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And Here We Go Again… She's Pregnant and Diabetic. Is She Really Different?

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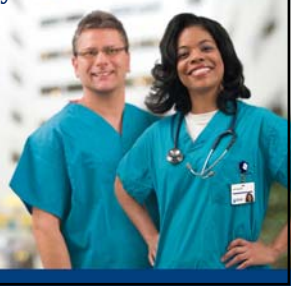

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Objectives

- Identify the prevalence of diabetes and pregnancy
- Discuss the normal physiologic changes of pregnancy that create a diabetogenic state
- Differentiate between gestational and pregestational diabetes
- Verbalize the fetal risk and infant morbidity related to the level of maternal hyperglycemia
- Discuss the implications strict metabolic control on pregnancy outcomes.

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Diabetes: What We Know….

- In the US, 23 million people have diabetes (CDC 2008)
- Prevalence of diabetes increased by 13.5% between 2005 and 2007 (NIDDKD, 2008)
- Almost 6 million people have diabetes that is undiagnosed (CDC, 2008)
- More than 8 million women in US have pregestational diabetes mellitus

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There Go Those OB People Again!

- Pregnancy + Diabetes =
  a. No difference, get over yourself!
  b. No clue…..
  c. Definite differences!

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Diabetes Mellitus: Women and Childbearing

- In the US, women over age 20 account for more than half the individuals with diabetes (CDC, 2008)
  - Only 25% of these women diagnosed (ADA, 2009)
- 6-7% of pregnancies are complicated by DM
  - Pregestational diabetes mellitus affects 1.3% of all pregnancies and increasing due to increase in Type 2 diabetes (Bell 2008; Lawrence 2008).
  - 90% of cases of diabetes in pregnancy are gestational
    - ½ of these women will develop diabetes later in life

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Diabetes On The Rise

- Aging population
- Urbanization
- *Obesity epidemic*
- Minority women
  - 50% non-Hispanic black women classified as obese (Hunt & Schuller, 2007)
- *Access to medical care*
- *Exposure of the fetus to hyperglycemia in utero*
- *Initiatives post delivery: skin to skin and promotion of exclusive breastfeeding*

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Pregnancy: A Diabetogenic State… What is it?

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Diabetogenic State: Carbohydrate, Protein, Fat Metabolism Changes in Pregnancy

- Goal: Create metabolic changes that will sustain the mother and allow continuous nutrients to the baby.
- Instigating factors: fetus and placental hormones
- **1st trimester changes(anabolic phase):**
  - Drop in fasting blood sugar
    - Insulin production and sensitivity slightly increases
    - Increased tissue response to insulin→ ↑glycogen and fat storage in liver and tissues
    - End of 1st trimester: insulin sensitivity decreases, with a responding ↑ in insulin production

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Diabetogenic State: Carbohydrate, Protein, Fat Metabolism Changes in Pregnancy

- **2nd to 3rd trimester changes (catabolic phase):**
  - Protein and fat breakdown with increased insulin resistance (50 – 75% 3rd trimester!)
    - Placental hormones (prolactin, HCS, cortisol, growth hormones): act as insulin antagonists
    - Maternal: maternal lipolysis → maternal fuel source
    - Maternal glucose sparing becomes fetal fuel by readily crossing placenta

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Blood Glucose Values in Pregnancy

	*Ideal	Goal
Fasting blood glucose	60-89 mg/dl	<90 mg/dl
1 hour postprandial	100-129 mg/dl	<140 mg/dl
Mean blood glucose	87 mg/dl	<100 mg/dl
Hemaglobin A_{1c}	2% - 5%	<7%

*demonstrated in women with neither diabetes nor carbohydrate intolerance during pregancy
Metzer et al, 2008

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Classification of Diabetes During Pregnancy

- Most common medical complication of pregnancy
- Pregestational: Overt, known diabetic prior to pregnancy
  - Type I: Autoimmune process that destroys the pancreatic B cells
  - Type II: Disease of insulin resistance and relative insulin deficiency
- Gestational: Diabetes diagnosed during pregnancy
  - Carbohydrate intolerance that begins or is first recognized during pregnancy

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White's Classification

- White's Classification
  - First developed in 1978
  - Emphasized end-organ derangement (eyes, kidneys, heart) and effect on pregnancy outcome
  - 2005: American College of Obstetricians and Gynecologists: no longer actively uses terminology

