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Improving reproductive performance in overweight/obese women with effective weight management

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Obesity and overweight are common conditions in the developed countries and they carry many health consequences, including some reproductive disorders. There is a very high prevalence of obese women in the infertile population and many studies have highlighted the link between obesity and infertility. A large proportion of infertile women have polycystic ovary syndrome (PCOS) which is also linked with increased risk of obesity and other metabolic anomalies. The association between obesity and/or PCOS and hyperinsulinaemia, hyperandrogenism and abnormal secretion of other hormones, such as leptin, underlies many reproductive disorders observed in this population. It has been demonstrated that weight loss can improve the fertility of obese women through the recovery of spontaneous ovulation, whereas others will have improved response to ovarian stimulation in infertility treatment. Therefore, it is proposed that following the initial assessment of infertility and body mass index or other measurement of obesity, various weight management interventions, including diet, exercise or pharmacotherapeutic approaches, should be considered for overweight and obese infertile women.

Key words: fertility fitness/obese/overweight/PCOS/weight loss

Introduction

There is great concern at the high prevalence of and the increasing trend to obesity worldwide, especially in Western societies. This is particularly evident in the USA where >50% of all women are overweight and 30% obese. In Australia, 67% of men are overweight or obese and 52% of women are overweight or obese which constitutes a marked increase over the last 20 years (Australian Institute of Health and Welfare, 2002). The consequent cost of obesity to national health systems is high (Anonymous, 2003) due to the increased morbidity and mortality, including the risk of several cancers associated with obesity (Calle *et al*., 1999, 2003). The worldwide trend of increasing obesity is attributable to a combination of reduced exercise, changing dietary composition and increased energy intake. While increased weight gain among young children is particularly evident in developed countries, changing lifestyles in developing countries will see the trend to obesity extend worldwide. Many ethnic groups who either migrate to Western societies or adopt a Western lifestyle are prone to obesity in their changed environment. Diamond (2003) has reviewed the epidemiology of diabetes in various populations; the data suggest that genetic tendencies to obesity are unmasked by geographical differences in food history. The thrifty gene hypothesis postulates the existence of metabolically thrifty genes that permit more efficient food utilization, fat deposition and rapid weight gain at occasional times of food abundance, thereby making the gene bearer better able to survive a subsequent famine. An alternative theory of the ‘thrifty phenotype’, based on experimental studies in animals, argues that the capacity for intergenerational metabolic adaptations to increased energy supply are easily exceeded among populations exposed to a ‘lean’ environment for even a single generation (Hales and Ozanne 2003).

Gynaecologists and reproductive scientists have encountered the reproductive consequences of a society increasing in weight as a higher frequency of women diagnosed with disorders of menstruation, infertility, diabetes mellitus in pregnancy and other significant sequelae (Sharpe and Franks, 2002). In addition, polycystic ovary syndrome (PCOS), is a condition characterized by hyperandrogenism and menstrual disturbances, further complicates the issue (Norman *et al*., 2002). At the same time, many advances have been made in recent years on the effect of weight reduction in improving reproductive function in overweight and obese infertile women, and there is now a better understanding of how weight reduction through dieting/exercising leads to improved reproductive performance. Finally, there have been interesting reports of how best to achieve and maintain weight loss through effective weight management.

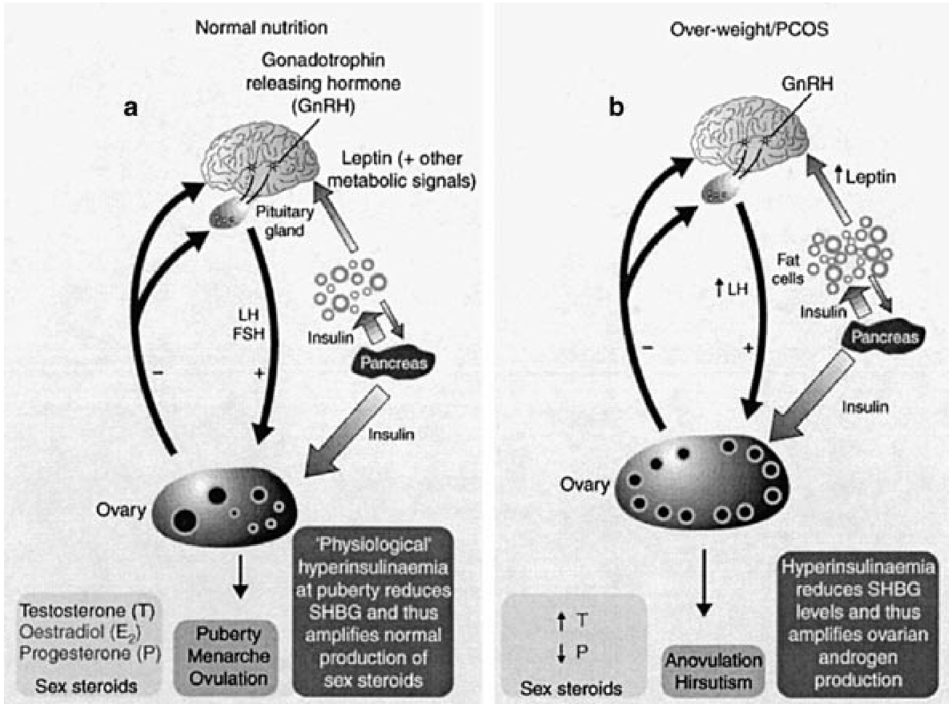

Figure 1. Hormonal mechanisms that link nutrition/diet and female fertility. (**a**) Normal ovarian function—resulting in normal puberty and reproductive competence—is controlled primarily by the gonadotrophins LH and FSH from the pituitary gland, the secretion of which is regulated by the brain hormone, GnRH. Nutrition is linked to the female reproductive system through the effects of a hormone emanating from fat cells (leptin) and by insulin from the pancreas, which alters the bioavailability of estradiol and testosterone by affecting production of SHBG (sex hormone-binding globulin) from the liver. Insulin can also function directly on the ovary. (**b**) In overweight women and/or those with polycystic ovary syndrome (PCOS), an increase in the number of fat cells results in a cascade of changes, involving increased leptin and insulin levels and a preferential increase in LH, but not FSH, levels. The net effect of these changes is to stimulate the partial development of follicles that secrete supranormal levels of testosterone, but which rarely ovulate (hence low progesterone). These changes are exacerbated by insulin-induced reduction in SHBG, which amplifies ovarian testosterone production/action. In addition, there is a genetic predisposition to PCOS. It should be noted that impaired fetal growth can also result in an increase in the number/size of fat cells and an increase in insulin resistance in adulthood, although the relationship to fertility and PCOS is still unclear. (From Sharpe and Franks, 2002; with permission.)

