Modern Management of Diabetes and Pregnancy

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Prevalence of Diabetes in Pregnancy in the United States of America

6,000,000 Pregnant Women Annually
Greater than 300,000 GDM + 300,000 T2DM + 7,000 T1DM

Evolution of GDM Criteria

<table>
<thead>
<tr>
<th></th>
<th>O'Sullivan</th>
<th>NDDG</th>
<th>Carp/Cous</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>90 mg/dl</td>
<td>105 mg/dl</td>
<td>95 mg/dl</td>
<td>95 mg/dl</td>
</tr>
<tr>
<td>1-hour</td>
<td>165 mg/dl</td>
<td>190 mg/dl</td>
<td>180 mg/dl</td>
<td>180 mg/dl</td>
</tr>
<tr>
<td>2-hour</td>
<td>145 mg/dl</td>
<td>165 mg/dl</td>
<td>155 mg/dl</td>
<td>155 mg/dl</td>
</tr>
<tr>
<td>3-hour</td>
<td>125 mg/dl</td>
<td>145 mg/dl</td>
<td>140 mg/dl</td>
<td>140 mg/dl</td>
</tr>
</tbody>
</table>

1973 - 2000

O'Sullivan. AJOG 1973;116:895
NDDG. Diabetes 1979;26:1039
Carpenter AJOG 1982;144:768
ADA Diab Care 2000;23(Suppl 2):S4
### Definition of Gestational Diabetes

<table>
<thead>
<tr>
<th>Group</th>
<th>Load (gm)</th>
<th>FBS (mg/dl)</th>
<th>1-hr</th>
<th>2-hr</th>
<th>3-hr (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADIPS</td>
<td>75</td>
<td>100</td>
<td></td>
<td></td>
<td>144</td>
</tr>
<tr>
<td>ADA</td>
<td>100</td>
<td>95</td>
<td>180</td>
<td>155</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>95</td>
<td>180</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>CDA</td>
<td>75</td>
<td>95</td>
<td>190</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>EASD</td>
<td>75</td>
<td>108</td>
<td></td>
<td></td>
<td>162</td>
</tr>
<tr>
<td>NDDG</td>
<td>100</td>
<td>105</td>
<td>190</td>
<td>155</td>
<td>145</td>
</tr>
<tr>
<td>WHO</td>
<td>75</td>
<td>126</td>
<td></td>
<td></td>
<td>140</td>
</tr>
</tbody>
</table>
HAPO Study Hypothesis

Hyperglycemia in pregnancy, less severe than overt DM, is independently associated with increased risk of adverse maternal, fetal and neonatal outcomes.

The HAPO Trial Study Design

HAPO was a 7-year prospective observational study following 23,325 pregnant women in 10 countries
75 gram Oral Glucose Tolerance Test
Fasting, One, and Two Hours Time Points

Central Laboratory

Clinical Coordinating Center

Data Coordinating Center

Field Centers

Australia
Barbados
Canada
China
Ireland
Israel
Singapore
Thailand
United Kingdom
United States

~25,000 pregnant women
Proposed Definition of GDM

Any one of the following:

<table>
<thead>
<tr>
<th>Glucose Category</th>
<th>% GDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting 92 mg/dl</td>
<td>alone 8.3%</td>
</tr>
<tr>
<td>1-hour 180 mg/dl</td>
<td>+ 5.7 = 14%</td>
</tr>
<tr>
<td>2-hour 153 mg/dl</td>
<td>+ 2.1 = 16.1%</td>
</tr>
<tr>
<td></td>
<td>+ 1.7 = 17.8%*</td>
</tr>
</tbody>
</table>

*1.7% were unblinded because of FPG ≥105 mg/dl &/or 2h ≥200 mg/dl

IADPSG. 25 March 2009
Definition of Gestational Diabetes Mellitus

- Glucose intolerance of variable degree with onset or first recognition during pregnancy
- Undiagnosed type 2 diabetic women would be classified as gestational diabetic women despite long-standing severe hyperglycemia
Are There Clinical Characteristics Independent of Gestational Week that Identify The Type 2 Diabetic Woman First Diagnosed with Hyperglycemia During Pregnancy?
Acanthosis nigricans is a brown to black, poorly defined, velvety hyperpigmentation of the skin, usually present in the posterior and lateral folds of the neck, the axilla, groin, umbilicus, and other areas.

The most common cause is insulin resistance, usually from type 2 diabetes mellitus.

Other causes are familial, obesity, drug-induced, malignant (gastric cancer), idiopathic, and Polycystic Ovary Syndrome.
Simply Look and Listen
Did your mother complain that your neck was dirty?

