Complications of Pregnancy

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Disclosures

• Abbott Point of Care, Inc.
  – Grant/Research Support
Objectives

• Describe the use of hCG in the diagnosis and management of ectopic and molar pregnancies

• Compare and contrast protocols for screening and diagnosing gestational diabetes mellitus

• Discuss the limitations of angiogenic markers as predictors of preeclampsia
Ectopic & Molar Pregnancy
Fertilization & Implantation

http://www.mhhe.com/socscience/sex/common/ibank/ibank/0112.jpg
Chorionic Villus

http://www.nucleusinc.com
hCG & Its Variants

• Dimeric glycoprotein hormone
  – α and β subunits
  – Maintains progesterone production by corpus luteum

• Numerous molecular forms of hCG present in pregnancy serum & urine
  – Dissociated or degraded molecules
  – No biological activity

Adapted from Cole L. Clin Chem 1997;43:2233-2243
hCG Concentrations During Pregnancy

- Detectable ~9-11 days after LH surge

- Serum concentrations increase progressively in early pregnancy
  - Doubling time ~48 hours
  - Peaks at 7-9 weeks of gestation

- Decrease until ~24 weeks then plateau
Ectopic Pregnancy

• Extrauterine implantation of blastocyst
  – ~95% occur in fallopian tube

• Incidence is estimated at 2% of all pregnancies

• Responsible for 5% of maternal deaths

• Classic symptoms
  – Abdominal/pelvic pain (95%)
  – Vaginal bleeding (70%)
  – May be asymptomatic until rupture

"Ectopic pregnancy" by Hic et nunc - Own work. Licensed under CC BY-SA 3.0 via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:Ectopic_pregnancy.svg#/media/File:Ectopic_pregnancy.svg
Diagnosis of Ectopic Pregnancy: Serial hCG

• Doubling time prolonged in ~60% of ectopic pregnancies
  – <53% increase in hCG in 48 h is 79% sensitive/99% specific

• Decreases seen in ~40% of ectopic pregnancies
  – >28% decrease in hCG in 48 h observed in 95% of miscarriages and 8% of ectopics

29% of ectopics have serial hCG results that increase/decrease like non-ectopic pregnancies!

Diagnosis of Ectopic Pregnancy: Transvaginal Ultrasonography

- Yolk sac should be evident at ≥39 days (5.5 weeks from LMP) after conception

- Considered to be definitive diagnosis of intrauterine pregnancy

http://www.obimages.net/other/the-first-trimester-normal-exam/

Barnhart KT. *NEJM* 2009;361:379-387
Diagnosis of Ectopic Pregnancy: hCG Discriminatory Zone

• Surrogate marker for gestational age
  – Concentration above which, if no IUP visualized by TVUS, a healthy singleton gestation is not present
  – 1,500-2,000 IU/L

• Not diagnostic of ectopic pregnancy
  – 11% of intrauterine pregnancies with no visualized sac have hCG >1,500 IU/L

• Discriminatory zone should not be used to determine the management of hemodynamically stable patient with suspected ectopic pregnancy

Barnhart KT. NEJM 2009;361:379-387
Diagnosis of Ectopic Pregnancy: Algorithm
Hydatidiform Moles

• Most common form of gestational trophoblastic disease
  – ~1 per 1,000 pregnancies

• Result from abnormalities in fertilization
  – Excess of paternal chromosomes

• Risk factors
  – Extreme maternal age (≤15 and ≥35 years)
  – Prior molar pregnancy

• Clinical features are non-specific
  – Vaginal bleeding, pelvic pressure/pain, enlarged uterus, hyperemesis gravidarum

• Essentially benign but carry an increased risk of persistent or malignant gestational trophoblastic neoplasia
Complete Hydatidiform Mole

**Feature**

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>46,XX or 46, XY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal/embryonic tissues</td>
<td>Absent</td>
</tr>
<tr>
<td>Trophoblastic proliferation</td>
<td>Diffuse “grape-like”</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Molar gestation</td>
</tr>
<tr>
<td>Postmolar malignant sequelae</td>
<td>15-20%</td>
</tr>
</tbody>
</table>
Partial Hydatidiform Mole

Dispermy

Karyotype:
- 69, XXX
- 69, XXY

Fetal/embryonic tissues: Present

Trophoblastic proliferation: Focal

Clinical presentation: Missed abortion

Postmolar malignant sequelae: 1-5%

http://library.med.utah.edu/WebPath
Diagnosis of Molar Pregnancy

• hCG
  – Usually higher than that observed with intrauterine or ectopic pregnancies of the same gestational age
  – hCG >100,000 IU/L more common in complete moles (45%) vs. partial moles (5%)

