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Role Of Lifestyle Modifications In The Management Of Polycystic Ovarian Disease (PCOD)

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Abstract

Polycystic ovary syndrome (PCOS) is a common endocrine disorder which has reproductive implications for women (i.e. anovulation and fertility) as well as metabolic implications (i.e. increased incidence of diabetes mellitus). Obesity, central obesity and insulin resistance are strongly correlated with the onset of PCOS and so, it is prudent to specifically target reducing these risk factors in the management of PCOS. Short term weight loss has been consistently shown to reduce insulin resistance while restoring ovulation and fertility. There are emerging changes in clinical practice regarding overweight women achieving weight loss, but in relation to monitoring we also have challenges regarding how to record and measure any potential changes that come with weight loss, with regards to long term risk factor considerations. The most recent evidence suggests that modest unequivocal lifestyle changes have a population indication that reduced the severity of impaired glucose tolerance and delayed the timeline of onset of diabetes mellitus, however this has not yet be prospective randomised controlled trial tested in women with PCOS. Guidelines for conservative management provide recommendation for maintenance sustainable weight loss through dietary and exercise approach to treating the condition. It should also be noted that other exogenous behaviours such as psychosocial stresses, tobacco use and alcohol consumption are also important factors to consider in managing PCOS.

Keywords: Polycystic ovary syndrome, diet, guideline, obesity ,physical activity, body fat distribution, sleep, cognitive behavioural therapy, quality of life, complementary medicine

Introduction

Polycystic ovary syndrome (PCOS) is a complicated heterogeneous endocrine disorder. The essential attributes of PCOS are biochemical and clinical hyperandrogenism accompanied by reproductive morbidity, including menstrual dysfunction and infertility (1). Moreover, PCOS is one part of a constellation of metabolic disorders that have been associated with cardiovascular disease and diabetes. The clustering of metabolic disorders, including insulin resistance, impaired glucose tolerance (IGT), dyslipidaemia, hyperuricaemia and hypertension have been called 'syndrome X' or the 'metabolic syndrome'. Typically, women with PCOS display one of the above metabolic disorders (2). About 20% of reproductive age women have morphological indications of polycystic ovaries (PCO) [3]. Nevertheless, PCO are not invariably related to the endocrine manifestations of menstrual dysfunction and hyperandrogenism [4]. Although there is debate regarding a diagnostic definition, the criteria established through a 1992 National Institutes of Health (NIH) consensus conference specify characteristics that are commonly utilized. Criteria that relies upon clinical (hirsutism and acne) and/or biochemical hyperandrogenism, irregular menses along with absence of other androgen disorders (i.e. congenital adrenal hyperplasia, hyperprolactinaemia or thyroid disorders). The presence of polycystic ovaries on ultrasound is not a requirement for diagnosis based on these criteria [5]. According to NIH criteria 4-8% of women of reproductive age present in PCOS (table 1)(6-8) The cause of PCOS is unclear, but it is believed to arise from an interaction between genetic and environmental factors [9]. Changing environmental factors is an important part of treatment prior to using pharmacological treatment (including clomid, gonadotrophins and agents that improve insulin sensitivity). In this review we will focus on the effects of changing lifestyle factors, including diet, exercise, smoking and patient's psychological perceptions of PCOS. The common use of anti-androgens and oral contraceptive pills in the treatment of PCOS will not be reviewed.

Fig. 1 Viewing lifestyle modifications through a whole person or holistic care lens. The key features of whole person or holistic care listed in the centre of the figure have been adapted from Thomas et al. [20]. 'Recognises individual personhood' relates to focusing on the unique needs of the person rather than the disease. 'Importance of therapeutic relationship' emphasises patient autonomy and responsibility. 'Acknowledges humanity of the doctor' considers the doctors' ability to self-reflect on how they engage in the care of the patient. 'Health as more than absence of disease' incorporates the mental, emotional, physical, environmental and social needs of the patient. 'Employs a range of treatment modalities' promotes continuity of care across health disciplines, and while it may include traditional, complementary and integrative medicine (TCIM), TCIM is not holistic if used in isolation and without adequate integration into conventional healthcare

DIET:

As a basic component in healthy weight management, a well-balanced diet with appropriate caloric intake and proportions of the specific macro-elements, protein, fat, and carbohydrate is important. BMI classification to determine body weight and waist circumference, is important for each patient. Overweight and obese patients require dietary intervention to obtain effective and sustainable weight loss. The Polish Diabetes Society (2015) [65] recommends a diet with reduced caloric intake based on individual energy requirements calculated from the resting metabolic rate (Respondek 2011) [64]. For example, a caloric deficit of 500-800 kcal a day which Holl was able and loses at a safe rate of 0.5-1 kg a week. However, once an individual loses weight, the weight loss itself may cause a drop in basal energy expenditure and to achieve weight loss takes longer as well. Because of this weight-loss patients require continual evaluation of the amount lost in order to monitor the decrease in weight and adjust current energy expenditure to account for baseline weight. Also, the amount of specific proportions of macroelements should be suited to the individual's preferences and needs; the IAC recommendations for macronutrient proportion could be as follows: protein 10-25% carbohydrates 46-65% fats 20-35% of total energy of the diet (PTD 2015) [65]. The right choice of products is essential for changing a diet, especially regarding glycaemic index. Glycaemic index (GI) measures how much blood glucose increases two hours after eating a product that has 50 grams of digestible carbohydrates. This increase is shown as a percentage compared to the same carbohydrate amount in white bread. Choosing products with a low glycaemic index (0–55) instead of those with an intermediate (56–70) or high GI (>70) leads to a lower rise in blood glucose and a smaller

insulin response. This is especially helpful for people with obesity, insulin resistance, or type 2 diabetes (Radulian et al. 2009, Marsh et al. 2010) [62,64].

