## RCTs on pregnant DM patients

<table>
<thead>
<tr>
<th>Study name</th>
<th>Setting</th>
<th>Population</th>
<th>Intervention vs. Control</th>
<th>Outcomes</th>
<th>Results</th>
<th>Study name</th>
<th>Design</th>
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<tbody>
<tr>
<td><strong>Embaby</strong> 2016</td>
<td>Egypt, urban</td>
<td>at increased risk for GDM due to obesity (BMI ≥ 30 kg/m²), age &gt; 25 yrs, 20-24th gestational wks, multigravida, physically active with ≥ 1 of the following 3 characteristics: history of macrosomia, abnormal glucose tolerance during previous pregnancy or first grade relative with DM2, no hypertension, GDM, medications that affects insulin secretion, serious pulmonary disease, cardiac, renal impairment and malignancy</td>
<td>n=40 100% female age (yrs): 29.2±3.8 BMI (kg/m²): 28.7±1.3 fasting glucose (mmol/l): 6.5±0.9 fasting insulin (IU/l): 15.78±1.58</td>
<td>IG: aerobic exercise program (walking on treadmill) three times weekly until the end of 37 wks of gestation + diet control. vs. CG: diet control with usual care given by obstetricians and midwives.</td>
<td>Duration: appr. 4 months</td>
<td><strong>El-Shamy</strong> 2018</td>
<td>RCT</td>
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<td>07/2014-02/2015</td>
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<td><strong>Strategies to increase physical activity</strong></td>
<td>Egypt, urban</td>
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<td><strong>El-Shamy</strong> 2018</td>
<td>Egypt, urban</td>
<td>GDM, age: 20-30 yrs, gestational age: 24-26 wks, BMI ≥ 30 kg/m², singleton live fetus, no high-risk pregnancy, bad obstetric situations or diseases, smoking, oral sedatives</td>
<td>n=30 100% female age (yrs): 24.2±2.8 BMI (kg/m²): 27±1.5</td>
<td>IG (n=15): acupressure + standard antenatal care vs. CG (n=15): standard antenatal care only</td>
<td>Duration: 12 weeks</td>
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<td>12/2016-05/2017</td>
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### Other non-pharmacological therapies

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<tr>
<td><strong>El-Shamy</strong> 2018</td>
<td>Egypt, urban</td>
<td>GDM, age: 20-30 yrs, gestational age: 24-26 wks, BMI ≤ 30 kg/m², singleton live fetus</td>
<td>n=30 100% female age (yrs): 24.2±2.8 75 g OGTT (mg/dl): fasting glucose: 129.05±0.6 2h postprandial: 146±1.65 BMi (kg/m²): 27±1.5</td>
<td>IG (n=15): acupressure + standard antenatal care vs. CG (n=15): standard antenatal care only</td>
<td>Duration: 12 weeks</td>
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### Results

- **Embaby 2016**
  - Fasting plasma glucose, Insulin level
  - Change to 37th week of gestation:
    - Fasting plasma glucose: Benefit for IG: 4.26±0.67 vs. 5.07±0.54 (p=0.0001)
    - Fasting insulin: Benefit for IG: 10.59±1.10 vs. 12.43±1.44 (p=0.0001)

- **El-Shamy 2018**
  - Primary: glycemic control, requirement for insulin, insulin resistance
  - Secondary: neonatal outcomes
  - Change over 3 months:
    - 75 g OGTT (mg/dl): Fasting: 116.1±0.1 vs. 118.2 ± 0.7
    - 2h postprandial: 125.3±1.2 vs. 127.3 ± 0.9
  - Complication (%): 5-min Apgar-Score < 7: 6.7 vs. 6.7 %
**Healthcare providers:***

**Utz 2018**  
*Marocco, urban / rural, primary care, 11/2016-02/2018*

Health centres with ≥ 30 monthly antenatal care consultations and all pregnant women with newly diagnosed GDM  
20 clinics were randomized → 10 in each group  
IG (n=120): first screening for GDM → positive tested women received counselling on nutrition and exercise  
vs. CG (n=95): routine practice

