European Society of Human Reproduction and Embryology

COURSE 3

"Developmental and therapeutic aspects of PCOS and androgen excess"

Special Interest Group Endocrinology

1 July 2007
Lyon, France

PRE-CONGRESS COURSE 3

Special Interest Group Endocrinology
"Developmental and therapeutic aspects of PCOS and androgen excess"

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PRE-CONGRESS COURSE 3 - PROGRAM

SIG Reproductive Endocrinology

"Developmental and therapeutic aspects of PCOS and androgen excess"

Course co-ordinators: N.S. Macklon (NL) and B.C. Tarlatzis (GR)

Course description: By addressing PCOS and Androgen Excess Disorders from a developmental context, a clear clinical approach to their diagnosis and management of both early and established disease is provided. In this course, a state-of–the-art update in the diagnosis and management of these important conditions is provided by leaders in the field, and a panel discussion addresses particularly controversial areas.

Target audience: Gynaecologists, Reproductive Endocrinologists and those in training.

Program

09.00 - 09.30: PCOS as a developmental disorder – ***B. Fauser (NL)***
09.30 - 09.45: Discussion

09.45 - 10.15: The origins and diagnosis of CAH – ***W. Arlt (UK)***
10.15 - 10.30: Discussion

10.30 - 11.00: Coffee break

11.00 - 11.30: The metabolic syndrome and PCOS – ***R. Norman (AUS)***
11.30 - 11.45: Discussion

11.45 - 12.15: Diagnostic approaches in PCOS and Androgen Excess – ***A. Balen (UK)***
12.15 - 12.30: Discussion

12.30 - 13.30: Lunch

13.30 - 14.00: Life style and PCOS – ***R. Norman (AUS)***
14.00 - 14.15: Discussion

14.15 - 14.45: Medical management of Hirsutism – ***A. Balen (UK)***
14.45 - 15.00: Discussion

15.00 - 15.30: Coffee break

15.30 - 16.00: Fertility treatment in PCOS – ***B. Fauser (NL)***
16.00 - 16.15: Discussion

16.15 - 16.45: Panel discussion – ***B.C. Tarlatzis (GR)***
16.45 - 17.00: Discussion

PCOS a developmental disorder

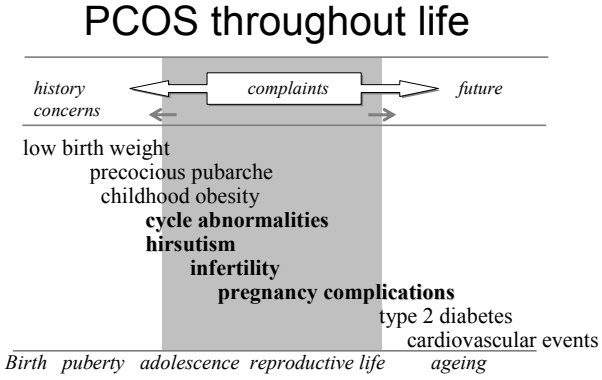
Prof. Bart CJM Fauser, M.D., Ph.D.
Department of Reproductive Medicine and Gynecology
University Medical Center
Utrecht
The Netherlands

Polycystic ovary syndrome is a complex genetic condition, suggesting that multiple genes are involved and that the full syndrome is expressed only when certain environmental factors are present. Historically the major focus of interest has been characteristic ovarian abnormalities and menstrual cycle distrubances. Moreover, these women frequently present with obesity, insulin resistance and other signs of metabolic disease. These women represent around 10% of the female population.

In a gynaecology practice, the great majority of these women present with anovulatory infertility. Patients may also been seen by either a general practicioner or a gynecologist due to complaints of hirsutism or cycle abnormalities. For hirsutism women may also visit a dermatologist, and at a young age these (obese) children may be referred to a pediatrician. At a later age, screening for emerging type 2 diabetes or the metabolic syndrome may occur at the internal medicine department. Hence, from an exclusive gynaecological condition, PCOS should now be considered at truly multi-disciplinary condition. Of course, preferred diagnostic interventions are dependent on age of the women and her complaint.

A recent meta-analysis has shown that pregnancy, delivery and off-spring is compromised in PCOS, even in case a singleton pregnancy is achieved. Both gestational diabetes and pregnancy induced hypertension is increased and birth weight of children is reduced. Presumably women presenting with pregnancy complications are more likely to suffer from complications herself after pregnancy. Moreover, limited follow-up studies suggested that female offspring more often presents with childhood obesity, early insulin resistance, cycle abnormalities and reduced fertility (i.e. the Barker hypothesis).

Many question remain, but future health of these PCOS children seems compromised. Much more reserach is needed to reliably assess future health risk for PCOS women, and hopefully identify individual risk factors and (lifestyle) strategies to prevent complications.



The metabolic syndrome and PCOS

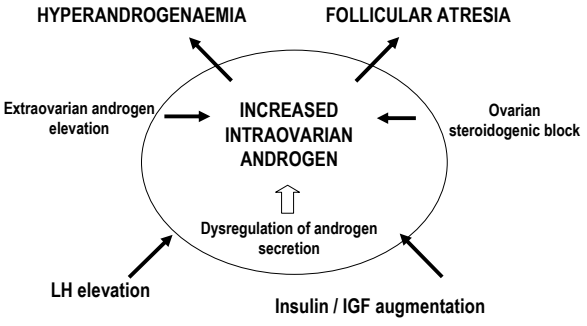
Robert Norman

Research Centre for Reproductive Health, University of Adelaide, The Queen Elizabeth Hospital , WCH and Repromed, South Australia

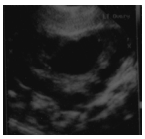
Learning objectives

- To understand the metabolic background of PCOS
- To understand current definitions of the metabolic syndrome
- To appreciate the variation in metabolic syndrome in PCOS
- To understand the relationship between adipose tissue and reproduction and insulin resistance
- To discuss options for prevention and treatment

Cardinal feature – ovarian hyperandrogenism



PCOS – a problem of perspective



Testosterone
LH:FSH ratio
Anovulation
Insulin resistance

Different diagnostic perspectives

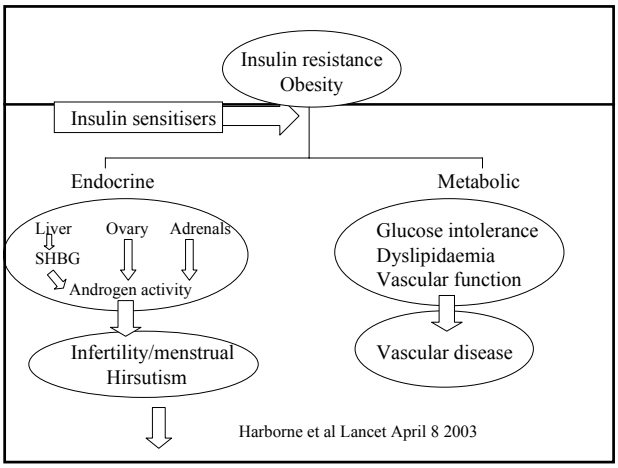
	Endocrinologist	Gynaecologist	
Menstrual problems	70% ⇧	47%	**<0.001**
Androgenisation	81% ⇧	59%	**<0.001**
Obesity	11%	8%	**NS**
PCO ultrasound	14%	61% ⇧	**<0.001**
Increased LH:FSH	24%	47% ⇧	**<0.001**
Insulin resistance	6%	11%	**NS**

Cussons et al 2004 (350 gynaecologists, 350 endocrinologists)

Different perspectives on investigations

	Endocrinologist	Gynaecologist	
LH,FSH	91%	94%	**NS**
Estradiol	64%	56%	**NS**
Testosterone	99%	92%	**NS**
17OHP	70% ⇧	46%	**<0.001**
DHEAS	80% ⇧	58%	**<0.001**
Glucose	89% ⇧	79%	**0.02**
Lipids	67% ⇧	34%	**<0.001**
Ovarian ultrasound	44%	91% ⇧	**<0.001**

Cussons et al 2004



Definition of metabolic syndrome

- ATPIII definition
- WHO definition
- IDDF definition
- Others

Why does metabolic syndrome matter?

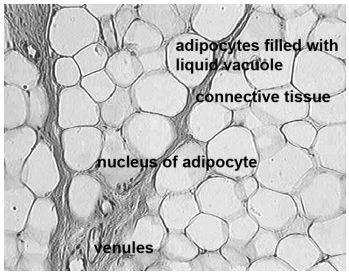
- Patient information
- Lifestyle change encouraged
- Potential long-term consequences
- Appropriate monitoring
- Appropriate therapy

Prevalence of metabolic syndrome

- Differences between countries and ethnicities
- Differences on weight
- Differences in different types of PCOS

Structure of Fat

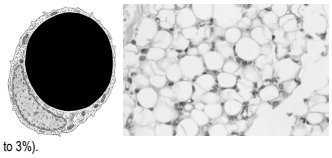
- Adipocytes
- Connective tissue matrix
- Nerve tissue
- Stromovascular cells
- Immune cells



Adipose tissue types

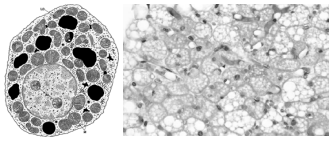
White adipose tissue (WAT)

- 60 to 85% lipid (90-99% being triglyceride)
- Small amounts of free fatty acids, diglyceride, cholesterol, phospholipid
- Minute quantities of cholesterol ester and monoglyceride
- The remaining is water (5 to 30%) and protein (2 to 3%).



Brown adipose tissue (BAT)

- Derives its colour from rich vascularization and densely packed mitochondria
- Polygonal in shape, have a considerable volume of cytoplasm and contain multiple lipid droplets of varying size. Their nuclei are round and almost centrally located.



Adipose tissue functions

White

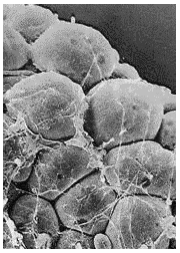
- Three functions:
  - Heat insulation,
  - Mechanical cushion
  - Energy source
- The average woman with 20% body fat has about one month of energy stored as fat

Brown

- Most prominent in newborn animals. In human infants it comprises up to 5% of body weight, then diminishes with age to virtually disappear by adulthood.
- Site of non-shivering thermogenesis (metabolic heat produced without the rapid contraction of muscles known as shivering).

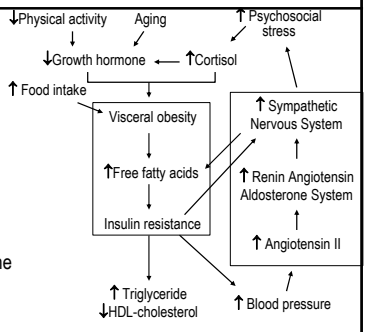
Function of Fat

- Storage of energy (triglycerides)
- Release of energy
- Insulation
- Secretion of hormones
- Metabolic regulation
- Other

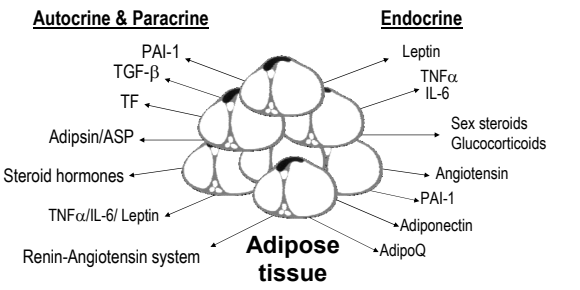


Fat metabolism

- Depends on energy requirements
- Regulated by nutrient, neural and hormonal signals
- Responds to insulin, adrenaline, growth hormone (GH), glucocorticoids



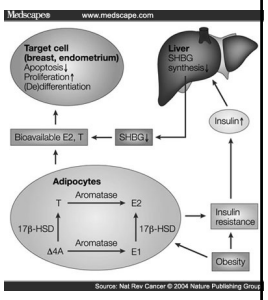
Hormones and other products



(Ahima and Flier, TEM 2000)

