational diabetes on pregnancy outcome. Crowther et al. NEJM 2005,352:2477-86.

Outcome	Intervention (n=490)	Routine care (n=510)	P value RR
Serious perinatal complication	1%	4%	0.01(.33)
Perinatal death	0%	1%	0.07
Shoulder dystocia	1%	3%	0.08(.46)
NICU admission	71%	61%	0.01(1.13)
Induction of labor	39%	29%	.001(1.36)
Cesarean delivery	31%	32%	
Preeclampsia	12%	18%	.02(.7)
Macrosomia	10%	21%	.001(.47)
Depression screen positive	8%	17%	.001(.46)
No difference in neonatal hypoglycemia; Apgar score, SGA, RDS, convulsions			



GDM SCREENING

4th International workshop on GDM

- **Universal screening**
high prevalence of type 2DM or risk factors
- **Selective screening**
Low risk population such as teenage clinics
- **Two step screen**
GCT followed by 3-h OGTT
- **One step screen**
75 gram 2-h OGTT



LOW RISK

- **TESTING NOT ROUTINELY REQUIRED IF:**
- **Caucasian ethnicity**
- **< 25 years**
- **Normal weight before pregnancy**
- **No family history of diabetes**
- **No history of abnormal glucose metabolism**
- **No history of poor obstetrical outcome**
- **4th international workshop on GDM Metzgar & Coustan 1998**



AVERAGE RISK

- **TESTING AT 24-28 WEEKS** or at first visit also recommended
- **Hispanic**
- **African American**
- **Native American**
- **Asian**
- **≥ 25 years**



HIGH RISK

- **TESTING AT 1ST VISIT AND REPEAT AT 24-28 WEEKS:**
- **Marked obesity**
- **Family history**
- **Prior Gestational diabetes**
- **Glycosuria or diabetic symptoms**
- **Previous macrosomia**
- **Previous Stillbirth**
- **Previous birth defect**



GLUCOSE CHALLENGE TEST

- **50- gram glucose load without regard to time of day or last meal.**
- **≥ 140 mg/dl detect 80% of GDM
14-18% will have positive screen**
- **≥ 130 mg/dl detect 90% of GDM
20-25% will have positive screen**

3 hour oral 100 gram glucose tolerance test

	National diabetes group 1979	Carpenter & Coustan 1982
Fasting	105	95
1 hr	190	180
2 hr	165	155
3 hr	145	140



Recommended Nutritional/Caloric Intake & Pregnancy wt gain

Dietary composition	50-60% carbohydrates 20% protein 25-35% fat with at least 10% unsaturated fatty acids	
Body mass index	Kcal/kg	Ideal wt gain (lb)
Underweight <19.8	36-40	28-40
Normal 19.8-26	30	25-35
Overweight 26.1-29	24	15-25
Obese >29	12-18	15-25



GDM A1 Counseling

- **Nutritional counseling**
 - Adequate nutrients for mother & fetus
 - To control glucose levels
 - To prevent starvation ketosis
- **Exercise**
- **Maternal & fetal risks**
- **Postpartum follow-up**

GDM A1 management

- Increased clinic visits
- FBS & 2HPPBS at home
- FBS & 2HPPBS during clinic visits
- Ultrasound for anatomy and fetal growth
- Weekly fetal testing from 36 weeks
- Start at 32 weeks if complications such as:
 - Advanced maternal age Hypertension
 - Previous stillbirth Preeclampsia
 - Tobacco or substance abuse



GDM A1 management

- **Weekly pelvic exam for Bishop's score from 37 weeks**
- **Induction after 37 weeks if favorable cervix**
- **Delivery by 41 weeks**
- **Consider elective cesarean delivery if EFW \geq 4500 grams**
- **Amniocentesis for elective cesarean delivery**
- **Induction if oligohydramnios, elevated umbilical artery SD ratio, non-reassuring FHRT or BPP \geq 6/10 at \geq 36 weeks**



Postpartum follow-up

- **75-g 2hr oral glucose test at 6-12 week after delivery**
- **If 75-g test normal, repeat minimum 3 yearly**
- **May recur in 2/3 of subsequent pregnancies**
- **May use low-dose oral contraceptives**
- **There is also increased risk of:**
 - **Hypertension**
 - **Abnormal serum lipid**
 - **Obesity**