Obesity, PCOS and reproductive disorders

Obesity, particularly in women with PCOS, can result in many reproductive disorders. This is due to the complex interaction between the pituitary gland, pancreas and ovary resulting in a changed hormonal secretion pattern (Figure 1) The original descriptions by Stein and Levinthal (1934) emphasized the association of obesity with PCOS. However, the use of hormone measurement and ultrasound led to a realization that not all patients with PCOS suffered from being overweight. Over a third to 50% of PCOS subjects are overweight or obese (Balen *et al*., 1995; Gambineri *et al*., 2002). Variation in body weight between PCOS populations in USA and Europe, attributed to genetic and lifestyle factors, has also been reported recently (Carmina *et al*., 2003). In PCOS women of Caucasian origin, it is found that the severity of both metabolic and clinical symptoms is positively correlated with the body mass index (BMI) (Norman *et al*., 1995). There is also evidence showing that even normal weight PCOS subjects have increased intra-abdominal fat (Yildirim *et al*., 2003).

In subfertile/infertile women with PCOS, overweight or obesity usually is more prevalent. The relative importance of PCOS status and overweight/obesity in this group of women is yet to be fully understood, although increasing evidence suggests that BMI contributes significantly towards the severity of many problems, such as the risk of miscarriage (Wang *et al*., 2002). Understanding the changed glucose metabolism and consequently modified androgen secretion in overweight/obese women with PCOS is the key for assessing the link between obesity and the risk of various reproductive disorders in this group of women. Leptin is another key link between obesity and reproductive disorder.

PCOS, insulin resistance and hyperandrogenism

Insulin resistance and compensatory hyperinsulinaemia have been consistently documented in lean and obese women with PCOS in comparison to weight-matched controls (Burghen *et al*., 1980; Chang *et al*., 1983; Moller and Flier, 1991; Dunaif, 1997). The severity of insulin resistance is reported to correlate with the severity of the clinical and metabolic phenotype of PCOS (Burghen *et al*., 1980; Robinson *et al*., 1993). Anovulatory women displaying hyperandrogenism and ovarian morphology consistent with PCOS are insulin resistant, whereas ovulatory women usually are not (Dunaif et al., 1985, 1987; Robinson *et al*., 1993).

As insulin resistance is influenced strongly by obesity in non-PCOS subjects (Beard *et al*., 1987), it was initially debated whether insulin resistance and hyperinsulinaemia are a primary metabolic disturbance of PCOS or a symptom of the obesity commonly observed in PCOS (Ovesen *et al*., 1993; Holte *et al*., 1994a, 1995). A synergistic interaction appears to exist with a degree of insulin resistance and hyperinsulinaemia in lean PCOS women augmented by the presence of obesity (Campbell and Gerich, 1990; Dunaif, 1997). The extent of this is still debatable, as not all women with PCOS exhibit hyperinsulinaemia and insulin resistance (Dale *et al*., 1992; Ehrmann *et al*., 1995). Discrepant results may in part be explained by the heterogeneity and complex aetiology of the syndrome, with lean and obese subgroups displaying varying insulin resistance and metabolic profiles (Acien *et al*., 1999). The presence of abdominal obesity is strongly associated with insulin resistance in subjects without PCOS (Hollmann *et al*., 1997). This additionally appears to hold true for both lean and obese women with PCOS, who may both exhibit increased abdominal obesity (Dale *et al*., 1992; Bringer *et al*., 1993), associated with increased insulin resistance (Pasquali *et al*., 1994).

An alternative mechanism for insulin resistance in PCOS that underlies the risk of developing into type II diabetes has been suggested. Deficient insulin action (Dunaif *et al*., 1995), β-cell dysfunction (Ehrmann *et al*., 1995), increased insulin secretion in response to dietary stimuli (Holte *et al*., 1994a,b) and decreased hepatic clearance of insulin (Ciampelli *et al*., 1997) are hypothesized to play an aetiological role in PCOS. Current research is attempting to elucidate its molecular and genetic rationale; as yet, no clear consensus has been reached.

Hyperinsulinaemia correlates positively with the presence of hyperandrogenism in obese and lean women with PCOS. The hyperandrogenism is postulated to result from both increased adrenal and ovarian androgen production (Rosenfield *et al*., 1990; Carmina *et al*., 1992; Ehrmann *et al*., 1992, 1995). These tissues do not appear to display insulin resistance whereas ovarian tissues may have selective resistance to insulin (Wu *et al*., 2003). This would agree with the suggested diverging insulin signalling in ovarian tissue (Nestler *et al*., 1998). Androgen overproduction has been reported both in unstimulated and LH-stimulated ovarian thecal cells (Gilling-Smith *et al*., 1997; Nelson *et al*., 1999) and in response to hyperinsulinaemia (Poretsky and Kalin, 1987). Hyperinsulinaemia has additionally been documented as decreasing serum sex hormone-binding globulin (SHBG) levels independent of obesity (Haffner, 1996). SHBG is produced in the liver and helps in the clearance and binding of testosterone. A low SHBG level will thus result in increased bioavailable testosterone (Plymate *et al*., 1988; Nestler *et al*., 1991).

While there is also abundant evidence associating an increased BMI with diabetes mellitus, subjects with PCOS in particular have a substantial added risk of glucose intolerance. In a study from Adelaide in women with PCOS (aged 20–30 years), 18% of women with a BMI >30 kg/m^2 had impaired glucose metabolism while 15% of women with normal glucose tolerance showed conversion to impaired glucose tolerance or frank diabetes when restudied 5–7 years later (Norman *et al*., 2001). The deterioration of glucose metabolism is significantly related to the initial weight (Wang *et al*., 2003). Conway *et al*. (1993) also showed that 8% of lean and 11% of obese women with PCOS had abnormal glucose tolerance.

PCOS and metabolic syndrome

The endocrine disturbances in PCOS can also result in long-term consequences. The insulin dysfunction previously discussed may lead to an increased occurrence of type II diabetes mellitus and impaired glucose tolerance (IGT) in later adult life (Dahlgren *et al*., 1992b; Legro *et al*., 1999). An increased incidence of hypertension has been reported in PCOS women compared to non-PCOS subjects (Dahlgren *et al*., 1992b; Holte *et al*., 1994b; Wild *et al*., 2000; Elting *et al*., 2001). The above attributes are found in both pre- and post-menopausal women (Dahlgren *et al*., 1992b), indicating a possible long-term risk associated with PCOS.

Together with increased abdominal obesity, this symptom clustering shows a striking similarity to the metabolic syndrome (Reaven, 1988). The predominance of these risk factors in women with PCOS may place them at a higher risk for cardiovascular and coronary heart disease later in life (Wild *et al*., 1990; Birdsall *et al*., 1997). Dahlgren *et al*. (1992a) showed in a retrospective study an increased risk profile (4–11 fold at ages 40–49 and 50–60 years) of myocardial infarction (MI) in women with PCOS compared to the general population. Increased activity of plasminogen activation inhibitor-I (PAI-I) and C-reactive protein (CRP) associated with increased risk of MI has been reported in PCOS (Sampson *et al*., 1996). There was also an increased fatal MI rate for women with irregular periods in the Nurses' Health Study (Rich-Edwards *et al*., 1994). Conversely, long-term follow-up studies have failed to demonstrate increased circulatory disease mortality with PCOS (Pierpoint *et al*., 1998). The lack of a uniform definition of PCOS until recently and the heterogeneous nature of this syndrome has limited our capacity to study the real association between PCOS and cardiovascular disease. A large, prospective, long-term follow-up study in a PCOS population with clear and extensive phenotyping of PCOS abnormalities at baseline is needed, as recently pointed out by Legro (2003).

