The Effects of Exercise and Nutritional Counseling in Women with Polycystic Ovary Syndrome

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Abstract

Purpose: To study the effects of a supervised exercise program combined with nutritional counseling on the hormonal aberrations associated with menstrual and reproductive function in women with Polycystic Ovary Syndrome (PCOS). **Methods:** Twelve females with a clinical, biochemical and ultrasonographic diagnosis of PCOS (age = 30.7 ± 1.3, weight = 98.1 kg ± 4.6, height = 1.6 m ± 0.02, BMI = 36.6 kg/m^2 ± 1.7, waist circumference = 98.7 cm ± 3.4) were randomly assigned to receive either exercise (EN; cardiovascular and resistance training 3 x/wk) plus nutritional counseling (1 x/wk; n = 7) or nutritional counseling only (N; 1 x/wk; n = 5) for a period of 12 weeks. Measurements of anthropometry, resting metabolic rate (RMR), selected hormones and ovarian follicle population were taken pre and post-intervention. **Results:** Repeated measures ANOVA revealed a greater decrease in sum of 5 skinfolds ($p = 0.05$) and a greater increase in estimated VO_{2max} ($p = 0.02$) in the EN group compared to the N group. There was a significant decrease in waist circumference ($p = 0.001$), waist:hip ratio ($p = 0.002$), and insulin levels ($p = 0.03$) in both the EN and N groups following the intervention, although there was no group x time interaction. There were no statistically significant changes in androgen or lipid levels or ovarian follicle population. Following the intervention, however, one subject in the EN group became pregnant. **Conclusion:** Although there were no statistically significant changes in the hormone levels, apart from the insulin, there was a trend towards an improved hormonal profile which occurred in the absence of weight loss. These findings suggest that exercise and nutritional counseling, in the absence of a

significant weight loss, may be beneficial in reversing the metabolic and reproductive abnormalities of PCOS.

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Glossary

Corpus luteum: The portion of the follicle that remains in the ovary after ovulation. If an egg is fertilized, it enlarges and releases hormones to support pregnancy but if conception does not occur, it degenerates.

Endometrium: The inner mucous membrane of the uterus, the thickness and structure of which varies with the phase of the menstrual cycle.

Follicle: The fluid-filled sac that surrounds the ovum (egg).

Follicle-stimulating hormone (FSH): The gonadotropin mostly responsible for promoting the recruitment of follicles and facilitating their growth.

Follicular atresia: The process by which oocytes are lost from the ovary by means other than ovulation.

Folliculogenesis: The process by which a primordial follicle grows and develops into a specialized graafian follicle with the potential to either ovulate its egg to be fertilized or die by atresia.

Gonadotropin-releasing hormone (GnRH): A hormone which stimulates the release of follicle-stimulating hormone and luteinizing hormone from the anterior lobe of the pituitary.

Hypothalamic-pituitary-ovarian axis: A regulatory system governing cyclic ovarian follicular maturation, the luteinizing hormone surge, ovulation and corpus luteum formation.

Luteinizing hormone (LH): The gonadotropin mostly responsible for promoting ovarian steroid secretion and inducing ovulation.

Negative feedback loop: The process whereby a hormone secreted by a target organ (ovary) signals the hypothalamopituitary unit so secretion of the stimulatory hormones (FSH and LH) can be readjusted to steady state.

Positive feedback loop: The process by which an estradiol signal originating from the mature graafian follicle stimulates the hypothalamopituitary unit to release GnRH, LH and FSH.

Progesterone: The main ovarian steroid produced by the corpus luteum. Also secreted by the follicle at the time of the gonadotropin surge.

CHAPTER 1

SCIENTIFIC FRAMEWORK

1.1 Introduction

As early as the 1930s, it was known that an association exists between disturbances in menstrual function and obesity (Bayer, 1939). In the mid 1930s an association between anovulation, (absence of ovulation), obesity, hyperandrogenism (excessive secretion of masculinizing hormones), and polycystic ovaries (ovarian enlargement from many small cysts) was first explained by Stein and Leventhal (1935). Although originally known as Stein-Leventhal Syndrome, this syndrome is now termed polycystic ovary syndrome (PCOS). In more recent years, and because of a greater understanding of PCOS, it is now defined as a heterogeneous syndrome characterized by persistent anovulation, oligomenorrhea or amenorrhea and hyperandrogenism in the absence of thyroid, pituitary or adrenal disease. In addition to the above, many women with PCOS may exhibit clinical characteristics such as hirsutism (adult male-pattern hair distribution in women), male-pattern balding, acne, obesity (Taylor, 1998) and now more notably, insulin resistance (Dunaif et al., 1997). Estimates from population-based studies indicate a prevalence of PCOS in 5% to 10% of women of reproductive age (Knochenhauer et al., 1998).

Currently, PCOS is described as the most common cause of anovulation resulting in infertility in adult women (Chang, 1996) and researchers agree it is one

of the most common reproductive endocrinological disorders affecting women (Knochenhauer et al., 1998). In addition to the role PCOS plays in the reproductive potential and fertility status of women, many other health risks are associated with this syndrome. These include an increased risk of developing type 2 diabetes, dyslipidemia, hypertension and subsequent cardiovascular disease (Solomon, 1999). From a health perspective, treating women with PCOS may not only result in the restoration of reproductive potential, but may also reduce their risk of developing the associated non-reproductive conditions.

It is well accepted that lifestyle modifications in the form of exercise and proper nutrition decrease the risk of developing these non-reproductive conditions, particularly type II diabetes. It has been reported that obese women with PCOS and insulin resistance have seven times the risk of developing type II diabetes compared with the general population (Dahlgren et al., 1992). Although previous research has involved primarily pharmacological therapy aimed at improving insulin sensitivity and inducing ovulation in this population, non-pharmacological treatment, primarily in the form of dietary restriction has also been used (Clark et al., 1995 and 1998). A less explored treatment option for women with PCOS comes in the form of exercise therapy. It is well known that exercise is one of the cornerstones in the treatment of type II diabetes, primarily because of its beneficial effects on improving insulin sensitivity (Hamdy, et al., 2001). As there are strong associations between insulin resistance, PCOS and the development of type II diabetes, we propose to determine the effects of a combined resistance and cardiovascular

exercise program on the metabolic and reproductive abnormalities associated with PCOS.

1.2 Review of Literature

To date, it is unclear whether PCOS is the expression of several disorders with differing etiologies, including anovulation, hyperandrogenism, polycystic ovaries, obesity (Berga, 1998) and insulin resistance (Dunaif et al., 1997), or if there is one single underlying cause. In order to address the causes of PCOS it is helpful to first understand ovarian development and ovulation.

The initial formation of the ovary begins as early as three weeks gestation. At approximately five weeks gestation, pre-meiotic germ cells, termed oogonia, begin the process of mitosis with the maximum number of oogonia in both ovaries reaching 6-7 million by 16-20 weeks gestation. During gestation weeks 8 to 13, meiotic cell division of oogonia begins, and at this stage the germ cells are termed primary oocytes. The primary oocytes are then surrounded by a single layer of granulosa cells, yielding primordial follicles. In the embryo, primordial follicles are first seen at 16 weeks of gestation, however follicular atresia in utero results in a decrease of primordial follicles to about 2 million with only approximately 300,000 remaining by puberty (Adashi et al., 1996). Until the time of puberty, the follicles do not continue further development, and of the remaining follicles, less than 1% (approximately 300-400) will reach ovulatory status during the reproductive years (Adashi et al., 1996; Speroff et al., 1999). At puberty however, follicular development resumes and continues until menopause (Yen et al., 1999).

During the reproductive years, hormonally controlled events are coordinated by the hypothalamic-pituitary-ovarian axis which controls the menstrual cycle (a series of changes in the endometrium of a non-pregnant female). The menstrual cycle parallels the activity of the ovaries and can be divided into three stages; the follicular phase, the ovulatory period and the luteal phase. In the ovary, a cohort of follicles are recruited to grow and mature during the follicular phase. Follicular maturation and release of the oocyte into the reproductive tract for fertilization (ovulation) occurs during the ovulatory phase. During the luteal phase, progesterone is secreted by the corpus luteum and secretory changes in the endometrium occur in preparation for implantation of a fertilized oocyte. The luteal phase ends and the follicular phase recurs when implantation fails to occur. Estrogen and progesterone levels decline, endometrial support declines, and menstruation begins.

The hypothalamus releases gonadotropin releasing hormone (GnRH) in response to levels of estrogen in the blood. A pulsatile release of GnRH modulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. The release of FSH stimulates the development of receptive ovarian follicles and permits the synthesis and secretion of estrogen from the follicles. The initial growth of follicles span several menstrual cycles and it is estimated that approximately 85 days are required for a follicle to mature to the preovulatory size (Adashi et al., 1996). Typically a cohort of up to 20 follicles respond to FSH, however, one dominant follicle from the cohort is selected to progress through a series of stages to maturity. Although the mechanism is

unknown by which a dominant ovulatory follicle is chosen, recruitment occurs early in the follicular phase of the menstrual cycle.

Growth of the primordial follicle to the preantral follicle occurs under the influence of FSH. FSH binds to receptors on the granulosa cells that surround the follicle to mediate cell growth and differentiation (Speroff et al., 1999). Adjacent to follicular granulosa cells, theca cells begin to arise from unspecialized mesenchymal cells in the stromal compartment. Under the influence of FSH, proliferation of the granulosa cells enlarge the follicle, yielding a secondary follicle. As the secondary follicle develops, the granulosa cells develop FSH, estrogen and androgen receptors. The preantral stage of the maturing follicle is reached as the granulosa cells constantly proliferate from a single layer to multiple layers of cells, while concomitantly differentiation of the theca cells occurs. The theca cells begin to acquire additional LH receptors and all are capable of steroidogenesis (Yen et al., 1999). In response to LH, steroidogenic activity of the theca cells results in the production of androgens. The conversion of androgens to estrogens is then mediated via an aromatase enzyme system. As aromatization occurs exclusively in the granulosa layer, diffusion of the androgens from the theca cells to the granulosa cells must occur (Speroff et al., 1999). In addition to proliferation and differentiation of the granulosa cells, FSH is also required to activate the aromatase enzyme, and thus initiates estrogen production, the predominant steroid produced (Speroff et al., 1999).

Follicular growth and steroidogenesis continue as the follicle reaches the antral stage. The FSH and estrogen work synergistically to increase the number of

FSH receptors within the granulosa cells of the follicle, making the follicle more FSH sensitive. A negative feedback of estrogen (released from the follicle) to the hypothalamus results in less FSH secretion from the anterior pituitary. Follicle selection occurs when a follicle which has maintained estrogen synthesis and formed numerous FSH receptors continues growth and development in an environment with less FSH. When this occurs, the antral follicle is selected to ovulate. As the FSH declines, and FSH support is withdrawn to the less developed follicles, that is, all but the selected follicle, aromatase activity decreases and atresia of the less developed follicles (non-dominant follicles) occurs. The granulosa cells of the antral follicle begin to acquire LH receptors, essential for follicular response to the ovulatory surge of LH. The preovulatory follicle continues synthesis of estrogen until the high level of estradiol induces the release of LH from the anterior pituitary (by a positive feedback response). The sharp LH surge ultimately leads to rupture of the dominant follicle into the reproductive tract (ovulation). When ovulation occurs, the corpus luteum begins to form from reorganization of the remaining granulosa and theca cellular material of the dominant follicle (Yen et al., 1999). The corpus luteum is maintained if conception and implantation occurs. In the absence of pregnancy, the corpus luteum regresses, estrogen and progesterone synthesis decline and a new cohort of follicles begins growth and development.

In women expressing polycystic ovary syndrome (PCOS), selection of a dominant follicle is rare, despite the presence of a population of small follicles. In the ovaries of women with PCOS, the number of primordial follicles are essentially the same as in normal ovaries, however, the number of growing follicles is about

twice that of normal ovaries (Adashi et al., 1996). As the follicles in PCOS women do not typically reach the 20-25 mm size and maturity of the dominant follicle that is selected to ovulate (Yen et al., 1999), it is proposed that the problem of folliculogenesis actually occurs at the level of selection of the dominant follicle (Adashi et al., 1996).

Selection of the dominant follicle is dependent upon FSH, and as this does not regularly occur in women with PCOS, it is suggested that the concentration of FSH is too low to trigger normal selection (Adashi et al., 1996). Granulosa cells in the small follicles of PCOS women are few in number, however, they do possess FSH receptors (Yen et al., 1999). Therefore, although these granulosa cells lack aromatase activity, they do have aromatization potential. Thus, it is theorized that the low aromatase activity in PCOS is due to inadequate levels of FSH (Yen et al., 1999), and as FSH is required for folliculogenesis, this may be the mechanism behind the absence of formation of a dominant follicle that is a precursor to ovulation. In addition to low and constant FSH levels, women with PCOS also display elevated LH concentrations (Yen et al., 1999). It is the elevated LH that causes an excessive production and secretion of androgens (Speroff et al., 1999). Consequently, in the absence of elevated levels of FSH, aromatase activity is not enhanced and selection and growth of a dominant follicle is inhibited and follicular atresia occurs (Speroff et al., 1999). It is believed that in the PCOS ovary, high androgen concentrations may inhibit follicular maturation, trigger follicular atresia (degeneration and resorption before the ovarian follicle reaches maturity) and ultimately cause anovulation which in turn prevents normal menstrual cycles

(Speroff et al., 1999). It has also been suggested that insulin acts synergistically with LH to stimulate androgen secretion (Adashi et al., 1996). As many women with PCOS have hyperinsulinemia, it is theorized that insulin-mediated stimulation of ovarian androgens contributes to the hyperandrogenism in this population (Adashi et al., 1996).

With PCOS, decreased aromatization of ovarian androgen to estrogen is associated with lower concentrations of sex-hormone binding globulin (SHBG), a specific protein carrier for androgens and estrogens. The production of SHBG is supported by estrogens and inhibited by androgens. Therefore under typical conditions women, who produce more estrogen than androgen, have twice the amount of SHBG than men (Yen et al., 1999). In PCOS women, when androgen levels exceed estrogen levels, a lower concentration of SHBG is observed and free androgen levels increase. When bound to SHBG, these sex steroids are unable to exert their effects, however when they are unbound (free), they are readily able to act at their target sites (Yen et al., 1999) and the masculinizing effects presented clinically as hirsutism and male-pattern balding may become apparent.

Although androgens are converted to estrogens in the ovarian follicle under the influence of FSH, aromatization can also occur in the liver, skin, brain and most notably in the muscle and adipose tissue, accounting for approximately 35-45% of aromatase activity (Yen et al., 1999). As adipose tissue is an extraglandular site of aromatization, the excess of adipose tissue present in obese women with PCOS can contribute to an increase in aromatase activity. The result of the increased conversion of androgens to estrogens causes constant levels of circulating estrogens

(Yen et al., 1999). Recent literature has indicated that approximately 50% of patients with PCOS are obese with abdominal fat distribution being the most common site of regional fat deposition (Talbott et al., 1995). Not only does excess adipose tissue play a key role in the reproductive status of women with PCOS (Franks, 1995), but more specifically abdominal fat distribution has been shown to have an influence on androgen and estrogen metabolism. Women with upper body obesity, commonly displayed in women with PCOS, have demonstrated higher rates of androgen production and increased free-testosterone levels. Conversely, women with gluteofemoral obesity typically present with elevated estrone levels due to aromatization of androstenedione (Yen et al., 1999).