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Modified White's classification of diabetes in pregnancy

Class	Description
A	Abnormal GTT at any age or of any duration treated only by diet therapy
B	Onset at age 20 years or older and duration of less than 10 years
C	Onset at age 10-19 years or duration of 10-19 years
D	Onset before 10 years of age, duration over 20 years, benign retinopathy, or hypertension (not preeclampsia)
D1	Onset before age 10 years
D2	Duration over 20 years
D3	Calcification of vessels of the leg (macrovascular disease), formerly called Class E
D4	Benign retinopathy (microvascular disease)
D5	Hypertension (not preeclampsia)
R	Proliferative retinopathy or vitreous hemorrhage
F	Nephropathy with over 500 mg/day proteinuria
RF	Criteria for both classes R and F
G	Many pregnancy failures
H	Evidence of arteriosclerotic heart disease
T	Prior renal transplantation
Gestational diabetes	
A1	Diet-controlled gestational diabetes
A2	Insulin-treated gestational diabetes

Classes B through T require insulin treatment.
GTT: glucose tolerance test.
Adapted from: Hare, JW, White, JR. Diabetes Care 1980; 3:394.

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Screening During Pregnancy

Routine Screening for Gestational Diabetes
- All patients are screened for gestational diabetes between 24-28 weeks gestation
- Patients at-risk screened earlier and with follow-up at 24-28 weeks gestation

Criteria for Early Screening for GDM
- Previous baby with macrosomia (>4 Kg.)
- First degree relative with diabetes
- Baby with anomaly or unexplained stillbirth
- Woman with PCO
- Obesity (>150% ideal)
- Previous glucose intolerance
- Diabetes symptoms
- Corticosteroid

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Routine Screening for Gestational Diabetes 1-Hour GTT

First step in screening
- 50 grams one hour glucose load in a non-fasting state
- Positive result is defined as 130,135 or 140 mg/dl
- Lower threshold – higher yield.
- Threshold of 130 mg/dl yields 90% but subjects more patients to 3-hour GTT

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Screening for Gestational Diabetes 3-Hour GTT

National Diabetes Data Group

- Fasting -105 mg/dl
- 1-hour - 190mg/dl
- 2-hour - 165 mg/dl
- 3-hour – 140 mg/dl

Carpenter – Coustan Criteria

- Fasting -95 mg/dl
- 1-hour - 180mg/dl
- 2-hour - 155 mg/dl
- 3-hour – 140 mg/dl

Adapted from Expert Committee for the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2000;23

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One Step Method for Gestation Diabetes Screening

- 75-g, 2-hour glucose tolerance test: 1 value ≥
  - FBS: 126 mg/dl
  - 1 hour plasma glucose 200 mg/dl
- Currently not endorsed by ACOG

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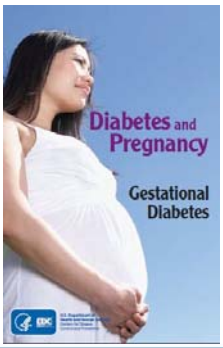

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Gestational Diabetes: Maternal and Fetal Effects

- Increased stillbirth rates
  - FBS>105 mg/dl associated with increased risk of stillbirth during the last 4 to 8 weeks of gestation (ADA, 1999)
- Macrosomic infants (>4500 g, ACOG 2000)
- Higher cesarean section rates

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Management of Gestational Diabetes

Pregnancy care
- Diet
  - 30kcal/kg/day
  - BMI>30: 30% calorie reduction
- Exercise
  - Physical activity reduced GM (Dempsey et al, 2004)
  - Resistance exercise ↓the need for insulin therapy in women overweight women with gestational diabetes (Brankston et al., 2004)

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Management of Gestational Diabetes

- Medications – only when glycemic control is a problem
  - Glyburide
  - Metformin
  - Insulin
- Glucose monitoring: ***postprandial monitoring***
  - DeVeciana et al, 1995: A_2 DM on insulin

	preprandial	1 hr pp
Neonatal Hypoglycemia	21%	3%
Macrosomia	42%	12%
CS Deliveries r/t Dystocia	39%	24%

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Management of Gestational Diabetes

- *Antepartum testing
- *Delivery/Intrapartum management
  - Elective induction?
  - Elective c-section?
- Postpartum care
  - Post delivery
  - 6 weeks – 12 weeks