Enzymes in sex steroid metabolism

- Steroid hormone prereceptor metabolism
  - C P450 – dependent aromatase
  - 3 βHSD, 3 αHSD
  - 11 βHSD1, 17 βHSD
  - 7 αhydroxylase
  - 17 αhydroxylase
  - 5 α reductase
- 100% oestrogen/ 50% testosterone in postmenopausal women
- C P450 aromatase and 17 βHSD highly expressed in adipose stromal cells and preadipocytes
- 17 βHSD : aromatase ↓ sc but ↑ visceral
- Aromatase knockout ↑ visceral fat, insulin resistance, ↑ lipids, hepatic

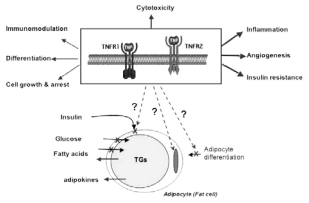


Tumour necrosis factor (TNF)

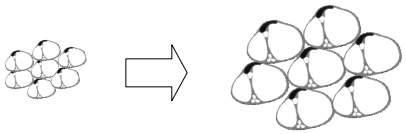
- 26 kDa transmembrane protein, cleaved to 17 kDa biologically active protein
- Type 1 and 2 TNFα receptors
- Adipose tissue adipocytes and stromovascular cells
- Associated insulin resistance
  - Infusion
  - TNF receptors
  - TNF α knockout

TNFα and reproduction

- Leads to insulin resistance
- Increased insulin effect on ovary (?PCOS)
- Differences between mice and humans



TNFα and obesity



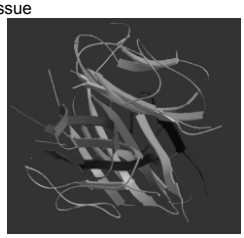
↑TNFα

↓ Food intake
↑ Energy expenditure
↑ Lipolysis ↓ Lipogenesis
↓ Insulin sensitivity
↓ GLUT4 LPL

-Obesity
- Insulin resistance
- Hypertension
- Hyperlipidemia

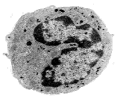
Adiponectin

- Specifically produced by adipocytes as a 30 kDa glycoprotein
- Higher in SC than visceral adipose tissue
- Adipo R-1 mainly in muscle and adipo R-2 mainly in liver
- Inverse association with insulin resistance and inflammatory states
- Increases with weight reduction and insulin-sensitising drugs
- Knockout and transgenic mouse models



Adiponectin and the immune system

ADIPONECTIN

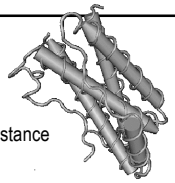


MONOCYTE
- Reduced TNF α and IL-6 production
- Increases IL-10 and IL-1 receptor antagonist

ENDOTHELIUM
Downregulation of adhesion molecules ICAM and VCAM by TNFα and resistin

(Fantuzzi, J Allergy Clin Immunol 2005)

Other proimflammatory cytokines



- IL-6
  - 22-27 kDa protein
  - Associated with obesity and insulin resistance
  - levels decrease with weight loss
  - ? IL6 CNS deficiency in obesity

Do circulating levels of proinflammatory cytokines alter reproductive function?

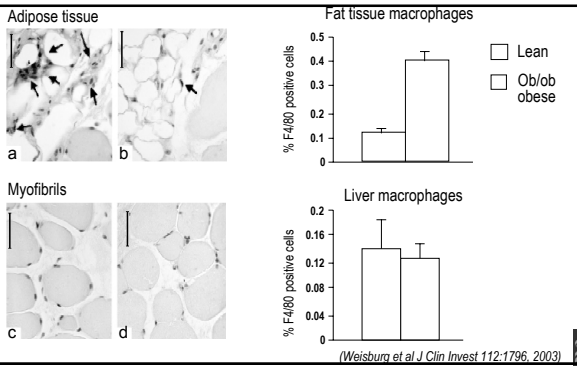
Other secretions

- **PAI-1**
  - Elevated in obesity and insulin resistance
  - Reduce with T2D's
  - TNFα increases PAI-1
- **Adipsin**
  - Required for enzyme production ASP which affects lipids and glucose
  - Promotes fatty acid uptake
- **Renin-Angiotensin system**
  - Renin, angiotensinogen, angiotensin I and II etc.
  - Correlated with obesity
- **Coagulation and complement**

Obesity and inflammation

- Circulating proinflammatory molecules eg cytokines, PAI-1
- White fat has 10% of stromovascular cells as CD14+ CD31+ macrophages
- Increased with adiposity in females
- Derived from bone marrow
- Migrate under the influence of leptin, MCP-1, adipocyte-conditioned medium

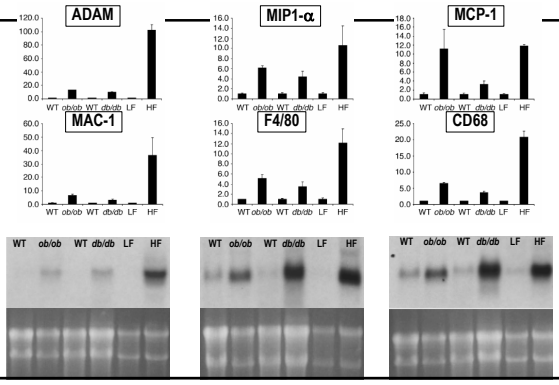
Macrophages in lean and obese mice



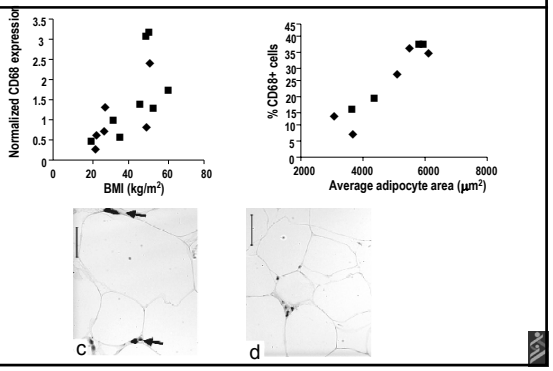
(Weisburg et al J Clin Invest 112:1796, 2003)

Inflammatory genes in obesity

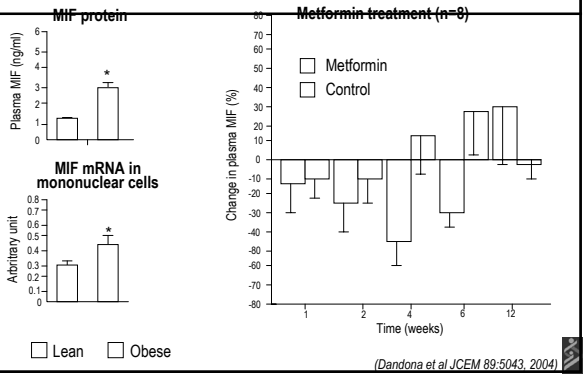
(Xu et al J Clin Invest 112:1821, 2003)



Increased macrophages in human fat



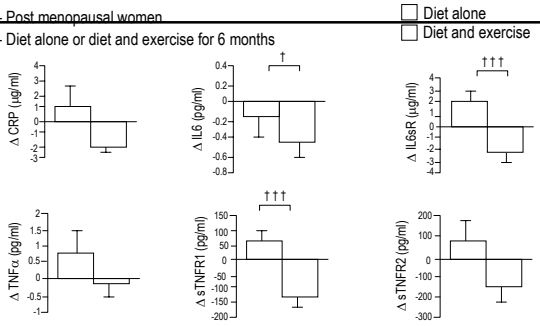
MIF protein and mRNA in human obesity



(Dandona et al JCEM 89:5043, 2004)

Diet and exercise in obesity

- Post menopausal women
- Diet alone or diet and exercise for 6 months

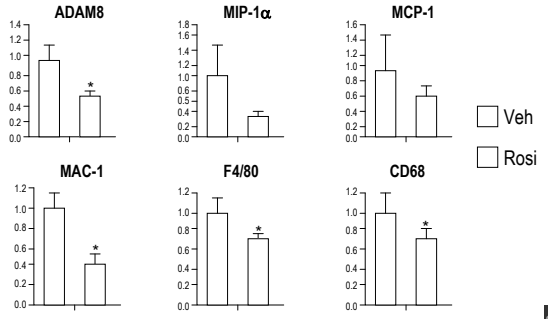


Diet and exercise but *not* diet alone reduced inflammatory cytokines

(You et al JCEM 89:1739, 2004)

PPARG reduces inflammation in obesity

- 12 week old C57B *ob/ob* mice treated with rosiglitazone 12mg/kg for 28 days



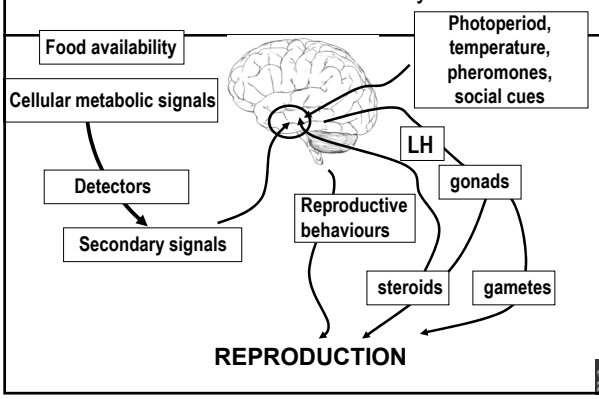
(Xu et al J Clin Invest 112:1821, 2003)

Adipose tissue and inflammation relationships

- **Cells**
  - Macrophages are a normal component of adipose tissue
  - Obesity is associated with increased numbers of macrophages in adipose tissue
  - Obesity is associated with the presence of activated macrophages in adipose tissue
  - There is cross-talk between adipocytes and lymphocytes in lymph nodes
- Molecules
  - Adipocytes produce many factors modulating immunity and inflammation
  - Leptin exerts mostly pro-inflammatory and immune-potentiating effects
  - Adiponectin exerts mostly anti-inflammatory effects
- Diseases
  - Low adiponectin levels in type II diabetes are a possible link to insulin resistance
  - Obesity seems to be associated with asthma, but the mechanism is unknown
  - Several conditions are associated with altered adipokine levels, but the significance of this observation is unclear

(Fantuzzi, J Allergy Clin Immunol 2005)

Areas of nutritional infertility



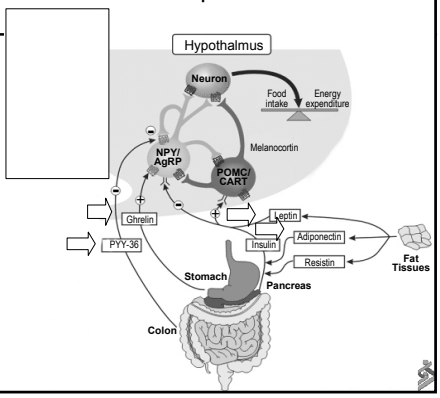
Gut –brain interactions and reproduction

PYY
Produced by intestine.
Action:
-Inhibits appetite
-Alters GNRH action

Leptin
-Produced by fat cells
Action
-Inhibits appetite

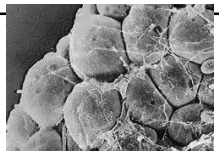
Adiponectin
Produced by adipose tissue.
Action: Decreases insulin resistance

Ghrelin
Produced by the stomach. Conveys information to the hypothalamus
Action: Stimulates appetite, enhances use of carbohydrates and reduces fat utilisation, increases gastric motility and acid secretion and reduces locomotor activity



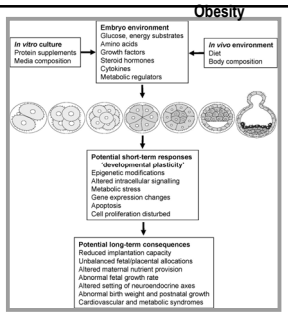
Fat signals for reproduction - leptin

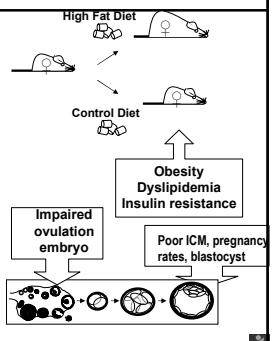
- Produced by fat
- Leptin ↓ with starvation
  Leptin ↓ with obesity
- Obesity in humans linked to leptin resistance to endogenous and exogenous hormone