Diagnosis of Class A2

- Insulin required if FBS > 95 mg/dl or 2HPPBS >120 mg on several occasions
- Insulin requiring gestational diabetes (Class A2) is managed like pre-gestational diabetes.
- Class A2 more likely if:
 - GCT >200mg,
 - 3hGTT with FBS \geq 100mg/dl
 - Any 3hGTT of \geq 200mg
 - Diagnosis before 24 weeks gestation



Maternal Complications

- **Urinary tract Infections**
- **Candidiasis**
- **Preeclampsia**
- **Cesarean delivery**
- **Genital trauma**
- **Polyhydramnios**
- **50% of GDM will develop overt diabetes within 20 years**



Neonatal Complications

- **Unexplained Stillbirths**
- **Macrosomia**
- **Shoulder dystocia**
- **Erbs' palsy and other birth trauma**
- **Hypoglycemia**
- **Respiratory distress syndrome**
- **Hypocalcaemia, hypomagnesia**
- **Neonatal jaundice, polycythemia**
- **Obesity, diabetes**



Maternal Complications (pre-gestation)

- **Worsening of retinopathy in Class R**
- **Increased mortality in Class H**
- **Diabetic ketoacidosis**
- **Hypoglycemia**
- **No effect on nephropathy**



Neonatal Complications (pre-gestation)

- **Abortions, embryonic delay**
- **Birth defects**
- **Hypertrophic/ congestive cardiomyopathy**
- **IUGR with Class C and worse**
- **Preterm delivery**

Threshold glucose levels

Perinatal mortality	Mean glucose level
3.8%	<100 mg/dl
16%	100-150
24%	>150
Optimum	100-115 mg/dl

Threshold glucose levels

Fetal macrosomia	Mean FBS
LGA rises (24%)	> 105 mg/dl
SGA rises (23%)	<86 mg/dl
Optimum(10%)	85-105 mg/dl
Optimum	Post-prandial <120 mg/dl

Threshold glucose levels

Fetal/neonatal defects	Mean glucose level
1.2 % anomalies	FBS=119 mg/dl, Post prandial = 142 mg/dl
10.9% anomalies	FBS= 133 mg/dl, Post prandial =164 mg/dl
Optimum	FBS < 120mg/dl, Post-prandial <140 mg/dl
Neonatal metabolic complications	<100 mg/dl



Insulin Therapy

- **Insulin dose**
 - **0.7 units/kg in 1st trimester**
 - **0.8 units/kg in 2nd trimester**
 - **0.9 units/kg in 3rd trimester**
- **In 1st trimester dose may decrease 10-25%**
- **In type 1 dose may increase by 10-20%**
- **In type 2 dose may increase 30-90%**



Insulin

- **Two thirds of insulin with breakfast**
 - **Intermediate /short acting ratio 2:1**
- **One third with dinner**
 - **Intermediate /short acting ratio 1:1**
- **May give intermediate insulin at bedtime to reduce fasting hypoglycemia**
- **May give short acting insulin with lunch if persistent elevated lunch levels**



Insulin Therapy

■ Time	Glucose (mg/dl)
■ Fasting	60-90
■ Premeal	60-105
■ Postmeal 1 hr	100-140
■ Postmeal 2 hr	100-120
■ 0200-0600	60-120
■ Usually check FBS & 2HPPBS	
■ In severe cases may add pre-meals, bedtime and 2-3 am blood glucose	

Insulin type

Insulin type	Onset	Peak action	Duration
Humalog Lispro	10 minutes	1 hour	2 hours
Regular insulin	20 minutes	2 hours	4 hours
NPH Insulin	1-2 hours	4 hours	8 hours



Oral Hypoglycemics

- **Insulin secretagogues**
 - **Sulfonylureas**
 - 1st generation
 - Tolbutamide
 - 2nd generation
 - Glyburide, Glypizide
 - **Meglitinides**
 - Repaglinide



Oral hypoglycemics

- Insulin sensitizers
- Biguanides
 - Metformin
- Thiazolidinediones
 - Pioglitazone
 - Troglitazone
- Alpha-glucosidase inhibitors
 - Acarbose
 - Miglitol