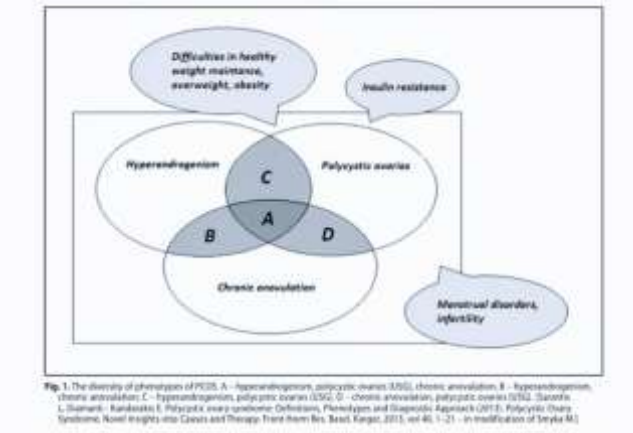

Fig. 1. The diversity of phenotypes of PCOS. A – hyperandrogenism, polycystic ovaries (USG), chronic anovulation; B – hyperandrogenism, chronic anovulation; C – hyperandrogenism, polycystic ovaries (USG); D – chronic anovulation, polycystic ovaries (USG). (Jasonska L, Duleba K., Kondzielski E. Polycystic ovary syndrome: Definitions, Phenotypes and Diagnostic Approach (2013). Polycystic Ovary Syndrome: Novel Insights into Causes and Therapy. Front Horm Res. Basel, Karger, 2013, vol 40, 1–21 – in modification of Smyka M.)

Additionally, eating low GI products boosts energy expenditure through thermogenesis and increases fat burning, which may help reduce body fat. It's important to note that the level of GI is affected not only by the type of product but also by how it is consumed and the other ingredients present in the diet at the same time (Radulian et al. 2009, Respondek 2011) [62,64]. To obtain the sustaining results, we must inform the patients that proper weight maintenance is related to making some general dietary changes, not quick restrictions and returning to old dietary habits.

VITAMIN D

Recent research on the pleiotropic effects of vitamin D has revealed a major role in developing risk factors for evolvement of cardiometabolic diseases: type 2 diabetes, arterial hypertension and metabolic syndrome.Cited research demonstrates that vitivamin D deficiency impacts the pathogenesis of insulin resistance, dyslipidaemia and mobilising inflammations and affects calcium metabolism. Additionally, vitamin D impacts levels of androgens and lead to regulation of the menstrual cycle and ovulation influencing fertility (Misiorowski 2012, Thomson et al. 2012, Brzozowska & Karowicz-Bilińska 2013) [68,67,66]. Research has shown that excess of adipose tissue in obese individuals decreases vitamin D bioavailability, due to sequestration within adipose tissue further research alludes to vitamin D that is previously sequestered being released to the blood stream through loss of body mass (Wąsowski et al. 2012). The outcome of the research comparing serum 25(OH)D of healthy women and women with PCOS has shown large differences.

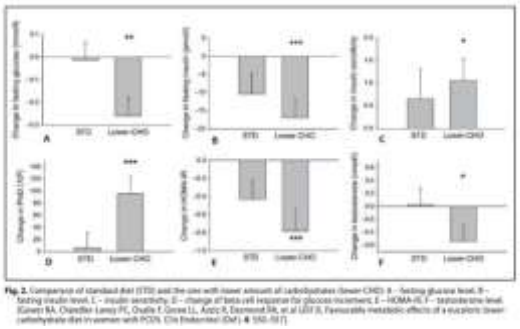

Fig. 2. Comparison of standard diet (STD) and the one with lower amount of carbohydrates (lower CHO). A – fasting glucose level, B – fasting insulin level, C – insulin sensitivity, D – change of beta cell response for glucose increment, E – HOMA-IS, F – testosterone level. (Gower BA, Chandler-Laney PC, Ovalle F, Goree LL, Azziz R, Desmond RA, et al. (2013). Favourable metabolic effects of a eucaloric lower-carbohydrate diet in women with PCOS. Clin Endocrinol (Oxf). 78: 160–167)

It is known that the 25(OH)D level is, indeed, reduced in obese women with PCOS (Thomson et al. 2012) [67]. Total need for vitamin D is derived from dermal synthesis with ultraviolet light and to a lesser degree food intake. Because of this latitude inhabited by the Polish population, they are at an increased risk for vitamin D deficiency, especially in the autumn-winter months. Furthermore, PCOS patients, due to their lack of acceptance in their appearance and lack of comfort in naked exposure, are at even greater risk for reduced dermal synthesis (Wąsowski et al. 2012, Kozłowski et al. 2014) [68]. Vitamin D supplementation is shown to be effective especially in the obese population and in patients with insulin resistance and low ovarian reserve is shown to decrease insulin resistance and is useful for infertility treatment (Brzozowska et al. 2013, Grzechocinska et al. 2013) [66,70].

Tab. 1. The factors influencing the level of glycaemic index of the products present in a diet.

Factors contributing to GI reduction:	Factors contributing to GI increment:
High fiber content	Low fiber content
High ratio of amylose to amylopectin	Low ratio of amylose to amylopectin
Presence of proteins and fats	Lack of other macronutrients
Presence of galactose and sucrose	Presence of fructose and lactose (but may contribute to insulin resistance and hepatic steatosis)
Raw products	Processed food: boiled, roasted, grinded
Slow food consumption	Fast food consumption

(Radulian G, Rusu E, Dragomir A, Posea M (2009). Metabolic effects of low glycaemic index diets. Nutr J 8: 1 – in modification of Smyka M.)

Many benefits associated with vitamin D intakeand the relative frequency of vitamin D deficiencies in the.ult population, the latest guidelines suggest vitamin Uniudientg (800 2000 IU/day)- supplementation forno arperiod of time in adults, depending on body mass,- from September to April - or year rsund in case of sufficient other synthesis. If obese increased"vitamin D supplementation" of 1600-4000 И iā/day. Piudowskyet al. 2013) [69].

