Reproductive outcome in women with body weight disturbances

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<table>
<thead>
<tr>
<th>Weight Status</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
</tr>
<tr>
<td>Obese</td>
<td>≥30.0</td>
</tr>
</tbody>
</table>

WHI report 1997
NIH, 1998
### Healthy range of body fat

<table>
<thead>
<tr>
<th>Age</th>
<th>Women (%)</th>
<th>Men (%)</th>
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</thead>
<tbody>
<tr>
<td>25-39</td>
<td>21-32</td>
<td>8-19</td>
</tr>
<tr>
<td>40-59</td>
<td>23-33</td>
<td>11-21</td>
</tr>
<tr>
<td>&gt;60</td>
<td>24-35</td>
<td>13-24</td>
</tr>
</tbody>
</table>
Body Fat

Essential Fat

- Bone marrow
- Organs
- Central nerve system
- Muscles

Women – 12% of TBW
- Breast, pelvis, hips, thighs

Men – 3% of TBW

(Pregnancy requires >50,000 calories over normal metabolic requirements. Lactation >500-1000 Cal/day)
Reproductive performance
The overweight male

Reproductive function is satisfactory

Normal semen analysis

Libido

BMI  Testosterone

Visceral fat

Improve insulin sensitivity

Test. Treat.
How low is too low for body fat percentage in women?

How Much Body Fat Do We Need?

Critical body weight of 47 kg is required for onset of cyclical ovarian activity.

Frisch & McArthur Science 1974:185;949-51
Frisch Hum. Reprod. 1987:2;521-33
A woman must have a minimum of 13-17% of body fat for regular menstruation.

Human ovarian function is extremely vulnerable to an energy imbalance.

- Luteal phase suppression
- Follicular phase suppression
- Ovulatory failure
- Oligomenorrhea
- Amenorrhea

Ellison, Am Anthropol 1990:2;933-52
About 1 – 5% of women suffer from “weight-related amenorrhea”


Indirect mechanism

signals ➔ hypothalamus ➔ GnRH ➔ Temperature control ➔ Changes in energy metabolism
Obesity

Environmental factors

Genetic

World epidemic with ever increasing incidence
Fat distribution

Peripheral (Gynaecoid)  Abdominal (Android)
Adipose tissue is a complex and highly active metabolic and endocrine organ.

Adipose tissue contains:
- Adipocytes
- Immune cells
- Connective tissue matrix
- Nerve tissue
- Stromovascular cells

White fat tissue
- 60-85% lipid (90-99% is triglyceride).
- Heat regulation
- Body Cushioning
- Energy storage

Brown fat tissue
- Rich vascularization
- Packed mitochondria
- Metabolic heat production without muscles contraction
Adipose tissue acts as an endocrine tissue

- Androgen
- Aromatase
- Estrogen
- Estradiol
- DHEA
- Androstenediol
- 17-beta hydroxysteroid dehydrogenase
- Esteron
Adipose tissue acts as an endocrine tissue

• Metabolites estrogen to 16-hydroxylated estrogen (high estrogen activity)
• Storage steroids hormone
• Stimulate insulin secretion
• Decrease liver production of SHBG allow high free levels of androgens

Frisch, Sci Am, 1998;258:88-95
Polycystic Ovarian Syndrome

Stein and Leventhal (1934)

- Most common endocrine disorder in women of reproductive age
- Affects 5-10% of the population


- ~20% of infertile females
- Short and long-term consequences on general and reproductive health
Obesity and reproductive disturbances

- Oligo-amenorrhea
- Hyper-androgenism

Overnourishment

- Overproduction of insulin
- Ovulation disruption
Abdominal obesity – 10-50% PCOD

Stein and Leventhal (1934)

Obesity and reproductive disturbances

Incidence
38-88%

Syndrome “O”

Overnourishment

Overproduction of insulin

Ovulation disruption
Prevalence of hyperinsulinemia and insulin resistance in PCOS

- In ~ 65% of obese PCOS women
- In ~ 20% of lean PCOS women

Arrest of follicular development

Hyperinsulinemia

In PCOD patients

Suppress liver production of SHBG

Free testosterone

Enhancement of pituitary LH pulse amplitude

Obesity
LH and IGF-I effect on theca cells

Cytochrome

p-450c 17-alpha activity

Androgen secretion

Non-obese

GH↑

LH↑

Key enzyme

Obese

Insulin resistance
Hyperinsulinemia

IGFBP-I↓

IGF-I↑

SHBG↓
How do we treat Infertility in Obese PCOD patients
Weight loss

Loss of 5% of TBW

Resumed ovulation in 90%

Pregnancy in 45%

>50% pregnancy per cycle

25% miscarriage compared with 75% for the same group

Clark et al. Hum Reprod 1995;10:2705-12
Loss of 4 kg

Resumed ovulation in 90%

Pregnancy in 77.6%

Miscarriage rate - 75% before losing weigh and 18% after (p<0.01)

Fulghesu et al. J.C.E.M. 1997

Estradiol (pmol/L) vs. Days from hCG injection

- Hyperins
- Normoins

P<0.01
Diameter >12 mm and < 16 mm

Number of follicles

Days from hCG injection

P<0.01
Fasting insulin levels

No. of Amps.

