

CURRENT PERSPECTIVES OF POLYCYSTIC OVARY SYNDROME (PCOS)

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Abstract: PCOS is now recognized as a variant of metabolic syndrome, which may include hyperinsulinemia, hyperlipidemia, diabetes mellitus, and possibly cardiac disease along with its conventionally recognized gynecological and dermatological manifestations. Several studies have suggested a high prevalence of PCOS of about 5-10% in women of reproductive age and its significance is increased even more in present context of rising incidence of obesity and metabolic syndrome as a important contributory factor. So in this article we reviewed the current guidelines for diagnosis of PCOS, its metabolic complication and current practice of treatment, our experience with metformin comparing to aldosterone, with better understanding its pathogenesis and management.

It is diagnosed on the basis of peripubertal onset of menstrual problems with clinical or biochemical hyper androgenism with radiological inputs on the basis of AES 2006 criteria. Obesity tend to be central in its distribution, insulin resistance is independently present in patients of pcos, showing a high degree of hyperinsulinemia and impaired glucose tolerance, on conducting our study on 168 north Indian adolescent girls with PCOS having a mean age of 22.6 years and that concluded that impaired fasting glucose (IFG) was noted in 6/168(3.57%), IGT in 49/168(29.16%) and diabetes in 15/168(8.92%) making the total prevalence of glucose intolerance as 41.60%. ideally the management should be aimed at addressing the basic defect of the whole metabolic constellation. Current management comprises treatment of the presenting symptoms, as well as any other abnormality discovered on investigation. We compared spironolactone and metformin in the management of various components of PCOS and observed that spironolactone (50 mg/day) appears to be better than metformin in the treatment of hirsutism and hormonal derangements of PCOS and has better patient tolerance at lower doses. The fact that superior positive effects of metformin on insulin sensitivity did not translate into proportionate clinical benefits in these PCOS subjects raises doubts about insulin resistance as a sole pathogenetic mechanism. Although metformin is classed as category 'B' drug but has been used widely for induction of ovulation with good efficacy either as a sole agent or in combination with clomiphene citrate with no specific neonatal complications, but there is inadequate evidence at present to suggests it use to prevent gestational diabetes or recurrent miscarriage and more studies are required.

INTRODUCTION

Initially called the Stein–Leventhal syndrome after its researchers in the 1930s, PCOS is now recognized to be a variant of metabolic syndrome which may include hyperinsulinemia, hyper-lipidemia, diabetes mellitus, and possibly cardiac disease, as well as the more conventionally recognized hirsutism, ovarian follicular atresia with anovulation, infertility, elevated androgen levels, endometrial cancer and obesity¹. This clustering of metabolic characteristics is almost similar to earlier described metabolic malady referred to as “Syndrome X” or metabolic syndrome by Gerald Reaven. Thus PCOS now should be viewed not just as a gynecological or dermatological disorder, but a sex limited manifestation of metabolic syndrome that involves multiple body systems and probably stems from a key pathogenic element called hyperinsulinemia.

PREVALENCE

PCOS is generally under diagnosed given the general concept about the condition among the practitioners. Clinicians should remember that menstrual abnormalities, such as cycles shorter than 21 days or longer than 35 days, are often associated with the condition. Many young women with these abnormalities are prescribed the oral contraceptive pill, which masks the condition until they try to achieve pregnancy. Several studies have suggested a prevalence of PCOS of 5%–10% in women

of reproductive age^{2,3}. Polycystic ovaries alone were found in 20%–25% of women in surveys in the United Kingdom and New Zealand⁴. There are no systematic prevalence studies from our country however the condition seems to be very common than west and it seems to be on rise in our population.

