

## **DEDICATION**

This is lovingly dedicated to my parents, Wayne and Sylvie, for their continued love, guidance and support throughout my life. To my siblings, Lauren, Troy and Dane and now, my wonderful husband, Andrew.

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## **ABSTRACT**

This double blind, randomised, placebo controlled study investigated the efficacy of ProgestoNat® cream in the treatment of menopausal syndrome in terms of subjective and objective data.

Menopause is defined as that point in time when permanent cessation of menstruation occurs following the loss of ovarian follicular activity. The perimenopause is the period just prior to the final menstrual period and is associated with the development of typical oestrogen deficiency symptoms such as hot flushes, night sweats, mood swings and loss of libido, to mention a few. The most widely used treatment for these symptoms is hormone replacement therapy. This form of treatment is effective for many women, but there are many risks and side effects associated with its use and there is a growing demand for natural alternatives, like natural progesterone creams. It is for this reason that the efficacy of ProgestoNat® cream was investigated as a natural alternative to hormone replacement therapy.

Thirty participants, experiencing natural menopause and meeting certain inclusion and exclusion criteria, were selected to participate in the study. The supervisor randomly allocated fifteen participants to the experimental group and fifteen participants to the placebo group. The placebo group was shared with a similar study testing the efficacy of *Dioscorea villosa* in the treatment of

menopausal syndrome (Macquet-Maurel, 2003). The objective results of this study were compared with the objective results of the ProgestoNat® group.

The subjects participating were required to attend three consultations with the researcher. Each consultation was held on day one to three of the menstrual cycle. If subjects had irregular menses, the consultations were held every 28 days.

During the first consultation the patient completed the Greene Climacteric Scale questionnaire. A registered, professional nurse then took a blood sample in order for the progesterone level to be measured. Each patient was given a bottle of ProgestoNat® cream or placebo cream.

After one menstrual cycle, or after 28 days had elapsed, the patients were requested to return for the second consultation. During this consultation only the Greene Climacteric Scale questionnaire was completed. The patients continued using the cream until day one to three of the following menstrual cycle, or on day 28 of the menstrual cycle.

At this time the third consultation was held. The Greene Climacteric Scale questionnaire was completed for the final time and a second blood sample was taken by the registered nurse for the progesterone level to be measured.

The results of the first questionnaire and blood test were used as a baseline for statistical analyses. As each group consisted of fifteen subjects ( $n=30$ ), non-parametric tests were used for data analysis. All statistical analyses were carried out using SPSS version 9.0.

The Mann Whitney U Test showed no statistical difference between the experimental and placebo groups with regard to both the subjective and objective data.

The Friedman's T Test indicated a statistically significant improvement between consultations for vasomotor symptom scores for group 1. In group 2, there was a statistically significant improvement between consultations for depression, anxiety and somatic symptom scores.

The Dunn procedure was then performed in order to determine which of the consultations were significantly different.

The Wilcoxon Signed Rank Test indicated that there was no statistically significant difference between the two progesterone measurements for both groups 1 and 2.

The Kruskal Wallis H Test revealed that there was no statistically significant difference between all three groups with regard to the objective data.

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# **CHAPTER 1**

## **INTRODUCTION**

### **1.1 Introduction**

In conventional terms, the menopause and its symptoms are viewed as a disorder or an illness caused by falling hormone levels. Menopause is actually a natural process as it is expected that every woman will experience menopause at some stage in her life, unlike a specific disease process. As viewed by the conventional medical profession, menopause is a hormone deficiency disease and can be corrected with hormone replacement therapy (HRT). However, there is a growing dissatisfaction among women taking HRT as they begin to experience the harmful side effects. An increasing number of women are seeking alternative routes. One of the more popular routes is natural progesterone therapy, however there is not sufficient research on this form of treatment to render it successful. There is much controversy about natural progesterone, thus the reason for this study.

### **1.2 Objectives**

**1.2.1** The first objective is to determine the efficacy of *ProgestoNat*<sup>®</sup> cream in the treatment of menopausal syndrome in terms of subjective data.

**1.2.2** The second objective is to determine the efficacy of *ProgestoNat*<sup>®</sup> cream in the treatment of menopausal syndrome in terms of objective data.

**1.2.3** The third objective is to compare the efficacy of *ProgestoNat*<sup>®</sup> cream with that of *Dioscorea villosa* cream (Macquet-Maurel, 2002) in terms of the objective data gathered in these two studies.

## **CHAPTER 2**

### **REVIEW OF THE RELATED LITERATURE**

#### **2.1 Definition**

Menopause is defined as that point in time when permanent cessation of menstruation occurs following the loss of ovarian follicular activity (Sonnendecker, 2001). The word 'menopause' refers to the last menstrual bleed and the diagnosis can only be made retrospectively (Cutler & Genovese-Stone, 2000). Menopause is diagnosed once twelve months have elapsed since the final menstrual period. Menopause means the cessation of menstruation, but the term is commonly used to include the perimenopausal years. This period is more correctly referred to as the climacteric (Llewellyn-Jones, 1999). The climacteric or perimenopause is the transitional phase during which reproductive function ceases. It is usually associated with a change in the length of the menstrual cycle and is often associated with the development of typical oestrogen-deficiency symptoms such as hot flushes and night sweats (Cutler & Genovese-Stone, 2000). The perimenopause covers the phase from ovulatory cycles with well-characterised hormone profiles to ovarian failure demonstrated by low oestrogen and high gonadotrophin levels (Morris & Rymer, 2001). The perimenopause is the period just prior to the final menstrual period, beginning at the onset of endocrinological and menstrual changes extending to the first year after the final menstrual period. The menopausal transition is that portion of the perimenopause that ends with the final menstrual period (Sonnendecker, 2001).



## **2.2 Incidence**

In the 1900's, the average age of menopause was approximately 48 years and mean female life expectancy was similar. The average age of menopause is now approximately 51.4 years and mean female life expectancy has lengthened to approximately 82 years. Therefore the average woman can now expect to spend approximately one third of her life in a postmenopausal state assuming normal age at menopause (Whitehead, 1999). Premature menopause is defined as menopause that occurs before the age of 40 years (Cutler & Genovese-Stone, 2000).

## **2.3 Physiology**

### **2.3.1 The Female Hormonal System**

The female hormonal system consists of three different hierarchies of hormones:

- gonadotrophin-releasing hormone (GnRH) from the hypothalamus
- The anterior pituitary hormones - follicle stimulating hormone (FSH) and luteinizing hormone (LH), and
- The ovarian hormones - oestrogen and progesterone.

The normal reproductive years of a woman are characterised by monthly rhythmical changes in the rates of secretion of these female hormones and corresponding changes in the sexual organs themselves. The principal oestrogen secreted by the ovaries is  $\beta$ -estradiol. The ovarian changes during the

sexual cycle are completely dependent on the anterior pituitary hormones (Guyton & Hall, 1997).

### **2.3.2 The Female Sexual Cycle**

There are three phases of the female sexual cycle: menstruation, preovulatory phase and the luteal phase.

Menstruation is caused by the sudden reduction of oestrogen and progesterone at the end of the female sexual cycle. Immediately after menstruation, FSH and LH are released from the pituitary gland and stimulate the development of the follicles in the ovary. The follicles undergo a series of developmental stages, and after approximately one week of growth, one of the follicles begins to outgrow the others. It becomes more highly developed than the others and secretes large amounts of oestrogen. This causes the remainder of the developing follicles to involute. This is known as the preovulatory phase. Approximately 2 days before ovulation, the rate of secretion of LH by the anterior pituitary gland increases markedly, causing final follicular growth and ovulation. Ovulation occurs approximately 14 days after the onset of menstruation (Guyton & Hall, 1997).

The ruptured follicle, under the influence of LH, undergoes rapid physical and chemical changes and becomes the corpus luteum. The corpus luteum secretes large quantities of oestrogen and progesterone. The large amounts of these two hormones cause a feedback effect to the hypothalamus to decrease the

secretion of both FSH and LH, preventing further follicles to grow. The corpus luteum begins to degenerate, decreasing the secretion of oestrogen and progesterone. The sudden reduction of these hormones results in menstruation. A new ovarian cycle then follows. (Guyton & Hall, 1997)

At menopause, only a few follicles still remain to be stimulated by FSH and LH. The production of oestrogens by the ovaries also decreases as the number of follicles approaches zero. As oestrogen production falls to a low level, the production of FSH and LH are no longer inhibited resulting in large quantities of FSH and LH being produced after menopause. (Guyton & Hall, 1997)

**Figure 2.1**

**Illustration of the approximate plasma concentrations of ovarian and gonadotrophin hormones and of ovarian follicular and endometrial growth during the normal female sexual cycle.**

(Solomon, Schmidt & Adragna, 1990)

## **2.4 Signs and Symptoms of Menopause**

The signs and symptoms that are associated with menopause are said to be caused by oestrogen deficiency. They are divided into three categories:

- Vasomotor symptoms - hot flushes and night sweats
- Genitourinary symptoms - dyspareunia, vaginal dryness, atrophic vaginitis, decreased libido, urgency and frequency of urination and recurrent cystitis
- Psychological symptoms - anxiety, poor memory, emotional lability, depression, insomnia, irritability and worry about aging (Nel, 1995).

### **2.4.1 Vasomotor Symptoms**

The vasomotor symptoms that occur during the climacteric include hot flushes and night sweats. The aetiology of these symptoms is complex and remains uncertain, but is possibly due to lability of the thermoregulatory centre in the hypothalamus, induced by falling oestrogen and progesterone levels (Morris & Rymer, 2001).

### **2.4.2 Genitourinary Symptoms**

Menopause is associated with regression of the reproductive organs. The vaginal mucosa becomes thinner and less lubricated due to decreasing oestrogen production. Atrophic vaginitis may occur, which can cause itching, burning, discomfort and vaginal bleeding may occur with sufficient thinning of the epithelium. The thinning vaginal mucosa results in painful intercourse. Sexual response can also diminish with decline in oestrogen levels. The epithelial lining

of the bladder and urethra undergo atrophic changes, resulting in increases in cystitis, urinary frequency, and incontinence. The epidermis thins, and skin loses some elasticity. There is generally a loss of axillary and pubic hair, with an increase in facial hair. Because the decline in ovarian function is usually gradual, a minority of women will also experience menstrual irregularity leading up to menopause, from prolonged and heavy menses to intermenstrual bleeding (Mattox, 1998).

### **2.4.3 Psychological Symptoms**

The psychological symptoms experienced during the menopause include depression and anxiety; symptoms such as panic attacks, lacking in energy, crying spells and irritability, to name a few (Greene, 1998).

