Obesity and Reproduction

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ESHRE Dubrovnic, 2010
Obesity has a negative impact on:
- spontaneous conception,
- miscarriage,
- pregnancy,
- long term health of children
  (congenital anomalies and metabolic disease)

Obesity is associated with reduced response to fertility treatment and variable impact on ongoing pregnancy rates

Obesity may affect safety of procedures:
- ability to see ovaries on scan,
- provide safe anaesthesia for procedures etc…
Should there be a cut off weight / BMI before any treatment?

- Reduced chance conception
- Increased risk miscarriage
- Increased rate of congenital anomalies
- Obstetrical problems
  (Gest DM, PET, delivery ....)

*Balen, Dresner, Scott & Drife
*BMJ 2006;332;434-435*
1. Obesity – the modern epidemic

2. Obesity and reproduction
   - infertility / outcome of treatments
   - polycystic ovary syndrome
   - mechanisms
   - miscarriage

3. Weight loss

4. Limits for treatment
Percentage population with BMI > 30 kg/m²
More than 12m adults (33% of men and 28% of women) and 1m children will be obese by 2010

19% of boys and 22% of girls (2-15y) will be obese

Having two obese parents → 5 x the risk of being obese
The runaway weight gain train: too many accelerators, not enough breaks

Brakes: Improved Lifestyle

Low socio-economic status

Disordered eating

Psychological dysfunction

Poor Health

No Exercise

Obesogenic Environment

Energy in > Energy out

Swinburn & Egger BMJ 2004;329:736
Medical Complications of Obesity

**Pulmonary disease**
- abnormal function
- obstructive sleep apnea
- hypoventilation syndrome

**Pancreatitis**

**Nonalcoholic fatty liver disease**
- Steatosis/steatohepatitis
- cirrhosis

**Gall bladder disease**

**Cancers**
- breast, uterus, cervix, prostate, kidney
- colon, esophagus, pancreas, liver

**Back pain**

**Stroke**

**Tiredness**

**Idiopathic intracranial hypertension**

+ Loss of vision

**Cataracts**

**Coronary heart disease**

**Diabetes**

**Dyslipidemia**

**Hypertension**

**Gynaecologic abnormalities**
- abnormal menses / infertility
- polycystic ovary syndrome
- gestational diabetes
- pre-eclampsia

**Oedema**

**Osteoarthritis**

**Phlebitis**
- venous stasis
- Venous thrombosis

**Gout**

**Liver diseases**
- steatosis/steatohepatitis
- cirrhosis

**Cataracts**

Tiredness

Idiopathic intracranial hypertension

+ Loss of vision

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Coronary heart disease

Diabetes

Dyslipidemia

Hypertension

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Oedema

Osteoarthritis

Phlebitis
- venous stasis
- Venous thrombosis

Gout

Liver diseases
- steatosis/steatohepatitis
- cirrhosis

Cataracts
Waist circumference - better than BMI

Figure 1  Prevalence (%) of predicted 10-yCHD risk ≥15% according to WHR and BMI in men aged 35–74 y.
1. Obesity – the modern epidemic

2. Obesity and reproduction
   - infertility / outcome of treatments
   - polycystic ovary syndrome
   - mechanisms
   - miscarriage

3. Weight loss

4. Limits for treatment
Body fat distribution and fertility

500 women receiving donor insemination

0.1 unit increase waist:hip → 30% ↓ conception

<table>
<thead>
<tr>
<th>W:H ratio</th>
<th>% pregnant after 12 cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.70</td>
<td>63%</td>
</tr>
<tr>
<td>0.7 – 0.75</td>
<td>51%</td>
</tr>
<tr>
<td>0.76 – 0.8</td>
<td>47%</td>
</tr>
<tr>
<td>0.81 – 0.85</td>
<td>41%</td>
</tr>
<tr>
<td>&gt; 0.85</td>
<td>32%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI</th>
<th>% pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20.0</td>
<td>40%</td>
</tr>
<tr>
<td>20.1-25</td>
<td>48%</td>
</tr>
<tr>
<td>25.1-30</td>
<td>48%</td>
</tr>
<tr>
<td>&gt;30</td>
<td>18%</td>
</tr>
</tbody>
</table>

hazard ratio 0.705, 95% CI 0.562-0.887

Zaadstra et al BMJ 1993; 306:484
Anovulatory infertility (WHO Group II)

- Infertility more likely with increasing BMI
  - Balen et al 1994

- BMI > 27 kg/m² ass. with reduced chance ovulation
  - Grodstein et al 1994

- Ovulation induction less effective if BMI > 28-30

- Greater risks in pregnancy if obese
  - (miscarriage, DM, delivery)
  - Gjoannaes et al 1984
The effect of obesity in women with polycystic ovary syndrome