PATHOGENESIS

The pathogenesis of PCOS is poorly understood, but plethora of evidence is favoring the insulin resistance with consequent hyperinsulinemia as the primary defect⁵. The theca cells, which envelop the follicle and produce androgens for conversion in the ovary to estrogen, are over-responsive to stimulation by circulating concentrations of insulin and leutenising hormone (LH) which are generally raised. The rise in LH levels itself is thought to be caused by the relatively high and unchanging concentrations of estrogens that may alter the control of this hormone by the hypothalamic–pituitary axis. This combination of raised levels of androgens, estrogen, insulin and LH explains the classic PCOS presentation of hirsutism, anovulation or dysfunctional bleeding, and disorder of glucose metabolism. Paradoxically, although the insulin regulatory molecules on the theca cells are responsive to insulin, those in the muscle and liver are resistant⁶.

DIAGNOSTIC CRITERIA

The diagnostic criteria for PCOS are generally based on peri-pubertal onset of menstrual problems with clinical or biochemical hyperandrogenism. The evolution of diagnostic criteria from NIH/NICHHD 1990⁷ through Rotterdam 2003 conference⁸ to current consensus by Androgen Excess Society

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2006 (AES)⁹ has however continued to put major thrust on hyperandrogenemia and anovulation (Table 1). The polycystic ovaries characterized by peripheral cysts (10 or more), less than 10 mm in size in an enlarged ovary with significant increase in the central stroma on ultrasound examination is particularly controversial as a criterion⁴. Most of the available literature on PCOS does not include the presence of polycystic ovaries as a diagnostic criterion. Moreover polycystic ovaries are also found in women with no evidence of menstrual dysfunction or hyperandrogenism¹⁰ and can also occur in early to mid-adolescence, in women with bulimia, recovery from anorexia nervosa, conditions of increased adrenal androgen production and hyperprolactinemia¹¹. In view of the multitude of components the index of suspicion should be high.

Table 1. Androgen Excess Society suggested criteria for the diagnosis of PCOS.

1. Hyperandrogenism: Hirsutism and/or Hyperandrogenemia and
2. Ovarian Dysfunction: Oligo- anovulation and/or polycystic Ovaries and
3. Exclusion of other androgen excess or related disorders

\$ Possibly excluding 21-hydroxylase-deficient non-classic adrenal hyperplasia, androgen-secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing's syndrome, the syndromes of severe insulin resistance, thyroid dysfunction, and hyperprolactinemia.

PRESENTATIONS OF PCOS

PCOS is a life long condition which may have effects at all ages, not just in the reproductive years (Table 2). The condition may have its origins in fetal life as researchers have claimed that the children with either intrauterine growth retardation or post-term birth are more prone to hyperinsulinism, premature pubarche and signs of PCOS early in reproductive life¹². **Teenagers** often have oligo- or amenorrhea, hirsutism, acne and weight disorders. **Women seeking to become pregnant** will have difficulties because of anovulation and menorrhagia is more common because of lack of ovulation and unopposed estrogen action. The absence of regular menstruation induced by progesterone withdrawal may lead to endometrial hyperplasia and uncontrolled bleeding. There is a theoretical risk of endometrial cancer and has been alleged to be four times more common and may even appear even in teenagers. However, recent studies have raised doubts about the validity of this dogma¹³. It is controversial whether miscarriage is increased in PCOS, or whether pregnancy loss is a result of excess body weight.

The incidence of obesity in women with PCOS varies between countries and ethnic groups. In the United States, about 50% of women with PCOS are overweight or obese, but this prevalence differs little from that in the general community. In our population with a cut-off of 25 Kg/m², 33.92% were