Glyburide

- **Class B drug sulfonylurea**
- **Does not cross human placenta**
- **Randomized study show:**
- **Good glycemic control 82% vs. 88%**
- **4% transferred to insulin**
- **Comparable rates of hypoglycemia, C/S rates, PIH.**



Comparison of Glyburide versus Insulin in Management of Gestational Diabetes Mellitus (53rd ACOG conference)

- **Objective: (49) glyburide vs. (48) insulin**
- **Glyburide was successful in 93% of GDM.**
- **May be better maternal & neonatal glucose control with insulin compared to glyburide but with no differences in birth weight.**
- **The insulin group seemed to include more severe diabetics.**
- **Insulin maybe more effective in severe diabetes but glyburide therapy overall may be more economical.**



Metformin

- Acts on liver and peripheral glucose uptake
- Not associated gain in weight
- Insulin has to be present
- Small molecule probably crosses placenta
- Risk of insulin fetopathy
- Conflicting inadequate reports(increased stillbirths, preeclampsia, birth defects, abortions, but decreased GDM)
- Don't use in pregnancy



Pre-gestational Diabetes

first trimester

- **Ultrasound for dating between 8-10 weeks gestation**
- **Schedule genetic counseling at first visit**
- **Fetal anatomical scan at 16-20 weeks**
- **Triple genetic screen at 15-20 weeks**
- **Fetal echocardiography at 18-22 weeks**



Pre-gestational diabetes

Initial Labs

- **CBC, electrolytes, LFT, HBA1C**
- **EKG**
- **24 hour urine collection for protein and creatine clearance**
- **Fundoscopy**
- **Thyroid function tests**
- **Urine culture**



Pre-gestational Diabetes Management

- **Basic ultrasound to assess fetal growth between 28-32 weeks**
- **Twice weekly fetal testing from 32 weeks**
- **Repeat basic ultrasound between 37- 38 weeks to r/o macrosomia**
- **If polyhydramnios or large for dates, evaluate glucose control and adjust insulin dosage.**



Pre-gestational Diabetes management

- **Schedule induction by 39 weeks**
- **Use sliding scale continuous insulin infusion in labor**
- **Monitor glucose levels q1-4 h in labor**
- **Hold morning insulin and use sliding scale if elective cesarean section**
- **Postpartum insulin requirements usually drop about 33-50%**
- **FBS of 120- 2HPPS of 200 mg/dl maybe acceptable post partum**




INDICATIONS FOR ADMISSION

- **Initial insulin therapy**
- **Uncontrolled blood sugars by home with:
FBS > 105 or 2HPPBS > 180 on 50% of tests**
- **Uncontrolled blood sugars by clinic test of:
FBS > 120; 2HPPBS > 180**
- **Suspected preeclampsia**
- **Suspected Infections**
- **Suspected fetal deterioration (IUGR, oligo,
abnormal BPP, elevated Doppler)**
- **Medical complications (emesis, renal,DKA)**



Diabetes Ketoacidosis

- **PRECIPITATING FACTORS**
- Poor compliance
- Infections
- Unrecognized new onset of diabetes
- **SPECIFIC FOR PREGNANCY**
- Hyperemesis gravidarum
- Betamimetics for tocolysis
- Corticosteroids for lung maturity



Diabetes Ketoacidosis ACUTE EMERGENCY

- 1% of pregnant type 1 DM
- Hyperglycemia glucose > 300mg/ml
- Serum ketones
- Metabolic acidemia (base excess \leq 4)
- **INADEQUATE INSULIN ACTION** with
- **excess STRESS HORMONES**
- **GLUCAGON** **CORTISOL**
- **CATHECOLAMINES** **GROWTH HORMONE**

