HAL
open science

Ovarian Function And Obesity – Interrelationship, Impact On Women's Reproductive Lifespan And Treatment Options

Dominik Rachoń, Helena Teede

To cite this version:

Dominik Rachoń, Helena Teede. Ovarian Function And Obesity – Interrelationship, Impact On Women's Reproductive Lifespan And Treatment Options. Molecular and Cellular Endocrinology, 2009, 316 (2), pp.172. 10.1016/j.mce.2009.09.026 . hal-00550247

HAL Id: hal-00550247

https://hal.science/hal-00550247

Submitted on 25 Dec 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Accepted Manuscript

Title: Ovarian Function And Obesity – Interrelationship, Impact On Women's Reproductive Lifespan And Treatment Options

Authors: Dominik Rachoń, Helena Teede

PII: S0303-7207(09)00523-1
DOI: doi:10.1016/j.mce.2009.09.026
Reference: MCE 7338

To appear in: *Molecular and Cellular Endocrinology*

Received date: 19-12-2008
Revised date: 2-9-2009
Accepted date: 28-9-2009

Please cite this article as: Rachoń, D., Teede, H., Ovarian Function And Obesity – Interrelationship, Impact On Women's Reproductive Lifespan And Treatment Options, *Molecular and Cellular Endocrinology* (2008), doi:10.1016/j.mce.2009.09.026

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

*Manuscript
ACCEPTED MANUSCRIPT

OVARIAN FUNCTION AND OBESITY – INTERRELATIONSHIP, IMPACT ON WOMEN'S REPRODUCTIVE LIFESPAN AND TREATMENT OPTIONS

Dominik Rachoń [1], Helena Teede [2]

1 Department of Clinical Nutrition, Medical University of Gdańsk, Poland.

2 The Jean Hailes Research Unit, School Public Health, Monash University, Melbourne, Victoria, Australia.

Word count 9 301

Corresponding author:
Dominik Rachoń, MD, PhD
Department of Clinical Nutrition,
Medical University of Gdańsk,
Dębinki 7, 80-211 Gdańsk, Poland
e-mail: drachon@amg.gda.pl

Accepted Manuscript

ACCEPTED MANUSCRIPT

ABSTRACT

Insulin resistance (IR) is a consequence of obesity, and in women it is often inextricably linked with ovarian function leading to clinical reproductive manifestations such as early menarche onset, subfertility and polycystic ovary syndrome (PCOS). Likewise, the dramatic fall in oestrogen production after menopause may contribute to weight gain and changes in adipose tissue distribution. Overall, women who are obese, especially those with reproductive complications including PCOS, have been identified as specific high risk subgroups for further progression through to prediabetes, type 2 diabetes mellitus (T2DM) and potentially cardiovascular disease (CVD). This review focuses on the interrelationship between the ovarian function and obesity as well as its treatment strategies.

Key words: obesity, ovaries, menarche, estrogens, androgens, polycystic ovary syndrome, menopause.

Accepted Manuscript

ACCEPTED MANUSCRIPT

Introduction

Transition from the ideal body weight into obesity is a result of an imbalance between caloric intake and physical inactivity. Insulin resistance (IR) is a consequence of obesity and in women it is often inextricably linked with ovarian function, leading to clinical reproductive manifestations across the female life continuum. Specifically, obesity in women manifests as a range of conditions that usually precede many of the acknowledged metabolic disturbances including prediabetes, diabetes and cardiovascular disease (CVD). These include early menarche, subfertility and polycystic ovary syndrome (PCOS). Likewise, at the end of the women's reproductive life, the cessation of ovarian function is also linked with the development of obesity as menopause precipitates abdominal weight gain and the associated adverse metabolic consequences. Overall, women who are obese, especially those with super-imposed reproductive complications including PCOS, have been identified as specific high risk subgroups for further progression through to prediabetes, type 2 diabetes mellitus (T2DM) and potentially CVD. Hence in female patients, practicing clinicians have a unique opportunity to identify those at greatest risk of obesity related metabolic complications early in life through the recognition of women with "reproductive insulin resistant conditions". These patients can then be targeted for early screening, lifestyle optimization, the prevention of the progression to prediabetes, diabetes and CVD as women age.

Earlier age of menarche onset and the risk of obesity in adult life

Data from several large retrospective studies have shown that girls who experience early menarche (before 11-12 years of age) have higher body mass index (BMI) in adult life compared to the late-maturing girls (Adair and Gordon-Larsen, 2001; Wang, 2002). However, the causal direction between earlier menarche and BMI is much debated. The mechanisms are also contentious but data from animal and human studies suggest that leptin may be the link between total body fat and the onset of menarche (reviewed by Shalitin S et al., 2003). Since sexual maturation depends on total body fat and tends to occur earlier in overweight and obese girls (Kaplowitz et al., 2001; Lee et al., 2007), it has been further suggested that childhood adiposity *per se* contributes to the development of obesity in adult life. In fact, it has been shown that nearly all the influence of early menarche on adult excess weight is a result of the influence of elevated relative weight on early maturation (Freedman et al., 2003; Must et al., 2005). Also, results from a prospective study conducted in Norway showed that early menarche onset was not associated with excess weight in girls that were relatively lean at the entry of the study (Bratberg et al., 2007).

Potentially this association between earlier menarche and adult obesity, heralds the beginning of the interaction between obesity and reproduction which spans across the female life continuum. This is in line with the results of a recent large population-based study (13,308 mainly white European women), the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC), showing that earlier age of menarche onset increases the risk of adult diabetes and this appears to be

ACCEPTED MANUSCRIPT

mediated by greater adult adiposity (Lakshman et al., 2008). These data support the advice that healthy lifestyle with adequate caloric intake and physical activity should be strongly advocated in childhood.

Obesity and subfertility in women

It is evident now that adipose tissue takes part in the metabolism of sex steroids and central obesity in women appears to impair reproduction even in the absence of PCOS. Potential mechanisms of subfertility in obese women include insulin resistance with its compensatory hyperinsulinemia, which stimulates ovarian androgen production, as well as increasing peripheral aromatization of androgens to estrogens. Altogether this may alter gonadotrophin secretion altering follicular development (reviewed by Diamanti-Kandarakis and Bergiele, 2001). In a recent cohort of 3029 consecutive subfertile couples it has been also shown that after adjusting for other confounding variables the probability of spontaneous pregnancy declined linearly with the women's body mass index (BMI) over 29 kg/m(2) (van der Steeg et al., 2008). These data suggest that obesity per se may impair reproduction in women.

PCOS and obesity

Polycystic ovary syndrome (PCOS) is the most frequent ovarian disorder in premenopausal women (Azziz et al., 2004) and obesity is a common feature in this endocrinopathy. Depending on the population studied, 20%-69% of women with PCOS are obese (BMI>30) and independent of obesity, women with PCOS have increased intraabdominal fat accumulation (Asuncion et al., 2000; Azziz et al., 2004; Carmina et al., 2007). Again in PCOS the causal direction between PCO and elevated BMI remains contentious.