270 PCOS receiving clomiphene citrate or gonadotrophins

Ovulation rate at 6 months:

<table>
<thead>
<tr>
<th>BMI Range</th>
<th>Ovulation Rate</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI 18-24 kg/m²</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>BMI 30-34 kg/m²</td>
<td>15.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI ≥35 kg/m²</td>
<td>12%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Al-Azemi et al. Arch Gynecol & Obst 2004; 270:205-10
The influence of body weight on response to ovulation induction with gonadotropins in 335 women with WHO Group II anovulatory infertility

Max BMI 35 kg/m², mean BMI 25.3 kg/m²

Increasing BMI significantly associated with:

- more antral follicles before stimulation
- more small & fewer intermediate sized follicles at ovulation
- more days of stimulation
- higher dose of gonadotrophins required
- no effect on ongoing pregnancy rates

Balen et al, BJOG 2006; 113: 1195
Predictors for outcome with gonadotropin ovulation induction in WHO Group II infertility: a meta-analysis

Degree of obesity positively correlated with amount of gonadotropin required:
weighted mean difference of 771 IU (95% CI 700-842)

Higher rate of cycle cancellation
(pooled OR 1.86, 95% CI: 1.13-3.06)

Reduction in ovulation rate
(OR 0.44, 95% CI: 0.31-0.61)

In those who ovulated:
no difference in pregnancy rates associated with obesity,
but negative association with insulin resistance
(pooled OR 0.29, 95% CI: 0.10 - 0.80)

*Mulders et al. Hum Reprod Update 2003; 9: 429-449*
Obesity and IVF

Pregnancy rates after IVF 50% lower if BMI > 30 kg/m² compared with women with BMI < 25 kg/m²

Body mass and probability of pregnancy during assisted reproduction treatment

3586 women who had ART in Adelaide, 25% PCOS

logistic regression analysis confirmed independent effect of body weight, linear reduction in fecundity with obesity p<0.001

<table>
<thead>
<tr>
<th>BMI</th>
<th>% achieving ≥1 pregnancy</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>45</td>
<td>0.81 (0.65-1.01)</td>
</tr>
<tr>
<td>20-24.9</td>
<td>48</td>
<td>1</td>
</tr>
<tr>
<td>25-29.9</td>
<td>42</td>
<td>0.81 (0.68-0.97)</td>
</tr>
<tr>
<td>30-34.9</td>
<td>40</td>
<td>0.73 (0.57-0.95)</td>
</tr>
<tr>
<td>&gt;35</td>
<td>30</td>
<td>0.50 (0.32-0.77)</td>
</tr>
</tbody>
</table>

Wang et al BMJ 2000; 321:1320
Impact of overweight and underweight on pregnancy outcome in IVF/ICSI

5019 IVF/ICSI in 2660 couples
Cumulative live birth rate 3 cycles:

BMI 18.5-24.9 kg/m²  50.3%  [95% CI  47.0 - 53.7]
BMI 25-29.9 kg/m²  44.9%  [95% CI  38.4 - 51.3]
BMI ≥30 kg/m²  41.4%  [95% CI  32.1 - 50.7]

Compared with BMI <25, if BMI > 30

OR of live birth 0.75 [95% CI  0.57-0.98] p=0.05
OR of early pregnancy loss 1.69 [95% CI  1.13-2.51] p=0.003

Fedorcsak et al, Hum Reprod 2004; 2523-2528
Miscarriage after IVF?

- 1018 patients treated with IVF (37% PCOS)

- Miscarriage - PCOS 25%,
  - normal ovaries 18%

- Multivariate logistic regression showed higher risk of miscarriage in PCOS due to obesity

Wang et al, 2001
Obesity and IVF

Some authors report no effect:

- yet complex interaction between body mass and body fat distribution

- the intensity of the stimulation protocol may overcome some of the adverse effects of obesity

*Lashan et al, Hum Reprod 1999; 14:712*
Obesity & Miscarriage

- ↑ risk of miscarriage in moderately obese (BMI 25–27.9 kg/m²)
  
  *Hamilton-Fairley et al Br J O G 1992;99:128*

- ↑ miscarriage after IVF & ICSI (BMI 25.8 to 30.8 kg/m²)
  

- BMI > 30 risk factor for miscarriage in oocyte recipients
  
Effect of overweight and obesity on assisted reproductive technology – systematic review

- Total of 1843 studies identified
- ART and obesity in 43 studies
- 14 fulfilled entry criteria
- All observational studies
- 3 Case control studies excluded