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Pregestational Diabetes

- Overt diabetes significantly affects pregnancy outcomes
- Complications to embryo, fetus and mother are directly associated with diabetes
- Successful outcome is related to glycemic control and degree of underlying cardiovascular and renal disease

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Management of Pregestational Diabetes

Prepregnancy Counseling
- Assessment of medical status
- Optimal Glycemic control
- Folic acid supplements

Prenatal Care
- Diet
- Exercise
- Glucose monitoring
- Oral hypoglycemic agents
- Insulin
- Antepartum Testing
- Delivery

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Management of Pregestational Diabetes

Preconception Counseling:
- Normalization of Hemoglobin A1C – at least within 1% of normal
- Evaluation of vascular disease
  - Retinal evaluation
  - Nephrology evaluation
- Nutrition
  - 30-35 kcal/kg./day
  - Folic acid replacement
- Institute glucose testing – fasting and 2-hour PP
- Exercise
- Start or refine insulin regiment

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Frequency of testing during pregnancy in women with pregestatonal diabetes

Test	Frequency
Hemoglobin A1C	Every 4 to 6 weeks
Blood glucose	Home measurements 4 to 8 times daily
Urine ketones	During period of illness; when any blood glucose value is >200 mg/dL (11.1 mmol/L)
Urine protein	Diptstick at office visits, quantitate 24 hour excretion each trimester in women with nephropathy
Serum creatinine	Each trimester in women with nephropathy
Thyroid function tests	Baseline measurements of serum free T4 and TSH
Eye examination	Baseline and then as necessary per retinal specialist

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Management of Pregestational Diabetes

Target Glucose Levels

- Fasting - 60-90 mg/dl
- Before lunch, dinner and bedtime snack - 60-100 mg/dl
- 1-hour postprandial - ≤ 140 mg/dl*
- 2-hour postprandial - < 120 mg/dl
- 3 am – 60-90 mg/dl

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Management of Pregestational Diabetes

Oral Anti-diabetic Agents:

- Women on these agents prior to pregnancy are advised to change to insulin prior to pregnancy
  - Better glucose control
  - Insulin does not cross placenta
  - Little is known about the effects of these agents on the early gestation
- Greater acceptability and compliance and less education than with insulin - need further studies for usage for Type 2 DM and GDM

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Management of Pregestational Diabetes

Oral Anti-diabetic Agents**:**

- Metformin (Beguanides)
  - Reduce peripheral insulin resistance
  - Inhibit gluconeogenesis
  - Reduce triglyceride concentrations
  - Does cross placenta
  - Study (Rowen 2008) – randomized controlled trial for the treatment of GDM – comparing insulin and Metformin - no increase in perinatal complications with a tendency to less severe neonatal hypoglycemia and maternal weight gain

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Management of Pregestational Diabetes

Oral Anti-diabetic Agents:

- Glyburide (2nd generation Sulfonylureas):
  - Enhances insulin secretion and peripheral sensitivity to insulin
  - Decreases hepatic clearance of insulin
  - Main side effect – hypoglycemia
  - Does not cross placenta – no evidence of fetal hyperinsulinemia
  - Randomized controlled study (Langer 2008) – treatment for GDM – found no difference in macrosomia or LGA infants

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Management of Pregestational Diabetes

- Glycosylated Hgb (HgbA1c)
  - Provides assessment of prior diabetic control
  - HgbA1c values:
    - Normal adults 2.2 – 4.4%
    - Good diabetic control 2.5 – 6%
    - Fair control 6.1 – 8%
    - Poor control >8%
  - Studies indicate an increased risk of congenital anomalies associated with elevated HbgA1c
    - < 6.9% - 0%
    - 7-8.5% - 5%
    - 10% - 25%

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Management of Pregestational Diabetes

Antenatal Care:

- Insulin requirement:
  - 1st trimester - 0.7- 0.8 units/kg/daym
  - 2nd trimester - 0.8 - 1.0 units/kg/day
  - 3rd trimester – 1.0 – 2.0 units/kg/day
- Insulin dosing:
  - Divided 2/3 in a.m. and 1/3 in p.m.
  - a.m. dose - 2/3 long-acting, 1/3 short-acting
  - p.m. dose – ½ long-acting, ½ short-acting

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Management of Pregestational Diabetes