PCOS commonly presents after menarche in adolescence. As a syndrome, it is characterized by a constellation of features with no specific diagnostic test and a great diversity in its clinical picture (Janssen et al., 2008). For the past 15 years, the identification of PCOS was based on the National Institute Health (NIH) diagnostic criteria which included the presence of biochemical or clinical hyperandrogenism and anovulation (excluding other secondary causes such as: thyroid dysfunction, non-congenital adrenal hyperplasia or hyperprolactinaemia) (Michelmore et al., 2001). According to these criteria, 4–8% of women in the general population have PCOS. However, in the 2003 European Society of Human Reproduction and Embryology (ESHRE) together with the American Society of Reproductive Medicine (ASRM) organized a consensus workshop where new criteria for the diagnosis of PCOS were developed. According to the ESHRE/ASRME consensus, PCOS can be diagnosed in a woman presenting with two out of the three of the following features: clinical and/or biological hyperandrogenism, chronic anovulation, or the presence of polycystic ovaries (PCO) on ultrasound. Current data on the prevalence of PCOS diagnosed according to the ESHRE/ASRM criteria in the

ACCEPTED MANUSCRIPT

general population is suggestive of greater PCOS prevalence compared to NIH diagnosed PCOS (Moran and Teede, 2009). What is more, there is an ongoing controversy over the ESHRE/ASRM definition of PCOS. The "ovulatory PCOS", and even more so, "non-hyperandrogenic PCOS" phenotypes, have received much criticism among practicing clinicians. A recent review by our group has suggested that the NIH PCOS groups may represent a more severe phenotype whereas the new ESHRE phenotypes including ovulatory and non-hyperandrogenic PCOS groups are less severe with metabolic features primarily related to excess weight, specifically increased abdominal fat (in press). In 2006 the Androgen Excess Society (AES) published a position statement pointing out that androgen excess is the key component of PCOS related to its clinical presentation as well as its long-term morbidity, and advocates the diagnosis of PCOS only to be made in the presence of hyperandrogenism (biochemical or clinical) (Azziz et al., 2006).

Insulin resistance (IR) is recognized to be the key pathophysiological feature of PCOS and a significant contributor to its reproductive and metabolic complications (Diamanti-Kandarakis, 2006). Nevertheless, the underlying mechanisms involved in IR in women with PCOS remain somewhat elusive (Kaufman et al., 2008). In the setting of IR and its subsequent hyperinsulinaemia, women with PCOS have increased risk of long-term sequelae, including increased risk of impaired glucose tolerance (IGT), T2DM nd cardiovascular disease (CVD), all exacerbated by coexistent obesity (Boudreaux et al., 2006). There is also emerging evidence that women with PCOS have a greater chance of developing GDM, with a recent meta-analysis reporting an OR of 2.94 (Ehrmann et al., 2006). Data from the epidemiological studies in general populations suggest that IR, independent of other risk factors, significantly increases the risk of CVD (Ruige et al., 1998; Rutter et al., 2005). Recent data suggests that the incidence of cardiovascular complications in insulin resistant and hyperinsulinemic women with PCOS is increased (Shaw et al., 2008). This is consistent with observations that, PCOS patients often display other indices of cardiovascular risk such as dyslipidaemia, high serum homocysteine and inflammatory markers (i.e. serum TNF and IL-6) (Diamanti-Kandarakis et al., 2007b; Guzelmeric et al., 2007; Atamer et al., 2008). They also present clinical features of premature atherosclerosis such as impaired pulse wave velocity (PWV), increased carotid intima media wall thickness (IMT), presence of carotid plaque, and increased coronary artery calcification (Carmina et al., 2008; Moran et al., 2008). Therefore, it is now recognised that treating IR in PCOS patients will effectively treat the symptoms and may also prevent the long-term sequelae of this endocrinopathy (De Leo et al., 2003).

Compensatory hyperinsulinaemia is also a significant contributor to the hyperandrogenism which is a common feature in IR women with PCOS (Diamanti-Kandarakis and Papavassiliou, 2006). Increased serum insulin stimulates ovarian androgen production, but also reduces sex hormone binding globulin (SHBG) production in the liver further increasing serum levels of free bio-available androgens (Azziz et al., 2005). Apart from reproductive (anovulation) and cosmetic (acne, alopecia, hirsutism)

ACCEPTED MANUSCRIPT

consequences of elevated serum androgens in women, emerging evidence also suggests that hyperandrogenaemia increases abdominal obesity, which in turn further aggravates existing IR (Pehlivanov and Orbetzova, 2007). Preadipocytes are known to have androgen receptors and high androgen levels have been shown to induce selective IR in cultured adipocytes (Belosi et al., 2006). Also, long term androgen administration in female-to-male transsexuals has been shown to induce the development of abdominal obesity and IR (Elbers et al., 2003). This is further supported by the effects of anti-androgens like spironolactone, which appear to reduce IR in some (Diamanti-Kandarakis and Panidis, 2007) but not all studies (Cenk Sayin et al., 2003). Also, in a placebo controlled study, the pure anti-androgen flutamide when administered in conjunction with a low-calorie diet to obese women with PCOS, improved hirsutism and hyperandrogenaemia and decreased intraabdominal fat depots (Gambineri et al., 2004; Gambineri et al., 2006). Conversely, molecules which are secreted by the intraabdominal adipose tissue (adipokines) may also promote ovarian androgen production. Data from animal experiments have shown, that TNF may directly stimulate proliferation and steroidogenesis in the rat theca cells (Roby and Terranova, 1990; Spaczynski et al., 1999) and is involved in the apoptosis and anovulation in the rat's ovary (Kaipia et al., 1996). Also, administration of leptin to female rats induces anovulation by direct ovarian effects (Duggal et al., 2000). Additionally, intra-abdominal fat tissue has been shown to express several enzymes involved in the metabolism of androgens which may further contribute to the hyperandrogenism in women with PCOS (Gambineri et al., 2002). Overall, hyperandrogenism and IR hyperinsulinaemia are both implicated in the adverse metabolic effects in women with PCOS, either directly or through an increased predilection for abdominal obesity.

In conclusion, IR and ovarian hyperandrogenism, which promotes the accumulation of intra-abdominal fat, appear to be the primary determinants of the metabolic abnormalities present in women with PCOS (Moran and Teede, 2009). Nevertheless, further studies are warranted to provide a greater understanding of the interactions between these three factors. Additionally, the optimal screening methods and treatment options for women with PCOS need to be developed. Some women who develop obesity often present signs of hyperandrogenism but having regular menses with no PCO in ultrasound. They do not fulfil the criteria for the diagnosis of PCOS. Nevertheless, IR together with compensatory hyperinsulinaemia also play a pathogenic role in the development of hyperandrogenaemia in these individuals. It is however unknown if such a state might predispose these women to the development of PCOS. Generic predisposition may also be involved here.

Non-pharmacological management of obesity in PCOS patients

IR and its compensatory hyperinsulinaemia play a crucial role in the development of central obesity in women with PCOS. Lifestyle studies to reduce IR in obese women with PCOS are limited by small numbers (n=6-40), lack of controls and variable methodologies used to evaluate IR. Although there are no long-term data on lifestyle change in PCOS, benefits including T2DM prevention would be

ACCEPTED MANUSCRIPT

expected (Moran et al., 2008). Short-term low calorie diets (4 weeks) with 6.6-9.0% weight loss have been shown to decrease IR (Hamilton-Fairley et al., 1993; Andersen et al., 1995). Studies of moderate caloric restriction for 2-15 months also gave positive outcomes (Pasquali et al., 1989). Encouragingly small reductions in weight (~5% body weight) have led to positive clinical improvements. Ideal dietary composition also requires clarification in patients with PCOS. In obese women with PCOS, varying protein content did not improve outcomes (Moran et al., 2003; Stamets et al., 2004). When similar energy and protein diets with variable fat contents were studied, effects on insulin levels, but not IR, were noted (Douglas et al., 2006). Currently, caloric restriction seems paramount and specific dietary recommendations require a greater evidence base (Moran et al., 2008). Although dietary control has been shown to have favourable metabolic effects not only in women with PCOS, long-term dietary restriction is generally difficult to maintain. Additionally, very low calorie diets usually alter metabolism by decreasing resting metabolic rate (RMR) which restrains further weight loss. Chronic exercise training increases RMR and is therefore always recommended as an adjunct to any caloric restriction (Moran et al., 2008). A pilot study conducted by Bruner et al. (2006) has shown that a combination of exercise and nutritional counselling in women with PCOS, as well as nutritional counselling alone, had favourable effects on waist girth, body fatness and fasting insulin levels, as well as a trend towards an increase in RMR in the exercise and nutrition group after completion of the intervention (Bruner et al., 2006). Recent studies investigating the effects of exercise in women with PCOS also showed that a 3-months structured exercise training programme caused significant improvement in cardiopulmonary functional capacity, decreased BMI, improved insulin sensitivity (Vigorito et al., 2007) and after 6-months even restored ovulation (Palomba et al., 2008). These data are consistent with the results on life-style intervention in T2DM where it is the first line treatment primarily due to favourable effects on IR, and cardiovascular risk factors (Hamdy et al., 2001). However, further research is warranted to inform on specific exercise prescriptions for women with PCOS and to explore the mechanisms underpinning efficacy of exercise interventions in PCOS and obesity.