non-obese and 66.08% in one study¹⁴. Obesity tends to be central (abdominal) in its distribution and even lean women with PCOS may have a fat distribution favouring central omental and visceral fat. **Insulin resistance** is independently related to PCOS, with women of normal weight with PCOS showing a degree of hyperinsulinaemia and impaired glucose disposal after meals and during glucose tolerance tests (oral or intravenous). It is uncertain whether this insulin resistance results from a specific genetic post-receptor defect, such as a defect in serine phosphorylation⁵ or whether it is comparable to the problem seen in type 2 diabetes. We compared spironolactone and metformin in the management of various components of PCOS and observed that spironolactone appears to be better than metformin in the treatment of hirsutism and hormonal derangements of PCOS and has a better patient tolerance at lower doses. The fact that superior positive effects of metformin on insulin sensitivity did not translate into the proportionate clinical benefit in these PCOS subjects raises doubts about insulin resistance as the sole pathogenetic factor⁴. Certainly, hyperinsulinemia is common but is difficult to interpret clinically, given the fact that it also results from obesity. There is some data which may be suggesting hyperinsulinemia as an epiphenomenon as our earlier observation^{14, 15}. **Glucose tolerance abnormalities and type 2 diabetes** are major complications in overweight women with PCOS. While fasting glucose level is usually normal postprandial glucose is abnormal as glucose disposal is impaired. We studied 168 north Indian adolescent girls with PCOS having a mean age of 22.6 years and concluded that impaired fasting plasma glucose (IFG) was noted in 6/168 (3.57%), IGT in 49/168 (29.16%) and diabetes in 15/168 (8.92%) making the total prevalence of glucose intolerance as 41.60%¹⁴. An excellent epidemiological study in the UK that followed up women with a histological diagnosis of PCOS

Table 2. Common Symptoms, signs and metabolic abnormalities of PCOS

Not all women with PCOS share the same symptoms:

1. Infrequent menstrual periods, no menstrual periods, and/or irregular bleeding
2. Hirsutism involving face, chest, stomach, back, thumbs, or toes
3. Acne vulgaris -moderate to severe
4. Male-pattern baldness or thinning hair
5. Acanthosis nigricans (patches of thickened and dark brown or black skin) on the neck, arms, breasts, or thighs
6. Skin tags in the armpits or neck area
7. Anxiety or depression
8. Sleep apnea syndrome
9. Overweight or obesity, usually central
10. Insulin resistance, glucose intolerance and type 2 diabetes
11. Hyperlipidemia
12. High blood pressure
13. Anovulation and infertility
14. High risk of coronary artery disease
15. Prothrombotic state
16. Elevated inflammatory markers like CRP, interleukins etc

after wedge resection of the ovaries found clear evidence of an increase in the rate of diabetes¹⁶ and confirmed the results of many other studies from the US and Europe. Hypertriglyceridaemia, increased concentrations of LDL and decreased concentrations of HDL cholesterol are common in women with PCOS, particularly if obese. Levels of plasminogen activator inhibitor-1 may also be raised, suggesting a chronic underlying sub inflammatory process. The association of PCOS and cardiovascular dysfunction is still under investigation and data has been conflicting. A higher than expected prevalence of PCOS has been reported among young women with angiographically proven narrowing of the coronary vessels; women with PCOS were also more likely to have sonographic evidence of premature obstruction of other large vessels^{17,18}. However, a UK study of medical records and death certificates of women with a histological diagnosis of PCOS revealed no evidence for an increase in myocardial infarction or other types of heart disease (Table 3).

	DIAGNOSTIC CRITERIA			
	FRANKS (USG) (N=300) (%)	CONWAY ET AL (USG) (N=556) (%)	GOLDZIEHER AND GREEN (HISTOLOGIC) (N=1079) (%)	GANIE M ASHRAF NICHHD# (N=168) (%)
Hirsutism	64	61	69	98
Acne	27	24	-	10.7
Obesity	35	35	41	60.2
Infertility	42	29	74	-
Amenorrhoea	28	26	51	10.7
Oligomenorrhoea	52	45	29	98.8
Regular menstrual cycle	20	25	158	0

Adapted from Ganie M A et al (Ref 14)

LABORATORY EVALUATION

History and general examination: These are required to elicit evidence of peripubertal menstrual dysfunction (age of menarche, duration of cycles, regularity, number of cycles in a year or cycle interval and flow) and hirsutism severity (as assessed qualitatively or semi quantitatively using the Ferriman–Gallwey score)¹⁹. Acne vulgaris, acanthosis nigricans, anthropometry especially waist circumference etc is to be noted. Mild clitoromegaly is not uncommon, but significant enlargement raises the possibility of virilisation. Gynecological examination is needed only to exclude other causes of bleeding and miscarriage.