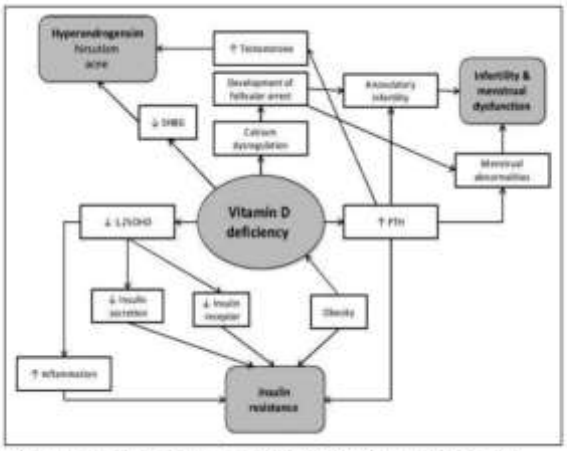

Fig. 1. The influence of vitamin D on hormone balances. (Thomson RL, Spedding S, Buckley JD (2012) Vitamin D in the Aetiology and Management of Polycystic Ovary Syndrome. Clin Endocrinol (Oxf). 77: 343–350)

Obesity in PCOS:

Rate of obesity in PCOS

Overweight and obesity have more prevalence in some newly developedand developing countries where people have adopted a western style of lifestyle and diet. Almost 50% of people are overweight in Australia and the USA, and women with PCOS tend to have BMI's outside the normal range (normal range BMI 19-25 kg m−2) and central distribution of adiposity. We are less certain about figures from other areas of the world for PCOS but the relative risk of obesity is likely to be higher in populations that are not as overweight as the USA (Tables 1,2).

Complications stemming from obesity in PCOS: insulin resistance:

Insulin resistance is well established to be important in the aetiology of the metabolic syndrome [2] and PCOS [13]. There is considerable evidence to suggest that hyperinsulinaemia, presumably due to insulin resistance, is present in a large proportion of cases of PCOS. The rise in insulin causes hyperandrogenaemia by stimulating thecal cell androgen production and suppressing sex hormone-binding globulin (SHBG) [13]. Obesity (especially when associated with abdominal distributions) increases metabolic and clinical manifestations of insulin resistance [14], and the effect of obesity on insulin metabolism in a woman with PCOS is potentialy worse than a woman who is similar in weight without PCOS. A number of investigators have documented that lean women with PCOS have insulin resistance, and overweight women with PCOS have more severe abnormalities than women with the same BMI without PCOS [13].

Obesity complications in the reproductive aspect of PCOS:

The increase in average BMI and tendency toward central adiposity have an unequivocal association with the risk factors for type 2 diabetes mellitus (T2DM), osteoarthritis, cardiovascular disease, sleep apnoea, breast and uterine cancer, and reproductive disorders [15,16]. Patients with overweight PCOS are less likely to conceive spontaneously or with medical assistance [17], are more likely to miscarry, more likely to have an abnormal fetal condition, and have a greater chance of complications during pregnancy (see Table 3).

Obesity complications in PCOS: impaired glucose tolerance and diabetes mellitus

Women with PCOS have a higher risk of developing T2DM in comparison to age- and weight-matched non-PCOS control women, with prevalence rates of 7.5-10% in the USA [1] (Fig. 1) and 17.7% in Thailand [2]. Impaired glucose tolerance (IGT) is a stage prior to T2DM and is present in 31.3-35% of women with PCOS in the USA [1] (Fig. 1) and 20.3% in Thailand [2]. The risk of developing hyperglycaemia is elevated with increasing BMI, and Legro et al. [12] documented increased rates of IGT and diabetes in obese (31.3%, 7.5%, respectively) compared with lean (10.3%, 1.5%, respectively) women with PCOS.

Table 1. Prevalence studies using NIH diagnostic criteria for polycystic ovary syndrome[a,b]

Subjects	PCOS diagnosis	Prevalence (%)	Obesity prevalence (%)[c]	Ref.
n = 192 Caucasian (Greece)	Oligomenorrhea: <8 cycles y HA: F-G score ≥6 Free T >95th centile Exclusion of other related disorders	6.8	38	[6]
n = 369 USA (n = 174 white, n = 196 black)	Oligomenorrhoea: ≤8 cycles y HA: F-G score ≥6 T/A /DHEAS >95th centile Exclusion of other related disorders	4.0	39	[7]
n = 154 Caucasian (Spain)	Oligomenorrhoea: >6 cycles length >35 days and/or nil bleeding for 3 consecutive months during last year HA: F-G ≥8/acne/alopecia T/DHEAS/FAI >95th centile Exclusion of other related disorders	6.5	10	[8]

[a]Abbreviations: A, androstenedione; DHEAS, dehydroepiandrosterone sulfate; FAI, free androgen index; F-G, Ferriman-Gallwey; HA, hyperandrogenism; NIH, National Institutes of Health; T, testosterone. [b]Adapted from Refs [6–8]. [c]Body mass index >30 kg m^{-2}.

We have demonstrated a very strong tendency across all studies for conversion from normoglycaemia to IGT over time [21] (consistent with observations by Ehrmann et al. [18]), with conversion also being strongly

related to BMI. Obese women (BMI >30 kg m−2) had a ten-fold increased risk, and overweight women (BMI 25-30 kg m−2) had a seven-fold increased risk of developing IGT or T2DM compared with normal weight (BMI <25 kg m−2) PCOS women [21]. Multiple investigators have demonstrated glucose abnormality detection (e.g., impaired glucose tolerance, T2DM) was accomplished best using oral glucose tolerance testing rather than a fasting glucose value [19-20] and that repeat testing, in particular those who have higher BMI, is important.

Table 2. Obesity prevalence estimates for women with polycystic ovary syndrome[a,b]

Subjects	PCOS diagnosis	Obesity prevalence (%)[c]	Ref.
n = 1079 (USA)	Histological features after wedge resection	41	[56]
n = 263 (UK)	Ultrasound	35	[57]
n = 1741 (UK)	Ultrasound	38	[58]
n =122 (Australia)	↑ serum T/A and ↓ SHBG Ultrasound	63	[4]

[a]Abbreviations: A, androstenedione; T, testosterone; SHBG, sex hormone-binding globulin. [b]Adapted from Refs [4,56–58]. [c]Body mass index >25 kg m^{-2}

Body fat distribution in PCOS:

Body fat distribution:

There is considerable evidence that upper body (‘android’ obesity) fat distribution is a significant predictor of cardiovascular disease and T2DM and that fat in the gluteofemoral ‘gynoid’ region is not [15]. Contemporary imaging (such as CT and MRI) has allowed for the compartmentalization of abdominal fat into intra-abdominal (or visceral) and subcutaneous fat (Fig. 2) There is robust evidence that insulation resistance and the metabolic syndrome correlate with the fat compartments that are primarily visceral fat [22]. Visceral fat probably accounts for much of the variation in insulin sensitivity observed among various populations. The visceral obesity phenotype carries the highest risk for cardiovascular and diabetic mortality and morbidity and for insulin resistance, dyslipidaemia, hypertension and left ventricular enlargement, despite the simplicity of the anthropometric estimates [15]. In a small cohort study on premenopausal women with a seven year follow-up there is evidence that visceral fat, as well as waist circumference, was significantly correlated with subsequent insulin resistance [23]. The observed relationship was linear and indicated that a decrease in visceral fat would be as likely to improve insulin resistance as a corresponding increase in visceral fat would be likely to result in an deterioration.