Findings

- Variable BMI cut off values
- Aggregated data on normal and low BMI
- Comparison groups: BMI of 25, 30, 35
- Inconsistent reporting of outcomes
- Live birth not reported in most studies
- No adjustment for confounders (e.g. age)
<table>
<thead>
<tr>
<th>Parameter (BMI cut-off)</th>
<th>Number of papers</th>
<th>Number of patients</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH dose (25 or 30)</td>
<td>2</td>
<td>5408</td>
<td>Highly sig increased dose in overweight</td>
</tr>
<tr>
<td>Cycle cancellation (25 or 30)</td>
<td>3</td>
<td>4039</td>
<td>Non-sig. trend to higher cancellation</td>
</tr>
<tr>
<td>Number of oocytes (25 or 30)</td>
<td>3</td>
<td>4039</td>
<td>Sig. fewer oocytes in overweight</td>
</tr>
<tr>
<td>OHSS (25 or 30)</td>
<td>2</td>
<td>1425</td>
<td>Non-sig. trend to increased OHSS in BMI&gt;30</td>
</tr>
<tr>
<td>Pregnancy rate (25 or 30)</td>
<td>5</td>
<td>7571</td>
<td>Trend to increased PR in lighter weight</td>
</tr>
<tr>
<td>Pregnancy rate (20-25 vs. &gt;25)</td>
<td>3</td>
<td>3694</td>
<td>Sig. lower PR in overweight</td>
</tr>
<tr>
<td>Pregnancy rate (35)</td>
<td>1</td>
<td>3146</td>
<td>Sig. lower PR in very overweight</td>
</tr>
<tr>
<td>Live birth (25 or 30)</td>
<td>2</td>
<td>3877</td>
<td>Non-sig. trend to increased LB in normal weight</td>
</tr>
<tr>
<td>Miscarriage (25)</td>
<td>8</td>
<td>6095</td>
<td>Non-sig. trend to increased losses in overweight</td>
</tr>
<tr>
<td>Miscarriage (30)</td>
<td>6</td>
<td>5652</td>
<td>Sig. increased losses in overweight</td>
</tr>
<tr>
<td>Miscarriage (35)</td>
<td>2</td>
<td>3376</td>
<td>Sig. increased losses in very overweight</td>
</tr>
</tbody>
</table>
Appraisal of existing evidence

- Limitations of existing evidence
- Values represent unadjusted odds
- Unable to rule out effect of age
- Inconsistency in cut-off values for BMI
- Few live birth data

Maheshwari et al, 2007
Effect of obesity on IVF

- Higher FSH requirement
- Lower oocyte yield
- Possibly lower pregnancy rates
- Higher miscarriage rates
- No evidence of effect on livebirth

Maheshwari et al, 2007
Conclusions of meta-analysis

- Negative effect of obesity on IVF
- Effect at several levels
- Results to be interpreted with caution
- Consensus to be reached on BMI limit
- Further work on obesity as predictor
- Meanwhile aim for optimum BMI in ART
1. Obesity – the modern epidemic

2. Obesity and reproduction
   - infertility / outcome of treatments
   - **polycystic ovary syndrome**
   - miscarriage
   - mechanisms

3. Weight loss

4. Limits for treatment
1741 Women with PCOS

OBESITY 40-50%

WEIGHT LOSS

↑ INSULIN

↑↑ ↑↑ ↑↑ ↑↑ INSULIN

Balen et al Hum Reprod 1995; 10: 2107
Obesity:

BMI – WHO criteria (overweight 25-30, obese > 30 kg/m²)

Waist Circumference > 80 cm
PCOS in South Asians and Caucasians living in the U.K.

S. Asians had significantly:

↓↓ ↓↓ age onset hirsutism  p < 0.01
↑↑ ↑↑ hirsutism, acne & acanthosis nigricans  p < 0.001
similar BMI & W:H

similar total Testosterone
↑↑ insulin and ↓ SHBG  p < 0.001

Wijeyaratne et al, Clin Endocrinol 2002; 57: 243
Wijeyaratne et al, Clin Endocrinol 2004; 60: 560
1. Obesity – the modern epidemic

2. Obesity and reproduction
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   - miscarriage

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Mechanisms?

Hyperinsulinaemia:

\[ \uparrow \text{androgens}, \downarrow \text{SHBG}, \text{worsens PCOS} \]
\[ \text{disrupts follicular maturation} \]
\[ \text{GnRH pulsatility} \rightarrow \text{LH secretion} \]

Leptin & Ghrelin:

\[ \text{receptors on endometrium, follicle, oocyte, embryo placenta, (testis)} \]

Endorphins:

\[ \text{GnRH pulsatility} \]

Cytokines, PAI-1, adiponectin, resistin, PYY3-36, glucocorticoids ....
Mechanisms?

Abnormal absorption & distribution of drugs ....