Pelvic ultrasound examination: Transvaginal ultrasound is the best imaging mode. Transabdominal ultrasound examination requires more expertise to get a good view, particularly in obese women. Ovarian morphology (total volume, thecal hyperechogenicity and 2-10 peripheral follicles) should be assessed in addition to measuring endometrial thickness⁴. Also it gives a clue about possible adrenal or ovarian lesion.

Hormone assays: There is no uniform opinion regarding the endocrine and metabolic workup for the routine clinics. Since the universally employed criteria (NIH/NICHHD) demand the exclusion of late-onset congenital adrenal hyperplasia (measurement of 17-hydroxyprogesterone), thyroid

dysfunction (thyroid-stimulating hormone), hyperprolactinemia (prolactin), Cushing’s syndrome (basal cortisol or overnight dexamethasone suppression) and androgen secreting tumors (androgen levels), however these tests can be omitted if the clinical features are not suggestive. Measurement of testosterone (total or adjusted for sex-hormone-binding globulin) is helpful to show hyperandrogenemia and to rule out an androgen-secreting tumor¹⁵. The serum progesterone may actually demonstrate the anovulation which is one of the major criterion. It is essential to exclude glucose intolerance with GTT using fasting and 2 hour post 75 gram value. It is not clear if insulin measurement is indicated, as the measurement is cumbersome and interpretation is difficult. GTT primed insulin levels can be used for calculating indices of insulin resistance such as the homeostasis model assessment [HOMA], AUCi, CIGMA or quantitative insulin sensitivity check index [QUICKI]) but for research purposes most investigators still use clamp technique^(20,21).

Other investigations: Assessment of lipid status (total and HDL cholesterol and triglyceride levels), liver functions, uric acid etc to quantitate metabolic risk. Laparoscopy of the pelvis, computed tomography and magnetic resonance imaging for fat content estimation, ovarian and adrenal anatomy are needed as research tools and under special clinical circumstances. Endometrial biopsy and hysteroscopy may be used to investigate unexplained vaginal bleeding.

MANAGEMENT OF PCOS

Ideally the management should be aimed at addressing the basic defect of the whole metabolic constellation. Current management comprises treatment of the presenting symptoms, as well as any other abnormalities discovered on investigation.

Lifestyle modification: Several studies have shown that weight loss can lead to resumption of ovulation within weeks^{22,23}. Clark and colleagues demonstrated that even a 5% reduction in body mass restores ovulation and fertility^{24,25} and devised a program of exercise and sensible eating that has become a model across the world for treating PCOS. Rapid changes in body composition and fat mass can be shown during lifestyle change. High-protein diets seem to be as effective as high-carbohydrate diets, provided that fat and total calories are comparable). While lifestyle changes are difficult to maintain, women seeking pregnancy are highly motivated, making this a first-line intervention in overweight women with PCOS^{22,25}. Longer-term changes in weight are more difficult to maintain. Lifestyle changes are a first-line intervention in women with PCOS who are overweight, have glucose intolerance and are hyperlipidemic.

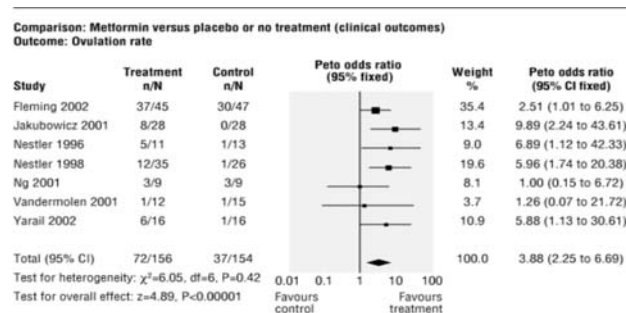
Pharmacotherapy

This includes many agents which may be beneficial in addressing the individual components, however the most popular therapy nowadays is insulin sensitizers as this is supposed to break the root cause of syndrome, the insulin

resistance.

