1-1-1985

The effects of vitamin B6 supplementation on premenstrual symptoms.

Kim Kendall
University of Massachusetts Amherst

THE EFFECTS OF VITAMIN B6 SUPPLEMENTATION ON PREMENSTRUAL SYMPTOMS

A Dissertation Presented

By

KIM ELIZABETH KENDALL

Submitted to the Graduate School of the
University of Massachusetts in partial fulfimment of
the requirements for the degree of

DOCTOR OF PHILOSOPHY

February 1985

Psychology

THE EFFECTS OF VITAMIN B6 SUPPLEMENTATION

ON THE PREMENSTRUAL SYNDROME

A Dissertation

by

KIM ELIZABETH KENDALL

Approved as to style and content by:

Bonnie R. Strickland

Bonnie R. Strickland, Chair

George W. Cobb

George W. Cobb, Member

Katherine V. Fite

Katherine V. Fite, Member

Patricia A. Wisocki

Patricia A. Wisocki, Member

Seymour M. Berger

Seymour M. Berger, Chair
Department of Psychology

ACKNOWLEDGEMENTS

I would like to thank the members of my Dissertation Committee, Bonnie Strickland, George Cobb, Katherine Fite and Pat Wisocki for their time, patience, and assistance. I am especially grateful for Professor Cobb's encouragement and assistance during the early stages of this project and for Professor Fite's valuable critiques of the final draft of this dissertation. Adrienne Paine, Barbara Morgan, Donna Motley, Lesley Tenney, Susan Craig, Audrey Getman, Susan Hunter, and Kate Bowman have my appreciation for their excellent work as research assistants. I am particularly grateful to all the women who graciously volunteered for this study, in spite of the minimal payment which was offered. Special thanks go to Arco Pharmaceuticals of Bohemea, NY and Stuart Pharmaceuticals of Wilmington, DE for their generous contributions of vitamin B6 supplements and placebo materials for this project. I would also like to thank all of my friends for their encouragement, and especially thank Corey Fagan, Barbara Morrell, Patricia Evans, Laura Kastner and Bram Fridhandler for their warmth and kindness over the last three years. Thanks also go to JoAnne Baranoski for her time, patience, and tremendous typing skills. Last, but by no means least, I would like to thank my advisor, Bonnie Strickland, for her unfailing support throughout my graduate student tenure at the University of Massachusetts and for her willingness to venture into less traditional areas of inquiry within the field of Clinical Psychology.

ABSTRACT

The Effects of Vitamin B6 Supplementation

on Premenstrual Symptoms

February, 1985

Kim Elizabeth Kendall, B.A., University of California/Davis

M.S., University of Massachusetts

Ph.D., University of Massachusetts

Directed by: Professor Bonnie Strickland

A double-blind controlled study of the effects of vitamin B6 supplementation on premenstrual symptoms was conducted. Fifty-six women who reported moderate to severe premenstrual mood changes participated in the study. Symptoms were monitored prospectively through daily home recordkeeping over a one month baseline period and a two month treatment period (3 months total). Subjects received daily supplements of 150 mg of vitamin B6 or the equivalent of a placebo over the entire two month treatment period. Analysis of covariance and t-test comparison results suggested that vitamin B6 may improve some premenstrual symptoms (including dysphoria) during periods of increased stress. Vitamin B6 was observed to have a general ability to improve subjective ratings of concentration level regardless of menstrual cycle phase. Data also suggested that a placebo in capsule form may be more effective than vitamin B6 in tablet form in ameliorating premenstrual symptoms. Future areas of inquiry and methodological concerns are discussed.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

CHAPTER I

INTRODUCTION

For centuries the monthly hormonal cycling in women has been associated with fluctuations in physical and psychological well-being. Through the ages, the effects of menstrual changes have variously influenced women in their cultures and legends. In this century, scientific documentation of these phenomena has begun to accumulate. For many women the monthly changes are associated with serious difficulties. Recent reviews have cited the increased incidence of psychiatric problems such as suicidal behavior and rate of hospitalizations for women during the premenstrum (Abramowitz and Balar, 1982; Berlin, Bergey and Money, 1982; Dalton, 1959; Jacobs and Charles, 1970; Smith, 1975; Steiner and Carroll, 1977), as well as increased criminal acts (Dalton, 1980). Although for most women, premenstrual symptoms do not require professional intervention, epidemiological evidence suggests that from 70% to 90% of all women report recurrent premenstural symptoms, and 20% to 40% of women experience some degree of temporary mental or physical dysfunction premenstrually (Reid and Yen, 1981). The premenstrual syndrome is widely variable among women. Some women become tense and irritable, while others feel depressed and lethargic. Physical symptoms may include headache, backache, fatigue, swelling and tenderness of breast or abdominal tissues, changes in appetite, migraine,

acne, seizures, and hypoglycemia (Smith, 1975; Reid and Yen, 1981). The relationship between physical and psychological symptoms has yet to be clarified; however, some researchers have recently attempted to identify symptom patterns or clusters, combining both physical and psychological symptoms (Endicott, Halbreich, Schacht and Nee, 1981; Haskett, Steiner, Osmun and Carroll, 1980; Moos, 1968).

A variety of pituitary, adrenal, and ovarian hormones -- at either excessive or insufficient levels, or in improper balance -- have been implicated as possible causes of premenstrual disturbances. Estrogen, progesterone, follicle stimulating hormone, luteinizing hormone, prolactin, ACTH, cortisol, and monoamine oxidase all show periodic changes in blood level in relation to the menstrual cycle. Renin, angiotensin, and aldosterone, which regulate body fluid blance, also fluctuate cyclically (Steiner and Carroll, 1977). The elimination of ovarian cyclicity through the administration of an agonist of gonadotropin-releasing hormone was shown to markedly reduce physical and behavioral premenstrual symptoms in a double-blind crossover study involving eight subjects diagnosed as having PMS (Muse, Cetel, Futterman and Yen, 1984). Nevertheless, no identifiable endocrine or physiologic markers have been found to distinguish women with the syndrome from those without (Reid and Yen, 1981). It is also clear that social, cultural, and psychological factors such as attitudes, expectancies, vulnerability to stress, and life style choice are salient factors which must be taken into account in any comprehensive investigation of this problem (Sherif, 1980).

While interrelated functioning of many of these substances has been documented in laboratory studies, the central mechanism leading to the premenstrual syndrome continues to elude researchers. Accumulated research evidence suggests that this syndrome is related to a dysfunction along the hypothalamic-pituitary-ovarian axis (Reid and Yen, 1981). It seems possible that in such a complex system of interacting substances and processes, the variety of premenstrual symptoms could result from any number of possible systemic imbalances, rather than from a single consistent underlying cause.

Because of the immediacy of the problem of widespread and debilitating premenstrual distress, it has been for many researchers and clinicians at least as important to discover means to alleviate symptoms, as it has been to identify underlying causes. Given the enormous complexity and variety of causal patterns suggested by the accumulated research, it is understandable that fruitful investigations of appropriate treatments have been extremely difficult to accomplish. Careful examination of the literature shows it to be frustratingly inadequate. Many popular remedies for menstrual and premenstrual distress have been untested or have been based on evidence from poorly controlled or uncontrolled clinical trials (Smith, 1975). Yet, vast numbers of women, with the collaboration of their physicians, subject themselves to chemical remedies of unknown effectiveness which may have serious side effects. Oral contraceptives, progesterone, and diuretic agents are three of the most widely used treatments, but the few well-controlled, double-blind studies in which these have been

studied, have failed to demonstrate their effectiveness (Steiner and Carroll, 1977). The possible risks of increased cancer and circulatory disorders suspected with the use of synthetic hormones are well known. Diuretics can have a variety of side effects, including depression (Huapaya and Ananth, 1980) -- one of the major symptoms associated with the premenstrual syndrome. Given these cautions, it is of particular importance to delineate treatments that are both safe and effective.

One of the main goals of this research was to develop a general methodology suitable for studying the menstrual cycle, to begin the delineation of particular variables that warrant further research, and to develop a rigorously controlled method for testing alternative treatments for various premenstrual symptoms.

Nutritional treatments have become increasingly popular, as a growing number of women prefer to avoid the use of drugs. Currently, there is no way for these women to make informed decisions regarding the effectiveness of nutritional treatments. Although it seems logical that some form of dietary supplementation might ameliorate premenstrual symptoms without the danger of side effects, very little controlled research has been done to test its effectiveness. Perhaps the most popular vitamin therapy for the premenstural syndrome currently involves dietary supplements of pyridoxine (vitamin B6). The purpose of this research was to determine whether dietary supplements of vitamin B6 can exert a beneficial effect on premenstrual depression and irritability in particular. The rationale for this treatment will be addressed later in this paper. The following is intended to be a brief review of

major research directions regarding the premenstrual syndrome.