Recent literature has suggested that insulin resistance (impaired insulin action at the receptor or post-receptor site), which is associated with abdominal obesity, can also affect reproductive status. In obese women with PCOS, an increased amount of abdominal fat has been demonstrated to be closely associated with a decrease in insulin sensitivity (Bringer et al., 1993) and hyperinsulinemia (Abate, 1996). It is theorized that there is an inverse relationship between the size of the adipocytes and the density of the insulin receptors. The possibility exists that the insulin resistance is due to a reduced density of insulin receptors on the hypertrophied adipocytes (Ivy et al., 1999). Since insulin resistance results in an inability of the body to clear glucose from the bloodstream, the consequence is an increased secretion of insulin from the pancreas which ultimately causes hyperinsulinemia (Ivy et al., 1999). The insulin resistance and hyperinsulinemia appears to play a role in PCOS as insulin has been shown to stimulate ovarian

androgen production (Speroff et al., 1999). It is suggested that insulin enhances the response of the granulosa cells to LH (Willis et al., 1996). The effect of LH on the maturing follicle is arrest of follicular growth, similar to what would occur during a normal menstrual cycle at the pre-ovulatory LH surge. However, in women with PCOS, this would result in anovulation because of a premature response to elevated LH by the ovarian follicle, ceasing its growth (Willis et al., 1996). It has also been suggested that insulin stimulates androgen synthesis in the theca cells and causes a decrease in hepatic synthesis of SHBG. As stated previously, a decrease in SHBG results in an increased amount of unbound androgen levels (Moghetti et al., 2000) which in this form can enter the cells and exert their biological effects (Yen, et al, 1999). It is still unknown whether the increased free androgen levels, the raised LH or both factors are responsible for the premature arrest of ovarian follicular growth and thus anovulation (Franks et al., 1999). Given this, the primary treatment of anovulation in this population involves interactions that would allow the ovarian follicle to mature, thereby inducing ovulation in women with PCOS.

Anovulatory women with PCOS seek medical intervention to control male pattern hair growth and correct menstrual irregularity. When pregnancy is desired, the most common approach in women with PCOS to induce ovulation is by means of pharmacological intervention. Clomiphene citrate (CC), a non-steroidal estrogen agonist/antagonist, is generally the first line of treatment used to induce ovulation in anovulatory women. This drug binds to hypothalamic estrogen receptors which causes an increase in the pulse frequency of GnRH; in turn, an increase in the secretion of LH and FSH results in maturation of the ovarian follicle and subsequent

ovulation (Yen et al., 1999). Ovulatory success rates with CC, as reported in the medical literature, are quite variable and range from 5% to 70% (Lobo et al., 1982; Opsahl et al., 1996). If a woman with PCOS fails to ovulate or conceive while on CC therapy, another treatment available is parenteral daily injections of FSH. Follicle-stimulating hormone therapy is very expensive and may result in ovarian swelling and pain, multiple ovulation (25%) with possible multi-fetal gestation of high order (>3) and ovarian hyperstimulation syndrome which can be life-threatening (Speroff et al., 1999). Hence, the use of FSH requires frequent estradiol assay and transvaginal ultrasonographic monitoring of the ovaries.

Recently, it has been suggested that oral agents such as metformin, commonly used to treat non-insulin-dependent diabetes mellitus, may be beneficial in the treatment of PCOS. Metformin works to increase insulin sensitivity, reducing insulin resistance and hyperinsulinemia (Yen et al., 1999) It's use has been shown to improve fertility in some women with PCOS. It is believed that insulin can directly stimulate ovarian androgen production by increasing LH-stimulated ovarian androgen synthesis (Iuorno & Nestler, 2001). It is believed that during folliculogenesis, high levels of LH cause abnormal growth and development of the theca cells. It is theorized that the follicles become atretic because of their hyperandrogenic microenvironment due to the greater number of theca cells which are subsequently stimulated by the high levels of LH (Adashi et al., 1996). Therefore, by improving insulin sensitivity and thus decreasing hyperinsulinemia, the production and secretion of LH could be regulated, allowing maturation of the ovarian follicle and subsequently ovulation. Metformin lowers glucose

concentrations and although the exact mechanism by which this occurs is still not fully established, it is thought that it improves both peripheral and hepatic sensitivity to insulin (AFHS Drug Information, 1998). Although improved insulin sensitivity is achieved with metformin, the decreased production of hepatic glucose attained by a reduction in gluconeogenesis is believed to be the primary effect of this drug (Speroff et al., 1999). Velazquez et al. (1994) found that 500 mg of metformin administered three times a day to 26 women with PCOS resulted in a significant reduction of androgen levels and reduced insulin levels along with normalization of menses. This finding encouraged further research on the effects of this insulin-sensitizing drug in the treatment of PCOS. Casimirri et al. (1997) demonstrated that treatment with metformin, 500 mg three times a day, combined with a low calorie diet for six months resulted in improved insulin and androgen levels, as well as menstrual cyclicity. The authors reported a decrease in BMI and visceral fat and concluded that based on these findings it was difficult to ascertain whether the positive effects of metformin were due to the drug itself or from the associated weight loss that occurred. A subsequent study has indicated that in the absence of weight loss, metformin was found to have no effect on hyperinsulinemia and hyperandrogenism in overweight women with PCOS (Ehrmann et al., 1997). The authors therefore concluded that metformin has no effect on ovarian steroidogenesis independent of weight loss.

More recently, metformin has been studied in conjunction with clomiphene citrate (CC) in an attempt to enhance the ovulatory responsiveness of obese, insulin-resistant women with PCOS. It was hypothesized that the inclusion of CC with

metformin would induce ovulation in an otherwise unresponsive group of women with PCOS who do not respond to metformin alone. When CC and metformin were combined, an ovulatory response rate of 90% occurred, compared to an 8% response rate in those receiving a placebo/CC combination (Nestler et al.,1998). As a significant decrease in serum insulin in the metformin and CC group occurred, the authors suggested that by decreasing insulin secretion, spontaneous ovulation with metformin either alone or combined with CC will occur. Based on these findings, the authors concluded that hyperinsulinemia impedes ovulation in obese women with PCOS.

As is the case with any medication, the risk of adverse effects exists. Previous investigations have not reported impaired fertility or carcinogenicity when metformin was given in dosages two to three times the maximum recommended human dose (AFHS Drug Information, 1998). It should be noted however, that these particular studies were based on animal models which are not always predictive of the human response. More recently, non-pharmacologic intervention strategies have been studied as therapeutic options for treating obese anovulatory women with PCOS. Lifestyle changes, specifically weight management in the form of diet and exercise, aimed at achieving a healthy body weight have also been shown to be effective. The rationale behind this form of treatment is centered around the association of obesity, insulin resistance and androgen levels. Diet and exercise have been used to treat obese type II diabetics by decreasing insulin resistance and body weight. It is thought that the beneficial effects of weight loss induced by diet and exercise in diabetics, namely the decrease in body weight and

improved insulin sensitivity, could be achieved in obese, anovulatory women with PCOS.

In obese women with PCOS, weight loss has been reported to enhance menstrual cyclicity and fertility rates, improve insulin sensitivity and reduce androgen and insulin concentrations (Pasquali et al., 1997). Kiddy et al. (1992) studied the endocrine and clinical effects of weight loss in obese PCOS women. Twenty-four obese (mean weight 91.5 kg) women with PCOS underwent a low-calorie, low-fat (approximately 30 g of fat per day) intervention diet for six to seven months. The women with a BMI of greater than 30 kg/m^2 were given the option of beginning the study on the Cambridge Diet (330 kcal/day) for four weeks, after which they would commence with the low fat 1000 kcal/day diet consumed by the other subjects. The authors did not report how many subjects were commenced on the Cambridge Diet for the initial four weeks. Thirteen of the initial 24 subjects attained a weight loss of greater than 5% (mean weight loss 11 kg) and demonstrated a fall of fasting serum insulin. Improved reproductive function was demonstrated in 82% of the anovulatory women. Specifically, 9 of the 11 amenorrheic/anovulatory women who lost greater than 5% of their body weight resumed regular menstrual cycles. In addition, five of these women with a long-standing history of infertility became pregnant after a weight loss of greater than 5% of their pre-treatment body weight. Conversely, only one of the eight anovulatory subjects who lost less than 5% of her pre-treatment body weight had improved reproductive function, conceiving after two months of the study. These results led the authors to conclude that although a 5% weight loss did not result in the subjects

reaching an ideal body weight, it did provide beneficial effects on ovarian function. Similarly, Franks et al. (1991) investigated the effects of a diet intervention on 24 obese (mean BMI 30.3 kg/m^2) women with PCOS. The subjects were placed on a 1000 calorie per day diet (nutritional composition not reported) for a period of six months. The data obtained on the 19 women who completed the study indicated that 68% (n=13) of the subjects lost more than 5% of their initial body weight. At the beginning of the study, 14 of the subjects had menstrual dysfunction and 9 subjects were infertile. After the diet intervention, 64% (n=9) of the subjects developed regular ovulatory cycles with 67% (n=6) of the initially infertile women becoming pregnant. A significant decrease in free testosterone and insulin concentrations, as well as an increase in SHBG, were also noted following the diet intervention. The authors concluded that SHBG levels are inversely related to insulin and that by reducing body weight by 5% or more, an improved biochemical profile (defined as decreases in free testosterone and insulin) and restoration of fertility can be achieved. Similar findings were also observed in a study by Hollmann et al. (1996) in which 35 obese (BMI $\geq$34.6 kg/m^2) women, aged 17-41 years and considered to be infertile, were studied. Although PCOS was not definitively diagnosed, all subjects displayed common characteristics of the disorder; 85% of the subjects were insulin resistant and all were obese and infertile. The subjects received dietary information and were instructed to reduce their weekly caloric intake to 5000-10,000 calories with a minimum protein intake of 40 g/day. In addition, the subjects were encouraged to increase their physical activity over an approximate eight month period, however no specific details regarding the

frequency, intensity or type of physical activity was provided. Following the weight-reducing diet, the average weight loss was 8.7 kg with improved menstrual function occurring in 80% (n=28) of the subjects with a subsequent pregnancy rate of 29% (n=10). Although plasma insulin levels were reduced, insulin resistance and hyperinsulinemia still persisted. The authors attributed this finding to the fact that although a reduction in weight was achieved, the subjects were still considered to be obese. The findings from this study support the previous work by Kiddy et al. (1992) and Franks et al. (1991), that improvements in insulin resistance and ovulatory status in obese, infertile women can be achieved with a reduction in body weight.

Although dietary control has been shown to produce favorable reproductive outcomes, long-term dietary restriction is generally difficult to maintain. Weight loss achieved through caloric restriction alone not only results in a higher likelihood of poor compliance to the diet, but the weight loss is rarely sustained (Huber-Buchholz et al., 1999). In addition, very low calorie diets have also been shown to adversely alter the body's metabolism, namely a decrease in resting metabolic rate (RMR; Wilmore & Costill, 1994). It is theorized that the decrease in RMR may occur because of the decrease in fat-free mass (FFM) which is associated with diet-induced weight loss (Ross et al., 2000). Conversely, it is suggested that exercise training may increase RMR by promoting an increase in FFM (Wilmore & Costill, 1994). The addition of chronic exercise as an adjunct to dietary treatment has the potential to decrease fat mass while preserving fat-free mass which is the goal of any weight loss program (Ross et al., 2000). In addition, exercise has been shown

to more favorably affect hypertrophic, compared to hyperplastic, fat cells (Ross et al., 2000). The predominant site of excess body fat in women with PCOS is in the abdominal region (Talbott et al., 1995) which is composed primarily of hypertrophic fat cells (Ross et al., 2000). For this reason, it has been suggested that exercise should be used as a strategy in treating obese women with PCOS. Clark et al. (1995) studied 13 infertile obese (mean BMI 38.7 kg/m^2) women, with a mean age of 30.9 years, all of whom had a documented past history of failure to respond to clomiphene citrate. Although not all of the subjects were diagnosed with PCOS (61% had PCOS), all subjects were anovulatory at the beginning of the study. The subjects attended weekly sessions two hours in length for six months. In the first hour, the subjects participated in an exercise program which initially consisted of one hour of low impact aerobics, gradually increasing to one hour of a walk/run and stair-climbing program. Diet and nutrition counseling took place in the second hour of each weekly session. After six months of intervention, 92% (n=12) of the women were ovulating spontaneously and a drop in insulin concentration was also reported. Based on these findings, the investigators concluded that weight loss through positive behavioral changes in exercise and diet over a six month period resulted in significant improvements in ovulation. Clark et al. (1998) later performed a similar study using a larger group (n=67) of obese, infertile women with a mean age of 31.6 years. The aim of the second study was to apply the same treatment to a larger sample size of women requiring fertility treatment. All the women had a BMI greater than 30 kg/m^2 and were infertile with 81% being anovulatory and 79% having PCOS. The same exercise and dietary counseling protocol employed by

Clark et al. in 1995 was used for a period of six months. At the beginning of the study, 69 subjects were anovulatory and following the treatment intervention, 90% of these women ovulated spontaneously. Although the average weight loss achieved at the end of the six months was 10.2 kg, the authors indicated that resumption of ovulation occurred by the fifth month with a mean weight loss of 6.5 kg.

Although improved ovulatory status following weight loss with diet and exercise was demonstrated by Clark et al. (1995 & 1998), there were possible limitations to their findings. For example, there was no random assignment into a treatment group and a control group. The subjects who were reported to have dropped out of the study due to work or other commitments were used as their control group as these subjects were still followed by the fertility clinic from which the sample population was taken. Subsequently, the investigators had no control on the dietary or physical activity patterns of these subjects. Although the treatment group was advised on gradual dietary changes, there was no follow up with regards to change in dietary habits during the study as the dietary assessments were only performed at the beginning and end of the study. As is the case with any questionnaire, the researcher relies on the accurate reporting by the subjects. The subjects were also encouraged to add two further exercise sessions per week to their physical activity regimen, in addition to the supervised program. It was assumed by the investigators that the subjects adhered to this advice because of the demonstrated weight loss, however, no data was collected on the frequency, type or duration of any additional physical activity performed by the subjects. An indication of overall

body fat and fat distribution was provided by BMI and waist and hip measurements respectively. However, a more comprehensive assessment such as skinfold measurements, specifically the sum of five skinfolds for overall body fat and the sum of two skinfolds for fat distribution would provide a more accurate description of body composition (Canadian Society for Exercise Physiology, 1996). This is of importance because the pattern of fat distribution, specifically abdominal fat, is more closely associated with menstrual irregularities. In addition, the latter study consisted of a population of women with mixed indications for fertility treatment, and thus the results cannot be generalized for obese, insulin resistant woman with PCOS.