Carefully controlled double-blind and crossover studies indicate that oestrogens have a tonic mental effect. Patients taking oestrogen supplementation show higher scores on psychometric evaluations, alleviating the psychogenic manifestations independent of vasomotor symptoms (Gambrell, 1997).

## **2.5 Long Term Consequences of Menopause**

The symptoms occurring at, or soon after, menopause may cause distress. However the long-term effects of oestrogen deficiency are far more devastating with consequences which may reduce life expectancy and degrade the quality of life. These are an increased risk of osteoporosis, cardiovascular disease and Alzheimer's disease (Llewellyn-Jones, 1999).

### **2.5.1 Osteoporosis**

Osteoporosis is defined as a metabolic bone disease characterised by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk (Ballard & Purdie, 1997). Osteoporosis is diagnosed according to bone mineral density (BMD). The World Health Organization (WHO) recently proposed that women with bone density values more than 2.5 standard deviations (SD) below the young adult mean value are to be considered as osteoporotic. Those women with bone density values between 1 and 2.5 SD below the young adult mean values are classified as osteopenic (Movsesyan, Tanko & Christiansen, 2002).

The two main factors for developing osteoporosis are a low bone mass, obtained at skeletal maturity as well as the magnitude and duration of subsequent bone loss. Peak bone mass is predominantly determined by genetic factors and occurs at skeletal maturity, whereas the rate of bone loss is determined by both genetic and environmental factors (Movsesyan, Tanko & Christiansen, 2002).

Osteoporotic fractures typically occur at the hip, spine and distal forearm. The incidence rate of fractures increases after the age of 45, while wrist fractures show a rising tendency in the 50's, vertebral fractures in the 60's and hip fractures in the 70's (Movsesyan, Tanko & Christiansen, 2002).

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At a cellular level bone remodelling consists of bone resorption, always followed by bone formation, a phenomenon called coupling. During an activation phase at the beginning of each remodelling cycle, osteoclasts excavate an erosion lacuna (Howship's lacunae) on the surface of the trabeculae in cancellous bone or a cavity within cortical bone. The osteoclasts are then replaced by osteoblasts that lay down osteoid within the resorption lacunae. Eventually the osteoid mineralises into bone. As the remodelling process starts with bone resorption, the information is apparently transmitted from the osteoblast to the osteoclast (Movsesyan, Tanko & Christiansen, 2002).

Menopause is the time when bone loss starts to accelerate from the existing peak bone mass (the maximum bone mass obtained at skeletal maturity). Bone loss occurs in the postmenopausal woman as a result of an increase in the rate of bone remodelling and an imbalance between the activity of osteoclasts and osteoblasts. When the processes of bone resorption and bone formation are not matched, the result is a remodelling imbalance that leads to bone loss (Movsesyan, Tanko & Christiansen, 2002).



It has been documented that clinical risk factors for osteoporosis include: white race, female sex, low body mass index, early menopause, positive family history for osteoporosis and smoking (Panidis et al. 2000).

### **2.5.2 Cardiovascular Disease**

The increase in the incidence of coronary heart disease (CHD) in women is not linearly related to age, being low in young women and increasing significantly in the sixth decade of life, which correlates with the onset of natural menopause. This has led investigators to hypothesise that menopause induced hormonal changes are independently associated with acceleration of the cardiovascular atherosclerotic process (Reis, 1997).

Oestrogen deficiency adversely affects lipid and lipoprotein metabolism, resulting in a significant increase in total and low-density lipoprotein (LDL) cholesterol and a reduction in the plasma level of the protective cholesterol, high-density lipoprotein (HDL). Triglycerides, which are an independent risk factor for CHD in women, also rise after menopause. Oestrogens appear to act as important regulators of arterial tone and oestrogen lack increases resistance to blood flow (Whitehead, 1999). It has been postulated that in premenopausal women circulating oestrogen acts directly on coronary arteries to inhibit the atherosclerotic process and that the loss of oestrogen during menopause is associated with acceleration of arterial lipid deposition, endothelial cell

hyperplasia and intimal thickening, which are early manifestations of atherosclerosis (Sturdee, 1997).

### **2.5.3 Alzheimer's Disease**

Dementia refers to the loss of cognitive or mental abilities. There are many forms of dementia, of which Alzheimer's disease (AD) is the commonest. AD is subdivided into early-onset disease (below 65 years) and late-onset disease (after 65 years). (Whitehead, 1999). There is considerable evidence that oestrogen has an effect on the central nervous system (CNS). Oestrogen deficiency may contribute to the neurodegenerative changes of the aging CNS and increase the incidence of senile dementia of the Alzheimer's type (Gambrell, 1997).

Two of the many findings in Alzheimer's disease are a decrease in dendritic spines and a deficiency of the cholinesterase enzymes necessary to reconvert the neurotransmitters to acetylcholine (Gambrell, 1997). Oestrogen is known to exert many metabolic and structural changes in the central nervous tissues. Case control studies are now also showing that the risk of Alzheimer's disease can be decreased by long-term oestrogen replacement therapy (Sturdee, 1997).

## **2.6 Treatment of Menopausal Symptoms**

### **2.6.1 Hormone Replacement Therapy**

Conventionally, menopause is treated with hormone replacement therapy (HRT). HRT was known as oestrogen replacement therapy, as oestrogen was the only hormone administered to patients. This is now referred to as unopposed therapy. Oestrogen therapy was founded in the 1930's, when injections of oestrogen were given for menopausal symptoms. It soon became clear that this unopposed therapy greatly increased the risk of endometrial and breast cancer. Oestrogen therapy quickly declined in popularity (Glenville, 1997).

Then, progestogen, the synthetic form of progesterone, was added to the therapy for ten to fourteen days each month. This is known as opposed hormone replacement therapy and is thought to be safer than the previous form of treatment. The main reasons for the addition of progestogen to HRT are to protect the endometrium from overstimulation by oestrogen and subsequent carcinoma, as well as to stimulate a regular bleed (Glenville, 1997).

Recently, there has been an explosion among investigators, clinicians and women themselves about all aspects of menopause. Of particular interest for clinicians is the role of hormone replacement therapy (HRT) in the management of symptoms. Despite all the benefits, HRT has not become universally accepted as a panacea for menopausal symptoms, given the fact that oestrogens, even in small doses, are related to several side effects. These either limit the duration of

treatment or decrease compliance or exclude certain female populations from the therapy. There is concern about the increased relative risk for breast cancer in women who receive HRT for extended time periods, a fact that limits long-term treatment in all women except those with vasomotor dysfunctions. Existing data support the view that long-term hormone replacement therapy is necessary in order to prevent osteoporosis or coronary disease. Even today, at the threshold of the 21<sup>st</sup> century, disagreements still exist and future research must focus on resolving them (Panidis et al. 2000).

#### Benefits of Hormone Replacement Therapy

- Relief of climacteric symptoms – vasomotor, genitourinary and psychological
- Protection against coronary heart disease
- Prevention of bone loss and vertebral fractures and maintenance of skeletal integrity

#### Risks and Concerns with Hormone Replacement Therapy

- Endometrial cancer
- Breast cancer
- Thrombo-embolic disease
- Hypertension
- Diabetes mellitus (Dreyer, 1999).

### Side Effects of Hormone Replacement Therapy

- Reactivation of uterine bleeding
- Breast tenderness
- Symptoms of hormone related fluid retention (Dreyer, 1999).

### Contraindications of Hormone Replacement Therapy

#### Absolute Contraindications:

- 1) Endometrial cancer
- 2) Breast cancer
- 3) Undiagnosed vaginal bleeding
- 4) Diseases of the liver, gallbladder or pancreas
- 5) History of thrombo-embolism
- 6) Other oestrogen-dependent neoplasms. (Nel, 1995).

#### Relative contraindications:

- 1) Endometrial hyperplasia
- 2) Leiomyomata
- 3) Endometriosis
- 4) Patients who smoke
- 5) Hypertension
- 6) Fibrocystic disease of the breasts
- 7) Migraine
- 8) Hepatic porphyria. (Nel, 1995).

### **2.6.2 Homoeopathy**

Homoeopathy is a self-consistent scientific system of medicinal therapy, developed in 1796 by Christian Friedrich Samuel Hahnemann (1755 – 1843) (Gaier, 1991). It is based on the principle of “like cures like”. This means that a medicine capable of producing certain effects when taken by a healthy human being is capable of curing any illness that displays similar effects. Medicines are administered in small doses, prepared by the process of potentisation; a step by step dilution and shaking-like action of the drug that makes it extremely powerful and simultaneously renders it harmless (Sankaran, 1997).

Siobahn Hagen (1995) has conducted research on homoeopathy and the menopause. The purpose of the research was to evaluate selected homoeopathic remedies for the menopausal syndrome, in terms of patient perception of the treatment, by means of questionnaires, in order to determine the effectiveness of the selected remedy on the menopausal syndrome. The two questionnaires used were the psychological general well-being index questionnaire (PGWB) and the patient perception questionnaire (PPER). Experimentally, the treatment and placebo groups did not show a significant statistical change between themselves in the amelioration of menopausal symptoms. It is significant, however that the treatment group did show a higher percentage improvement over the placebo group. The PGWB showed a 33% greater improvement over the placebo group; and the PPER showed a 40% greater improvement over the placebo group (Hagen, 1995).

Sinden Domleo (2002) has also conducted research on the menopause. The purpose of the study was to evaluate the efficacy of the homoeopathic remedy, Folliculinum 30CH in the treatment of menopausal syndrome. The conclusion of the study was that Folliculinum 30CH is ineffective in the treatment of menopausal symptoms in terms of the patients' perception (Domleo, 2002).

### **2.6.3 Nutritional Therapy**

Another alternative approach to treating menopause is diet and lifestyle.

#### Diet

The most important dietary recommendation may be to increase the amount of plant foods, especially those high in phytoestrogens, while reducing the amount of animal foods in the diet. There is also a protective effect with consumption of fruit and vegetables (Pizzorno & Murray, 1999)

Foods high in phytoestrogens include fennel, celery, parsley, soy, nuts, whole grains, apples and alfalfa. A high intake of phytoestrogens is thought to explain why hot flushes and other menopausal symptoms rarely occur in cultures consuming a predominantly plant-based diet. Soy is especially important in the diet of menopausal women as it aids the relief of atrophic vaginitis and is thought to help in the prevention of breast cancer. The isoflavones and phytosterols of soybeans produce a mild oestrogenic effect. Another useful effect of soy is its

protection of LDL cholesterol from oxidation, an effect of great significance for the prevention of cardiovascular disease (Pizzorno & Murray, 1999).