Over nutrition effects on poor outcomes

Overnutrition
Obesity

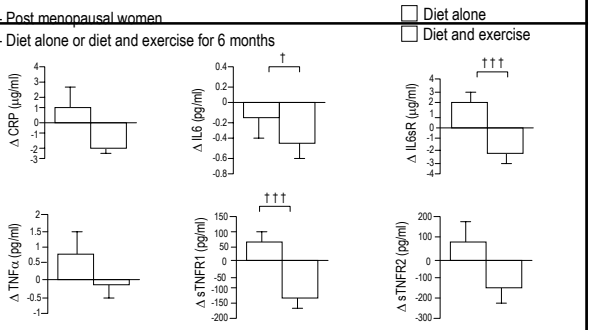




Fleming et al Biol Reprod 71, 1046–1054 (2004)

Diet and exercise in obesity

- Post menopausal women
- Diet alone or diet and exercise for 6 months



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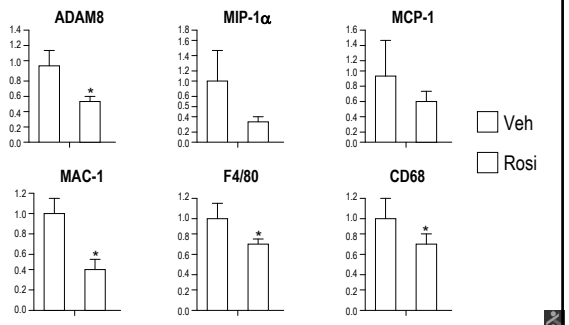

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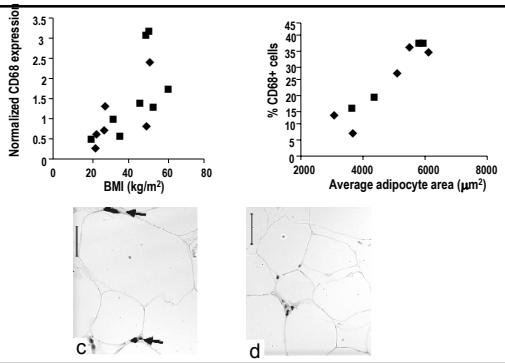


Rotterdam criteria and metabolic syndrome

- University of Iowa reproductive endocrine clinic
- 258 patients and ATPIII criteria
- All features (58%) 37%
- Hyperandrogenaemia and oligomenorrhoea (14%) 40%
- Hyperandrogenism and PCO (14%) 42%
- Oligomenorrhoea and PCO (13%) 20%
- Controls 8%

Shroff et al Fert Steril 2007

Iowa study

- BMI and BP less in oligomenorrhoea and PCO
- Glucose and insulin resistance the same
- Lipids the same between groups

Asian women in Thailand with IDF criteria

- 175 patients with PCOS in Thailand
- Prevalence 35% using IDF criteria

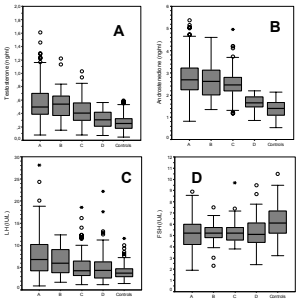
Gynaecological Endocrinol 23:153, 2007

What is the effect of androgens?

- 309 European women with PCO morphology
- 191 had oligomenorrhoea and hyperandrogenism (PHO)
- 76 had raised androgens and normal periods (PH)
- 42 had oligomenorrhoea and normal androgens (PO)
- 76 controls

- Insulin sensitivity: PO=C, PO<PHO
- Metabolic syndrome PO=C, PO<PHO
- LH levels PO>C, PHO>C

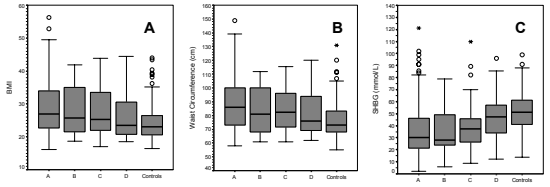
Rotterdam and endocrine differences



	Hyperandrogenism	Oligo-anovulation	PCO
A 61%	YES	YES	YES
B 7%	YES	YES	NO
C 16%	YES	NO	YES
D 17%	NO	YES	YES

Dewailly et al unpublished

Rotterdam and endocrine differences



Dewailly et al unpublished

Options for treatment

- Prevention
- Early diagnosis
- Lifestyle changes
- Metformin

Diagnostic approaches in Polycystic Ovary Syndrome and Androgen Excess

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Learning Objectives

1. Define the polycystic ovary syndrome (PCOS)
2. List the investigations required to diagnose PCOS
3. Define hyperandrogenism
4. Define menstrual cycle disturbances
5. Define the morphological characteristics of a polycystic ovary

Introduction

The polycystic ovary syndrome (PCOS) is a heterogeneous collection of signs and symptoms that gathered together form a spectrum of a disorder with a mild presentation in some, whilst in others a severe disturbance of reproductive, endocrine and metabolic function. Key features include menstrual cycle disturbance, hyperandrogenism and obesity. There are many extra-ovarian aspects to the pathophysiology of PCOS, yet ovarian dysfunction is central. At a recent joint ASRM/ESHRE consensus meeting a refined definition of the PCOS was agreed: namely the presence of two out of the following three criteria: 1) Oligo- and/or anovulation; 2) Hyperandrogenism (clinical and/or biochemical); 3) Polycystic ovaries, with the exclusion of other aetiologies (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004). The morphology of the polycystic ovary, has been redefined as an ovary with 12 or more follicles measuring 2-9 mm in diameter and/or increased ovarian volume (>10 cm^3) (Balen *et al,* 2003).

There is considerable heterogeneity of symptoms and signs amongst women with PCOS and for an individual these may change over time (Balen et al, 1995). Polycystic ovaries can exist without clinical signs of the syndrome, which may then become expressed over time. A gain in weight is associated with a worsening of symptoms whilst weight loss may ameliorate the endocrine and metabolic profile and symptomatology. Elevated serum concentrations of insulin are more common in both lean and obese women with PCOS than weight-matched controls.

What is polycystic ovary syndrome?

Despite the recent ESHRE/ASRM consensus meeting, controversy still existed over a precise definition of the "syndrome" and whether or not the diagnosis should require confirmation of polycystic ovarian morphology. The generally accepted view is that a spectrum exists, ranging from women with polycystic ovarian morphology and no overt abnormality at one end, to those with polycystic ovaries associated with severe clinical and biochemical disorders at the other end. Using a combination of clinical, ultrasonographic, and biochemical criteria, the diagnosis of PCOS is usually reserved

for those women who exhibit an ultrasound picture of polycystic ovaries, and who display one or more of the clinical symptoms (menstrual cycle disturbances, hyperandrogenism), and/or one or more of the recognized biochemical disturbances (elevated LH, testosterone, androstenedione, or insulin).

Hyperandrogenism

Hyperandrogenism may be determined by clinical or biochemical parameters. The clinical manifestations of androgen excess being hirsutism, alopecia and acne. The presence of hirsutism is the key feature but this is a relatively subjective diagnosis and few physicians in clinical practice actually use standardized scoring methods. Furthermore, there are significant racial differences, with hirsutism may being significantly less prevalent in hyperandrogenic women of Eastern Asian origin, or in adolescence, whilst being more prevalent in women from Southern Asia (that is the Indian subcontinent) (Wijeyeratne *et al,* 2002).

The presence of acne after adolescence is thought also to be a relatively good indicator of hyperandrogenism, although studies are somewhat conflicting regarding the exact prevalence of androgen excess in these patients. Most patients with PCOS have evidence of biochemical hyperandrogenemia, and circulating androgen levels may also represent an inherited marker for androgen excess. However, it has been shown that some patients with PCOS may not demonstrate an overt abnormality in circulating androgens (Balen *et al*., 1995; Laven *et al*., 2002).

Testosterone is bound both to sex hormone binding globulin (SHBG) and albumin. The measurement of total testosterone is probably all that is required in order to exclude the presence of an androgen secreting tumour. In other words the value of measuring testosterone is primarily to help to exclude other causes of androgen excess. The measurement of free testosterone (T) or the free T (free androgen) index (FAI) may also be used for assessing for hyperandrogenemia (Imani *et al*., 2000). Methods for the assessment of free T include equilibrium dialysis, calculation of free T from the measurement of sex hormone binding globulin and total T, or ammonium sulfate precipitation.

A few patients with PCOS may have isolated elevations in dihydroepiandrosteronesulphate (DHEAS). Furthermore androstenedione may be more elevated in patients with 21-hydroxylase deficient non-classic adrenal hyperplasia than PCOS (Laven *et al*., 2002), although the paucity of normative and clinical data with DHEAS and androstenedione preclude their routine measurement.

Ultrasound definitions of the polycystic ovary

Polycystic ovaries are commonly detected by ultrasound or other forms of pelvic imaging, with estimates of the prevalence in the general population being in the order of 20% - 33% (Polson et al 1988, Michelmore et al 1999). However, not all women with polycystic ovaries demonstrate the clinical and biochemical features which define the polycystic ovary syndrome (PCOS). While it is now clear that ultrasound provides an excellent technique for the detection of polycystic ovarian morphology,

identification of polycystic ovaries by ultrasound does not automatically confer a diagnosis of PCOS.

The transabdominal ultrasound criteria of Adams *et al* (1986) defined a polycystic ovary as one which contains, in one plane, at least 10 follicles (usually between 2 and 8 mm in diameter) arranged peripherally around a dense core of ovarian stroma or scattered throughout an increased amount of stroma. When scattered through the stroma it was suggested that the cysts were usually 2-4 mm in diameter (Adams *et al,* 1985).

The multicystic ovary is one in which there are multiple ($\geq$ 6) cysts, usually 4 – 10 mm in diameter with normal stromal echogenicity (Adams *et al,* 1985). This is the characteristic appearance during puberty and in women recovering from hypothalamic amenorrhoea – both situations being associated with follicular growth without consistent recruitment of a dominant follicle. There may be confusion amongst inexperienced ultrasonographers, radiologists and gynaecologists, hence the need for careful consideration of the clinical picture and endocrinology. Polycystic ovaries are evident in adolescent girls as a distinct entity from multi-cystic ovaries. Indeed it appears that PCOS manifests for the first time during the adolescent years, which are critical for future ovarian and metabolic function (Balen & Dunger 1996).

Jonard *et al,* (2003) studied 214 women with PCOS (oligo-/amenorrhoea, elevated serum LH and/or testosterone, and/or ovarian area > 5.5 cm^2) and 112 with normal ovaries to determine the importance of follicle number per ovary (FNPO). A 7MHz transvaginal ultrasound scan was performed and three different categories of follicle size analysed separately (2-5, 6-9 and 2-9 mm). The mean FNPO was similar between normal and polycystic ovaries in the 6-9 mm range but significantly higher in the polycystic ovaries in both the 2-5 and 2-9 mm ranges (Jonard *et al,* 2003). Within the 2-5 mm range there were significant positive correlations with serum testosterone, androstenedione and LH concentrations. There was an inverse correlation within the 6-9 mm range between FNPO and testosterone, body mass index (BMI) and fasting insulin concentrations and a positive correlation with inhibin B concentrations. The mean FNPO in the 2-5 mm range was significantly greater in the polycystic ovaries than the controls, whilst it was similar in the 6-9 mm range. A FNPO of $\geq$ 12 follicles 2-9 mm gave the best threshold for the diagnosis of PCOS (sensitivity 75%, specificity 99%) (Jonard *et al,* 2003). The authors suggest that intra-ovarian hyperandrogenism promotes excessive early follicular growth up to 2-5 mm, with more follicles able to enter the growing cohort which then become arrested at the 6-9 mm size. A new definition of the polycystic ovary is proposed: increased ovarian area (> 5.5 cm^2) or volume (> 11 cm^3) and/or the presence of $\geq$ 12 follicles of 2-9 mm diameter (as a mean of both ovaries) (Jonard *et al,* 2003).