Events leading to DKA

- Insulin lack
- Stress hormones



- Hyperglycemia



- Hypereosmolality



- Osmotic diuresis

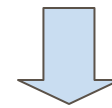
- Dehydration

- Electrolyte loss

- Hypotension



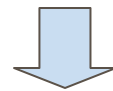
Insulin lack



ketones, low intracellular K⁺

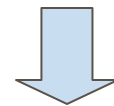


metabolic acidosis



hyperventilation

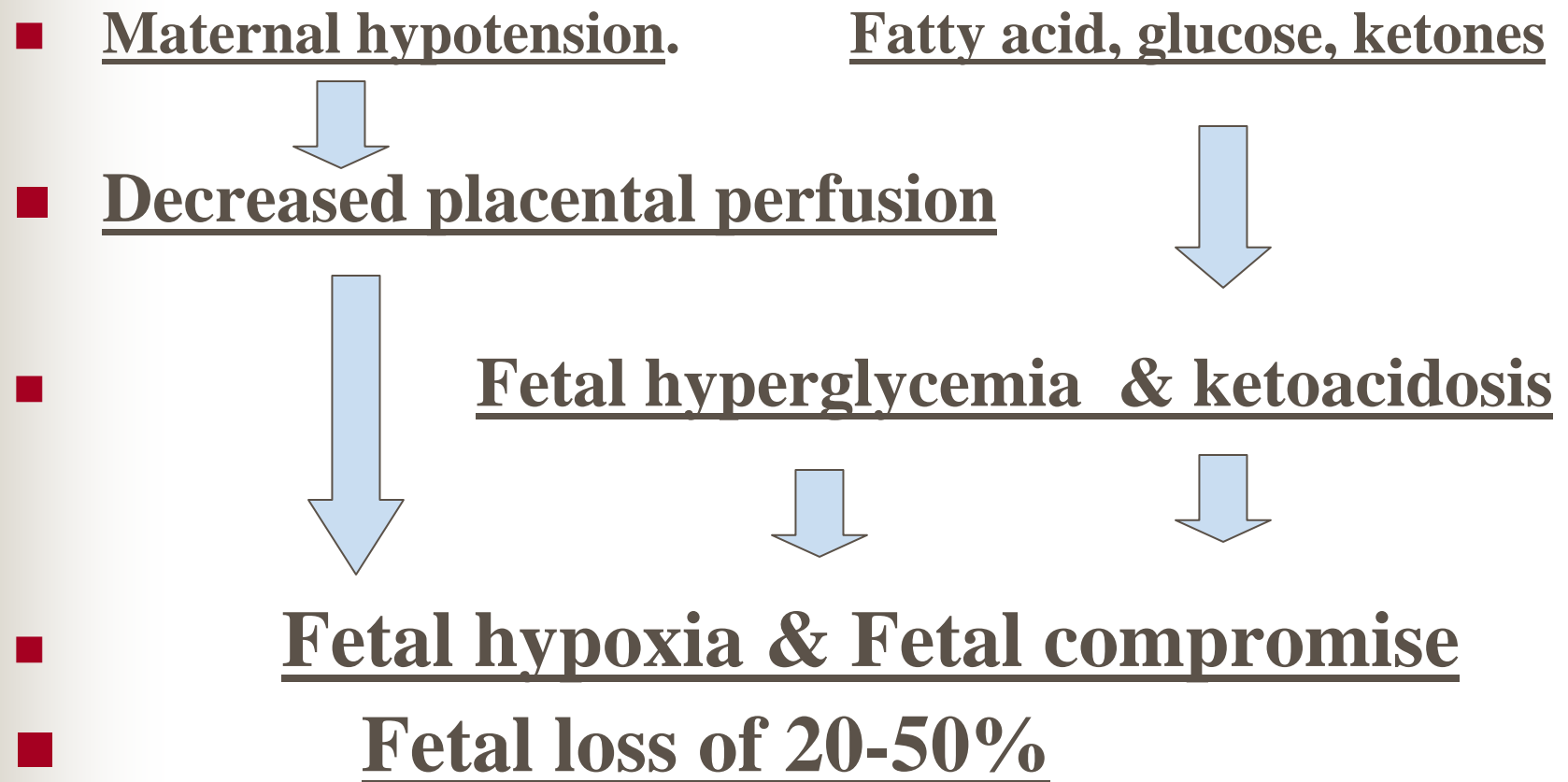
fruity odor



SHOCK & DEATH

Diabetes Ketoacidosis

Fetal Consequence



Diabetic Ketoacidosis

Insulin	<p>10-20 U IV bolus, or 0.1 U/kg IV bolus then 5-10 U/hr</p> <p>Double infusion rate if glucose level not decreased by 25% in 2 hours when glucose \leq 150mg/dl</p> <p>Reduce to 1-2 U/hr Start ADA diet</p> <p>Start SC NPH & regular insulin</p>
Fluid	<p>0.9%NaCl at 1000 ml/hr x 1hr</p> <p>1000 ml over 2 hrs, 250 mL/hr thereafter</p> <p>Change IV to D5NS when glucose < 250 mg/dl</p> <p>Replace H2O loss in 12-24 hr(mean 5-10 L)</p>