↓ Intrafollicular hCG, affects oocyte quality

Carrell et al 2001, RBM Online 3:109
Hyperinsulinaemia and miscarriage

- Hyperinsulinaemia is a risk factor for EPL
- Glycodelin: immunoregulatory peptide protects implantation
- ↓ glycodelin and IGFBP-1 in pregnancies that miscarry
- Metformin therapy may increase glycodelin and IGFBP-1

Nestler, 2003
Plasminogen activator inhibitor (PAI-1)

- Glycoprotein
- Potent inhibitor of fibrinolysis
- Elevated in PCOS, hyperinsulinemia
- High levels are risk factor for EPL in PCOS

Craig et al F&S 2002; 78:487
Glueck et al F&S 2000;74:394
Carrington, Rai, Regan 2005 (abs)
Hyperinsulinemia

Hyperinsulinemia associated with

- Obesity
- High plasminogen activator inhibitor activity (PAI) = hypofibrinolysis

Craig et al F&S 2002; 78:487
Glueck et al F&S 2000;74:394
Carrington, Rai, Regan 2005 (abs)
Hyperinsulinaemia and miscarriage

- Hyperinsulinaemia is a risk factor for EPL
- Associated impairment of fibrinolytic response during implantation
- Homozygosity for the 4G/4G polymorphism in the PAI1 gene promotor found more often in PCOS and rec misc

Craig et al F&S 2002; 78:487
Glueck et al F&S 2000;74:394
Carrington, Rai, Regan 2005 (abs)
Metformin therapy:
lower insulin
  E2
  T, FAI
  VEGF

High androgens inversely related to [PP14]
Conclusions

- Women who have PCOS have higher rates of miscarriage than women with normal ovaries.

- Obesity, hyperinsulinemia, high concentrations of LH, androgens and PAI-1 may all be involved.

- Treatment to reduce weight, LH, insulin and androgen levels may improve the miscarriage rate.
A multi-centre randomised, placebo-controlled, double-blind study, of combined life-style modification & metformin in obese patients with PCOS

- 8 centres U.K., co-ordinated by Leeds
- Placebo controlled, double blind RCT
- 6 months metformin 850mg b.d.
- 143 women randomised, with BMI > 30 kgm⁻²
  
  mean BMI 38 kgm⁻²

power 0.90 for significance 0.05, requires 55 per arm of study)

Randomised 143

Metformin 69
- Withdrew 13
- Completed 56

Placebo 74
- Withdrew 8
- Completed 66
Metformin vs Placebo

Significant increase in number of cycles, and fall in BMI and waist circumference in both groups

No difference in ovulation rate between the groups

Improvements seen in those who lost weight in either group

A randomised double blind clinical trial comparing clomifene citrate plus metformin with clomifene citrate plus placebo in newly diagnosed PCOS

228 women with PCOS

Randomly allocated to receive either metformin 2000 mg/d or placebo for 1 month

Then clomifene citrate 50 up to 150 mg for 6 ovulations or until CC-resistance

BMI ~ 28 kg/m²

_Moll et al, BMJ; 332: 1485_
### Ovulation per dosage clomifene citrate

<table>
<thead>
<tr>
<th>Dosage</th>
<th>CC + metformin</th>
<th>CC + placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC 50mg</td>
<td>49/80 (61%)</td>
<td>50/92 (54%)</td>
<td>0.36</td>
</tr>
<tr>
<td>CC 100mg</td>
<td>27/44 (61%)</td>
<td>35/53 (66%)</td>
<td>0.63</td>
</tr>
<tr>
<td>CC 150mg</td>
<td>8/17 (47%)</td>
<td>13/23 (57%)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

*Moll et al. BMJ 2006; 332: 1485*
### Ovulation, pregnancy and spontaneous abortion rates

<table>
<thead>
<tr>
<th></th>
<th>CC + metformin</th>
<th>CC + placebo</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ovulation</strong></td>
<td>n=111</td>
<td>n=114</td>
<td></td>
</tr>
<tr>
<td></td>
<td>71 (64%)</td>
<td>82 (72%)</td>
<td>0.89 (0.7 - 1.1)</td>
</tr>
<tr>
<td><strong>Ongoing Pregnancy</strong></td>
<td>44 (40%)</td>
<td>52 (46%)</td>
<td>0.87 (0.6 - 1.2)</td>
</tr>
<tr>
<td><strong>Spontaneous Abortion</strong></td>
<td>13 (12%)</td>
<td>12 (11%)</td>
<td>1.11 (0.5 - 2.3)</td>
</tr>
</tbody>
</table>

*Source: Moll et al BMJ 2006; 332: 1485*
Discontinuation due to side effects:

16% versus 5% (95% CI 5 - 16%)