Obesity and leptin

Leptin plays a potentially important role in human infertility given the discovery of its regulatory effect on fertility in the mouse (Castracane and Henson, 2002). There is a strong correlation between serum leptin concentrations and body fat (Maffei *et al*., 1995; Considine *et al*., 1996; Vicennati *et al*., 1998) and BMI (Chapman *et al*., 1997) in humans. Leptin levels have also been reported to be increased in women with PCOS (Brzechffa *et al*., 1996; Vicennati *et al*., 1998) although this was not supported by many other studies (Chapman *et al*., 1997; Rouru *et al*., 1997; Gennarelli *et al*., 1998). There is no clear explanation for this inconsistency, although the complex interrelation between leptin and body weight, obesity, body fat distribution and many other factors means that studies with large sample size and proper statistical analysis are required for delineating the relationship. On the other hand, there is a consistent positive association between leptin levels and obesity (Brzechffa *et al*., 1996; Chapman *et al*., 1997; Rouru *et al*., 1997; Gennarelli *et al*., 1998; Vicennati *et al*., 1998) and non-obese women of PCOS were not hyperleptinaemic (El Orabi *et al*., 1999). Given the well-established effect of leptin on ovarian steroidogenesis and ovulation in rodents (Duggal *et al*., 2000; Ryan *et al*., 2002, 2003) and in humans (Agarwal *et al*., 1999; Brannian *et al*., 1999; Loffler *et al*., 2001), it can be speculated that the high concentration of leptin might have a role in the pathogenesis of PCOS and reproductive disorders influenced by obesity.

Obesity and menstrual disorder

Classic studies by Mitchell and Rogers (Mitchell, 1953) and Hartz *et al*. (1979) showed that obesity was present at a 4-fold higher rate in women with menstrual disturbances than in women with normal cycles. Forty-five per cent of amenorrhoeic women were obese whereas only 9–13% of women with normal periods were overweight. Furthermore, anovulation was strongly associated with obesity: grossly obese women had a rate of menstrual disturbance 3.1-fold more frequent than women in the normal weight range (BMI 18.5–25.0 kg/m^2). Teenage obesity was positively correlated with menstrual irregularity later in life and obesity was correlated with abnormal and long cycles, heavy menstrual flow and hirsutism. Lake *et al*. (1997) studied women at ages 7, 11, 16, 23 and 33 years and found obesity in childhood and the early 20s increased the risk of menstrual problems [odds ratio (OR) 1.75 and 1.59 respectively]. Women who were overweight (BMI 23.9–28.6 kg/m^2) and obese (>28.6 kg/m^2) at 23 years of age were respectively 1.32 and 1.75 times more likely to have menstrual difficulties. Girls with menarche at 9, 10 or 11 years were more likely to have menstrual problems at 16.5 years (OR 1.45 for mild and 1.94 for severe menstrual abnormality), as confirmed by Ibanez *et al*. (1998).

The presence of PCOS may further aggravate the effect of obesity on menstrual functions. Of 1741 UK subjects with PCOS, 70% had menstrual disturbances and only 22% had normal menstrual function if their BMI was >30 kg/m^2 (Balen *et al*., 1995). Kiddy *et al*. (1992) found that obese subjects with PCOS had an 88% chance of menstrual disturbance compared to 72% in non-obese subjects with PCOS.

In the Nurses' Health Study II (n = 101 073 women), women with long or highly irregular menstrual cycles (⩾40 days length) had a significantly increased relative risk (RR) of developing type II diabetes mellitus compared to women with a regular menstrual cycle (26–31 days) (RR = 2.08) after adjustment for BMI. This risk was more marked in obese women although lean women with menstrual irregularity also had an increased risk of type II diabetes mellitus (RR of 1.67, 1.74 and 3.86 for BMI at age 18 of <25, 25–29 and ⩾30 respectively) (Solomon *et al*., 2001). This indicates that reproductive dysfunction is associated with an increase in metabolic morbidity that is only partially mediated by weight.

Obesity and infertility

Many multiparous women are obese, indeed most obese women are able to achieve pregnancy readily. In support of this, a large study of fertile women did not show any relationship between conception rates and weight or BMI (Howe *et al*., 1985). However, obese and overweight women are over-represented in gynaecological and reproductive medicine clinics. Obesity in the teenage years is more common among married women who never became pregnant than for married women who did become pregnant (Hartz *et al*., 1979). The Nurses' Health Study reported that in 2527 married infertile nurses, the relative risk of ovulatory infertility was 1.3-fold higher (95% CI 1.2–1.6) in the group with a BMI range of 24–31 kg/m^2 and 2.7-fold higher (2.0–3.7) in women with a BMI >32 kg/m^2 (Rich-Edwards *et al*., 1994). More recent data from this group show that ovulatory infertility can be largely attributable to overweight and a sedentary lifestyle (Rich-Edwards *et al*., 2002). Grodstein *et al*. (1994a) showed that anovulatory infertility in 1880 infertile women and 4023 controls was more common in those with a BMI of >26.9 kg/m^2 (RR 3.1, 2.2–4.4) Even high normal to slightly overweight levels may have an effect on fertility.

Weight during childhood did not predict adult fecundity, but weight at 23 years did if the woman was obese (OR 0.69, 0.56–0.87). Obese women at 23 years were less likely to become pregnant within 12 months than women of normal weight, while infertility rate was 33.6% in obese women versus 18.6% in normal weight women (Lake *et al*., 1997).

Zaadstra *et al*. (1993) found that the upper quartile of BMI (>33.1 kg/m^2) in a group of apparently normal women who were undergoing donor insemination led to a reduced chance of pregnancy (OR 0.43). This was a particularly significant study because few of the women required medication to stimulate ovulation. Kusakari *et al*. (1990) in Japan found that obesity was related to anovulation and/or infertility and Balen *et al*. (1995) also found that obesity was correlated with higher infertility rates. In 204 North American women (Green *et al*., 1988), there was a reduced fertility rate among women who were >20% of ideal body weight (OR 2.1)—this did not apply to women who had previously been pregnant. Indeed, obese or overweight subfertile or infertile women have a lower success rate during infertility treatment (Koloszar *et al*., 2002). Several reports confirmed the independent effect of BMI on fecundity in infertile women treated by assisted reproductive technology; with very obese women having half the odds of conception compared to moderate BMI women (Wang *et al*., 2000; Wittemer *et al*., 2000; Nichols *et al*., 2003) although complex interaction between various factors, including infertility aetiology and body fat distribution, may obscure such a relationship (Lashen *et al*., 1999). It has been suggested that intrafollicular hCG concentrations are related to BMI, and this may explain the concurrent decrease in embryo quality and pregnancy rates (Carrell *et al*., 2001). Imani *et al*. (2000) found that free androgen index and leptin are the most prominent endocrine predictors of ovarian response during ovulation induction by clomiphene citrate. However, more research will be needed for a better understanding of the association.