### Nutritional Supplements

Studies conducted on vitamin E supplementation proved to relieve hot flushes and vaginal complaints as well as improving the blood supply to the vaginal wall when taken for at least 4 weeks. Vitamin E oil, creams, ointments or suppositories can be used topically to provide symptomatic relief of atrophic vaginitis. Vitamin E is usually quite effective in relieving the dryness and irritation of atrophic vaginitis as well as other forms of vaginitis (Pizzorno and Murray, 1999).

Hesperidin, as with many other flavonoids, is known to improve vascular integrity and relieve capillary permeability. Combined with vitamin C, hesperidin may be effective in relieving hot flushes. In a clinical study, 94 women were given a formulated combination of hesperidin and vitamin C daily. At the end of one month, symptoms of hot flushes were relieved in 53% of the patients and reduced in 34%. There were also improvements noted in nocturnal leg cramps, nose bleeds and easy bruising (Pizzorno and Murray, 1999).

### **2.6.4 Lifestyle Alterations**

The avoidance of alcohol, chocolate, coffee and spicy foods is recommended during menopause as they are thought to aggravate hot flushes.



Regular exercise can reduce the frequency of hot flushes and help in the prevention of heart disease. Weight bearing exercise such as walking, running and light, weight training may protect the bones.

Some women claim that soaking in a tepid bath for 20 minutes each morning prevents hot flushes for the rest of the day (Wilmont, 1999).

### **2.6.5 Phytotherapy**

Phytotherapy is an empirical system of medicine that employs only plant remedies (derived from trees, ferns, seaweed, lichens or other vegetation) destined to support the healing life force (Gaier, 1991).

Many plants have shown to exert a tonic effect on the female hormonal system. Most of their effect is believed to be a result of phytoestrogens in the plants as well as the plant's ability to improve blood flow to the female organs (Pizzorno & Murray, 1999).

Phytoestrogens are naturally occurring constituents in many plants. Legumes are particularly rich in oestrogenic isoflavones while cereals are rich in oestrogenic lignans. Pacific rim nations eating a diet rich in soy, experience less severe menopausal symptoms, whilst several chronic diseases of menopausal women including breast cancer, colon cancer and atherosclerotic cardiovascular disease have a much lower incidence than in Western countries. Some studies have been done to explore the potential benefit of these compounds. Results indicated cardioprotective benefits without increasing the risk of endometrial and breast cancer in menopausal women (Brincat, Galea & Muscat Baron, 1997).

Phytoestrogens are compounds which, are derived from plants yet which have an affinity for the estradiol receptor. There are many classes of phytoestrogens. The two which have received the most attention are the lignans and the isoflavones. Lignans are present in many fibre rich foods while the isoflavones are confined to legumes, particularly soya beans. In postmenopausal women, gonadotrophin levels are reduced and oestrogen-like changes in vaginal cytology occur following administration of phytoestrogens. It has also been reported that soy protein isolate added daily to the diet substantially reduced the frequency of hot flushes in climacteric women (Sonnendecker, 2001).

The four most useful herbs in the treatment of hot flushes are *Angelica sinensis* (Dong Quai), *Glycyrrhiza glabra* (Licorice), *Vitex agnus-castus* (Chasteberry), *Cimicifuga racemosa* (Black cohosh) (Pizzorno & Murray, 1999).

Dong Quai is predominantly regarded as a 'female' remedy. This herb has demonstrated good uterine tonic activity. The administration of this herb to mice resulted in an increase of uterine weight and of glucose utilization by the liver and uterus. These effects reflect oestrogenic activities. Its effectiveness in relieving hot flushes may be a combination of the herb's mild oestrogenic effects and other components acting to stabilize blood vessels (Pizzorno & Murray, 1999).

The medicinal use of Licorice root dates back several thousand years. Licorice is believed to lower oestrogen while simultaneously raising progesterone levels. It

is believed that the oestrogen-like activity of licorice is helpful in relieving menopausal symptoms (Pizzorno & Murray, 1999).

The chaste tree is native to the Mediterranean. Its berries have long been used for female complaints. Scientific investigation has shown chaste berry has profound effects on pituitary function. It is possible that its beneficial effects in menopause are due to altering LH and FSH secretion (Pizzorno & Murray, 1999).

Black cohosh was used widely for the relief of menstrual cramps and menopause. Clinical studies have shown that this herb relieves hot flushes, depression and vaginal atrophy. Most patients report noticeable benefits within four weeks after the onset of cimicifuga therapy (Pizzorno & Murray, 1999).

Ginkgo biloba is another herb that is often indicated in menopausal women for its effects on the vascular system. It may be especially useful in improving both cold hands and feet and the forgetfulness which accompanies menopause (Pizzorno & Murray, 1999).

*Dioscorea villosa* is yet another herb that is gaining popularity in treating menopausal complaints. It is more commonly known as wild yam, is a native plant of North and Central America, the wild yam was first used medicinally by the Aztecs and Maya because of its pain-relieving qualities. Later, European settlers used it for treating joint pain and colic. Recently, wild yam has been

recognised for its ability to mimic certain hormones, especially progesterone, and it is believed to relieve menopausal or premenstrual symptoms. Most of these claims remain scientifically unproved. Wild yam contains a substance called *Diosgenin*, which can be converted to progesterone in a laboratory, but the human body is unable to make this conversion. Wild yam also acts as a muscle relaxant, antispasmodic, anti-inflammatory and has pain-relieving properties. The alkaloids and steroidal saponins account for these effects. This action suggests that wild yam may be of particular value for digestive disorders such as diverticulitis, Crohn's disease and irritable bowel syndrome. It can also improve menstrual cramps and the pain associated with endometriosis (Wilmont, 1999).

## **2.7 Natural Progesterone**

Natural progesterone therapy is becoming increasingly popular in treating menopause. The theory behind this form of therapy is; at menopause the finely tuned balance between oestrogen and progesterone in a woman's body is disturbed. Oestrogen levels fall drastically at menopause but the level of progesterone falls even further leaving a state known as oestrogen dominance. The administration of natural progesterone is believed to bring the hormone levels back into balance (Kenton, 1996).

The level of progesterone produced daily in a woman's body can vary, depending on whether she is pre-menopausal, post-menopausal or pregnant. Progesterone is synthesized in the body from cholesterol via the hormone pregnenolone.

Progesterone itself can be converted into cortico-steroids and testosterone.

Progesterone also affects the behaviour of other hormones; its most vital role is ensuring survival of the foetus (Rushton & Bond, 1999).

Natural progesterone is the name, which has been acquired by the progesterone that is produced in a laboratory for placing into creams or tablets for supplementation. The word 'natural' used in this context means that the progesterone made in the laboratory has exactly the same chemical structure as progesterone made in the body. This means that it is natural to the body and recognised as identical to the progesterone produced by a woman herself.

Progesterone is made in the laboratory from saponins. These are steroid-like substances found in plants. The most commonly used is *diosgenin*, which is found in Mexican wild yams. This substance is treated in the laboratory and in a simple three-stage cascade process, is converted into progesterone. It is then micronised to facilitate easy absorption (Rushton & Bond, 1999).

A growing number of doctors and women in Europe and North America report that natural progesterone banishes the common symptoms of menopause such as hot flushes, vaginal dryness, depression, irritability, anxiety and lack of libido, to mention a few. They also believe it has the ability not only to prevent osteoporosis but to reverse it. (Kenton, 1996).

## **CHAPTER 3**

### **MATERIALS AND METHODS**

#### **3.1 Sample Selection**

Subjects were selected according to certain inclusion and exclusion criteria.

##### **3.1.1 Inclusion Criteria**

Subjects had to be between 40-55 years of age and experiencing at least 2 major and 1 minor of the following symptoms:

##### **Major Symptoms**

- Hot flushes
- Menstrual irregularities
- Dry vaginal canal / painful intercourse
- Irritability and mood changes

##### **Minor Symptoms**

- Headaches
- Stress incontinence
- Memory loss
- Loss of libido
- Tinnitus
- Bleeding gums

(Margolis, 2002)

### **3.1.2 Exclusion Criteria**

- Subjects who are on hormone replacement therapy (HRT) or any other treatment (including herbal remedies) for menopausal symptoms.
- Subjects experiencing premature menopause or any other condition in which oestrogen production is deficient.
- Subjects who have had a total hysterectomy.
- Subjects who are on any other medication such as thyroxin, psychotropic drugs or corticosteroids which may affect the presentation of menopausal symptoms.

Subjects who met with all the parameters were given a patient information letter (see Appendix A) and were required to sign an informed consent form (see Appendix B) before participating in the study.

### **3.2 Sample Distribution**

Thirty patients were selected by convenience sampling and randomly divided into two equal groups. Group 1 formed the experimental group, receiving *ProgestoNat*<sup>®</sup> cream, and group 2 formed the placebo group and received a placebo cream.

The data gained from the patients in the placebo group (group 2) was shared with a concurrent study of similar methodology (The efficacy of *Dioscorea villosa* cream in the treatment of menopausal syndrome, Macquet-Maurel 2003) and vice versa. This was possible, as the placebo applications used in the two

studies are identical in terms of ingredients, appearance, dosage and posology. The subjective and objective measures in the two studies are also identical. Given the above-mentioned similarities between the two studies, the third objective of this study was proposed. The placebo cream given to group 2 was indistinguishable from the experimental cream. It contained the identical combination of ingredients with the exception of *Diosgenin*, the active ingredient of *ProgestoNat*® cream.

Natura Homoeopathic Laboratories (a registered homoeopharmaceutical company) prepared the creams according to the standards set out in the British Pharmacopoeia (British Pharmacopoeia, 1999). The experimental treatment consisted of an aqueous cream base comprising seven base substances (i.e. *Aloe vera* (1%), *Borage oil* (3%), *Calendula officinalis* (1%), *Echinacea angustifolia* (1%), *Evening primrose oil* (1%), *Piper methysticum* (1%), *Symphytum officinale* (1%) and Vitamin E (1%). This base substance was then impregnated with the test substance, *Diosgenin* at 2% volume to volume (see Appendix E).

### **3.3 Randomisation**

This research project was conducted in a randomised double blind placebo controlled manner. The supervisor, Dr D. Naude randomly allocated either group 1 or group 2 to a list of numbers from 1 – 30. A number was then allocated to each patient sequentially, thereby placing them in one of the two groups. The researcher was not aware of the status of each patient. The researcher explained



to the participants that there was a 50% chance that they will be placed in the placebo group. As compensation, the patients in group 2 were offered free treatment for menopausal syndrome after the study.

### **3.4 Treatment**

The subjects participating were required to attend three consultations with the researcher. Each consultation was held on day one to three of the menstrual cycle. If subjects had irregular menses, the consultations were held every 28 days.

During the first consultation the patient completed the Greene Climacteric Scale questionnaire (See Appendix D). A registered, professional nurse then took a blood sample in order for the progesterone level to be measured.