Fernando Botero
Acanthosis Nigricans

Relationship between BMI and A1C

\[ y = 2.9125x + 17.74 \]

\[ R^2 = 0.1089 \]

\( P < 0.05 \)
Two distinct groups? A separation of A1C can be seen at 5.3%

Relationship between Systolic Blood Pressure and A1C above and below 5.3%
Time To Turn The Tide
Type 2 Diabetes Diagnosed During Pregnancy

Use Clinical Criteria to Diagnose Type 2 Diabetes During Pregnancy

Proposal 2008
At Time of Diagnosis
Use Clinical Criteria to Diagnose Type 2 Diabetes During Pregnancy

- Elevated Glucose on the Glucose test
- Elevated Blood Pressure (> Two Standard Deviations above the mean (> 105 mmHg)
- Elevated A1C (> 5.3 %) at time of diagnosis
- Elevated BMI (based on pregnancy weight)
- Evidence of Acanthosis nigricans (any degree)
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Modified Pedersen Hypothesis

Fetal Hyperglycemia

Stimulates fetal pancreas

Fetal Hyperinsulinemia

Glucose

? Sulfonylureas
Metformin

Insulin

IgG-antibody-bound Insulin

Placenta

Fetus

Mother
Magnetic Resonance Image of Pregnancy Complicated by Diabetes

Normoglycemia

Hyperglycemia


"Hyperglycemic Peaks" & Risk of Macrosomia

Santa Barbara County Health Care Services  
(4,000 Pregnant Women Per Year)  
Universal Screening Yields 300 - 400 Diabetic Women Per Year  

Make Diagnosis  
Self Blood glucose monitoring  
4 per day (Fasting and 1-hour postprandial)  
Teach carbohydrate restricted diet  
One Week Later  
Begin insulin if Fasting > 90 mg/dl and or 1-hour > 120 mg/dl  

Evidence that Early Treatment Improves Outcome in Pregnancies Complicated By Hyperglycemia  

Evidence Continued!

Macrosomia Rate
Coetzee E et al. 1985-2007
No treatment: 40%
Metformin: 20%
Sulfonylureas: 20%
Insulin: 12%

Langer et al. NEJM 2001
Glyburide: 20%
Insulin: 20%

Coetzee and Jovanovic Debate. Diabetes Care, November 2007

Metformin versus Insulin for the Treatment of Gestational Diabetes

Janet A. Rowan, M.B., Ch.B., William M. Hague, M.D., Wanzhen Gao, Ph.D., Malcolm R. Batin, M.B., Ch.B., M. Peter Moore, M.B., Ch.B., for the MiG Trial Investigators

N Engl J Med
May 8, 2008
Normoglycemia is The Goal for Therapy

Treatment Must Target
The Postprandial Glucose
to Prevent Macrosomia

Insulin Requirements for Pregnant Diabetic Women

Physiological Serum Insulin Secretion Profile

Plasma Insulin (µU/ml)

Breakfast  Lunch  Dinner

Time

Insulin Antibodies Relate to Diabetes Duration and Do Not Impact Glucose Control

Insulin antibody titer IgG (µU/mL)

r=0.73

Years of treatment with conventional insulin

Primary Structure of Human Insulin

A-chain

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

B-chain

NH_{2} 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

Rapid-Acting Insulin Analogue

Commercially Available in 1995

Monomeric Insulin

Regular Human Insulin

Serum Insulin (pmol/L)

Time (h)

0 2 4 6 8 10

0 100 200 300 400 500 600 700 800

0.2 U/kg SQ
### Primary Structure of Lys(B28), Pro(B29)-Insulin (β-Chain; N-terminal)

<table>
<thead>
<tr>
<th></th>
<th>Gly</th>
<th>Glu</th>
<th>Phe</th>
<th>Tyr</th>
<th>Thr</th>
<th>Pro</th>
<th>Lys</th>
<th>Thr</th>
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</thead>
<tbody>
<tr>
<td>Human Insulin</td>
<td>23</td>
<td>24</td>
<td>25</td>
<td>26</td>
<td>27</td>
<td>28</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Lispro</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Maternal Hyperglycemia - 1-Hour Postprandial Glucose Concentration

- **Blood Glucose ≥ 120 mg/dL**
  - **Breakfast**: ±0.40 ± 0.30
  - **Lunch**: ±0.54 ± 0.51
  - **Supper**: ±0.54 ± 0.51
  - **TOTAL**: ±0.47 ± 0.49

*Statistically significant difference*

Jovanovic L et al. Diabetes Care 1999
Insulin Antibody Findings:
Lispro and Aspart Both Not More Immunogenic Than Human Regular

Primary Structure of Asp(B28)-Insulin (β - Chain; N - terminal)
**Postprandial Glycemic Control in GDM**

**Aspart versus Human Regular Insulin**

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>Insulin (µU/mL)</th>
<th>C-peptide (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