Women with central obesity take longer to become pregnant, indicating that fat distribution plays a role in the chance of becoming pregnant. Zaadstra *et al*. (1993) have shown that fertile women with central adiposity take longer to become pregnant than women of the same BMI with peripheral adiposity. Even lean women with PCOS have a significantly higher amount of body fat than controls (Kirchengast and Huber, 2001). There is also an association between central adiposity, anovulatory cycles and hyperinsulinaemia in adolescent girls born small for gestational age (SGA) (Ibanez *et al*., 2002). Ibanez *et al*. found that ovulation was restored following metformin treatment and a reduction in abdominal fat mass. The mechanism of this effect is uncertain but it is well known that increased central fat distribution is associated with a higher level of circulating insulin and other features of the metabolic syndrome.

Obesity, miscarriage and other adverse pregnancy outcomes

Weight excess is associated with an increased risk of miscarriage. In a study of primiparous women seeking a spontaneous pregnancy (Hamilton-Fairley *et al*., 1992), 11% of women with a BMI 19–24.9 kg/m^2, 14% with BMI 25–27.9 kg/m^2 and 15% of those

>28 kg/m^2 miscarried (OR 1, 1.26 and 1.37 respectively). Women >82 kg are more likely to miscarry than thinner women (OR 2.7 for 82–95 kg and 3.4 for >95 kg) (Bohrer and Kemmann, 1987) while even a mild increase in BMI (25–28 kg/m^2) leads to a significantly higher risk of pregnancy loss (OR 1.37, 1.18–1.60) following gonadotrophin ovulation induction in some series (Hamilton-Fairley *et al*., 1992; Pettigrew and Hamilton-Fairley, 1997). In pregnancies achieved by assisted reproduction treatment, we also showed a marked increase in the risk of miscarriage in overweight and obese women independent of PCOS (Wang *et al*., 2002). Another recent study in women receiving donated oocytes also observed obesity as an independent risk factor for miscarriage (Bellver, 2003). Obesity is also a risk factor for early pregnancy loss after assisted reproduction treatment (Fedorcsak *et al*., 2000), although it was found unrelated to preclinical pregnancy loss (Winter *et al*., 2002).

The adverse effect of overweight and obesity on pregnancy and obstetric outcome is well known. Some of the American studies on massively obese women indicate high health risks and resultant increased costs to the health system (Galtier-Dereure *et al*., 2000), for example cost in increased requirement for infertility treatment (Rich-Edwards *et al*., 2002). High pre-pregnancy weight is associated with an increased risk of pregnancy-induced hypertension, toxaemia, gestational diabetes, urinary infection, macrosomia, Caesarean section, and increased hospitalization (Fridstrom *et al*., 1999; Michlin *et al*., 2000). PCOS *per se* seemed to have little effect on pregnancy outcomes other than increased risk of gestational diabetes (Mikola *et al*., 2001), although studies with large sample size are needed to distinguish the effect of PCOS and the confounding effect of overweight and obesity.

Obesity and response to infertility treatment

Most studies show conclusive evidence that increasing BMI is associated with an increased requirement for clomiphene citrate. In several of these, large doses of clomiphene (up to 200 mg per day) were required to ensure ovulation in the heaviest women (Shepard *et al*., 1979; Lobo *et al*., 1982; Friedman and Kim 1985; Dickey *et al*., 1997). Doses of gonadotrophins required to induce ovulation are also increased in anovulatory women and those requiring ovarian stimulation for any reason (McClure *et al*., 1992). Increased weight and BMI in PCOS lead to impaired response to standard doses of clomiphene citrate, although most obese women with this condition will respond to larger doses (Crosignani *et al*., 1994). Fedorcsak *et al*. (2001) showed that obesity, independent from hyperinsulinaemia, was related to lower oocyte recovery on IVF and increased total FSH requirements for stimulation. A similar observation has been made with gonadotrophin ovulation induction in non-PCOS women (Loh *et al*., 2002).

Improvement of reproductive function through weight management and dietary intervention

Weight loss may impact on reproductive functioning for several reasons, which broadly encompass the effect of a reduction in fat and/or lean tissue mass, related changes in some endocrinological parameters and metabolism and even improvement in self-esteem. The effect of weight loss on reproductive functioning depends on initial body weight and probably the amount of weight lost. Modest weight losses of ~10% in obese women have been demonstrated to be effective in improving hormonal profiles, menstrual regularity, ovulation, and pregnancy rates (Falsetti *et al*., 1992; Kumar *et al*., 1993; Clark *et al*., 1995; Galletly *et al*., 1996; Hollmann *et al*., 1996; Norman and Clark, 1998). Interventions over as little as 4 weeks with weight losses of 5–10% of initial body weight can reduce hyperandrogenism and circulating insulin (Hamilton-Fairley *et al*., 1993; Clark *et al*., 1995; Clark *et al*., 1998; Huber-Buchholz *et al*., 1999; Wahrenberg *et al*., 1999). In addition, the intergenerational tracking of maternal adiposity through perinatal mechanisms indicates a potential to reduce the risk of obesity in the offspring by controlling obesity in the mother (Foreyt and Poston, 1998).

Weight loss improves insulin resistance and hormone profile

Attenuating insulin resistance has become a target in normalizing hyperandrogenism and anovulation in PCOS. Weight loss improves insulin sensitivity and short-term reproductive fitness in overweight women and PCOS subjects and is additionally crucial for improving short- and long-term metabolic health. This can be accomplished through dietary control and exercise with the overall aim of energy expenditure exceeding energy intake over a short or medium period. Caloric restriction improves insulin sensitivity measured through euglycaemic hyperinsulinaemia clamps (Andersen *et al*., 1995; Holte *et al*., 1995), fasting glucose:insulin ratios (Pasquali *et al*., 1986), homeostasis model assessment (Moran *et al*., 2003), oral glucose tolerance test (OGTT)-stimulated insulin (Pasquali *et al*., 1989; Hamilton-Fairley *et al*., 1993; Jakubowicz and Nestler, 1997) and fasting insulin (Kiddy *et al*., 1989; Botwood *et al*., 1995; Wahrenberg *et al*., 1999; Pasquali *et al*., 2000; Van Dam *et al*., 2002).

Weight loss in PCOS women also decreases hyperlipidaemia (Andersen *et al*., 1995; Moran *et al*., 2003) and ovarian cytochrome P450c17α activity (Jakubowicz and Nestler, 1997) and improves adipocyte lipolysis (Wahrenberg *et al*., 1999). Following weight loss, metabolic and endocrine variables were improved to a level similar to that of BMI-matched non-PCOS controls (Holte *et al*., 1995), indicating a positive role of dietary treatment in restoring reproductive and metabolic function to overweight women with PCOS.