Antepartum Fetal Surveillance
- Viability/dating scan
- Maternal alpha-fetoprotein screening at 16-20 weeks
- Detailed anatomy scan at 18-20 weeks
- Echocardiogram @ 20-22 weeks
- Serial U/S for growth in 2nd and 3rd trimester
- Antenatal assessments with NST/BPP weekly from 32-36 weeks, then twice weekly

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Management of Pregestational Diabetes

Intrapartum Management
- Elective delivery @ 39 weeks or with amniocentesis-documented pulmonary maturity
- IV insulin – mixed in saline solution – 1:1 concentration and t titrate to maintain blood glucose - 70-120 mg/dl
- IV dextrose – BS < 70 mg/dl or with ketonuria

Scheduled Cesarean Section
- Administer long-acting insulin but hold short-acting insulin
- Hourly glucose monitoring

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Intrapartum Insulin Management

STANDARD INSULIN PROTOCOL

For blood glucose (mg/dL):	Insulin GTT (units)	IVF (at 125 cc/hour)
<100	0	D5 NS
100-110	1	D5 NS
111-130	2	D5 NS
131-150	3	NS
151-170	4	NS
171-190	5	NS
191-210	6	NS
211-230	7	NS
231-250	8	NS

TJUH MFM proposed protocol, 2012

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Postpartum Management

- Insulin requirement – decreases
  - Reduce antepartum insulin dosing by ½
  - Restart oral agents if effective
- Breastfeeding
  - Supplement with 500 extra kcal compared to non-pregnant

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COMPLICATIONS: SO, WHAT DOES THIS MEAN TO MOM AND BABY???

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Maternal Complications of Diabetes

- Hypoglycemia
  - Increased with pregnancy/concern about patient recognition of glucose < 60mg/dl
- Cardiovascular Complication
  - Worsening of DM associated vasculapathies
  - Hypertension
  - Preeclampsia
  - Placental insufficiency
- Preterm Labor

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Maternal Complications of Diabetes

Diabetic Ketoacidosis

- Life threatening emergency – 5-10% of all pregnancies complicated by PGDM
- Most common in Type I diabetes
- Acute decompensation with cardinal features of dehydration and alteration in sensorium
- Characterized by hyperglycemia, ketonemia and acidosis
- Absolute or relative lack of insulin

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DKA and Pregnancy: What is Different

- DKA at lower glycemic levels
  - Check for ketones when blood glucose >200mg/dl
- To delivery or not to delivery…..

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Case Study: DKA

- 29 year old G3 P0020 at 30 weeks gestation presents to triage with complaints of flu symptoms, nausea, and fatigue. Has not felt fetal activity since the previous day. C/O contractions q 2-5 minutes. Initial baseline FHR 180's and flat
- History of Type II DM on insulin pump

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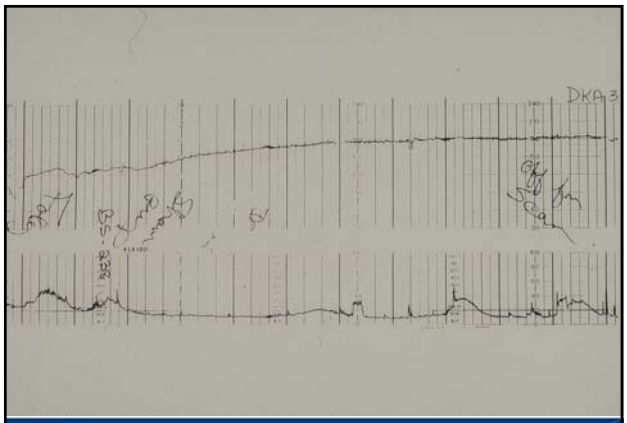

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Management Plan

- Deliver????
- Stabilize and deliver?