**Primary:** birthweight
**Secondary:** maternal weight gain, glucose control, pregnancy complications.

Follow-up visits:
- 7.5±4.9 vs. 3.8±3.3 (p=0.001)
- FBG within the norm: better with IG
- <1/3 of all values: 7.6 vs. 32.6 %
- 1/3-2/3 of all values: 17.8 vs. 32.6 %
- >2/3 of all values: 74.6 vs. 34.8 %

Macrosomia (birthweight>4000 g): 3.5 vs. 18.4 % (p<0.001)

**Pharmacological strategies**

**Ashoush 2016**  
*Egypt, urban, tertiary care, 01/2014-11/2014*

GDM, mothers with 26–32-week GDM (oral 2-h 75 G glucose tolerance test) singleton pregnancies, failure of satisfactory glyemic control despite adequate diet and exercise for ≥ 1 wk

no fetal anomalies on ultrasonography, other pregnancy complications, known intolerance to metformin or risk factors for lactic acidosis

n=95  
100% female age (yrs): 31.8±3  
HbA1c (%): 5.75 ± 0.55  
75g OGTT (mg/dl)
- fasting: 106.05±4.6
- 1h:310.25±11.6
- 2h:176.65±9.4  
BMI (kg/m²): 31.2±1.4

IG (n = 47):
- metformin (initial total dose 1000 mg/d with meals, increase by 500 or 850 mg every 1 or 2 wks toward target or up to a maximum dose of 2500 mg/d until delivery, addition of insulin if needed)

vs. CG (n = 48):
- regular insulin + neutral protamine Hagedorn (3:7) (starting dose 0.7 units/kg*), adjusted to achieve adequate glycemic control at increments of 1 unit/10 mg glucose higher than the desired cut-off, short action insulin whenever needed)  
**Duration:** until delivery

**Primary:** successful maternal glycemic control
**Secondary:** maternal BMI, glycemic control parameters, maternal weight gained during pregnancy, side effects to metformin, mode of delivery, gestational age at delivery, neonatal birthweight, macrosomia, neonatal hypoglycemia, neonatal death, congenital anomalies, admission to neonatal intensive care unit

Until delivery:
- fasting glucose during treatment (mg/dl): better with IG:
  - during the last wk: 78±3.1 vs. 79.9±3.7 (p=0.008)
  - during the last 2 wks: 78.9±3.5 vs. 80.8±4.7 (p=0.029)
- maternal hypoglycaemia (%): no difference: 6.25 vs. 12.5 (p=0.254)
- neonatal hypoglycaemia (%): 12.8 vs. 14.6 (p=0.001)
- Maternal weight gain (Kg): 4.4 ± 0.6 vs. 5.1 ± 0.8 (p=0.001)
- neonatal congenital anomalies (%): 2.1 vs. 2.1 (p=0.747)
- headache (%): 27.3 (metformin+insulin) vs. 5.6 (metformin monotherapy) vs. 0% (insulin monotherapy)
- neonatal ICU admission (%): 8.5 vs. 10.4 (p= 0.514)