Overview of Regulation of the Menstrual Cycle

The brain controls the interacting activities of the hypothalamus, pituitary, and ovaries, thereby controlling release of hormones. The ovaries provide feedback signals to the brain-pituitary system which, in turn, responds by adjusting the amount and type of hormone to be released. Most menstrual disorders are commonly due to disturbances in the brain-pituitary portion of this regulatory system. An understanding of these interacting components is necessary in order to examine physiological and psychological factors that may be involved in the premenstural syndrome. This section is intended to summarize, in a general way, the physiological processes which regulate a normal menstrual cycle.

The average menstrual cycle lasts 28 days and begins on the first day of menses (period of menstrual bleeding). The first half of a cycle is the follicular phase, and the luteal phase makes up the second half. The follicular and luteal phases are divided by ovulation which occurs at midcycle, or approximately at day number 14, and again are divided by the onset of the menses. The first half of the follicular phase includes the menses and the second half of this phase begins on the 6th or 7th day of the menstrual cycle (Yen, 1981). Other authors have chosen to further subdivide the luteal phase into the early luteal phase, late luteal, and premenstrual periods (Rossi and Rossi, 1980); days 17-21, 22-24, and 25-28, respectively comprising these subdivisions.

During the early follicular phase, the hypothalamus signals the pituitary which, in turn, releases follicle stimulating hormone (FSH). FSH encourages the follicles in the ovaries to begin to grow and mature and produce estrogen. The second half of the follicular phase is marked by an increase in the release of estradiol and esterone. Estradiol rises slowly at first, and then rapidly to a peak, stimulating the release of luteinizing hormone (LH) by the pituitary. One day later, a peak surge of LH is seen which stimulates the rupture of a follicle and the release of an ovum (egg). As estrogen levels rise, FHS levels decrease. Several days before the surge of LH, levels of androgens, testosterone and progesterone are also beginning to rise due to increased activity in the follicles. Ovulation is accompanied by an abrupt surge in LH-FSH, which lasts about 36 hours, followed by release of the ovum 24 hours later. Once the ovum is released, LH continues to influence the follicle to become the progesterone producing corpus luteum (yellow body). Progesterone levels rise and estrogen levels fall abruptly. Progesterone produced by the corpus luteum stimulates the lining of the uterus to prepare for the implantation of the ovum which is on its way via the fallopian tubes. Peak progesterone levels are reached about 8 days after the LH surge. Parallel, but smaller increases are seen in 17α-hydroxyprogesterone, estradiol, and esterone, while LH and FSH continue to decline. The corpus luteum has a lifetime of about 14 days. (Interestingly, both estrogen and progesterone produced by the luteal tissue seem to destroy this same tissue, forming a self-destruct mechanism.) If the ovum is not

fertilized, or it is fertilized too late for it to develop sufficiently by the time it reaches the uterus, it is unable to implant itself in the lining of the uterus, leading to a decline in progesterone and a further decline in estrogen in the late luteal phase. This decline may initiate local production of prostaglandins, which are thought to promote vasoconstriction, as well as other factors involved in the process of sloughing off and expelling the lining of the uterus. At the end of the luteal phase, or the beginning of the menses, FHS levels begin to rise again to initiate the growth of the follicles for the next cycle (Carlson, 1977; Yen, 1981).

Other factors have been linked to the premenstrual syndrome, because they also fluctuate over the menstrual cycle. Cortisol levels are higher during the follicular phase than the luteal phase. Aldosterone (an electrolyte-regulating hormone of the adrenal cortex) is two times higher during the luteal phase than the follicular phase, peaking the 9th or 10th day before menses and dropping rapidly 6 or 7 days before menstrual bleeding begins (Steiner and Carroll, 1977). Corticosterone and desoxycorticosterone show a similar pattern. Progesterones and estrogens induce the formation of angiotensin which initiates and parallels fluctuations in levels of aldosterone (Steiner and Carroll, 1977).

It has been hypothesized that one or several of these factors related to the normal menstrual cycle may be an imbalance and, therefore, may be responsible for the premenstrual syndrome (PMS). The following

is intended to be a review of the major theories of dysfunction which physiologists have explored in relationship to the PMS.

Estrogen Excess - Progesterone Deficiency

Since 1931, it has been proposed that an excess of estrogen might be responsible for the PMS. More recently, reports have documented increased levels of estrogen and decreased levels of progesterone on women with the PMS (Bäckström and Carstensen, 1974; Munday, Brush and Taylor, 1977, 1981). Unbalanced estrogen production could be responsible for fluid retention, breast swelling, abdominal swelling, abnormal carbohydrate metabolism, as well as mood changes seen in the PMS. Other studies have found that levels of estrogen and progesterone withdrawal, not an improper estrogen:progesterone ratio, might be responsible for the PMS (Kutger and Brown, 1972). Although it was thought that the administration of natural or synthetic progesterones might, therefore, alleviate the PMS, there have been no large double-blind studies demonstrating the usefulness of either progesterone or testosterone therapy in treating the PMS (Reid and Yen, 1981; Smith, 1975).

Treatment of the PMS with progesterone is still fairly popular in clinics (Reid and Yen, 1981). Indirect evidence for the possible effectiveness of progesterone therapy came with research on oral contraceptives which showed that contraceptives which were highly estrogenic made premenstrual symptoms worse and those that were strongly progesterogenic improved premenstrual dysphoria. Oral contraceptives

were reported to both lessen and worsen premenstrual symptoms. Controlled studies by Coppen, Milne, Outram and Weber and by Jordheim (see Steiner and Carroll, 1977) failed to confirm the effectiveness of oral contraceptives in treating the PMS.

Synthetic progesterones, when studied in a controlled manner, do not seem to be more effective in treating the PMS than a placebo (Jordheim, 1972; Reid and Yen, 1981; Sampson, 1979; Swyer, 1955). Again, however, uncontrolled studies continue to support the notion that progesterone treatment can be useful (Berlin, Bergey and Money, 1982; Dalton, 1980; Kerr, Day, Munday, Brush, Watson and Taylor, 1980).

It is interesting that several of these authors (Munday, Brush and Taylor, 1981) later reverse themselves and conclude that it is unlikely that progesterone plays an important role in the PMS, since the greatest progesterone deficit occurs at the mid-luteal phase (days 8 to 9 premenstrually) before symptoms are most severe. They also feel that the estrogen:progesterone ratio does not appear to differ markedly in the PMS, but suggest that there does appear to be a large difference in estrogen levels at the time of most severe symptoms (days 1 to 4 premenstrually). High premenstrual levels of estrogen have also been cited as a possible factor in the PMS by Bäckström and Carstensen (1981).

Estrogen is known to affect neurotransmitter concentrations. High estrogens are usually associated with low norepinephrine concentrations (La Torre, 1974). It is possible that estrogen could affect behavior in different ways depending on the levels of progesterone

present (Munday, Brush and Taylor, 1981). Low levels of estrogen are known to correlate with high levels of monoamine oxidase which, in turn, may deplete catecholamines (Abramowitz, Baker and Fleischer, 1982; La Torre, 1974). This evidence, along with research which has shown that oral contraceptives are associated with increased levels of premenstrual depression, suggest that estrogens may have a role in the PMS, and one that is more important than the role progesterone may play (Smith, 1975).

Aside from the effects that estrogen and progesterone may have on catecholamine levels and subsequent changes in mood, both estrogen and progesterone are thought to affect changes in fluid retention which occur premenstrually. Estrogen may be involved in premenstrual fluid retention by increasing synthesis and activity of plasma renin and angiotensin II. Renin and angiotensin II are known to raise blood pressure through vasoconstriction. They also increase the output of aldosterone, a hormone which affects the fluid and electrolyte balance of the body (Reid and Yen, 1981). Progesterone may also have a role in modulating fluid retention and blood pressure, again by affecting the activity of plasma renin and the secretion of aldosterone. It has been suggested that in this case, progesterone and not estrogen is primarily responsible for the rise in renin and aldosterone seen during the luteal (premenstrual) phase (Reid and Yen, 1981).

Aldosterone, Vasopressin and Angiotensin

In normal and PMS women, aldosterone levels are similar. However, it seems that women with the PMS may excrete larger quantities of aldosterone than controls. It is possible that increased secretion of aldosterone might result from stress and/or decreased dopamine activity levels (Reid and Yen, 1981). But, a recent report by Munday, Brush and Taylor (1981) found that there were no differences between PMS women and controls in aldosterone levels. This finding has been supported by studies which have shown that lowering aldosterone levels by administering spirolactone (an aldosterone antagonist) was no more effective than placebo in alleviating premenstrual symptoms (Smith, 1975).