Each patient was given a bottle of ProgestoNat<sup>®</sup> cream or placebo cream. A metered dose (20 mg) (one pump action) of the cream was applied every night, on a rotational basis to the face, neck, upper chest, breasts, inner arms and thighs, palms of hands and soles of feet.

After one menstrual cycle, or after 28 days had elapsed, the patients were requested to return for the second consultation. During this consultation only the Greene Climacteric Scale questionnaire was completed. The patients continued

using the cream in the same manner until day one to three of the following menstrual cycle, or on day 28 of the menstrual cycle.

At this time the third consultation was held. The Greene Climacteric Scale questionnaire was completed for the final time and a second blood sample was taken by the registered nurse for the progesterone level to be measured.

The results of the first questionnaire and blood test were used as a baseline for statistical analyses.

### **3.5 Measurement**

#### **3.5.1 Subjective Data**

The Greene Climacteric Scale questionnaire was used to assess measurement of participants on a subjective level. This questionnaire is a standard measure of menopausal symptoms used for comparative and replicative purposes. The scale is based on menopausal symptoms that are divided into four groups, namely psychological (anxiety and depression), somatic, vasomotor and sexual. Each symptom is given a score ranging from 0 to 3, with 0 representing no symptom experienced and 3 representing extreme symptoms. Since menopause is a multifaceted phenomenon, symptoms may come from different domains and have different aetiologies, therefore each group of symptoms is totalled separately and not added together to give a single score (Greene, 1998).

### **3.5.2 Objective Data**

Objective measurement was assessed through blood tests. Two blood samples were taken. One sample was drawn before commencement of treatment and one sample at the end of the treatment. The level of progesterone was measured in each sample and a comparison of the progesterone level was noted between sample one and two. The blood samples were tested at the Nelson Mandela School of Medicine, University of Natal, Department of Chemical Pathology. The blood samples were centrifuged at 3000rps for 10 minutes. The serum was poured into a tube and stored at -20°C. This process was performed for each blood sample within two hours of drawing the blood. The progesterone test was performed on all the serum samples simultaneously at the end of the study. This was done in order to minimise error and ensure standardisation. Data obtained at the first consultation served as a baseline measurement for statistical purposes. The method of analysis used was Elecsys Progesterone II, a product of Roche Diagnostics corporation.

## **3.6 Data Analysis**

### **3.6.1 Statistical Methods**

The two variables of interest in this study were the subjective data (i.e. the Greene Climacteric Scale questionnaire) and the objective data (i.e. the blood progesterone measurements). The score of symptoms from the questionnaire were tabulated after every consultation for statistical analyses to be made. Three

sets of symptom scores and two progesterone readings were taken for each subject.

As each group consisted of fifteen subjects (n=30), non-parametric tests were used for data analysis.

### **3.6.2 Statistical Analysis**

- i) The first purpose of the analysis was to determine whether there were significant differences between the two groups with respect to the variables of interest. This was carried out using the Mann-Whitney U test.
- ii) The second purpose was to determine whether there were significant improvements within each of the groups with respect to the variables of interest, using the Friedman's T-Test and the Dunn procedure where necessary.
- iii) The Wilcoxon Signed Rank Test was used to determine if there were any improvements within each of the groups with regard to the objective data (i.e: blood results).
- iv) The Kruskal Wallis H Test was used to determine any improvements between group 1 (ProgestoNat®), group 2 (placebo) and group 3 (*Dioscorea villosa*) with regard to objective data.

The significance level will be set at  $\alpha = 0.05$  and decisions will be made using appropriate p-values.

All statistical analyses were carried out using SPSS version 9.0.

### **Mann-Whitney U Test**

This is a test which is used for inter group comparisons. It will determine if there is a difference between group 1 (ProgestoNat ®) and group 2 (placebo) with respect to the variables of interest (objective and subjective data).

### Hypothesis Testing

The null hypothesis,  $H_0$ , states that there is no difference between the two groups with respect to the variables of interest. The alternative hypothesis,  $H_1$ , states that there is a difference between the two groups.

### Decision Rule

At the  $\alpha = 0.05$  level of significance, the decision rule states that if  $p > \alpha$  the null hypothesis  $H_0$  will be accepted. If  $p < \alpha$  the null hypothesis will be rejected.

### **Friedman's T Test and Dunn Procedure**

Friedman's T test was used for intra-group comparison of the subjective data.

This test was used to determine improvement between the consultations for both group 1 and group 2.

### Hypothesis Testing

The null hypothesis  $H_0$  states that there is no improvement within the respective group with respect to the variable of interest. The alternative hypothesis  $H_1$  states that there is an improvement within the respective group.

### Decision Rule

At the  $\alpha = 0.05$  level of significance, the decision rule states that if  $p > \alpha$ , the null hypothesis  $H_0$  will be accepted. If  $p < \alpha$  the null hypothesis  $H_0$  will be rejected.

If the null hypothesis is rejected (i.e:  $p < 0.05$ ), then the Dunn procedure is performed. This is performed in order to determine which of the consultations are different.

### **Wilcoxon Signed Rank Test**

This test is used for intra-group comparison of the objective data. It is used to determine improvements between the two progesterone measurements within group 1 and group 2.

### Hypothesis Testing

The null hypothesis  $H_0$  states that there is no improvement within the respective group with respect to the variable of interest. The alternative hypothesis  $H_1$  states that there is an improvement within the respective group.

### Decision Rule

At the  $\alpha = 0.05$  level of significance, the decision rule states that if  $p > \alpha$  the null hypothesis  $H_0$  will be accepted. If  $p < \alpha$  the null hypothesis  $H_0$  will be rejected.

### **Kruskal Wallis H Test**

This test was used for inter group comparisons of the objective data between group 1 (ProgestoNat®), group 2 (placebo) and group 3 (*Dioscorea villosa*).

### Hypothesis Testing

The null hypothesis  $H_0$  states that there is no improvement between the three groups with respect to the variable of interest. The alternative hypothesis  $H_1$  states that there is an improvement between the three groups.

### Decision Rule

At the  $\alpha = 0.05$  level of significance, the decision rule states that if  $p > \alpha$ , the null hypothesis  $H_0$  will be accepted. If  $p < \alpha$  the null hypothesis  $H_0$  will be rejected.

## **CHAPTER 4**

### **RESULTS**

#### **4.1 Introduction**

This chapter displays the subjective statistical results acquired from the Greene Climacteric Scale questionnaire as well as the objective results obtained from the progesterone measurements.

#### **4.2 Admissibility of the Data**

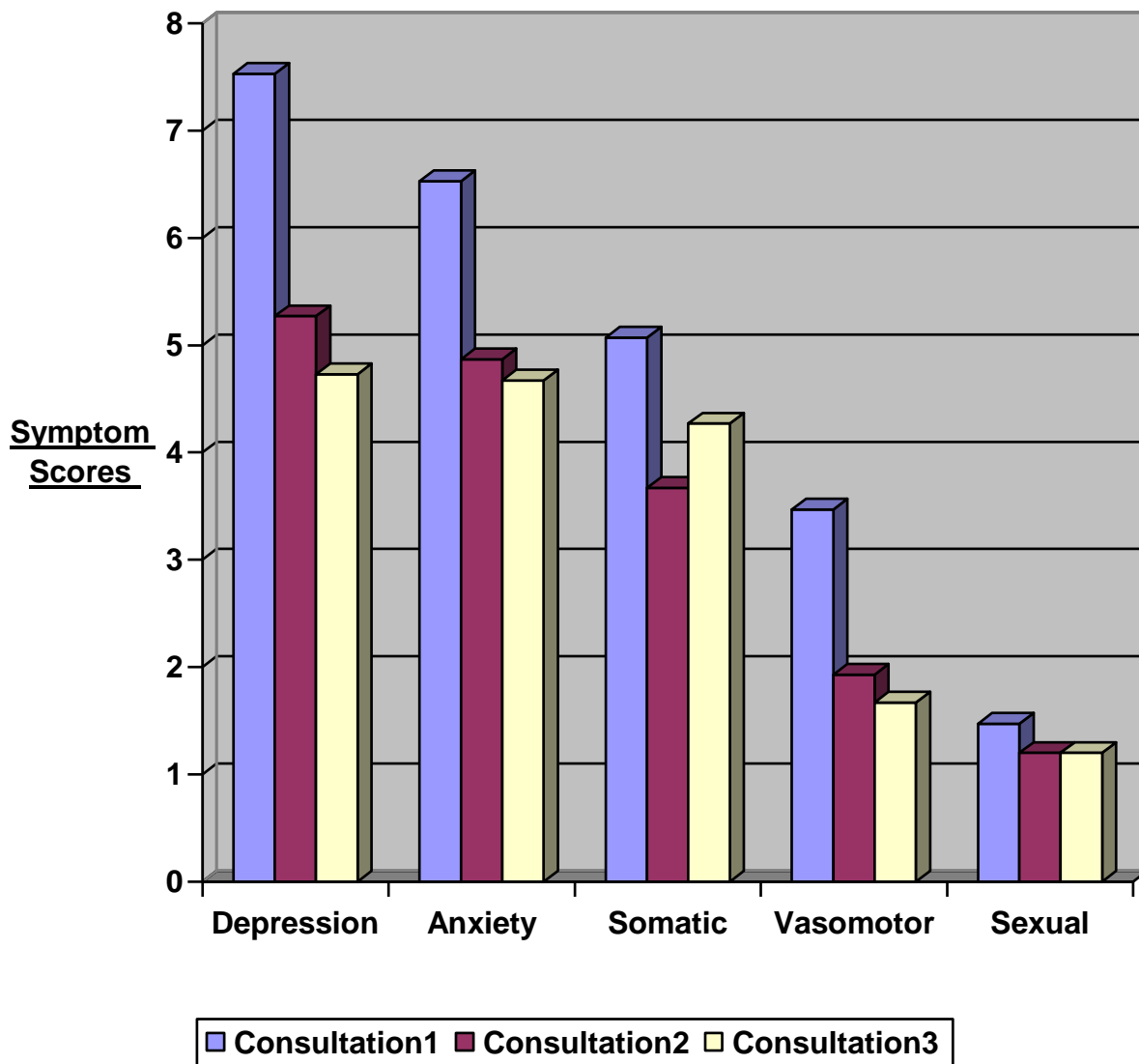
Only the data acquired in this study were used for the statistical analyses displayed in this chapter.