The increased echodensity of the polycystic ovary is a key histological feature (Hughesdon 1982) but is a subjective assessment that may vary depending upon the setting of the ultrasound machine and the patient's body habitus. Normal stromal echogenicity is said to be less than that of the myometrium, which is a simple guide that will take into account the setting of the ultrasound machine. Stromal echogenicity has been described in a semi-quantative manner with a score for normal (=1), moderately increased (=2) or frankly increased (=3) (Pache *et al,* 1991). Dewailly *et al,* (1994) designed a computer assisted method for standardizing the assessment of

stromal hypertrophy. Patients with hyperandrogenism, of whom 68% had menstrual cycle disturbances were compared with a control group and a group with hypothalamic amenorrhoea. There was no correlation between LH and androstenedione (A) concentrations. Stromal area, however, correlated significantly with A and 17OHP, but not testosterone, LH or insulin concentrations; cyst area did not correlate with endocrine parameters (Dewailly *et al,* 1994). Thus it was suggested that the analysis of ovarian stromal area is better than quantification of the cysts in polycystic ovaries.

In summary, the morphology of the polycystic ovary, has been redefined as an ovary with 12 or more follicles measuring 2-9 mm in diameter and/or increased ovarian volume (>10 cm^3) (Balen *et al,* 2003).

Exclusion of Related Disorders

In order to establish the diagnosis of PCOS it is important to exclude other disorders with a similar clinical presentation, such as congenital adrenal hyperplasia, Cushing's syndrome and androgen secreting tumors. The measurement of total testosterone is usually sufficient in most populations. In some populations, however, 21-hydroxylase deficient non-classic adrenal hyperplasia (NCAH) is more prevalent than in others and this can be excluded by measuring a basal morning 17-hydroxyprogesterone level, with cut-off values ranging between 2 and 3 ng/ml.

If the patient presents with oligo/anovulation it is necessary to measure serum follicle-stimulating hormone (FSH), luteinising hormone (LH) and estradiol (E_2) levels in order to exclude hypogonadotropic hypogonadism (low FSH, LH and E2) or premature ovarian failure (high FSH, LH and low E2). PCOS is part of the spectrum of normogonadotropic normo-estrogenic anovulation (WHO 2). A measurement of prolactin should also be performed to exclude hyperprolactinemia, although women with PCOS as a sole diagnosis may sometimes have moderately elevated serum prolactin concentrations (Balen *et al,* 1995).

Conclusion

The polycystic ovary syndrome is a true syndrome with varied manifestations in different populations and between different populations. With recent increase in understanding of the pathophysiology of PCOS and the recognition of the importance of ultrasound in defining the morphology of the polycystic ovary the syndrome has now been defined as the presence of two out of the following three criteria: 1) Oligo- and/or anovulation; 2) Hyperandrogenism (clinical and/or biochemical); 3) Polycystic ovaries, with the exclusion of other aetiologies.

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Lifestyle and PCOS

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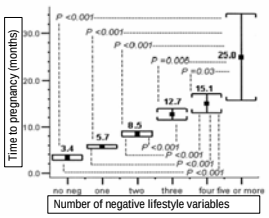
Outline of the talk

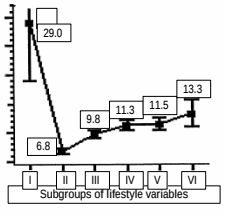
- What is the evidence base for lifestyle aspects having a bad effect on fertility and health?
- What is the evidence for lifestyle intervention being effective?
- How do we deliver lifestyle changes to our patients?

Evidence –based knowledge of harm ⇨ Evidence- based knowledge of intervention success ⇨ Health care delivery of lifestyle intervention

Negative lifestyle and fertility

(Hassan and Killick Fertility and Sterility 81:384, 2004)





Negative factors include:

1. Women's smoking >15 cigarettes/day
2. Men's smoking >15 cigarettes/day
3. Men's alcohol >20 units/week
4. Women's coffee/tea intake>7 cups/day
5. Women's weight >70 kg
6. Social deprivation score >60
7. Women's age >35 years, and/or partners' age >45 years at the time of discontinuing contraception

Women's BMI in kg/m2 were:

(I) 19 (IV) 30–34
(II) 19–24 (V) 35–39
(III) 25–29 (VI) 39

Obesity and reproduction – bad synergies

Prior to pregnancy

Increases length of time to pregnancy, menstrual disorders, miscarriage and may require more drugs

During pregnancy

Increases gestational diabetes, congenital abnormalities, high blood pressure, instrumental and operative delivery, fetal and neonatal death

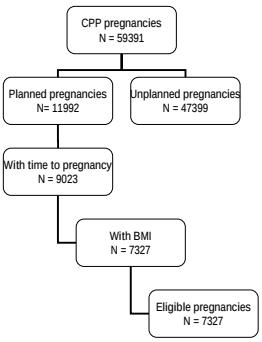
After pregnancy

Increases diabetes mellitus, high blood pressure, endometrial cancer, cardiovascular disease, musculoskeletal problems

Obesity and infertility

- Abundant evidence for infertility in overweight women on natural cycles regardless of menstrual regularity
  - *Green et al 1988, Zaadstra et al 1993, Rich-Edwards et al 1994, Lake et al 1997, Bolumar et al 2000, Hassan and Killick 2004, Gessink Law et al 2007*
- Evidence for reduced success of ovulation induction and ART in overweight women
  - Wang et al 2000, Bellver et al 2003, Legro et al 2007
- Evidence for increased success in reproductive outcomes in overweight women with lifestyle intervention
  - *Groups in UK (Franks), Italy (Pasquali), Australia (Norman), USA (Hoeger, Legro)*

Collaborative Perinatal Project (1959-1965)



- After adjusting for age, chances of fecundability were different for BMI
  - Underweight 0.94 (0.86-1.03)
  - Normal weight 1.0
  - Overweight 0.84 (0.77-0.92)
  - Obese 0.72 (0.63-0.83)
- Chance of conceiving per cycle reduced 8% overweight and 18% in overweight woman
- Takes 3 months longer to become pregnant in overweight and 9 months longer in obese women for 75% to become pregnant

Gesink Law et al Hum Reprod 2007

Pre-pregnancy weight - risk of adverse outcomes

BMI		Nullipara	Multipara
			OR
<20	**Lean**	**1.0**	**1.0**
20-24.9	**Normal**	**2.2 (1.2-4.1)**	**0.9 (0.6-1.3)**
25-29.9	**Overweight**	**3.2 (1.6-6.2)**	**1.1 (0.7-1.8)**
30-	**Obese**	**4.3 (2.0-9.3)**	**2.0 (1.1-2.3)**

167750 Swedish women pre-pregnancy 1992-3 followed through pregnancy

Cnattingius et al N Engl J Med. 1998 338:147-52.

Pre-pregnancy obesity complications/fetal death

	OR
Gestational diabetes	3.60 (3.2-3.9)
Genital tract infection	1.30 (1.07-1.56)
Wound infection	2.24 (1.91-2.64)
Urinary tract infection	1.39 (1.18-1.63)
Pyrexia	1.29 (1.13-1.48)
Pre-eclampsia	2.14 (1.8-2.5)
Induction of labour	1.70 (1.64-1.76)
Emergency LSCS	1.83 (1.74-1.93)
Elective LSCS	1.72 (1.62-1.83)
PPH	1.39 (1.32-1.46)
Major PPH	1.44 (1.30-1.60)

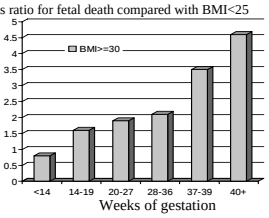
Sebire et al Int J Obesity 2001 25:1175-1182

287213 English women pre-pregnancy followed through pregnancy

Pre-pregnancy obesity complications/fetal death

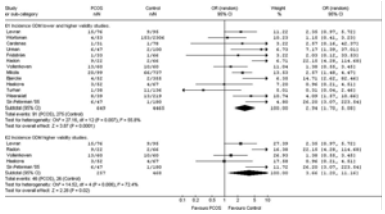
Nohr et al Obstet Gynecol. 2005 106:250-9.

Adjusted hazards ratio for fetal death compared with BMI<25

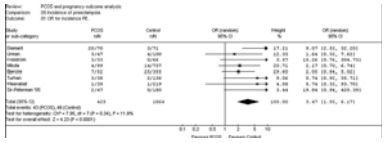


54405 Danish women pre-pregnancy followed through pregnancy

PCOS pregnancies – diabetes and pre-eclampsia



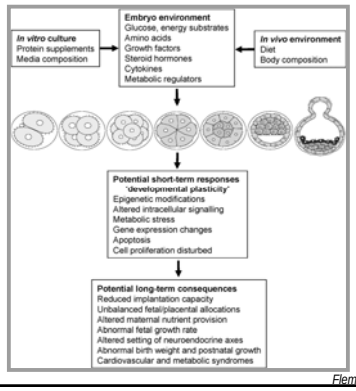
Gestational diabetes



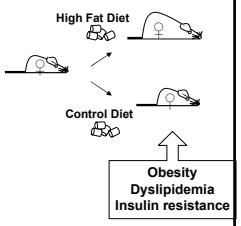
Pregnancy induced hypertension

Boomsma et al Human Reproduction Update, Vol.12, No.6 pp. 673–683, 2006

Over nutrition effects on poor outcomes



Overnutrition
Obesity

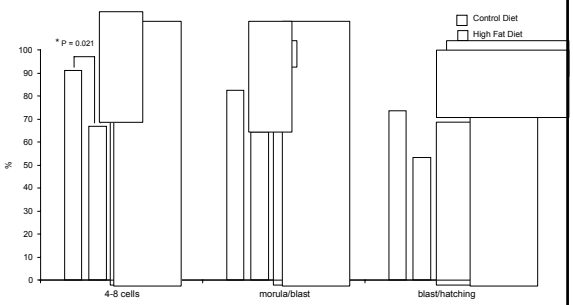


Obesity
Dyslipidemia
Insulin resistance

Fleming et al Biol Reprod 71, 1046–1054 (2004)

On-time blastocyst development

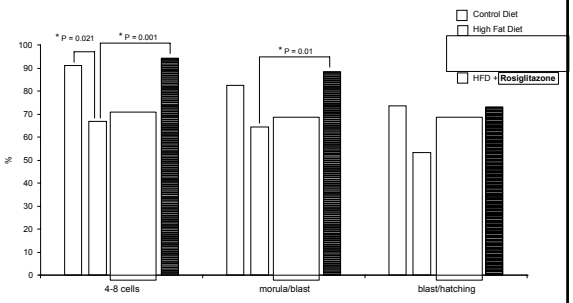
Percent fertilized mouse oocytes to reach developmental targets on-time



Minge, Lane, Norman and Robker 2006

On-time blastocyst development

Percent fertilized oocytes to reach developmental targets on-time



Minge, Lane, Norman and Robker 2006

IVF and obesity 2004-2006

IVF cycles
N = 1545

Women undergoing first cycle IVF
N = 940

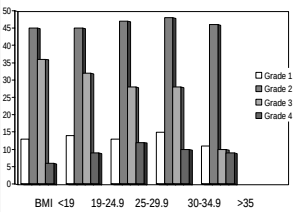
Women undergoing egg recovery
N = 932

Women having embryo transfer
N = 820

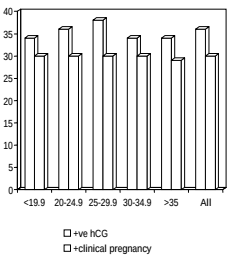
Standard IVF cycles with downregulation by GnRH agonists, recombinant FSH, hCG and luteal support

Embryo quality and pregnancy – IVF 2004-6

Embryo grading – not different



Pregnancy rates – not different



Other lifestyle issues in PCOS

- Smoking
- Stress
- Medication
- Diet and exercise
- Sexual activity

Homan et al Human Reproduction Update 2007

Conclusion 1

- Question: What is the evidence base for lifestyle aspects having a bad effect on fertility and health?
- Answer: Many lifestyle factors impact on fertility and health

Evidence –based knowledge of harm ⇨

Weight disorders

Smoking

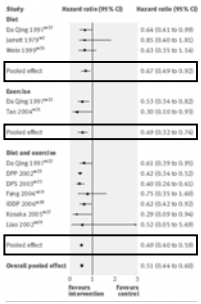
Stress

Other

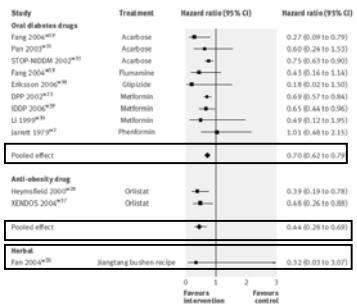
Lifestyle changes - fertility and reproductive health