• Transvaginal ultrasound to observe characteristic findings

Berkowitz RS, et al. NEJM 2009;360:1639-1645
hCG in Management of Molar Pregnancy

- Successful treatment leads to progressive decline in hCG
- Serial hCG to monitor for postmolar GTN
- ACOG: Weekly hCG until non-detectable for 3 weeks then monthly for 6 months

Case Study

- 25 yo female with positive home pregnancy test and LMP 36 days earlier presents to ED for vaginal bleeding. Serum hCG was 250 IU/L (normal, ≤5). TVUS revealed a 0.58 cm candidate for gestational sac in the uterus. Serial hCG testing performed over the next several days.
## Case Study

<table>
<thead>
<tr>
<th>Time (d)</th>
<th>hCG (IU/L)</th>
<th>hCG change from previous (%)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>250</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>-16</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>232</td>
<td>+10</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>171</td>
<td>-26</td>
<td>Uterine aspiration</td>
</tr>
<tr>
<td>8</td>
<td>120</td>
<td>-30</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>148</td>
<td>+23</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>Not determined</td>
<td>NA</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>13</td>
<td>130</td>
<td>-12</td>
<td>None</td>
</tr>
<tr>
<td>16</td>
<td>130</td>
<td>0</td>
<td>None</td>
</tr>
</tbody>
</table>

- Physician asks about potential interferences.

Case Study

1. Why was serial hCG testing performed on this patient?

2. Why was the physician concerned about possible interferences in the hCG tests?
Case Study Resolution

• Declining hCG over time suggested miscarriage but ectopic pregnancy could not be ruled out

• Interventions did not reduce hCG as quickly as physician anticipated

• Studies done by lab failed to provide any evidence of interferences

• Lab advised continued monitoring of hCG over time

• One week later patient began menses; serum hCG was undetectable

Gestational Diabetes Mellitus
Gestational Diabetes Mellitus (GDM)

• Most frequent metabolic complication of pregnancy

• Any degree of glucose intolerance with onset or first recognition during pregnancy that is not overt diabetes

• Accounts for 90% of diabetes in pregnancy

• Prevalence varies due to population tested, race, ethnicity, age, body composition, and different screening and diagnostic criteria
  – Traditionally stated as ~7% of all pregnancies (range 1-25%)
Pathophysiology of GDM

Mother
- ↓ Insulin availability (resistance)
- ↑ Glucose

Placenta
- Anti-insulin hormones: Human placental lactogen, Estrogens, Progesterone

Fetus
- Pancreas
- ↑ Insulin
- Excess nutrient storage
- Macrosomia
- Hypoglycemia
## Consequences of GDM

<table>
<thead>
<tr>
<th>Maternal Morbidity</th>
<th>Fetal Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypertension</td>
<td>• Macrosomia (excessive birth weight)</td>
</tr>
<tr>
<td>• Preeclampsia</td>
<td>• Neonatal hypoglycemia</td>
</tr>
<tr>
<td>• Increased likelihood of C-section</td>
<td>• Polycytemia</td>
</tr>
<tr>
<td>• Development of diabetes after pregnancy</td>
<td>• Increased perinatal mortality</td>
</tr>
<tr>
<td></td>
<td>• Congenital malformation</td>
</tr>
<tr>
<td></td>
<td>• Hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>• Respiratory distress syndrome</td>
</tr>
<tr>
<td></td>
<td>• Hypocalcemia</td>
</tr>
</tbody>
</table>
Risks of adverse outcomes increase progressively with maternal hyperglycemia

- Fasting glucose
- 1-Hr glucose
- 2-Hr glucose

### A Birth Weight >90th Percentile

**Glucose Category**

- Frequency (%)

### B Primary Cesarean Section

**Glucose Category**

- Frequency (%)

### C Clinical Neonatal Hypoglycemia

**Glucose Category**

- Frequency (%)

### D Cord-Blood Serum C Peptide >90th Percentile

**Glucose Category**

- Frequency (%)

**F: <75 mg/dL**
- 1: <106 mg/dL
- 2: <91 mg/dL

**F: >99 mg/dL**
- 1: >211 mg/dL
- 2: >177 mg/dL

**mg/dL x 0.0555 = mmol/L**
Screening and Diagnostic Testing for GDM

• Performed at 24-28 weeks of gestation because identifying and treating GDM decreases fetal and maternal morbidity
  – Particularly macrosomia, shoulder dystocia, and preeclampsia

• Most commonly done by oral glucose tolerance tests (OGTT)

• One- or two-step approaches
  – Two Step
    • Screening test first (non-fasting; 50 g load; 1 h plasma glucose)
    • Diagnostic test for abnormal screens (fasting; 100 g load; 3 h OGTT)
  – One Step
    • Omit screening test
    • Diagnostic testing (fasting; 75 g load; 2 h OGTT)
# GDM Testing Protocols