Pharmacological management of obesity in PCOS patients

Lifestyle interventions may not be adequate or sustainable. In these cases, pharmacological therapies may have a role in the treatment of PCOS related obesity with a lack of understanding on the mechanisms underpinning the interaction between obesity, IR and reproductive function; current therapies are blunt tools and are of limited efficacy.. Since central obesity is also associated with IR, insulin sensitizers have been used to control body weight gain in patients with PCOS. Most of the data comes from the studies on metformin, a biguanide which is widely used in patients with T2DM for more then half a century. Although, metformin treatment in patients with PCOS has been shown to improve insulin sensitivity in numerous studies, its effects on body weight and central obesity are inconsistent. In one double blind, placebo controlled study metformin has been shown to reduce body

ACCEPTED MANUSCRIPT

weight (Fleming et al., 2002). However, data from our group and from other investigations show that metformin treatment reduces IR without any effects on body weight (Moghetti et al., 2000; Meyer et al., 2007). Also, conclusions from the recent Cochrane review point out that although metformin is an effective treatment for anovulation in women with PCOS and there is some evidence of benefit on parameters of the metabolic syndrome (reduction of fasting insulin levels, blood pressure and low-density lipoprotein cholesterol) there seems to be no effect on BMI or abdominal obesity (Lord et al., 2003). Data from the studies in diabetes only suggest prevention of weight gain with metformin, rather than weight loss, but no long term studies are available to clarify this in PCOS. The effects of other insulin sensitizers such as glitazones have also been evaluated in patients with PCOS. Data from the largest randomized placebo controlled trial, showed that troglitazone decreased serum insulin and androgen levels, improved menstrual cyclicity and restored ovulation in women with PCOS but also increased body weight (Azziz et al., 2001). However, due to its hepatotoxicity, troglitazone has been withdrawn from the market. Limited studies have looked at pioglitazone, which reduces serum insulin and androgens, and may restore menstrual cyclicity and ovulation in women with PCOS (Brettenthaler et al., 2004). However, data in diabetes shows glitazones promote weight gain and with potential teratogenic effects, the use of these drugs in obese reproductive age patients with PCOS may be limited (Pi-Sunyer, 2008).

Sibutramine is a selective serotonin and noradrenaline re-uptake inhibitor approved for the long-term management of obesity. Its primary mechanism of action is increased satiety, although some evidence also suggests increased energy expenditure could play a role in sibutramine-induced weight loss (Poston and Foreyt, 2004). Data from the recent studies on the use of sibutramine in obese patients with PCOS clearly show that treatment with this drug for 6 months together with lifestyle intervention, results in weight reduction and may also decrease hyperandrogenaemia and IR (Sabuncu et al., 2003; Florakis et al., 2008; Lindholm et al., 2008). Treatment with orlistat, a potent inhibitor of gastric and pancreatic carboxyl-ester lipase which impairs digestion of dietary fats, combined with hypo-caloric diet apart from decreasing body weight also led to a reduction of serum insulin and androgen levels in obese PCOS patients (Jayagopal et al., 2005; Diamanti-Kandarakis et al., 2007a; Panidis et al., 2008). Further progress in basic science research into the mechanisms of interaction between IR and obesity will potentially lead to discovery of future therapeutic targets and more research is needed.

Bariatric surgery in the treatment of PCOS related obesity

Bariatric surgery is the most invasive treatment strategy of obesity in PCOS patients. Although, it may lead to a substantial weigh loss (>50% of basal body fat) and a complete resolution or improvement of PCOS symptoms, T2DM, hyperlipidaemia, hypertension and obstructive sleep apnea in simple obesity (Buchwald et al., 2004), it is not devoid of complications. Therefore, bariatric surgery should only be advocated to morbidly obese individuals after careful evaluation of the risk-to-benefit ratio. According to the current National Institute of Health clinical recommendations, surgical

ACCEPTED MANUSCRIPT

treatment of obesity should be considered when BMI is greater than 40 or greater than 35 in patients with a high-risk obesity-related condition following failure of other treatments for weight control (reviewed by Bult et al., 2008) . Results from an uncontrolled study assessing the effect of bariatric surgery in morbidly obese women with PCOS also reported sustained weight loss and complete resolution of all features defining PCOS, including hirsutism, hyperandrogenism, menstrual irregularity, anovulation, IR and metabolic abnormalities (Escobar-Morreale et al., 2005). In another study examining gastric bypass in overweight women with PCOS, a 56.7% weight loss over 1 year decreased hirsutism and improved menstrual cyclicity as well as natural conception (Eid et al., 2005). Nevertheless, these data need to be re-evaluated and supported by larger long-term controlled trials.

The use of oral contraceptive pills (OCP) in obese PCOS patients

Oral contraceptive pills (OCP) are very often first line therapy in women with PCOS. Apart from restoring menstrual cyclicity providing endometrial protection they also decrease the clinical symptoms of hyperandrogenaemia (acne/hirsutism). Nevertheless, the use of OCP in obese women with PCOS raises a number of concerns. High dose OCP (≥35ug of ethynylestradiol/day) appear to increase IR in both PCOS and non-PCOS populations, potentially having adverse long term consequences (Morin-Papunen et al., 2000; Meyer et al., 2007). Additionally, obesity has a significant impact on the risk of venous thromboembolism risk (Ageno et al., 2008) which can be further aggravated by the use of OCP (Martinez and Avecilla, 2007). Data from recent research also point out to the role of a progestin type used however, further studies are warranted. Nevertheless, the use of OCP in obese women with PCOS should be limited to only those where it is indicated and at the lowest possible dose. Patients should also always be informed of the potential complications of such a treatment. Also, in order to provide endometrial protection, the use of a cyclic (10-14 days/month), preferably metabolically neutral progestagen (i.e. dydrogesteron or fourth generation progestagen) for the induction of endometrial shredding can be considered. Again a grater mechanistic/basic science understanding of the interaction between estrogen and progestin therapy and IR could have future therapeutic implications.

Conclusions on obesity in PCOS

Central obesity and hyperandrogenism are underpinned by IR in PCOS as an important aetiological factor. Targeting IR may improve the course of this syndrome and reduce complications such as T2DM. Life style modification including dietary restriction and regular physical training should be the first line therapy. If these are inadequate, or unsustainable pharmacological therapies can be offered. Metformin does not appear to reduce body weight but in PCOS it has been shown to induce ovulation, have favourable metabolic advantages and one can speculate that they may reduce the progression to T2DM. Sibutramine or orlistat can be indicated if lifestyle change is inadequate. The use of OCP in obese women with PCOS should be limited to only those patients where it is indicated.

ACCEPTED MANUSCRIPT

Low dose OCP should be preferred. Bariative surgery is effective but should be reserved to those with morbid obesity where lifestyle change is unsuccessful. Ultimately a greater understanding of the mechanistic interactions between IR, obesity, hyperandrogenism is needed to guide advances in future therapies for this common condition.

Menopause, hormonal changes and obesity

Menopause is a term used to describe the last physiological menstrual period in a woman's life. In clinical practice, menopause is diagnosed retrospectively when the absence of regular menses lasts for at least 12 months (Lund, 2008). It is due to the aging of the ovary resulting from the exhaustion of ovarian follicles (Wise et al., 1996) causing infertility and a progressive loss of its hormonal activity (Greendale and Sowers, 1997). Loss of ovarian oestrogen production is the key pathophysiological event responsible for the consequences of menopause. These not only include so called oestrogen deficiency symptoms such as "hot flushes", increased sweating, insomnia, depression and *dyspareunia* but also impact long-term health.