#### **4.3 Bar Charts**

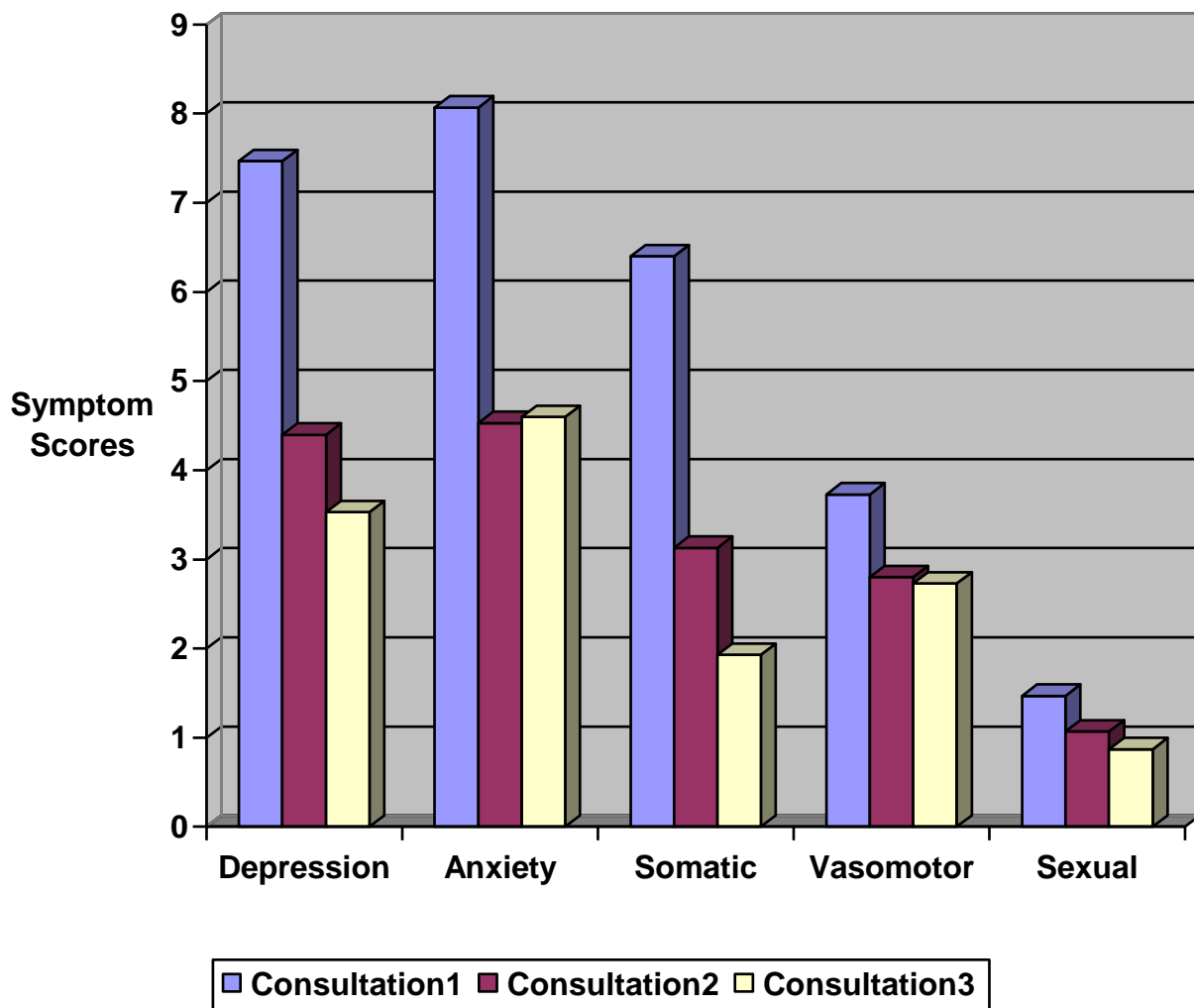
The following bar charts were used to represent the findings of the Greene Climacteric Scale questionnaire for all three consultations for both Group 1 (ProgestoNat®) and group 2 (placebo). The bar charts were also used to represent the comparison of the two blood progesterone measurements for all three groups, group 3 being *Dioscorea villosa* (Macquet-Maurel, 2003), as previously mentioned.



**Figure 4.1 Bar Chart Representation of the Subjective Data  
from Group 1 (Experimental)**



**Figure 4.2 Bar Chart Representation of the Subjective Data  
from Group 2 (Placebo)**



## **MANN WHITNEY U TEST**

### **Inter Group Comparison of the Subjective Data between Group 1 and Group 2**

**Table 4.1**

<b>SYMPTOM</b>	<b>CONSULTATION 1</b>	<b>CONSULTATION 2</b>	<b>CONSULTATION 3</b>	<b>CONCLUSION</b>
<b>Depression</b>	0.950	0.520	0.529	No Differences
<b>Anxiety</b>	0.169	1.000	0.586	No Differences
<b>Somatic</b>	0.154	0.736	0.103	No Differences
<b>Vasomotor</b>	0.659	0.154	0.167	No Differences
<b>Sexual</b>	1.000	0.829	0.381	No Differences

### **Conclusion**

All the tabulated p values are greater than 0.05. Therefore, the null hypothesis  $H_0$  is accepted. (There is no statistical difference between the two groups with regard to the subjective data)

**Inter Group Comparison of the Objective Data between Group 1 and Group 2**

**Table 4.2**

<b>BLOOD SAMPLE</b>	<b>P-VALUE</b>	<b>CONCLUSION</b>
<b>Sample 1</b>	0.868	No Difference
<b>Sample 2</b>	0.330	No Difference

**Conclusion**

All the tabulated p values are greater than 0.05. Therefore, the null hypothesis  $H_0$  is accepted. (There is no statistical difference between the two groups with regard to the objective data)

## **FRIEDMAN'S T TEST**

### **Intra-Group Comparison of the Subjective Data for Group 1**

**Table 4.3**

<b>SYMPTOM</b>	<b>P-VALUE</b>	<b>CONCLUSION</b>
<b>Depression</b>	0.108	No Difference
<b>Anxiety</b>	0.098	No Difference
<b>Somatic</b>	0.125	No Difference
<b>Vasomotor</b>	0.000	Difference
<b>Sexual</b>	0.102	No Difference

### **Conclusion**

At the  $\alpha = 0.05$  level of significance, the test indicated a statistically significant improvement between consultations for vasomotor symptom scores for group 1.

This means that the null hypothesis was rejected because  $p < 0.05$ . The Dunn procedure was then applied to establish which of the consultations were different. (See Dunn procedure below)

The test indicated that there was no statistically significant difference between consultations for the depression, anxiety, somatic and sexual symptom scores for group 1. This means that the null hypothesis was accepted because  $p > 0.05$ .

The Dunn procedure was therefore not applied in this case.

## **Intra-Group Comparison of the Subjective Data for Group 2**

**Table 4.4**

<b>SYMPTOM</b>	<b>P-VALUE</b>	<b>CONCLUSION</b>
Depression	0.002	Difference
Anxiety	0.005	Difference
Somatic	0.000	Difference
Vasomotor	0.477	No Difference
Sexual	0.069	No Difference

### **Conclusion**

At the  $\alpha = 0.05$  level of significance, the test indicated a statistically significant improvement between consultations for depression, anxiety and somatic symptom scores for group 2. This means that the null hypothesis was rejected because  $p < 0.05$ . The Dunn procedure is then applied to establish which of the consultations were different. (See Dunn procedure below)

At the  $\alpha = 0.05$  level of significance, the test indicated that there was no statistically significant difference between consultations for the vasomotor and sexual symptom scores for group 2. This means that the null hypothesis was accepted because  $p > 0.05$ . The Dunn procedure was therefore not applied in this case.

## **THE DUNN PROCEDURE**

If the null hypothesis,  $H_0$ , is rejected for Friedman's T-Test (i.e:  $p < 0.05$ ), then the Dunn procedure is performed. This is performed in order to determine which of the consultations are different.

Dunn Procedure - EQUATION: If  $R_j$  and  $R_{j'}$  are the  $j^{\text{th}}$  and  $j'^{\text{th}}$  treatment rank totals, then  $R_j$  and  $R_{j'}$  are declared significantly different if:

$$|R_j - R_{j'}| \geq z \sqrt{\frac{bk(k+1)}{6}}$$

Where:

$b$  = number of blocks (i.e: the total number of patients in the group)

$k$  = number of treatments (i.e: the total number of consultations)

$z$  = a value in the standard normal probabilities table corresponding to  $1 - [\alpha/k(k-1)]$

$\alpha$  = experimentwise error rate

(Daniel, 1978)

If  $\alpha = 0.15$ ,  $k = 3$ , then  $z = 1.96$

Therefore the above equation = 10.73

### Dunn procedure for group 1 – Vasomotor symptom scores

**Table 4.5**

		<b>RANK TOTALS</b>
<b>VASOMOTOR</b>	<b>CONSULTATION 1</b>	41
	<b>CONSULTATION 2</b>	26
	<b>CONSULTATION 3</b>	23

### **Conclusion**

Difference between consultation1 and 2:

$|R_1 - R_2| = |41 - 26| = 15$ , which is  $> 10.73$ . Therefore, there is an improvement between 1<sup>st</sup> and 2<sup>nd</sup> consultations for vasomotor scores.

Difference between consultation1 and 3:

$|R_1 - R_3| = |41 - 23| = 18$ , which is  $> 10.73$ . Therefore, there is an improvement between 1<sup>st</sup> and 3<sup>rd</sup> consultations for vasomotor scores.

Difference between consultation 2 and 3:

$|R_2 - R_3| = |26 - 23| = 3$ , which is  $< 10.73$ . Therefore, there is no difference between 2<sup>nd</sup> and 3<sup>rd</sup> consultations for vasomotor scores.



**Dunn procedure for group 2 – Depression, Anxiety and Somatic symptom scores**

**Table 4.6**

		<b>RANK TOTALS</b>
<b>DEPRESSION</b>	CONSULTATION 1	40
	CONSULTATION 2	28.5
	CONSULTATION 3	21.5
<b>ANXIETY</b>	CONSULTATION 1	39
	CONSULTATION 2	26.5
	CONSULTATION 3	24.5
<b>SOMATIC</b>	CONSULTATION 1	41.5
	CONSULTATION 2	27.5
	CONSULTATION 3	21

**Table 4.7**

	<b><math>R_1 - R_2</math></b>	<b><math>R_1 - R_3</math></b>	<b><math>R_2 - R_3</math></b>
<b>DEPRESSION</b>	7.5	13.5	6
<b>ANXIETY</b>	11	17.5	6.5
<b>SOMATIC</b>	20	16	-4

## **Conclusion**

There was a significant improvement between the 1<sup>st</sup> and 3<sup>rd</sup> consultations for the depression symptom scores.

There was a significant improvement between the 1<sup>st</sup> and 2<sup>nd</sup> as well as the 1<sup>st</sup> and 3<sup>rd</sup> consultations for the anxiety symptom scores.