Table 3. Impact of obesity on reproduction[a,b]

Condition	Associated risks
Menstruation	↑ risk of menstrual dysfunction: amenorrhoea, oligomenorrhoea and menorrhagia
Infertility	↑ risk of ovulatory and anovulatory infertility: anovulation, poor response to fertility drugs
Miscarriage	↑ risk of miscarriage, spontaneously and after infertility treatment
Glucose intolerance	↑ risk of impaired glucose tolerance and type 2 diabetes mellitus
Infertility treatment	↑ requirement for clomiphene citrate/gonadotrophin ovulation induction. ↓ success rate for IVF/ICSI/GIFT pregnancies
Pregnancy	↑ prevalence of pregnancy-induced hypertension, gestational diabetes, Caesarean section and Down's syndrome

[a]Abbreviations: GIFT, gamete intrafallopian transfer; ICSI, intracytoplasmic sperm injection; IVF, in-vitro fertilization. [b]Adapted from Ref. [59].

Fat distribution in PCOS:

Although the compartmentalization of fat in PCOS has not been well studied, it is well-established

that women with PCOS have a propensity to store abdominal fat as defined by waist to hip ratio (WHR) [12]. However, WHR is a simple estimation of visceral fat and others have shown that even with a similar WHR, women with PCOS have greater intra-abdominal fat than controls [24]. When imaging methods that are more sensitive have been used, non-obese women with PCOS had a significantly greater amount of total and trunk fat, with similar lower body fat mass compared to controls [25] Women with PCOS and higher levels of abdominal fat distribution have higher levels of fasting insulin, atherogenic lipids, luteinizing hormone, estrone and androstenedione than women with PCOS and peripheral fat distribution at the same body weight level [4]. Holte and colleagues [26] have shown that there is a linear relationship between the amount of abdominal fat and insulin resistance through the entire BMI spectrum in both PCOS and controls. The increased differences in insulin resistance at high BMI between obese controls and women with PCOS does appear to be accounted for by controlling for abdominal fat mass. If

visceral mass is a major factor in PCOS, it seems likely that interventions to reduce visceral fat mass will improve both PCOS and the manifestations of metabolic syndrome. Conversely, therapies that can impact PCOS but do not modify visceral fat mass - such as ovulation induction agents that do not stimulate insulin - are expected to provide little or no benefit in terms of metabolic health. It is also documented that even with modest weight loss, there is a substantial reduction in visceral fat, which can improve metabolic markers [15]. Because waist-hip ratio and BMI correlate poorly with visceral fat reduction, waist circumference itself is the best direct measure of reduction in visceral fat [23].

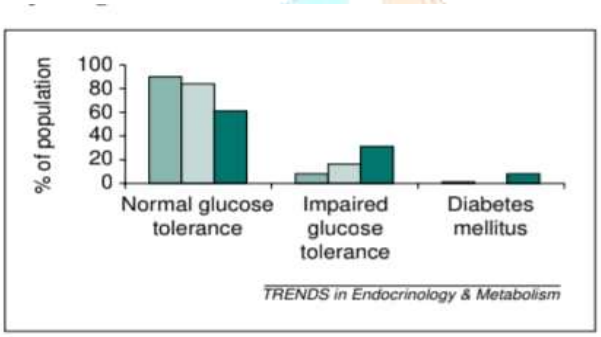

Fig. 1. Glucose tolerance in polycystic ovary syndrome (PCOS) assessed by 75 g oral glucose tolerance test in women with PCOS (dark green); age-, weight- and ethnicity-comparable reproductive normal control women (light green); and US women aged 20–44 years from Second National Health and Nutrition Survey (medium green). The figure shows prevalence rates for normal glucose tolerance, impaired glucose tolerance and undiagnosed diabetes mellitus according to WHO criteria. Reproduced, with permission, from Ref. [60].

Lifestyle change and PCOS:

Short-term weight loss and PCOS

PCOS treatment should target both normalizing short-term hyperandrogenism and anovulation as well as reducing metabolic risks. A primary concern is preventing and treating IGT and T2DM: by pharmacotherapy or ideally by lifestyle alteration. Total weight loss and loss of a substantial amount of visceral fat are key treatment approaches. The reproductive and metabolic advantages from weight loss are believed to occur from a reduction in circulating insulin. The initial use of insulinsensitizing drugs like metformin and the thiazolidenediones have shown beneficial metabolic and clinical effects (reviewed in Ref. [27]). The benefits of weight loss on clinical and biochemical PCOS have been consistently documented (reviewed in Ref. [28]). Studies of shortterm weight-loss treatment (four to eight weeks) have documented effects of decreased abdominal fat [26,29], androgenicity [26], insulin resistance and serum insulin [26,29] and improved lipid levels [29]. Clinical, reports of improvements in menstrual cyclicity and fertility [26,30] and hirsutism [30].

Lifestyle interventions in the non-PCOS population:

For mitigation of diabetic complications and mortality Whether or not these benefits are sustained in the long term are unknown. Additionally, although risk factors forT2DM are mitigated, these studies do not measure whether T2DM prevalence is actually reduced. The diabetes literature shows diet and exercise will reduce the risk of T2DM [31]. In a prospective study over 4 years in overweight individuals with IGT (n=523), a modest weight loss (4.2 kg in year one) with diet and exercise intervention, resulted in a 58% reduction in risk of developing diabetes when compared to a control group (0.8 kg weight loss) [32].