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Admission: Delivery Room

- Contracting q 2-5 minutes: administered terbutaline 0.25 mg SQ as tocolytic
- IV hydration
- Initial Labs
  - ABG: pH - 7.26; PCO2 -19; PO2 - 111; HCO3 - 8; BD - 16
  - CBC: WBC - 11.6; Hgb - 16.9; Hct - 48.1; plt - 231
  - Chemistry: Na - 121; K - 6.1; CL - 84: Bun - 27; Glucose - 600; creatinine 1.6; anion gap 27;
  - BOHB: 77.3 mg/dl
  - LFT's WNL

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Arterial Blood Gas Values

	Non-Pregnant	Pregnant	Patient	Fetus
pH	7.35-7.45	7.40-7.45	7.26	7.25-7.35
pO2 (mm Hg)	85-100	101-108	111	20-30
pCO2 (mm Hg)	36-44	27-32	19	40-50
Bicarb (mEq/L)	24-30	18-21	16	<10

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DKA Case Presentation

- Management
  - IV hydration - initially 2 liters/hr ; then 250/hr.
  - Continuous cardiac monitoring/ VS q 30 minutes
  - IV insulin - 20 units regular insulin /hour
  - O2 via face mask after SATs decreased to 94%
  - Glucose monitoring
    - 12:45 pm - 620 gm/dl
    - 15:30pm - 300 gm/dl
  - IV insulin up to 25/hr
  - Vaginal exam - 2cm/1/2cm long/ floating
  - Toco monitoring – contractions - every 2 minutes

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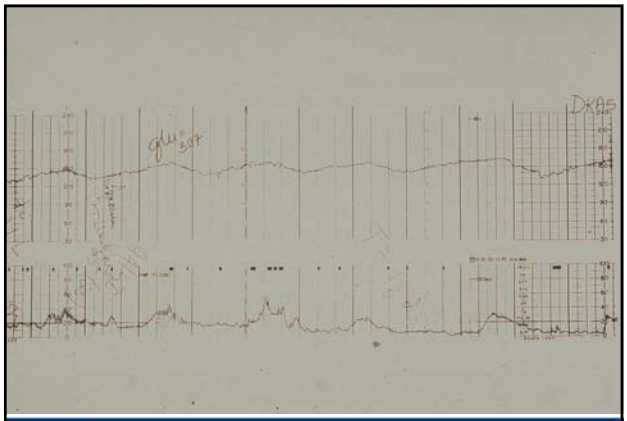

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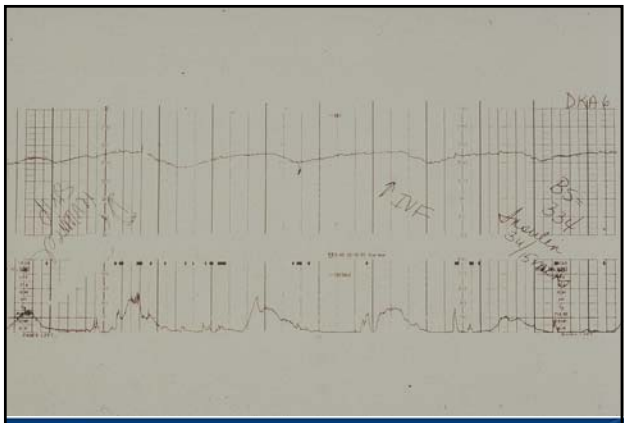

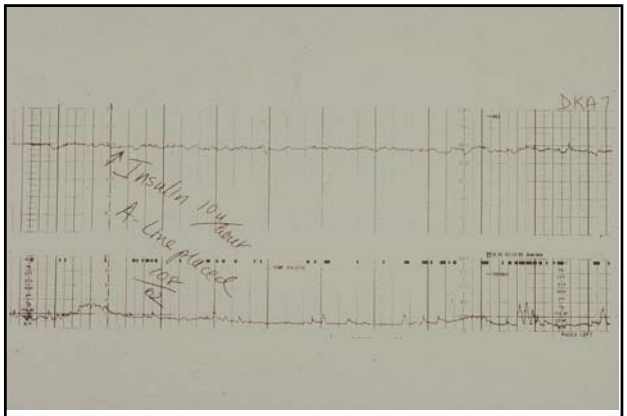

Post Intervention Gas Results:

- pH: 7.42
- pCO2: 26
- pO2:114
- BD: 6.0
- O2Sat: 98%

Outcome: DKA

- Delivered by elective cesarean section at 38 weeks gestation
- Apgars: 8/9
- Weight: 9 lbs 4 oz

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Management of DKA

- Goals:
  - Find and correct cause
  - Lower serum glucose and restore fluid volume
  - Correct acidosis and correct electrolyte balance
  - Assure fetal well-being

