Insulin therapy in gestational diabetes mellitus

October 15, 2015

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Contents

• Introduction

• Insulin therapy
  – Target
  – Insulins (human insulin and analogs)
  – Real practice

• Summary
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• Introduction

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• Summary
• Gestational diabetes mellitus (GDM)
  
  – associated with adverse outcomes in pregnancy, such as preeclampsia, Cesarean delivery, macrosomia, and birth trauma.

  – increased risk of conversion to type 2 diabetes over time.
Treatment of GDM

- Medical nutrition therapy (MNT)
- Pharmacotherapy (Insulin)
  - preferred over oral anti-diabetic agents due to its better safety and efficacy to achieve good glycemic control
- Treating mild cases of GDM → dilemma
< Treating mild GDM cases >

Analysis 1.11. Comparison 1: Any specific treatment versus routine antenatal care (subgroups by type of specific treatment), Outcome II: **Birthweight > 4000 g.**

Review: Treatments for gestational diabetes

Comparison: Any specific treatment versus routine antenatal care (subgroups by type of specific treatment)

Outcome: Birthweight > 4000 g

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Specific treatment</th>
<th>Routine ANC</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Package of treatment for mild GDM</td>
<td>49/506</td>
<td>110/524</td>
<td>[ ]</td>
<td>100.0 %</td>
<td>0.46 [ 0.34, 0.63 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>506</strong></td>
<td><strong>524</strong></td>
<td>[ ]</td>
<td><strong>100.0 %</strong></td>
<td><strong>0.46 [ 0.34, 0.63 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 49 (Specific treatment), 110 (Routine ANC)

Heterogeneity: not applicable

Test for overall effect: Z = 4.83 (P < 0.00001)

Test for subgroup differences: Not applicable
## Analysis 1.12. Comparison 1 Any specific treatment versus routine antenatal care (subgroups by type of specific treatment), Outcome 12 Birthweight > 90th centile.

### Review:
Treatments for gestational diabetes

### Comparison:
1. Any specific treatment versus routine antenatal care (subgroups by type of specific treatment)

### Outcome:
12 Birthweight > 90th centile

### Study or subgroup | Specific treatment | Routine ANC | Risk Ratio | Weight | Risk Ratio |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>1 Specific dietary advice</td>
<td>8/32</td>
<td>7/36</td>
<td>-</td>
<td>25.3%</td>
<td>1.29 [0.53, 3.15]</td>
</tr>
<tr>
<td>Bancroft 2000</td>
<td>2/16</td>
<td>4/13</td>
<td>-</td>
<td>17.0%</td>
<td>0.41 [0.09, 1.88]</td>
</tr>
<tr>
<td>Ford 1997</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>48</td>
<td>49</td>
<td>-</td>
<td><strong>42.3%</strong></td>
<td><strong>0.93 [0.44, 1.97]</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Diet plus insulin for mixed severity</td>
<td>4/63</td>
<td>15/63</td>
<td>-</td>
<td>57.7%</td>
<td>0.27 [0.09, 0.76]</td>
</tr>
<tr>
<td>Langer 1989</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>63</td>
<td>63</td>
<td>-</td>
<td>57.7%</td>
<td>0.27 [0.09, 0.76]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>111</td>
<td>112</td>
<td>-</td>
<td>100.0%</td>
<td>0.55 [0.30, 0.99]</td>
</tr>
</tbody>
</table>

- Total events: 10 (Specific treatment), 11 (Routine ANC)
- Heterogeneity: $\chi^2 = 1.62$, df = 1 ($P = 0.20$); $I^2 = 38\%$
- Test for overall effect: $Z = 0.18$ ($P = 0.86$)
- 2 Diet plus insulin for mixed severity
- Langer 1989
- Heterogeneity: not applicable
- Test for overall effect: $Z = 2.48$ ($P = 0.012$)

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Alwan N et al. *Cochrane Database Syst Rev* 2009;8:CD003395
< Treating mild GDM cases >

### Analysis 1.17.
Comparison 1: Any specific treatment versus routine antenatal care (subgroups by type of specific treatment), Outcome 17: Composite outcome in infant (death, shoulder dystocia, nerve palsy, bone fracture).