Like aldosterone, vasopressin, another component of the renin-angiotensin system which is released by the pituitary, constricts blood vessels and raises blood pressure. Estrogen may regulate vasopressin release. Evidence has linked vasopressin to water retention seen premenstrually and there are some reports, from inadequately controlled studies, showing the effectiveness of vasopressin antagonists on PMS symptoms (Reid and Yen, 1981).

Steiner and Carroll (1977) feel that the renin-angiotensin system is not likely to be involved in the PMS. The fact that aldosterone activity levels drop six days before menstruation begins, suggests that it is not likely that aldosterone is related to dysphoria and water retention seen in the late luteal phase. This notion is further substantiated by reports that changes in the renin-angiotensin system do

not occur in anovulatory cycles. Premenstrual depression and dysphoria, however, do occur in anovulatory cycles, suggesting that angiotensin is not responsible for mood changes seen premenstrually (Steiner and Carroll, 1977). It is interesting to note that progesterone levels also do not fluctuate in anovulatory cycles, again suggesting that progesterone does not play a role in premenstrual dysphoria (Adamopoulos, Loraine, Lunn, Coppen and Daly, 1972; Steiner and Carroll, 1977).

Prolactin

Prolactin has complex influences on gonadal functions and is responsible for initiating lactation and promoting the growth of breast tissue. Levels of prolactin (PRL) fluctuate with the menstrual cycle, having higher levels during the luteal phase than the follicular, with peak levels occurring at ovulation. It also seems that PRL levels can vary greatly from woman to woman and from day to day (Reid and Yen, 1982; Steiner and Carroll, 1977). PRL levels remain elevated during the late luteal phase, while levels of estrogen and progesterone are dropping. High levels of PRL are thought to inhibit ovulation, and at the time of Steiner and Carroll's review (1977), several authors had found abnormally high levels of PRL in women with premenstrual tension. More recent studies reviewed by Reid and Yen (1981) have failed to confirm this finding. Several researchers have tried to treat the PMS with bromocriptine, a substance which suppresses the release of PRL by the pituitary, and contradictory results have been found.

Rein and Yen argue that although most researchers in this area assume that PRL is responsible for fluid retention and that it is, therefore, responsible for premenstrual fluid retention (as well as perhaps other premenstrual symptoms), it has not been established that PRL has osmoregulatory effects in humans. These authors suggest that PRL may indirectly affect the PMS by increasing dopamine activity, which in turn might improve moods or reverse water retention. Reid and Yen (1981) were, nevertheless, unable to conclude that PRL per se is an important factor in premenstrual tension.

De La Fuente and Rosenbaum (1981), based on Steiner and Carroll's 1977 review, proposed that excess levels of PRL may interact with ovarian hormones to produce premenstrual symptoms featured by depression when estrogen is low, and featured by irritability-hostility when progesterone levels are low. They support this hypothesis with the finding that postpartum depression usually occurs at a time when PRL levels are above normal and estrogen and progesterone levels have dropped. It seems, though, that these authors did not have access to the more recent findings reviewed by Reid and Yen which suggest that PRL is not involved in the PMS.

A more recent study, not mentioned in the review by Reid and Yen, also supports the view that PRL is not a major factor in the PMS. Bäckström and Aavaag (1981), in earlier work, had found lowered levels of progesterone during the luteal phase in women with the PMS. They had hypothesized that these lowered levels of progesterone might be explained by fluctuations in PRL, since this hormone is thought to influence

steroid hormone production and can cause the corpus luteum to produce insufficient amounts of progesterone. Fifteen women diagnosed as having the PMS were compared to 17 controls. The mean PRL levels for the PMS group was not significantly different from that of controls, even when those women with less severe PMS were excluded and when possible effects of sampling time were analyzed. Again, it seems that PRL does not, in itself, play a major role in the PMS.

Endorphins and MSH

Endogenous (within the body) opiate receptors have recently been discovered and may be involved in many central nervous system (CNS) disorders. Halbreigh and Endicott (1981) have hypothesized that decreases in endorphins may be involved in premenstrual depression, while an increase may contribute to anxious-agitated premenstrual depression. High levels of endorphins occur during pregnancy and after birth and, therefore, may be involved in postpartum depression. Since endorphins, like exogenous (external) opiates have an euphoric effect, it has been proposed that endorphins may be involved in mania and depression. Endorphins may also affect dopamine and serotonin levels associated with depression directly, or indirectly by inhancing dopamine turnover. Drugs such as naloxone and naltrexone, which block the activity of endorphins, can induce symptoms of increased sexual desire and dysphoria which are rarely seen together clinically, but have been reported together premenstrually.

Prolactin levels may be higher in women with premenstrual tension (see above) and since dopamine inhibits the release of prolactin, elevated prolactin may indicate decreased dopamine activity. Endorphins may also affect prolactin levels directly, since all opiates are known to stimulate prolactin.

Opiates interact with norepinephrine, serotonin and acetylcholine, increasing their synthesis. Serotonin is thought to be related to changes in depression, irritability, pain sensitivity and sexual desire, which are changes frequently seen during the premenstrum (Halbreich and Endicott, 1981).

Reid and Yen (1981) have also hypothesized a role for endorphins in the PMS and have reviewed other research which may link endorphins to this syndrome. Endorphins have an antidiuretic effect, increasing the release of vasopressin (known to regulate fluid retention and modulate other pituitary functions). Endogenous opiates also affect glucose metabolism (blood sugar levels) by eliciting the release of glucagon and insulin, resulting in hyperglycemia (high blood sugar) in humans and secondary hyperinsulism (chronically elevated levels of insulin). Disturbances in glucose metabolism have been found premenstrually, particularly hypoglycemic (low blood sugar) conditions, which could be caused by withdrawal of opiates (Reid and Yen, 1981). Opiates inhibit appetite and thirst. They may also inhibit the action of prostaglandin E_1. Prostaglandin E_1 stimulates fluid secretion in the small intestines. Inhibition of this action may result in constipation often associated with opiates. The analgesic effects of opiates

involve cyclic adenosine monophosphate which is stimulated by prostaglandins. Changes in appetite, pain sensitivity, constipation and diarrhea are fairly common premenstrual symptoms.

Like Halbreich and Endicott (1981), Reid and Yen (1981) postulate an abberant release of, or sensitivity to endorphins in the PMS. Additionally, they hypothesize that melanocyte-stimulating hormone (MSH) may also be involved in the PMS. This hormone is known to increase awareness of environmental stimuli and enhance arousal and attention. The fact that MSH, like the endorphins, is influenced by sex hormones and influences pituitary activity makes it a likely candidate for a role in the PMS as well.

Melanocyte-stimulating hormone (MSH) is a peptide from the anterior pituitary that influences the deposition of pigment in the body. Sex hormones appear to have a role in the regulation of synthesis and release of MSH, estrogen promotes its synthesis, but inhibits its release, while progesterone enhances release of MSH. In humans, MSH influences adaptive behavior through its ability to enhance arousal and attention and to increase awareness of environmental stimuli. Even though there is not direct evidence for MSH having a role in the PMS, the fact that it is known to affect arousal and attention, to stimulate levels of growth hormone, LH and FSH in humans, and it is known to act in concert with endorphins, suggests that MSH may modulate mood, behavior, and functioning of the pituitary along with endorphins (Reid and Yen, 1981):

> Endorphin-induced inhibition of central biogenic amine systems (norepinephrine, serotonin and dopamine) may produce mood changes, increased appetite and thirst. Mastodynia (breast swelling), fluid retention, constipation, and abdominal bloating in individual cases may result from endorphin incited increases in the levels of prolactin and vasopressin and the inhibitory effect of endorphins on prolactin action within the bowel (constipation). Withdrawal of endogenous opiate stimulus affords relief from these complaints, but may trigger new symptoms. Increased activity of biogenic amine systems may produce rapid improvement in mood and relief from mastodynia, edema and bloating. Release from opiate inhibition of prostaglandin action may explain headaches and loose stool which frequently accompany the onset of menstruation. In exceptional cases, an excessive rebound to dopaminergic hyperfunction may explain the development of late premenstrual hyperactivity, irritability, aggressive and hostile behavior, or psychosis...Differing amounts of gonadal steroid levels from month to month and from person to person may account for the heterogeneous and variable clinical manifestations of this disorder. (Reid and Yen, 1981)

Androgens and Testosterone-Estradiol Binding Globulin

Androgens have been thought to influence sexual desire in women and both increases and decreases in libido have been noted during premenstruum. Bäckström and Aavaag (1981) compared the levels of testosterone and testosterone-estradiol binding globulin (TeBG) in 15 women diagnosed with PMS and 17 normal controls of approximately the same age. Diagnosis of PMS was determined based on the development of mental symptoms regularly every premenstrual week, cessation of the symptoms at the start of menstruation, and no symptoms during the remainder of the cycle. Mean plasma testosterone levels did not differ significantly in the PMS group; however, when overall luteal phase concentrations were calculated, TeBG binding capacity was higher in the PMS group. Because

active testosterone is thought to be in the unbound form, higher levels of TeBG binding capacity suggest an overall increase in bound (inactive) testosterone and a decrease in active (unbound) testosterone, resulting perhaps in a physiologically less active supply of testosterone in spite of the fact that mean testosterone concentrations did not differ between the two groups of women.