Costs (Egyptian pounds): 89.66±0.96 vs. 174.9±11.1 (for monotherapies)
<table>
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<tr>
<th>Study</th>
<th>Country</th>
<th>Region</th>
<th>Time Frame</th>
<th>Eligibility</th>
<th>n</th>
<th>Age (yrs)</th>
<th>BMI (kg/m²)</th>
<th>Gestational Age</th>
<th>GDM Pre-Existing DM</th>
<th>Treatment Details</th>
<th>Primary</th>
<th>Secondary</th>
<th>Change from enrolment to delivery</th>
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<tbody>
<tr>
<td>Beyuo 2015</td>
<td>Ghana, urban</td>
<td>urban</td>
<td>01/2013-12/2013</td>
<td>Pregnant women with DM2 or GDM (plasma glucose ≥7 mmol/l after an overnight fast or plasma glucose concentration ≥11.1 mmol/l 2 hours after a 75 g glucose drink), 20-30 wks gestation, age: 18-45yrs, eligible for insulin therapy. No T1DM, DM2 who have previously failed to achieve glycemic control on metformin monotherapy, allergies to metformin.</td>
<td>104</td>
<td>33.3±4.6</td>
<td>3.1±6.6</td>
<td>28.7±3.7</td>
<td>56.7 % with median duration of 4 (1-15) yrs</td>
<td>IG (n=52): Metformin (starting with 500 mg / d, gradually increase over 2 wks to a maximum dose of 2500 mg/d, insulin was added if necessary) vs. CG (n=52): insulin treatment (daily dose 0.3 IU/kg, titrated to achieve the glycemic targets, if necessary, admission to the ward and therapy with soluble insulin). Duration: until delivery.</td>
<td>Primary: 2-hour post prandial blood glucose (2HPG)</td>
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<td>Secondary: fasting glucose, 1HPG, maternal weight gain, pregnancy outcome and feto-neonatal outcomes.</td>
<td>Change from enrolment to delivery: glycemic control (mmol/l): fasting glucose: no difference: 6.42±0.98 vs. 6.62±1.57 (p=0.928) 1HPG: no difference: 8.95±1.27 vs. 9.62±1.44 (p=0.078) 2HPG: benefit for IG: 7.84±1.43 vs. 9.05±1.89 (p=0.004)</td>
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<td>Ibrahim 2014</td>
<td>Egypt, urban</td>
<td>urban</td>
<td>08/2011-04/2012</td>
<td>GDM or pre-existing DM, gestational age 20-34 wks with insulin resistance. No DM1, secondary diabetes or liver or renal impairment.</td>
<td>90</td>
<td>29.8 ± 5.4</td>
<td>31.83 ± 3.23</td>
<td>28.7±3.7</td>
<td>56.7 % with median duration of 4 (1-15) yrs</td>
<td>IG (n=46): Metformin (1500 mg, raised to 2000 mg) without increasing insulin dose. Patients switched to CG if treatment was not successful to control blood glucose concentrations. CG (n=44): insulin dose was increased according to the standard protocol.</td>
<td>Primary: maternal glycemic control (fasting glucose ≤95 mg/dl and 2-HPG ≤120 mg/dl)</td>
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<td>Secondary: maternal bouts of hypoglycemia, need for another hospital admission for uncontrolled diabetes during pregnancy, gestational age at delivery, mode of delivery, birth weight, birth trauma, congenital anomalies, Apgar score, neonatal hypoglycemia, need for neonatal intensive care unit admission, adverse neonatal outcomes.</td>
<td>Complications:</td>
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<td>23.3 vs. 30.8 % had fetal macrosomia</td>
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<td>1 new-born in each group had congenital malformations</td>
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<td>7 vs. 38.5 % had neonatal hypoglycemia</td>
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<td>18.6 vs. 41 % had NICU admission</td>
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<td>0 vs. 5.1 % had stillbirths</td>
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<td>11.6 vs. 25.6 % with respiratory distress syndrome</td>
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<td><strong>BMI</strong></td>
<td>Body mass index; <strong>CG</strong></td>
<td>Control group; <strong>CI</strong></td>
<td>Confidence interval; <strong>DM</strong></td>
<td>diabetes mellitus; <strong>DM2</strong></td>
<td>type 2 diabetes; <strong>FPG</strong></td>
<td>fasting plasma glucose; <strong>GDM</strong></td>
<td>gestational diabetes; <strong>HbA1c</strong></td>
<td>haemoglobin A1c; <strong>1 / 2HPG</strong></td>
<td>1 / 2-hour post prandial blood glucose; <strong>IG</strong></td>
<td>intervention group; <strong>n</strong></td>
<td>number of participants; <strong>MD</strong></td>
<td>mean difference; <strong>MDa</strong></td>
<td>adjusted mean difference; <strong>OGTT</strong></td>
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**Supplementary Table 4:** Characteristics and results of studies on pregnant women with DM