Metformin: Use of the insulin-sensitising drug metformin at doses of 500–2500 mg daily is controversial, but appears valuable in increasing menstrual cyclicity and pregnancy rate.^{26–29} Recent systematic reviews suggest that the drug has efficacy for ovulation induction, either as a sole agent or in combination with clomiphene citrate²⁸. It has been widely used for this purpose, and no specific neonatal complications have been described, despite it being classed as “category B” drug. There is inadequate evidence at present to suggest its use in pregnancy to prevent gestational diabetes or recurrent miscarriage, but there are some studies underway to address the issue (Fig 1).

Fig 1. Metanalysis of studies investigating benefit of metformin in ovulation of induction in PCOS *



Adopted from Lord J M (Ref 28)

The new insulin-sensitising agents, the “glitazones”- troglitazone (now discontinued), rosiglitazone and pioglitazone- have been shown to be very effective for ovulation induction. There is greater concern about the effects on the fetus of these drugs compared with metformin, and they should not be used by women trying to become pregnant²⁹.

Clomiphene citrate: This is an oral oestrogen antagonist that raises circulating concentrations of FSH and induces follicular growth in most women with PCOS and anovulation. The initial regimen is 25–50 mg per day for 5 days. Therapy can be monitored by estrogen levels, follicular ultrasound examination and luteal progesterone level (> 20 nmol/L). Failure of response is associated with high body mass index and high androgen levels. Doses up to 200 mg per day can be used before failure of response is established. In the rare situation in which side effects limit treatment, tamoxifen can be used. Both treatments increase the risk of multiple pregnancies. Combination of clomiphene citrate and metformin has been used successfully in a subset for ovulation induction²⁷.

Gonadotrophin treatment: Ovulation induction with gonadotrophins such as FSH has proved successful for at least three decades, but demands skill and experience to avoid multiple pregnancies and ovarian hyper stimulation syndrome. Patients start on low-dose recombinant FSH administered subcutaneously. Monitoring of ovarian response involves ultrasound examination, often with oestradiol measurement. Human chorionic gonadotrophin is given when one follicle

reaches 16–20 mm in size. Any more than two follicles of an appropriate size gives the risk of multiple pregnancies. Multiple gonadotrophin cycles may be required to achieve pregnancy, but this approach is preferable before more invasive procedures, such as in-vitro fertilization.

In-vitro fertilization: Provided there is no problem other than anovulation, this has little place in the management of infertility resulting from PCOS. Ovulation induction by a skilled reproductive endocrinologist is preferable to in-vitro fertilisation because of the risks of hyperstimulation and multiple pregnancy with the latter procedure.

Surgical Treatment

Wedge resection of the ovaries has been abandoned because of concerns about pelvic adhesions, another cause of subfertility, and loss of valuable ovarian tissue. Ovarian diathermy or laser drilling has been used in recent years with apparently good results; a recent systematic review comparing drilling with clomiphene citrate and gonadotrophins proved equivalence in the studies examined. However, like wedge resection, this surgery may produce pelvic adhesions. Destructive surgery to the ovary should be used only after extensive discussion with the patient and not because the ovaries are found to be polycystic incidentally during routine laparoscopy.