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DKA - Case Presentation #2

29 year-old G2 P1001 at 28 weeks (confirmed by 9-week U/S) presented to L&D

- Consistent prenatal care - 28 week labs not done
- Past medical history - negative; Past Ob history - term SVD with no complications
- Presented with history of increased thirst, urinary frequency and N/V for 2 weeks
- Today - worsening S/S; decreased fetal movement since a.m. and contractions every 2 minutes, no bleeding or LOF

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DKA Case Presentation

Initial Evaluation
- Vital signs:
  - T-99.2; P – 126 bpm; RR – 32 bpm; BP - 107/62 mmHg.
- Fingerstick glucose- 476 gm/dl
- Pulse oximetry - 99%
- Urine dip:
  - +3 ketones; +4 glucose; SG - 1.015

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DKA Case Presentation

- Initial Labs
  - ABG: pH - 7.26; PCO2 -18; PO2 – 106; BD - 19
  - CBC: WBC - 11.6; Hgb - 16.9; Hct - 48.1; plt - 231
  - Chemistry: Na - 121; K - 6.1; CL - 84: Bun - 27; Glucose - 1121; creatinine 1.6; anion gap 27;
  - BOHB: 77.3 mg/dl
  - LFT's WNL

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Arterial Blood Gas Values

	Non-Pregnant	Pregnant	Patient	Fetus
pH	7.35-7.45	7.40-7.45	7.26	7.25-7.35
pO2 (mm Hg)	85-100	101-108	106	20-30
pCO2 (mm Hg)	36-44	27-32	18	40-50
Bicarb (mEq/L)	24-30	18-21	8	<10

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Fetal Status with Maternal DKA

- Viable fetus - continuous electronic fetal monitoring
- Lateral position
- Oxygen
- Hydration
- Correct maternal acidosis/hypovolemia

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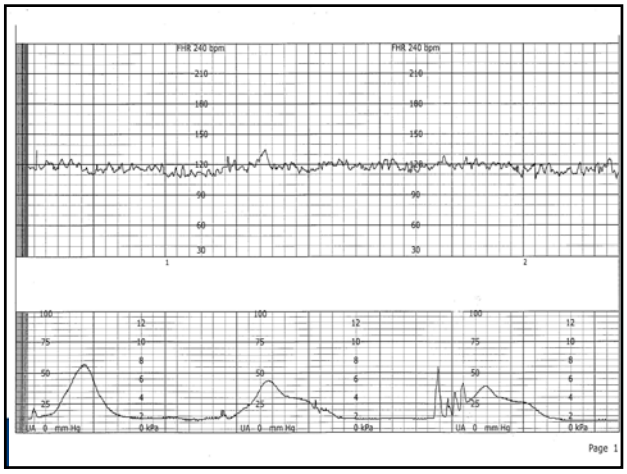

Management of DKA

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  - Find and correct cause
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DKA Case Presentation

- Management
  - IV hydration - initially 2 liters/hr ; then 250/hr.
  - Continuous cardiac monitoring/ VS q 30 minutes
  - IV insulin - 20 units regular insulin /hour
  - O2 via face mask after SATs decreased to 94%
  - Glucose
    - 12:45 pm - 818 gm/dl
    - 13:45pm - 575 gm/dl
  - IV insulin up to 25/hr
  - Vaginal exam - 2cm/1/2cm long/ floating
  - Toco monitoring – contractions - every 2 minutes

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DKA Case Presentation

- Intrapartum Care
  - Arterial line inserted – labs and BP monitoring
  - ABG's - 7.21/24/360/9/16.7
  - Chemistry - 138/3.8/110/527/24/1.4
  - K - rider 20 meq over 2 hours
  - BHOB – 55mg/dl;
  - Coagulation studies - WNL
  - V.E. - 7cm/100%/floating (14:45)
  - Ineligible for regional anesthesia
  - Morphine IVP for pain management
  - I&O/ 2500 cc/1850cc (IV fluids increased to 500cc/hour)

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DKA Case Presentation

- Delivery
  - Patient 10 cms @ 3:30pm
  - AROM for clear fluid
  - SVD - stillborn female - wt. 1500 gms
- Initial Postpartum laboratory studies
  - ABG's - 7.22/29/106/12/14.4
  - Chemistry - 141/4.0/116/442/21/1.2
  - BOHB - 31.9; phosphate - 1.9

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DKA Case Presentation

- 24- Hour Follow-up
  - I&O - 6315cc's/3005cc's
  - Labs:
    - Chemistry: 143/120/11/4.3/16/0.7/292
    - ABG's: 7.28/33/143/15/10.7
    - BOHB - 10.1mg/dl