Maureen Dalton (1981) also compared levels of TeBG binding capacity of 50 women with severe PMS and 50 age-matched controls. She hypothesized that changes in the binding capacity might be responsible for changes in total estradiol concentrations which had been previously reported in the literature. Her PMS group differed, however, from other studies; all 50 women had suffered severe premenstrual symptoms leading to mental hospitalization, suicide attempts, criminal offenses and premenstrual violence. Dalton found that the PMS group had significantly lower TeBG binding capacity in contrast to the findings of Bäckström and Aavaag (1981). Like Bäckström and Aavaag, she also found no differences in total testosterone or estradiol concentrations. She hypothesized that perhaps a defect in the liver might affect production of TeBG. Dalton's findings suggest that higher levels of active or unbound testosterone and estradiol may exist at the tissue level. Her findings are more consistent with researchers who have found high estrogen and low progesterone levels in women with PMS.

MAO Activity Levels

Another factor which has been implicated in the PMS is monoamine oxidase (MAO), an enzyme which catalyzes the formation of aldehydes, ammonia and hydrogen peroxide. Substances which inhibit MAO activity increase the activity of dopamine, serotonin and norepinephrine in the brain. Due to this effect on catecholamines, MAO inhibitors are sometimes used as antidepressants (Miller and Keane, 1978). MAO activity levels may be altered in the PMS. High levels of MAO activity have been found in premenstrual women and it has been speculated that progesterone could stimulate MAO activity and be responsible for the depression seen in some women premenstrually (Abramowitz, Baker and Fleisher, 1982; Steiner and Carroll, 1977). Some doubt has been cast on this hypothesis because other authors have found that MAO activity levels did not correlate with a global scale of menstrual mood variations (Steiner and Carroll, 1977).

Vitamin A

The use of vitamin A in the treatment of premenstrual pain was accidentally discovered in 1947 by Simkins, after having administered the vitamin to treat hyperthyroidism (Block, 1960). Carotene is thought to inactivate thyroxin and, therefore, reduce thyroid hyperactivity which often exists premenstrually. It has also been postulated that vitamin A may inactivate estrogen in the liver and, in this way, compensate for premenstrual increased estrogen levels. Block (1960) reported that vitamin A was most useful in reducing symptoms of headache and tension. Unfortunately, his study was not well designed. Two other reports of the effectiveness of vitamin A

have been reviewed by Reid and Yen (1981); however, none of these reports have been substantiated and the topic deserves further exploration. It is interesting to note that vitamin A intake may be comprised in a large portion of our population. Lower income groups of white and black females are more likely to have vitamin A intake levels below standard. It is extimated that between 18-23% of these women may be below intake norms (NES, 1971-72). Data indicate that vitamin A intake is a major public concern for Spanish-Americans in low income states (Ten-State Nutrition Survey, 1966-70).

Vitamin B6

Reid and Yen (1981) have done the best review of the theoretical grounds for the use of vitamin B6 (pyridoxine) in the treatment of the PMS. Vitamin B therapy has been advocated since the 1940's. During this period it was thought that vitamin B-complex deficiency might lead to an excess of estrogen in the PMS. Biskind and Biskind (1943) had noticed that a vitamin B deficiency in rats impaired estrogen metabolism, while androgens continue to be inactivated, leading to an imbalance in the estrogen-androgen equilibrium. They reported successful treatment of the PMS with vitamin B, as well as successful treatment of some symptoms of menopause, menorrhagia (excessive menstruation), cystic mastitis (breast cysts), and metrorrhagia (irregular menses) in women who showed signs of vitamin B deficiency, glossitis (inflamed tongue) and cheilosis (fissured and

scaled lips) were the most common of these symptoms. Women were frequently treated initially with parental doses of vitamin B, rather than oral therapy, as impaired absorption often occurs in nutritional deficiency. In 1948, during the war, Zondek and Brezezinsky (1948) studied 14 women who showed severe signs of vitamin B deficiency and found no signs of impaired estrogen degradation in these women. Their findings diminished the popularity of vitamin B therapy.

Interst in vitamin B therapy revived when it was discovered that it acts as a coenzyme (pyridoxal phosphate) in the synthesis of dopamine and serotonin (Reid and Yen, 1981). Due to this revived interest and popularization of vitamin megadoses, cases of vitamin B toxicity have been reported when taken in amounts ranging from 2 to 5 grams per day (Shcaumburg, Kaplan, Windeback, Vick, and Rasmus, 1983; Pleasure and Bowen, 1983). Toxic doses of pyridoxine may cause widespread, non-specific axonal degeneration affecting large and small myelinated fibers and result in impaired sensation, gait and coordination. These symptoms, in some cases, have only been partially reversible.

An estrogen-induced deficiency of the enzyme pyridoxal phosphate) has been suggested as a possible factor in depression in women on oral contraceptive and in women with the PMS (Adams, Wynn, Rose, Seed, Folkard and Strong, 1973; Adams, Wynn, Seed and Folkard, 1974; Herzberg, Draper, Johnson and Nicol, 1971; Rose, 1979). Rose (1978) speculated that estrogen might alter vitamin B6 distribution and induce enzymes which compete for available B6. Women on oral contraceptives do show a disturbance of this metabolic pathway which can be corrected by a pyridoxine supplement

(Winston, 1973). Because there are many such enzyme reactions which are pyridoxine dependent, it has been suggested that a vitamin B6 deficiency might manifest itself in various ways clinically and that depression may be only one manifestation of such a deficiency (Winston, 1973). It is possible that a deficiency of pyridoxine could contribute to other symptoms seen with oral contraceptives and in the PMS. Several recent studies have documented an association between low vitamin B6 serum levels and depression in research comparing depressed patients with non-depressed patients and controls (Carvey Williams and Sheffield, 1979; Nobbs, 1974; Russ, Hendricks, Chrisley, Kaliu and Driskell, 1983).

Disturbed glucose levels are observed in women on oral contraceptives (Winston, 1973) and have been reported in women premenstrually. More recent evidence suggests that carbohydrate tolerance is increased premenstraully and this might account for cravings often reported by women at this time (Reid and Yen, 1981). Vitamin B6 supplements have been shown to improve the impaired glucose tolerance curve seen in women on oral contraceptives (Winston, 1973). In a well-controlled study, vitamin B6 supplements were shown to be effective in reducing premenstrual levels of depression in women on oral contraceptives (Adams et al., 1978).

Three controlled studies have been done examining the possibility that vitamin B6 supplements might alleviate dysphoria associated with the PMS. In one study (Stokes and Mendels, 1972), 13 women with

PMS, who served as their own controls, were given either placebo or vitamin B6 supplements in a double-blind manner. These authors found no differences in moods between the vitamin and the placebo periods as measured by the Moos menstrual distress questionnaire. The results of this study are difficult to evaluate, because full details of the protocol, subjects, and results have never been published. Supplements were given monthly for an 18-day period prior to and including the first few days of the menses and dosages were not specified in this report, but are likely not to have exceeded 50 mg/day. Four women showed a tendancy toward improvement on the vitamin; however, this result was not significant. It may be that inadequate dosages were given or that they were given for too brief a period. It is also possible that subtle effects due to vitamin supplementation would not appear with a sample size of only 13. Further methodological issues will be discussed later in this paper. Mattes and Martin (1983) used a souble-blind, placebo controlled crossover procedure to evaluate the fffect of 50 mg of pyridoxine given ten days prior to menstruation on premenstrual depression in three women. Each woman reported subjective decreases in premenstrual depression while on vitamin B6 supplementation vs. placebo condition. Abraham and Hargrove (1980) used a similar procedure and demonstrated a significant response of carefully defined symptoms to vitamin B6 in doses of 500 mg per day compared to placebo. This study, unfortunately, also used a small sample size and, therefore, is difficult to generalize from.

The fact that vitamin B6 plays a role in the synthesis of dopamine and serotonin led other researchers to postulate that this vitamin might alter prolactin levels, since dopamine and serotonin are involved in the control of prolactin release. Serotonin activity has been shown to facilitate a rise in prolactin, whereas dopamine inhibits this release (McIntosh, 1976). Initial studies showed that vitamin B6 could depress prolactin secretion and, therefore, inhibit lactation and restore menses in women with amenorrhea (Delitala, Masala, Alagna and Devilla, 1976; McIntosh, 1976; Reid and Yen, 1981). Several subsequent studies reviewed by Reid and Yen have failed to demonstrate similar effects. These studies make it seem less likely that vitamin B6 might affect disorders which result from excess prolactin levels.