The relationship between changes in insulin sensitivity, luteinizing hormone and ovulation patterns after lifestyle modifications were investigated in a group of 18 infertile, anovulatory, obese women between the ages of 22 and 39 years with PCOS (Huber-Buchholtz et al., 1998). The investigators used the same dietary and exercise protocol employed by Clark et al. (1995) for their intervention. It was hypothesized that a change in exercise patterns and sensible eating in these women would lead to an improvement in insulin sensitivity, resulting in a decrease in luteinizing hormone and consequently a rise in ovulation rate and pregnancy. The subjects chose either group or individual diet and exercise counseling sessions, which were provided for a period of six months. At the end of the six months, a weight loss of 2-5% from the subjects' initial weight was demonstrated. The subjects showed a 71% improvement in insulin sensitivity and a 39% decrease in luteinizing hormone levels associated with a subsequent return of menstrual

function and fertility. The authors therefore concluded that lifestyle modifications through exercise and sensible eating patterns leads to an improvement in reproductive function. As with previous investigations, the authors reported that these changes occurred with minimal weight loss, an encouraging finding for obese, infertile women. Similar to the limitations proposed by Clark et al. (1995 & 1998), the study design by Huber-Buchholz et al. (1999) did not employ random assignment.

Obesity has an independent effect on insulin resistance (Dunaif, 1997), and is often a characteristic of anovulatory females. Improved ovulatory function may be achieved by increasing insulin sensitivity as a result of a decrease in body weight. Although few studies have been performed on the effects of weight control in the form of lifestyle modifications such as diet and in particular exercise, it is suggested that weight loss does improve spontaneous ovulation and should be considered as the first line of therapy proposed to obese PCOS women, prior to any pharmacological treatment (Galtier-Dereure et al., 1997). The correlation between obesity and a possible blunted response to clomiphene citrate further suggests that weight reduction achieved through positive lifestyle changes in the form of exercise and proper nutrition may be beneficial by inducing ovulation. In addition, obesity and insulin resistance are further associated with an abnormal lipid profile; specifically increased triglycerides, increased low-density lipoprotein cholesterol (LDL-C) and decreased high density lipoprotein cholesterol (HDL-C; Yen et al., 1999). The treatment of dyslipidemia by exercise has proved to be beneficial with respect to lowering triglyceride and raising HDL-C concentrations (American

College of Sports Medicine, 1997). When combined with a low-calorie diet to further induce weight loss, decreases in total cholesterol and LDL-C have also been reported (American College of Sports Medicine, 1997). The measurement and treatment of abnormal lipid levels is important in this population because an abnormal lipid profile is often observed in women with PCOS. Further, the combination of insulin resistance, an abnormal lipid profile and central obesity may increase the risk of cardiovascular disease and the development of overt diabetes in an already susceptible population (Speroff et al., 1999). Therefore, the objective of this study is to examine the effects of aerobic and resistance exercise training, combined with nutritional counseling on body composition, insulin sensitivity, selected hormones and lipid profiles to improve the ovulatory status of women with polycystic ovary syndrome.

1.3 Statement of the Problem and Hypotheses

1.3.1 Statement of the Problem

There is very limited research available on the effect of exercise on menstrual irregularities and reproductive function in the overweight woman. The impact of exercise on menstrual irregularities and reproductive function has primarily focused on very lean women who participate in strenuous exercise. One of the main reproductive disturbances of obese women has involved women with polycystic ovary syndrome (PCOS). Although obesity is the major health concern in this subset of women, PCOS also involves many other endocrinopathies. It has been suggested that weight loss achieved through lifestyle modifications, by means

of hypocaloric diets, and to a lesser extent exercise, has improved reproductive function in women with PCOS. To date, randomized trials with treatment and control groups have not been completed in the few studies which have involved exercise.

The purpose of this study, therefore, was to determine the effects of a supervised cardiovascular and resistance exercise program on the hormonal aberrations associated with menstrual and reproductive function in women with PCOS. Specifically, the effect of exercise and nutritional counseling on insulin, androgen and lipid levels was observed in this cohort of women. Body composition, specifically patterns of body fatness, resting metabolic rate, cardiorespiratory fitness and nutritional practices were also measured. Random assignment into a treatment (exercise and nutritional counseling group; EN) and a control (nutritional counseling only; N) group was employed.

1.3.2 Hypotheses

It was hypothesized that a supervised exercise program with dietary counseling would result in a decrease in body fatness, which would subsequently normalize the dependent variables studied. It was hypothesized that there would be a decrease in fasting insulin, LH:FSH ratio and low-density lipoprotein cholesterol, with an increase in sex-hormone binding globulin and high-density lipoprotein cholesterol. It was also hypothesized that a decrease in the above variables would occur as a result of the exercise program and in the absence of a significant change in body weight.

1.3.3 Limitations

1. The results of this study can only be applied to the population from which the subjects represent.
2. The benefits achieved by a cardiovascular and resistance training program relies on the adherence to the exercise program by the subjects.
3. The dietary habits could not be controlled, therefore the food intake estimation relies on the accurate reporting of the subjects with regards to portion sizes and actual food consumed.
4. It was assumed that the weight loss in the nutrition only group was achieved by changes in their dietary intake and that the subjects did not undertake any other forms of weight loss, i.e. severe dietary restriction, during the course of the intervention.

CHAPTER 2

METHODS

2.1 Study Design

A treatment-control experimental design was used to make comparisons between subjects receiving exercise and nutritional counseling (EN) or nutritional counseling only (N). To observe the effects of a 12 week cardiovascular and resistance training exercise program, the subjects were randomly assigned to receive either exercise and nutritional counseling or nutritional counseling only. Pre- and post-testing was conducted on all participants on the dependent variables assessed, including body composition (body mass index, waist circumference, sum of five skinfolds, waist to hip ratio), insulin sensitivity, androgen levels, fasting lipid levels, ovarian follicle population, cardiorespiratory fitness, resting metabolic rate and nutritional practices. The above measures were obtained prior to and at the completion of the study.

2.2 Participants

Exclusion criteria included the presence of thyroid disease, increased prolactin levels, and increased dehydroepiandrosterone sulfate (DHEAS) levels which were measured during the pre-screening assessment prior to enrollment into the study. In addition, any other cardiovascular, respiratory or endocrinological diseases which required the use of prescribed medication resulted in exclusion from

the study. The subjects were asked to refrain from taking oral contraceptive pills and therefore were counseled on barrier methods of contraception. Pregnancy tests were performed on all subjects and those with a positive result were excluded. Subjects were also excluded if they were currently smoking. Inclusion criteria included overweight women (body mass index > 27 kg/m^2) with irregular menstrual cycles and a diagnosis of polycystic ovary syndrome (PCOS) based on biochemical and ultrasonographic techniques.

The required sample size was based on the previous literature regarding expected changes in body weight (-0.6 kg ± 0.4) and fat mass (-1.3 kg ± 0.2) associated with an endurance and resistance exercise program. The calculated value indicated a sample size of approximately 20 subjects in each group would have 80% power to detect a difference in means with a level of significance set at $p = 0.05$. Subject recruitment was attempted through a newspaper advertisement, an advertisement (Appendix A) that was distributed to each of the three Saskatoon hospitals (Royal University Hospital, St. Paul's Hospital, Saskatoon City Hospital) as well as information sent to various family physician offices. Due to difficulties with subject recruitment, the study took place over a total of 34 weeks with a staggered starting time for three groups outlined below.

A total of 12 sedentary, untrained adult females in their reproductive years (mean age = 30.7 ± 4.6 years), with a clinical and biochemical diagnosis of polycystic ovary syndrome (PCOS) were voluntarily recruited for participation in the proposed study. The subjects were moderately obese, determined by a body mass index (BMI) of greater than 27 kg/m^2 (mean BMI = 36.6 ±5.9 kg/m^2)

according to the standards outlined by the American College of Sports Medicine (1997). The subjects also displayed central obesity determined by waist circumference (mean waist circumference = 98.9 ±11.9 cm) as outlined by the National Institute of Health (1998). The subjects did not have impaired glucose tolerance, determined by a pre-screening oral glucose tolerance test (OGTT). All individuals gave informed written consent (Appendix B) according to the guidelines established by the University of Saskatchewan Advisory Committee on Ethics in Human Experimentation prior to participating in the study. The participants' names were then randomly drawn from a hat and assigned into either the EN group (n=7) or the N group (n=5). As indicated previously, staggered starting times resulted in three groups of women. Group 1 consisted of four subjects (EN = 2, N = 2), group 2 had five subjects (EN = 3, N = 2) and group 3 had three subjects (EN = 2, N = 1). Table 3.1 describes the subjects' baseline anthropometric characteristics.

2.3 Procedures

Prior to beginning the study protocol, all subjects were assessed by a gynecologist in the Department of Obstetrics, Gynecology and Reproductive Science at Royal University Hospital, Saskatoon, SK. The purpose of this visit was to confirm the diagnosis of PCOS. Each subject completed a questionnaire (Appendix D) regarding menstrual history, medical history, physical activity habits and weight loss history. A complete assessment was then carried out by the gynecologist which included a complete physical examination, hematological

assessment, pregnancy status, as well as transvaginal ultrasonography. After acceptance into the study, the subjects were then given a standard dose of progesterone to induce withdrawal bleeding in an effort to prevent dysfunctional uterine bleeding prior to initiation of the intervention. Further baseline determinations of body composition, resting metabolic rate (RMR), cardiorespiratory fitness and nutritional measures were then carried out. The duration of the study for each group was 12 weeks.

2.3.1 Exercise Program

The subjects in the EN group participated in a 12 week supervised exercise program, which focused on weight loss, as this has shown to improve the symptoms of PCOS (Huber-Buchholz et al., 1999 & Clark et al., 1995). The exercise program was conducted three days a week and consisted of a 10 minute warm up period on the treadmill or bicycle, followed by 30 minutes of cardiorespiratory exercise such as treadmill walking and/or stationary cycling at a moderate intensity level of 70-85% of their age-predicted maximum heart rate. To ensure each subject was exercising at a moderate intensity, Polar Heart Rate monitors were used to monitor heart rates during the exercise sessions.

Each exercise session also included a supervised resistance training component composed of twelve exercises: biceps curl, lat pulldown, leg curl, leg extension, shoulder press, chest press, leg press, hip abduction, hip adduction, hip flexion, hip extension and back extension. After familiarization with the resistance training equipment and program, each subsequent session began with two sets of 10

repetitions at a comfortable baseline weight. When three sets of 15 repetitions of each exercise were completed comfortably, the weight was then increased by approximately five percent or 2.2 kg (whichever was greater). All training sessions were conducted in the R.J. Williams Building, College of Kinesiology at the University of Saskatchewan. Each exercise session was recorded in a training log (Appendix E) by the subjects and the supervisor. The subjects were also encouraged to participate in physical activity such as walking on the alternate days when not at the supervised program and were given an activity log (Appendix F) to complete with regards to their physical activity outside of the structured program.

2.3.2 Nutritional Counseling

All the women were required to attend one-hour group nutritional seminars once a week conducted by the researcher and a registered dietitian. They were counseled on long-term nutritional strategies including: (1) Determining caloric requirements, (2) Canada's Food Guide to Healthy Eating, (3) serving sizes and portion sizes, (4) daily fat consumption targets, (5) diet strategies and goals for weight loss, (6) shopping tips for healthy food choices, (7) meal planning, (8) food preparation and modification, and (9) other weight-related topics specific to carbohydrate, fat and protein, fiber, water and key nutrients.

2.3.3 Measurements

2.3.3.1 Body Composition

Body composition was measured at baseline and at the conclusion of the study as it has been shown that women with higher waist/hip ratios displaying abdominal obesity have higher androgen levels (Pasquali et al., 1993). Skinfold measurements were taken from five sites (subscapular, supra-iliac, umbilical, posterior thigh and anterior thigh sites) and were measured as outlined by the Canadian Society for Exercise Physiology (1996a). Initial skinfolds were taken at all five sites and recorded to the nearest 0.2 mm. The procedure was repeated to obtain a second measurement at all five sites and the mean of the two measurements was recorded. When the difference between the first and second measurement of a particular skinfold was greater than 0.4 mm, a third measurement was taken. From the three measurements, the two measures that were more closely matched in value were used. When all three measures were equidistant apart, the mean of all three measurements from that site were used. The final measurements from each skinfold site were then summed. Waist and hip circumferences were measured to obtain the waist:hip ratio. To determine waist girth, a tape measure was positioned horizontally at the level of the noticeable waist narrowing. The measurement was read at the end of a normal expiration. When the point of narrowing was not found, an indeterminate waist was approximated by finding the lateral level of the 12^{th} or lower floating rib and taking the girth at that site. Each subject stood with her legs together and hip girth was determined. The tape measure was positioned horizontally around the hips at the greatest posterior protuberance of the buttocks.

Each girth measurement was taken twice and recorded to the nearest 0.5 cm. When the difference between the first and second girth was greater than 0.5 cm, a third girth was taken and the average was determined from all three measurements. All skinfold and girth measurements were taken by the same tester.

2.3.3.2 Biochemical Markers

After a minimum twelve hour fast, blood samples were drawn from each subject for determination of fasting insulin and lipid profiles. Fasting insulin levels were analyzed using the Immulite 2000 chemiluminescent immunoassay system (Diagnostic Product Corporation, Los Angeles, CA, USA). The lipid analysis included total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (Tg) and TC/HDL ratio. Total cholesterol, HDL and Tg were analyzed using the automated SYNCHRON LX System (Beckman Coulter, Inc., Fullerton, CA, USA). The LDL cholesterol was calculated from values obtained on TC, HDL and Tg (LDL = TC – HDL – (Tg/2.2)). The TC/HDL ratio was also determined from the calculated values for each. Blood samples were also drawn to determine follicle-stimulating hormone (FSH) and luteinizing hormone (LH) as well as total testosterone, sex-hormone binding globulin (SHBG) and free androgen index (FAI). The FSH and LH levels were measured by microparticle enzyme immunoassay (MEIA) technology using the AxSYM System (Abbott Laboratories, Abbott Park, IL, USA). Total testosterone was analyzed using the Abbott architect (Abbott Laboratories, Abbott Park, IL, USA). Sex-hormone binding globulin was analyzed using the Immulite

2000 chemiluminescent immunoassay system (Diagnostic Product Corporation, Los Angeles, CA, USA). The free androgen index (FAI) was calculated from the results of the total testosterone and SHBG (testosterone/SHBG). All samples were drawn and analyzed immediately by Phlebotomy Services of Saskatoon District Health, were obtained pre and post-testing and were drawn in the morning at approximately the same time of day after a 12 hour fast.