Moll et al BMJ 2006; 332: 1485
CC and/or metformin alone or in combination

626 anovulatory PCOS

Metformin vs Placebo 2000 mg / day

Clomiphene or Placebo 50 – 150 mg for 5d

6 cycles or 30 weeks

Mean BMI ~ 35 kg/m²

CC and/or metformin alone or in combination

<table>
<thead>
<tr>
<th></th>
<th>CC</th>
<th>M</th>
<th>CC + M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conception/ovulation</td>
<td>39.5%</td>
<td>8.4%</td>
<td>46.0%</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>8.3%</td>
<td>20.8%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Live birth</td>
<td>22.5%</td>
<td>7.2%</td>
<td>26.8%</td>
</tr>
<tr>
<td></td>
<td>(47/209)</td>
<td>(15/208)</td>
<td>(56/209)</td>
</tr>
</tbody>
</table>

CC superior to metformin and combination confers no advantage in achieving live birth

Revised Cochrane Meta-analysis
Metformin vs placebo or no treatment: Body weight

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Metformin Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baillargeon 2004</td>
<td>61.4</td>
<td>1.6</td>
<td>28</td>
<td>61.4</td>
<td>1.6</td>
<td>30</td>
<td>96.3%</td>
<td>0.00 [-0.82, 0.82]</td>
<td></td>
</tr>
<tr>
<td>Kelly 2002</td>
<td>91</td>
<td>24</td>
<td>10</td>
<td>94</td>
<td>31</td>
<td>10</td>
<td>0.1%</td>
<td>-3.00 [-27.30, 21.30]</td>
<td>-3.00 [-27.30, 21.30]</td>
</tr>
<tr>
<td>Lord 2006</td>
<td>94.7</td>
<td>27.1</td>
<td>16</td>
<td>94.9</td>
<td>15.5</td>
<td>15</td>
<td>0.3%</td>
<td>-0.20 [-15.62, 15.22]</td>
<td>-0.20 [-15.62, 15.22]</td>
</tr>
<tr>
<td>Pasquali 2000</td>
<td>94</td>
<td>17</td>
<td>10</td>
<td>97</td>
<td>18</td>
<td>8</td>
<td>0.2%</td>
<td>-3.00 [-19.33, 13.33]</td>
<td>-3.00 [-19.33, 13.33]</td>
</tr>
<tr>
<td>Tang 2006</td>
<td>99</td>
<td>15</td>
<td>56</td>
<td>99.2</td>
<td>17.3</td>
<td>66</td>
<td>2.0%</td>
<td>-0.20 [-5.93, 5.53]</td>
<td>-0.20 [-5.93, 5.53]</td>
</tr>
<tr>
<td>Trolle2007</td>
<td>92.9</td>
<td>19</td>
<td>42</td>
<td>96.1</td>
<td>21.1</td>
<td>45</td>
<td>0.9%</td>
<td>-3.20 [-11.63, 5.23]</td>
<td>-3.20 [-11.63, 5.23]</td>
</tr>
<tr>
<td>Vandermolen 2001</td>
<td>96.9</td>
<td>26.53</td>
<td>11</td>
<td>106.9</td>
<td>23.2</td>
<td>14</td>
<td>0.2%</td>
<td>-10.00 [-29.84, 9.84]</td>
<td>-10.00 [-29.84, 9.84]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>173</td>
<td></td>
<td></td>
<td>188</td>
<td></td>
<td>100.0%</td>
<td></td>
<td>-0.06 [-0.87, 0.75]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.70, df = 6 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

OR  -0.06  95% CI  -0.87, 0.75

Metformin versus placebo or no treatment: Live birth rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Metformin Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng 2001</td>
<td>1</td>
<td>9</td>
<td>2</td>
<td>9</td>
<td>79.6%</td>
<td>0.44 [0.03, 5.93]</td>
</tr>
<tr>
<td>Yarali 2002</td>
<td>1</td>
<td>16</td>
<td>0</td>
<td>16</td>
<td>20.4%</td>
<td>3.19 [0.12, 84.43]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>100.0%</td>
<td>1.00 [0.16, 6.39]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

Live birth rate: OR 1.00 95% CI 0.16, 6.39

### Metformin versus Clomiphene Citrate: Live birth Rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Metformin</th>
<th>Clomifene</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Legro 2007</td>
<td>15</td>
<td>208</td>
<td>47</td>
<td>209</td>
</tr>
<tr>
<td>Palomba 2005</td>
<td>26</td>
<td>50</td>
<td>9</td>
<td>50</td>
</tr>
<tr>
<td>Zain 2008</td>
<td>4</td>
<td>42</td>
<td>7</td>
<td>41</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>300</strong></td>
<td><strong>300</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 45, 63

Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%

Test for overall effect: Z = 4.25 (P < 0.0001)