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Management of Diabetic Ketoacidosis

- Maternal mortality – rare
  - Profound hypovolemic shock
  - Prolonged uncorrected acidosis
  - Myocardial infarction
  - Cardiac arrhythmias
  - Correction of acidosis, dehydration and lower glucose < 150mg/dl - prognosis for mother and fetus greatly improves

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Management of Diabetic Ketoacidosis

- Fetal Effects
  - Hyperglycemia can lead to excessive fetal diuresis
  - Ketoacids can lead to fetal metabolic acidosis
  - Doppler studies demonstrate abnormal flow in the umbilical and middle cerebral arteries of the fetus
  - Fetal heart rate tracings – minimal or absent variability, lack of accelerations and presence of late decelerations
  - Delivery delayed until mother stabilized and fetal testing remains abnormal
- Fetal mortality
  - Up to 10% even with aggressive management

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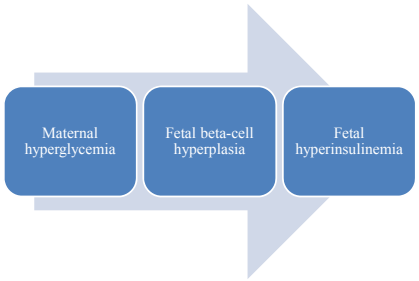

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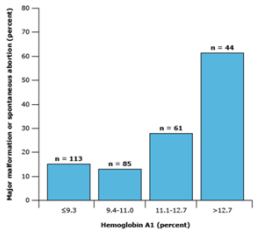
Deleterious effect of poor glycemic control on fetal outcome



Combined incidence of major malformation and spontaneous abortion according to the hemoglobin A1 (HbA1) value during the first trimester of pregnancy in 303 women with type 1 diabetes. The risk rose markedly at HbA1 values above 11 percent (approximately equivalent to a HbA1c value of 8.5 percent). Other studies have found an increase in risk at HbA1c values above 9.5 percent.

Data from: Greene MF, Hare JW, Cloherty JP, et al, Teratology 1989; 39:225.

LightDate

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Fetal &Neonatal Complications of Diabetes

Fetal Complications
- IUFD
- IUGR
- Anomalies
- Macrosomia

Neonatal Complications
- Prematurity
- RDS
- Hypoglycemia
- Birth Injury

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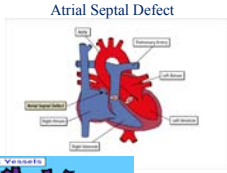
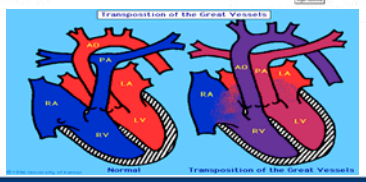
Congenital Cardiac Anomalies Associated with Pregestational Diabetes Mellitus

Ventricular Septal Defect

Atrial Septal Defect





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Central Nervous System and Skeletal System Associated with Pregestational Diabetes Mellitus

Neural Tube Defect

Caudal Regression

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Neonatal Complications Associated with Diabetes Mellitus

Macrosomia

1. ACOG defined as BW> 4500grams
2. Difficult antenatal diagnosis
3. C/S suggested -EFW >4500g
4. Avoid operative delivery EFW> 4000g and prolonged 2nd stage
5. Increased of birth injury

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Fetal/Neonatal Complications Associated with Diabetes Mellitus

- Intrauterine Growth Restriction
  - Placental insufficiency occurs with increase frequency with pregestational diabetes and is usually associated with preeclampsia
  - Preeclampsia is increased with advanced diabetes and vascular complications

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Neonatal Complications Associated with Diabetes Mellitus

- Preterm Delivery
  - Pregestational diabetes –risk factor for preterm delivery – study from NICHD – analyzed 461 pregnancies
    - 9% of PDM compared to 4.5% non-diabetic spontaneously delivered prior to 35 weeks
    - 7% of diabetic compared to 2% non-diabetic underwent indicated PTD

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Diabetes Mellitus in Pregnancy

Future:

- Management continues to improve
  - Preconceptual care
  - Expert care during pregnancy
  - Adherent participants
- Excellent perinatal outcome nearly identical to non-diabetic women

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