There was a significant improvement between the 1<sup>st</sup> and 2<sup>nd</sup> as well as the 1<sup>st</sup> and 3<sup>rd</sup> consultations for the somatic symptom scores.

## **WILCOXON SIGNED RANK TEST**

### **Intra Group Comparison of the Objective Data for Group 1 and 2**

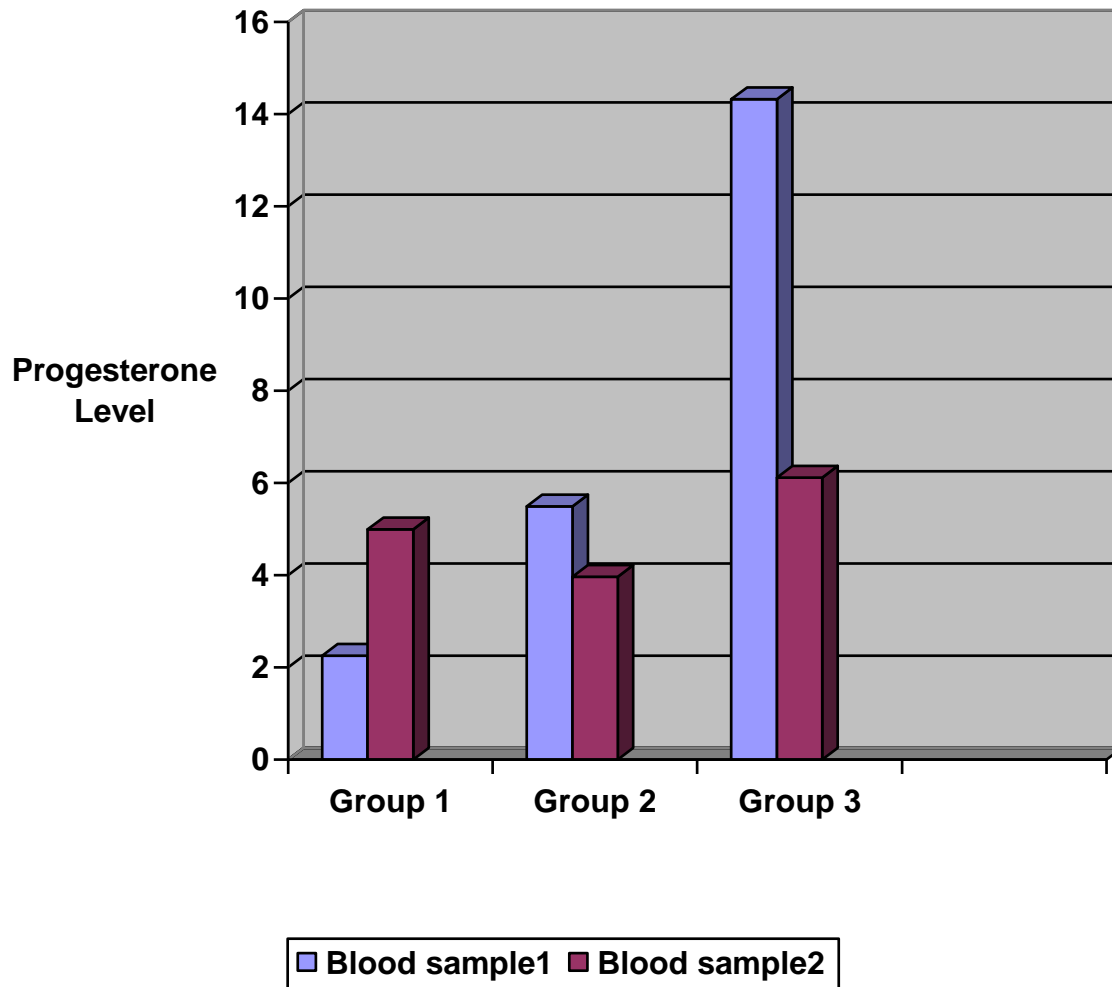
**Table 4.8**

<b>BLOOD SAMPLE</b>	<b>P-VALUE</b>	<b>CONCLUSION</b>
Group 1	0.307	No Difference
Group 2	0.156	No Difference

### **Conclusion**

At the  $\alpha = 0.05$  level of significance, the test indicated that there was no statistically significant difference between the two progesterone measurements for both group 1 and group 2. This means that the null hypothesis was accepted because  $p > 0.05$ .

**Figure 4.3 Bar Chart Representation of the Comparison of the Objective Data for All Three Groups**



**Group 1 = ProgestoNat® Experimental Group**

**Group 2 = Placebo Group**

**Group 3 = *Dioscorea villosa* Group**

## **KRUSKAL WALLIS H TEST**

### **Inter Group Comparison of the Objective Data between Group 1, 2 and 3**

**Table 4.9**

<b>BLOOD SAMPLE</b>	<b>P-VALUE</b>	<b>CONCLUSION</b>
Sample 1	0.95	No Difference
Sample2	0.350	No Difference

### **Conclusion**

At the  $\alpha = 0.05$  level of significance, the test revealed that there is no statistically significant difference between these groups with regard to the objective data (The null hypothesis was accepted).

## **CHAPTER 5**

### **DISCUSSION**

The purpose of this study was to evaluate the efficacy of ProgestoNat® cream in the treatment of menopausal symptoms with regard to subjective and objective data; as well as comparing the efficacy of this cream with that of *Dioscorea villosa* (Macquet-Maurel,2003) in terms of the objective data gathered in these two studies.

The results of this study indicated a statistically significant improvement with regard to the subjective data.

The experimental group showed a statistically significant improvement between consultations for the vasomotor symptom scores from the questionnaire. These improvements appeared between the 1<sup>st</sup> and 2<sup>nd</sup> consultations as well as the 1<sup>st</sup> and 3<sup>rd</sup> consultations.

The placebo group showed a statistically significant improvement between consultations for depression, anxiety and somatic symptom scores from the questionnaire. For the depression scores, the improvement was between the 1<sup>st</sup> and 3<sup>rd</sup> consultations and for the anxiety and somatic scores; the improvement was between the 1<sup>st</sup> and 2<sup>nd</sup> as well as the 1<sup>st</sup> and 3<sup>rd</sup> consultations.

The experimental group had improvement in one of the five symptom scores, whereas the placebo group had improvement in three of the five symptom scores. This observation could be attributed to various factors.

The base substances of the cream, excluding the active ingredient, may have had more of a therapeutic effect than initially expected. Although there is no evidence to state that the base ingredients are active, it may be a possibility that they were active considering the substantial improvement within this placebo group. The reason that these base substances were included in the cream was that this cream is a registered product that is marketed in pharmacies and health shops and was selected by the researcher as the menopausal cream on which these clinical trials would be run.

The 'placebo effect' is another consideration. It is the psychological or psychophysiological effect of this treatment cream, which had a therapeutic intent for the subjects' menopausal symptoms and through a psychological mechanism, this cream containing no active ingredients, had a very powerful and positive effect on the subjects. The result of the placebo cream being more effective than the treatment cream has proved to be an interesting point of discussion. If this improvement in the placebo group is in fact due to the placebo effect, then surely the improvement in the treatment group could also be attributed to the placebo effect?

This raises the point of the accuracy of the Greene Climacteric Scale questionnaire. Many of the questions in the questionnaire are not only relevant to menopause but other health conditions as well. For example 'shortness of breath', this symptom is relevant to menopause, however it is also a typical symptom of smoking and other lung pathologies. 'Feeling tired or lacking energy' is definitely a symptom experienced during the menopause but it is also a common symptom of the anaemias. In the same manner 'heart beating quickly or strongly' is also a common symptom of any cardiac pathology. Therefore, to critically evaluate this questionnaire, the results reflected by it may be inaccurate, relevant to the menopause and therefore the subjective results obtained may not have been a true reflection of the improvement of symptoms in menopausal syndrome with regard to this study.

There was no statistical significance with regard to the objective data in this study. The ProgestoNat® experimental group revealed no statistical difference as illustrated by the Wilcoxon Signed Rank Test. In the bar chart representation, comparing all three groups, it does seem as though there is a positive result in group 1, however these are the mean blood progesterone levels. As revealed by the Kruskal Wallis H Test, there is no statistical difference between all three groups.

There were only two blood measurements taken. This may have made a difference to the results. Measurements taken more frequently, possibly every week and over a longer period of time may have exhibited different results.



However, these extra tests were not possible due to a limited budget. Also, in order to determine whether the progesterone is in fact being absorbed, one must not only conduct blood tests but saliva tests as well (Rushton and Bond, 1999). The other factor to consider is the test conducted on the blood, if in fact it was accurate each and every time. This test conducted on the blood to measure the progesterone level, usually detects the form of progesterone manufactured by the body. This test can therefore be questioned as to whether it is indeed sophisticated enough to detect and recognise this 'natural progesterone' found in the cream.

In order for ProgestoNat® cream to be considered effective in the treatment of menopausal syndrome, it should show a significantly better therapeutic effect than the placebo. This was only indicated in the vasomotor category of the menopausal symptoms. ProgestoNat® is therefore rendered an effective form of treatment for vasomotor symptomatology in the menopause.

### **Difficulties Encountered**

Environmental and social factors play a vital role in one's everyday life. These circumstances influenced the subjects' participation. It was difficult on few occasions to record psychological and physical symptoms, differentiating between hormonal imbalance and coincidental life events. The somatic variable of the questionnaire posed difficulty, as many of the symptoms such as joint

pains and headaches may be unrelated to the menopause, although their onset may have been coincidental.

Patient compliance was essential for this study and required discipline and dedication from the subjects.

## **CHAPTER 6**

### **CONCLUSION AND RECOMMENDATIONS**

#### **6.1 Conclusion**

ProgestoNat®, is effective in treating vasomotor symptoms of menopausal syndrome. This is a very valuable fact, as vasomotor symptoms are the most common reason for treatment requests during the menopause and they have the most negative impact on quality of life, of all the symptoms.

The conclusion of this study is that the natural progesterone cream, ProgestoNat®, is an ineffective form of therapy for menopausal syndrome in terms of the objective data as revealed by the Wilcoxon Signed Rank Test.

#### **6.2 Recommendations**

- The sample size used in further investigations should be larger in order to obtain greater statistical accuracy. This was not possible in this case due to budget limitations.
- The trial was run over November, December and January. This holiday making and festive time of the year may not have been completely conducive to the study. Although not reported, subjects may have lacked discipline during this time. The psychological effects often experienced during this busy season could have also affected the results of the study.