Again, three studies have assessed the clinical usefulness of vitamin B6 supplementation for the PMS (Abraham and Hargrove, 1980; Mattes and Martin, 1983; Stokes and Mendels, 1972). The possibility that supplementation may be useful needs further substantiation (Reid and Yen, 1981). This is especially true in light of recent evidence which suggests that a significant portion of Americans might be vitamin B deficient. Deficiencies of pyridoxine, thiamin, and riboflavin (B vitamins) often occur hand-in-hand. It is difficult to estimate their rate of occurrence separately; however, clinical signs of overall vitamin B deficiency can be observed in a substantial portion of children and adults (2-18%) in the United States (NES, 1971-72).

Lithium

Treatment of the PMS with lithium has been explored due to the cyclic nature of the syndrome and symptoms of depression which commonly exist. In these ways, the PMS resembled psychiatric disturbances for which lithium is the treatment of choice (Steiner and Carroll, 1977). Steiner and Carroll (1977) have carefully reviewed the research in this area and the later review by Reid and Yen (1981) does not include more recent work regarding the use of lithium to treat the PMS.

Several researchers in the late 60's and early 70's reported a good effect of lithium in treating the PMS. In 1974, two controlled studies by Singer, Cheng and Schou (1974) and Mattsson and Von Schoultz (1974), both double-blind, did not find lithium to be more effective than placebo in treating the PMS. The women in Singer's study (n=19) showed equal improvement under both conditions, but 12 of these women also suffered from other psychiatric conditions throughout the remainder of the cycle which suggests that this sample did not represent the PMS as it is commonly defined. Mattsson's PMS group did meet the normal criteria: regularly recurring symptoms which appear 7-8 days prior to the menses and are relieved by the first or second day of the menses and do not occur at any point during the remainder of the cycle. This study did, however, fail to differentiate between subgroups of PMS symptomatology, i.e., anxiety-tension, depression, irritability, and fluid retention

(Steiner and Carroll, 1977). Failure to make these distinctions is common in the PMS literature. More recently, researchers have been advocating the importance of distinguishing among various PMS symptom typologies, since it is possible that these subgroups may be the result of different underlying causes (Halbreich, Endicott and Schacht, 1982; Haskett, Steiner, Osmun and Carroll, 1980; Osborn, 1981; Sampson and Prescott, 1981; Steiner and Carroll, 1977). In the Mattsson study, placebo was found to be the most effective treatment, followed by a diuretic, with lithium the least effective of the three treatments. Steiner and Carroll (1977) conclude that the effectiveness of lithium in treating various subtypes of the PMS is still an open question. It should be kept in mind, however, that the same criticism (failure to distinguish among symptom typologies) could be made of most PMS research to date.

The relationship between premenstrual changes and mental disorder has been explored, but results have been inconsistent (Endicott, Halbreich, Schacht and Nee, 1981; Halbreich, Endicott and Schacht, 1982; Haskett, Steiner, Osmun and Carroll, 1980). Again, the direction of recent work is toward delineating between PMS and premenstrual worsening of psychiatric disorders. Authors who have selected women with only PMS have concluded that PMS is not typically a syndrome of anxiety or depression in the usual diagnostic sense and that it should not be thought of as a model for recurrent affective disorders (Haskett, Steiner, Osmun and Carroll, 1980). This

finding suggests that lithium treatment may not be useful in the PMS, since the rationale for the use of lithium was originally based on the resemblance of the PMS to cyclic affective disorders.

Psychological-Personality Variables

The unusually strong placebo effect seen in most premenstrual research suggests that psychological and social factors may be involved in the PMS (Gonzalez, 1981; Jordheim, 1972; Mattsson and von Schoultz, 1974; Sampson, 1979; Watts, Dennerstein and De La Horne, 1980). The myriad of seemingly unrelated symptoms associated with the PMS led many to hypothesize that the PMS was a psychosomatic disorder as early as 1938. Unresolved oedipal conflicts and/or marital conflicts were postulated as the source of this disorder. Women were thought to be unconsciously expressing stress or poor attitudes toward womanhood through their menstrual symptoms (Reid and Yen, 1981). Authors have reported correlations between premenstrual changes and disturbed attitudes toward menarche and the menses, guilt around sexual feelings, severe medical and gynecological histories, poor marital adjustment, and high neuroticism scores (Reid and Yen, 1981).

Although not of high quality, the psychoanalytic literature shows a similar picture (Steiner and Carroll, 1977). In one study, questionnaires were sent to 103 women and it was concluded that, for these women, menstrual problems were related to traumatic menarche experiences (Shainess, 1961). Other analysts have postulated that the mother-daughter relationship is important in determining future

attitudes toward menstruation and femininity in general (Deutsch, 1944). Fortin, Wittkower and Kalz (1958), May (1976), and Paulson (1961) also associated rejection of the feminine role and sexual guilt with premenstrual symptoms. This view may still be prevalent today. It would be interesting to conduct a survey of attitudes toward the PMS among medical and psychiatric professionals.

Premenstrual symptoms have been correlated with various personality factors. Coppen and Kessell (1963) found that neurotic patients showed the highest premenstrual irritability. Similarly, Watts, Dinnerstein and De La Horne (1980) found that women with the PMS scored higher on trait anxiety and neuroticism scales, as well as had more negative attitudes toward their bodies, genitals, sex and masturbation than controls. In 1975, Smith, in his review of this literature, concluded that the evidence suggested that tense, anxious individuals, possibly having negative attitudes toward their sex role, are more likely to complain of premenstrual irritability, even though nonneurotic women may suffer the same symptoms. In the case of neurotic individuals, however, it is difficult to determine which comes first, the cart or the horse, premenstrual problems or neurotic tendencies.

Somewhat in contrast to Smith's conclusion, Blank, Goldstein and Chatterjee (1980), in a more recent review of this literature, concluded that although some evidence suggests that severity of prementstrual symptoms may in part reflect underlying personality variables, the bulk of recent literature casts serious doubts on this

hypothesis. In particular, these authors cited recent dissertations by Kleinsasser (1976), DiNardo (1975), and Seagull (1974) which attempted to correlate neuroticism, sociability, self-sufficiency, introversion-extroversion, dominance-submission, self-confidence, locus of control, body attitudes, adequacy of functioning, and adjustment with premenstrual symptoms. All three authors found that these measures do not fluctuate with the menstrual cycle or with severity of the PMS. Seagull (1974) concluded that mood and behavior do fluctuate over the cycle, but that personality factors do not. Only introversion-extroversion seemed to have any predictive value, with introverted women tending to rest more, avoid social contact and report lowered performance efficacy levels during the menstrual phase of their cycle (Kleinsasser, 1976).

Sociological-Attitudinal Variables

Sociological studies have suggested that social expectations in many cultures provide women with the opportunity to express stress and malaise, to regress and to be absent from work around the time of menstruation. Smith (1975) reviewed the work of authors who suggest that these social expectations produce a self-fulfilling prophecy effect for many women. Gough (1975) administered psychological inventories to 201 young women. He found that the women who reported the greatest amount of menstrual distress were low on socialization and high on femininity subscales of the California Personality Inventory. The opposite trend was seen in women who reported the lowest

amounts of menstrual distress. As mentioned above, Watts, Dennerstein and Horne (1980) found that women with PMS showed more negative attitudes toward their bodies, genitals, sex and masturbation than controls. Tarpin (1976) found similar relationships between negative sexual attitudes and premenstrual distress. May (1976) speculated that premenstrual tension may be associated with helplessness or loss of self-control during menstruation in women who he found to be more assertive, less traditional, and having fewer inhibitions. He further hypothesized that women who became depressed premenstrually were expressing another kind of anxiety or the view that menstruation is an unclean and shameful process. May's hypothesis that helplessness and loss of self-control may be associated with premenstrual tension is contradicted by Seagull's (1974) findings that measures of self-sufficiency and locus of control do not vary over the menstrual cycle.

Based alone on the high placebo response rate seen in premenstrual research, it seems fair to assume that personality and social-attitudinal factors play a role in the development and expression of premenstrual symptoms. It is also likely, however, based on the physiological literature, that somatic factors play as large, if not larger, role in influencing the PMS (Parker, 1960; Reid and Yen, 1981; Smith, 1975; Steiner and Carroll, 1977). It seems clear that psychological and physiological interactions are inseparable and circular in their ability to influence each other. It is probably

futile to attempt to rate either factor as more or less important. The most useful model seems to be one that conceptualizes a complex, and perhaps circular, pattern of interaction and feedback between psychological-social and physiological variables.