These hormonal changes have been associated with the development of several chronic conditions including the emergence of the metabolic syndrome (MS) and its consequences such as T2DM and CVD (Carr, 2003). Central obesity is the main feature of the MS and the results from the majority of studies suggest that menopause has a strong impact on the intra-abdominal fat deposition. Data from animal experiments, clearly show that ovariectomy (ovx) in rats causes weight gain and increased abdominal adipose tissue accumulation. Conversely, treatment of ovx rats with oestrogen or any substance with estrogenic potential (i.e. phytoestrogens) attenuates ovariectomy induced weight gain and visceral fat deposition (Rachoń et al., 2007a; Rachoń et al., 2007b). Consistently, aromatase deficient or oestrogen receptor alpha (ERα) knockout mice develop obesity and related metabolic abnormalities again suggesting that oestrogen deprivation may play a pivotal role in postmenopausal weight gain in women (Heine et al., 2000; Jones et al., 2006). Ovarian androgen production appears to be relatively unaffected by menopause and the adrenal glands continue to secrete androgen precursors such as dehydroepiandrosterone-sulfate (DHEA-S) and androstendione, which in the absence of high oestrogen levels leads to the state of relative hyperandrogenism (Wich and Carnes, 1995).

However, data from human studies are somewhat inconsistent and influenced by several factors such as the methodology used to assess body fat distribution and the confounding effect of age (Tchernof and Poehlman, 1998). Most of the studies using anthropometric measurements (waist circumference or waist to hip ratio) failed to detect an effect of menopause on weight gain and central fat distribution (Zamboni et al., 1992; Pasquali et al., 1994). However, studies using radiologic techniques such as computed tomography or dual x-ray absorptiometry (DEXA) showed that menopause may lead to the accumulation of intra-abdominal fat tissue (Tremollieres et al., 1996; Toth et al., 2000). What is more,

Accepted Manuscript

ACCEPTED MANUSCRIPT

data from the few longitudinal studies suggest that menopause predisposes to the development of central obesity (Poehlman et al., 1995; Bjorkelund et al., 1996).

The dramatic fall in serum oestrogen levels together with relative hyperandrogenism may be responsible for weight gain and changes in adipose tissue distribution after menopause (Svendsen et al., 1993). Data from several animal experiments clearly show that oestrogen deficiency in ovx rats may increase food intake (Gray and Wade, 1981; Pedersen et al., 2001) and decrease adipose tissue lipolysis (Darimont et al., 1997), spontaneous physical activity (Roy and Wade, 1975), and energy expenditure (Heine et al., 2000; Pedersen et al., 2001). Also, it has been shown that hypoestrogenemia in ovx rats causes central leptin insensitivity and increases hypothalamic neuropeptide Y levels and thereby contribute to excess fat accumulation (Ainslie et al., 2001). Results from human studies have also demonstrated that women who became postmenopausal had significantly greater reductions in resting metabolic rate and lower physical activity levels compared to their premenopausal controls (Ravussin et al., 1988; Poehlman et al., 1995). Other factors involved in fat metabolism are also likely to be involved. Using real-time PCR analysis, Misso et al. (2005) have compared the expression of various genes involved in fat metabolism in subcutaneous abdominal and gluteal fat in premenopausal, postmenopausal and postmenopausal women treated with oestrogen. Levels of transcripts encoding genes associated with insulin sensitivity (adiponectin, peroxisome proliferator-activated receptor gamma and fatty acid transporter) were significantly greater in gluteal fat from oestrogen depleted postmenopausal women than in fat from oestrogen treated or premenopausal subjects. In contrast, levels of transcripts for acetyl CoA carboxylase alpha, long chain acyl CoA dehydrogenase and hormone sensitive lipase were significantly greater in abdominal fat from premenopausal women than either postmenopausal groups. Also Ferrara et al. (2002) compared in vitro abdominal and gluteal sc adipose tissue metabolism in postmenopausal and perimenopausal women. Despite similar fat cell size and beta-adrenergic receptor and postreceptor (dibutyryl-cAMP)-stimulated lipolysis, basal lipolysis was 77% lower in gluteal adipose cells from postmenopausal compared with perimenopausal women. In addition, adipose tissue lipoprotein lipase (AT-LPL) activity was significantly higher in the postmenopausal compared with perimenopausal women in both gluteal and abdominal adipose cells. These findings indicate that menopause transition is associated with changes in adipose tissue metabolism, which may contribute to the accumulation of body fat after menopause.

It is not yet clear if menopause per se leads to an increase in insulin resistance (IR). Results from several studies show that postmenopausal women have higher fasting glucose and insulin levels compared with premenopausal controls (Dallongeville et al., 1995; Poehlman et al., 1995; Lynch et al., 2001). However, data from all studies using the euglycemic-hyperinsulinemic clamp technique, strongly suggest that aging and central obesity make a major contribution to the development of IR in women after menopause (DeNino et al., 2001; Guthrie et al., 2001). Hence, increased IR after

Accepted Manuscript

ACCEPTED MANUSCRIPT

menopause may be secondary to increased adiposity and potentially exacerbated by reduced physical activity.

Lifestyle modification in the treatment of postmenopausal obesity

Weight loss and physical exercise are the main approaches in the non-pharmacological therapy of postmenopausal central obesity (Simkin-Silverman et al., 2003; Dubnov-Raz et al., 2007). Apart from the reduction of daily caloric intake, aerobic physical activity should be advocated since it has been shown to increase visceral adipocyte lipolysis (reviewed by Poirier and Despres, 2001). In contrast, regular endurance training may improve insulin sensitivity independent of total weight loss (Igwebuike et al., 2008). Also, it has been shown that exercise blunts declines in lipolysis and fat oxidation after dietary-induced weight loss in obese postmenopausal women (Nicklas et al., 1997). Based on a systemic review of randomized controlled trials, early postmenopausal women (50-65 yrs) are likely to benefit from 30 minutes of daily moderate walking in one to three bouts combined with a resistance training programme twice a week (Asikainen et al., 2004).

Pharmacological and surgical treatment of obesity in postmenopausal women

Pharmacological therapy of obesity in postmenopausal women should only be considered as an adjunct to hypocaloric diet and exercise. All the licensed drugs such as orlistat and sibutramine have shown to be effective and are reasonably tolerated (reviewed by Samat et al., 2008). However their use should only be limited to women in whom lifestyle interventions are unfeasible or unsustainable. Treatment with metformin can also be considered, especially in those at risk of diabetes as prevention of both weight gain (ADOPT study) and diabetes (PPP study), however further research is needed (Gokcel et al., 2002).

Bariatric surgery is the most effective long-term treatment for obesity in terms of weight loss, health risks, and improvement in quality of life. In the largest study (n=16 155, 78.8% females) evaluating the risk of all-cause early postsurgical mortality among older patients (60% were ≥ 45 yrs) undergoing open bariatric surgery the rates of 30-day, 90-day, and 1-year mortality for women were 1.5%, 2.1% and 3.7%, respectively and were strongly associated with advancing age. Patients aged 65 years or older had a substantially higher risk (Flum et al., 2005). Therefore, the risk-to-benefit ratio should be considered on an individual basis

The use of hormone replacement therapy (HRT) in postmenopausal women with obesity

Although most intervention trials on the effects of HRT showed that oestrogen use in postmenopausal women may prevent or delay the increase in intra-abdominal fat accumulation and IR (Espeland et al., 1997; Gambacciani et al., 1997) such treatment in obese women should be prescribed with caution and only where indicated. Obesity not only increases breast cancer risk (Modugno et al., 2006) but also enhances the risk of thrombo-embolic complications such as deep vein thrombosis or pulmonary

ACCEPTED MANUSCRIPT

embolism. Therefore, it is advocated that the use of HRT in obese women should be given in lowest effective doses and preferably through parenteral route (i.e. transdermal patches or gels) (Rachoń and Teede, 2008). The type of progestin used in those who have an intact uterus may also have a strong impact on insulin sensitivity and body weight. Therefore, the fourth generation progestins or retroprogestagens (i.e. dydrogesteron) which are devoid of androgenic effects and are metabolically neutral, seem to be more appropriate in HRT in obese postmenopausal women (Sitruk-Ware, 2004). These assumptions however warrant further studies.