2.3.3.3 Transvaginal Ultrasound

Transvaginal ultrasound was used to determine the presence of a polycystic ovarian population of follicles and to determine the presence of a corpus luteum as well as changes in the endometrium. Although ultrasonography has primarily been used as a diagnostic tool for gynecological disorders in the past, transvaginal sonography of the female reproductive organs has been shown to be an effective technique to provide evidence that ovulation has occurred. Transvaginal ultrasonography is also able to provide reliable information on ovarian follicle number and size (Pache et al., 1990). One of the clinical characteristics in women with PCOS is the presence of numerous small follicules, approximately 2-10 mm in size (Speroff et al., 1999) which can be easily detected on transvaginal ultrasound.

The number of ovarian follicles was assessed in the plane of largest ovarian dimension in both transverse and sagittal planes. Endometrium thickness and pattern (A-D) was also recorded (Fleischer et al., 1990; Fleischer et al, 1986). All transvaginal ultrasounds were performed by the same gynecologist in the

Department of Obstetrics, Gynecology and Reproductive Sciences at Royal University Hospital, Saskatoon, SK.

2.3.3.4 Cardiorespiratory Fitness

Cardiorespiratory fitness was determined by the Astrand and Ryhming submaximal cycle ergometer test conducted on a Monark 818E cycle ergometer. This protocol is the standard submaximal cycling test for determining cardiorespiratory fitness as outlined by the Canadian Society for Exercise Physiology (1996b). Subjects pedaled at 50 rpm for six minutes at a work rate that elicited a steady-state heart rate between 120 and 150 beats per minute. When the participants did not reach this desired steady state in heart rate, they continued to exercise for another minute. Maximal oxygen uptake was estimated using the normative data of Astrand and Rodahl (1977).

2.3.3.5 Resting Metabolic Rate

The resting metabolic rate of each participant was measured by a Sensormedics VMAX 29 series metabolic cart (Yorba Linda, CA). The VMAX 29 employs an analyzer module, pneumatics module, and an AST 486 desktop computer; mass flow sensor, 16% oxygen, 4% CO_2 calibration cylinder with gas valve and calibration syringe. It provides an open-circuit, indirect method of calorimetry through the use of a dilution test. All subjects were instructed to fast for at least 12 hours prior to their testing. In addition, they were instructed to avoid any form of exercise training for at least 48 hours, attain a minimum of 8 hours of sleep the night before and to avoid any activity requiring excessive movement the

morning of the testing. After measurements of height and weight were recorded, each subject rested in the supine position for approximately 15 minutes. A ventilated hood was then placed over the participant's head. Room air was inhaled and exhaled into the hood which was attached to the gas analyzers via a collection tube. The baseline RMR measurements continued until the subject reached a "steady state" defined as five consecutive readings (separated by at least 1 minute) with exhaled volume values within 5% of their previous values. All participants were tested in the morning at approximately the same time of day. Resting energy expenditure was estimated using measured respiratory exchange ratio to establish the caloric equivalent of VO_2 (oxygen consumed; Barszteinm, Elwyn, Askanazi & Kinney, 1989).

2.3.3.6 Nutritional Practices

Individual nutrient intakes were determined by three 24-hour dietary recalls (Appendix I) conducted prior to and following the intervention. Twenty-four hour dietary recall is the most commonly used method to assess the actual food intakes (McQuaid-Cox, 1990). It is a valid tool to obtain actual food intakes at a group level by covering a wide range of ages, social backgrounds, and occupations (Karvetti & Knuts, 1985). The technique is quick, easy and has low subject burden (McQuaid-Cox, 1990). The subjects were asked to recall the types and amounts of food and beverages that they had consumed over the previous 24 hours. Three recalls were performed covering one weekend day and two weekdays. Food consumption data obtained from the 24-hour recalls were analyzed for energy and

nutrient content with FUEL Nutrition Software 2.1a (LogiForm International Inc., Saint-Foy, QB, Canada). Diets of the participants were assessed for adequacy by comparing individual and mean intakes with the Canadian Recommended Nutrient Intakes (Canada, Health & Welfare, 1990) and foods consumed to Canada's Food Guide to Healthy Eating (Canada, Health & Welfare, 1992).

2.4 Statistical Analysis

A 2 (treatment and control groups) X 2 (baseline and post-test) analysis of variance (ANOVA) was performed for each dependent variable which included anthropometry (weight, BMI, waist circumference, W:H, SO5S), biochemical markers (LH:FSH, insulin, SHBG, free androgen index, testosterone), lipid profile (LDL, HDL, triglycerides, total cholesterol (TC) and TC/HDL ratio), resting metabolic rate, predicted maximum oxygen consumption and transvaginal ultrasonographic changes (left and right ovarian follicle population). A one-way ANOVA was used to assess the significance of differences between groups on the dependent variables assessed. Tukey's post hoc analysis was performed if there was a significant finding. Statistical significance was set at $P<0.05$. All values are expressed as the mean ± the standard error.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Results

3.1.1 Anthropometry

Anthropometric measurements of the participants are shown in Table 3.1. No significant difference between the intervention or control groups were observed at baseline in body weight, BMI, waist circumference, waist to hip ratio (W:H) or sum of 5 skinfolds (SO5S), indicating that both groups were relatively homogenous. The anthropometric measurements also confirm that both groups were moderately obese based on the criteria outlined by the Canadian Society for Exercise Physiology (1996a).

Following the intervention program, no significant difference in body weight ($p = 0.12$; Figure 3.1) or BMI ($p = 0.12$; Figure 3.2) was observed between the groups. There was a significant decrease in waist circumference in both the intervention and control groups ($p = 0.001$) following the intervention program, although there was no group x time interaction. Figure 3.3 showed a 5% decrease in the EN group (98.3 ± 5.0 to 93.1 ± 4.8 cm) and the N group (99.8 ± 5.0 to 94.8 ± 5.4 cm). Similarly, Figure 3.4 showed there was a significant decrease in the W:H ($p=0.002$) for both groups following the intervention program. There was a 3% decrease in the EN group (0.81 ± 0.02 to 0.79 ± 0.02) and a 4% decrease in the N group (0.85 ± 0.02 to 0.82 ± 0.02), however there was no significant difference

between the groups following the intervention. The data on the sum of skinfolds showed a significant group x time interaction ($p=0.05$) following the intervention (Figure 3.5). Post hoc analysis revealed there was a greater decrease in the EN group compared to the N group ($p=0.03$). There was a 12% decrease in the EN group (173.6 ± 8.3 to 152.1 ± 7.6 mm) while the N group decreased by 3% (176.3 ± 12.6 to 171.4 ± 12.1 mm).

Table 3.1
Baseline and post-intervention anthropometric subject characteristics. All values are means ± SE.

Characteristics	**EN Group (n=7)**		**N Group (n=5)**	
	Pre	**Post**	**Pre**	**Post**
Age (years)	32.3 ± 1.0	32.3 ± 1.0	28.4 ± 2.7	28.4 ± 2.7
Body weight (kg)	100.5 ± 6.7	99.7 ± 7.5	94.8 ± 6.2	91.7 ± 4.9
BMI (kg/m^2)	36.2 ± 2.0	35.9 ±2.2	37.1 ± 3.4	35.9 ± 3.0
Waist Girth (cm)	98.3 ± 5.0	93.1 ± 4.8	99.8 ± 5.0	94.8 ± 5.4
W:H ratio	0.81 ± 0.02	0.79 ±0.02	0.85 ± 0.02	0.82 ± 0.02
SO5S (mm)	173.6 ± 8.3	152.1 ± 7.6	176.3 ± 12.6	171.4 ± 12.1

BMI = body mass index; W:H = waist to hip ratio; SO5S = sum of five skinfolds (subscapular, iliac crest, abdominal, anterior thigh, posterior thigh).

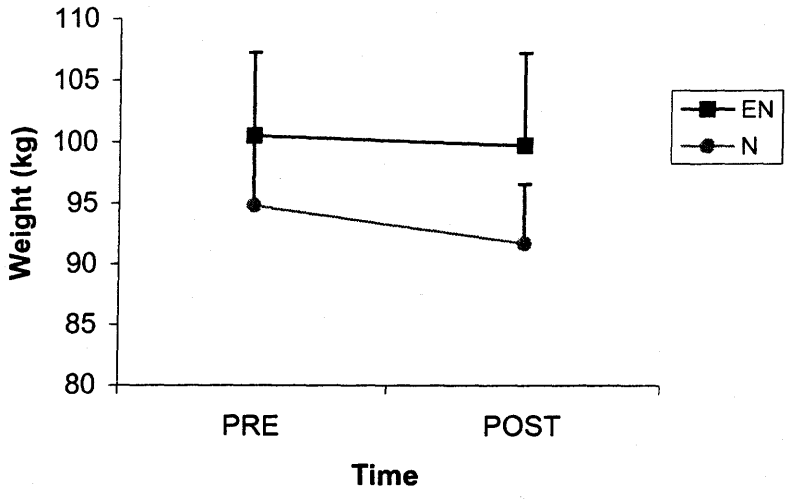

Figure 3.1: Changes in body weight following 12 weeks of exercise and nutritional counseling (EN; n=7) and nutritional counseling only (N; n=5). Values are the mean ± SE.

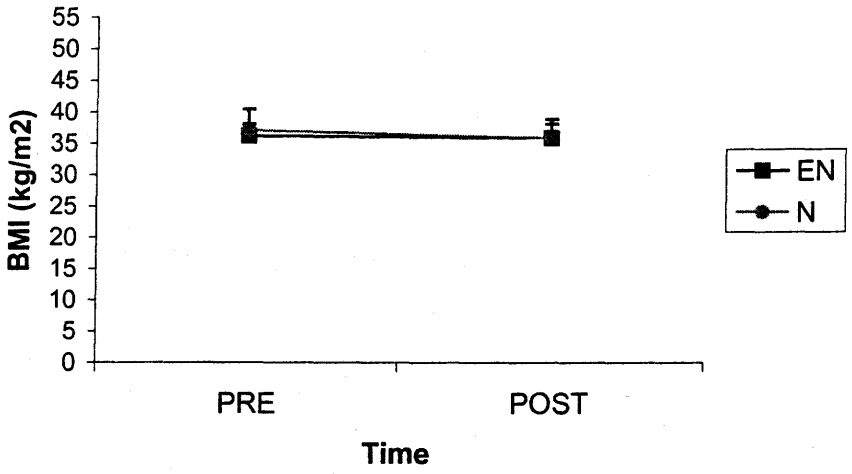

Figure 3.2: Changes in body mass index (BMI) after 12 weeks of exercise and nutritional counseling (EN; n=7) or nutritional counseling only (N; n=5). Values are the mean ± SE.

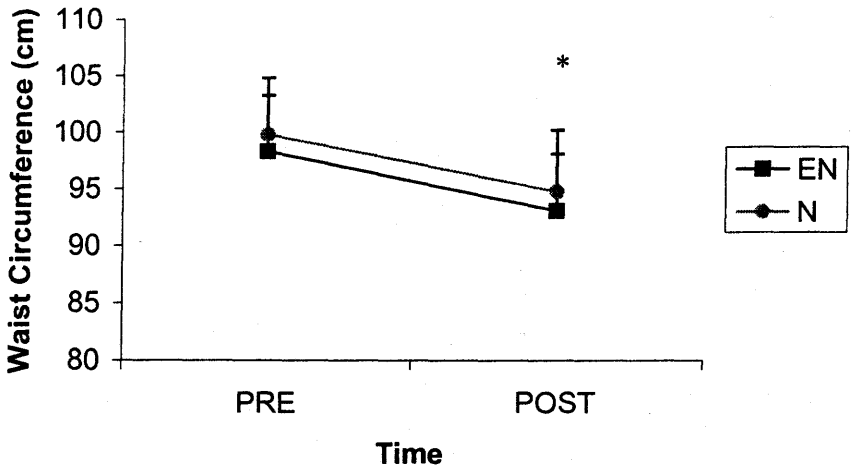

Figure 3.3: Changes in waist circumference after 12 weeks of exercise and nutritional counseling (EN; n=7) or nutritional counseling only (N; n=5). Values are the mean ± SE.
*Significantly different from baseline.

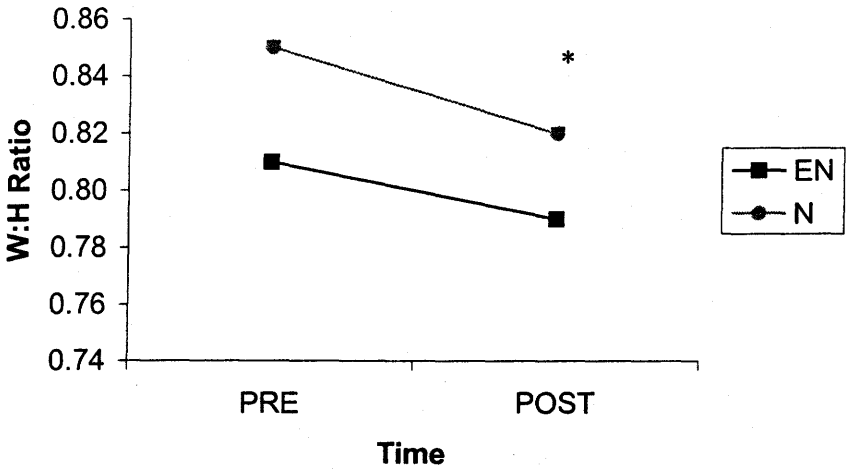

Figure 3.4: Changes in waist:hip ratio (W:H) after 12 weeks of exercise and nutritional counseling (EN; n=7) or nutritional counseling only (N; n=5). Values are the mean ± SE.
*Significantly different from baseline.

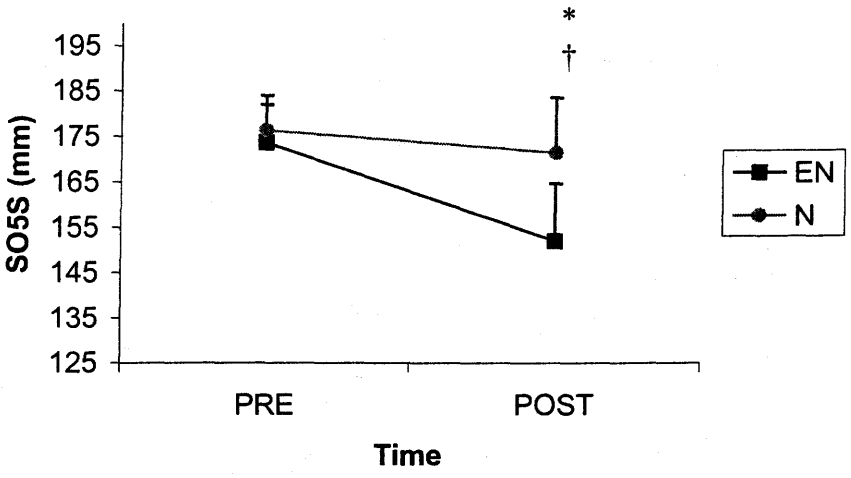

Figure 3.5: Changes in sum of five skinfolds (SO5S; subscapular, iliac crest, abdominal, anterior thigh, posterior thigh) after 12 weeks of exercise and nutritional counseling (EN; n=7) or nutritional counseling only (N; n=5). Values are the mean ± SE.
*Significantly different from baseline.
†EN group significantly different from N group.