Performance

Feminists have long argued that fluctuations in the menstrual cycle and concommitant fluctuations in hormonal levels ("raging hormones") do not render women incompetent or unreliable in terms of performance on the job or elsewhere. In fact, this arguement is well supported by the literature (Blank, Goldstein and Chatterjee, 1980).

An exception is some work of Dalton's, reviewed by Tasto and Insel (1977), which suggests that lowered performance may occur in adolescent women during menstruation. She studied school girls in an English boarding school and found that forgetfulness increased menstrually in the girls who were more intelligent and free of psychological stress. She has also found lowered examination performance in similar studies. It is not clear how well conducted these projects were.

Blank, Goldstein and Chatterjee (1980) have reviewed the performance literature more extensively. Mild decreases in performance were found premenstrually and menstrually in a study by Stocker (1974). Contrary to these findings, is the work of Berstein (1977) who found no differences between premenstrual/menstrual and intermenstrual academic performance in a sample of college women. Both

Golub (1974) and Summer (1972) found no differences in intellectual test scores over the menstrual cycle, although Golub's subjects made subjective reports and had expectations to the contrary. (It is interesting to speculate about the meaning of these negative expectations.) Zimmerman and Parlee (1973) also support these findings. Basic sensory-motor processes , such as reaction time and concentration time showed no changes. This trend also seems to be true for speech fluency (Silverman and Zimmer, 1976).

In spite of Dalton and Stocker's findings, the literature fairly consistently challenges the social stereotype that women are not as competent during the premenstrual and menstrual phases of the cycle. But for women who suffer from severe PMS, this may not be the case.

Research Objectives

Although it seems logical that some form of dietary supplementation might ameliorate premenstrual symptoms (indeed, vitamin therapy has dramatically increased in popularity among lay people in recent years), very little controlled research has been done to test the effectiveness of nutritional supplementation in treating the PMS.

Renewed interest in vitamin B6 therapy occurred with the discovery that this vitamin acts as a coenzyme in the biosynthesis of the neurotransmitters dopamine and serotonin. Both of these neurotransmitters have been implicated in a variety of disorders of mood and behavior (Reid and Yen, 1981). Vitamin B6 is involved

in many other metabolic activities, including protein synthesis, converting glycogen to glucose to provide energy for muscle tissue, the production of red blood cells, proper functioning of nervous tissue, and the metabolism of certain fatty acids (Robertson, Flinders and Godfrey, 1976). In view of the many decarboxylase and transaminase reactions that are vitamin B6 dependent, it is likely that a functional deficiency of pyridoxine would manifest itself in several ways clinically, and not only as depression (Winston, 1973). This potential for multiple manifestations is attractive in relationship to the PMS, given the variety of symptoms that can be associated with this syndrome.

Along with dopamine and serotonin synthesis, vitamin B6 has been linked to improper glucose metabolism (Winston, 1973), estrogen metabolism (Biskind and Biskind, 1943), prolactin levels (McIntosh, 1976), and premenstrual depression in women on oral contraceptives (Adams et al., 1973). Many normal American diets may be marginal in vitamin B6 content, since 75% of this vitamin is removed by food processing such as milling and heat (Robertson et al., 1976). It has recently been estimated that 2-18% of the population may be vitamin B deficient (NES, 1971-72).

The possibility that pyridoxine may be useful in treating the PMS still needs further substantiation (Reid and Yen, 1981). Given the facts mentioned above, it is likely that nutritional supplementation of pyridoxine might have beneficial effects on premenstrual symptoms and in particular, premenstrual depression.

The present research effort was designed to examine the effects of vitamin B6 supplementation on the premenstrual syndrome. If vitamin B6, in fact, has beneficial effects on physiological functioning, these beneficial effects should eventually act to decrease premenstrual dysphoria, and perhaps other symptoms as well. One would expect to see a decrease in reported depression, irritability, tension, and anxiety during the premenstruum. This research was specifically designed to assess the hypothesis that vitamin B6 may exert beneficial effects over time on levels of depression and anxiety.

Preliminary Research Findings

To examine the effectiveness of pyridoxine supplementation on premenstrual symptoms, a pilot study was designed using a double-blind crossover procedure. Advertisements were placed in local newspapers asking for volunteers. These women were screened based on the following selection criteria: women could not be taking any oral contraceptives, be on any regular medication or in poor health. They had to be between the ages of 20 and 40 and have fairly regular menstrual cycles. Volunteers were told that they would receive a token sum if they completed at least four months of the study and an additional sum if they completed the entire six months of the study. Approximately 80 telephone responses were screened and 40 of these callers were recruited for an initial interview and data collection. Of the 30 subjects who agreed to begin the home record keeping, a

final sample of 9 subjects completed six months of a parallel study examining the effects of dietary sodium intake, and only 4 subjects completed six months of the pyridoxine pilot study.

Baseline data were collected over the first two months of the project. During this time, a routine of home record keeping and three monthly office visits was established. Subjects were asked to fill out 12 questionnaire packets per month. These 12 packets were filled out starting on day one of the cycle, for the first three days of menstruation. The second group of packets was filled out for three days during the follicular phase and prior to ovulation. (Interviewers carefully worked out individual schedules with each woman according to the expected length of her cycle.) The third set of questionnaires was filled out for three days during the luteal phase (about 10 days prior to menstruation), and the final set was filled out as nearly as possible to the last three days before the onset of the next cycle. The rationale for this approach was based on the need to gather data from different phases of the cycle, yet minimize the time and effort that would be demanded from volunteers. It was found, however, that even for subjects who reportedly had regular cycles, there was enough variation in their cycle length to make it difficult to accurately calculate the phases, so that in a number of instances women started their next cycle while filling out the premenstrual packet, or conversely, ended up not starting the next cycle for a considerable time following what was to have been the premenstrual set of questionnaires. This problem

will be addressed in the research described here. In addition to home records, subjects were asked to come into the research office three times per cycle to deliver their completed questionnaires and to have their weight and blood pressure checked.

After baseline data were gathered for two complete cycles, the experimental procedure was begun. Each of the 4 subjects was randomly assigned to take either the placebo or the vitamin B6 supplement, 3 times per day, one tablet with each meal, totalling 150 mg/day. No other dietary changes or manipulations were made. After a two month period the crossover was begun and the groups were reversed. Interviewers who met with subjects and supplied them with the tablets were blind to the condition of the subject.

Home record keeping included the short form of the Zuckerman and Lubin (1965) Multiple Affect Adjective Check List, which has scales measuring levels of depression, anxiety and hostility. It also included the Moos Menstrual Distress Questionnaire (MDQ), which has a number of scales reflecting a variety of affective, behavioral, and physical menstrual cycle symptoms (Moos, 1968). In addition to these standard instruments, the packets included food frequency check lists with a representative assortment of common foods which were scored for rough indications of sodium intake, sugar intake, and total intake, as well as B6 and potassium intake. Finally, the packet contained a brief questionnaire asking subjects to assess their appetite, activity level, number of experienced stressors, and food cravings.

Thirty-six subjects completed the baseline period of two months. Average scores for the four phases of the cycle were calculated using these subjects' data. These averages revealed a U-shaped pattern if plotted over the month. Increasing levels of negative affect were seen menstrually, followed by lower levels during the mid-cycle phases (follicular and luteal), with a gradual increase in negative affect occurring again during the premenstrual phase of each cycle. This U-shaped pattern was seen in all of the measures of dysphoric mood. As might be expected, arousal (positive affect) showed the opposite pattern, increasing in the mid-cycle phases and decreasing in the menstrual and premenstrual phases.

In order to examine the data for overall changes in moods between the baseline, treatment and placebo phases of the study, an average over all phases of the cycle was calculated. When these overall baseline, placebo, and treatment phase means were calculated on the 4 subjects in the B6 study, all mood measures except hostility and arousal were lowered under both the placebo and the treatment conditions. Both the Moos and the MAACL measures of anxiety and depression showed this trend, and it was also seen in the Moos measure of amount of mood swing. The additional decline associated with vitamin B6 supplementation, beyond that consistently seen under the placebo condition, was usually small. The largest increased effects of B6 were seen in the Moos measures of depression and mood swing, although placebo effects followed closely behind.

Treatment with B6 was consistently more effective than treatment with placebo alone. But these differences were small.

When similar comparisons were made looking at water retention and menstrual pain, treatment with vitamin B6 made a greater improvement than placebo. As might be expected, declines during the menstrual and the premenstrual phases of the cycle accounted for the largest portion of the overall decline in the pain and water retention measures. Hostility and arousal (positive affects) do not seem to have been affected by B6 supplementation.

