Critical Care in Obstetrics: An Innovative and Integrated Model for Learning the Essentials
Diabetic Ketoacidosis in Pregnancy

Jeffrey C. Faig, M.D., FACOG, FACP

Clinical Professor, Department of Obstetrics & Gynecology
Stanford University

Society for Maternal-Fetal Medicine
I have no conflicts of interest to disclose
Outline

- Learning Objectives
- Background/Pathophysiology
- Pregnancy Risks
- Pregnancy Complications
- Diagnosis
- Treatment
- Summary
- Evidence
Learning Objectives

- Understand the pathophysiology of DKA
- List complications with DKA
- Understand how pregnancy increases the risk of DKA
- Describe complications for the maternal-fetal unit with DKA in pregnancy
- List diagnostic criteria for DKA
- Outline the treatment for DKA
Background

- DKA is one of the most serious medical complications of pregnancy
- Maternal mortality ~ 1%
  - Decreased from 5-15%
- Fetal mortality ~ 9%
  - Decreased from 50-85%
- PTB common, from PTL or medical intervention
Incidence

- Incidence 1-2% diabetic patients/year (decreased from 10-20% in 1970s)
- Perinatal Mortality also decreasing

**Table 1. Incidence of diabetic ketoacidosis in pregnancy**

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Incidence, % (No.)</th>
<th>Perinatal Mortality Rate, % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lufkin et al. (1)</td>
<td>7.9 (18/228)</td>
<td>27.8 (5/18)</td>
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<td>Kilvert et al. (2)</td>
<td>1.7 (11/635)</td>
<td>22</td>
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<tr>
<td>Montoro et al. (3)</td>
<td>3.9 (22/560)</td>
<td>35 (7/20)</td>
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<tr>
<td>Chauhan et al. (4)</td>
<td>22</td>
<td>35</td>
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<td>1986–1991</td>
<td>3</td>
<td>10</td>
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<tr>
<td>Cullen et al. (5)</td>
<td>2 (11/520)</td>
<td>9 (1/11)</td>
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</table>
Risk Factors

- Emesis
  - Hypovolemia, ↓ CHO, ↓ insulin
- \(\beta\)-sympathomimetics
  - Hyperglycemia, FFA, and ketones via gluconeogenesis, glycogenolysis, lipolysis
- Infection
  - reduces glucose utilization by up to 50%
  - Urinary tract, lungs, soft tissue, sinuses, skin, teeth, chorioamnionitis
- Poor Rx compliance
  - ↓ insulin
- Insulin pump failure
- Undiagnosed diabetes
- Glucocorticoids
  - ↑ insulin resistance
- MD management error
Pathophysiology

- Inadequate insulin action
  - DM1 absolute/DM2 relative
- Perceived hypoglycemia at target cells — liver, muscle, adipose
- Exaggerated counter regulatory response:
  - Increased glucagon and catecholamines
  - Hyperglycemia
  - Acidemia
  - Osmotic diuresis
  - Electrolyte depletion
Inadequate insulin action

Perceived hypoglycemia at target cells – liver, muscle, adipose

Ketones & FFA released by liver and fat

Glucouria, Ketonuria → Electrolyte depletion

Hyperglycemia

Osmotic Diuresis

1. Without insulin from the pancreas, glucose from food is unable to be processed by the body.

2. The liver produces more glucose to feed the body, but without insulin, the glucose accumulates in the bloodstream.

3. Without glucose for energy, the body breaks down fat. Ketones (toxic acids) are the by-product of fat metabolism and build up in the bloodstream (ketoacidosis). This can be fatal, causing heart rhythm abnormalities.

4. Ketones and glucose are transferred into the urine.

5. The kidneys utilize water to empty the bloodstream of excess glucose and ketones.

6. Water is lost (voided) along with excess glucose and ketones. The loss of water leads to dehydration, which worsens the ketoacidosis in a vicious cycle and causes low blood pressure and shock.
Pathophysiology

- Inadequate insulin action leads to:
  - ↑ hormone sensitive lipase
    - Lipolysis, release of FFA and ketone bodies
- Tissue level hypoglycemia leads to:
  - Release of glucagon, epinephrine leading to:
    - gluconeogenesis/hyperglycemia
    - glycogenolysis
    - muscle breakdown
    - decreased peripheral uptake of glucose
    - decreased FFA storage
Pathophysiology