3.1.2 Cardiovascular Fitness

Table 3.2 illustrates there was no significant difference in cardiorespiratory fitness between the intervention and control groups at baseline. These results indicate both groups had a low fitness level as outlined by the Canadian Society for Exercise Physiology (1996). Following the intervention program, the data on the predicted maximal oxygen consumption shows a significant group x time interaction ($p = 0.02$). Post hoc analysis revealed there was a greater increase in the EN group compared with the N group ($p = 0.04$). Figure 3.6 shows there was a 42% increase in the EN group (22.6 ± 2.1 to 32.0 ± 2.9 $ml \cdot kg^{-1} \cdot min^{-1}$) and a 5% increase in the N group (23.9 ± 2.5 to 25.0 ± 4.2 $ml \cdot kg^{-1} \cdot min^{-1}$).

3.1.3 Resting Energy Expenditure

Baseline measurements of resting energy expenditure (REE) indicates there was no significant difference between the intervention and control groups (Table 3.2). Following the intervention, no significant difference in REE was observed between the two groups ($p = 0.63$; Figure 3.7). However, the EN group increased by 9% (1485 ± 177 to 1610 ± 146) whereas the N group decreased by 1% (1596 ± 107 to 1586 ± 103).

3.1.4 Ovarian Follicle Population

At baseline, there was no difference between the groups for the number of ovarian follicles in either the right or left ovaries (Table 3.2) with all subjects having an ovarian follicle population consistent with the diagnosis of PCOS. Following the

intervention, there were no significant differences in ovarian follicle population in either ovary between the groups (right ovary p = 0.50, left ovary p = 0.37; Figure 3.8). Due to poor visualization of the left ovary on transvaginal ultrasound, one subject was excluded from this analysis.

Table 3.2
Baseline cardiovascular fitness scores, resting energy expenditure values and ovarian follicle population. All values are means ± SE.

Characteristic	EN Group (n=7)	N Group (n=5)
VO_2 ($kg \cdot min^{-1} \cdot min^{-1}$)	22.6 ± 2.1	23.9 ± 2.5
REE (kcal/day)	1485 ± 177	1596 ± 107
PCO-R	49 ± 7	47 ± 8
PCO-L	35 ± 5	33 ± 4 (n=4)

VO_2 = oxygen consumption; RMR = resting energy expenditure, PCO-R = number of ovarian follicles on the right ovary; PCO-L = number of ovarian follicles on the left ovary.

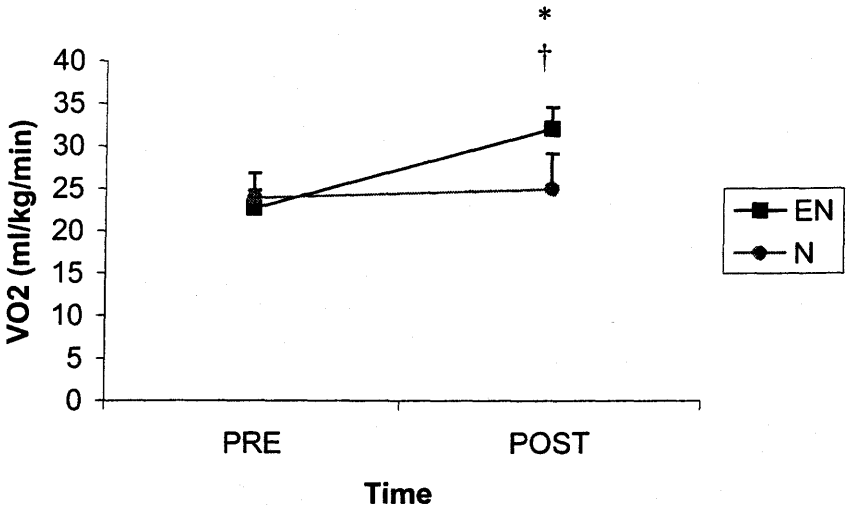

Figure 3.6: Changes in predicted maximal oxygen consumption (VO2max) after 12 weeks of exercise and nutritional counseling (EN; n=7) or nutritional counseling only (N; n=5). Values are the mean ± SE.
*Significantly different from baseline.
†EN group significantly different from N group.

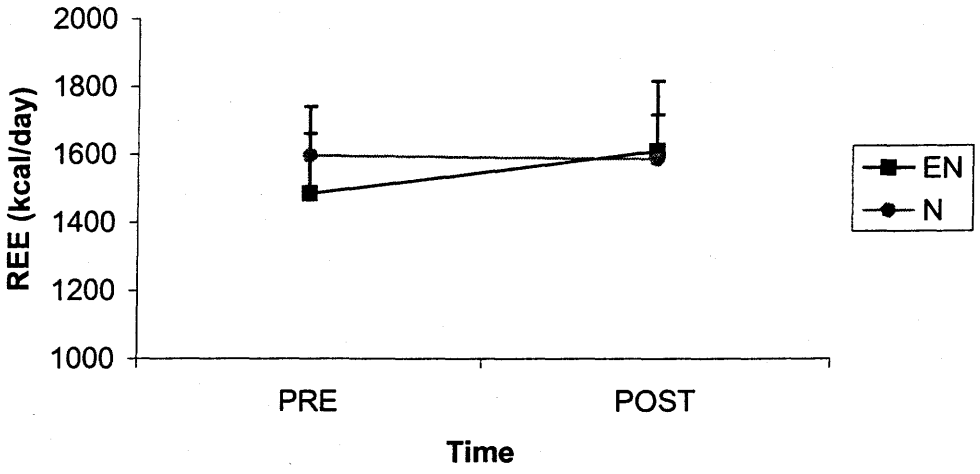

Figure 3.7: Changes in resting energy expenditure (REE) after 12 weeks of exercise and nutritional counseling (EN; n=7) or nutritional counseling only (N; n=5). Values are the mean ± SE.

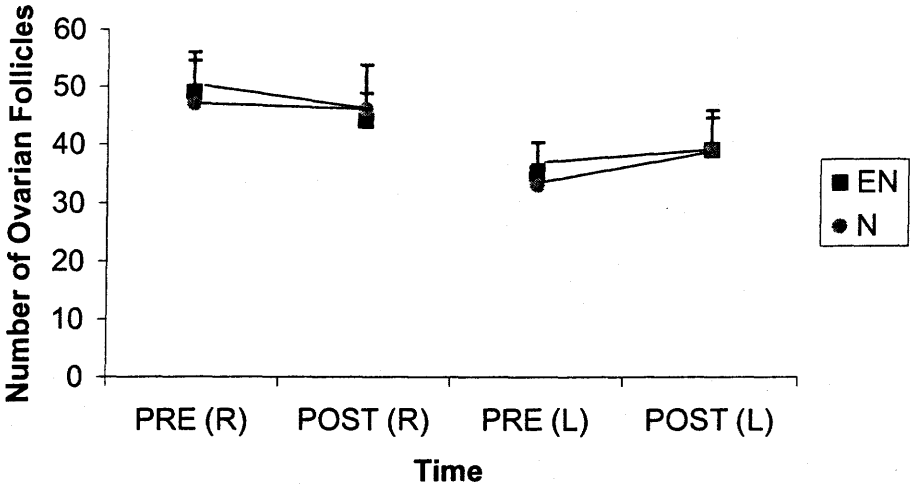

Figure 3.8: Changes in right (R) and left (L) ovarian follicle population after 12 weeks of exercise and nutritional counseling (EN; n=7) or nutritional counseling only (N; n=4). Values are the mean ± SE.

3.1.5 Hormone Levels

There were no significant differences between the groups for baseline measurements of LH:FSH and fasting insulin levels (Table 3.3). Following the intervention, there was no significant difference of LH:FSH ($p = 0.20$; Figure 3.9) between the groups. The data on two subjects in the EN group were excluded due to laboratory error for one subject and a positive pregnancy test for the other subject. There was a significant decrease in fasting insulin levels within both groups following the intervention ($p = 0.03$). Figure 3.10 shows the EN group had a 29% decrease (116.7 ± 42.2 to 82.5 ± 20.8 pmol/L) while the N group had a 55% decrease (233.8 ± 86.4 to 105.0 ± 24.6 pmol/L), however these differences were not significant between the two groups. The data on one subject from both the EN and N groups were excluded in this analysis due to laboratory error.

3.1.6 Androgen Levels

There were no significant baseline differences between the intervention and control group for sex-hormone binding globulin (SHBG), total testosterone or free androgen index (FAI; Table 3.3). Due to laboratory error, one subject from the N group was excluded for the following data. Following the intervention, there were no significant differences in SHBG ($p = 0.50$; Figure 3.11), testosterone ($p = 0.61$; Figure 3.12) or FAI ($p = 0.89$; Figure 3.13) either within or between the two groups.

Table 3.3
Baseline hormone and androgen assays. All values are means ± SE

Characteristic	EN Group	N Group	Normal Range
LH:FSH (U/L)	2.2 ± 0.6 (n=5)	2.0 ± 0.4 (n=5)	<1.0
Fasting insulin (pmol/L)	116.7 ± 37.7 (n=6)	233.8 ± 77.4(n=4)	72.0 - 100.0
SHBG (nmol/L)	26.4 ± 4.3 (n=7)	17.1 ± 4.9 (n=4)	18.0 - 114.0
Testosterone (nmol/L)	3.0 ± 0.3 (n=7)	3.1 ± 1.0 (n=4)	0.5 - 4.1
FAI	13.9 ± 2.6 (n=7)	20.3 ± 4.6 (n=4)	0.0 - 8.5

LH:FSH = luteinizing hormone to follicle stimulating hormone ratio; SHBG = sex-hormone binding globulin; FAI = free androgen index.

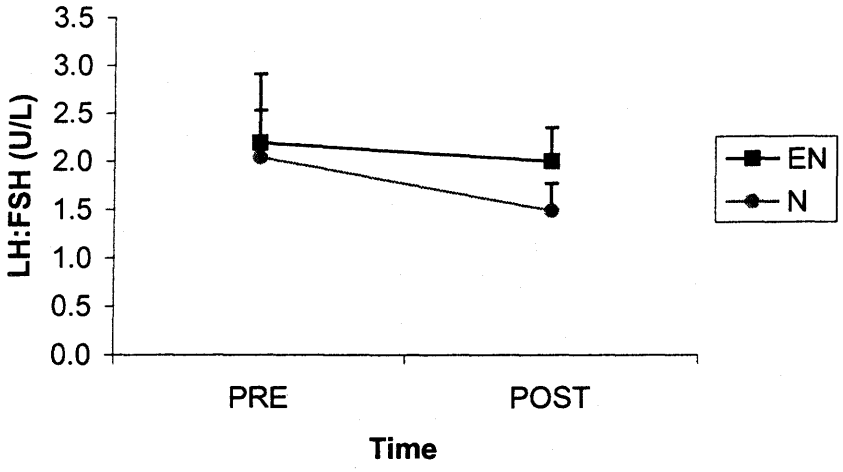

Figure 3.9: Changes in luteinizing hormone to follicle stimulating hormone ratio (LH:FSH) after 12 weeks of exercise and nutritional counseling (EN; n=5) or nutritional counseling only (N; n=5). Values are the mean ± SE.

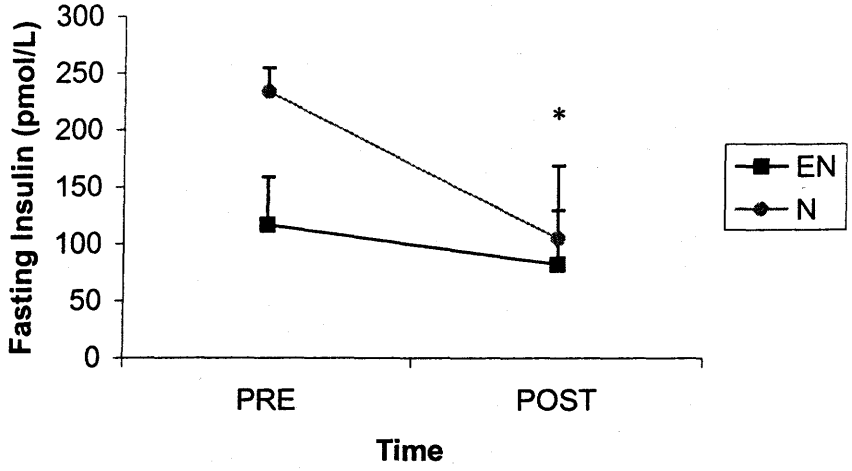

Figure 3.10: Changes in fasting insulin levels after 12 weeks of exercise and nutritional counseling (EN; n=6) or nutritional counseling only (N; n=4). Values are the mean ± SE.
*Significantly different from baseline.

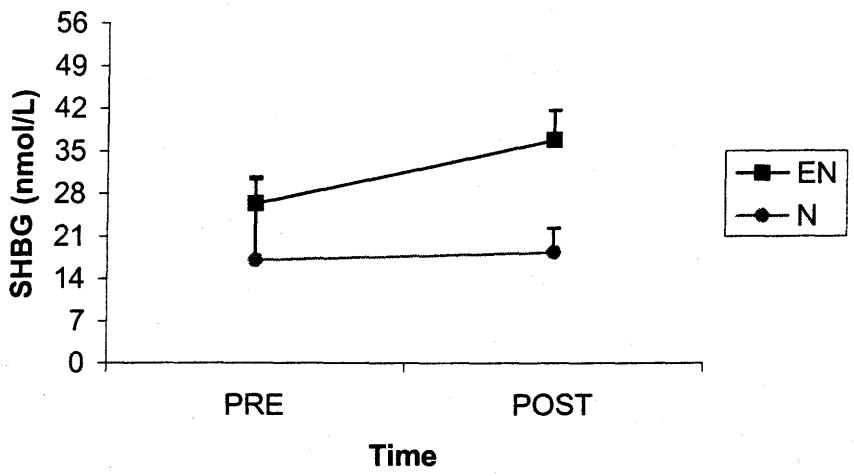

Figure 3.11: Changes in sex-hormone binding globulin (SHBG) after 12 weeks of exercise and nutritional counseling (EN; n=7) or nutritional counseling only (N; n=4). Values are the mean ± SE.