With a sample size of 4, these results are very likely to reflect chance variation. But declines in levels of depression, anxiety, mood swing, water retention, and menstrual pain suggested that further research was needed to examine the possibility that B6 supplementation might be significantly more beneficial than treatment with placebo in ameliorating the negative affect experienced premenstrually and menstrually.

Discussion of Methodology

The pilot study was handicapped due to small sample size and large amounts of variability in measurements, making it difficult to detect what are perhaps subtle effects on mood levels resulting from changes in dietary intake. Variability was introduced by inaccurate calculation of menstrual cycle phase, seasonal changes, random life events affecting within subject variability, age differences, and perhaps differential responses from a variety of premenstrual subtypes. The most serious problem overall seemed to be

the extreme variability of subject responses from cycle to cycle. As might be expected, moods and food intake are highly responsive to external stimuli as well as to menstrual cycle phases. Seasonal influences -- including holidays, weather, and semester endings for students -- can mask more subtle cyclic effects. Using more subjects or investigating individual patterns more carefully by using a longer time period are possible approaches to this problem.

The willingness of subjects to keep records was encouraging. In follow-up interviews, subjects tended to object to the record keeping the least, and to the office visits the most, suggesting that future increases in the amount of home record keeping demands would be feasible. Matching subjects for age and symptom typology would lessen between-subject variability. Recruiting several separate groups of volunteers, each overlapping one month in their participation, would control for some variation due to seasonal changes and academic schedules. It was also found to be important not to rely on retrospective reports on menstrual symptom severity, since this pilor revealed an interesting discrepancy between retrospective reports of symptoms and daily reports of symptoms.

Before formally introducing the methods adopted for this research, it would be useful to summarize comments other researchers in this field have made regarding methodology in addition to the considerations mentioned above.

Defining severity and subclassifying premenstrual changes recently have become more important factors in PMS research. The etiology of the PMS still remains obscure and the major reason for this obscruity may be the wide variation in definition found in this field. The importance of descriptive clarity, reliability of measurement and classification has been highlighted in recent articles (Halbreich, Endicott, Schacht and Nee, 1982; Steiner, Haskett and Carroll, 1980).

Most researchers have used a single definition of premenstrual syndrome that combines different dimensions of change or symptoms that might be seen premenstrually (Halbreich et al., 1982). Moos (1969) has attempted to delineate dimensions of premenstrual change to some extent by factor analyzing common symptomatology (47 items) into 8 symptom clusters: pain, water retention, concentration, behavioral change, autonomic reactions, negative affect, arousal, and a control scale. These scales also allow for some assessment of severity. More recently, Steiner, Haskett and Carroll (1980) have attempted to develop more specific criteria for the premenstrual syndrome. They have developed two scales for rating the severity of premenstrual symptoms based on a study of women with severe premenstrual symptoms and no evidnece of symptoms at other phases of their menstrual cycle, and who had reported premenstrual dysphoria for at least six consecutive cycles. From this data and previous research, these authors established a research diagnostic criteria

for a single premenstrual tension syndrome.

Based on the work of Moos and the authors above, a new assessment, the Premenstrual Assessment Form (PAF) has been developed which attempts to further delineate subtypes of mood, behavior and physical changes be defining inclusion and exclusion criteria with cut-off points to aid in differentiation (Halbreich, Endicott and Schacht, 1982; Halbreich, Endicott, Schacht and Nee, 1982). The diagnostic criteria developed by Steiner, Haskett and Carroll (1980) was used in this research to verify that subjects did, in fact, suffer from the PMS. The PAF was used to further differentiate between symptom typologies when possible.

Consistent with the findings of the pilot study are reports by other researchers that retrospective ratings are frequently discrepant from data obtained daily throughout the menstrual cycle. It has been suggested that the mood of a subject on the date which the rating is undertaken may be responsible for this discrepancy (May, 1976; Sampson and Prescott, 1981). Assessing premenstrual symptoms at a predetermined time can be difficult, since the menstrual cycle is generally somewhat unpredictable from month to month (Sampson and Prescott, 1981). This problem was of major significance in our pilot study. Also, if there is no record of a subject's scores during non-premenstrual phases, there is no way to assess symptom patterns. Daily or every-other-day recording of symptoms appears to be the most reliable method of assessing symptom patterns and degree of severity

(Rossi and Rossi, 1980; Sampson and Prescott, 1981). It is still possible that social stereotypes might influence how subjects rate their moods and symptoms; however, with a controlled experimental design and large enough sample sizes, treatment effects should still appear if they exist.

Sampson and Prescott (1981) recommend self-ratings of moods and physical symptoms over observed behavior or rater assessments. In assessing treatment, observable behavioral events are normally going to be too few in number to indicate response to therapy and there is no agreement about whether measures such as the galvanic skin response and reaction time are related to symptom severity. Rater assessments are usually weakly correlated with self-ratings when based on projective tests and interviews suffer from the same drawbacks as retrospective ratings.

Among the self-rating methods which are available and commonly used are individual checklists using a 3-4 point scale or a 10 cm line scale, more general anxiety and depression scales (Beck depression scale, Zuckerman and Lubin check list), or the Moos Menstrual Distress Questionnaire (MDS), which is specifically designed to assess menstrual cycle symptomatology. The MDQ appears to be the most widely used self-rating scale in PMS research (Sampson and Prescott, 1981).

Statistical problems can result in assessing whether a treatment is better than a placebo when there is a high placebo response, as

in the case of PMS. It is, therefore, necessary to have an untreated cycle before assessing treatment response and to ensure that a subject actually does fit the diagnostic criteria for PMS. This research project has been designed with these considerations in mind.

CHAPTER II

METHOD

Setting

This study was primarily conducted in the home environment. Subjects were asked to keep daily records of their moods and menstrual cycle symptoms. These records were filled out by each subject in the evening to insure, as much as possible, that similar conditions prevailed when ratings of moods and other symptoms were recorded.

One monthly visit to the research office was required. The visits were scheduled according to individual cycles so that they occurred during the mid-cycle phase. Follow-up interviews with participants from the pilot study indicated that subjects were most reluctant to make office visits and least reluctant to keep home records. It was hypothesized that subjects would be more willing to make office visits when they occurred during the mid-cycle phase, rather than during perhaps more difficult menstrual and premenstrual phases of the cycle. The number of appointments were reduced from 3 to 1/month, and record keeping was increased from a total of 12 days/month (divided into four 3-day segments) to daily record keeping. Length of participation was reduced from six months to three months in duration. The goal of these modifications was to maximize the number of participants by minimizing the time commitment, but intensifying record keeping demands.

Subjects

Fifty-five women participated as subjects. Subjects were recruited on a voluntary basis and received $12.00 upon completion of the study. Advertisements were placed in local newspapers and university bulletins. Approximately 110 telephone responses were screened and 83 of these callers were recruited for an initial interview.

Initial in-person research office appointments were scheduled for women who met the following criteria: Absence of oral contraceptives and an I.U.D.; lack of regular medications and any serious medical problems; women had to be planning to stay in the area and not be planning a pregnancy; women could not be taking more than a common daily vitamin supplement; and they must have reported regular recurring premenstrual mood changes that were moderate to severe in nature and noticeable to friends or relatives. Women also had to have a fairly regular menstrual cycle. Women who reported that they occasionally skipped cycles were not allowed to participate. The mean age of the participants was 28, and ages ranged between 17 and 41.

Initial interviews involved further description of symptoms and their timing. These interviews provided an in-depth description of the study to volunteers and details about home record keeping were provided. Women were then asked if they were willing to participate for three monthly cycles. These interviews were conducted by trained undergraduate research assistants.

Of the 74 subjects who agreed to begin the home record keeping, a final sample of 55 subjects completed three months of the study.

This tally represents a 26% dropout rate and is a marked improvement over the 57% dropout rate seen in our pilot study. This improvement suggests that minimizing time commitment and intensifying record keeping did act to maximize the number of participants.

Research Design

A placebo controlled, double-blind procedure was used. In order to avoid crossover effects, as well as minimize time commitment on the part of volunteers, this project did not use a crossover design balanced for crossover effects as was used in the pilot study. Because it was hypothesized that seasonal influences -- holidays, weather, and semester endings for students -- might mask more subtle cycle effects on mood, three separate groups of subjects were run (GI, GII, GIII), each for a three-month period, at three times of the year, such that each group overlapped in duration with the previous group in an attempt to balance for seasonal effects. Figure 1 illustrates when each group of subjects began in the study, the range of duration of their participation, and where they overlapped in time. Holidays and exams, which are thought to be particularly stressful times of the year, are noted in the figure.