**OR 0.30 95% CI 0.17, 0.52**

---

Metformin plus ovulation induction agent vs ovulation induction agent alone: Ovulation Rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.3.1 PCOS and clomifene sensitive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jakubowicz 2001</td>
<td>26</td>
<td>28</td>
<td>22</td>
<td>28</td>
<td>5.5%</td>
<td>3.55 [0.65, 19.37]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>26</td>
<td>28</td>
<td>22</td>
<td>28</td>
<td>5.5%</td>
<td>3.55 [0.65, 19.37]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>26</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.46 (P = 0.14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3.3.2 PCOS and clomifene resistant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hwu 2005</td>
<td>17</td>
<td>40</td>
<td>5</td>
<td>40</td>
<td>8.2%</td>
<td>5.17 [1.68, 15.98]</td>
<td></td>
</tr>
<tr>
<td>Kocak 2002</td>
<td>21</td>
<td>27</td>
<td>4</td>
<td>28</td>
<td>6.8%</td>
<td>21.00 [5.21, 84.66]</td>
<td></td>
</tr>
<tr>
<td>Malkawi 2002</td>
<td>11</td>
<td>16</td>
<td>3</td>
<td>12</td>
<td>5.6%</td>
<td>6.60 [1.23, 35.44]</td>
<td></td>
</tr>
<tr>
<td>Ng 2001</td>
<td>4</td>
<td>9</td>
<td>1</td>
<td>9</td>
<td>3.4%</td>
<td>6.40 [0.55, 74.89]</td>
<td></td>
</tr>
<tr>
<td>Sturrock 2002</td>
<td>5</td>
<td>12</td>
<td>4</td>
<td>14</td>
<td>5.8%</td>
<td>1.79 [0.35, 9.13]</td>
<td></td>
</tr>
<tr>
<td>Vandermolen 2001</td>
<td>9</td>
<td>12</td>
<td>4</td>
<td>15</td>
<td>5.4%</td>
<td>8.25 [1.45, 46.86]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>116</td>
<td>118</td>
<td>35.2%</td>
<td></td>
<td>6.55 [3.40, 12.63]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>67</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.05; Chi² = 5.36, df = 5 (P = 0.37); I² = 7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.61 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3.3.3 PCOS and clomifene sensitivity not defined</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>El-Biely 2001</td>
<td>35</td>
<td>45</td>
<td>29</td>
<td>45</td>
<td>9.3%</td>
<td>1.93 [0.76, 4.90]</td>
<td></td>
</tr>
<tr>
<td>Khorram 2006</td>
<td>7</td>
<td>16</td>
<td>1</td>
<td>15</td>
<td>3.9%</td>
<td>10.89 [1.14, 103.98]</td>
<td></td>
</tr>
<tr>
<td>Legro 2007</td>
<td>582</td>
<td>964</td>
<td>462</td>
<td>942</td>
<td>12.9%</td>
<td>1.58 [1.32, 1.90]</td>
<td></td>
</tr>
<tr>
<td>Moll 2006</td>
<td>84</td>
<td>141</td>
<td>98</td>
<td>168</td>
<td>11.9%</td>
<td>1.05 [0.67, 1.66]</td>
<td></td>
</tr>
<tr>
<td>Sahin 2004</td>
<td>38</td>
<td>51</td>
<td>34</td>
<td>55</td>
<td>9.8%</td>
<td>1.81 [0.79, 4.15]</td>
<td></td>
</tr>
<tr>
<td>Zain 2008</td>
<td>38</td>
<td>41</td>
<td>24</td>
<td>41</td>
<td>7.1%</td>
<td>8.97 [2.37, 33.91]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1279</td>
<td>1291</td>
<td>59.2%</td>
<td></td>
<td>2.75 [1.48, 5.11]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>803</td>
<td>650</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.42; Chi² = 29.18, df = 6 (P &lt; 0.00001); I² = 79%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.20 (P = 0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CC resistant**

OR 6.55 95% CI 3.40, 12.63

**CC sensitive**

OR 2.75 95% CI 1.48, 5.11

**All**

OR 3.93 95% CI 2.32, 6.65

Heterogeneity: Tau² = 0.55; Chi² = 53.17, df = 13 (P < 0.00001); I² = 73%
## Metformin plus ovulation induction agent vs ovulation induction agent alone: Live Birth Rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legro 2007</td>
<td>56</td>
<td>47</td>
<td>209</td>
<td>50.7%</td>
<td>1.26 [0.81, 1.97]</td>
<td></td>
</tr>
<tr>
<td>Moll 2006</td>
<td>21</td>
<td>31</td>
<td>111</td>
<td>36.5%</td>
<td>0.62 [0.33, 1.17]</td>
<td></td>
</tr>
<tr>
<td>Sahin 2004</td>
<td>3</td>
<td>3</td>
<td>10</td>
<td>3.4%</td>
<td>0.88 [0.13, 5.82]</td>
<td></td>
</tr>
<tr>
<td>Vandermolen 2001</td>
<td>4</td>
<td>1</td>
<td>12</td>
<td>0.9%</td>
<td>7.00 [0.66, 73.93]</td>
<td></td>
</tr>
<tr>
<td>Zain 2008</td>
<td>7</td>
<td>7</td>
<td>41</td>
<td>8.6%</td>
<td>1.00 [0.32, 3.16]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>384</td>
<td>389</td>
<td>791</td>
<td>100.0%</td>
<td>1.04 [0.75, 1.46]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 91 vs 89