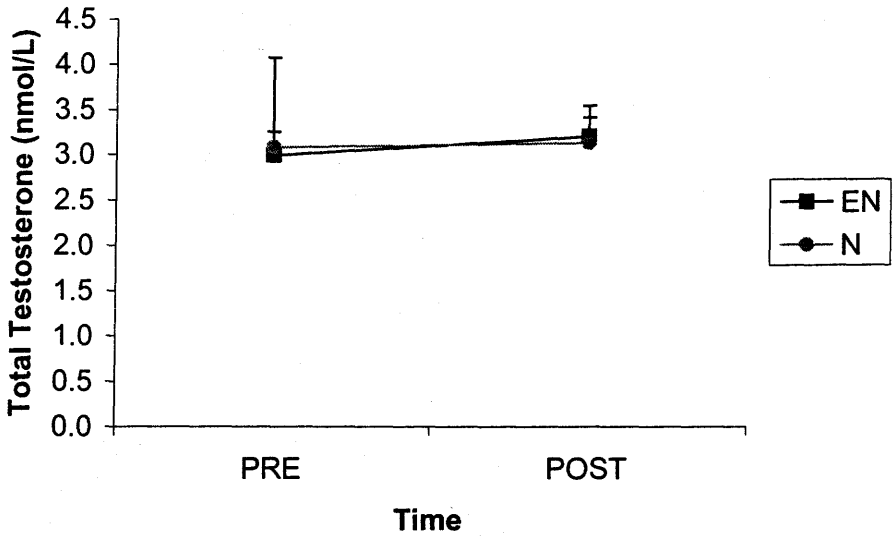

Figure 3.12: Changes in testosterone level after 12 weeks of exercise and nutritional counseling (EN; n=7) or nutritional counseling only (N; n=4). Values are the mean ± SE.

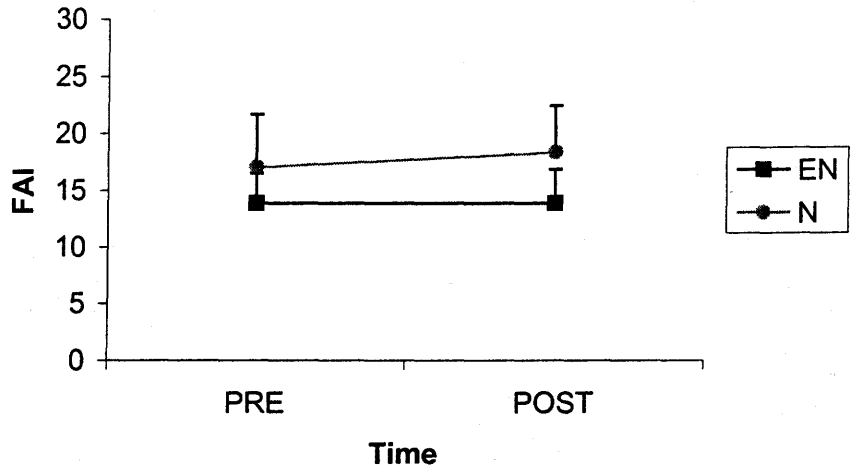

Figure 3.13: Changes in free androgen index (FAI) after 12 weeks of exercise and nutritional counseling (EN; n=7) or nutritional counseling only (N; n=4). Values are the mean ± SE.

3.1.7 Lipid Profile

Baseline assessment of HDL (high density lipoprotein), LDL (low density lipoprotein) Tg (triglycerides), TC (total cholesterol and HDL/TC (high density lipoprotein to total cholesterol ratio) revealed no significant differences between the intervention and control groups (Table 3.4). The data collected on the lipid profile following the intervention showed no significant differences in HDL ($p = 0.76$; Figure 3.14), LDL ($p = 0.81$; Figure 3.14), Tg ($p = 0.84$; Figure 3.14), TC ($p = 0.96$; Figure 3.14) or HDL/TC ($p = 0.91$; Figure 3.14) within or between the intervention and control groups.

3.1.8 Fertility Status

Following the intervention the diagnosis of PCOS remained in all but one subject in the EN group who became pregnant during the intervention. It is interesting to note that the two previous pregnancies in this individual were achieved by the use of clomiphene citrate. Although all the women in the EN group, and all but one woman in the N group reported a spontaneous menstrual cycle during the intervention, it should be mentioned that the cycles were variable and therefore cannot be directly attributed to the intervention.

Table 3.4
Baseline blood lipid analysis. All values are means ± SE.

Characteristic	EN Group (n=7)	N Group (n=5)	Normal Range
HDL (mmol/L)	1.15 ± 0.09	1.22 ± 0.20	0.09 - 2.20
LDL (mmol/L)	2.75 ± 0.30	2.74 ± 0.28	2.00 - 3.40
Tg (mmol/L)	1.07 ± 0.13	1.13 ± 0.16	0.60 - 2.30
TC (mmol/L)	4.38 ± 0.35	4.47 ± 0.44	3.80 - 5.20
TC/HDL	3.93 ± 0.35	3.94 ± 0.52	3.40 – 4.40

HDL = high density lipoprotein; LDL = low density lipoprotein; Tg = triglycerides; TC = total cholesterol; TC/HDL = total cholesterol to high density lipoprotein ratio.

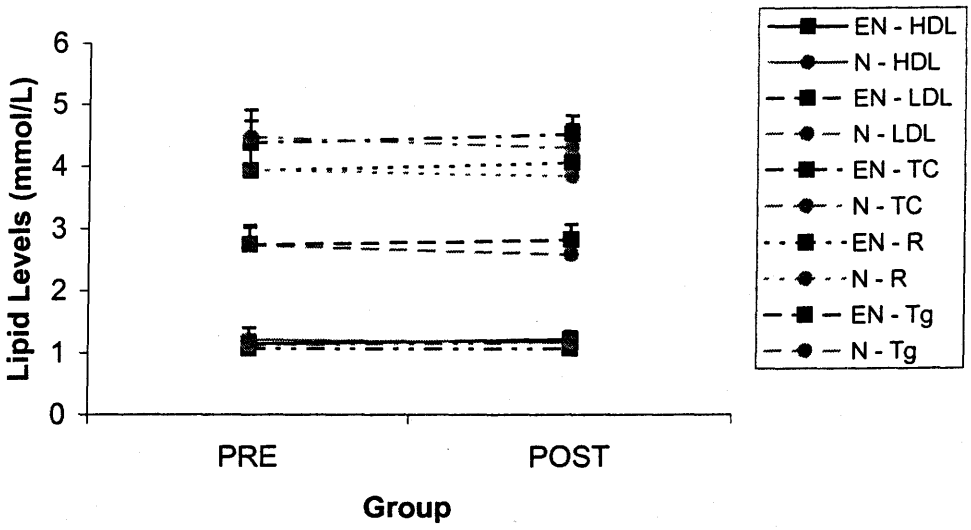

Figure 3.14: Changes in lipid profile after 12 weeks of exercise and nutritional counseling (EN; n=7) or nutritional counseling only (N; n=5). Values are the mean ± SE.

3.2 Discussion

The literature to date has suggested that dietary-induced weight loss improves the ovulatory status of women with PCOS (Franks et al., 1991; Kiddy et al., 1992; Hollmann et al., 1996), however, there is a lack of research on the effect of exercise on this population. It has previously been shown that weight loss, independent of exercise, improves the insulin resistance (Guzick et al., 1994; Holte et al., 1995) and hyperinsulinemia (Pasquali et al., 1989; Kiddy et al., 1992) in obese women with PCOS. As insulin resistance is now believed to be a key player in the pathogenesis of PCOS, we wanted to determine if exercise would exert the same beneficial effects as the diet-induced weight loss in obese women with PCOS. Randomized controlled studies of affected women are limited, especially with regard to lifestyle modification. As previous research has focused almost primarily on dietary modifications, we elected to randomize the women into a treatment group (exercise and nutritional counseling; EN) or a control group (nutritional counseling only; N) to determine the effectiveness of an exercise program in this population. The purpose of this study therefore was to determine the effects of a supervised exercise program combining cardiovascular and resistance training on the metabolic and hormonal aberrations associated with the menstrual and reproductive function in obese women with PCOS. Specifically, we wanted to determine the effects of exercise on body composition, primarily patterns of body fatness, and resting metabolic rate. It was hypothesized that changes in these variables following the intervention would result in improved fasting insulin, androgen and lipid levels as well as enhance the reproductive status in women with polycystic ovary syndrome.

As many women with PCOS may be unaware of their diagnosis until they try to conceive, improved reproductive function is one of their primary goals. The design of this study therefore allowed us to provide a form of 'treatment' (i.e. nutritional counseling) for all the subjects regardless of their randomization.

The findings of the present study revealed that the combination of exercise and nutritional counseling, as well as nutritional counseling alone provided favorable effects on some of the variables assessed. Specifically there were significant decreases in waist girth, body fatness and fasting insulin following the intervention. Although the reductions in waist girth and fasting insulin were similar between the two groups, there was a greater decrease in body fatness as a result of the exercise. Interestingly, these changes occurred in the absence of a significant weight loss, which is a potentially important finding in this population. Based on the previous literature, it has been suggested that improvements in the biochemical profile of women with PCOS occurs with a weight loss of 5% or greater of initial body weight (Kiddy et al., 1992; Franks et al., 1991). The data from this study, however, suggests a trend towards an improvement in the biochemical profile with a body weight reduction of as little as 1%. This suggests that factors other than a reduction in body mass, such as a decrease in body fatness, specifically in the abdominal region, may be important in this population.

The anthropometric data revealed small non-significant decreases in body weight (EN 1%, N 3%) and BMI (EN 1%, N 3%). These findings support the previous literature regarding exercise and decreases in body weight. It has been suggested that in the absence of caloric restriction, exercise provides a modest

decrease in body weight (Rippe & Hess, 1998; Utter et al., 1998), particularly with the addition of resistance training (Ballor et al., 1988; Cullinen et al., 1998). When different modes of exercise are compared, it has been found that aerobic-type exercise (i.e. run/walk or cycling) yielded an average weight loss of 0.6 kg after 17 weeks of exercise whereas weight training resulted in an average increase in body weight of 0.3 kg following 10 weeks of training (Ballor & Keesey, 1991). When these two modes of exercise are combined, it is reasonable to assume that minimal loses of body mass would occur due to the suspected increase in fat-free mass. Conversely, it has been reported that exercise training may result in moderate to large losses in body fat (Wilmore, 1983; Bray et al., 1990; Hill et al., 1994). The data from the present study does suggest that there was a decrease in body fatness given the significant decreases in waist girth (EN 5%, N 5%), waist:hip ratio (EN 3%, N 4%) and sum of five skinfolds (EN 12%, N 3%). These changes in body fatness are perhaps more relevant in view of the findings from previous research regarding exercise and abdominal obesity. Previous research has indicated that exercise in the absence of weight loss is not associated with a decrease in abdominal obesity and that a modest weight loss of 2 kg results in only a small reduction in waist circumference (Ross et al., 2000). Conversely, the data from this study indicates that a weight loss of approximately 1-3% of body weight (approximately 0.8-3.1 kg) resulted in a significant reduction in abdominal obesity (5.0-5.3 cm decrease; $p = 0.001$). The mean waist circumference at the conclusion of the study was less than 95 cm and although a waist circumference of >88 cm is considered to be a high risk for women (National Institute of Health, 1998), the trend towards a

decrease is an important finding in this population due to the significant metabolic risks associated with an increased waist circumference (American College of Sports Medicine, 1997). Although previously it has been suggested that visceral obesity exacerbates an individual's metabolic risks, i.e. insulin resistance and abnormal lipid profile (Despres & Lamarche, 2000), it has also been suggested that the accumulation of subcutaneous fat correlates well with total body fat which also results in impaired insulin action (Lemieux et al., 1993). It is interesting to note that although the N group had a slightly greater weight loss than the EN group (3% vs. 1% respectively), the changes in waist circumference were the same (5%). This may be attributed to the possible increase in FFM with a subsequent loss of fat mass in the EN group while the N group may have had decreases in FFM. Ballor and Keesey (1991) have reported that regular exercise may lead to a modest loss of weight and fat mass and increase in FFM with weight training producing a more substantial increase in FFM. As such, Van Zant (1992) reported that using total body weight as an assessment of the effectiveness of exercise may underestimate the loss of fat mass due to the exercise.

In addition to a significant loss in waist girth in both groups, there was also a significant decrease in W:H within the whole group (EN 3%, N 4%; $p = 0.002$). Although the baseline W:H measurements would be classified as a moderately high health risk (Williams, 1999), as they ranged from 0.81 to 0.85, these values may not be indicative of this populations' true risk of metabolic complications. The combination of an increased BMI (>30 kg/m^2) and waist circumference (> 88 cm) significantly increases the risk of developing type II diabetes, hypertension and

cardiovascular disease (National Institute of Health, 1998). A possible explanation for the somewhat misleading W:H ratio is that although these women were considered markedly overweight to obese based on BMI (American College of Sports Medicine, 1997), a correspondingly high hip circumference may have masked their degree of obesity. For this reason, it is felt that the changes in waist circumference as a measure of central obesity is more relevant to this population with regards to associated risk reduction.

There was also a significant decrease in the sum of five skinfolds (SO5S) in the EN group compared to the N group (12% vs.3%; $p = 0.03$) which indicates a change in body fatness. These findings suggest that resistance training and cardiovascular exercise improved the pattern of body fatness in these women. The results suggest that the decrease in SO5S came not only from the change in waist circumference but also from other areas as well, as the waist circumference in both groups decreased the same degree. It is known that excess weight carried in the abdominal area increases the risk of developing metabolic complications (American College of Sports Medicine, 2000), therefore the combination of significant reductions in body fatness in the absence of a significant weight loss may be encouraging to the obese woman with PCOS as large reductions in body weight may not be as essential to improve their metabolic risk profile.

Although the changes in resting metabolic rate (RMR) that occurred following the intervention program did not reach statistically significant levels in either group, there was almost a 10% increase in the EN group while the N group demonstrated a 1% decrease. The role of exercise in increasing RMR is equivocal,

however it has been suggested that small increases in RMR are beneficial in increasing daily caloric expenditure (Wilmore & Costill, 1994). The close association between RMR and FFM suggests that the addition of the resistance training component may have been beneficial in increasing the RMR of the EN group. It is believed that an increase in FFM results in an increase in RMR as muscle tissue is more metabolically active that fat tissue (Williams, 1999). It is postulated that an increase in FFM occurred in the EN group, as the data indicates a significant decrease in waist circumference, W:H and SO5S with a minimal decrease in body weight. However, a direct measurement of FFM was not obtained and therefore this assumption cannot be definitively confirmed. It has been suggested that exercise is very important to prevent a decline in RMR in women who diet to reduce weight (Lennon et al., 1984). As there was a significant decreased total caloric intake (EN 16%, N 13%; $p = 0.04$) following the intervention, the results suggest that there was a trend towards a beneficial effect on RMR due to the exercise, although this failed to reach statistical significance.