Prevention of diabetes mellitus meta-analysis

Diet/exercise



Drugs



Lifestyle modification works in reproduction

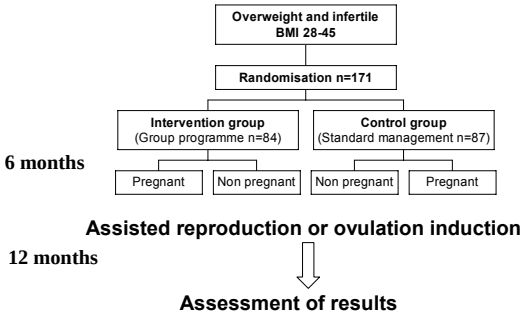
- Small amount of weight loss restores menstrual periods *(Clark et al 1994)*
- Weight loss improves ART outcomes *(Clark et al 1998)*
- Weight loss improves metabolic outcomes *(Huber-Buccholz et al)*
- Weight loss in groups is better than individually
- Confirmed in several centres around the world

A successful approach to lifestyle modification

Fertility Fitness for Women

Difficult to sustain over more than 15 years

Randomised trial of lifestyle intervention and fertility



Results of RCT

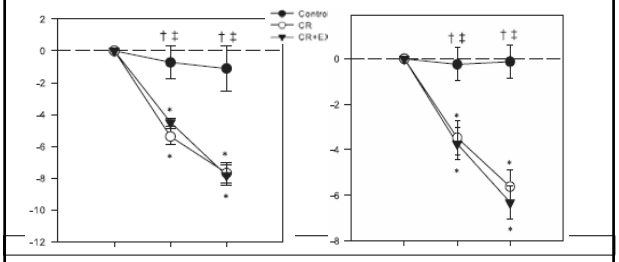
	Control n =87	Intervention n = 84
Weight loss (kg)	1.3 (0.2)	4.7 (0.3) *
Pregnancies at 18months	18 (21.4%)	53 (61%) *
Miscarriage	3 (16.6%)	6 (11.3%)
ART pregnancies	9%	37% *
Spontaneous pregnancies	11%	24% *

* $p<0.001$

Exercise and PCOS

- Vigorito et al (JCEM 2007) randomised 90 PCOS subjects to exercise or no exercise
  - *Exercise increased peak oxygen consumption and maximal workload*
  - *Exercise reduced weight, CRP and insulin resistance*
- Redman et al (JCEM 2007) studied women with calorie restriction of 25% (CR), control or CR (12.5%) and exercise (EX) *12.5% increase calorie use for 3 months*

Exercise can substitute for diet

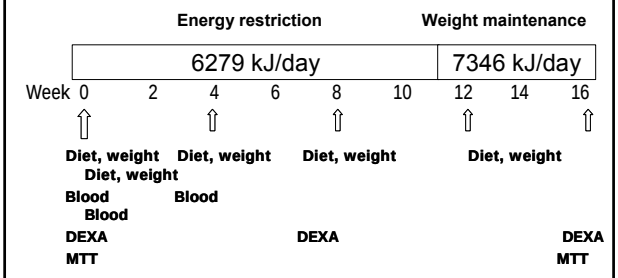


Weight over 3 months

Fat free mass over 3 months

Redman et al JCEM 2007

Carbohydrate vs protein isocaloric diets



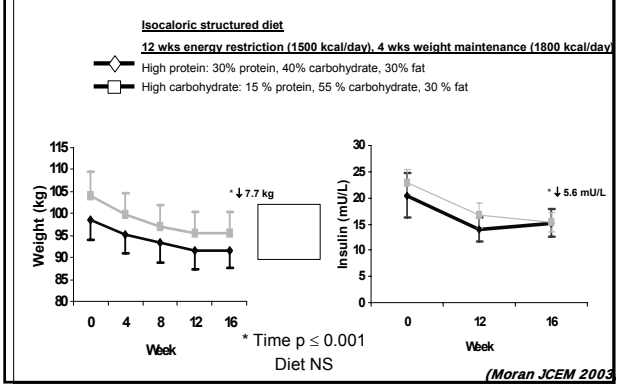
Blood: Fasting venous leptin, insulin, glucose, ghrelin, HOMA assessment of insulin resistance

DEXA: Body composition

MTT: Meal tolerance test

Moran et al JCEM 2003

High protein and high carbohydrate diets equally effective

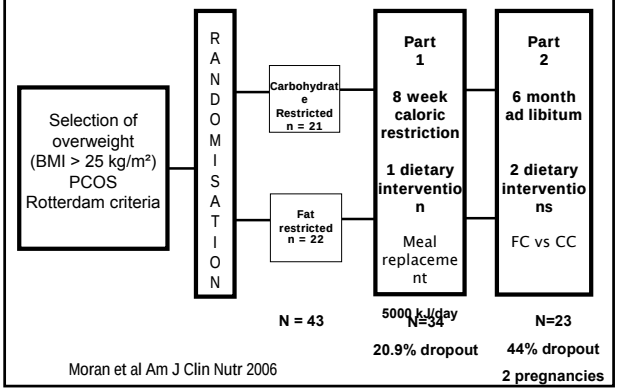


* Time $p \leq 0.001$

Diet NS

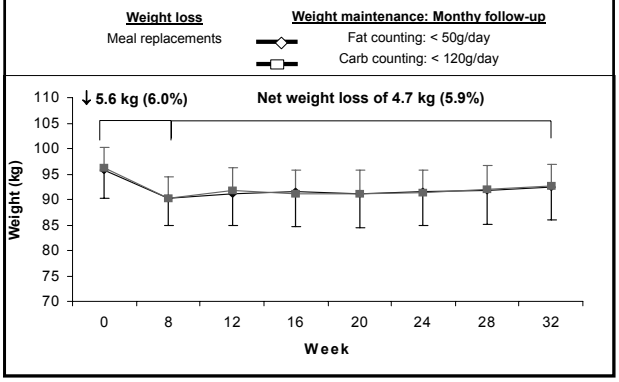
(Moran JCEM 2003

Study design – 6 month dietary intervention

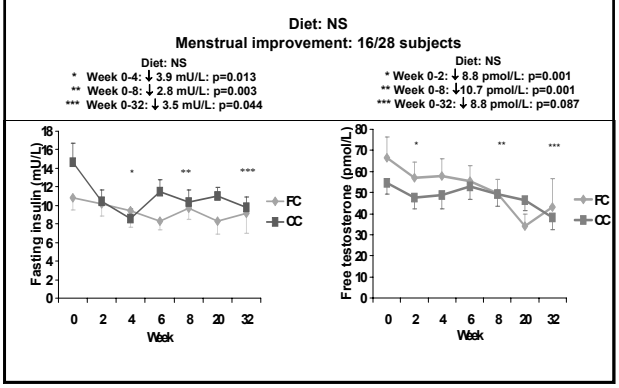


Moran et al Am J Clin Nutr 2006

Results: Weight loss – 6 month dietary intervention



Insulin and free testosterone – 6 month dietary intervention

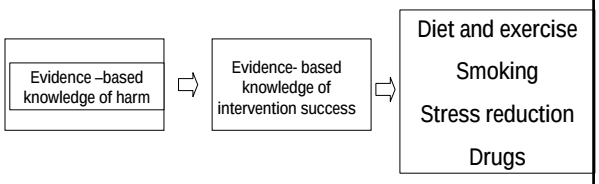


Dietary elements in PCOS

- Slow weight loss is safer than rapid weight loss in management
- While rapid weight loss is effective for weight loss and metabolic change, ketotic conditions are potentially dangerous for fertility (*Tsagareli et al 2006)*
- Low calories more important than macronutrient composition ie high carbohydrate equivalent to high protein for the same calories *(Moran et al, Stamerts et al)*
- Dietary composition of iron, trans fats and vegetable protein may be involved in the lack of ovulation *(Nurses' Health Study)*
- Reduction in calories in diet may be traded for increase in caloric use by exercise *(Ravuissen et al 2007)*

Conclusion 2 – lifestyle intervention may work

- Question: What is the evidence for lifestyle intervention being effective?
- Answer: Some but not enough evidence



How do we introduce lifestyle change?

- Medical and nursing attitudes
- Change individual approaches
- Group activities
- Health pathways
- Reproductive lifescripts

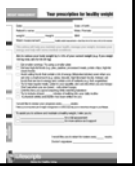
Medical and nursing attitudes - Adelaide

- Interview with 10 doctors in the clinic
  - *Most said they discussed smoking and weight*
  - *Few discussed anything else re lifestyle*
- Case note examination of same doctors
  - *Senior doctors documented weight and smoking discussion*
  - *Other had no documentation or treatment recommendations*
- Few doctors had any rational approach to help with lifestyle interventions
- Patients did not want health messages when presenting for fertility

Approach to lifestyle – current research

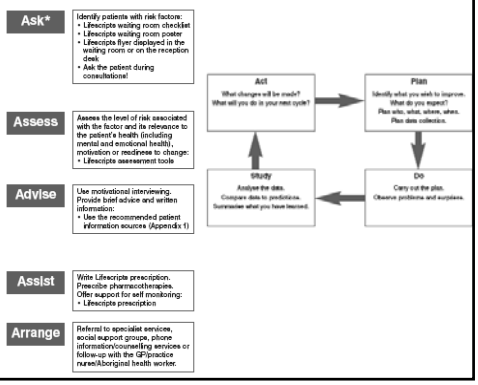
Doctor patient awareness campaigns ⇨ **Individual and couple interview re lifestyle** ⇨ Reproductive health pathway planning

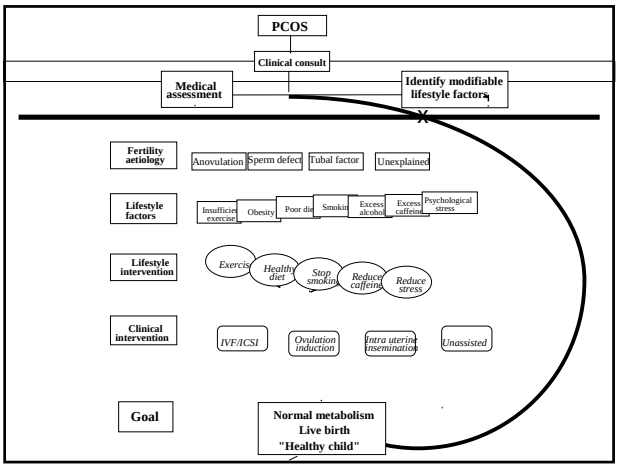
Reproductive health lifescript ⇦ Reproductive health information sheets ⇦ Provision of lifestyle resources

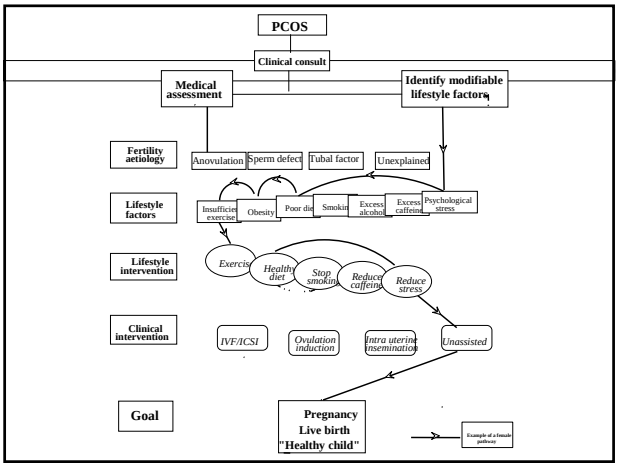


Motivational interviewing for lifestyle change

- Ask
- Assess
- Advise
- Assist
- Arrange




PCOS
Clinical consult
Medical assessment
Identify modifiable lifestyle factors
Fertility aetiology
Anovulation
Sperm defect
Tubal factor
Unexplained
Lifestyle factors
Insufficient exercise
Obesity
Poor diet
Smoking
Excess alcohol
Excess caffeine
Psychological stress
Lifestyle intervention
Exercise
Healthy diet
Stop smoking
Reduce caffeine
Reduce stress
Clinical intervention
IVF/ICSI
Ovulation induction
Intra uterine insemination
Unassisted
Goal
Normal metabolism
Live birth
"Healthy child"