- Demographically, there were only subjects from two different racial groups who volunteered for the study. Thus, it is recommended that further investigations should include a greater racial diversity.
- In future studies the base substances should be excluded, therefore excluding the possibility of effects being attributed to the base substances.
- Future studies should be run over at least a period of six months to possibly gain more accurate results.
- Future studies of this nature should include more frequent blood analyses as well as saliva tests to increase accuracy of the results.

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## **APPENDIX A**

### **INFORMATION WITH REGARDS TO RESEARCH PROJECT**

#### **TITLE OF RESEARCH PROJECT:**

The efficacy of *Dioscorea villosa* and *ProgestoNat*<sup>®</sup> creams in the treatment of menopausal syndrome.

#### **NAME OF SUPERVISOR:**

Dr David Naude M.Tech (Hom) (TN)

#### **NAME OF RESEARCH STUDENTS:**

Louise Macquet-Maurel

Taryn McTeer

Dear Patient,

The aim of this study is to evaluate the effectiveness of *Dioscorea villosa* (Wild yam) and *ProgestoNat*<sup>®</sup> creams in the treatment of menopausal syndrome.

Forty-five people will be required to complete this study. Each participant will be randomly allocated to one of three equal groups. The selection criteria requires that patients be between 40 – 55 years of age and currently experiencing at least two major and one minor of the following symptoms:

#### **Major symptoms:**

- Hot flushes
- Menstrual irregularities
- Dry vaginal canal / painful intercourse
- Irritability and mood changes

#### **Minor symptoms:**

- Headaches
- Poor bladder control
- Memory loss
- Loss of libido
- Ringing in the ears
- Bleeding gums

Patients who fall into any of the following categories will be excluded from the study:

- Patients who are on hormone replacement therapy (HRT) or any other treatment (including herbal remedies) for menopausal symptoms.
- Patients experiencing premature menopause or any other condition in which oestrogen production is deficient.

- Patients who have had a total hysterectomy.
- Patients who are on other medication such as thyroxin, psychotropic drugs or corticosteroids which may affect the presentation of menopausal symptoms.

Each group will receive a different treatment in order to determine which treatment is more effective. One group will receive a cream containing *Dioscorea villosa* tincture. Another group will receive *ProgestoNat*® cream, which contains *Diosgenin*, also referred to as 'natural' progesterone. The last group will receive a control cream. This is a cream that is unmedicated, but indistinguishable from the other creams. All three creams will contain the following added ingredients:

- *Aloe vera*
- Borage oil
- *Calendula officinalis* (Marigold)
- *Echinacea angustifolia*
- *Evening primrose oil*
- *Piper methysticum* (Kava Kava)
- *Symphytum officinale* (Comfrey)
- Vitamin E

#### Benefits of the study:

The benefit of this study is that the participants in the treatment groups will be given free treatment for their symptoms of menopausal syndrome. The control group will be given the option of free treatment at the end of the study. There will also be an opportunity to increase their knowledge of menopause.

#### Remuneration:

No remuneration will be offered to participants of this study.

#### Procedure of the study:

Each participant will be required to attend three consultations with the researcher. During each consultation the patient will fill in a questionnaire regarding the symptoms they are experiencing. A blood sample will be taken by a registered nurse at the beginning of the study, and again at the end of the study. The progesterone level in the blood will be measured. No other tests will be performed on the blood sample. The results of the blood tests will be made available to the patients. Each consultation will take place on day 1 – 3 of the menstrual cycle (i.e. The first to the third day of the start of menstrual bleeding). If menstruation does not occur, the following consultation will be held on day 35 of the menstrual cycle. The length of the study will be 2 cycles. At the end of the study the questionnaires and blood test results will be compared and analysed to ascertain which treatment provides the best results.

Confidentiality:

All the results are confidential and will only be viewed by the researcher, and supervisor.

Risks and Discomfort:

Complications are not expected from either of the treatments nor the control, however you have the option of withdrawing from the study without motivation. The only slight discomfort experienced may be that of acquiring the blood sample, however this will be performed by a registered nurse according to stringent safety protocol.

You are kindly asked not to alter your lifestyle in any way for the duration of the study and to refrain from using any other form of treatment for the symptoms you are experiencing, as this may alter the outcome of treatment and thus the results of the study. You are free to treat any unrelated conditions accordingly, but please inform the researcher if this occurs.

The treatment is supervised by a qualified homoeopath and is free of charge. In case of any queries or problems that may arise during the study, please contact:

Louise Macquet-Maurel      Tel: 0837826462

Taryn McTeer                      Tel: 0836616286

Dr David Naude                      Tel: 2042041 (Durban Institute of Technology)

Thank-you for your participation in this study

Kind Regards

Louise Macquet-Maurel and Taryn McTeer  
(Final year homoeopathy students)

Patient Name: \_\_\_\_\_ Signature: \_\_\_\_\_  
(in block letters)

Witness Name: \_\_\_\_\_ Signature: \_\_\_\_\_  
(in block letters)

## IMINININGWANE YOPHANDO OLWENZIWAYO

### ISIHLOKO SOPHANDO OLWENZIWAYO:

Ukusebenza kwe *Dioscorea villosa* ne *ProgestoNat*<sup>®</sup> imithi esetshenzisela ukwelapha kokuvaleka kokuya esikhathini.

### IGAMA LOMQEQESHI UMSIZI:

Dr David Naude M.Tech (Hom) (TN)

### IGAMA LOMFUNDI OPHANDAYO:

Louise Macquet-Maurel

Taryn McTeer

Siguli Esithandekayo,

Injongo yaloluphando ukuthola ukusebenza kahle komithi obizwa ngokuthi *iDioscorea villosa* ne *ProgestoNat*<sup>®</sup> okuwu khilimu abalwa nokuvaleka kokuya esikhathini.

Kuyodingeka abantu abangamashumi amane nanhlano ukwenza loluphando. Ilowo nalowo oyobamba iqhaza uyofakwa ngokungakhethiwe kwelinye lamaqoqo amathathu alinganayo. Indlela okukhethwe ngayo ifuna ukuba iziguli zibe neminyaka ephakathi kwamashumi amane nanhlano kuya emashumini amahlanu nanhlano ubudala abakhombisa okungenani izinkomba ezimbili ezinkulu nenkomba eyodwa yalokhu okulandelayo:

#### Izinkomba ezinkulu:

- Ukuzwela ukushisa nokujuluka kungashisi
- Ukuya esikhathini ngendlela engamukelekile
- Ukoma ngaphanzi / nobuhlungu uma uya ocansini
- Ukushesha ukucasuka nokungahlali ujabulile

#### Izinkomba ezincane:

- Ukuphathwa ikhanda
- Ukuhluleka ukubamba umchamo
- Ukukhohlwa
- Ukungalangazeleli ukuya ocansini
- Izindlebe ezidumayo
- Izinsini ezophayo

Iziguli ezingena kuloluhla olulandelayo ziyosuswa zingabe zisaba ingxenye yaloluphando:

- Iziguli vele esezelashelwa khona ukuvaleka
- Iziguli ezizithola zivaleka ngaphambi kwesikhathi
- Iziguli esezakhishwa isibeletho
- Iziguli ezelashelwa ezinye izifo

Ilelo naleloqoqo liyonikezwa ukwelashwa okwahlukile khona kuzobonakala ukuthi iyiphi indlela eyelapha ukwedlula enye. Iqoqo lokuqala liyonikezwa ukhilimu ofakwe iDioscorea villosa. Iqoqo lesibili liyonikezwa ukhilimu iProgestoNat® one Diosgenin. Iqoqo lesithathu lithole ukhilimu ongenamuthi kodwa ongeke ukwazi okulehlukanisa kuneminye one placebo kuphela. Bobathathu labokhilimu bayoba nalezithako ezilandelayo:

- *Aloe vera*
- *Borage oil*
- *Calendula officinalis* (Marigold)
- *Echinacea angustifolia*
- *Evening primrose oil*
- *Piper methysticum* (Kava kava)
- *Symphytum officinale* (Comfrey)
- Vitamin E

#### Imiphumela yalokukuhlolwa:

Imiphumela yalokukuhlolwa ukuthi zonke iziguli ezibambe iqhaza kuloluphando zithole ukwelashwa mahlala izinkomba zokuvaleka kokuya esikhathini. Iqoqo lokugcina lona liyonikwa ithuba lokuzikhethela ukuthi liyafuna yini ukwelashwa ekupheleni kophando. Bayothola futhi ithuba lokwazi kabanzi ngokuvaleka kokuya esikhathini.

#### Ukukhokheleka:

Bonke abathathe iqhaza kuloluphando angeke bakhokhelwe.

#### Indlela okuyokhutshwa ngayo:

Ilowo nalowo oyobamba iqhaza kuloluphando, kuyomele abonane nomphandi izihlandla ezintathu. Kuleso nalesosikhathi bebonana, isiguli kuyomele sigcwalise siphendule imibuzo ngezinkomba ezizibonayo nezizizwayo. Umhlengikazi oqeqeshiwe uyothatha igazi kuleso nalesosiguli ngaphambi kokubamba iqhaza kulolucutshungulo kanjalo futhi noma seluphelile. Izinga le progesterone egazini liyokalwa. Akukho okunye ukuhlolwa okuyokwenziwa egazini elithathiwe. Ukubonana kwesiguli nomcubonguli kuyokwenzeka njalo osukwini lokuqala kuya kwelesithatho sokuya esikhathini kuleyonyanga. Ubude bokuhlolwa kuyokuba izinyanga ezimbili. Ekupheleni kokuhlolwa konke okuyobe kusetsenziswa kuyobe sekuqhathaniswa kulutshungulwe ukuze kutholakale ukuthi iliphi ikhambi elisebenza kahle uma kuqhathaniswa lawa amathathu.

#### Ubumfihlo:

Yonke imiphumela eyotholakala iyoba imfihlo futhi iyobonwa kuphela ilowo ocubulungayo kanjalo nalowo omsizayo.

Ubucayi nokungakhululeki:

Abukho ubungozi obuyotholakala ngokusebenzisa noma iliphi elinye lalamakhambi kodwa isiguli sivumelekile ukuhoxa ekubeni ingxeny yaloluphando ngaphandle kokunikeza isizathu. Okuyikhona kungakhululeki okuyozwiwa iziguli ilokho kokuthatha igazi kodwa lokho kuyokwenziwa umhlengikazi oqeqeshiwe futhi oyoqiniseka ukuthi usebenzisa izinto ezifanele ukwenza lokho futhi esebenzisa izinto ezihlanzekile.

Uyacelwa ukuthi ungashintshi indlela yakho yokuphila ngesikhathi kwenziwa loluphando futhi kungabibikho mithi oyisebenzisayo okwalesikhathi njengoba ukwenza njalo kungakhinyabeza imiphumela yalokukuhlolwa. Uvumelekile ukwelapha olunye uhlobo lwesifo ongazithola usunaso inqobo nje uma kungesiso lesi okuohandwa ngaso kodwa futhi kufanele wazise umphandi ngalesosimo.