<table>
<thead>
<tr>
<th>Approach</th>
<th>Criteria</th>
<th>Screening test cutoff (mg/dL)</th>
<th>Fasting (mg/dL)</th>
<th>1 hour (mg/dL)</th>
<th>2 hour (mg/dL)</th>
<th>3 hour (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Step (100 g load)</td>
<td>Carpenter &amp; Coustan</td>
<td>130, 135, or 140</td>
<td>95</td>
<td>180</td>
<td>155</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>NDDG</td>
<td></td>
<td>105</td>
<td>190</td>
<td>165</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>CDA</td>
<td></td>
<td>95</td>
<td>191</td>
<td>160</td>
<td>NA</td>
</tr>
<tr>
<td>1-Step (75 g load)</td>
<td>WHO</td>
<td>NA</td>
<td>92-125</td>
<td>180</td>
<td>153-199</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>IADPSG</td>
<td>NA</td>
<td>92</td>
<td>180</td>
<td>153</td>
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</tr>
</tbody>
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NDDG: National Diabetes Data Group  
CDA: Canadian Diabetes Association  
WHO: World Health Organization  
IADPSG: International Association of Diabetes and Pregnancy Study Groups

\[ \text{mg/dL} \times 0.0555 = \text{mmol/L} \]
## GDM Testing Protocols

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<th>3 hour (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Step (100 g load)</td>
<td>Any 2 values abnormal</td>
<td>130, 135, or 140</td>
<td>95</td>
<td>180</td>
<td>155</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>Carpenter &amp; Coustan</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>CDA</td>
<td>140</td>
<td>95</td>
<td>191</td>
<td>160</td>
<td>NA</td>
</tr>
<tr>
<td>1-Step (75 g load)</td>
<td>Any 1 value abnormal</td>
<td>NA</td>
<td>92-125</td>
<td>180</td>
<td>153-199</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Endocrine Society &amp; ADA</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
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**ACOG & ADA**

**Endocrine Society & ADA**

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\[ \text{mg/dL} \times 0.0555 = \text{mmol/L} \]
GDM Screening Tests

• Glucose challenge test
  – Non-fasting, 50 g load, 1 h plasma glucose
  – Cutoffs
    • 130 mg/dL: 88-99% sensitive; 66-77% specific
    • 140 mg/dL: 70-88% sensitive; 69-89% specific

• Fasting plasma glucose
  – Performs worse than glucose challenge test at identifying GDM

• HbA$_{1c}$
  – No threshold had good enough sensitivity/specificity for use as screening test


\[ \text{mg/dL} \times 0.0555 = \text{mmol/L} \]
GDM Diagnostic Tests

100 g 3 h OGTT
Established in 1964
Cutoffs not outcome-based
Fasting: ≥95 1 h: ≥180 2 h: ≥155 3 h: ≥140
(2 or more above cutoff)
~4-7% GDM

75 g 2 h OGTT
Established in 2008
Cutoffs outcome-based (HAPO)
Fasting: ≥92 1 h: ≥180 2 h: ≥153
(1 or more above cutoff)
~18% GDM

mg/dL x 0.0555 = mmol/L

Controversies

• ACOG recommends against adoption of the 1-step approach and criteria because it will
  – Increases the incidence of GDM
  – Increase prenatal visits for fetal/maternal surveillance
  – Increase interventions without clear demonstration of improvements in maternal and neonatal outcomes
  – Increase health care costs

Use of 1-step testing improved outcomes and was cost-effective

<table>
<thead>
<tr>
<th></th>
<th>2-step</th>
<th>1-step</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1,750</td>
<td>1,526</td>
</tr>
<tr>
<td>GDM prevalence</td>
<td>10.6%</td>
<td>35.5%</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>6.4%</td>
<td>5.7%</td>
</tr>
<tr>
<td>C-section</td>
<td>25.4%</td>
<td>19.7%</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>4.6%</td>
<td>3.7%</td>
</tr>
<tr>
<td>NICU admission</td>
<td>8.2%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Costs</td>
<td>Higher due to more C-sections and NICU admissions</td>
<td>Higher for provider visits, insulin, and glucose self-monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>€-14,358 per 100 women</td>
</tr>
</tbody>
</table>

All outcomes significantly decreased in 1-step population

Alternatives

• Serial glucose monitoring
  – Periodic random fasting glucose testing for women at high risk for GDM

• Fasting plasma glucose
  – Concentrations <85 mg/dL identify those who do not have GDM (LR- = 0.25) (Donovan L, et al. Ann Intern Med 2013;159:115-122)

• Meal/candy
  – Typically lack sensitivity and are not validated in large studies
  – None endorsed by ADA or ACOG

mg/dL x 0.0555 = mmol/L
Case Study

• A 34 yo Hispanic woman in her 2\textsuperscript{nd} pregnancy is seen for prenatal care at 24 weeks gestation. Past obstetric history relevant for spontaneous vaginal delivery of a 9 lb, 8 oz. male infant at 40 weeks gestation 8 years ago. Family history reveals that her mother has type 2 DM. A urine dipstick test shows 3+ glycosuria and negative ketones.