Conclusions on obesity after menopause

The dramatic fall in serum oestrogen levels together with relative hyperandrogenism may contribute to weight gain and changes in adipose tissue distribution after menopause. Hypocaloric diets and physical exercise are the main approaches in postmenopausal excess weight. Pharmacological interventions have a limited role and should be only considered as an adjunct therapy in those patients where lifestyle interventions are unfeasible or unsustainable. Although, bariatric surgery is an effective treatment option for long-term reduction of body weight and amelioration of obesity-related complications, it should be only offered to those who are morbidly obese after carefully outweighing the risk-to-benefit ratio. The use of HRT in obese women is not contraindicated and may have favourable metabolic effects, however it should be used with caution and preferably be parenteral (i.e. trandermal patches or gels). Fourth generation progestins or retroprogestagens, which appear metabolically neutral, should also be used in preference.

Conclusion

IR is a consequence of obesity, which in turn is a result of an excessive caloric intake and physical inactivity. In women obesity is often inextricably linked with ovarian function, leading to clinical reproductive manifestations across the female life continuum. These include early menarche, subfertility and PCOS. Likewise, at the end of the women's reproductive life, the cessation of the ovarian function is also linked with the development of obesity as menopause precipitates abdominal weight gain and its adverse metabolic consequences. Overall, women who are obese, especially those with reproductive complications including PCOS, have been identified as specific high risk subgroups for further progression through to prediabetes, T2DM and potentially CVD. Hence in female patients, practicing clinicians have a unique opportunity to identify those at greatest risk of obesity related metabolic complications early in life through the recognition of women with "reproductive insulin resistant conditions". The challenges for researchers include unlocking the mechanisms of IR and the interaction between obesity, hyperandrogenism, reproduction, fertility and hormonal changes and menopause. This is vital to future therapeutic advances.

Accepted Manuscript

ACCEPTED MANUSCRIPT

Conflict of interest

The authors report no conflict of interest.

Sources of funding

Dr. Dominik Rachoń is a fellow of The Group of Eight European Fellowship 2007.

Prof. Helena Teede is a National Health and Medical Research Council (NHMHC) Research Fellow.

Accepted Manuscript

ACCEPTED MANUSCRIPT

REFERENCES

Adair, L.S. and Gordon-Larsen, P., 2001. Maturational timing and overweight prevalence in US adolescent girls. Am. J. Public Health 91, 642-4.

Ageno, W., Becattini, C., Brighton, T., Selby, R. and Kamphuisen, P.W., 2008. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation 117, 93-102.

Ainslie, D.A., Morris, M.J., Wittert, G., Turnbull, H., Proietto, J., Thorburn, A.W., 2001. Estrogen deficiency causes central leptin insensitivity and increased hypothalamic neuropeptide Y. Int. J. Obes. Relat. Metab. Disord. 25, 1680-8.

Andersen, P., Seljeflot, I., Abdelnoor, M., Arnesen, H., Dale, P.O., Lovik, A. and Birkeland, K., 1995. Increased insulin sensitivity and fibrinolytic capacity after dietary intervention in obese women with polycystic ovary syndrome. Metabolism 44, 611-6.

Asikainen, T.M., Kukkonen-Harjula, K. and Miilunpalo, S., 2004. Exercise for health for early postmenopausal women: a systematic review of randomised controlled trials. Sports Med 34, 753-78.

Asuncion, M., Calvo, R.M., San Millan, J.L., Sancho, J., Avila, S. and Escobar-Morreale, H.F., 2000. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J. Clin. Endocrinol. Metab. 85, 2434-8.

Atamer, A., Demir, B., Bayhan, G., Atamer, Y., Ilhan, N. and Akkus, Z., 2008. Serum levels of leptin and homocysteine in women with polycystic ovary syndrome and its relationship to endocrine, clinical and metabolic parameters. J Int Med Res 36, 96-105.

Azziz, R., Ehrmann, D., Legro, R.S., Whitcomb, R.W., Hanley, R., Fereshetian, A.G., O'Keefe, M. and Ghazzi, M.N., 2001. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. J. Clin. Endocrinol. Metab. 86, 1626-32.

Azziz, R., Woods, K.S., Reyna, R., Key, T.J., Knochenhauer, E.S. and Yildiz, B.O., 2004. The prevalence and features of the polycystic ovary syndrome in an unselected population. J. Clin. Endocrinol. Metab. 89, 2745-9.

Azziz, R., Marin, C., Hoq, L., Badamgarav, E. and Song, P., 2005. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. J Clin Endocrinol Metab 90, 4650-8.

Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H.F., Futterweit, W., Janssen, O.E., Legro, R.S., Norman, R.J., Taylor, A.E. and Witchel, S.F., 2006. Position statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J. Clin. Endocrinol. Metab. 91, 4237-45.

Belosi, C., Selvaggi, L., Apa, R., Guido, M., Romualdi, D., Fulghesu, A.M. and Lanzone, A., 2006. Is the PCOS diagnosis solved by ESHRE/ASRM 2003 consensus or could it include ultrasound examination of the ovarian stroma? Hum Reprod 21, 3108-15.

Bjorkelund, C., Lissner, L., Andersson, S., Lapidus, L. and Bengtsson, C., 1996. Reproductive history in relation to relative weight and fat distribution. Int J Obes Relat Metab Disord 20, 213-9.

Boudreaux, M.Y., Talbott, E.O., Kip, K.E., Brooks, M.M. and Witchel, S.F., 2006. Risk of T2DM and impaired fasting glucose among PCOS subjects: results of an 8-year follow-up. Curr Diab Rep 6, 77-83.

Bratberg, G.H., Nilsen, T.I., Holmen, T.L. and Vatten, L.J., 2007. Early sexual maturation, central adiposity and subsequent overweight in late adolescence. a four-year follow-up of 1605 adolescent Norwegian boys and girls: the Young HUNT study. BMC Public Health 7, 54.

Brettenthaler, N., De Geyter, C., Huber, P.R. and Keller, U., 2004. Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism, and ovulatory dysfunction in women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 89, 3835-40.

Bruner, B., Chad, K. and Chizen, D., 2006. Effects of exercise and nutritional counseling in women with polycystic ovary syndrome. Appl. Physiol. Nutr. Metab. 31, 384-91.

Buchwald, H., Avidor, Y., Braunwald, E., Jensen, M.D., Pories, W., Fahrbach, K. and Schoelles, K., 2004. Bariatric surgery: a systematic review and meta-analysis. Jama 292, 1724-37.

Accepted Manuscript

ACCEPTED MANUSCRIPT

Bult, M.J., van Dalen, T. and Muller, A.F., 2008. Surgical treatment of obesity. Eur J Endocrinol 158, 135-45.

Carmina, E., Bucchieri, S., Esposito, A., Del Puente, A., Mansueto, P., Orio, F., Di Fede, G. and Rini, G., 2007. Abdominal fat quantity and distribution in women with polycystic ovary syndrome and extent of its relation to insulin resistance. J. Clin. Endocrinol. Metab. 92, 2500-5.

Carmina, E., Bucchieri, S., Mansueto, P., Rini, G., Ferin, M. and Lobo, R.A., 2008. Circulating levels of adipose products and differences in fat distribution in the ovulatory and anovulatory phenotypes of polycystic ovary syndrome. Fertil Steril.