Location of adipose tissue reduction is also important in restoring metabolic and reproductive function (Holte *et al*., 1995; Huber-Buchholz *et al*., 1999). Holte *et al*. (1995) additionally demonstrated that weight loss in women resulted in reduction of truncal– abdominal fat and that endocrine and metabolic improvements between intervention and control groups were removed after adjusting for truncal–abdominal fat. Weight loss also decreases hyperandrogenism (measured as decreases in free androgen index, free or total testosterone and increases in SHBG) and improves menstrual function, ovulation and fertility (Kiddy *et al*., 1989; Pasquali *et al*., 1989; Kiddy *et al*., 1992; Hamilton-Fairley *et al*., 1993; Botwood *et al*., 1995; Holte *et al*., 1995; Jakubowicz and Nestler, 1997; Van Dam *et al*., 2002; Moran *et al*., 2003). Less consistently documented are changes in LH with reductions (Pasquali *et al*., 1989), increases (Van Dam *et al*., 2002) and no changes reported (Kiddy *et al*., 1992; Holte *et al*., 1995; Jakubowicz and Nestler, 1997).

Although it is anecdotally reported that women with PCOS have difficulty in achieving and maintaining weight loss, this has not been specifically examined. No differences in weight loss have been observed between subjects with and without PCOS following isocaloric 5000–6000 kJ/day (1190–1428 kcal/day) diets for 2–7 months (Jakubowicz and Nestler, 1997; Pasquali *et al*., 2000) and in our unpublished study in subjects with (n = 20) and without PCOS (n = 12) over 4 months of energy restriction. This has not been investigated under less restrictive or self-managed dieting regimes. It is suggested that women with PCOS may exhibit possible abnormalities in energy expenditure. While resting energy expenditure (REE) does not differ between women with PCOS and weight-matched controls (Segal and Dunaif, 1990; Robinson *et al*., 1992), postprandial thermogenesis (PPT) has been found either not to differ (Segal and Dunaif, 1990) or to be decreased (Robinson *et al*., 1992) in women with PCOS. Robinson *et al*. (1992) calculated that this difference in PPT between PCOS and controls would account for a weight gain of 1.9 kg per year if maintained in the long-term.

Weight loss improves reproductive functions

When fertility is a problem, the primary goal of treatment is to normalize serum androgens and restore reproductive function, simply achieved by reducing insulin resistance through a decrease in weight and abdominal fat. Studies of weight loss through lifestyle modification have indicated that improvements in fertility occur with modest weight loss (~5% of initial body weight) and study-end BMI of >30 kg/m^2 (Kiddy *et al*., 1992; Hollmann *et al*., 1996). Crosignani *et al*. (2003) recently showed that there is a parallel improvement in anthropometric indices, ovarian physiology and fertility rate induced by diet. Foreyt and Poston (1998) also suggested that modest weight losses of ~10% of initial weight are effective in improving hormonal profiles, menstrual regularity, ovulation, and pregnancy rates.

In 11/25 women who responded to weight loss with improvements in menstrual cyclicity (ovulation and menstrual cycle length), a significant reduction in fasting insulin and homeostasis model assessment insulin resistance index (HOMA) was observed compared to subjects who showed no improvement in menstrual cyclicity with weight loss (Moran *et al*., 2003). Where PCOS is present, this is consistent with the proposed aetiology of insulin resistance. It would be of great clinical use to be able to identify these subjects prior to commencement of a treatment strategy in order to target successful interventions.

Short- and long-term management of weight loss

Weight management for women has been vigorously recommended by many authors (Hoeger 2001; Norman *et al*., 2002). Short-term weight loss has been achieved in overweight PCOS subjects with very low calorie diets (VLCD) (330–421 kcal/day) (Kiddy *et al*., 1989; Hamilton-Fairley *et al*., 1993; Andersen *et al*., 1995; Wahrenberg *et al*., 1999; Van Dam *et al*., 2002) and moderate caloric restriction (1000–1500 kcal/day for 3–6 months) (Pasquali *et al*., 1986, 1989, 2000; Kiddy *et al*., 1992; Andersen *et al*., 1995; Holte *et al*., 1995; Jakubowicz and Nestler, 1997; Moran *et al*., 2003). There is evidence that energy restriction alone, independent of weight loss, improves reproductive parameters (Moran *et al*., 2003), which has implications for the management of infertility compared to the longer-term prevention of co-morbidities.

Despite the short-term benefits of severe caloric restriction, sustained long-term weight loss is more difficult to achieve (Wadden 1993), and if weight is regained the manifestations of PCOS may return. In a review of 17 studies of long-term outcome for dietary treatment of obesity in general populations, Ayyad and Andersen (2000) concluded that ~15% of subjects maintain weight loss (all or 9–11 kg) with success rates of up to 14 years of observation. Although physical activity, behaviour modification and continued support are associated with attenuating weight regain (Ayyad and Andersen, 2000), it is unclear which dietary strategies are optimal in a free-living situation. Some evidence indicates that weight is maintained more effectively and compliance is increased when an *ad libitum* low fat, high carbohydrate dietary pattern (~30% of daily energy as fat and 55% as carbohydrate) is followed over longer periods of time, compared to fixed energy diets. Toubro and Astrup (1998) compared 1 year weight maintenance with an *ad libitum* low fat, high carbohydrate diet after 13.5 kg initial weight loss in 43 obese adults; 65% of the *ad libitum* group and 40% of the fixed energy group maintained a weight loss of >5 kg after 2 years. In a cross-sectional study, Shick *et al*. (1998) assessed the dietary patterns of 438 subjects from the National Weight Control Registry who maintained a weight loss of 30 kg for 5.1 years. Subjects who successfully maintained weight reported continued consumption of a low energy and low fat diet. A systematic evaluation of six randomized controlled trials using partial meal replacement plans for weight management suggests that these types of interventions can safely and effectively produce significant sustainable weight loss and improve weight-related risk factors of disease (Heymsfield *et al*., 2003). The efficacy of this approach in PCOS has not been assessed.

Finally, pharmacotherapeutic approaches may also be an option for long-term weight loss maintenance. Sibutramine and orlistat are two weight loss drugs currently approved for obesity treatment, which have been associated with significantly greater weight loss than that seen with dieting alone (Thearle and Aronne, 2003) but there is little work reported using these drugs in the context of improving fertility or infertility treatment, such as assisted reproductive techniques or ovulation induction, so it will not be further discussed here.