- Final common pathway
  - Cardiac dysfunction
  - Decreased tissue perfusion, including placenta
  - Acute renal injury
  - Maternal & Fetal acidemia
  - NRFHT
    - Decreased variability
    - Decelerations
    - Bradycardia
  - Shock, Coma, Death
Pregnancy Risks
Pregnancy increases DKA risk - Diabetogenic state

- Glucose continually absorbed by fetoplacental unit
  - ~ 150 gm/day 3rd trimester
  - Augmented 5x ↑ placental transporter (GLUT-1)
- Increased insulin resistance
  - HPL, cortisol, prolactin, progesterone, placental GH
Pregnancy Risks

- Pregnancy increases DKA risk — Diabetogenic State
  - Decreased GI motility
    - Progesterone — increased CHO absorption
  - Metabolic hallmarks of pregnancy
    - Fasting hypoglycemia
    - Fasting ketonuria
    - Hyperinsulinemia
Pregnancy Pathophysiology

- Pregnancy increases DKA risk – increased alveolar minute ventilation
  - Progesterone-induced respiratory alkalosis
  - Increased NaHCO₃⁻ excretion
  - Decreased renal buffering capacity
- Compensated respiratory alkalosis
  - “Normal” pregnancy pH 7.43
    - pCO₂ 30 mm Hg/HCO₃⁻ 19-20 mEq/l
Pathophysiology of Diabetic Ketoacidosis

Decreased effective circulating insulin
Increased insulin counter-regulatory hormones
- glucagon, catecholamines, cortisol, growth hormone

Insulin sensitive tissue effects

- muscle
  - decreased glucose utilization

- liver
  - increased hepatic glucose production
    - increased gluconeogenesis
    - increased glycogenolysis
  - increased ketogenesis
  - increased lipolysis

- adipose

Hyperglycemia

Glucosuria

Osmotic diuresis

Metabolic acidosis

Vomiting, decreased oral intake

Dehydration
Ketone Body Metabolism

- FFA oxidized & converted to ketoacids in liver
  - $\beta$-hydroxybutyrate and acetoacetate
  - Acetoacetate decarboxylated to acetone: fruity odor of breath

- Glucagon augments production 300%
Ketogenesis

- Fat-derived energy generated in the liver
- Utilized by brain, heart, kidney, skeletal muscles when limited CHO
- Supply 30-40% of needs after 3 day fast
- Production 2-3x baseline during pregnancy –
  - Detectable in ~30% of 1st morning urines
  - Freely cross placenta
Pregnancy Complications
Pregnancy Complications

- Metabolic acidosis
  - Ketone bodies from liver
  - Lactate from peripheral hypoperfusion
- Hyperglycemia
  - Gluconeogenesis/glycogenolysis
  - Glucagon, epinephrine, growth hormone, cortisol
- Osmotic diuresis
  - Worsens hypoperfusion, hyperglycemia, acidemia
- Hyperkalemia
  - Inhibited entry of $K^+$ into cells from ↓ insulin
  - Release of $K^+$ from muscle breakdown
Maternal Implications

- Osmotic diuresis
  - ↓ Utero-placental blood flow
- Acidemia (ketones/lactate)
  - ↓ Cardiac output
- Hyperkalemia
  - Ectopy
Fetal Implications

- Osmotic diuresis
  - Decreased tissue perfusion

- Acidemia
  - Transfer of ketone bodies across placenta
  - Lactate from ↓ tissue perfusion
  - Limited fetal buffering ability

- ↑ O₂ demand
  - Hyperinsulinemia

- ↓ O₂ availability
  - Maternal ↓ PO₄⁻, ↓ 2,3 DPG - ↑ affinity of maternal Hgb for O₂
Fetal Implications

- Nonreassuring FHT
  - Decreased variability
  - Late decelerations
  - Severe bradycardia
- Fetal loss rate ~ 9%
Fetal Implications

- Long term data of adverse effects on survivors lacking
- Possible association between maternal plasma ketone levels and lower IQ scores or decreased mental development scoring during 2\textsuperscript{nd} year of life
- Nevertheless, stabilize mother prior to expedited delivery
Diagnosis
Clinical Presentation