Heterogeneity: \( \chi^2 = 5.79, \text{df} = 4 (P = 0.22); I^2 = 31\%

Test for overall effect: \( Z = 0.25 (P = 0.80) \)

OR 1.04 95% CI 0.75, 1.46

---

Cochrane Update: PCOS and Metformin

- There is no evidence that metformin improves live birth rates whether it is used alone (Pooled OR = 1.00, 95% CI 0.16 to 6.39) or in combination with clomiphene (Pooled OR = 1.48, 95% CI 1.12 to 1.95).

- However, clinical pregnancy rates are improved for metformin versus placebo (Pooled OR = OR 3.86, 95% C.I. 2.18 to 6.84) and for metformin and clomiphene versus clomiphene alone (Pooled OR =1.48, 95% C.I. 1.12 to 1.95).

Tang et al, Cochrane Database, Jan 10, 2010
Insulin sensitising agents in PCOS:
ESHRE/ASRM Consensus, 2007

• No clear role of metformin in management of anovulatory infertility either alone or in combination

• No evidence of improvement in pregnancy outcome

*Human Reproduction 2008; 23:462*
*Fertility & Sterility 2008; 89: 505*
*RCOG Scientific Advisory Committee Guideline, 2008*
1. Obesity – the modern epidemic

2. Obesity and reproduction
   - infertility / outcome of treatments
   - mechanisms
   - polycystic ovary syndrome
   - miscarriage

3. Weight loss

4. Limits for treatment
Components of a healthy diet

- **Fruit and vegetables**
  - At least 5 portions daily

- **Bread, other cereals and potatoes**
  - At least 5 portions daily

- **Meat, fish and alternatives**
  - 2–3 portions daily

- **Foods containing fat**
  - 0–3 portions daily

- **Foods containing sugar**
  - 0–3 portions daily

- **Milk and dairy foods**
  - 2–3 portions daily

---

Weight management in PCOS

Energy restriction lowers insulin

↑ IGFBP-1  ↓ IGF-1

Androgen synthesis down-regulated

Kiddy et al 1992; Poretsky et al 1999
Weight management in PCOS

Abdominal (truncal) fat loss most significant in PCOS
A loss of weight of 5 - 10% → 30% reduction in visceral fat

↓ hyperandrogenism and hyperinsulinaemia
and restore reproductive function even if BMI still > 30 kg/m²

↑ spontaneous ovulation
↑ response to ovulation induction
↓ miscarriage rate

Moran & Norman 2004
Holte et al JCEM 1995 80:2586
Weight loss and exercise

BMI > 30, > 2y anovulatory infertility, CC resistance

13/18 completed 6 month study:
weight loss $\rightarrow$ improved endocrinology
all ovulated
11 conceived (5 naturally)

Clark et al H. Rep 1995 10:2705
Weight loss in PCOS vs non-PCOS women

Women with PCOS may have reduced BMR and disturbed eating patterns.

But no differences in weight loss in women with PCOS or normal ovaries following isocaloric 5000-6000 kj/day diets for 2-7 months.

Jakubowitcz & Nestler JCEM 1997; 82:556
Pasquali et al JCEM 2000; 85:2767
“Eat less and exercise more? That’s the most ridiculous fad diet I’ve heard of yet!”
“Eat less and exercise more? That’s the most ridiculous fad diet I’ve heard of yet!”

- **Energy requirements**
  - 2000 kcal
- **Intended calorie intake**
  - 1500 kcal
- **Daily calorie deficit**
  - 500 kcal
- **Weekly calorie deficit**
  - 3500 kcal
- **1 lb = 3500 kcal)**
- **1 lb fat per week = 1 lb fat per month = 1 lb fat per 3 months = 1 lb fat per year**

- **Calorie Deficit**
  - One night off: \(4000 \times \text{kcal} = >1\text{lb fat}
  - One week of dedicated dieting: \(500 \times 7 = 3500 \text{kcal} = 1\text{lb FAT}\)
## Types of Diet