**Review:** Treatments for gestational diabetes

**Comparison:** 1. Any specific treatment versus routine antenatal care (subgroups by type of specific treatment)

**Outcome:** 17. Composite outcome in infant (death, shoulder dystocia, nerve palsy, bone fracture)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Specific treatment</th>
<th>Routine ANC</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Package of treatment for mild GDM</td>
<td>Crowther 2005</td>
<td>7/506</td>
<td>23/524</td>
<td>100.0 %</td>
<td>0.32 [ 0.14, 0.73 ]</td>
</tr>
</tbody>
</table>

**Total (95% CI):**
- Total events: 7 (Specific treatment), 23 (Routine ANC)
- Heterogeneity: not applicable
- Test for overall effect: Z = 2.70 (P = 0.0069)
- Test for subgroup differences: Not applicable

Alwan N et al. *Cochrane Database Syst Rev* 2009;8:CD003395
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# Current glycemic target

<table>
<thead>
<tr>
<th>Targets</th>
<th>Fasting</th>
<th>1 h postmeal</th>
<th>2 h postmeal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 95 mg/dl</td>
<td>&lt; 140 mg/dl</td>
<td>&lt; 120 mg/dl</td>
</tr>
<tr>
<td></td>
<td>(&lt;5.3 mmol/l)</td>
<td>(&lt; 7.8 mmol/l)</td>
<td>(&lt; 6.7 mmol/l)</td>
</tr>
</tbody>
</table>

Metzger BE et al. *Diabetes Care* 2007;30 Suppl 2:S251-60
Patterns of glycemia in normal pregnancy

Hernandez TL et al. Diabetes Care 2011;34:1660-8
Mean pattern of glycemia

Suggested Postprandial Targets based on +1SD from weighted means:
1-hour: <122 mg/dL
2-hour: <110 mg/dL

FBG 71±8 mg/dL
2-hour PP 99±10 mg/dL
1-hour PP 109±13 mg/dL
24-hour Mean BG 88±10 mg/dL
Table 1—Probability of antenatal insulin treatment as generated by risk model compared with actual insulin use

<table>
<thead>
<tr>
<th>Probability (%) of insulin treatment predicted by risk model</th>
<th>Low risk</th>
<th>Medium risk</th>
<th>High risk</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>10.1–20</td>
<td>20.1–30</td>
<td>30.1–40</td>
<td>40.1–50</td>
</tr>
<tr>
<td>0.1</td>
<td>1.9</td>
<td>9.7</td>
<td>18.7</td>
<td>22.7</td>
</tr>
<tr>
<td>Percentage of whole cohort with this calculated risk</td>
<td>33.3</td>
<td>20.8</td>
<td>27.6</td>
<td>35.7</td>
</tr>
<tr>
<td>Percentage of patients actually requiring insulin in each risk band</td>
<td>0.1</td>
<td>0.7</td>
<td>5.2</td>
<td>13.0</td>
</tr>
<tr>
<td>Percentage of patients requiring insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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Insulin treatment

• Antenatal insulin treatment
  → designed to mimic the physiologic insulin secretion by pancreas.

• Women with GDM produce insulin endogenously, but cannot support the increased insulin requirement to counter the diabetogenic placental hormones to maintain euglycemia.
Human insulin (1)

• Regular insulin (RI) / neutral protamines Hagedorn (NPH)
  – standard insulins which have been used for treatment of diabetes in pregnancy.