**Study Duration**

<table>
<thead>
<tr>
<th>Antibodies (B/T%)</th>
</tr>
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<tbody>
<tr>
<td>BAS</td>
</tr>
<tr>
<td>6 WKS</td>
</tr>
<tr>
<td>TERM</td>
</tr>
<tr>
<td>6 WKS PP</td>
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</tbody>
</table>

**Insulin Treatment and Antibodies**

- MDI with RHI+NPH (n=8)
- MDI with IAsp+NPH (n=8)

**Pettitt DJ, Jovanovic L et al Diabetes Care 26 2003.**
Type 1 Diabetic Women

Safety and Efficacy of Insulin Analogues in the Treatment of Type 1 Diabetic Women During Pregnancy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>n</th>
<th>Congenital Malformations</th>
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<tbody>
<tr>
<td>Diamond and Kormas</td>
<td>1997</td>
<td>3</td>
<td>2</td>
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<td>Rosen et al.</td>
<td>1998</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Calle-Pascual et al.</td>
<td>1999</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Cohen et al.</td>
<td>1999</td>
<td>30</td>
<td>1</td>
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<td>Garg et al.</td>
<td>1999</td>
<td>28</td>
<td>2</td>
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<td>Jovanovic et al.</td>
<td>1999</td>
<td>19</td>
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</tr>
<tr>
<td>Alawi</td>
<td>2001</td>
<td>31</td>
<td>0</td>
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<tr>
<td>Battacharyya et al.</td>
<td>2001</td>
<td>103</td>
<td>1</td>
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<tr>
<td>Idama et al.</td>
<td>2001</td>
<td>7</td>
<td>0</td>
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<td>Patmore et al.</td>
<td>2001</td>
<td>76</td>
<td>4</td>
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<td>Persson et al.</td>
<td>2001</td>
<td>16</td>
<td>0</td>
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<tr>
<td>Scherbaum et al.</td>
<td>2002</td>
<td>33</td>
<td>3</td>
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</table>

Total before 2004: 352, 14
**Diabetes Education Faculty Meeting**

### Neonatal Outcomes & Human Regular Insulin Use During Pregnancy

**Commercially available 1985**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Publication Year</th>
<th>Time Frame</th>
<th>Country</th>
<th>n</th>
<th>Malformations</th>
<th>Malformation rate</th>
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<tbody>
<tr>
<td>Diabetes Control and Complications Trial</td>
<td>1996</td>
<td>1983-93</td>
<td>USA</td>
<td>191</td>
<td>9</td>
<td>4.7%</td>
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<tr>
<td>Casson et al.</td>
<td>1997</td>
<td>1990-94</td>
<td>UK</td>
<td>351</td>
<td>33</td>
<td>9.4%</td>
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<tr>
<td>Schaefer-Graf et al.</td>
<td>2000</td>
<td>1987-95</td>
<td>USA</td>
<td>416</td>
<td>37</td>
<td>8.9%</td>
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<tr>
<td>Suhonen et al.</td>
<td>2000</td>
<td>1988-97</td>
<td>Finland</td>
<td>704</td>
<td>30</td>
<td>4.3%</td>
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<tr>
<td>Gunton et al.</td>
<td>2000</td>
<td>1989-98</td>
<td>Australia</td>
<td>63</td>
<td>7</td>
<td>11.1%</td>
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<tr>
<td>Vaarasmaki et al.</td>
<td>2000</td>
<td>1986-90</td>
<td>Finland</td>
<td>280</td>
<td>16</td>
<td>5.7%</td>
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<tr>
<td>Bhattacharyya et al.</td>
<td>2001</td>
<td>1993-2000</td>
<td>UK</td>
<td>57</td>
<td>4</td>
<td>7.0%</td>
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<tr>
<td>Sheffield et al.</td>
<td>2002</td>
<td>1991-2000</td>
<td>USA</td>
<td>410</td>
<td>25</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

Range: 4.3-11.1%
Mean: 6.1%

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### Proving The Null Hypothesis:

**Insulin Lispro Does Not Cause Malformations**

The Observation of 500 Exposed Pregnancies

- 496 Women
- 533 Pregnancies
- 542 Offspring
- 500 Live births
- 27 Major congenital anomalies
- 2 Minor congenital anomalies
- 31 Spon. Abortions
- 7 Elect. Abortions
- 4 Stillborn

**5.4%**
Malformations Are Related to Glucose Not Type of Insulin


NovoRapid® – Insulin Aspart Study Results 332 Births

- Congenital malformations – Total of 15
  6 in Aspart and 9 in Human Regular
- Spontaneous abortions – Total of 24
  11 in Aspart and 13 in Human Regular
- Mean postprandial glucose concentrations significantly lower in the Aspart group versus HI group after randomization and reminded significantly lower for the duration of the Trial