- Hyperventilation
- Altered mental status
- Dehydration
- Weakness
- Vomiting
- Polyuria
- Fruity odor
Workup - Approach

- Careful Hx/PE – *seek out risk factors*

- Laboratory workup
  - Glucose, electrolytes, BUN/creat, LFT’s, amylase
  - $Mg^{++}$, $P04^{=}$
  - CBC with diff
  - UA, culture
  - ABG
  - Serum ketones
  - Blood cultures

- Imaging
  - CXR

- Additional evaluation as indicated
Workup - Labs

- Glucose > 250-300 mg/dl
  - May be lower in pregnancy, even < 200
- ↑ BUN, ↑ creatinine
- ↓ PO$_4^-$ (due to binding to ketoacids)
- ↓ Na$^+$
  - Hyperglycemia dilutes plasma Na$^+$ by 1.6 mEq/l for every 100 mg/dl increase in glucose
- pH < 7.3
- HCO$_3^-$ < 15 mEq/l
  - Increased anion gap/ketonemia
  - Anion Gap = (Na$^+$ - (Cl$^- +$ HC0$_3^-$))
  - Normal 12 mEq/liter ± 2
    - Base deficit > 4 mEq/L
Workup - Ketones

- Serum ketones
  - Quantitative testing for $\beta$-hydroxybutyrate has replaced traditional nitroprusside test
  - More desirable since present in 3-10 x higher concentration than acetoacetate
Diagnostic Pitfalls

- Consider DKA at low or even normal levels of glycemia, especially in setting of:
  - Vomiting
  - ↓ CHO intake
  - Continuous glucose uptake by placenta and fetus
  - ↓ insulin self administration, insulin pump malfunction or prolonged skin site use activation of hormone sensitive lipase: ↓ insulin activity

- FFA and ketone body production occur in pregnancy despite relative normoglycemia
Management
Management - Overall Strategy

Maternal

Causes
- Thorough history and physical
- Rule out infection (UA/Urine Cx, CXRAYS)
- Treat underlying cause

Volume repletion
- Estimate fluid deficit (~100 mL/kg)
- Place Foley catheter
- Monitor Ins/Outs
- Correct 75% total deficit in 1st 24 hours
- Start with isotonic fluid (eg, 0.9% NS)
- Convert to D5 0.45 NS when FSBG <250 mg/dL
- Replete electrolytes
- Stop fluids once estimated deficit corrected

Hypoglycemia
- Begin insulin therapy
- FSBG hourly
- Treat initially with regular insulin via IV (with continuous drip or hourly bolus)
- Continue until AG closed, ketosis cleared
- Start SQ insulin therapy prior to stopping IV insulin

Labs
- BMP, Mag/Phos every 2-4 hours
- Replete K+ once <5 mmol/L (ensure normal renal function)
- ABG every 2 hours
- Serum/Urine ketones every 2 hours (until resolved)

Fetal
- Initiate fetal monitoring
- Left lateral decubitus, oxygen to improve fetal environment
- Stabilize maternal condition PRIOR to considering delivery
Useful Calculations

- **Anion gap**
  - $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$
  - $\text{Nml} \ 12 \pm 2$

- **Serum Osm**
  - $2(\text{Na}^+ + \text{K}^+) + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8}$

- **Corrected Na$^+$(mEq/L)**
  - measured Na$^+ + \left(\frac{\text{plasma glucose (mg/dl)} - 100}{100}\right) \times 1.6$

- **Total body water deficit**
  - $(0.6 \times \text{body weight(kg)} + 1 - (140/\text{serum Na}^+))$
IV hydration

- Increases tissue perfusion
- Reduces acidemia
- Improves cardiac function
- Reduces glucose by hemodilution
- Increases renal loss of glucose
IV hydration

- Use 0.9% NaCl
- Assume fluid deficit of 4-10 liters (100 ml/kg)
  - Goal = correcting 75% of deficit over 24 hrs
    - 1 liter/hr for 2 hrs
    - then 250-500 ml/hr
- Foley catheter/hourly urine output
- NS until glucose < 250 mg/dl, then D$_5$ 1/2 NS
- Check electrolytes, glucose, A/G q 4-6h
**IV Hydration**