• Subcutaneous injection of RI  self-associates to form hexamers
  → need to disassociate into the monomeric form
  → absorption through the capillary wall

• The time required for disassociation is responsible for delayed absorption leading to a slower onset of action compared to endogenous insulin, resulting in increased risk of post-meal hyperglycemia.
Human insulin (2)

• NPH
  – Duration of action about 16–18 h (unable to provide once-daily basal insulin)
  – Night-time administration
    → results in an unphysiologic rise in insulin concentration in the early-morning hours → risk of hypoglycemia.

• Unfavorable pharmacokinetics of RI and NPH make aggressive glycemic control difficult.

• Insulin analogs: Overcome the PK limitations of RI / NPH
## Pharmacologic characteristics of insulins

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Time of Action</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset, h</td>
<td>Peak, h</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart</td>
<td>&lt;0.25</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>Glulisine</td>
<td>&lt;0.25</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>Lispro</td>
<td>&lt;0.25</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>Regular</td>
<td>0.5–1.0</td>
<td>2–3</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detemir</td>
<td>1–4</td>
<td>—(^a)</td>
</tr>
<tr>
<td>Glargine</td>
<td>1–4</td>
<td>—(^a)</td>
</tr>
<tr>
<td>NPH</td>
<td>1–4</td>
<td>6–10</td>
</tr>
</tbody>
</table>
• Insulin aspart
  – position 28 on the β-chain: proline → aspartic acid

  – fast dissociation of hexamers into monomers in subcutaneous tissue → very rapid onset of action

  – approved for use in pregnancy
## Efficacy and safety of aspart in pregnancy

**Table 3** Efficacy and safety of insulin aspart in pregnancy

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>n</th>
<th>Type of diabetes</th>
<th>Type of insulin</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou and Fan [17]</td>
<td>CT</td>
<td>80</td>
<td>GDM</td>
<td>Aspart versus regular</td>
<td>Comparable efficacy and safety. No significant inter-group difference in outcomes of pregnant women &amp; their babies</td>
</tr>
<tr>
<td>Heller et al. [18]</td>
<td>RCT</td>
<td>99</td>
<td>T1DM</td>
<td>Aspart versus regular</td>
<td>Initiation of insulin aspart preconception rather than during early pregnancy may result in a lower risk of severe hypoglycemia</td>
</tr>
<tr>
<td>Lloyd et al. [19]</td>
<td>RCT</td>
<td>322</td>
<td>T1DM</td>
<td>Aspart versus NPH</td>
<td>More live births at term, without increasing total costs</td>
</tr>
<tr>
<td>Hod et al. [20]</td>
<td>RCT</td>
<td>322</td>
<td>T1DM</td>
<td>Aspart versus regular</td>
<td>Fetal outcome comparable with a tendency toward fewer fetal losses and preterm deliveries</td>
</tr>
<tr>
<td>Mathiesen et al. [16]</td>
<td>RCT</td>
<td>322</td>
<td>T2DM</td>
<td>Aspart versus NPH</td>
<td>Reduced major hypoglycemia and lower postprandial glycemia</td>
</tr>
<tr>
<td>Pettitt et al. [21]</td>
<td>RCT</td>
<td>27</td>
<td>GDM</td>
<td>Aspart versus regular</td>
<td>More effective in decreasing postprandial glucose levels, Overall safety and effectiveness comparable.</td>
</tr>
<tr>
<td>Di Cianni et al. [22]</td>
<td>RCT</td>
<td>96</td>
<td>GDM</td>
<td>Aspart versus lispro  versus regular</td>
<td>Both RAIs associated with better postprandial maternal glucose control and anthropometric measures in newborns</td>
</tr>
<tr>
<td>Pettitt et al. [23]</td>
<td>RCT</td>
<td>15</td>
<td>GDM</td>
<td>Aspart versus regular versus no insulin</td>
<td>Better lowering postprandial excursions in aspart group</td>
</tr>
<tr>
<td>Lindholm et al. [24]</td>
<td>Case–control</td>
<td>886</td>
<td>T1DM and T2DM</td>
<td>Aspart versus regular</td>
<td>Antibodies specific to insulin aspart were rare; their levels remained undetectable in most patients throughout the studies, with mean levels below the upper normal limit</td>
</tr>
</tbody>
</table>