In addition to the beneficial anthropometric changes in the EN group, it was also expected that significant increases in predicted maximal oxygen consumption (VO_{2max}) in the EN group would occur. This was confirmed as the data indicated that there was a 42% increase ($p = 0.005$) in relative VO_{2max} in the EN group following the intervention compared with a 5% increase in relative VO_{2max} in the N group. To account for changes in body weight, the absolute VO_{2max} was calculated which yielded similar results. There was a 41% increase ($p = 0.008$) in the EN group with no change in the N group. The increased VO_{2max} in this population may

serve to reduce their metabolic risk. Endurance exercise training has been shown to improve insulin action and metabolic risk profiles in obese individuals (Despres & Lamarche, 2000). The literature also suggests that low cardiorespiratory fitness is associated with metabolic abnormalities (Whatley et al., 1999). Improvements in cardiorespiratory fitness in women with PCOS may serve to reduce the metabolic abnormalities such as insulin resistance, compensatory hyperinsulinemia and abnormal lipid profiles that are associated with this syndrome.

One of the metabolic abnormalities in women with PCOS is the presence of insulin resistance and compensatory hyperinsulinemia that is also associated with excess abdominal obesity (Speroff et al., 1999). Although hyperinsulinemia and insulin resistance are apparent in both obese and non-obese women with PCOS, they are greater in the obese women. Because of the increased metabolic risks associated with central obesity, we elected to examine the obese PCOS population in the present study. Following the intervention, there was a significant decrease in fasting insulin levels within both the EN and N groups (EN 29%, N 55%; $p<0.03$). Although the magnitude of change between the two groups was not significant, the larger decrease in the N group compared to the EN group was somewhat surprising. It was hypothesized that as a result of the exercise training and subsequent decreases in body fatness, that the EN group would have demonstrated enhanced results compared to the N group. It is well recognized that exercise is one of the cornerstones in treating diabetics because of its beneficial effect on improving insulin sensitivity (American College of Sports Medicine, 1997). It was hypothesized that improvements in insulin sensitivity would result in decreasing the

compensatory hyperinsulinemia associated with PCOS as a result of the exercise intervention. Although previous literature involving dietary modifications has also shown beneficial results with respect to insulin levels (Franks et al., 1991, Kiddy et al., 1992, Guzick et al., 1994, Pasquali et al., 1997), the dietary interventions in these studies ranged from 330 kcal/day to 1000 kcal/day. While the data from this study reflects a 13% decrease in total caloric intake in the N group, the total caloric intake decreased by approximately 287 kcal/day. In addition, although there was a slight decrease in fat intake (approximately 4%), the proportion of dietary fat still exceeded 30% of the total diet. Additionally, there was a slight decrease in carbohydrate intake (approximately 9%) which resulted in carbohydrates accounting for 52% of the total intake. There was however, a 42% increase in protein intake. It has been suggested that a higher protein (45%) hypoenergetic diet may be beneficial in reducing fasting insulin levels in obese hyperinsulinemic individuals (Baba et al., 1999), however the protein intake in the N group only accounted for 19% of the total energy intake. The slightly greater decrease in fasting insulin in the N group compared to the EN group may also be explained by the similar reduction in waist circumference however the N group also achieved a slightly greater, albeit insignificant, weight loss than the EN group (3% vs. 1%). As the weight loss in both groups was not significant, these results indicate that even in the absence of weight loss, significant changes in insulin levels can be achieved by changes in body composition.

Research in women with PCOS has reported another interesting link which exists between excess abdominal obesity and insulin resistance. Abnormal lipid

profiles are commonly associated with PCOS (Talbott et al., 2001) and it has been suggested that women with PCOS and insulin resistance display decreased HDL-C levels and increased LDL-C and triglyceride levels (Yen et al., 1999). Although there were no abnormalities detected in these variables in either group at baseline in the present study, it is interesting to note that the EN group had a 6% increase in HDL-C compared to a 3% decrease in HDL-C in the N group. This supports previous findings that exercise has a beneficial effect on HDL-C (American College of Sports Medicine, 1997). While there was no change in triglyceride level in the EN group, there was a 4% increase in the N group. These results further support the beneficial effects of exercise on triglyceride levels (American College of Sports Medicine, 1997). The small changes in lipids following the study may be due to the relatively normal lipid profiles at baseline. It is expected that small, if any, changes would occur in the lipid profile in the absence of hyperlipidemia. As well, an intervention of 12 weeks may not have be long enough to elicit the changes in the lipid profile due to exercise alone. However, the findings of the present study are of particular importance in this population as the clinical characteristics of PCOS parallel the risk factors for cardiovascular disease (CVD). It has been shown that women with PCOS are comparable to those with diabetes and other insulin-resistant states with regards to their risk of developing CVD (Amowitz & Sobel, 1999). The literature indicates there is an increased risk of atherosclerosis in diabetes (Garg, 1998), and because of the clinical similarities between PCOS and diabetes, interventions that result in lower triglyceride levels and increased HDL-C levels may reduce or delay the onset of a cardiovascular event.

In addition to the metabolic complications of android obesity in women with PCOS, increased abdominal fat deposition is associated with decreased levels of sex-hormone binding globulin (SHBG) and increased synthesis of androgens (Speroff et al., 1999). Following the intervention there was a 39% increase in SHBG in the EN group compared to an 8% increase in the N group. Although these results were not significant, the trend suggests that the observed changes in body fatness, characterized by decreases in waist circumference, W:H ratio and SO5S, resulted in beneficial effects on the level of SHBG, particularly in the EN group where significant changes in body fatness were observed. It has been shown previously that decreased levels of SHBG are associated with increased free androgen levels (Yen et al., 1999) and it is speculated that with a rise in SHBG, a subsequent decrease in free-testosterone would be apparent. Unfortunately, due to a change in laboratory policy, these measurements were not available. The Department of Laboratory Medicine at Saskatoon District Health indicated that the analysis of free-testosterone was no longer available, and was replaced with the Free Androgen Index (a ratio of testosterone/SHBG). We were therefore unable to report on any associations between an increase in SHBG and decrease in free-testosterone levels.

The excessive production and secretion of androgens in PCOS is related to the raised LH:FSH ratio (Speroff et al., 1999), which is a diagnostic criterion for PCOS. Following the intervention, there was a decrease in the LH:FSH ratio of 9% in the EN group and 27% in the N group, however these results were not found to be significant either within or between the groups. The absence of a statistically

significant change in LH:FSH ratio may be due to the single sample obtained. Although the LH:FSH ratio in this study was used primarily for clinical purposes to confirm the diagnosis of PCOS, it is suggested that for future research, the average of three samples taken approximately 15 minutes apart be used to obtain a more accurate LH:FSH ratio. As well, the insignificant change in the LH:FSH ratio may partially contribute to the lack of demonstrable change in ovarian follicle population in either the intervention or control group. The mechanism by which this occurs involves the elevation of LH. The increased LH:FSH ratio results from the increase in LH as well as low levels of FSH (Yen et al., 1999). Because an increase in LH and inadequate levels of FSH are believed to arrest follicular growth of the maturing follicles, it would follow that without a significant decrease in the LH:FSH ratio, there would not be a decrease in ovarian follicle population. However, failure to detect a difference which actually exists (type II error) may be due to the small sample size. The insignificant change in ovarian follicle population may also be explained by the duration of the study. A time period of three months may have been insufficient to detect any significant changes in ovarian follicle population since the lifespan of a normal ovarian follicle may extend several months (Speroff et al., 1999). It is suggested that it takes approximately 85 days for a follicle to reach pre-ovulatory status (Speroff et al., 1999) and therefore a study length of 90 days may have been inadequate to detect any changes. In addition, the use of transvaginal ultrasonography in the present study was to confirm the diagnosis of a polycystic ovarian population of follicles by measuring total number of follicles. To overcome observer variability encountered by measuring the total number of

follicles, it is suggested that a representative sample of the ovary be used in future research.

The obvious limitation of the study is the relatively small sample size. A small sample size increases the risk of a type II error; failing to detect a difference which actually exists. As stated previously, the diagnosis of PCOS may only become apparent in women when they are trying to conceive. Because of the duration of the intervention (12 weeks) as well as the possibility of randomization into a control group, many of the women who inquired about the study were unwilling to delay treatment beyond the 12 weeks. This ultimately resulted in a relatively small sample size. The results of the present study may also have been limited by the duration. An extended intervention may have also provided more insight into the beneficial effects of the exercise on the metabolic parameters assessed. For example, it is estimated that the beneficial effects of exercise training on lipid levels may take up to nine months to be achieved (American College of Sports Medicine, 1997). It is encouraging, however, to note that over a 12-week, period, there were significant positive changes in body fatness and fasting insulin levels, two factors known to contribute to PCOS.

CHAPTER 4

CONCLUSIONS

4.1 Conclusions

The findings from the present study suggests that lifestyle modifications in the form of aerobic and resistance exercise with the addition of nutritional counseling may provide beneficial effects with regards to the metabolic profile of obese women with PCOS. Although there were improvements in body fatness in both the control group (N) and the treatment group (EN), the magnitude of change was greater in the treatment group. The significant decrease in fasting insulin as well as the tendency towards improved sex hormones, in the absence of a significant weight loss, suggests that changes in body composition, specifically a decrease in body fatness, may be more significant than changes in body mass in benefiting this population. Individuals who embark on an exercise program in an effort to lose substantial amounts of body weight often become discouraged because of the time involved to induce aesthetic changes. It may be encouraging to the obese woman with PCOS that although a decrease in body weight may initially be most desirable, a decrease in body fatness, primarily in the abdominal region, may improve their metabolic and hormonal profiles with only minimal losses in body mass. These findings may therefore be beneficial in motivating these individuals to continue with positive lifestyle modifications on a long-term basis.

4.2 Future Research

In order to further address the fertility status of obese women with PCOS, future research should be directed towards obtaining a larger sample size and an intervention of a longer duration. An intervention of a longer duration may be beneficial in determining changes in the menstrual cycle and the ovarian follicle population. It is also recommended that accurate reporting of changes in the menstrual cycle, specifically the pattern and duration of the cycles, be obtained to determine any possible effects due to exercise. In addition, to overcome observer variability by measuring the total number of follicles, a representative sample of the ovary should be evaluated through the use of transvaginal ultrasonography.

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APPENDIX A

Hospital Recruitment Advertisement

Do you have Polycystic Ovary Syndrome (PCOS)?

Are you overweight?

Do you have irregular periods?

Are you between the ages of 15 and 40?

If you currently are not taking any medications, you may be eligible to participate in our study

For further information

Please call Brenda Lindstrom at 653-9023
College of Kinesiology
or
Dr. Donna Chizen at 966-8623
Department of Obstetrics, Gynecology & Reproductive Sciences, College of Medicine

University of Saskatchewan
All information is confidential

APPENDIX B

Participant Informed Consent

Brenda Lindstrom BSc (Kin)
College of Kinesiology,
University of Saskatchewan
653-9023

Donna R. Chizen MD, FRCSC
Associate Professor
Department of Obstetrics, Gynecology &
Reproductive Sciences
Royal University Hospital
University of Saskatchewan

Karen Chad PhD
Associate Professor
College of Kinesiology,
University of Saskatchewan

CONSENT FORM

The Effect of Exercise and Nutritional Counselling in Women with Polycystic Ovary Syndrome

The majority of women with polycystic ovarian syndrome (PCOS) are overweight. Many women with PCOS also have problems with irregular egg release (ovulation) causing irregular menstrual periods and extra hair growth that is typical for men. Research has shown that there appears to be a link between the hormonal changes of PCOS and difficulty using blood sugars. Women with PCOS have been shown to have a mild form of insulin resistance that may change the way blood sugar is used so that gaining weight is easier. It has been suggested that women with PCOS may also be at risk to develop diabetes and heart disease in later life.

Lifestyle changes such as diet adjustments combined with exercise have been shown to reduce weight in both men and women who are diabetic. Diabetics who exercise have an improved sensitivity to insulin. Because it has been shown that overweight women with PCOS have a mild form of insulin resistance, it is possible that similar lifestyle changes will result in weight loss.

This study will allow us to look at changes in hormone levels of women with PCOS who complete a supervised exercise program along with nutritional counselling. We expect that diet and exercise will be helpful by: decreasing weight, total body fat especially in the abdominal area, decreasing male hormone levels, blood fats and improving insulin sensitivity. The long-term benefits could be to decrease your risk for heart disease and diabetes if similar diet and exercise continues after the study is completed. The long-term effects of a decrease in male hormone levels may be less male hair growth, regular ovulation and regular periods.

The procedures will involve an initial interview which will involve the completion of a questionnaire regarding menstrual and pregnancy history, medical history, and physical examination, by Dr. Donna Chizen of the Department of Obstetrics, Gynecology and Reproductive Sciences. A vaginal ultrasound examination of the ovaries and uterus will be done by Dr. Chizen or colleague/female assistant. In addition, venous blood tests will be taken and a 2-hour glucose tolerance test will be arranged prior to beginning the study in order to exclude diabetes. Measurements of height, weight and fat pattern will be done, as well as determining your resting metabolic rate.

This study will take place over a period of 12 weeks. Women in this study will be in either the exercise and diet counselling group or will be asked to carry out their usual daily activities. The exercise sessions will include a warm up, aerobic exercise and weight training for approximately one hour, three times each week. The intensity of the aerobic exercise will be monitored by heart rate. Diet counselling will be provided at regular intervals.

Women in both groups will be asked to record food eaten during a 24-hour period on three separate days. At a midpoint and at the end of this study period, repeat blood testing, measures of body fat, weight and vaginal ultrasound will be repeated.

Women will be excluded from this study if found to have diabetes or other health problems such as adrenal hyperplasia. Women will also be excluded if they require the use of regular medication that will alter hormonal status or may affect their participation in an exercise program. Women will also be excluded if they are not overweight, as determined by height, weight and body mass calculation or if they do not have polycystic ovarian syndrome as diagnosed by history, ultrasound examination and blood tests.

The possible risks of this study include muscle soreness and discomfort as a result of exercise, which should decrease as the exercise program progresses. Bruising at the site of the blood test and minor discomfort upon insertion of the vaginal ultrasound probe may also be experienced.

There may be unforeseen risks during the study and after it is completed.

The individual is free to withdraw from the study at any time and this withdrawal will not affect your access to services at the university or at the hospital.

The individual's identity will remain confidential during and after the study.

Should any questions arise in regard to this research study, please contact the principle investigator, Dr. Karen Chad at 966-6511 or research assistant Brenda Lindstrom at .

The researchers involved in the project will advise the individual of any new information that may have a bearing on the individual's decision to continue in the study.

Participants will receive regular feedback throughout their participation in the study. In addition, at the conclusion of the study, participants will receive a copy of their own individual results as well as a copy of any potential publications arising from this research study.

If you require clarification concerning the ethical aspects of your participation in this study, you may contact the Office of Research Services, University of Saskatchewan at (306) 966-4053.

I agree to participate in the study as described and the contents of the consent document have been explained to me. I understand the contents of the consent. I have received a copy of the consent for my records.