Carr, M.C., 2003. The emergence of the metabolic syndrome with menopause. J. Clin. Endocrinol. Metab. 88, 2404-11.

Cenk Sayin, N., Gucer, F., Balkanli-Kaplan, P., Ali Yuce, M. and Yardim, T., 2003. Insulin resistance and lipid profile in women with polycystic appearing ovaries: implications with regard to polycystic ovary syndrome. Gynecol Endocrinol 17, 387-96.

Dallongeville, J., Marecaux, N., Isorez, D., Zylbergberg, G., Fruchart, J.C. and Amouyel, P., 1995. Multiple coronary heart disease risk factors are associated with menopause and influenced by substitutive hormonal therapy in a cohort of French women. Atherosclerosis 118, 123-33.

Darimont, C., Delansorne, R., Paris, J., Ailhaud, G. and Negrel, R., 1997. Influence of estrogenic status on the lipolytic activity of parametrial adipose tissue in vivo: an in situ microdialysis study. Endocrinology 138, 1092-6.

De Leo, V., la Marca, A. and Petraglia, F., 2003. Insulin-lowering agents in the management of polycystic ovary syndrome. Endocr Rev 24, 633-67.

DeNino, W.F., Tchernof, A., Dionne, I.J., Toth, M.J., Ades, P.A., Sites, C.K. and Poehlman, E.T., 2001. Contribution of abdominal adiposity to age-related differences in insulin sensitivity and plasma lipids in healthy nonobese women. Diabetes Care 24, 925-32.

Diamanti-Kandarakis, E. and Bergiele, A., 2001. The influence of obesity on hyperandrogenism and infertility in the female. Obes Rev 2, 231-8.

Diamanti-Kandarakis, E., 2006. Insulin resistance in PCOS. Endocrine 30, 13-7.

Diamanti-Kandarakis, E. and Papavassiliou, A.G., 2006. Molecular mechanisms of insulin resistance in polycystic ovary syndrome. Trends Mol. Med. 12, 324-32.

Diamanti-Kandarakis, E., Katsikis, I., Piperi, C., Alexandraki, K. and Panidis, D., 2007a. Effect of long-term orlistat treatment on serum levels of advanced glycation end-products in women with polycystic ovary syndrome. Clin. Endocrinol. (Oxf) 66, 103-9.

Diamanti-Kandarakis, E. and Panidis, D., 2007. Unravelling the phenotypic map of polycystic ovary syndrome (PCOS): a prospective study of 634 women with PCOS. Clin Endocrinol (Oxf) 67, 735-42.

Diamanti-Kandarakis, E., Papavassiliou, A.G., Kandarakis, S.A. and Chrousos, G.P., 2007b. Pathophysiology and types of dyslipidemia in PCOS. Trends Endocrinol Metab 18, 280-5.

Douglas, C.C., Gower, B.A., Darnell, B.E., Ovalle, F., Oster, R.A. and Azziz, R., 2006. Role of diet in the treatment of polycystic ovary syndrome. Fertil Steril 85, 679-88.

Dubnov-Raz, G., Pines, A. and Berry, E.M., 2007. Diet and lifestyle in managing postmenopausal obesity. Climacteric 10 Suppl 2, 38-41.

Duggal, P.S., Van Der Hoek, K.H., Milner, C.R., Ryan, N.K., Armstrong, D.T., Magoffin, D.A. and Norman, R.J., 2000. The in vivo and in vitro effects of exogenous leptin on ovulation in the rat. Endocrinology 141, 1971-6.

Ehrmann, D.A., Liljenquist, D.R., Kasza, K., Azziz, R., Legro, R.S., Ghazzi, M.N. and Group, P.C.T.S., 2006. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. Journal of Clinical Endocrinology & Metabolism 91, 48-53.

Eid, G.M., Cottam, D.R., Velcu, L.M., Mattar, S.G., Korytkowski, M.T., Gosman, G., Hindi, P. and Schauer, P.R., 2005. Effective treatment of polycystic ovarian syndrome with Roux-en-Y gastric bypass. Surgery for Obesity & Related Diseases 1, 77-80.

Elbers, J.M., Giltay, E.J., Teerlink, T., Scheffer, P.G., Asscheman, H., Seidell, J.C. and Gooren, L.J., 2003. Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. Clin. Endocrinol. (Oxf) 58, 562-71.

Accepted Manuscript

ACCEPTED MANUSCRIPT

Escobar-Morreale, H.F., Botella-Carretero, J.I., Alvarez-Blasco, F., Sancho, J. and San Millan, J.L., 2005. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. J Clin Endocrinol Metab 90, 6364-9.

Espeland, M.A., Stefanick, M.L., Kritz-Silverstein, D., Fineberg, S.E., Waclawiw, M.A., James, M.K. and Greendale, G.A., 1997. Effect of postmenopausal hormone therapy on body weight and waist and hip girths. Postmenopausal Estrogen-Progestin Interventions Study Investigators. J Clin Endocrinol Metab 82, 1549-56.

Ferrara, C.M., Lynch, N.A., Nicklas, B.J., Ryan, A.S. and Berman, D.M., 2002. Differences in adipose tissue metabolism between postmenopausal and perimenopausal women. J Clin Endocrinol Metab 87, 4166-70.

Fleming, R., Hopkinson, Z.E., Wallace, A.M., Greer, I.A. and Sattar, N., 2002. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. J. Clin. Endocrinol. Metab. 87, 569-74.

Florakis, D., Diamanti-Kandarakis, E., Katsikis, I., Nassis, G.P., Karkanaki, A., Georgopoulos, N. and Panidis, D., 2008. Effect of hypocaloric diet plus sibutramine treatment on hormonal and metabolic features in overweight and obese women with polycystic ovary syndrome: a randomized, 24-week study. Int J Obes (Lond) 32, 692-9.

Flum, D.R., Salem, L., Elrod, J.A., Dellinger, E.P., Cheadle, A. and Chan, L., 2005. Early mortality among Medicare beneficiaries undergoing bariatric surgical procedures. Jama 294, 1903-8.

Freedman, D.S., Khan, L.K., Serdula, M.K., Dietz, W.H., Srinivasan, S.R. and Berenson, G.S., 2003. The relation of menarcheal age to obesity in childhood and adulthood: the Bogalusa heart study. BMC Pediatr. 3, 3.

Gambacciani, M., Ciaponi, M., Cappagli, B., Piaggesi, L., De Simone, L., Orlandi, R. and Genazzani, A.R., 1997. Body weight, body fat distribution, and hormonal replacement therapy in early postmenopausal women. J Clin Endocrinol Metab 82, 414-7.

Gambineri, A., Pelusi, C., Vicennati, V., Pagotto, U. and Pasquali, R., 2002. Obesity and the polycystic ovary syndrome. Int J Obes Relat Metab Disord 26, 883-96.

Gambineri, A., Pelusi, C., Genghini, S., Morselli-Labate, A.M., Cacciari, M., Pagotto, U. and Pasquali, R., 2004. Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. Clin. Endocrinol. (Oxf) 60, 241-9.

Gambineri, A., Patton, L., Vaccina, A., Cacciari, M., Morselli-Labate, A.M., Cavazza, C., Pagotto, U. and Pasquali, R., 2006. Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. J. Clin. Endocrinol. Metab. 91, 3970-80.

Gokcel, A., Gumurdulu, Y., Karakose, H., Melek Ertorer, E., Tanaci, N., BascilTutuncu, N. and Guvener, N., 2002. Evaluation of the safety and efficacy of sibutramine, orlistat and metformin in the treatment of obesity. Diabetes Obes Metab 4, 49-55.

Gray, J.M. and Wade, G.N., 1981. Food intake, body weight, and adiposity in female rats: actions and interactions of progestins and antiestrogens. Am J Physiol 240, E474-81.

Greendale, G.A. and Sowers, M., 1997. The menopause transition. Endocrinol Metab Clin North Am 26, 261-77.