Magon N et al. *J Obestet Gynecol India* 2014;64:82-90
Rapid-acting insulin analogs - aspart

N = 322, T1DM, aspart vs. regular insulin

Aspart is safe and effective as RI in pregnant women (with T1DM)

Mathiesen ER et al. Diabetes Care 2007;30:771-6
Insulin concentrations during 4-h meal tests

Pettitt DJ et al. Diabetes Care 2003;26:183-6
Glucose concentrations during 4-h meal tests

Pettitt DJ et al. Diabetes Care 2003;26:183-6
Rapid-acting insulin analogs - lispro

- Insulin lispro
  - inverting lysine at position 28 ↔ proline at position 29 on the β chain
  - quick dissociation of hexamers into monomers in subcutaneous tissue → has a very rapid action.
  - approved by US FDA for use during pregnancy
### Efficacy and safety of lispro in pregnancy

**Table 4** Efficacy and safety of insulin lispro in pregnancy

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>n</th>
<th>Type of diabetes</th>
<th>Type of insulin</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colatrella et al. [26]</td>
<td>Retrospective</td>
<td>89</td>
<td>T1DM and GDM</td>
<td>Lispro protamine versus NPH</td>
<td>Pregnancy outcome was similar, except for a lower insulin requirement.</td>
</tr>
<tr>
<td>Durnwald et al. [25]</td>
<td>Prospective</td>
<td>107</td>
<td>T1DM and T2DM</td>
<td>Lispro versus regular</td>
<td>Improved glycemic control and lower total insulin requirements. Perinatal outcomes similar between women treated with both types of insulin.</td>
</tr>
<tr>
<td>Cypryk et al. [27]</td>
<td>Retrospective</td>
<td>71</td>
<td>T1DM</td>
<td>Lispro versus regular</td>
<td>Comparable course of pregnancy and the perinatal outcome</td>
</tr>
<tr>
<td>Persson et al. [28]</td>
<td>RCT</td>
<td>33</td>
<td>T1DM</td>
<td>Lispro versus regular</td>
<td>Reduced postprandial glycemia after breakfast and slightly higher rate of hypoglycemia</td>
</tr>
<tr>
<td>Batthacharyya et al. [29]</td>
<td>Retrospective</td>
<td>157</td>
<td>GDM</td>
<td>Lispro versus regular</td>
<td>Significant decrease in HbA1c levels and greater satisfaction</td>
</tr>
<tr>
<td>Jovanovic et al. [30]</td>
<td>RCT</td>
<td>42</td>
<td>GDM</td>
<td>Lispro versus regular</td>
<td>Less hypoglycemic episodes before breakfast; less postprandial hyperglycemia; more reduction in HbA1c levels at the 3rd trimester</td>
</tr>
</tbody>
</table>
Rapid-acting insulin analogs - glulisine

- Insulin glulisine
  - the latest rapid-acting insulin analog
  - Its pharmacologic action profile is similar to both insulin lispro and insulin aspart.
  - but not yet approved for pregnancy usage
Long-acting insulin analogs - detemir

• Insulin detemir
  – a long-acting recombinant human insulin analog
  – has been approved for use in pregnancy (2012)
    (FDA pregnancy category B classification)
  – provides with a long-acting insulin analog option
    in management of pregnancy diabetes
Long-acting insulin analogs - detemir
Compared with neutral protamine lispro, detemir exhibited a flatter PD profile.
Blood glucose values were similar for detemir and netural protamin lispro
## Table 5: Efficacy and safety of insulin detemir in pregnancy