Ukwelashwa kuzobe kubhekwe kabanzi umuntu oqeqeshwe kabanzi kulomkhakha kanti futhi kumahala. Uma kwenzeka ufuna incazelo noma ufisa ukwanzi kabanzi ngesikhathi luqhubeka uphando, ukhululekiwe ekutheni uxhumane nalaba abalandelo:

Louise Macquet-Maurel Tel: 0837826462

Taryn McTeer Tel: 0836616286

Dr David Naude Tel: 2042041 (Durban Institute of Technology)

Siyabonga ukubamba iqhaza kwakho kuloluphando.

Ozithobayo

Louise Macquet-Maurel and Taryn McTeer

(Final year homoeopathy students)

Igama Lesiguli: \_\_\_\_\_ Isignature: \_\_\_\_\_  
(Bhala ngamagama amakhulu)

Igama Lofakazi: \_\_\_\_\_ Isignature: \_\_\_\_\_  
(Bhala ngamagama amakhulu)

## APPENDIX B

### INFORMED CONSENT FORM

TITLE OF RESEARCH PROJECT:

The efficacy of *Dioscorea villosa* and *ProgestoNat*<sup>®</sup> cream in the treatment of menopausal syndrome.

NAME OF SUPERVISOR:

Dr David Naude M.Tech(Hom)(TN)

NAME OF RESEARCH STUDENTS:

Louise Macquet-Maurel

Taryn McTeer

DATE: \_\_\_\_\_

PLEASE CIRCLE THE APPROPRIATE ANSWERS:

- |   |        |
|---|--------|
| 1. Have you read the research information sheet?  | YES/NO |
| 2. Have you had the opportunity to ask questions regarding the study?   | YES/NO |
| 3. Have you received satisfactory answers to your questions?  | YES/NO |
| 4. Have you received enough information about this study?   | YES/NO |
| 5. Do you agree not to discuss any of the particulars of your treatment with any other study participants?  | YES/NO |
| 6. Who have you spoken to with regards to this study?<br>_____.   |        |
| 7. Do you fully understand the implications of your involvement in this study?  | YES/NO |
| 8. Do you understand that you are free to withdraw from this study:<br>1. At any time<br>2. Without having to give reason for withdrawing, and<br>3. Without affecting your future health care? | YES/NO |
| 9. Do you agree to voluntarily participate in this study?   | YES/NO |

If you have answered no to any of the above, please obtain the information before signing

Patient name: \_\_\_\_\_ Signature: \_\_\_\_\_  
(In block letters)

Witness name: \_\_\_\_\_ Signature: \_\_\_\_\_  
(In block letters)

Research Student name: \_\_\_\_\_ Signature: \_\_\_\_\_



ISIHLOKO SOPHANDO OLWENZIWAYO:

Ukusebenza kwe *Dioscorea villosa* ne *ProgestoNat*® imithi esetshenzisela ukwelapha kokuvala kokuya esikhathini.

IGAMA LOMQEQESHI UMSIZI:

Dr David Naude M.Tech (Hom) (TN)

IGAMA LOMFUNDI OPHANDAYO:

Louise Macquet-Maurel

Taryn McTeer

USUKU: \_\_\_\_\_

Kokolozela izimpendulo ezifanelo:

1. Kungabe ulifundile iphepha locwaningo? YEBO/CHA
2. Kungabe ulitholile ithuba lokubuza imibuzo ngalolucwaningo? YEBO/CHA
3. Kungabe ugculisekile ngezimpendulo ozitholile? YEBO/CHA
4. Kungabe ulutholile ulwazi olwenele ngalolucwaningo? YEBO/CHA
5. Kungabe oyavuma ukungadingidi imininingwane emayelana nokwelashwa nabanye ababambe iqhaza kulolucwaningo? YEBO/CHA
6. Ubani osukhulume naye maqondana nalolucwaningo?  
\_\_\_\_\_.
7. Uyayiqondisisa imibandela yokuthatha inxaxheba kuloluphando? YEBO/CHA
8. Kungabe uyazi ukuthi ukhululekile ekuhoxeni kuloluphando:
  1. Noma nini
  2. Ngaphandle kokunikeza isizatho.
  3. Ngaphandle kokuba nomthalela ekulashweni kwakho? YEBO/CHA
9. Kungabe uyavuma ukuba ingxenye yaloluphando ngokuthanda kwakho? YEBO/CHA

**Uma uphendule ngokuthi cha kwe minye yalemibuzo engenhla, uyacelwa ukuba uthola ulwazi ngaphambi kokusayina.**

Igama lesiguli: \_\_\_\_\_ Isignature: \_\_\_\_\_  
(Bhala ngamagama amakhulu)

Igama lofakazi: \_\_\_\_\_ Isignature: \_\_\_\_\_  
(Bhala ngamagama amakhulu)

Igama lomfundi ocwaningayo: \_\_\_\_\_ Isignature: \_\_\_\_\_

## **APPENDIX C**

### **CONTENTS OF CREAM**

Aloe vera 1%	-	Anti-inflammatory and anti-irritant effect on the Skin.
Borage oil	-	A rich source of omega-3 fatty acids.
Calendula officinalis D2	-	Antiseptic, antifungal and anti-inflammatory effect on the skin.
Echinacea angustifolia D2	-	Used topically to treat tired, stressed skin.
Evening primrose oil	-	A rich source of omega-3 fatty acids. Relieves symptoms of premenstrual syndrome and breast pain.
Piper methysticum D2	-	Soothes skin and relieves tension and anxiety.
Symphytum officinale D2	-	Promotes healthy growth of skin cells and healing of skin blemishes. Improves tone and texture of skin.
Vitamin E 1%	-	Has anti-oxidant, free radical scavenging and anti-ageing properties.

This Appendix is not intended for Subjects. The contents of the cream are included in the information letter – Appendix A.

## **APPENDIX D**

### **THE GREENE CLIMACTERIC SCALE (Greene, 1998)**

NAME: .....

DATE: .....

NUMBER: .....

Please indicate the extent to which you are bothered at the moment by any of these symptoms by placing a tick in the appropriate box.

<b>SYMPTOMS</b>	<b>Not at all</b>	<b>A little</b>	<b>Quite a bit</b>	<b>Extremely</b>	<b>Score 0-3</b>
1. Heart beating quickly or strongly					
2. Feeling tense or nervous					
3. Difficulty in sleeping					
4. Excitable					
5. Attacks of panic					
6. Difficulty in concentrating					
7. Feeling tired or lacking energy					
8. Loss of interest in most things					
9. Feeling unhappy or depressed					
10. Crying spells					
11. Irritability					
12. Feeling dizzy or faint					
13. Pressure or tightness in head or body					
14. Parts of body feel numb or tingling					
15. Headaches					
16. Muscle and joint pains					
17. Loss of feeling in hands or feet					
18. Breathing difficulties					
19. Hot flushes					
20. Sweating at night					
21. Loss of sexual interest					

Psychological (1-11) = \_\_\_\_\_

Somatic (21) = \_\_\_\_\_

Depression (7-11) = \_\_\_\_\_

Vasomotor (19-20) = \_\_\_\_\_

Anxiety (1-6)= \_\_\_\_\_

Sexual (21) = \_\_\_\_\_

**THE GREENE CLIMACTERIC SCALE (Greene, 1998)**

IGAMA: .....

USUKU: .....

NUMBER: .....

Uyacelwa ukuthi usho izinga elikuhluphayo okwamanje mayelana nalezinkomba ezilandelayo ngokufaka uphawo esikhaleni esifanele.

Izinkomba	Akukho nhlobo	Kukhona kancane	Kukhona kakhudlwana	Kakhulu	Umphumela 0-3
1. Inhliziyo eshaya ngamandla noma kakhulu					
2. Ukuzizwa ungakhululekile					
3. Ukuba nokunzima ekulaleni					
4. Ukujabula kakhulu					
5. Ukwesaba					
6. Ukungakwazi ukulalelisa					
7. Ukuzizwa ukhathele					
8. Ukuzithola ungajathuliswa izinto eziningi					
9. Ukuzizwa udangele					
10. Ukuzizwa unomunyu kuthi khala					
11. Ukushesha ukucasuka					
12. Ukuzizwa unenzululwane noma ukuguleka					
13. Ikhandla noma umzimba oqinile					
14. Ukudikiza nokungawezwa amanye amalunga omzimba					
15. Ukuphathwa ikhandla					
16. Imisipha namalunga omzimba abuhlungu					
17. Izandla nezinyawo eziphelelwe imizwa					
18. Ukuba nobunzima bokuphefumula					
19. Ukushiselwa					
20. Ukujuluka ebusuku					
21. Ukulahlekelwa uthando lokuya ocansini					

Psychological (1-11) = \_\_\_\_\_

Somatic (21) = \_\_\_\_\_

Depression (7-11) = \_\_\_\_\_

Vasomotor (19-20) = \_\_\_\_\_

Anxiety (1-6) = \_\_\_\_\_

Sexual (21) = \_\_\_\_\_

## **APPENDIX E**

### **METHOD OF MANUFACTURE OF AQUEOUS CREAM**

#### **MATERIALS:**

Emulsifying Ointment	300g
Phenoxyethanol	10g
Purified water, freshly boiled and cooled, Sufficient to produce	1000g

#### **METHOD:**

The phenoxyethanol was dissolved in sufficient purified water at about 60°C to produce a total weight of about 700g. The emulsifying ointment was melted, and the phenoxyethanol solution was added when both were at about 60°C, and mixed. The cream was gently stirred until cool and sufficient purified water was added to produce 1000g, and mixed (British Pharmacopoeia, 1999).

*Diosgenin* was then added to the aqueous cream at 2% volume to volume, using a secondary emulsifier to facilitate the incorporation . The incorporation was performed at a temperature of 45°C. The following ingredients were then added at 1% volume to volume: *Aloe vera*, *Calendula officinalis*, *Echinacea augustifolia*, *evening primrose oil*, *Piper methysticum*, *Symphytum officinale* and *Vitamin E*. *Borage oil* was added at 3% volume to volume.

Note: *Diosgenin* is a sterol in the plant *Dioscorea villosa* (Wild Yam). It is extracted from *Dioscorea villosa* and converted by chemical transformation to 'bio-equivalent ' or 'natural' progesterone. The active ingredient, *Diosgenin*, is extracted and manufactured into a powder by Infinity Industries Inc. in New York, for Natura Laboratories. The aqueous based cream is medicated with this powder at 2% volume to volume.