- Avoid Lactated Ringers
  - LR is hypotonic – reduces serum osmolality and promotes cerebral edema

<table>
<thead>
<tr>
<th></th>
<th>NA</th>
<th>K</th>
<th>CL</th>
<th>pH</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>142</td>
<td>4</td>
<td>103</td>
<td>7.4</td>
<td>HCO3- 25 mEq/L</td>
</tr>
<tr>
<td>Normal Saline</td>
<td>154</td>
<td>0</td>
<td>154</td>
<td>5.4</td>
<td></td>
</tr>
</tbody>
</table>
| Ringer’s Lactate | 130 | 4  | 109 | 6.5 | Lactate 28 mEq/L  
Ca++ 3 meq/L  |
IV insulin

- Eliminate perceived intracellular hypoglycemia
  - inhibit hormone sensitive lipase, prevent ketogenesis
- Reduce exaggerated counter-regulatory response

- Dosing
  - 0.1 unit/kg bolus (~ 10 units) then 0.1 unit/kg/hr
  - Double rate if glucose does not ↓ by 50-75 mg/dl over first hour
  - Capillary blood glucose (finger stick) q 1h
  - Continue 1-2 units/hr after normoglycemia established
  - Continue until after initial subcut injection
Potassium

- Deficit 5-10 mEq/kg body weight – calculate
  - Insulin shifts $K^+$ into cells
  - Keto-acids bind $K^+$, excrete in urine
- Replace with 20 mEq/l KCl in NS infusion or 10 mEq KCl/100 ml NS infused over 1 hour piggyback
- *Defer replacement until adequate renal function established*
- Keto-acids bind phosphate
- Phosphaturia and total body $\text{PO}_4^{\text{2-}}$ deficit
- Replace with 10-20 mEq $\text{KPO}_4^{\text{2-}}$/liter for each 10-20 mEq $\text{K}^+$
- Defer replacement until adequate renal function established
HCO$_3^-$

- Administered due to concern for adverse effects of severe acidosis
  - Impaired cardiac function, CHF, vascular collapse

- Cautions
  - May cause fluid retention, cerebral edema
  - Rapid and complete normalization of maternal pH and pCO$_2$ may
    - Increase fetal pCO$_2$
    - Impair fetal ability to maintain adequate O$_2$ transfer
Bicarbonate treatment

- Bicarbonate does not appear to favorably influence outcomes if pH > 6.9
- Below 6.9-7.0, consensus to administer even if value unproven

Dosing:

- NaHCO$_3$ 1 ampule (44 mEq) in 1 liter of 0.45% NaCl as needed to raise pH > 7.0
Management Pitfalls

- Volume
  - Avoid cessation of replacement after glucose normalized
    - Acidemia still present, takes much longer to clear than hyperglycemia
    - Correction of volume critical to resolution of acidemia
  - Continue volume replacement until calculated fluid replacement normalized
**Management Pitfalls**

- **Insulin**
  - Beware discontinuation too soon
    - Acidemia still present
    - Follow anion gap, serum ketones
  - Continue at 1-2 units/hr IV after normoglycemia established
  - Maintain D₅ infusion if glucose <250 mg/dl
  - Continue IV until after 1st subcutaneous dose administered
Management Pitfalls

- Preterm Labor
  - Avoid β-sympathomimetics
    - Stimulate gluconeogenesis, glycogenolysis and lipolysis
    - Increase glucose, FFA, ketones
  - Give Betamethasone for usual indications
    - Follow BGs carefully after administration
      - Increased glucose intolerance
      - Increased insulin requirement
Summary
Summary

- DKA has a high risk of fetal & maternal morbidity
- Pregnancy physiology increases the risk of DKA
- Early, aggressive treatment with fluids
  - Use 0.9% NaCl
  - IV insulin until anion gap is closed
  - IV glucose if BG <250
  - Correction of electrolytes
Avoid management pitfalls

Volume
- Continue replacement until after glucose and calculated fluid replacement normalized

Insulin
- Beware premature discontinuation
- Continue IV until after 1st SQ dosing

Avoid β-sympathomimetics
- Stimulate gluconeogenesis, glycogenolysis and lipolysis
- Increase glucose, FFA, ketones
Evidence
Evidence level III

Thank You for Your Attention!

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