<table>
<thead>
<tr>
<th>Diet Type</th>
<th>Fat</th>
<th>CHO</th>
<th>Protein</th>
<th>Alcohol</th>
<th>% kJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>34</td>
<td>49</td>
<td>14</td>
<td>3</td>
<td>% kJ</td>
</tr>
<tr>
<td>Low-fat, high-CHO, low-protein</td>
<td>30</td>
<td>55</td>
<td>15</td>
<td>-</td>
<td>% kJ</td>
</tr>
<tr>
<td>Very-low-fat, very high-CHO</td>
<td>15</td>
<td>70</td>
<td>15</td>
<td>-</td>
<td>% kJ</td>
</tr>
<tr>
<td>Moderate-CHO, moderate-protein</td>
<td>30</td>
<td>40</td>
<td>30</td>
<td>-</td>
<td>% kJ</td>
</tr>
<tr>
<td>Moderate-protein, very-low-CHO</td>
<td>55</td>
<td>15</td>
<td>30</td>
<td>-</td>
<td>% kJ</td>
</tr>
</tbody>
</table>

Increasing dietary protein and reducing glycaemic index may be of benefit but still requires more evidence w.r.t. reproductive function.
Weight Reduction:
RCOG Guidelines, 2007

No evidence for one type of diet

Strategies may include pharmacotherapy (e.g. Orlistat)

Bariatric surgery

Avoid pregnancy during rapid weight loss
XENDOS: Xenical compared with placebo

Adapted from Torgerson JS et al. Diabetes Care 2004; 27: 155–161
The role of bariatric surgery in the management of female fertility

Sam Scholtz, Carel Le Roux, Adam Balen

Roux-en-Y
Gastric Bypass

Gastric
Banding

Avoid pregnancy during rapid weight loss
Long term weight loss maintenance

Obesity surgery and PCOS

- 12 patients: 100% resolution of menstrual abnormalities
- Normalisation of sex hormones and SHBG
- Significant improvements in hirsutism

Moreale et al, JCEM 2005
Pregnancy post obesity surgery

- Timing of conception controversial
- Less preeclampsia, GDM and macrosomia
- ? Fetal programming
- Higher rate of IUGR and C sections
- Low threshold for imaging / surgical exploration if maternal complications suspected
- Clinical trial needed for consensus ("Bambini" RCT)

References:
1. Obesity – the modern epidemic

2. Obesity and reproduction
   - infertility / outcome of treatments
   - mechanisms
   - polycystic ovary syndrome
   - miscarriage

3. Weight loss

4. Limits for treatment
Obesity and Reproduction

- Should there be a cut-off?
- Is it possible to define a cut-off? Should this be based on BMI, waist circ, metabolic measurements, other “health parameters”?
- Should there be a different cut-off for different procedures/treatments?
- Should a defined cut-off come into play when placed on waiting list or should a patient not be allowed onto a list until weight has reduced?
- How absolute can we be?
BFS Guidelines, 2007

“Treatment should be deferred until BMI < 35 kg/m$^2$ although in those with more time (under 37y, normal ovarian reserve) a weight reduction to < 30 kg/m$^2$ is preferable”

Conversion rates over time

67 obese PCOS,
mean age 32.5y & BMI 28.7 kg/m²
Followed up with 75g GTT, mean time 6.2y
At start: 54 normal, 13 Impaired Glucose Tolerance

Normoglycaemic: 9% IGT 8% Type 2 DM
IGT: 15% normal 54% Type 2 DM

Relative risk of converting: If BMI < 25 1
25-30 7.1 (3.3-11.0)
> 30 10.2 (3.9-16.5)

Increased weight gain in women with PCOS

17,200 calories per annum ≡ 1.9 kg of fat excess in PCOS versus normal

Increased weight and insulin resistance:

↓ SHBG
↑ androgens
anovulation
Gestational DM
Type 2 DM
Cardiovascular disease

Franks, 2006
PCOS and hyperinsulinaemia

30-50% Obese PCOS develop IGT or Type 2 DM by 30y

82% premenopausal women with Type 2 DM have PCO
- 52% of these had PCOS
- no difference in metabolic profile in those with or without symptoms

Conn et al, Clin Endo 2000; 52: 81
Ethnicity and insulin resistance in PCOS

Comparison between Caribbean-Hispanic PCOS and non-Hispanic PCOS with controls

C-H had similar androgens but ↑ insulin resistance

Insulin resistance genetically transmitted, with ↑ prevalence in Pima Indians and Mexican Americans

Dunaif et al, Diabetes, 1993; 42: 1462
• Ovulatory C-H women had normal reproductive function, despite same degree of insulin resistance as white PCOS women

• Susceptibility factors for PCOS extend beyond presence of insulin resistance

Dunaif et al, Diabetes, 1993; 42: 1462
Insulin response to glucose load higher in Asian Indian women with PCOS than Caucasian PCOS

*Norman et al, F & S 1995; 63:58*