Hod M et al. AJOG 2007
### Long-Acting Insulin Analogue: Glargine

- **Glargine**: No multi-national trials but
  - 2006: 8 Published Letters to the Editor
    - Total 32 pregnant women with Type 1 Diabetes
  - 2007 EASD: 3 Posters
    - Total 187 pregnant women with Type 1 Diabetes
- **Total**: 219

### Insulin Detemir in Type 1 Diabetes and Pregnancy Trial: Randomized to Receive NPH or Detemir (and Aspart)

- **First patient**: May 2007
- **Completion**: April 2010

**Perinatal Outcome**
1. Composite pregnancy outcome
2. Presence of major malformations
3. Live born infants
4. Insulin antibodies in live born infants
5. Cord blood insulin Detemir
6. Adverse events

**Maternal End Points**
1. A1C and FPG
2. 8-point profiles during pregnancy and hypos
3. Retinopathy and nephropathy
4. Mode of delivery
5. Insulin antibodies
6. Adverse events
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**Insulin Algorithm: NPH Three Times a Day**  
Aspart or Lispro Before Meals and Snacks

- **Breakfast:** Aspart or Lispro
- **Lunch:** Aspart or Lispro
- **Dinner:** Aspart or Lispro

**Variable Basal Rate Continuous Subcutaneous Insulin Infusion Pump**  
Insulin Lispro or Insulin Aspart

- **Breakfast**
- **Lunch**
- **Dinner**

**Basal Infusion**

- **4:00**
- **8:00**
- **12:00**
- **16:00**
- **20:00**
- **24:00**
- **4:00**
- **8:00**

Plasma Insulin
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DIEP Study
Progression of retinopathy

- Pregnancy?
- Tight control?
- Elevated glycohemoglobin?
Progression of Retinopathy

2 step increase
>2 step increase
NPDR to PDR

No Retinopathy
Microaneurysms only
Mild NPDR
Moderate NPDR and worse

2 or more step Progression of Retinopathy

DIEP
DCCT-Intensive
DCCT-Control
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- Experienced observer
- Pupillary dilation
- Darkened room

LASER PHOTOCOAGULATION THERAPY
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MiniMed® Continuous Glucose Monitoring System (CGMS)
Glucose Sensor Profile: Unrecognized “Peaks”

Macrosomia Despite Normoglycemia: Results of Ten “Well-controlled” GDM

<table>
<thead>
<tr>
<th>BG (mg/dL)</th>
<th>BG (mmol/L)</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;120</td>
<td>&gt;6.7</td>
<td>1.8</td>
<td>1.0</td>
<td>2.6</td>
</tr>
<tr>
<td>&gt;130</td>
<td>&gt;7.2</td>
<td>1.5</td>
<td>0.8</td>
<td>2.1</td>
</tr>
<tr>
<td>&gt;140</td>
<td>&gt;7.8</td>
<td>1.3</td>
<td>0.7</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Jovanovic L et al. Diabetes Technology and Therapeutics 2002
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Glucose Sensors

Transdermal Sensor¹,²

Wired and Wireless Continuous Sensors³,⁴

Implantable Sensors⁵

Near Infrared Sensor⁶


Peak postprandial connective fluid glucose is at 72 minutes as measured by CGM whereas peak postprandial capillary finger stick blood glucose is at 60 minutes
Glucocorticoid Treatment in Preparation for Premature Delivery

Use of Continuous Glucose Sensing to Guide Therapy in Twin Gestation
Why Do Some Diabetic Women Have Normal Weight Infants Despite Documentation of Maternal Hyperglycemia?

Factors that Determine Size at Birth

- **Growth Restriction**
  1. Smoking
  2. Multiple gestation
  3. Race
  4. Maternal age
  5. Diabetes mellitus-vasculopathy
  6. Maternal malnutrition
  7. Maternal and paternal physiognomy
  8. Hypertension
  9. Genetic
  10. Altitude

- **Growth Promotion**
  1. Parity
  2. Postdatism
  3. Race
  4. Maternal age
  5. Diabetes mellitus-hyperglycemia
  6. Maternal Obesity
  7. Maternal and paternal physiognomy
  8. Genetic
  9. Male gender
  10. Insulin antibodies
The Villain is Maternal Hyperglycemia

However, the fetus is an “Accomplice” in its destiny

The “Fidgety Fetus Hypothesis” suggests an “energy in, energy out” relationship as a determinant of birth weight

Recent reports have examined the “fidget gene” in lean and obese adults, and suggest that individual differences in activity level are biologically determined.

Studies Designed To Prove The Fidgety Fetus Hypothesis

Fetal Heart Rate Accelerations and Fetal Activity
Corrected birth weight percentile vs. FHR accelerations/20minutes

INACTIVE
ACTIVE
dividing line between an inactive and active fetus
90th Percentile

View and Opinion from Santa Barbara, California
Normoglycemia before, during and after all pregnancies complicated by diabetes results in a normal baby