1. What tests should be done to evaluate the patient's glucose tolerance?

1. How is the diagnosis of GDM established?
Case Study Resolution

• The patient presents with several risk factors for GDM
  – Age, ethnicity, 1st degree relative with DM

• Glycosuria should prompt blood glucose testing before she leaves the clinic
  – 193 mg/dL

• Patient instructed to return the next morning for a fasting plasma glucose
  – 143 mg/dL

• Does she have GDM?
  – Fasting glucose is >126 mg/dL
  – Diagnosis is overt diabetes mellitus

\[
\text{mg/dL} \times 0.0555 = \text{mmol/L}
\]
Preeclampsia
Preeclampsia

• New onset of hypertension and either proteinuria or end-organ dysfunction after 20 weeks of gestation in a previously normotensive woman

• Occurs in 5-8% of pregnancies worldwide
  – 1.5 to 2x higher in first pregnancies

• 90% of cases are late onset (≥34 weeks); 10% are early onset (<34 weeks)

• Delivery of the placenta is the only treatment
Pathophysiology

- Abnormal placentation
- Normal
  - Invasive cytotoxophoblasts replace maternal endothelial cells of spiral arteries
  - Increased capacity and blood flow to placenta

Pathophysiology

• Preeclampsia
  – Incomplete cytotrophoblast invasion
  – Spiral arteries remain intact and capable of vasoconstriction
  – Placental underperfusion, hypoxia, and ischemia

• Placental release of anti-angiogenic factors that cause widespread maternal systemic endothelial dysfunction
  – Clinical manifestations of preeclampsia

Major Risk Factors for Preeclampsia

- Past history of preeclampsia
- Nulliparity
- Pregestational diabetes
- Chronic renal disease
- Chronic hypertension
- Obesity
- Family history of preeclampsia
- Multiple gestation
Clinical Manifestations of Preeclampsia

**Signs & Symptoms**

- Hypertension
- Persistent headache/visual disturbances
- Edema
- Upper abdominal/epigastric pain

**Laboratory abnormalities**

- Microangiopathic hemolytic anemia
- Elevated transaminases
- Thrombocytopenia (<100,000/μL)

**Fetal Consequences**

- Growth restriction
- Oligohydramnios

**HELLP Syndrome**

- Hemolysis
- Elevated Liver enzymes
- Low Platelets
Diagnosis of Preeclampsia

<table>
<thead>
<tr>
<th>Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure</td>
</tr>
<tr>
<td>• Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection)</td>
</tr>
<tr>
<td>• Protein/creatinine ratio greater than or equal to 0.3*</td>
</tr>
<tr>
<td>• Dipstick reading of 1+ (used only if other quantitative methods not available)</td>
</tr>
</tbody>
</table>

Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:

<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Platelet count less than 100,000/microliter</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Impaired liver function</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Elevated blood concentrations of liver transaminases to twice normal concentration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary edema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Cerebral or visual symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Each measured as mg/dL.

ACOG. Obstet Gynecol 2013;122:1122–1131
Diagnosing vs. Predicting Preeclampsia

Not a problem

Problem

Can’t prevent + Can’t cure = Why predict?
Serum Angiogenic Factors

- Alterations in serum concentrations of VEGF, PIGF, sFlt-1, and sEng
  - Precede the onset of clinical preeclampsia by several weeks to months
  - Correlate with disease severity
  - Normalize after delivery

Serum Angiogenic Factors

• The prevalence of preeclampsia in the general obstetrical population is relatively low

• A clinically useful test needs high sensitivity and specificity to confidently predict or exclude development of the disease
Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis

Author’s conclusions PlGF, sFLT1 and sENG showed modest but significantly different concentrations before 30 weeks of gestation in women who developed pre-eclampsia. Test accuracies of all four markers, however, are too poor for accurate prediction of pre-eclampsia in clinical practice.

Sensitivities ranged from 18% to 32% at 95% specificity

Kleinrouweler CE, et al. BJOG 2012;119:778-787
Summary

• hCG is a valuable test in the assessment and management of ectopic and molar pregnancies

• Identifying pregnant women with GDM is needed to decrease fetal and maternal morbidity

• No clinically available tests perform well in distinguishing women who will develop preeclampsia from those who will not