Using insulin-sensitizing agents

Therapeutic use of insulin-sensitizing agents such as metformin, diazoxide, troglitazone and D-chiro-insotol (a mediator of the action of insulin at the receptor level) in the treatment of PCOS have resulted in amelioration of hyperinsulinaemia and hyperandrogenism (Nestler *et al*., 1989; Velazquez *et al*., 1994; Dunaif *et al*., 1996; Nestler *et al*., 1999; Pasquali *et al*., 2000; Ibanez *et al*., 2003). This provides both support for the link between hyperinsulinaemia and hyperandrogenism and an additional potential pharmaceutical target for improvement of both conditions. It has thus been postulated that hyperinsulinaemia is a key metabolic abnormality in PCOS. Metformin, however, is not effective for grossly obese women (Ehrmann *et al*., 1997). Some studies found that metformin induced weight loss (Wong and Wong, 2003) although this remains to be confirmed (Siraj, 2003). The use of metformin for infertile women with PCOS receiving infertility treatment has become popular in the last few years. A recent systematic review found that metformin is effective, alone

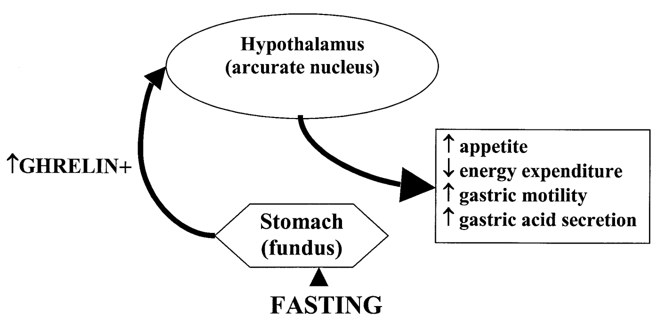

Figure 2. The physiological pathway of ghrelin function. Ghrelin, a 28 amino acid acylated peptide, is secreted into the circulation primarily by the endocrine cells in the stomach and acts on the hypothalamus to influence appetite, energy expenditure and the functions of digestive system.

or together with ovulation induction agent, for the ovulation induction of PCOS women (Lord *et al*., 2003).

Appetite, ghrelin and weight management

Discrepancies in appetite regulation may exist. Some investigators have claimed that bulimia is a common finding in PCOS, but others have not confirmed this. There has been much interest in the appetite regulation function by hormone ghrelin (Figure 2). Ghrelin is a 28 amino acid acylated peptide produced primarily by the endocrine cells in the stomach and is secreted into the circulation (Kojima *et al*., 1999). It stimulates growth hormone (GH) secretion through its action as an endogenous ligand for the hypothalamic–pituitary growth hormone secretagogue receptor (GHS-R) The GHS-R is widespread throughout the body, indicating multiple roles for ghrelin in addition to its GH-secreting actions. In particular, ghrelin has been implicated as an important regulatory peptide in a number of physiological processes in the brain and the periphery including food intake, body weight regulation and endocrine pancreatic function and glucose metabolism (Muccioli *et al*., 2002).

Ghrelin increases sharply immediately prior to onset of feeding. Once feeding has commenced, plasma ghrelin drops to reach a trough 1–2 h post-meal before returning to baseline values (Cummings *et al*., 2001, 2002; English *et al*., 2002). In obesity, fasting ghrelin is decreased (Tschop *et al*., 2001) and the post-prandial decrease may be impaired (English *et al*., 2002), potentially compromising meal termination. Following weight loss, fasting ghrelin increases and the impaired post-meal response normalizes (Cummings *et al*., 2002). These data support a potential role of ghrelin in the pathogenesis of human obesity.

There is a paucity of data on ghrelin homeostasis in PCOS. Fasting ghrelin is decreased in subjects with PCOS compared to controls in some (Pagotto *et al*., 2002; Schofl *et al*., 2002) but not all (Orio *et al*., 2003) studies. Pagotto *et al*. (2002) additionally observed no change in fasting plasma ghrelin following 7 months of a hypocaloric diet (1200–1400 kcal/day) for either PCOS (n = 10) or non-PCOS (n = 10) age- and weight-matched subjects (Pagotto *et al*., 2002). However, in a pilot study, our group observed higher fasting plasma ghrelin in non-PCOS compared to PCOS overweight subjects and a greater increase in fasting ghrelin for non-PCOS subjects following 16 weeks of weight loss (Moran *et al*., 2003). There was a greater improvement in postprandial ghrelin response following weight loss for non-PCOS compared to the PCOS subjects (unpublished data). There is thus a suggestion that both fasting and postprandial ghrelin homeostasis is impaired in PCOS and that weight loss may partially restore normal ghrelin homeostasis. This indicates that ghrelin is down-regulated in obesity with the consequence of decreasing satiety signals with feeding, potentially leading to a predisposition to overconsumption for subjects with PCOS.

The benefit of weight management through lifestyle change

In some studies, a reduced emphasis was put on caloric restriction while more emphasis was placed on lifestyle changes. These included educating subjects on the adoption of general healthy eating practices in conjunction with moderate amounts of low-intensity exercise (Clark *et al*., 1995, 1998; Huber-Buchholz *et al*., 1999). These principles may be easier to sustain than a lifestyle change and thus are likely to improve lifelong maintenance of a healthy weight. The effect of exercise on improving insulin sensitivity independent of weight loss has also been documented (Goodyear and Kahn, 1998). Lifestyle changes can also aid in normalizing hyperlipidaemia and hypertension in reducing the risk for cardiovascular disease and diabetes mellitis, including the 25% reduction of fasting insulin and triglycerides and 10% reduction in weight and blood pressure (Noakes *et al*., 1999).

Longer-term lifestyle studies indicate that improvements in fertility occur with modest weight loss (~5% of initial body weight) and study-end BMI of >30 kg/m^2. Clark *et al*. (1995) conducted a prospective study including a weight loss component to determine whether it could help infertile, overweight, anovulatory women. A weekly programme of behavioural change in relation to exercise and diet for 6 months resulted in an average weight loss of 6.3 kg, a restoration of ovulation in 12 of the 13 subjects and pregnancy in 11 women. Fasting insulin and testosterone concentrations dropped significantly. A further study (Clark *et al*., 1998) of the same protocol involved 67 anovulatory women in an exercise and dietary intervention for 6 months. Women in the study lost an average of 10.2 kg or 3.7 kg/m^2 (10% reduction of BMI) with 60 of the 67 anovulatory subjects resuming spontaneous ovulation. Of these women, 52 achieved a pregnancy, 45 of which resulted in a live birth. A low fat (~30% of energy and saturated fat ~10% of energy), moderate protein and moderate carbohydrate intake and increased consumption of fibre, wholegrain breads and cereals and fruit and vegetables in conjunction with moderate regular exercise (30–60 minutes/day) is proposed to aid in weight loss and maintenance both in the general population and in obese infertile women with PCOS (Scalzo, 2000).

Furthermore, lifestyle modification through diet and exercise programmes in obese subjects with PCOS improves psychological parameters (self-esteem, anxiety, mean depression scores and scores on general health questionnaire) (Galletly *et al*., 1996) in addition to reproductive outcomes (Clark et al., 1995, 1998; Huber-Buchholz *et al*., 1999). While the effect of long-term weight loss on reduction in diabetic risk has not been studied specifically in PCOS, lifestyle change with altered diet and increased physical activity is associated with significant reduction in the risks of developing diabetes mellitus in the general population (Knowler *et al*., 2002). Furthermore, these interventions are superior to those of medication such as metformin

(Doggrell, 2002; Diabetes Prevention Program Research Group, 2002).