Diabetic Ketoacidosis

K⁺	If high, KCl at 20mEq/hr + urine output If low or normal, KCl at 20mEq/hr ASAP Reduce rate by 50% if oliguric Monitor EKG, serum K⁺
HCO₃	If pH <7.0 give to raise pH to 7.0 If pH 7.0-7.2 ± small amount (>88mEq)
General	Naso gastric tube and bladder catheter Electrolytes BUN Creatinine Ketones Glucose CBC ABG urine output q1-4 hr Infection: identify and treat Low dose heparin

ANOMALIES

ANOMALY (5-10%)	RR	% risk
All cardiac defects(38%)	18x	8.5%
All CNS defects(10%)	16x	5.3%
Anencephaly	13x	
Spina bifida	20x	
Genito urinary defects	5x	
absent kidney	4x	
polycystic kidney	4x	
double ureter	23x	
Musculoskeletal(15%)		
(caudal regression)	252x	



Fuel Mediated Teratogenesis

- **HYPERGLYCEMIA**
- **Fasting glucose**
- **Preconceptual care**
- **Arachidonic acid deficiency**
- **Myo-inositol deficiency**
- **Free oxygen radicals**
- **Ketones**



Risk of birth defect based on HbA1C

- | | |
|-------------------|----------|
| ■ HbA1C <7% | low risk |
| ■ HbA1C 7.2-9.1% | 14% risk |
| ■ HbA1C 9.2-11.1% | 23% risk |
| ■ HbA1C >11.2% | 25% risk |



MACROSOMIA

Asymmetrical

- occurs in 20- 50 %
- Pancreatic islet hyperplasia
- Increased adiposity, muscle mass & organomegaly
- Head not affected with disproportionate increase in shoulders and trunk
- Morbidity: Shoulder dystocia, birth trauma, acidosis, hypoglycemia, jaundice, obesity
- Decreased by good glucose control

Shoulder dystocia rates

Birthweight (grams)	Shoulder Dystocia %		P value
	Diabetic	Nondiabetic	
4000-4249	3.1	2.7	NS
4250-4449	7.4	5.2	.03
4500-4749	27.9	8.1	<.01
4750-4999	55.6	14.8	<.01
≥ 5000	62.5	9.8	<.01

Sonographic predictors of macrosomia/shoulder dystocia

Authors	N AGA/LGA	Diagnostic test	sen	spe	ppv	npv
Elliot	70(47/23)	Chest Diameter-BPD ≥1.4cm	87	72	61	92
Bochner	201	AC > 90%(30-33wks)	88	83	56	96
Landon	79(48/31)	AC ≥ 1.2 cm /wk(32-39wk)	84	85	79	89
Mintz	43(20/23)	Shoulder width > 12 mm	83	90		
Cohen	31	AD-BPD ≥ 2.6 cm	100	46	30	100



Route of Delivery

- **Shoulder dystocia & brachial plexus injury increase with birth weight**
- **Cesarean section mainly eliminates risk**
- **Ultrasonic Fetal weight threshold can result decreased injury**
- **Benefits of C/S must be weighed against economic cost and morbidity**
- **Ultrasound EFW is best means of detecting fetal overgrowth(80-90% sensitivity)**

Toronto-tri hospital trial

Group	Macrosomia (>4kg)	C/S rate
Non-diabetic controls n=2940	14%	20%
Treated type 2 DM n=143	10.5%	34%
Untreated GDM n=115	29%	30%



Recommendations

- **US preventive Services Task Force states that there is insufficient evidence to recommend for or against screening for gestational diabetes (2003)**



Reasons to screen

- **50% of GDM develop type 2 DM**
- **Reduces macrosomia & birth trauma**
- **Reduce programming for obesity & diabetes**
- **May improve well-being**

**THANK
YOU**



THE END