PCOS
Clinical consult
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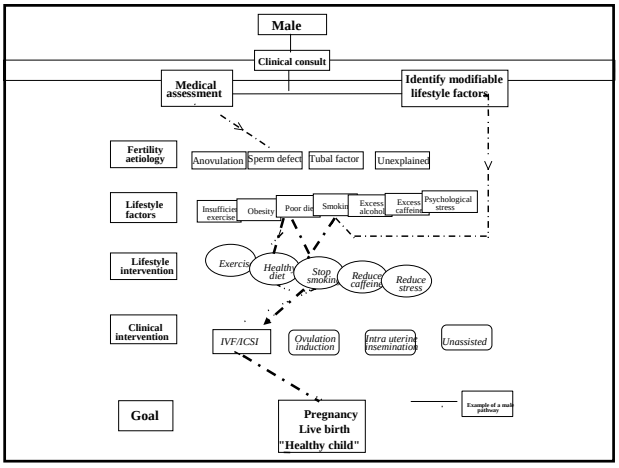
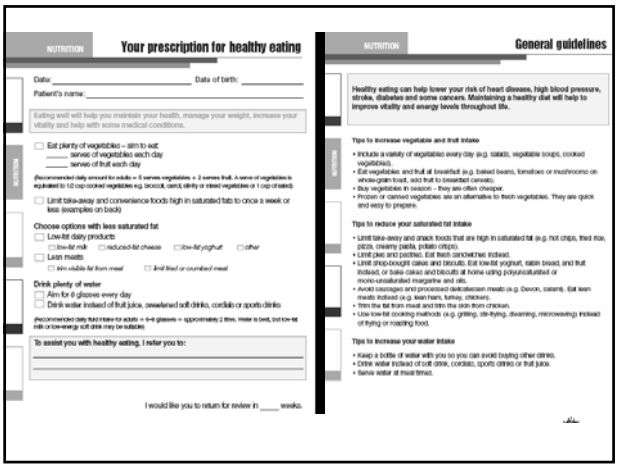
Excess alcohol
Excess caffeine
Psychological stress
Lifestyle intervention
Exercise
Healthy diet
Stop smoking
Reduce caffeine
Reduce stress
Clinical intervention
IVF/ICSI
Ovulation induction
Intra uterine insemination
Unassisted
Goal
Pregnancy
Live birth
"Healthy child"
Example of a female pathway


Male
Clinical consult
Medical assessment
Identify modifiable lifestyle factors
Fertility aetiology
Anovulation
Sperm defect
Tubal factor
Unexplained
Lifestyle factors
Insufficient exercise
Obesity
Poor diet
Smoking
Excess alcohol
Excess caffeine
Psychological stress
Lifestyle intervention
Exercise
Healthy diet
Stop smoking
Reduce caffeine
Reduce stress
Clinical intervention
IVF/ICSI
Ovulation induction
Intra uterine insemination
Unassisted
Goal
Pregnancy
Live birth
"Healthy child"
Example of a male pathway



NUTRITION

Your prescription for healthy eating

Date: _____ Date of birth: _____

Patient's name: _____

Eating well will help you maintain your health, manage your weight, increase your vitality and help with some medical conditions.

NUTRITION

- ☐ Eat plenty of vegetables – aim to eat:
  - _____ serves of vegetables each day
  - _____ serves of fruit each day

(Recommended daily amount for adults = 5 serves vegetables + 2 serves fruit. A serve of vegetables is equivalent to 1/2 cup cooked vegetables e.g. broccoli, carrot, stirfry or mixed vegetables or 1 cup of salad)

- ☐ Limit take-away and convenience foods high in saturated fats to once a week or less (examples on back)

Choose options with less saturated fat

- ☐ Low-fat dairy products
  - ☐ low-fat milk ☐ reduced-fat cheese ☐ low-fat yoghurt ☐ other
- ☐ Lean meats
  - ☐ trim visible fat from meat ☐ limit fried or crumbed meat

Drink plenty of water

- ☐ Aim for 6 glasses every day
- ☐ Drink water instead of fruit juice, sweetened soft drinks, cordials or sports drinks

(Recommended daily fluid intake for adults = 6–8 glasses = approximately 2 litres. Water is best, but low-fat milk or low-energy soft drink may be suitable)

To assist you with healthy eating, I refer you to:

_____

_____

I would like you to return for review in ____ weeks.

NUTRITION

General guidelines

Healthy eating can help lower your risk of heart disease, high blood pressure, stroke, diabetes and some cancers. Maintaining a healthy diet will help to improve vitality and energy levels throughout life.

Tips to increase vegetable and fruit intake

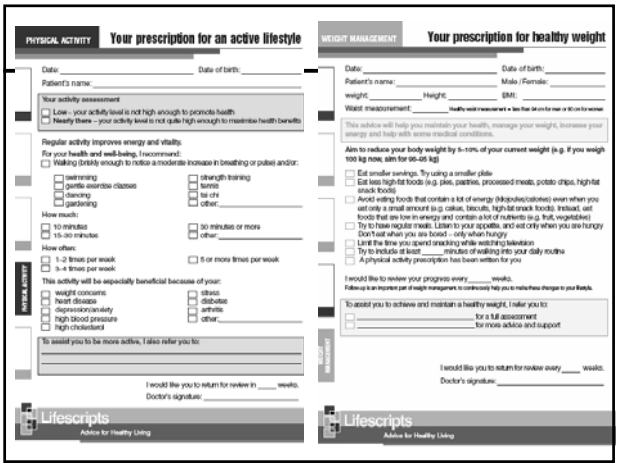
- Include a variety of vegetables every day (e.g. salads, vegetable soups, cooked vegetables).
- Eat vegetables and fruit at breakfast (e.g. baked beans, tomatoes or mushrooms on wholegrain toast, add fruit to breakfast cereals).
- Buy vegetables in season – they are often cheaper.
- Frozen or canned vegetables are an alternative to fresh vegetables. They are quick and easy to prepare.

Tips to reduce your saturated fat intake

- Limit take-away and snack foods that are high in saturated fat (e.g. hot chips, fried rice, pizza, creamy pasta, potato crisps).
- Limit pies and pasties. Eat fresh sandwiches instead.
- Limit shop-bought cakes and biscuits. Eat low-fat yoghurt, raisin bread, and fruit instead, or bake cakes and biscuits at home using polyunsaturated or mono-unsaturated margarine and oils.
- Avoid sausages and processed delicatessen meats (e.g. Devon, salami). Eat lean meats instead (e.g. lean ham, turkey, chicken).
- Trim the fat from meat and trim the skin from chicken.
- Use low-fat cooking methods (e.g. grilling, stir-frying, steaming, microwaving) instead of frying or roasting food.

Tips to increase your water intake

- Keep a bottle of water with you so you can avoid buying other drinks.
- Drink water instead of soft drink, cordials, sports drinks or fruit juice.
- Serve water at meal times.



PHYSICAL ACTIVITY

Your prescription for an active lifestyle

Date: _____ Date of birth: _____

Patient's name: _____

Your activity assessment

- ☐ Low – your activity level is not high enough to promote health
- ☐ Nearly there – your activity level is not quite high enough to maximise health benefits

Regular activity improves energy and vitality.

For your **health and well-being**, I recommend:

- ☐ Walking (briskly enough to notice a moderate increase in breathing or pulse) and/or:
  - ☐ swimming
  - ☐ gentle exercise classes
  - ☐ dancing
  - ☐ gardening
  - ☐ strength training
  - ☐ tennis
  - ☐ tai chi
  - ☐ other: _____

How much:

- ☐ 10 minutes
- ☐ 15–30 minutes
- ☐ 30 minutes or more
- ☐ other: _____

How often:

- ☐ 1–2 times per week
- ☐ 3–4 times per week
- ☐ 5 or more times per week

This activity will be especially beneficial because of your:

- ☐ weight concerns
- ☐ heart disease
- ☐ depression/anxiety
- ☐ high blood pressure
- ☐ high cholesterol
- ☐ stress
- ☐ diabetes
- ☐ arthritis
- ☐ other: _____

To assist you to be more active, I also refer you to:

_____

_____

_____

I would like you to return for review in ____ weeks.

Doctor's signature: _____

Lifescripts
Advice for Healthy Living

WEIGHT MANAGEMENT

Your prescription for healthy weight

Date: _____ Date of birth: _____

Patient's name: _____ Male / Female: _____

weight: _____ Height: _____ BMI: _____

Waist measurement: _____ Healthy waist measurement = less than 94 cm for men or 80 cm for women

This advice will help you maintain your health, manage your weight, increase your energy and help with some medical conditions.

Aim to reduce your body weight by 5–10% of your current weight (e.g. if you weigh 100 kg now, aim for 95–95 kg)

- ☐ Eat smaller servings. Try using a smaller plate
- ☐ Eat less high-fat foods (e.g. pies, pastries, processed meats, potato chips, high-fat snack foods)
- ☐ Avoid eating foods that contain a lot of energy (kilojoules/calories) even when you eat only a small amount (e.g. cakes, biscuits, high-fat snack foods). Instead, eat foods that are low in energy and contain a lot of nutrients (e.g. fruit, vegetables)
- ☐ Try to have regular meals. Listen to your appetite, and eat only when you are hungry. Don't eat when you are bored – only when hungry
- ☐ Limit the time you spend snacking while watching television
- ☐ Try to include at least _____ minutes of walking into your daily routine
- ☐ A physical activity prescription has been written for you

I would like to review your progress every _____ weeks.

Follow-up is an important part of weight management, to continuously help you to make these changes to your lifestyle.

To assist you to achieve and maintain a healthy weight, I refer you to:

- ☐ _____ for a full assessment
- ☐ _____ for more advice and support

I would like you to return for review every ____ weeks.

Doctor's signature: _____

Lifescripts
Advice for Healthy Living

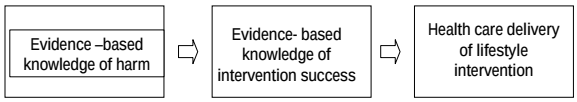
Why does our advice fail?

1. GP/obstetrician: Lack of information regarding fertility
   - Poor knowledge and convictions
   - Poor personal example
2. Patient factors
   - Message seen as health and not fertility related
   - Lifestyle change not seen as treatment
3. Reproductive specialist:
   - Expectation that high-tech will work well – and it often does!
   - Doctor personality too judgemental or conflict avoiding
   - Message directed at female rather than couple
4. Paramedical staff
   - Accessibility and information

Lifestyle changes - conclusions

- Lifestyle modification is important in the approach to infertility
- A group approach to lifestyle modification is superior to individual attempts to lose weight
- Weight loss alone is not critical to success in overcoming infertility related to excess weight – caloric restriction is more critical
- All overweight women should be in a lifestyle modification programme prior to medical intervention
- Need research on how does this program work
  - metabolic changes
  - behavioral changes

- Question: How do we deliver lifestyle changes to our patients?
- Answer: This is the major area for research if we want effective change



Evidence for lifestyle issues in PCOS

- Systematic review of lifestyle affected factors and fertility published by *Homan et al Human Reproduction Update 2007*

Definite	Possible	None
Weight disorders	Stress	Many others
Age	Caffeine	
Smoking	Alcohol, drugs	

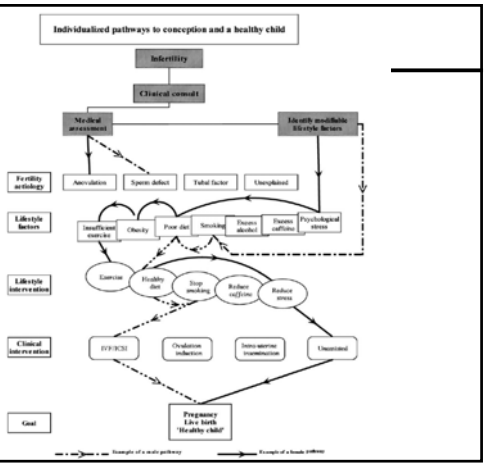
Acknowledgements

- Lisa Moran, Manny Noakes, Peter Clifton – CSIRO
- Gillian Homan
- Leanne Redman, other students
- NHMRC Program grant funds