Addressing a number of lifestyle factors can improve long-term reproductive and metabolic health. Exercise aids in management of infertility through reducing insulin resistance (Goodyear and Kahn, 1998), limiting lean muscle mass loss in weight loss (Garrow and Summerbell, 1995) and aiding in maintenance of a reduced weight (Skender *et al*., 1996). Furthermore, combining exercise and dietary intervention together will increase the success of the regime (Skender *et al*., 1996; Frost *et al*., 2002). Systematic reviews indicate that improved weight maintenance is aided enormously by exercise (Fogelholm *et al*., 2000). Smoking is a major risk factor for female sub-fertility, expressed as time to pregnancy and early pregnancy loss, for pre-term birth and low birthweight in babies (Satcher, 2001; Winter *et al*., 2002). High levels of alcohol intake have been associated with reduced fertility and increased risk of spontaneous abortion (Grodstein *et al*., 1994b). Cognitive behaviour therapy and reduction of psychosocial stressors can aid both in weight loss and maintenance of the reduced weight (Wing, 1992; Skender *et al*., 1996). Attempting weight loss in a group environment additionally provides psychological support (Galletly *et al*., 1996). Modifying additional factors such as alcohol consumption, smoking, cognitive behaviour therapy and use of a group environment can increase the long-term success and maintenance of weight loss and reproductive and metabolic improvements and has been previously successfully applied (Clark *et al*., 1995, 1998; Huber-Buchholz *et al*., 1999).

Dietary interventions: what diet?

The most important determinant of dietary intervention for weight loss is energy balance, though for many other reasons various types of diet have been proposed and tested. Most studies have looked at carbohydrate-deplete, fat-depleted diets with caloric restriction as the model for long-term sustained weight loss. However, some consumer support groups promote high protein, low carbohydrate or low glycaemic index (GI) diets as being more effective for therapeutic outcomes in this condition. There is no definite evidence to support or refute this approach. Long-term weight loss may be more effective with low fat, high carbohydrate diets comprising unrefined foods such as whole-grain, pasta, brown rice, etc., but the evidence for this is inconsistent and remarkably limited (Saltzman *et al*., 2001; Poppitt *et al*., 2002). None of these studies have been conducted in women with PCOS.

The traditional food pyramid emphasizes a low fat, high carbohydrate diet with secondary emphasis on unrefined carbohydrate. Recent research recommends actively restricting foods high in glycaemic load such as potatoes and refined grain products such as white bread; limiting dairy products to one or two servings a day; replacing unhealthy saturated fat with healthier unsaturated vegetable oils; and emphasizing whole grains, fruits and vegetables (Willett and Stampfer, 2003). The greater emphasis on a diet lower in glycaemic load through minimizing refined carbohydrate and using unsaturated fats more liberally is the key feature of this pyramid, although whether this approach is successful as a strategy to achieve energy restriction has not been directly tested other than in one very short-term (6 day) small trial (Dumesnil *et al*., 2001). There are many diets on offer to consumers and few have any scientific credibility. However, recent publications have shown that mortality is reduced by adherence to a Mediterranean diet (Hu, 2003; Trichopoulou *et al*., 2003) and the use of high protein, low carbohydrate diets has been shown to be associated with better and more sustained weight loss (Foster *et al*., 2003).

Alternative strategies suggest that increasing dietary protein or reducing dietary glycaemic/load may aid in weight loss. Increasing dietary protein at the expense of carbohydrate is proposed to aid weight loss through an increased satiating and thermogenic effect of protein, but evidence for the latter is limited (Raben, 2002). It may also increase insulin sensitivity through preserving lean body mass in weight loss. Decreasing dietary glycaemic load is proposed to improve cardiovascular risk profile and is additionally proposed to aid weight loss through an increased satiating effect of low GI foods.

Dietary protein: the effect of increasing dietary protein in weight loss/weight maintenance

Baba *et al*. (1999) reported a decreased fall in resting energy expenditure (REE) with weight loss in a high protein (HP) compared to a low protein (LP) diet (–555.7 kJ compared to –1614.1 kJ). However, Luscombe *et al*. (2003) showed a similar reduction in REE for both HP and LP diets. This may be explained by the difference in protein intake between the two studies (45% compared to 28% respectively for the HP diets) and we propose to repeat these measurements with an increased protein intake (35–40% of daily intake). In short-term studies, e.g. 24 h, HP diets increase postprandial thermogenesis (PPT) and REE compared to high carbohydrate or fat diets with equal calories (Robinson *et al*., 1990; Mikkelsen *et al*., 2000; Luscombe *et al*., 2002). Luscombe *et al*. (2003) reported a 28% increased thermic effect of feeding for a HP compared to a LP meal, corresponding to a difference of 1.3 kg in weight over 6 months. With the potential for reduced PPT in PCOS (Robinson *et al*., 1992), this may lead to significant differences in weight loss or maintenance. We propose that a further increase in dietary protein (35–40% of daily intake) may aid in weight loss and maintenance of a reduced weight by minimizing the normal fall in energy expenditure seen in weight loss.

While greater decreases in weight and fat composition were observed with HP compared to LP *ad libitum* diets (Skov *et al*., 1999), no significant differences have been observed in isocaloric diets for weight and body fat (Lean *et al*., 1997; Luscombe *et al*., 2002; Moran *et al*., 2003). In a prior weight loss study in women with type II diabetes, we observed a greater decrease in total (5.3 versus 2.8 kg) and abdominal (1.3 versus 0.7 kg) fat for a HP compared to a LP diet (Parker *et al*., 2002). These studies modestly increased protein (30% of daily intake); a more substantial increase (35–40%) has not yet been explored for >4 weeks. Protein is more satiating than carbohydrate or fat (Poppitt *et al*., 1998), as shown by a 2000 kJ energy intake difference between *ad libitum* HP and LP diets (Skov *et al*., 1999). This increased satiating effect may aid dietary compliance or weight maintenance, particularly in a free-living situation. Qualitatively Layman *et al*. (2003) reported a greater level of satiety and satisfaction following 10 weeks of an isocaloric HP (30% protein) compared to a LP (16% protein) diet.

Oral and intravenous protein or amino acids stimulate insulin release, both singly and synergistically with glucose (Gannon *et al*., 1988). Clinically, Baba *et al*. (1999) reported no difference in fasting insulin levels between HP and LP diets. However, a 17% decrease in insulin sensitivity was reported for a HP compared to a

Table I. Glycaemic index (GI) of some low fat foods

Food group	Low GI <55	Moderate GI 55–70	High GI >70
Breakfast cereals	Porridge, rice, bran, Kelloggs All Bran™, Kellogg's Sultana Bran™	Mini Wheats™, Kelloggs Nutrigrain™, Kelloggs Sustain™, Uncle Toby's Vita Brits™	Sanitarium Puffed Wheat™, Kelloggs Rice Bubbles™, Kelloggs Cornflakes™, Sanitarium Weet Bix™
Grains, pasta, bread	Mahatma Premium Classic™ brand rice, pasta (all types), mixed grain bread, fruit loaf	Basmati rice, white bread	Calrose™, white rice, brown rice, wholemeal bread
Vegetables and legumes	Beans (soy, kidney, baked), lentils	Pontiac variety potato, new potato, sweet potato	Baked potato, instant potato
Fruit	Apple, grapes orange kiwifruit	Banana, pineapple, raisins, rockmelon	Watermelon
Dairy foods	Milk (plain or flavoured), low-fat ice cream, flavoured yoghurt		
Beverages	Apple juice	Cordial, soft drinks, orange juice	Lucozade™
Snacks and Confectionery		Popcorn, boiled-type lollies	Jelly beans
Sugars	Fructose (fruit sugar), lactose (milk sugar)	Sucrose (table sugar), honey	Glucose, maltose (in malt)

