Problems of Obesity and Early Pregnancy

Prof T C Li
Professor of Reproductive Medicine & Surgery
Sheffield
Obesity and Reproductive Problems

• Infertility
• Miscarriage
• Recurrent Miscarriage
• Ectopic pregnancy
• Late pregnancy complications
Study 1

Meta-analysis

BMI & miscarriage rate
The effect of increased body mass index on the risk of miscarriage: a meta-analysis
Study design

- Meta analysis
- MEDLINE (1964 - 2006)
- All methods of conception
- Patients with a BMI of $\geq 25$ kg/m$^2$ Vs Normal BMI
- 16 studies
## Obesity & Miscarriage

**Study** or sub-category | **High BMI** | **Normal BMI** | **OR (random)** | **Weight** | **OR (random)** | **Quality** | **D - E** | **Variance**
--- | --- | --- | --- | --- | --- | --- | --- | ---
Al-Azemi 2004 | 10/35 | 0/36 | | | | D | 0.00 | 2.14
Bair 2006 | 3/158 | 2/177 | | | | D | 0.00 | 0.85
Belver 2003 | 21/105 | 36/255 | | | | D | 0.00 | 0.09
Belver 2007 | 111/572 | 257/1613 | | | | D | 0.00 | 0.02
Dohrer 2006 | 40/295 | 35/320 | | | | D | 0.00 | 0.06
Fedorcsak 2000 | 28/79 | 68/304 | | | | D | 0.00 | 0.07
Fedorcsak 2004 | 98/745 | 279/1839 | | | | D | 0.00 | 0.02
Hamilton-Fairley | 9/12 | 8/29 | | | | D | 0.00 | 0.62
Lachen 2004 | 237/1644 | 394/3288 | | | | D | 0.00 | 0.01
Loveland 2001 | 5/24 | 3/42 | | | | D | 0.00 | 0.61
Styne-Gross 2005 | 46/112 | 51/207 | | | | D | 0.00 | 0.06
Van Swieten 2005 | 9/51 | 12/101 | | | | D | 0.00 | 0.22
Wang 2001 | 103/397 | 97/509 | | | | D | 0.00 | 0.03
Weng 2002 | 80/771 | 13/1508 | | | | D | 0.00 | 0.07
Winter 2002 | 55/396 | 124/701 | | | | D | 0.00 | 0.03
Wittemer 2000 | 7/89 | 11/222 | | | | D | 0.00 | 0.25

**Total (95% CI):** 5545 | 11151 | 1.67 | [1.25, 2.25]

**Total events:** 862 (High BMI), 1395 (Normal BMI)

**Test for heterogeneity:** CHI² = 64.63, df = 15 (P < 0.00001), I² = 84.1%

**Test for overall effect:** Z = 3.42 (P = 0.0006)

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M Metwally, K Ong, WL Ledger, TC Li, Fertil Steril 2007
Subgroup analysis
Ovulation induction

<table>
<thead>
<tr>
<th>Study</th>
<th>High BMI</th>
<th>Normal BMI</th>
<th>OR (fixed)</th>
<th>Weight</th>
<th>OR (fixed)</th>
<th>Quality</th>
<th>D - E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al-Azemi 2004</td>
<td>10/85</td>
<td>0/36</td>
<td>16.89</td>
<td>10.15</td>
<td>0.58, 178.05</td>
<td>D</td>
<td>0.00</td>
<td>2.14</td>
</tr>
<tr>
<td>Hamilton-Fairley</td>
<td>9/12</td>
<td>8/29</td>
<td>32.20</td>
<td>7.88</td>
<td>1.69, 36.72</td>
<td>D</td>
<td>0.00</td>
<td>0.62</td>
</tr>
<tr>
<td>Balen 2006</td>
<td>3/158</td>
<td>2/177</td>
<td>50.91</td>
<td>1.69</td>
<td>0.28, 10.27</td>
<td>D</td>
<td>0.00</td>
<td>0.85</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>255</td>
<td>242</td>
<td></td>
<td>100.00</td>
<td>5.11, 14.83</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 22 (High BMI), 10 (Normal BMI)

Test for heterogeneity: Ch² = 1.97, df = 2 (P = 0.37), P = 0%
Test for overall effect: Z = 3.00 (P = 0.003)
### IVF/ICSI

**Review:** obesity and miscarriage (Version 05)
**Comparison:** 01 obesity and miscarriage
**Outcome:** 02 miscarriage after IVF/ICSI