NAME _____ _____
Print Signature

WITNESS _____ _____
Print Signature

RESEARCHER _____ _____
Print Signature

APPENDIX C

Certificate of Approval

University of Saskatchewan
Advisory Committee on Ethics in Human Experimentation

November 24, 2000

Certificate of Approval

INCIPAL INVESTIGATOR	COLLEGE	BMC#
Chad	Kinesiology	2000-190

STITUTION(S) WHERE RESEARCH WILL BE CONDUCTED (STUDY SITE)

llege of Kinesiology
J. Williams Building

Department of Obstetrics, Gynecology and Reproductive Services
Royal University Hospital

ONSORING AGENCIES

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ie Effects of Exercise and Nutritional Counseling in Obese Women with Polycystic Ovary Syndrome

IGINAL APPROVAL DATE	EXPIRY DATE
tober 4, 2000	November 1, 2001

RTIFICATION UPDATE	APPROVED ON
dvertisement	November 24, 00

ERTIFICATION

ie University Advisory Committee on Ethics in Human Experimentation (UACEHE) has reviewed the above-med research project including the protocol and consent form, if applicable. The proposal was found to be ceptable on ethical grounds. The principal investigator has the responsibility of ensuring that the authorized search is carried out according to governing law. This Certificate of Approval is valid for the above time period ovided there is no change in experimental procedures.

NGOING REVIEW REQUIREMENT(S)

ie UACEHE will require the submission of an annual status report prior to the expiry date of November 1, 2001.

PPROVED.

.W. Quest, Chair
niversity Advisory Committee on
thics in Human Experimentation

ease send all correspondence to:

Office of Research Services
University of Saskatchewan
Room 210 Kirk Hall, 117 Science Place
Saskatoon, SK S7N 5C8
Phone: (306) 966-4053 Fax: (306) 966-8597

APPENDIX D

Baseline Medical Questionnaire

Women with Polycystic Ovary Syndrome:
Study of The Effect of Exercise and Nutritional Counselling

Family Physician	
Name (last, first, middle} **Maiden Name** **Former Marriage Name** **Married / Common-law** since: **Single**	
Address **City** **Postal Code**	
Saskatchewan Health #	
Birth Date (day/month/year) **Age**	
Racial Origin	
Business Phone # **Occupation** or **Student Status** **Home Phone #**	
Medications	
Allergies (drugs, foods) What reactions did you have?	
Smoking? Fill in answer:	Non Smoker _____; Quit ____months ____years ago Smoker _____; ___cigarettes/day; other tobacco_____
Alcohol Use	Type & amount used each day or week
Rubella Immunity	
Blood Group / Rh Type	(if known)

Women with Polycystic Ovary Syndrome:
Study of The Effect of Exercise and Nutritional Counselling

Weight **Height** **BMI** (we will calculate)	Pounds Kilograms Feet/inches Centimeters
Extra Hair Growth **Hair type** (circle) **Hair removal**	Mustache, chin, sideburns, belly, thighs, back, other:_____ Fine, coarse Bleaching, plucking, waxing, electrolysis
Menstrual History (please fill in blanks or circle)	Age at time of first period of bleeding: _____ Do your menstrual periods occur regularly/ predictably? Yes/No How many days from the beginning of one period to the beginning of the next period? Average____ days; Shortest #____days; Longest #_____ days; [ie no average–vaginal bleeding happens every 15 -90 days] How many days do you bleed? _____ to _____ days; Do you pass clots? _____ Do you spot / bleed between periods? _____ Pain with bleeding? Mild ( ) Moderate ( ) Severe ( ) Pain medication needed: _____ Where is pain? Pelvis, lower back, thighs other _____ Do you bleed after sexual intercourse?
Contraception What did you use before? What are you using now?	Oral contraceptives Dates?_____ Reason to stop_____ Intrauterine Device Dates?_____ Reason to stop_____ Diaphragm Dates?_____Reason to stop_____ Condom Dates?_____ Reason to stop_____ Tubal sterilization Date?_____ Vasectomy Date?_____ Other None
Fertility Concerns	Are you trying to become pregnant? Yes No If yes, for how long? Do you know when you are most fertile?
Sexual History	Heterosexual, Homosexual, Bisexual Any difficulties?

Women with Polycystic Ovary Syndrome:
Study of The Effect of Exercise and Nutritional Counselling

Past Medical Problems (thyroid, diabetes, hormones, bowel / bladder / asthma/ muscle or joint problems/ other [specify])	[List year of treatment]
Past Surgeries (appendicitis, bowel, joints, bone)	[List year of treatment, physician, hospital, city]
Past Fertility Treatments (Ovulation drugs, metformin, inseminations)	
Past Fertility Tests (x-ray dye test, laparoscopy, other surgery)	
Psychiatric Illness (depression, other)	
Family History of Illness (thyroid disease, diabetes, heart disease, stroke, cancer, other)	
Pregnancy History	Number of pregnancies _____ Dates: Number of livebirths _____ Number of miscarriages _____ D&C needed? Pregnancy termination? Ectopic pregnancy? Time to get pregnant? Therapy to get pregnant?

Women with Polycystic Ovary Syndrome:
Study of The Effect of Exercise and Nutritional Counselling

Physical Activity Habits	
In a typical week (7 days), how often do you perform physical activity that increases your heart rate and will cause sweating? (circle one)	At least 3 times. Normally once or twice. Rarely or never.
If you are physically active, how long have you been active for?	_____months _____ years
What type of physical activity do you normally do (walking, swimming, gardening, weight training)? Please provide details.	
When you are physically active, do you feel that you: (circle one)	Make an intense effort. Make a moderate effort. Make a light effort.
In general, would you say that your current level of fitness is: (circle one)	Very good. Good. Average. Poor. Very Poor.

Women with Polycystic Ovary Syndrome:
Study of The Effect of Exercise and Nutritional Counselling

Weight Loss History Have you lost any weight within the past six months? (circle one) If yes, how much? Was this weight loss intentional? (circle one) If yes, what did you do to lose the weight (i.e. exercise, diet, pills)? Please provide details.	 Yes No _____pounds Yes No
Diet History Are you currently following a specific diet plan? (circle one) If yes, please provide details.	 Yes No

Women with Polycystic Ovary Syndrome:
Study of The Effect of Exercise and Nutritional Counselling

Release of Medical Information Form

Please sign this form so that we may obtain needed medical records from any doctor or hospital to help with your care

Sincerely ,

Donna R. Chizen, MD. FRCSC

Royal University Hospital
Room 4509
Hospital Drive,
Saskatoon, S7N 0S9

To whom it may concern:

I agree with the release of pertinent medical information as requested by Dr. D.R. Chizen

Print Name	Signature	Date

APPENDIX E

Exercise Training Log

Exercise Training Log

Name_____ Date_____

#	Exercise	Weight (lbs)	Reps in Set #1	Reps in Set #2	Reps in Set #3	Total Reps
1	Leg Press					
2	Chest Press					
3	Lat. Pulldown					
4	Shoulder Press					
5a	Right Hip Abduction					
5b	Left Hip ABduction					
6a	Right Hip ADduction					
6b	Left Hip ADduction					
7a	Right Hip Flexion					
7b	Left Hip Flexion					
8a	Right Hip Extension					
8b	Left Hip Extension					
9	Leg Extention					
10	Leg Curl					
11	Biceps Curl					
12	Back Extention					
Warm-up	Cardio Machine	Cardio Time (min)	Speed (mph) or Resistance	Grade	Cool-down (min)	Target HR Achieved

Target Heart Rate_____

APPENDIX F

Daily Activity Log

Daily Activity Log

Participant's Name_____

Date (Month & Day)	Activity Performed	Duration (minutes)
Monday		
Tuesday		
Wednesday		
Thursday		
Friday		
Saturday		
Sunday		

APPENDIX G

Participant Guidelines for Baseline Testing

Name_____

Appointment Date & Time_____

You will have three tests performed on this date. These include a measurement of your metabolism which will take approximately ½ hour, an assessment of your current level of fitness performed on a stationary bicycle, and which will take about 20 minutes. Measurements of your height, weight and fat pattern which also be done and will also take approximately 20 minutes. The total time for this testing will take approximately 1½ hours. Below are some guidelines which I will ask you to follow to ensure the accuracy of the testing. If you have any questions, please do not hesitate to contact me at .

Thank you,
Brenda

Guidelines for Testing

1. **Do not eat or consume any liquids, except water, for 12 hours before the test.**
2. **Do not perform any exercise training within 48 hours of the test.**
3. **If possible, try to get a minimum of 8 hours of sleep the night before the test.**
4. **Do not walk to the site of testing and try to do as little as possible the morning of the test. For example, do not vacuum, or do any other activity which requires a lot of movement.**
5. **Please wear comfortable shoes and clothing, preferably shorts and a short-sleeved shirt, for the bicycle test and measurements of fat pattern.**

All testing will be done at the R.J. Williams Building, College of Kinesiology at the University of Saskatchewan. This building is located on Cumberland Ave, one block off of College Drive. I will meet you at the main doors of the building (located in the middle of the building on Cumberland Ave.) and take you to the lab for your testing. I thank you in advance for participating in my research study.

APPENDIX H

Participant Anthropometric Data Sheet

Participant Anthropometric Data Sheet

Name:_____ **Phone:**_____

Age:_____

Defining criteria for Polycystic Ovary Syndrome (PCOS)

_____Ultrasound

_____Increased androgen levels

_____LH:FSH > 1

_____Clinical amenorrhea/ oligomenorrhea and hirsutism

Anthropometric Measurements

Measurement	**Baseline**				**Post-test**			
Weight (kg)								
Height (m)								
BMI (kg/m2)								
Waist girth (cm)								
Hip girth (cm)								
Waist:hip ratio								

Skinfold Measurement (mm)	**Baseline**			**Record**	**Post-test**			**Record**
Subscapular								
Suprailiac								
Umbilical								
Front thigh								
Rear thigh								

APPENDIX I

Three-Day Food Record

INTRODUCTION

This booklet is used to record your detailed daily food intake. It is meant to give the researchers some idea of your usual dietary intake. Therefore, it is very important that you do not alter your eating habits while taking part in this study. In other words, do not let the fact that you are writing down what you eat influence your choice of foods. The names of the participants in this study will be kept confidential.

The usefulness of the results of this study depends on the accuracy with which you record your daily food intake. Please write down full details on all the food and drink that you consume each day.

INSTRUCTIONS

1) The purpose of this diary is to record all the food (including drinks) which you eat for a three day period. The three day period should include 2 weekdays and 1 weekend day.

2) Two pages are provided for each day of the three day period.

3) After each meal or snack that you eat, please write down in detail each separate food item you consumed - including the type of food (e.g. processed cheese) and the amount of food in household measures (e.g. 1 cup of cooked spaghetti). A meal will have to be listed by its separate parts (e.g. fried steak - 8 oz., french fries - 1 cup, coleslaw - 3 tbsp.)

4) The best way to record the information is by carrying this diary around with you wherever you go. Before going to sleep, you should look over the diary to check that you have not missed anything. Remember to include snacks!

5) If you eat fast food, you can just list the type of food you ate (e.g. 1 Big Mac, 1 large fires, 1 chocolate milkshake).

6) The following pages explain the use of household measures, and the description of foods. A sample day's diet sheet is given. Please take the time to read these pages as it will help to make your diet record more accurate.

1) Please use household measures. For example:

cup: vegetables, cereal, fruit, milk, beverages
tablespoon: sauces, fats
teaspoon: sugar, honey, drink mix
slices: bread, bacon
fractions: 1/6 pie.

2) State the <u>type</u> of food eaten. For example:

Milk: homo, 2%, 1%, skim, goat's
Cheese: processed, Swiss, spread
Bread: enriched white, 60% whole wheat, sweet cinnamon bun, bran muffin
Cereal: Sugar Pops, Miniwheats, granola
Meat: hamburger, fried chicken - breasts, scrambled eggs, cod fillets
Others: strawberry jam, Becel margarine, Caesar dressing, oatmeal cookies.

3) State the <u>amount</u> of food eaten. For example:

Cheese: 1" cube cheddar
3 tbsp lite cream cheese
1/4 cup 2% creamed cottage cheese
Fruit: 1/2 cup canned peaches (in heavy syrup)
12 grapes
1 medium banana
Bread: 2 slices 100% whole wheat
1 large kaiser
Cereal: 3/4 cup corn flakes
1 shredded wheat biscuit
Meat: 1 cup baked beans with pork
2 cups tuna casserole (tuna, cream of mushroom soup, noodles, peas)
4 thin slices roast beef

Vegetables: 2 slices cucumber
1/2 cup boiled cabbage

4) Include manner of cooking: fried, boiled, raw.

5) Remember all alcoholic drinks.

Here is a Sample:

Date: Sat., Dec. 14th (Day 3)

Time	Food Description	Amount	
9:30a.m.	Waffles-white flour	3, 8"x4"	ea.
	syrup-Aunt Jemima	1/2 cup	
	yogurt-peach	125ml	
	coffee, 1 tsp. sugar	1 cup	
	milk (2%)	1/4 cup	
10:30	Chocolate chip cookies	3	
	coffee, 1 tsp. sugar	1 cup	
	milk (Half & Half-10%)	1/4 cup	
12:30	Sandwich		
	-2 slices whole wheat bread	2 slices	
	-mozarella cheese (3"x1/4"x2")	2 slices	
	-salami	4 slices	
	-lettuce	1 leaf	
	-butter	1 tsp.	
	-mayonaise	1 tsp.	
5:30	Spagherri	1 cup	
	meat sauce	1/2 cup	
	garlic toast	2 slices	
	(Continue on the next page if your need		
	it) Leave Code column blank.		

Here is a Sample:

Date: Sat., Dec. 14th (Day 3)

Time	Food Description	Amount	
9:30a.m.	Waffles-white flour	3, 8"x4"	ea.
	syrup-Aunt Jemima	1/2 cup	
	yogurt-peach	125ml	
	coffee, 1 tsp. sugar	1 cup	
	milk (2%)	1/4 cup	
10:30	Chocolate chip cookies	3	
	coffee, 1 tsp. sugar	1 cup	
	milk (Half & Half-10%)	1/4 cup	
12:30	Sandwich		
	-2 slices whole wheat bread	2 slices	
	-mozarella cheese (3"x1/4"x2")	2 slices	
	-salami	4 slices	
	-lettuce	1 leaf	
	-butter	1 tsp.	
	-mayonaise	1 tsp.	
5:30	Spagherri	1 cup	
	meat sauce	1/2 cup	
	garlic toast	2 slices	
	(Continue on the next page if your need		
	it) Leave Code column blank.		

APPENDIX J

Baseline and post-intervention dietary intakes

Table A1
Baseline and post-intervention dietary intakes. All values are means ± SE.

	EN Group		N Group	
Macronutrient	**Pre**	**Post**	**Pre**	**Post**
Carbohydrate (%)	42 ± 2.57	47 ± 4.52	57 ± 13.12	52 ± 4.85
Protein (%)	15 ± 1.32	19 ± 1.09	13 ± 0.97	19 ± 1.17
Fat (%)	33 ± 4.41	33 ± 3.95	32 ± 10.05	31 ± 3.67
Calories	2388 ± 149.0	2013 ± 195.36	2199 ± 646.29	1912 ± 457.07