LP diet (Piatti *et al*., 1994). In weight loss, reduction of lean body mass (LBM) has important implications for maintaining metabolic rate and improving insulin sensitivity through increasing skeletal muscle insulin-mediated glucose uptake. While no positive effect of increasing dietary protein on sparing LBM was found (Skov *et al*., 1999), Piatti *et al*. (1994) found a decreased reduction in LBM with increasing dietary protein through an effect of proteolysis and maintenance of whole-body nitrogen levels. Piatti et al. increased dietary protein more severely (45% protein) than Skov et al. (25% protein). Furthermore, an increased ratio of fat/LBM loss was reported with weight loss with an isocaloric HP (30% protein) compared to a LP diet (16% protein) (6.36 compared to 3.92 kg) (Layman *et al*., 2003). A prior study also indicated that total LBM was preserved to a greater extent in weight loss in hyperinsulinaemic females on a HP (30% protein) compared to a LP diet (15% protein) (–0.1 kg compared to–1.5 kg) (Farnsworth *et al*., 2003).

Significant improvements in total cholesterol, triglycerides and low-density lipoprotein cholesterol (LDL-C) are observed in studies with no weight loss (Wolfe and Piche, 1999) for HP compared to LP diets. In overweight women with PCOS, we observed a 10% decrease in high-density lipoprotein (HDL-C) for a LP diet with no change for a HP diet after weight loss (Moran *et al*., 2003). In weight loss, improvements in total cholesterol/HDL-C (Moran *et al*., 2003), triglycerides (Layman *et al*., 2003) and total cholesterol and LDL-C (Parker *et al*., 2002) were reported for isocaloric HP compared to LP diets. For *ad libitum* LP and HP diets, Skov *et al*. (1999) demonstrated a reduction in plasma triglycerides for the HP diet with no change for the LP diet. However, these changes in lipids are not consistently reported. Farnsworth *et al*. (2003) also noted a greater lowering of plasma triglycerides on the HP diet in hyperinsulinaemic women.

Glycaemic load: the effect of altering glycaemic load in weight loss/weight maintenance

Glycaemic index (GI) is a classification index of carbohydrate foods based on their effects on blood glucose response over 2 h, and glycaemic load (GL) is the product of the GI and the amount of dietary carbohydrate (Jenkins *et al*., 1984). Table I lists GI grouping of some common types of food. Dietary GI and GL are positively associated with risk of coronary artery disease and type II diabetes (Salmeron *et al*., 1997; Liu *et al*., 2000). Clinical intervention studies have shown that weight maintenance low GI diets may lower daylong glucose levels, glycated haemoglobin (HBA1c), triglyceride and total cholesterol concentrations compared to high GI diets (Brand *et al*., 1991). The effect of low GI diets on improving insulin sensitivity is more controversial. Jarvi *et al*. (1999) documented 27% lower fasting insulin after 24 days following a low GI diet compared to a high GI diet. However, no differences in insulin sensitivity were found between the two diets.

Reduced GI foods have been shown to result in increased satiety, decreased hunger and lower voluntary food intake in 15/16 single day studies (Brand-Miller *et al*., 2002). This has not been investigated in longer-term weight loss settings, but a reduced *ad libitum* energy intake may also occur (Brand-Miller *et al*., 2002). In this scenario, increasing dietary protein will also decrease the GL through decreasing the total amount of carbohydrate. An additive effect may additionally exist between the two factors. A significant recent study (Dumesnil *et al*., 2001) examined low GI–low fat–HP *ad libitum* diet compared to the conventional American Heart Association (AHA) moderate protein high carbohydrate diets for the treatment of the atherogenic metabolic risk profile over 6 days. This is the first study to examine the combined effects of increasing dietary protein and decreasing dietary GI. The AHA diet was associated with significant increases in hunger and decreases in satiety whereas the low GI–low fat–HP *ad libitum* diet reduced energy intake by 25%. The low GI–low fat–HP diet was associated with an improved metabolic risk profile whereas the AHA diet increased triglycerides by 28% and decreased HDL-C by 10% (Dumesnil *et al*., 2001). It is possible that a HP–low GI diet may optimally improve glycaemic control, lipid profiles and insulin sensitivity compared to other dietary interventions. A HP–low GI diet may also aid in long-term weight loss and maintenance of a reduced weight due to the increased satiating effects of low GI foods compared to other dietary interventions but this has yet to be confirmed.

Summary and recommendation for weight management of infertile patients

There is well-established evidence for the detrimental effect of overweight and obesity on women's reproductive function; this is further complicated by the presence of PCOS in many infertile women. In addition, the distribution of body fat is also related to the reduction or even loss of fertility. So far, most research has indicated that overweight and obese conditions lower the concentration of SHBG and increase androgen, insulin and leptin secretion and insulin resistance, leading to hyper-insulinaemia and hyperandrogaenmia. However, there is limited understanding of the details of how these changes affect human reproductive function. On the other hand, weight loss has been shown to improve metabolic function, hormonal profile and lead to marked recovery or improvement of reproductive function.

Therefore the recommendation for overweight/obese patients with infertility is closely related to the ramification of this problem. They should have their height, weight and waist circumference recorded at their first consultation and at regular intervals thereafter. Once the patient has been classified as overweight or obese, then weight management should be offered as a first line treatment option.

Dietary intervention and increased physical activity remain the optimal treatment strategy for overweight/obese women with PCOS. A relatively small weight loss (~5 kg) can improve insulin resistance and hyperandrogenism, menstrual function and fertility, and large changes in weight may not be needed to restore reproductive function. Weight loss can also improve long-term metabolic health and realistic and achievable target weight loss goals can be set for women. Obesity and overweight can be treated by a variety of strategies including dietary management, physical activity, behaviour modification, pharmacotherapeutic treatment and surgery. Dietary management with lifestyle modification as an objective should be adopted initially with pharmacological and other interventions reserved for use when weight-loss regimes have proved unsuccessful.

Since the overall emphasis is to achieve and maintain a reduced weight, attempts should be made to establish sensible eating patterns and a healthy lifestyle. A number of alternative dietary approaches to the conventional low fat–high carbohydrate regime such as partly modified diets or moderately HP–lower carbohydrate diets which are consistent with a healthy eating plan may assist in maintaining an energy restricted diet. The other lifestyle factors, such as alcohol intake, smoking and psychosocial stressors, should also be addressed. A group environment can provide support for weight loss and maintenance of weight loss. At the same time, it is necessary to tailor intervention to an individual's weight and current dietary and exercise patterns. The use of a dietician is warranted to aid in the evaluation of dietary intake and eating patterns and in individualizing an appropriate dietary approach.

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