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>High BMI n/N</th>
<th>Normal BMI n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
<th>Quality</th>
<th>D - E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dokters 2006</td>
<td>40/295</td>
<td>35/320</td>
<td>-</td>
<td>-</td>
<td>12.13 [0.79, 2.07]</td>
<td>D</td>
<td>0.00</td>
<td>0.06</td>
</tr>
<tr>
<td>Fedorcsak 2000</td>
<td>28/79</td>
<td>58/304</td>
<td>-</td>
<td>-</td>
<td>11.98 [1.12, 3.25]</td>
<td>D</td>
<td>0.00</td>
<td>0.07</td>
</tr>
<tr>
<td>Fedorcsak 2004</td>
<td>98/745</td>
<td>279/1639</td>
<td>-</td>
<td>-</td>
<td>13.06 [0.65, 1.00]</td>
<td>D</td>
<td>0.00</td>
<td>0.02</td>
</tr>
<tr>
<td>Loveland 2001</td>
<td>5/24</td>
<td>3/42</td>
<td>-</td>
<td>-</td>
<td>5.47 [0.74, 15.61]</td>
<td>D</td>
<td>0.00</td>
<td>0.61</td>
</tr>
<tr>
<td>Van Swieten 2005</td>
<td>9/51</td>
<td>12/101</td>
<td>-</td>
<td>-</td>
<td>6.62 [0.51, 1.32]</td>
<td>D</td>
<td>0.00</td>
<td>0.22</td>
</tr>
<tr>
<td>Wang 2001</td>
<td>97/509</td>
<td>103/397</td>
<td>-</td>
<td>-</td>
<td>12.84 [0.49, 0.92]</td>
<td>D</td>
<td>0.00</td>
<td>0.03</td>
</tr>
<tr>
<td>Wang 2002</td>
<td>80/771</td>
<td>18/1508</td>
<td>-</td>
<td>-</td>
<td>11.95 [3.70, 16.11]</td>
<td>D</td>
<td>0.00</td>
<td>0.07</td>
</tr>
<tr>
<td>Winter 2002</td>
<td>85/396</td>
<td>124/701</td>
<td>-</td>
<td>-</td>
<td>12.74 [0.53, 1.06]</td>
<td>D</td>
<td>0.00</td>
<td>0.03</td>
</tr>
<tr>
<td>Whiteman 2000</td>
<td>7/39</td>
<td>11/222</td>
<td>-</td>
<td>-</td>
<td>9.32 [0.61, 1.37]</td>
<td>D</td>
<td>0.00</td>
<td>0.25</td>
</tr>
</tbody>
</table>

**Total (95% CI):** 2969/5434

**Total events:** 419 (High BMI), 653 (Normal BMI)

Test for heterogeneity: Chi² = 53.05, df = 8 (P < 0.00001), P = 91.4%
Test for overall effect: Z = 1.51 (P = 0.13)
### Oocyte donation

**Review:** obesity and miscarriage (Version 05)

**Comparison:** 01 obesity and miscarriage

**Outcome:** 03 miscarriage after oocyte donation

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>High BMI n/N</th>
<th>Normal BMI n/N</th>
<th>OR (random)</th>
<th>Weight %</th>
<th>OR (random)</th>
<th>95% CI</th>
<th>Quality</th>
<th>D - E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belver 2003</td>
<td>21/105</td>
<td>36/255</td>
<td></td>
<td>20.58</td>
<td>1.52</td>
<td>[0.84, 2.75]</td>
<td>D</td>
<td>0.00</td>
<td>0.09</td>
</tr>
<tr>
<td>Belver 2007</td>
<td>11/572</td>
<td>257/1613</td>
<td></td>
<td>52.05</td>
<td>1.27</td>
<td>[0.99, 1.63]</td>
<td>D</td>
<td>0.00</td>
<td>0.02</td>
</tr>
<tr>
<td>Styne-Gross 2005</td>
<td>46/112</td>
<td>51/207</td>
<td></td>
<td>27.06</td>
<td>2.13</td>
<td>[1.30, 3.49]</td>
<td>D</td>
<td>0.00</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>789</td>
<td>2075</td>
<td></td>
<td>100.00</td>
<td>1.52</td>
<td>[1.10, 2.09]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total events:** 178 (High BMI), 344 (Normal BMI)

**Test for heterogeneity:** Chi^2 = 3.46, df = 2 (P = 0.18), I^2 = 42.2%

**Test for overall effect:** Z = 2.56 (P = 0.01)

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[Graph or chart showing data distribution]
Obesity and Reproductive Problems

- Infertility
- Miscarriage
- Recurrent Miscarriage
- Ectopic pregnancy
- Late pregnancy complications
Study 2

Impact of BMI on miscarriage rate in women with recurrent miscarriage
Miscarriage rates for different BMI categories for all pregnancies ($n = 844; P > 0.05$) and the first pregnancy after referral ($n = 491; P > 0.05$).