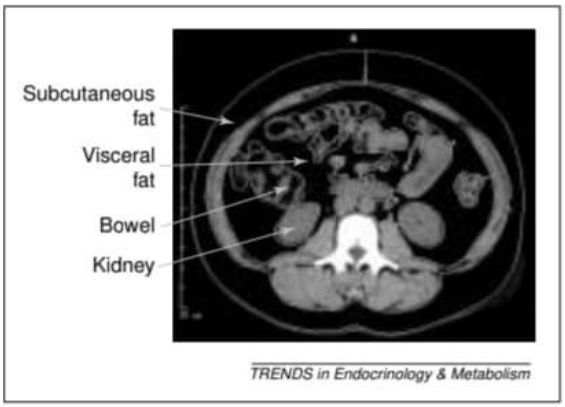

Fig. 2. Computerized tomography scan of abdomen at L2 level to illustrate visceral abdominal fat and subcutaneous abdominal fat.

Elements adopted were regular exercise and a diet low in trans and saturated fats and high in fibre. In a 16-year follow-up study (n=84 941), the incidence of T2DM was 90% lower where lifestyle factors included a BMI ≤ 25 kg m−2, a diet high in cereal fibre and polyunsaturated fat and low in saturated fats and trans fats, low glycaemic load, exercise, regularly not smoking and alcohol in moderation [33].

Box 1. NIH clinical guidelines for long-term treatment of overweight and obesity. Adapted from Ref. [35].

- Sensible diet and changed eating habits for long term.
- Effective physical activity programme sustainable long term.
- Behaviour modification, reduction of stress, well-being.
- Combination of dietary and behavioural therapy and increased physical activity.
- Social support by physician, family, spouse and peers.
- Smoking cessation and reduction in alcohol consumption.
- Avoidance of 'crash diets' and short-term weight loss.
- Minor roles for drugs involved in weight loss.
- Avoidance of aggressive surgical approaches for majority.
- Adaptation of weight-loss programmes to meet individual needs.
- Long-term observation, monitoring and encouraging of patients who have successfully lost weight.

Lifestyle modification has demonstrated equal effectiveness as pharmacological intervention in reducing the onset of T2DM in individuals without PCOS. The Diabetes Prevention Program involved an RCT that compared lifestyle intervention (150 min per week of exercise and a low-fat diet) to metformin (850 mg twice per day) and placebo in overweight participants (n=3234) with IGT. Early results demonstrated that lifestyle intervention reduced the risk of transition to diabetes by 58%, while metformin reduced risk by 31% [34]. Therefore weight loss via lifestyle modification should be a primary treatment outcome for PCOS, with pharmacological intervention being a relevant option, primarily in cases where weight-loss attempts have failed.

Long-term weight reduction & PCOS

Although short-term weight loss through moderate or severe caloric deficit can be effective, it is unlikely that long-term weight loss can be maintained. Once weight is regained, the symptoms of PCOS, as well as the long term morbidity and mortality risk, will likely return. The NIH clinical guidelines for the long-term management of overweight and obesity clearly state the importance of attainable and sustainable goals, including integrative diet modification, physical activity and behaviour modification (Box 1) [35]. These principles of weight maintenance are consistent with those examined in diabetic populations, in the long term.

The Role of Diet Composition:

Current lifestyle guidelines for PCOS suggest a low fat (~30% of energy; saturated fat ~10% of energy), moderate protein (~15%) and high carbohydrate diet (~55%) with increased fibre, wholegrain breads and cereals, fruit and vegetables for a reduction of associated mortality and morbidity and improvement of insulin sensitivity [36]. These principles are consistent with the NIH recommendations for dietary therapy for weight loss and maintenance [35] and the dietary regimes recommended from the diabetes intervention trials [32-34].

The impact of dietary composition on consumer interest is more exciting than weight loss alone. Emerging approaches suggested to treat obesity and PCOS advocate for increasing dietary protein at the expense of carbohydrate. It has been suggested that these diets facilitate greater weight loss due to the high satiety of protein in comparison to carbohydrate or fat [37], and may be beneficial for insulin sensitivity via maintenance of lean body mass [38]. However, these dietary regimens specifically have not been examined in PCOS and require further research before recommendations can be made.

Stressors from a psychosocial context and reproductive health:

Numerous authors have demonstrated that women with
PCOS experience more stress and have a poorer
Self image than controls [39]. Galletly et al. [40] showed significant improvement in psychological variables, including self-esteem, anxiety, mean depression scores and scores on the general health questionnaire. Cronin et al. [41] have developed a health-related quality-of-life questionnaire for women with PCOS with emotional and mood concerns being a major focus of the items. Since NIH guidelines for weight loss feature behaviour therapy and an adjustment of psychological factors, any lifestyle program should include behaviour therapy and a better understanding of the psychological background of women with PCOS.

Caffeine, smoking, and reproductive health:

The link between caffeine and fertility is not clear. Caanet al. [42] and Curtis et al. [43] found no impact of caffeine on pregnancy rates or fecundability. On the other hand,

studies reported higher odds for delayed conception and reduced fecundability with caffeine intake of 300 mg per day or more [44] and over 500 mg per day [45]. There may be confounding effects between caffeine and smoking [44]. Smoking is a significant risk factor for female subfertility, measured by time to pregnancy, preterm birth, and low birth weight in babies [46]. Alarmingly, many women with PCOS are smokers. About 50% of women visiting our clinic in Adelaide are current smokers, which is roughly double the population rate for the same age group. Smoking serves many psychological roles. People often believe it helps with weight control, self-esteem, comfort, and a sense of control. However, the long-term effects eventually undermine these reasons. Stopping smoking is crucial for all women, but it is challenging due to the complex and powerful reasons people smoke.

Alcohol and reproduction health:.
Observational data suggests a J-shaped relationship between alcohol consumption and cardiovascular disease risk, In terms of reproductive outcomes, Grodstein et al. [47] found a reduced fertility and increased spontaneous abortion risk in heavy-drinking women. However, low levels of alcohol consumption show inconsistent findings. Low levels of consumption were associated with decreased fertility with five drinks per week [48], while Olsen et al. [49] found an association between alcohol and subfecundity only at high levels of exposure. consumption could be of benefit. Further detailed and specific research is required to confirm this interpretation of the available literature. The extent to which these observations can be applied to PCOS needs to be tempered by the apparent low threshold below which the effects of alcohol consumption outweigh its beneficial effects. If women are seeking to conceive, or are already pregnant, the quantity of alcohol consumed should be no more than the minimum for safe consumption. However, one of the groups who may find that low or moderate alcohol consumption is beneficial may be women with PCOS. More detailed and formal research is needed to validate this interpretation of the current literature.