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>n</th>
<th>Type of diabetes</th>
<th>Type of insulin</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Callesen et al. [35]</td>
<td>Retrospective</td>
<td>113</td>
<td>T1DM</td>
<td>Insulin detemir versus glargine</td>
<td>Hemoglobin A1c levels and the incidence of severe hypoglycemia were comparable at 8 weeks. Proportion of pre-eclampsia, preterm delivery, and infants LGA was also comparable in both groups.</td>
</tr>
<tr>
<td>Hod et al. [34]</td>
<td>RCT</td>
<td>274</td>
<td>T1DM</td>
<td>Insulin detemir versus NPH</td>
<td>Well tolerated, comparable perinatal outcomes and no safety issues.</td>
</tr>
<tr>
<td>Lambert and Holt [13]</td>
<td>Case report</td>
<td>1</td>
<td>T1DM</td>
<td>Insulin detemir</td>
<td>Bedtime detemir may indeed favor improved glycemic control during pregnancy, reducing the risk of hypoglycemia.</td>
</tr>
<tr>
<td>Mathiesen et al. [36]</td>
<td>RCT</td>
<td>310</td>
<td>T1DM</td>
<td>Insulin detemir versus NPH insulin</td>
<td>Non-inferior; fasting plasma glucose (FPG) was significantly lower; Major and minor hypoglycemia rates during pregnancy were similar between groups.</td>
</tr>
<tr>
<td>Shenoy et al. [37]</td>
<td>Retrospective</td>
<td>18</td>
<td>T1DM and T2DM</td>
<td>Insulin detemir</td>
<td>Maternal outcomes were satisfactory, with only one woman having severe hypoglycemia, and no progression of retinopathy or nephropathy.</td>
</tr>
<tr>
<td>Lapolla et al. [32]</td>
<td>Retrospective</td>
<td>10</td>
<td>T1DM</td>
<td>Insulin detemir</td>
<td>Glycemic control improved, and HbA1c progressively decreased. None of the women developed or underwent progression of diabetic retinopathy, and none had diabetic nephropathy or neuropathy.</td>
</tr>
</tbody>
</table>
Long-acting insulin analogs - detemir

N = 310, T1DM, detemir vs. NPH

Detemir : solid line
NPH : dotted line

Mathiesen ER et al. *Diabetes Care* 2012;35:2012-7
Long-acting insulin analogs - glargine

• Insulin glargine
  – lasting for about 24 h
  – Currently, the use of insulin glargine in pregnancy is not approved
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Insulin requirements in pregnancy

- Pre-conception: ~ 0.8 units/kg
- First trimester: ~ 0.7 units/kg
- Second trimester: ~ 0.8 units/kg
- Third trimester: 0.9~1.0 units/kg
- Near term: insulin requirements may decrease again
- Morbidly obese woman: 1.5~2.0 units/kg
- Twin pregnancies (in GDM): doubling of insulin requirement
Insulin requirement in pregnant women with T1DM

Garcia-Patterson A et al. Diabetologia 2010;53:446-51
Insulin dosing schedule

A. Insulin analogue* at morning, afternoon, and evening meals, with Long-acting Insulin^ at night.

B. Insulin analogue* at morning and afternoon meals, with NPH at evening and night meals.

C. Bolus Insulin at morning, afternoon, and evening meals, with Basal Infusion at night.
Insulin dosing schedule

• Dosing schedules (for example)
  – morning: 2/3 of the total daily dose (2 NPH : 1 RI)
  – evening: 1/3 of the total daily dose (1 NPH : 1 RI)
  – NPH → protamine lispro or protamine aspart
  – RI → lispro or aspart
Insulin dosing schedule

• Dosing schedules (for example)
  – Detemir + short acting insulins (4 injections/day)
  – bed time as detemir (40–50 % of the total daily insulin requirement)
  – remaining insulin is divided into three doses with each meal.
  – Titration of insulin dose is based upon frequent self-monitoring of blood glucose.
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Summary

- To lower the risk of perinatal complications, treatment of GDM is very important.

- Newer insulins, aspart, lispro and detemir, provide better glycemic control than human insulin.

- When we treat women with GDM, patient centered approach is very important.
Thank you for your attention ~