Reversing the basic defects in PCOS by metformin is currently considered to address the all components but some additional modalities are needed for the symptomatic treatment of the disturbing problems. **Hirsutism** treatment classically has been by: the oral contraceptive pill (e.g., ethinylloestradiol 35 µg plus cyproterone acetate 2 mg daily for 21 of 28 days); cosmetic measures (e.g., laser electrolysis, bleaching, waxing or shaving); oral estrogen and cyproterone acetate (oestradiol valerate 2 mg daily and cyproterone acetate 50 mg for 14 days a month); spironolactone (75–200 mg daily); or other drugs, such as the antiandrogen flutamide or the antifungal agent ketoconazole. We found low dose spironolactone (50 mg /day) as better tolerated agent with excellent efficacy almost comparable to metformin by 6 months. These drugs either reduce androgen production or inhibit androgen-binding to the receptor. Response times for drugs can be from 3 -6 months. Obesity can be managed by drugs like sibutramin, orlistat or rimonabant. Menstrual dysfunction, including irregular periods, can be managed by administration of progestins (e.g., medroxyprogesterone acetate or norethisterone) or the oral contraceptive pill. Endometrial hyperplasia should be assessed by ultrasound examination, endometrial biopsy or hysteroscopy, and can be treated by hormonal therapy, such as the oral contraceptive pill or progestins.

LONG-TERM MANAGEMENT

Some investigators have suggested prophylactic use of metformin in young teenagers and older women to avoid the problems of the metabolic syndrome. This approach is

probably premature at present and may not be recommended. Advice about improved exercise and diet is more rational, given the abundant data on the role of lifestyle change in preventing and treating problems of glucose metabolism, hyperlipidemia, future fertility etc. Adult and young women with PCOS require ongoing surveillance to detect impaired glucose tolerance, hyperlipidemia, endometrial hyperplasia and consequent complications. Obese women, in particular, require regular (possibly annual) glucose tolerance testing because of the potential for rapid progression from normal to impaired glucose tolerance and diabetes. Thus key in reducing the mortality and morbidity because of many disorders stemming from this condition is to early recognition of the syndrome.

REFERENCES

- Lobo RA, Carmina E. The importance of diagnosing the polycystic ovary syndrome. *Ann Intern Med* 2000; 132: 989-993.
- Knochenhauer ES, Key TJ, Kahsar-Miller M, et al. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab* 1998; 83: 3078-3082.
- Diamanti-Kandarakis E, Kouli CR, Bergiele AT, et al. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. *J Clin Endocrinol Metab* 1999; 84: 4006-4011.
- Polson DW, Adams J, Wadsworth J, et al. Polycystic ovaries—a common finding in normal women. *Lancet* 1988; 1: 870-872.
- Dunaif A, Segal KR, Futterweit W, et al. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 1989; 38: 1165-1174.
- Stankiewicz M, Norman R. Diagnosis and management of polycystic ovary syndrome: a practical guide. *Drugs*. 2006;66:903-912.
- Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine F, editors. *Polycystic ovary syndrome*. Boston: Blackwell, 1992: 377-384.
- The Rotterdam ESHRE/ASRM sponsored PCOS Consensus WORKSHOP GROUP 2004. Revised 2003 consensus on diagnostic criteria and long term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;19: 41-47.
- Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E et al. Position statement: Criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: An Androgen Excess Society Guideline. *J Clin Endocrinol Metab* 2006;91:4237-4245.
- Farquhar CM, Birdsall M, Manning P, et al. The prevalence of polycystic ovaries on ultrasound scanning in a population of randomly selected women. *Aust N Z J Obstet Gynaecol* 1994; 34: 67-72.
- Adams J, Polson DW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. *Br Med J (Clin Res Ed)* 1986; 293: 355-359.
- Ibanez L, Potau N, Ferrer A, et al. Anovulation in eumenorrheic, nonobese adolescent girls born small for gestational age: insulin sensitization induces ovulation, increases lean body mass, and reduces abdominal fat excess, dyslipidemia, and subclinical hyperandrogenism. *J Clin Endocrinol Metab* 2002; 87: 5702-5705.
- Hardiman P, Pillay OS, Atiomo W. Polycystic ovary syndrome and endometrial carcinoma. *Lancet* 2003; 361: 1810-1812.
- Ganie MA, Khurana M L, Eunice M, Gupta N, Dwivedi S N, Gulati M, and Ammini A.C. Prevalence of Glucose intolerance among adolescent and young women with polycystic ovary syndrome in India. *Indian J Endocrinol Metab* VI (1) 9-14:2004.
- Ganie MA, Khurana M L, Eunice M, Gulati M, Dwivedi S N, Gupta N and Ammini A.C. Comparison of efficacy of metformin with spironolactone in the management of polycystic ovary syndrome: An open labeled study. *J Clin Endocrinol Metab* 89:2756-2762, 2004.
- Norman RJ, Masters L, Milner CR, et al. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. *Hum Reprod* 2001; 16: 1995-1998.
- Wild S, Pierpoint T, McKeigue P, et al. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. *Clin Endocrinol (Oxf)* 2000; 52: 595-600.
- Talbot EO, Guzik DS, Sutton-Tyrrell K, et al. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. *Arterioscler Thromb Vasc Biol* 2000; 20: 2414-2421.
- Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab* 1961; 21: 1440-1447.
- Abassi F, Reaver GM. Evaluation of the quantitative insulin sensitivity index as an estimate of insulin sensitivity in humans. *Metabolism* 2002; 51: 235-237.
- Legro RS, Finegood D, Dunaif A. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 1998; 83: 2694-2698.
- Pasquali R, Antenucci D, Casimirri F, et al. Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss. *J Clin Endocrinol Metab* 1989; 68: 173-179.
- Clark A M, Ledger W, Galletly C, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod* 1995; 10: 2705-2712.
- Clark A M, Thornley B, Tomlinson L, et al. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod* 1998; 13: 1502-1505.
- Moran LJ, Noakes M, Clifton PM, et al. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003; 88: 812-819.
- Norman RJ, Kidson WJ, Cuneo RC, et al. Metformin and intervention in polycystic ovary syndrome. *Endocrine Society of Australia, the Australian Diabetes Society and the Australian Paediatric Endocrine Group. Med J Aust* 2001; 174: 580-583.
- Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. *Cochrane Database Syst Rev* 2003; (3): CD003053.
- Lord JM, Flight IHK, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 2003; 327: 951.
- Azziz R, Ehrmann D, Legro RS, et al. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2001; 86: 1626-1632.