Exercise and reproductive health:
Women with PCOS are a specific group of individuals who would likely derive significant benefit from exercise on a routine basis. Exercise increases insulin sensitivity, both through direct actions in the muscle with regards to metabolism and through indirect help with weight control[52]. In addition, the potentially very good effects of physical activity are likely not to come from a large amount of weight loss changes, actual body shape changes,
and even modest exercise may be beneficial. This point is important because many individuals deal with visible body shape as a main point of reference for success from exercise and may find themselves discouraged when this change is not apparent. It should be highlighted that a small change in energy expenditure or weight loss is associated with a large increase in potential benefits[53]. Exercise should become a routine and necessary component of an overall healthy lifestyle management aimed at maintaining long-term health.

The Fertility Fitness programme:
In Adelaide [53-55] has applied these principles to the management of PCOS (Box 2). This programme comprises dietetic and psychological intervention and centres around adopting consistent healthy food choices and moderate amounts of low-intensity physical activity in a communal setting. Small weight losses (2-5%) have produced statistically significant reductions in waist fat [53] and improvements in psychological outcomes [52], androgen levels [54], insulin resistance [53] and ovulation and fertility [53-55]. Clark et al. [55] reported normal ovulation was restored in 60/67 previously anovulatory women, improved pregnancy in 52/67 women, and a decrease in the rate of miscarriage (from 75% pre-intervention to 18% post-intervention). This provides reasonable evidence that sustained adoption of these principles in a primary care setting would be able to prevent women with PCOS from developing IGT and T2DM and may also have a beneficial long term management of

reproductive and endocrine fitness.

Box 2. The Fertility Fitness Programme. Adapted from Ref. [61].

- Information about role of weight and body composition in reproductive disorders.
- Agreement to seek lifestyle changes for at least six months.
- Group meeting with partners to explain the course.
- Weekly meetings for 2–2.5 h with women.
- Gentle aerobic exercises for 1 h (walking, stepping etc.).
- Lecture/seminar for 1 h (good eating – nutrition/alcohol/smoking/caffeine, psychological aspects, medical information etc.).
- Put into practice for next six months.
- If return of periods, pregnancy etc., no further medical treatment.
- If disorder persists after six months, offer appropriate medical treatment.

The Nature of FSH induction by GnRH:

The follicle-stimulating hormone (FSH), which is a major regulator of mammalian gonadal function, is induced by the peptide gonadotropin-releasing hormone (GnRH) but the extent to which the induction is direct or indirect (and the in vivo relevance of each type of induction) remains unclear. Two advances now allow us to address these questions, which are central to understanding FSH regulation. The first is the use of transformed LβT2 gonadotropes to define essential promoter sequences of FSHB(the gene for the FSH-β subunit) required for induction by GnRH and/or other factors; the second is our ability to express FSHB promoter-reporter constructs in transgenic mouse gonadotropes to determine the physiological significance of promoter elements identified from studies using LβT2 cells. Here, we summarize previous work on GnRH induction of FSH, and we propose questions and a plan for the future.

Follicle-stimulating hormone (FSH)

It is responsible for gonadal development in mammals. It is necessary for egg production [1,2] and is also essential for spermatogenesis [1,3], particularly in primates [4]. This α-β heterodimer is only found in pituitary gonadotropes [5]. Its synthesis and/or secretion can decrease and/or increase >20-fold in vivo [highest in gonadectomized animals [6], lowest in mammals given chronic gonadotropin-releasing hormone (GnRH) agonists [7] or antagonists [8,9]], and it naturally fluctuates five- to sevenfold during the estrous cycle [10 12]. Although steroids can modulate steroid hormones, steroid hormone actions are often species specific. One thing that seems constant in all species, is that GnRH [13] and members of the transforming growth factor β (TGF-β) superfamily [14-18], which GnRH may also regulate [19], stimulate synthesis of FSH. GnRH induction of FSHB (gene that encodes the FSH-β subunit) transcription is rate-limiting for total FSH production and also account for the great majority of FSH secretion [20-22]. Therefore, to understand GnRH induction of FSH, it is necessary to understand transcriptional induction of FSHB by both GnRH and members of the TGF-β family.Member of the transforming growth factor β superfamily [14-18], which GnRH may also regulate [19]. FSHB (gene that encodes the FSH-β subunit) transcription is considered the rate-limiting step for total FSH production and accounts for most FSH secretion [20-22]. Therefore, to understand GnRH induction of FSH it will be necessary to understand transcriptional induction of FSHB by GnRH and TGF-β family members.

GnRH and TGF-β family members

They stimulate in vivo FSHB. It is clear that GnRH plays a role in robust FSH synthesis and secretion. Some investigators have immune bioneutralized GnRH in animals to demonstrate that approximately 50-67% of serum FSH is GnRH-dependent [23]. Comparable levels of GnRH involvement have been revealed using GnRH antagonists [8,9] or chronic GnRH agonist treatment [7] to block GnRH actions in vivo (Fig. 1a) [13]. Studies with hpg GnRH-deficient mice reveal that serum FSH is 60% lower in the female and lower still (87%) in hpg males [24]. Restoration of the genetic defect in hpg mice completely restores FSH production and reproductive competence [24]. Thus, it is clear that GnRH has importance to FSH production in vivo. Some members of the TGF-β superfamily are also known to induce FSH. The strongest of these agonists are the activins [14-17], and some bone morphogenetic proteins (BMP6 and -7) have recently been implicated [18]. In fact, when follistatin, a bioneutralizing molecule that binds and neutralizes activins and BMPs, is used, serum levels of FSH in rats decline rapidly and faster than rats treated with GnRH antagonists. Thus, the activins and

BMPs are much stronger inducers than GnRH.