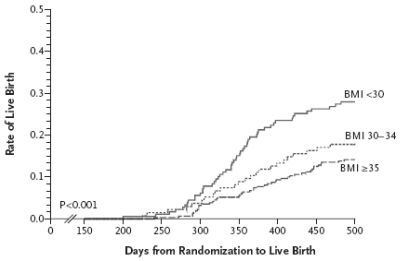
- Growth of technical side of ART defeats attempts at lifestyle intervention
- Aim to provide holistic care
- Evidence based care

Methods: Phase 2 Dietary intervention

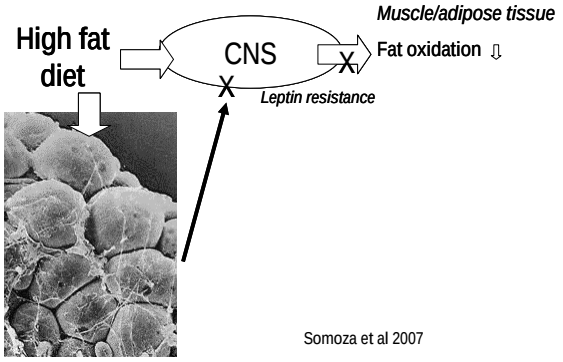
- Assessing a dietary education strategy
  - Semi-ad libitum intervention: list of ad libitum foods provided
  - Both groups educated on **low GI and low saturated fat choices**
- DIET 1: Fat counting (FC)
  - **Limited to 50 g fat/day**
    - AIM: < 30 % fat > 55 % carbohydrate
- DIET 2: Carbohydrate counting (CC)
  - **Limited to 120 g CHO/day**



Effect of BMI on treatment outcomes

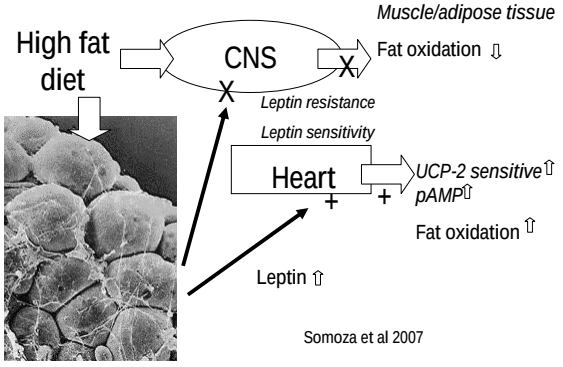


Leptin resistance following high fat diets



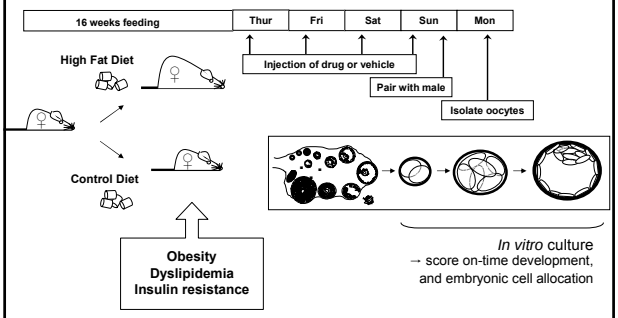
Somoza et al 2007

Leptin resistance following high fat diets



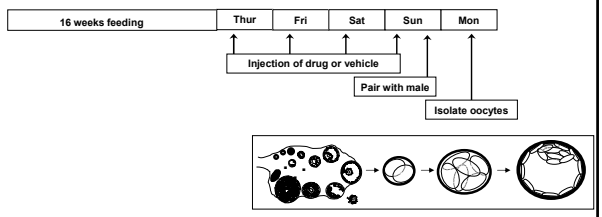
Somoza et al 2007

Obesity effects protocol



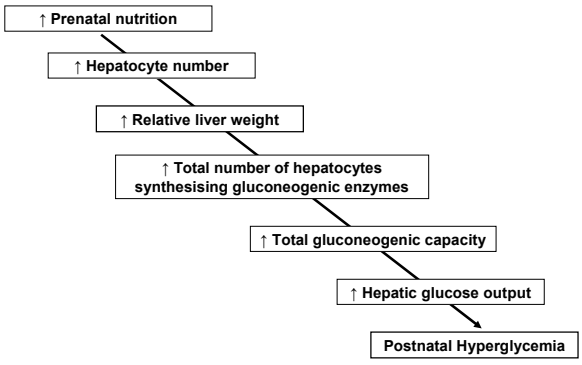
Minge, Lane, Norman and Robker 2006

Obesity effects protocol

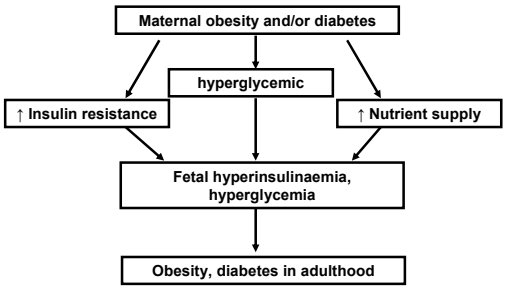


Minge, Lane, Norman and Robker 2006

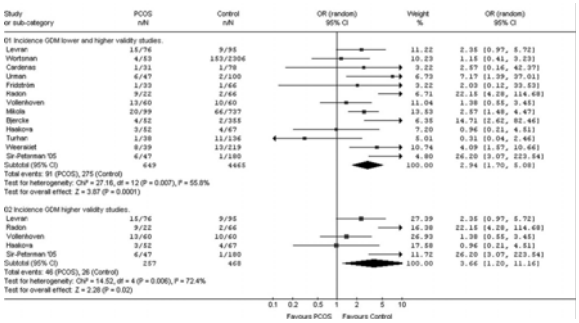
Obesity prepregnancy and fetal risks



Maternal overnutrition and offspring development



Outcomes of PCOS pregnancies –gestational diabetes



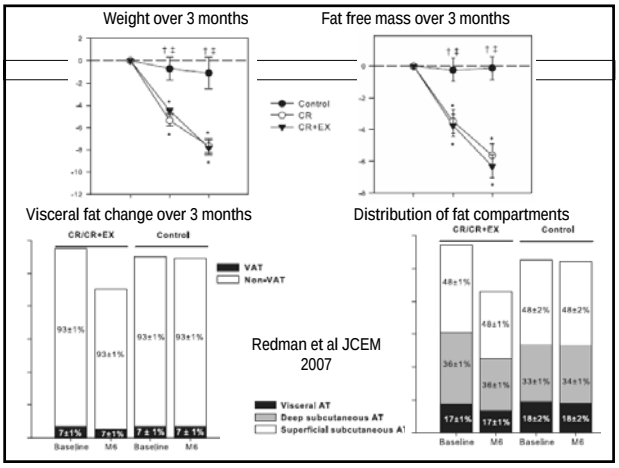
Boomsma et al Human Reproduction Update, Vol.12, No.6 pp. 673–683, 2006

Lessons on diet

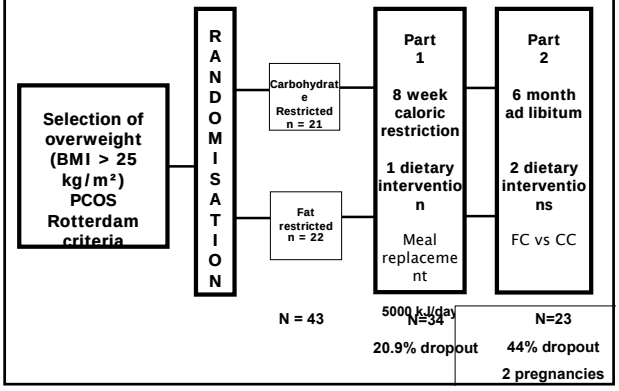
- Calories more important than dietary composition
  - High carbohydrate vs High protein
  - High protein may be better tolerated
- Short term restriction may be all that is needed
  - Acute caloric restriction *(Kiddy et al, Moran et al)*
- Consumer interest in glycaemic index diets
  - No real evidence of benefit
- Role of added metformin needs attention *(Pasquali et al, Ibanez)*
- Short-term reproductive effects but long-term problems with pregnancy health and later metabolism

Modern IVF overcomes effects of obesity

- 1545 consecutive ART cycles 2004-2005
- Analysis on first cycle only
- Each person only represented once
- 940 women represented in the database
- 834 reached egg recovery
- 820 reached embryo transfer
- Standard IVF cycles with downregulation by GnRH agonists, recombinant FSH, hCG and luteal support



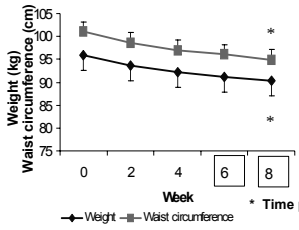
Methods: Study design



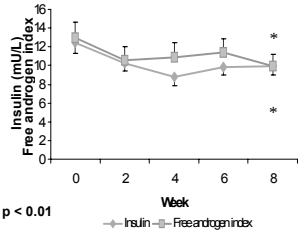
Diet induces good weight loss

8 weeks of energy restriction: Meal replacements 2x day + snacks/low fat meal
Dietary intake/day: 1170 kcal, 21 % fat, 24 % protein, 53 % carbohydrate

Weight ↓ 5.6 kg
Waist circumference ↓ 6.1 cm



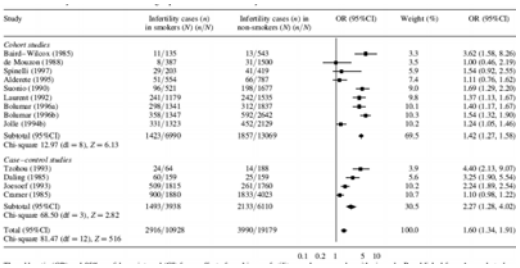
Insulin: ↓ 2.8 mU/L
Free androgen index: ↓ 3.1



* **Time p < 0.01**

(Moran 2006 AJCN)

Evidence base for adverse effects of smoking



Evidence for lifestyle issues in PCOS

- Systematic review of lifestyle affected factors and fertility published 2007 (Homan et al Human Reproduction Update)
- Definite evidence: weight, smoking, age
- Possible evidence: stress, alcohol, caffeine, drugs
- No evidence: Everything else

A group approach

Fertility Fitness for Women

What is the evidence for lifestyle interventions being effective?

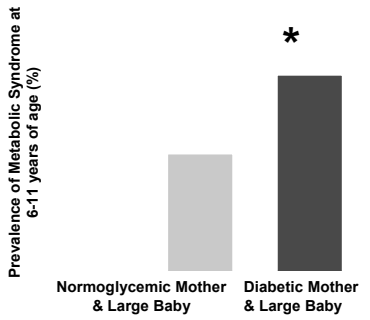
- Dietary interventions
- Exercise
- Role of drugs
- Stress reduction techniques

PCOS is associated with increased risk of problems

- Maternal
  - Gestational diabetes
  - Pregnancy-induced hypertension
  - Pre-eclampsia
  - Delivery by Caesarean section
- Neonatal
  - Admission to neonatal intensive care
  - Perinatal mortality
  - Premature delivery

Boomsma et al Human Reproduction Update.12:673–683. 2006

Maternal hyperglycemia increases risk of metabolic syndrome in childhood



Boney et al. Pediatrics.2005

Medical Management of Hirsutism

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Introduction

Women with PCOS are plagued by a variety of peripheral androgen excess disorders, including hirsutism, acne and androgenic alopecia These all originate in the pilosebaceous unit (PSU), the common skin structure that gives rise to both hair follicles and sebaceous glands. Androgen excess most commonly leads to hirsutism. Androgen can be viewed as a growth factor for stimulating development of the pilosebaceous unit (PSU), but it is just one among many factors that may contribute to its life cycle. Hyperinsulinemia, commonly found in women with PCOS may also contribute to the activation of the PSU. Paradoxically, androgens can exert opposite effects on the hair follicles of the scalp, causing conversion of terminal follicles to vellus-like follicles, a process termed miniaturization. This effect may lead to the development of androgenic alopecia in women or male pattern baldness characterized by frontal and sagittal scalp hair loss. Androgens can also cause increased sebum production and abnormal keratinization of the PSU, contributing to the development of seborrhea and acne evident at puberty and in women with androgen excess.