R = 0.6, p < 0.003

Homburg et al. Hum Reprod 1996
R = 0.6, p < 0.004

Homburg et al. Hum Reprod 1996
Dimethylbiguanide

Multiple mechanisms of action:

- Inhibition of gluconeogenesis in the liver
- Enhanced peripheral uptake of glucose
- Increased intestinal use of glucose
- Decreased fatty acid oxidation
61 women with BMI >28

USA  Venezuela  Italy

PCOS

26 women received - Placebo
35 women received - Metformin 1500 mg/day

1  14  28  35

Prog. >25 nmol/L

P<0.001

1 ovulated
14 ovulated

Effects of metformin on ovarian function and metabolic factors in PCOS

• Randomized double-blind placebo controlled trial
• Frequent blood sampling (twice weekly)

47 women received - Placebo
13% ovulated
P<0.01

49 women received - Metformin 850 mg b.i.d.
23% ovulated

14 weeks

Fleming et al. JCEM 2002
Metformin dosing in obese women with PCOS

- **29 < BMI < 37**
  - 1000 mg/day
  - or
  - 1500 mg/day

- **BMI > 37**

  • Significant weight reductions in all groups
  • Higher dose not more effective

Harborne and Fleming ASRM 2002 O-89
Complications during pregnancy
Meta-analysis of pregnancy outcome

Early miscarriage

Boomsma et al. Hum Reprod 2006;12:673

720 patients vs. 4505 controls

<table>
<thead>
<tr>
<th>BMI</th>
<th>Spon. Abor.</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>17%</td>
<td>0.94</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>18%</td>
<td>1.0</td>
</tr>
<tr>
<td>25-29.9</td>
<td>22%</td>
<td>1.29</td>
</tr>
<tr>
<td>30-34.9</td>
<td>27%</td>
<td>1.71</td>
</tr>
<tr>
<td>&gt;35</td>
<td>31%</td>
<td>2.19</td>
</tr>
</tbody>
</table>
270 women, who were treated for infertility

Pregnancy rate - 45.2%, live birth rate – 37.8%

**Fig. 3** The effect of obesity on conception and obstetric outcome

Al-Azemi et al. Arch Gynecology 2003
Figure 6. Body weight (BMI) of recipient is important for oocyte donation (Bellver et al., 2003). * = p<.05.
Obesity to Pregnancy-related Complications – BMI >35

Preeclampsia (5 – fold increase)
Stillbirths after 28 weeks gestation (3 – fold increase)
Early neonatal death (3.5 – fold increase)
Large-for-gestational-age infants (4 – fold increase)

Cedergen MI, Obstet Gynecol 2004
A Swedish, population-based cohort study (n=805,275)
Cnattingius et al NEJM 1998
Gestational diabetes

General population – 1-3% GDM

Obese women – 17% GDM

PCOS and risk of type II diabetes

- 10-20% type II diabetes (within 10 years)

*Linne et al. BJOG 2002, 109:1227*
Delivery complications

Rate of CS planned and acute – 2 x higher

Complications

- Blood loss
- Infection
- Dehiscence
- Hernia formation
Newborn complications

During delivery

Head trauma
Shoulder dystocia
Brachial plexus lesions
Fractures of the clavicle
## Newborn complications >30 BMI

### Birth defects

<table>
<thead>
<tr>
<th>Defect</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spina bifida</td>
<td>3.5</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>3.3</td>
</tr>
<tr>
<td>Heart defects</td>
<td>2.0</td>
</tr>
<tr>
<td>Multiple anomalies</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Possible explanations – hyperglycemia, elevated insulin, elevated estrogen

# Impact of obesity on reproduction

<table>
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<tr>
<th>Condition</th>
<th>Associated risks</th>
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<tbody>
<tr>
<td>Menstruation</td>
<td><em>Menstrual dysfunction: Amenorrhea, oligomenorrhea</em></td>
</tr>
<tr>
<td>Infertility</td>
<td><em>Anovulatory infertility, poor response to ovulatory drugs</em></td>
</tr>
<tr>
<td>Miscarriage</td>
<td><em>Increase risk</em></td>
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*Rich-Edwards et al AJOG 1994*
Any effort should be invested in education and understanding the complications of high BMI before and during pregnancy.