Conclusion:

Short-term dietary intervention investigations have shown that weight loss can restore reproductive fitness and hyperandrogenism and improve metabolic variables in overweight women with PCOS as a group. Long-term investigations of lifestyle change with diabetic populations demonstrate sustained improvement. While there have been no investigations to identify the long-term effects of weight loss in PCOS, lifestyle modification is the focus of the Australian Fertility Fitness Programme run out of Adelaide, Australia. Lifestyle modification is the best initial management strategy for obese women with a desire to enhance their reproductive function and metabolic fitness, thus it should be the primary aim of treatment for overweight women with PCOS. Pharmacological management strategies, including the use of insulin-sensitizing agents, should be routinely viewed as a secondary management option. The principles of lifestyle modification that are likely to bring greatest benefit in overweight women with PCOS, include moderate training exercise, reduced smoking, dietary modification, and a decrease of psychosocial stressors. Group-based approaches offer their own levels of value in terms of support and can ease providers identifying ease to manage lifestyle modification principles. Future studies should identify the impact of varying dietary composition on reproductive fitness and metabolic fitness in PCOS, and inform future studies investigating the relative impact of psychosocial stressors, caffeine, smoking and alcohol in PCOS (box 3).

Box 3. Lifestyle modification suggested for treatment of polycystic ovary syndrome (PCOS) in overweight women

- Moderate exercise (≥30 min day^{-1}).
- Dietary modification (fat ≤30% daily intake, ↓ saturated and trans fat and glycaemic load, ↑ fibre and polyunsaturated fat).
- For weight loss, establishing an energy deficit of 500–1000 kcal day^{-1}.
- Reduction of psychosocial stressors.
- Cessation of smoking.
- Moderate alcohol consumption.
- Moderate caffeine consumption.
- Group interaction/intervention to provide support and assist implementing changes.

References:

1 Lobo, R.A. and Carmina, E. (2000) The importance of diagnosing the polycystic ovary syndrome. Ann. Intern. Med. 132, 989-993

2 Reaven, G. (1999) Syndrome X: 10 years after. Drugs 58 (Suppl. 1), 19-20; discussion 75-82

3 Farquhar, C.M. et al. (1994) The prevalence of polycystic ovaries on ultrasound scanning in a population of randomly selected women. Aust. N. Z. J. Obstet. Gynaecol. 34, 67-72

4 Norman, R.J. et al. (1995) Metabolic approaches to the subclassification of polycystic ovary syndrome. Fertil. Steril. 63, 329-335

5 Zawdaki, J. and Dunaif, A. (1992) Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In Polycystic Ovary Syndrome.Current Issues in Endocrinology and Metabolism (Vol. 4) (Dunaif, A. et al., eds), pp. 377-384, Blackwell Scientific

6 Diamanti-Kandarakis, E. et al. (1999) A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. J. Clin. Endocrinol. Metab. 84, 4006-4011

7 Knochenhauer, E.S. et al. (1998) Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J. Clin. Endocrinol. Metab. 83, 3078-3082

8 Asuncion, M. et al. (2000) A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J. Clin. Endocrinol. Metab. 85, 2434-2438

9 Legro, R.S. (1999) Polycystic ovary syndrome.Phenotype to genotype. Endocrinol. Metab. Clin. North Am. 28, 379-396

10 Legato, M.J. (1997) Gender-specific aspects of obesity. Int. J. Fertil. Womens Med. 42, 184-197

11 AIHW. (2000) Australia's Health 2000: The Seventh Biannual Health Report of the AIHW, Australian Institute of Health and Welfare

12 Rebuffe-Scrive, M. et al. (1989) Anthropometric variables and metabolism in polycystic ovarian disease. Horm. Metab. Res. 21, 391-397

13 Dunaif, A. (1997) Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr. Rev. 18, 774-800

14 Abate, N. et al. (1995) Relationships of generalized and regional adiposity to insulin sensitivity in men. J. Clin. Invest. 96, 88-98

15 Despres, J.P. et al. (2001) Treatment of obesity: need to focus on high risk abdominally obese patients. BMJ 322, 716-720

16 Zaadstra, B.M. et al. (1993) Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. BMJ 306, 484-487

17 Wang, J.X. et al. (2000) Body mass and probability of pregnancy during assisted reproduction treatment: retrospective study. BMJ 321, 1320-1321

18 Ehrmann, D.A. et al. (1999) Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 22, 141-146

19 Legro, R.S. et al. (1999) Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J. Clin. Endocrinol. Metab. 84, 165-169

20 Weerakiet, S. et al. (2001) Prevalence of type 2 diabetes mellitus and impaired glucose tolerance in Asian women with polycystic ovary syndrome. Int. J. Gynaecol. Obstet. 75, 177-184

21 Norman, R.J. et al. (2001) Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. Hum. Reprod. 16, 1995-1998

22 Barzilai, N. et al. (1999) Surgical removal of visceral fat reverses hepatic insulin resistance. Diabetes 48, 94-98

23 Lemieux, S. et al. (1996) Seven year changes in body fat and visceral adipose tissue in women. Association with indexes of plasma glucose-insulin homeostasis. Diabetes Care 19, 983-991

24 Holte, J. et al. (1994) Enhanced early insulin response to glucose in relation to insulin resistance in women with polycystic

ovary syndrome and normal glucose tolerance. J. Clin. Endocrinol. Metab. 78, 1052-1058

25 Kirchengast, S. and Huber, J. (2001) Body composition characteristics and body fat distribution in lean women with polycystic ovary syndrome. Hum. Reprod. 16, 1255-1260

26 Holte, J. et al. (1995) Restored insulin sensitivity but persistently increased early insulin secretion
after weight loss in obese women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 80, 2586-2593

27 Iuorno, M.J. and Nestler, J.E. (2001) Insulin-lowering drugs in polycystic ovary syndrome. Obstet. Gynecol. Clin. North Am. 28, 153-164

28 Hoeger, K. (2001) Obesity and weight loss in polycystic ovary syndrome. Obstet. Gynecol. Clin. North Am. 28, 85-97

29 Andersen, P. et al. (1995) Increased insulin sensitivity and fibrinolytic capacity after dietary intervention in obese women with polycystic ovary syndrome. Metabolism 44, 611-616

30 Kiddy, D.S. et al. (1992) Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. Clin. Endocrinol. (Oxf.) 36, 105-111

31 Pan, X.R. et al. (1997) Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 20, 537-544

32 Tuomilehto, J. et al. (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New Engl. J. Med. 344, 1343-1350

33 Hu, F.B. et al. (2001) Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. New Engl. J. Med. 345, 790-797

34 Diabetes Prevention Program Research Group (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin.
New Engl. J. Med. 346, 393-403