Assessment of Hirsutism and Balding

The methodology for the assessment of hirsutism, and response to treatment has been poorly validated (Barth 1996). Hirsutism scores are notoriously subjective and even the most frequently utilized standard of subjective hirsutism scores, the modified Ferriman-Gallwey score, utilizes non-midline, non-androgen dependent body hair to make the diagnosis. A subjective scale is important for discriminating unwanted excess hair with a diffuse distribution (hypertrichosis) from hirsutism.

Treatment of Hirsutism

Treatment options include cosmetic and medical therapies. As drug therapies may take six to nine months or longer before any improvement of hirsutism is perceived physical treatments including electrolysis, waxing and bleaching may be helpful whilst waiting for medical treatments to work. For many years the most ‘permanent’ physical treatment for unwanted hair has been electrolysis. It is time-consuming, painful and expensive and should be performed by an expert practitioner. Regrowth is not uncommon and there is no really permanent cosmetic treatment but the last few years have seen much development in the use of laser and photothermolysis techniques. There are many different types of laser in production and each requires evaluation of dose intensity, effectiveness and safety. The technique is promising, being faster and more effective than shaving, waxing or chemical depilation. Repeated treatments are required for a near permanent effect because only hair

follicles in the growing phase are obliterated at each treatment. Hair growth occurs in three cycles so six to nine months of regular treatments are typical. Patients should be appropriately selected (dark hair on fair skin is best), and warned that complete hair removal cannot be guaranteed and some scarring may occur. At present it is not widely available and is still an expensive option.

Medical regimens should stop further progression of hirsutism and decrease the rate of hair growth. Adequate contraception is important in women of reproductive age as transplacental passage of anti-androgens may disturb the genital development of a male fetus. Most medical methods, while improving hirsutism do not produce the dramatic results women desire, and treatment is often palliative rather than curative. In general, combination therapies appear to produce better results than single agent approaches (Azziz et al 1994; De Leo et al 2000), however randomized trials have not established a primary treatment for hirsutism. The choice of combination therapies remains empiric, with variations on a theme as to the best combination. In terms of ameliorating the effects of androgen excess on the pilosebaceous unit, there are a triumvirate of targets to focus on: decreasing production of androgens, decreasing bioavailability of androgens and opposing the action of androgens. In terms of directly affecting the cell cycle in the PSU, there is a single agent available, eflornithine hydrochloride crème.

Anti-Metabolite: Eflornithine hydrochloride crème

Eflornithine hydrochoride crème is marketed under the brand name VANIQA. Eflornithine is a potent and irreversible inhibitor of the enzyme, ornithine decarboxylase, which is necessary for the production of polyamines, which are important for cell migration, proliferation, and differentiation. Inhibition of this enzyme limits cell division and function. It is given as a 13.9% crème of eflornithine hydrochloride, and applied to affected areas twice a day for a minimum of four hours each. Two randomized double-blind placebo controlled trials involving 594 women (both pre- and post-menopausal) have been conducted. The publication of these studies in peer reviewed journals should yield further information about their efficacy (Balfour & McClellan 2001). These studies lasted 24 weeks with a an 8 week follow-up phase with no treatment. In these clinical trials 32% of women showed marked improvement after 24 weeks compared with 8% of placebo treated and benefit was first noted at 8 weeks. A total of 58% of subjects experienced some overall improvement. Eflornithine agent was generally well tolerated with the most common side effects being stinging of the skin (8.5% of patients on eflornithine compared with 2.5% on placebo) and skin rash (2.8% in the eflornithine group compared with 1.5% of the placebo group). Eflornithine is pregnancy category C, with no known human or animal teratogenecity or toxicity - although theoretically an anti-mitotic, anti-proliferative, and anti-differentiation agent should be avoided during pregnancy and used cautiously in a population of women seeking pregnancy. There appears to be minimal systemic absorption and circulation of the topical eflornithine when it is only applied to the face. While it has not specifically been studied in other areas of the body, theoretically it would be effective for other midline areas of terminal hair.

Androgen Suppressive Therapy

Women with documented hyperandrogenemia would theoretically benefit most from suppressive drugs, although in actual practice the clinical response to this type of therapy does not correlate with androgen levels. Suppression of ovarian androgen secretion has been achieved with oral contraceptives, progestins, or GnRH analogue treatment. Glucocorticoids have also been used to suppress adrenal hyperandrogenism, although are not recommended because of their adverse effect on insulin resistance.

Combined Oral Contraceptive Pills

COCPs can lower ovarian androgen production by suppressing gonadotropins and indirectly suppressing ovarian androgen biosynthesis. They can markedly increase SHBG levels by the estrogen effects on the liver. And, depending on the type of progestin chosen, they can also serve as androgen receptor antagonists. A number of observational or non-randomized studies have noted improvement in hirsutism on the oral contraceptive . Few studies have compared varying types of oral contraceptives and no pill has been shown to be superior in treating hirsutism in PCOS.

Onset of action may be prolonged, and is measured in months, if not years. One observational study of long term effects noted that mild-moderate hirsutism took 36-60 cycles to resolve (Falsetti et al, 2001). It was still present in about a third of women, though ameliorated in severe cases, after 60 cycles (Falsetti et al, 2001). Acne may respond in a shorter time period (12-24 m) and may experience a greater remission rate. A number of studies have found additive benefit when the oral contraceptive pill is combined with other treatment modalities, such as flutamide or with spironolactone.

The best oral contraceptive for women with PCOS is unknown, although arguably the pill containing a progestin that also functions as an anti-androgen, such as cyproterone acetate is the best theoretical choice. A new combined oral contraceptive Yasmin (Schering Healthcare Ltd) has recently been developed, containing ethinyl oestradiol 30 mcg and a new progestogen drospirenone (5 mg). Drospirenone is derived from 17α spironolactone, unlike most other current progestogens which are derived from 19-nortestosterone and therefore may have androgenic effects. Several studies have shown that drospirenone has a similar pharmacological profile to that of natural progesterone with clinically relevant anti-mineralocorticoid and anti-androgenic effects. Drospirenone increases SHBG levels three to four-fold. It also works as an antimineralocorticoid and its use may favor weight maintenance or even weight loss. These anti mineralocorticoid effects preclude its use in women with renal disease or hyperkalemia, Additional benefit in terms of hirsutism is obtained by its antagonistic properties (much like spironolactone) at the level of the androgen receptor. Thus theoretically, this combination OCP would improve all three targets in the triumvirate of androgen action.

Anti-Androgen Therapy

These compounds antagonize the binding of testosterone and other androgens to the androgen receptor. As a class therefore they are teratogenic, and pose risk of feminization of the external genitalia in a male fetus should the patient conceive. This is one reason to use them in combination therapy with OCP to prevent unexpected pregnancy. There may be additional benefits of this class of agents, including direct inhibition of steroidogenesis. Androgen antagonism may result in improvements in other metabolic variables such as insulin sensitivity and circulating lipids. All appear to offer some benefit, although the best choice for hirsutism is unknown. Randomized trials have found that spironolactone, flutamide and finasteride all have similar efficacy in improving hirsutism.

Spironolactone

Although spironolactone has had a long and extensive use as an anti-androgen and multiple clinical trials have been published showing a benefit, the overall quality of the trials and small numbers enrolled have limited the ability of a meta-analysis to document its benefit in the treatment of hirsutism (Lee et al 2000). Spironolactone, a diuretic and aldosterone antagonist, also binds to the androgen receptor with 67% of the affinity of dihydrotestosterone. It has other mechanisms of action, including inhibition of ovarian and adrenal steroidogenesis, competition for androgen receptors in hair follicles, and direct inhibition of 5-alpha-reductase activity. The usual dose is 25-100 mg twice a day and the dose is titrated to balance efficacy with avoiding side effects. There is a dose response effect and a long period before benefit is observed - 6 months or more. About 20% of the women will experience increased menstrual frequency and this is one reason for combining spironolactone therapy with a combined oral contraceptive pill. The medication also has potential teratogenicity as an anti-androgen, although exposure has rarely resulted in ambiguous genitalia in male infants. Acne has also been successfully treated with spironolactone. Thus despite extensive published experience with spironolactone, much of the treatment basis for hirsutism is empiric.

Flutamide

Flutamide is another nonsteroidal anti-androgen which has been shown to be effective against hirsutism in observational trials. The most common side effect is dry skin but its use has rarely been associated with hepatitis and liver failure and so is not recommended for young women with PCOS. A dose of 250 mg/d is given. There is greater risk of teratogenicity with this compound and contraception should be used. The mechanism, even with this agent can be debated as there is evidence to suggest that anti-androgens may also improve insulin sensitivity in hyperandrogenic women.

Finasteride

There are two forms of the enzyme 5α-reductase, type 1 predominantly found in the skin and type II, predominantly found in the prostate and reproductive tissues. Finasteride inhibits both forms and is available as a 5 mg tablet for the treatment of prostate cancer and a 1 mg tablet for the treatment of male alopecia. It has been found to be effective for the treatment of hirsutism (Moghetti et al 1994). Finasteride is better tolerated than other anti-androgens with minimal hepatic and renal toxicity, but has the highest and clearest risk for teratogenicity in a male fetus and adequate contraception must be used.

Insulin Sensitizing Agents

A recent Cochrane database analysis of the efficacy of metformin in PCOS found only one study adequately designed to evaluate hirsutism, and this showed no treatment effect. There were no studies for androgenic alopecia. However the meta-analysis did show a significant improvement in hyperinsulinemia and free androgen levels with the use of metformin in women with PCOS. Further study is needed to detect differences between classes of insulin sensitizing agents, and prolonged benefit over a longer duration of study.

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Fertility treatment in PCOS

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Polycystic ovary syndrome is a complex genetic condition, diagnosed based on oligo/anovulation, hyperandrogenemia and polycystic ovaries. Moreover, these women frequently present with obesity, insulin resistance and other signs of metabolic disease. These women represent around 10% of the female population. The incidence may further rise due to the ongoing epidemic of obesity resulting from changes in diet and life style habits.

In a gynaecology practice, the great majority of these women present with anovulatory infertility. In fact, it is suggested that at least 20% of all infertility is due to PCOS. The medical treatment of these women aiming to restore normo-ovulatory cycles is referred to as ovulation induction. This approach is under increasing pressure in relation to the widespread use of assisted reproduction (ovarian hyperstimulation and intra-uterine insemination, or IVF) or surgical procedures such as laparoscopic ovarian cautery.

Recently, an ESHRE/ASRM sponsored cencensus workshop on ovulation induction strategies in PCOS has been organised in Thessaloniki, Greece. In brief; Life style and diet changes should be recommended and actively encouraged to all obese PCOS women. Clomiphene citrate remains the first line drug of choice, despite relatively low efficacy. A recently published, large, multi-center, comparative trial convincingly demonstrated poor outcomes associated with the use of insulin sensitising agents for ovulation induction. Despite initial positive experience with aromatase inhibitors, well powered randomized trials need to show its efficacy and safety before this compound can be recommended for large scale clinical use. As second line treatment both gonadotropins or ovarian cautery can be applied depending on patient (and doctor) preference. The major shortcoming of even low-dose, step-up gonadotropin protocols is the increased chances for multiple gestation. The drawback of the surgical approach is the relatively low efficacy, required additional drugs is many women. However, multiple pregnancies following ovarian cautery are negligible. There is no need for IUI in addition to ovulation induction. IVF should be considered as third line treatment after failed ovulation induction.

Overall, ovulation induction treatment is effective and singleton live birth rates of over 70% have been described. Several studies have been published describing features upon initial screening predicting outcomes of various steps of ovulation induction. This development holds promise for more patient tailored treatment algorithms in the future. This may eventually identify (older) patients that qualify for assisted reproduction at an earlier stage. In this respect, IVF and single embryo transfer may be an attractive alternative proposition.

Learning objective

1. Understand that ovulation induction is a valid treatment option which should not be replaced by assisted reproduction techniques.
2. Understand why clomiphene citrate remains the drug of choice for first line ovulation induction.

3. Understand how arguments in favour of gonadotropins or ovarian cautery as preferred second line intervention should be balanced.
4. Understand how prediction models could be applied to develop more patient tailored treatment approaches in ovulation induction