Where is the problem?
Study 3

Impact of BMI on Endometrial function in women with recurrent miscarriage:
a retrospective study

M Metwally, E Tuckerman, SM Laird, WL Ledger, TC Li, RBM Online 2007
Subjects

145 unexplained RM

BMI

BMI <25
n=74

BMI >25
n= 71
Methodology

• Morphology: dating criteria of Noyes
• Immunohistochemistry
  – Steroid receptors
  – LIF
  – Leucocyte subpopulations
Aim

- LIF
- E&P receptor
- morphology
- CD+
## Endometrial Morphology

<table>
<thead>
<tr>
<th></th>
<th>BMI &lt; 25 (n=74)</th>
<th>BMI ≥ 25 (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPD</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Normal development</td>
<td>59</td>
<td>54</td>
</tr>
</tbody>
</table>

P > 0.05
<table>
<thead>
<tr>
<th>Receptor</th>
<th>BMI&lt;25 n= 16</th>
<th>BMI&gt;25 n= 17</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stromal P</td>
<td>270.0 (53.0)</td>
<td>260 (68.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Glandular P</td>
<td>240.0 (139.0)</td>
<td>225.0 (340.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Luminal P</td>
<td>255.0 (148.0)</td>
<td>220.0 (148.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Stromal E</td>
<td>119.0 (114.0)</td>
<td>145.0 (130.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Glandular E</td>
<td>170.0 (141.0)</td>
<td>110.0 (133.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Luminal E</td>
<td>146.5 (125.0)</td>
<td>125.0 (135.0)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>BMI&lt;25</td>
<td>BMI&gt;25</td>
<td>p</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>---------</td>
<td>----</td>
</tr>
<tr>
<td>N=13</td>
<td></td>
<td>n=16</td>
<td></td>
</tr>
<tr>
<td>CD45</td>
<td>23.3 (13-35)</td>
<td>21.0 (14-29)</td>
<td>NS</td>
</tr>
<tr>
<td>CD56</td>
<td>8.4 (5-28)</td>
<td>8.3 (4-16)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4</td>
<td>2.5 (1-5)</td>
<td>2.5 (0.5-7)</td>
<td>NS</td>
</tr>
<tr>
<td>CD3</td>
<td>3.6 (2-7)</td>
<td>3.9 (0-8)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Conclusion

• A modest increase in BMI does not appear to have a major adverse effect on:
  — Endometrial morphology
  — Oestrogen and progesterone receptors
  — Leucocyte populations
• Negative correlation between BMI and LIF expression
• a strong case to conduct a prospective study to further examine LIF expression in women with high BMI, especially in women who are severely or morbidly obese
Study 4

Impact of BMI on endometrial protein profile (Proteomic) of women with recurrent miscarriage:
a prospective study
Proteomics: the way forward?
Is obesity associated with an endometrial defect? An endometrial proteomic analysis of obese women with recurrent miscarriage

M Metwally, WL Ledger, TC Li
The Jessop Wing, Sheffield, UK
Obesity and the endometrium

- Suggested from clinical studies using the oocyte donation model Bellver et al, F&S, 2007
- Suggested from tissue studies:
  - Steroid receptors
  - Endometrial leukocytes
  - Endometrial morphology
  - Leukemia inhibitory factor

  Metwally et al, RBM online, 2006
Aim of study

• To map the protein structure of the endometrium in women with increased BMI and recurrent miscarriage.

• To determine if an alteration in the endometrial protein profile may reflect an endometrial cause for the increased risk of miscarriage in women with this condition.
### Materials and methods

#### Recurrent miscarriage
- Obese: 12
- Normal: 4

#### Controls
- Obese: 2
- Normal: 3

**Mid-luteal endometrial biopsy**
Proteomics

- Extraction and labelling of proteins
- 2D gel electrophoresis
- Image Analysis: quantification of differences in protein expression
- Principle components analysis
- Protein identification: mass spectrometry
2D gel electrophoresis
Proteomics

• Extraction and labelling of proteins
• 2D gel electrophoresis
• Image Analysis: quantification of differences in protein expression
• Principle components analysis
• Protein identification: mass spectrometry
Interpretation

• Obesity has a positive impact on Haptoglobin
  – glycoprotein synthesised in the liver
  – binds excess haemoglobin protecting the kidneys in cases of intravascular haemolysis
  – important component of the body’s response to inflammatory conditions
  – Mediator of endothelial dysfunction

• Chain A pre albumin and beta globulin: Markers of endothelial dysfunction

• Evidence for a local inflammatory reaction
Study 5

Impact of BMI on embryo quality in women undergoing assisted conception: a retrospective study
The embryo?

- Difficult to assess
- Many grading systems
- Inter and intra-observer variability

Baxter Bendus et al., 2006
## Embryo quality markers

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Overweight</th>
<th>obese</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryo grade</td>
<td>2</td>
<td>1.9</td>
<td>2.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Embryos discarded</td>
<td>4.5</td>
<td>4.0</td>
<td>6.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Utilisation rate</td>
<td>49%</td>
<td>50%</td>
<td>31%</td>
<td>0.01</td>
</tr>
<tr>
<td>Embryos cryopreserved</td>
<td>1.1</td>
<td>0.9</td>
<td>0.2</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Metwally et al, RBM Online, 2007
Where is the problem?

Both
Obesity and Reproductive Problems

- Infertility
- Miscarriage
- Recurrent Miscarriage
- Ectopic pregnancy
- Late pregnancy complications
Conclusions

• Obesity increases the risk of miscarriage and recurrent miscarriage
• Obesity affects embryo quality
• Obesity adversely affect endometrial function