35 NIH (1998) Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults: evidence report. J. Obesity Res. 6 (Suppl. 2), S51-S209

36 Anonymous. (2000) Case problem: dietary recommendations to combat obesity, insulin resistance, and other concerns related to polycystic ovary syndrome. J. Am. Dietetic Assoc. 100, 955-957; discussion 957-960

37 Mikkelsen, P.B. et al. (2000) Effect of fat-reduced diets on 24-h energy expenditure: comparisons between animal protein, vegetable protein, and carbohydrate. Am. J. Clin. Nutr. 72, 1135-1141

38 Piatti, P.M. et al. (1994) Hypocaloric high-protein diet improves glucose oxidation and spares lean body mass: comparison to hypocaloric high-carbohydrate diet. Metabolism 43, 1481-1487

39 Downey, J. et al. (1989) Mood disorders, psychiatric symptoms, and distress in women presenting for infertility evaluation. Fertil. Steril.
52, 425-432

40 Galletly, C. et al. (1996) Improved pregnancy rates for obese, infertile women following a group treatment program. An open pilot study. Gen. Hosp. Psychiatry 18, 192-195

41 Cronin, L. et al. (1998) Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). J. Clin. Endocrinol. Metab. 83, 1976-1987

42Caan, B. et al. (1998) Differences in fertility associated with caffeinated beverage consumption. Am. J. Public Health 88, 270-274

43 Curtis, K.M. et al. (1997) Effects of cigarette smoking, caffeine consumption, and alcohol intake on fecundability. Am. J. Epidemiol. 146, 32-41

44 Stanton, C.K. and Gray, R.H. (1995)

Effects of caffeine consumption on delayed conception.
Am. J. Epidemiol. 142, 1322-1329

45 Bolumar, F. et al. (1997) Caffeine intake and delayed conception: a European multicenter
study on infertility and subfecundity. European Study Group of Infertility Subfecundity. Am. J. Epidemiol. 145, 324-334

46 Satcher, D. (2001) Women and Smoking. A Report of the Surgeon General. Centres for Disease Control

47 Grodstein, F. et al. (1994) Infertility in women and moderate alcohol use. Am. J. Public Health 84, 1429-1432

48 Jensen, T.K. et al. (1998) Does moderate alcohol consumption affect fertility? Follow up study among couples planning first pregnancy. BMJ 317, 505-510

49 Olsen, J. et al. (1997) Does moderate alcohol intake reduce fecundability? A European multicenter study on infertility and subfecundity. European Study Group on Infertility and Subfecundity. Alcohol. Clin. Exp. Res. 21, 206-212

50 Flanagan, D.E. et al. (2000) Alcohol consumption and insulin resistance in young adults. Eur. J. Clin. Invest. 30, 297-301

51 Kiechl, S. et al. (1996) Insulin sensitivity and regular alcohol consumption: large, prospective, cross sectional population study (Bruneck study). BMJ 313, 1040-1044

52 Kovacs, G. and Wood, C. (2001) The current status of polycystic ovary syndrome. Aust. N. Z. J. Obstet. Gynaecol. 41, 65-68

53 Huber-Buchholz, M.M. et al. (1999) Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J. Clin. Endocrinol. Metab. 84, 1470-1474

54 Clark, A.M. et al. (1995) Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Hum. Reprod. 10, 2705-2712

55 Clark, A.M. et al. (1998) Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. Hum. Reprod. 13, 1502-1505

56 Goldzieher, J.W. and Green, J.A. (1962) The polycystic ovary, I: clinical and histological features. J. Clin. Endocrinol. Metab. 22, 325328

57 Kiddy, D.S. et al. (1990) Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: an analysis of 263 consecutive cases. Clin. Endocrinol. (Oxf.) 32, 213-220

58 Balen, A.H. et al. (1995) Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. Hum. Reprod. 10, 2102111

59 Norman, R.J. and Clark, A.M. (1998) Obesity and reproductive disorders: a review. Reprod. Fertil.
Dev. 10, 55-63

60 Dunaif, A. and Thomas, A. (2001) Current concepts in the polycystic ovary syndrome. Annu. Rev. Med. 52, 401-419

61 Norman, R.J. and Clark, A.M. (2000) Lifestyle factors in the aetiology and management of polycystic ovary syndrome. In Polycystic Ovary Syndrome (Kovacs, G.T. ed.), Cambridge
University Pre

62. Constantino D, Minozzi G, Minozzi F, Guaraldi C (2009). Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. Eur Revfor Med Pharmacol Sci. 13: 105-110.

63.Marsh KA, Steinbeck KS, Atkinson FS, Petocz P, Brand-MillerJC (2010). Effect of a low glycemic index compared with a conventional healthy diet on polycystic ovary syndrome. Am J Clin Nutr. 1: 83-92.

64. Stranska Z, Matoulek M , Vilikus Z ,

Svacina S , Stransky P (2011). Aerobic exercise has beneficial impact on atherogenic index of plasma in sedentary overweigh and obese women. Neuro Endocrinol Lett. 32 (1): 102-108.

65.Standardy leczenia dietetycznego otyłości prostej osób dorosłych. Stanowisko Polskiego Towarzystwa Dietetyki 2015 (2015) [Dietary treatment's standards of adults' simple obesity (In Polish to English abstract)]. Dietetyka. 8.

66. Brzozowska M, Karowicz-Bilińska A (2013). The role of vitamin D deficiency in the etiology of polycystic ovary syndrome disorders. Ginekol Pol. 84: 456-460

67. Thomson RL, Spedding S, Buckley JD (2012). Vitamin D in the Aetiology and Management of Polycystic Ovary Syndrome. Clin Endocrinol (Oxf). 3: 343-350.

68. Misiorowski W (2012). Role of vitamin D deficiency in cardiovascular disease. Postępy Nauk Med. 11: 900-905

69. Thomas H, Mitchell G, Rich J, Best M. Defnition of whole person care in general practice in the English language literature: a systematic review. BMJ Open. 2018;8(12):e023758.

70. Grzechocińska B, Dąbrowski FA, Cyganek A, Wielgoś M (2013). The role of vitamin D in impaired fertility treatment. Neuro Endocrinol Lett. 34 (8): 756-62.