LITERATURE REVIEW

IMPACT OF OBESITY AS A MORTALITY PREDICTOR IN HIGH-RISK PATIENTS WITH MYOCARDIAL INFARCTION OR CHRONIC HEART FAILURE: A POOLED ANALYSIS OF FIVE REGISTRIES

Jawdat Abdulla, Lars Køber, Steen Z. Abildstrøm, et.al *European Heart Journal* 2008; 29: 594-601.

The objective of the study was to explore the influence of obesity on prognosis in high-risk patients with myocardial infarction (MI) or heart failure (HF). Individual data of 21 570 consecutively hospitalized patients from five Danish registries were pooled together. After a follow-up of 10.4 years, all-cause mortality using multivariate model and adjusted hazard ratios (HR) with 95% confidence intervals were calculated. Compared with normal weight [body mass index (BMI) 18.5–24.9 kg/m²], obesity class II (BMI ≥35 kg/m²) was associated with increased risk of death in patients with MI but not HF [HR = 1.23 (1.06–1.44), *P* = 0.006 and HR = 1.13 (0.95–1.36), *P* = 0.95] (*P*-value for interaction = 0.004). Obesity class I (BMI 30–34.9 kg/m²) was not associated with increased risk of death in MI or HF [HR = 0.99 (0.92–1.08) and 1.00 (0.90–1.11), *P* > 0.1]. Pre-obesity (BMI 25–29.9 kg/m²) was associated with decreased death risk in MI but not HF [HR = 0.91 (0.87–0.96), *P* = 0.0006 and 1.04 (0.97–1.12), *P* = 0.34] (*P*-value for interaction = 0.007). Underweight (BMI < 18.5 kg/m²) patients were in increased death risk regardless of MI or HF [HR = 1.54 (1.35–1.75) and 1.37 (1.18–1.59), *P* < 0.001]. In patients with MI but not HF, the relationship between BMI and mortality is U-shaped with highest mortality in underweight and obese class II, but lowest in the other BMI classes.