Guthrie, J.R., Ball, M., Dudley, E.C., Garamszegi, C.V., Wahlqvist, M.L., Dennerstein, L. and Burger, H.G., 2001. Impaired fasting glycaemia in middle-aged women: a prospective study. Int J Obes Relat Metab Disord 25, 646-51.

Guzelmeric, K., Alkan, N., Pirimoglu, M., Unal, O. and Turan, C., 2007. Chronic inflammation and elevated homocysteine levels are associated with increased body mass index in women with polycystic ovary syndrome. Gynecol Endocrinol 23, 505-10.

Hamdy, O., Goodyear, L.J. and Horton, E.S., 2001. Diet and exercise in type 2 diabetes mellitus. Endocrinol Metab Clin North Am 30, 883-907.

Hamilton-Fairley, D., Kiddy, D., Anyaoku, V., Koistinen, R., Seppala, M. and Franks, S., 1993. Response of sex hormone binding globulin and insulin-like growth factor binding protein-1 to an oral glucose tolerance test in obese women with polycystic ovary syndrome before and after calorie restriction. Clin. Endocrinol. (Oxf) 39, 363-7.

ACCEPTED MANUSCRIPT

Heine, P.A., Taylor, J.A., Iwamoto, G.A., Lubahn, D.B. and Cooke, P.S., 2000. Increased adipose tissue in male and female estrogen receptor-alpha knockout mice. Proc Natl Acad Sci U S A 97, 12729-34.

Igwebuike, A., Irving, B.A., Bigelow, M.L., Short, K.R., McConnell, J.P. and Nair, K.S., 2008. Lack of dehydroepiandrosterone effect on a combined endurance and resistance exercise program in postmenopausal women. J. Clin. Endocrinol. Metab. 93, 534-8.

Janssen, I., Powell, L.H., Crawford, S., Lasley, B. and Sutton-Tyrrell, K., 2008. Menopause and the metabolic syndrome: the Study of Women's Health Across the Nation. Arch Intern Med 168, 1568-75.

Jayagopal, V., Kilpatrick, E.S., Holding, S., Jennings, P.E. and Atkin, S.L., 2005. Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. J. Clin. Endocrinol. Metab. 90, 729-33.

Jones, M.E., Boon, W.C., Proietto, J. and Simpson, E.R., 2006. Of mice and men: the evolving phenotype of aromatase deficiency. Trends Endocrinol Metab 17, 55-64.

Kaipia, A., Chun, S.Y., Eisenhauer, K. and Hsueh, A.J., 1996. Tumor necrosis factor-alpha and its second messenger, ceramide, stimulate apoptosis in cultured ovarian follicles. Endocrinology 137, 4864-70.

Kaplowitz, P.B., Slora, E.J., Wasserman, R.C., Pedlow, S.E. and Herman-Giddens, M.E., 2001. Earlier onset of puberty in girls: relation to increased body mass index and race. Pediatrics 108, 347-53.

Kaufman, R.P., Baker, T.E., Baker, V.M., DiMarino, P. and Castracane, V.D., 2008. Endocrine and metabolic differences among phenotypic expressions of polycystic ovary syndrome according to the 2003 Rotterdam consensus criteria. American Journal of Obstetrics & Gynecology 198, 670e1-670e10.

Lakshman, R., Forouhi, N., Luben, R., Bingham, S., Khaw, K., Wareham, N. and Ong, K.K., 2008. Association between age at menarche and risk of diabetes in adults: results from the EPIC-Norfolk cohort study. Diabetologia 51, 781-6.

Lee, J.M., Appugliese, D., Kaciroti, N., Corwyn, R.F., Bradley, R.H. and Lumeng, J.C., 2007. Weight status in young girls and the onset of puberty. Pediatrics 119, e624-30.

Lindholm, A., Bixo, M., Bjorn, I., Wolner-Hanssen, P., Eliasson, M., Larsson, A., Johnson, O. and Poromaa, I.S., 2008. Effect of sibutramine on weight reduction in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Fertil Steril 89, 1221-8.

Lord, J.M., Flight, I.H. and Norman, R.J., 2003. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane. Database. Syst. Rev., CD003053.

Lund, K.J., 2008. Menopause and the menopausal transition. Med Clin North Am 92, 1253-71, xii.

Lynch, N.A., Nicklas, B.J., Berman, D.M., Dennis, K.E. and Goldberg, A.P., 2001. Reductions in visceral fat during weight loss and walking are associated with improvements in VO(2 max). J Appl Physiol 90, 99-104.

Martinez, F. and Avecilla, A., 2007. Combined hormonal contraception and venous thromboembolism. Eur J Contracept Reprod Health Care 12, 97-106.

Meyer, C., McGrath, B.P. and Teede, H.J., 2007. Effects of medical therapy on insulin resistance and the cardiovascular system in polycystic ovary syndrome. Diabetes Care 30, 471-8.

Michelmore, K., Ong, K., Mason, S., Bennett, S., Perry, L., Vessey, M., Balen, A. and Dunger, D., 2001. Clinical features in women with polycystic ovaries: relationships to insulin sensitivity, insulin gene VNTR and birth weight. Clin Endocrinol (Oxf) 55, 439-46.

Misso, M.L., Jang, C., Adams, J., Tran, J., Murata, Y., Bell, R., Boon, W.C., Simpson, E.R. and Davis, S.R., 2005. Differential expression of factors involved in fat metabolism with age and the menopause transition. Maturitas 51, 299-306.

Modugno, F., Kip, K.E., Cochrane, B., Kuller, L., Klug, T.L., Rohan, T.E., Chlebowski, R.T., Lasser, N. and Stefanick, M.L., 2006. Obesity, hormone therapy, estrogen metabolism and risk of postmenopausal breast cancer. Int J Cancer 118, 1292-301.

Moghetti, P., Castello, R., Negri, C., Tosi, F., Perrone, F., Caputo, M., Zanolin, E. and Muggeo, M., 2000. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-

Accepted Manuscript

ACCEPTED MANUSCRIPT

month trial, followed by open, long-term clinical evaluation. J. Clin. Endocrinol. Metab. 85, 139-46.

Moran, L.J., Noakes, M., Clifton, P.M., Tomlinson, L., Galletly, C. and Norman, R.J., 2003. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 88, 812-9.

Moran, L.J., Hutchison, S.K., Meyer, C., Zoungas, S. and Teede, H.J., 2008. A comprehensive assessment of endothelial function in overweight women with and without polycystic ovary syndrome. Clin. Sci. (Lond).

Moran, L.J. and Teede, H.J., 2009. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. Hum. Reprod. Update. 15, 477-88.

Moran, L.J., Pasquali, R., Teede, H.J., Hoeger, K.M. and Norman, R.J., 2008. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertility and sterility. [Epub ahead of print]Morin-Papunen, L.C., Vauhkonen, I., Koivunen, R.M., Ruokonen, A., Martikainen, H.K. and Tapanainen, J.S., 2000. Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. J. Clin. Endocrinol. Metab. 85, 3161-8.

Must, A., Naumova, E.N., Phillips, S.M., Blum, M., Dawson-Hughes, B. and Rand, W.M., 2005. Childhood overweight and maturational timing in the development of adult overweight and fatness: the Newton Girls Study and its follow-up. Pediatrics 116, 620-7.

Nicklas, B.J., Rogus, E.M. and Goldberg, A.P., 1997. Exercise blunts declines in lipolysis and fat oxidation after dietary-induced weight loss in obese older women. Am. J. Physiol. 273, E149-55.

Palomba, S., Giallauria, F., Falbo, A., Russo, T., Oppedisano, R., Tolino, A., Colao, A., Vigorito, C., Zullo, F. and Orio, F., 2008. Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. Hum Reprod 23, 642-50.

Panidis, D., Farmakiotis, D., Rousso, D., Kourtis, A., Katsikis, I. and Krassas, G., 2008. Obesity, weight loss, and the polycystic ovary syndrome: effect of treatment with diet and orlistat for 24 weeks on insulin resistance and androgen levels. Fertil Steril 89, 899-906.

Pasquali, R., Antenucci, D., Casimirri, F., Venturoli, S., Paradisi, R., Fabbri, R., Balestra, V., Melchionda, N. and Barbara, L., 1989. Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss. J. Clin. Endocrinol. Metab. 68, 173-9.

Pasquali, R., Casimirri, F., Labate, A.M., Tortelli, O., Pascal, G., Anconetani, B., Gatto, M.R., Flamia, R., Capelli, M. and Barbara, L., 1994. Body weight, fat distribution and the menopausal status in women. The VMH Collaborative Group. Int J Obes Relat Metab Disord 18, 614-21.

Pedersen, S.B., Bruun, J.M., Kristensen, K. and Richelsen, B., 2001. Regulation of UCP1, UCP2, and UCP3 mRNA expression in brown adipose tissue, white adipose tissue, and skeletal muscle in rats by estrogen. Biochem Biophys Res Commun 288, 191-7.

Pehlivanov, B. and Orbetzova, M., 2007. Characteristics of different phenotypes of polycystic ovary syndrome in a Bulgarian population. Gynecol Endocrinol 23, 604-9.

Pi-Sunyer, F.X., 2008. The effects of pharmacologic agents for type 2 diabetes mellitus on body weight. Postgrad Med 120, 5-17.

Poehlman, E.T., Toth, M.J. and Gardner, A.W., 1995. Changes in energy balance and body composition at menopause: a controlled longitudinal study. Ann. Intern. Med. 123, 673-5.

Poirier, P. and Despres, J.P., 2001. Exercise in weight management of obesity. Cardiol. Clin. 19, 459-70.

Poston, W.S. and Foreyt, J.P., 2004. Sibutramine and the management of obesity. Expert Opin Pharmacother 5, 633-42.

Rachoń, D. and Teede, H., 2008. Postmenopausal hormone therapy and the risk of venous thromboembolism. Climacteric 11, 273-9.

Rachoń, D., Vortherms, T., Seidlova-Wuttke, D. and Wuttke, W., 2007a. Effects of dietary equol on body weight gain, intra-abdominal fat accumulation, plasma lipids, and glucose tolerance in ovariectomized Sprague-Dawley rats. Menopause 14, 925-32.

ACCEPTED MANUSCRIPT

Rachoń, D., Vortherms, T., Seidlova-Wuttke, D. and Wuttke, W., 2007b. Dietary daidzein and puerarin do not affect pituitary LH expression but exert uterotropic effects in ovariectomized rats. Maturitas 57, 161-70.

Ravussin, E., Lillioja, S., Knowler, W.C., Christin, L., Freymond, D., Abbott, W.G., Boyce, V., Howard, B.V. and Bogardus, C., 1988. Reduced rate of energy expenditure as a risk factor for body-weight gain. N Engl J Med 318, 467-72.

Roby, K.F. and Terranova, P.F., 1990. Effects of tumor necrosis factor-alpha in vitro on steroidogenesis of healthy and atretic follicles of the rat: theca as a target. Endocrinology 126, 2711-8.

Roy, E.J. and Wade, G.N., 1975. Role of estrogens in androgen-induced spontaneous activity in male rats. J Comp Physiol Psychol 89, 573-9.

Ruige, J.B., Assendelft, W.J., Dekker, J.M., Kostense, P.J., Heine, R.J. and Bouter, L.M., 1998. Insulin and risk of cardiovascular disease: a meta-analysis. Circulation 97, 996-1001.

Rutter, M.K., Meigs, J.B., Sullivan, L.M., D'Agostino, R.B., Sr. and Wilson, P.W., 2005. Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham Offspring Study. Diabetes 54, 3252-7.

Sabuncu, T., Harma, M., Harma, M., Nazligul, Y. and Kilic, F., 2003. Sibutramine has a positive effect on clinical and metabolic parameters in obese patients with polycystic ovary syndrome. Fertil Steril 80, 1199-204.

Samat, A., Rahim, A. and Barnett, A., 2008. Pharmacotherapy for obesity in menopausal women. Menopause Int 14, 57-62.

Simkin-Silverman, L.R., Wing, R.R., Boraz, M.A. and Kuller, L.H., 2003. Lifestyle intervention can prevent weight gain during menopause: results from a 5-year randomized clinical trial. Ann. Behav. Med. 26, 212-20.

Sitruk-Ware, R., 2004. New progestogens: a review of their effects in perimenopausal and postmenopausal women. Drugs Aging 21, 865-83.

Shalitin, S., Phillip, M., 2003. Role of obesity and leptin in the pubertal process and pubertal growth--a review. Int. J. Obes. Relat. Metab. Disord. 27, 869-74.

Shaw, L.J., Bairey Merz, C.N., Azziz, R., Stanczyk, F.Z., Sopko, G., Braunstein, G.D., Kelsey, S.F., Kip, K.E., Cooper-Dehoff, R.M., Johnson, B.D., Vaccarino, V., Reis, S.E., Bittner, V., Hodgson, T.K., Rogers, W. and Pepine, C.J., 2008. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health--National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. J Clin Endocrinol Metab 93, 1276-84.

Spaczynski, R.Z., Arici, A. and Duleba, A.J., 1999. Tumor necrosis factor-alpha stimulates proliferation of rat ovarian theca-interstitial cells. Biol. Reprod. 61, 993-8.

Stamets, K., Taylor, D.S., Kunselman, A., Demers, L.M., Pelkman, C.L. and Legro, R.S., 2004. A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. Fertil Steril 81, 630-7.

Svendsen, O.L., Haarbo, J., Hassager, C. and Christiansen, C., 1993. Accuracy of measurements of body composition by dual-energy x-ray absorptiometry in vivo. Am. J. Clin. Nutr. 57, 605-8.

Tchernof, A. and Poehlman, E.T., 1998. Effects of the menopause transition on body fatness and body fat distribution. Obes Res 6, 246-54.

Teede, H.J., Meyer, C. and Norman, R.J., 2005. Insulin-sensitisers in the treatment of polycystic ovary syndrome. Expert Opin Pharmacother 6, 2419-27.

Toth, M.J., Tchernof, A., Sites, C.K. and Poehlman, E.T., 2000. Effect of menopausal status on body composition and abdominal fat distribution. Int J Obes Relat Metab Disord 24, 226-31.

Tremollieres, F.A., Pouilles, J.M. and Ribot, C.A., 1996. Relative influence of age and menopause on total and regional body composition changes in postmenopausal women. Am. J. Obstet. Gynecol. 175, 1594-600.

van der Steeg, J.W., Steures, P., Eijkemans, M.J., Habbema, J.D., Hompes, P.G., Burggraaff, J.M., Oosterhuis, G.J., Bossuyt, P.M., van der Veen, F. and Mol, B.W., 2008. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. Hum Reprod 23, 324-8.

Accepted Manuscript

ACCEPTED MANUSCRIPT

Vigorito, C., Giallauria, F., Palomba, S., Cascella, T., Manguso, F., Lucci, R., De Lorenzo, A., Tafuri, D., Lombardi, G., Colao, A. and Orio, F., 2007. Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 92, 1379-84.

Wang, Y., 2002. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics 110, 903-10.

Wich, B.K. and Carnes, M., 1995. Menopause and the aging female reproductive system. Endocrinol Metab Clin North Am 24, 273-95.

Wise, P.M., Krajnak, K.M. and Kashon, M.L., 1996. Menopause: the aging of multiple pacemakers. Science 273, 67-70.

Zamboni, M., Armellini, F., Milani, M.P., De Marchi, M., Todesco, T., Robbi, R., Bergamo-Andreis, I.A. and Bosello, O., 1992. Body fat distribution in pre- and post-menopausal women: metabolic and anthropometric variables and their inter-relationships. Int J Obes Relat Metab Disord 16, 495-504.

Accepted Manuscript