All subjects were asked to describe their menstrual cycle symptoms in detail and were asked to describe an average day's food intake. All women were asked to keep baseline home records for a period of one menstrual cycle, beginning on day number one of their next cycle. Volunteers were then asked to take a vitamin B6 supplement or a placebo three times per day, or once with each meal, totalling 150 mg/day

FIGURE 1. Range of duration and overlap of Groups I, II, and III across seasons with holiday, exam, and tylenol scare periods highlighted. In Group I, 50% of the subjects were in the third month of the study during the stressful winter exam and holiday season. In Group II, 59% of the subjects were in the first month, or baseline phase of the study during the holiday season.

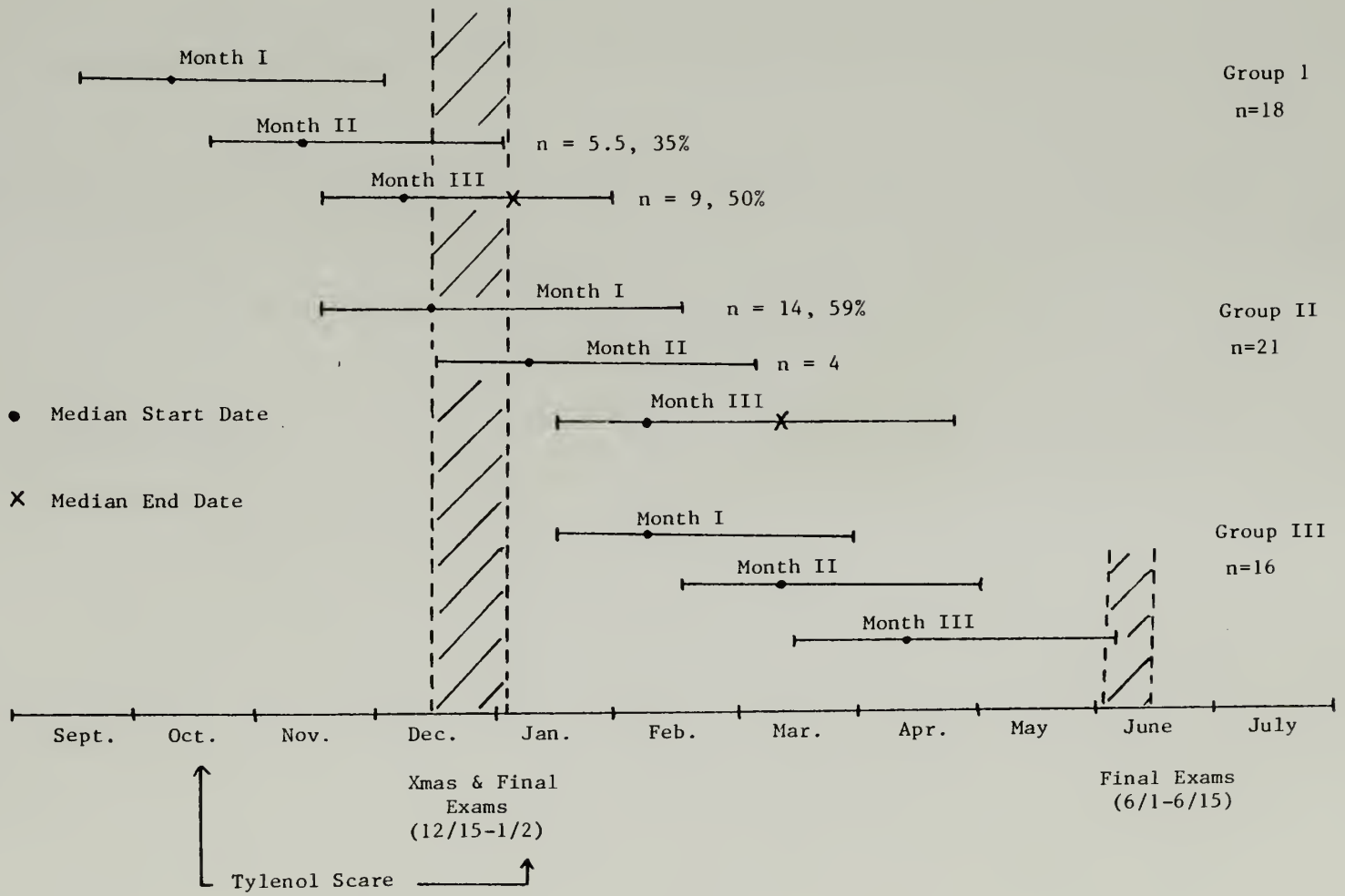

Month I
Month II
n = 5.5, 35%
Month III
n = 9, 50%
Group 1
n=18
Month I
n = 14, 59%
Month II
n = 4
Month III
Group II
n=21
Median Start Date
Median End Date
Month I
Month II
Month III
Group III
n=16
Sept.
Oct.
Nov.
Dec.
Jan.
Feb.
Mar.
Apr.
May
June
July
Xmas & Final
Exams
(12/15-1/2)
Final Exams
(6/1-6/15)
Tylenol Scare

Figure 1

for those on the vitamin B6 supplement. Subjects in Group I received a matching small white tablet form of placebo and vitamin B6. Subjects in Group II and Group III received placebo and vitamin B6 in matching brown gelatin capsules. This aspect of the study was not planned. The serendipity of this procedure led to seeing differential placebo effects, as will be discussed in the results section.

Subjects were blind to the treatment, as were their interviewers. In order to assure uniformity of groups, subjects were matched for age and premenstrual symptomatology as closely as possible and then randomly assigned to receive either the vitamin or placebo. Interviewers were balanced across subjects for age and condition. No significant differences in baseline scores were seen between any of the three groups (Table 1) and demographic characteristics matched as well (see Table 2). Volunteers continued their home record keeping for two cycles while on the placebo or vitamin supplement. At the end of the entire three month period, subjects were told which condition they were under, received payment, and a full description of the study, including a description of their own menstrual cycle variations in mood and other symptoms.

Procedures and Measures

The constructs of interest in this study were mood and physical symptoms. A pretest measure of general menstrual cycle symptoms was given to each subject at the intial interview in order to differentiate between those who fit diagostic criteria for PMS (Steiner, Haskett and

Table 1

Summary of Paired t-Test Comparisons on Baseline Levels between Groups I, II, and III (none significant)

	Group I	Group II	Group III	F-ratio	d.f.
1. Anxiety-Semantic Differential (α=.005):					
Cycle Average					
Ave.	5.185	5.489	4.983	0.840	53
S.D.	1.361	0.879	1.426		
Premenstrual Phase					
Ave.	6.118	6.052	5.726	0.255	53
S.D.	1.730	0.994	2.352		
2. Depression-Semantic Differential (α=.005):					
Cycle Average					
Ave.	4.880	5.285	4.803	1.150	53
S.D.	1.233	0.780	1.221		
Premenstrual Phase					
Ave.	5.655	5.639	5.610	0.004	53
S.D.	1.582	1.030	1.966		
3. All Negative Affect-Semantic Differential (α=.005):					
Cycle Average					
Ave.	5.097	5.545	5.111	1.080	53
S.D.	1.240	0.761	1.306		
Premenstrual Phase					
Ave.	5.941	6.020	5.816	0.083	53
S.D.	1.600	0.914	2.053		
4. Perceived Stress Level-Semantic Differential (α=.005):					
Cycle Average					
Ave.	5.114	4.884	4.659	0.666	53
S.D.	1.345	1.018	1.082		
Premenstrual Phase					
Ave.	5.249	4.540	4.997	0.841	53
S.D.	1.842	1.469	2.010		

Table 1 (continued)

	Group I	Group II	Group III	F-ratio	d.f.
5. Menstrual Pain-MDQ-T (α =.005):					
Cycle Average					
Ave.	2.245	2.108	2.123	0.397	53
S.D.	0.477	0.391	0.680		
Premenstrual Phase					
Ave.	2.278	2.409	2.510	0.438	53
S.D.	0.647	0.701	0.844		
6. Poor Concentration-MDQ-T (α =.005):					
Cycle Average					
Ave.	1.747	1.650	1.576	0.521	53
S.D.	0.467	0.461	.0552		
Premenstrual Phase					
Ave.	1.963	1.841	1.906	0.141	53
S.D.	0.731	0.585	0.880		
7. Behavior Changes-MDQ-T (α =.005):					
Cycle Average					
Ave.	1.717	1.571	1.513	0.929	53
S.D.	0.501	0.320	0.552		
Premenstrual Phase					
Ave.	1.796	1.682	1.677	0.194	53
S.D.	0.658	0.547	0.776		
8. Autonomic Symptoms-MDQ-T (α =.005):					
Cycle Average					
Ave.	1.320	1.344	1.374	0.078	53
S.D.	0.394	0.374	0.445		
Premenstrual Phase					
Ave.	1.500	1.545	1.531	0.028	53
S.D.	0.454	0.722	0.591		

Table 1 (continued)

	Group I	Group II	Group III	F-ratio	d.f.
9. Water Retention-MDQ-T (α =.005):					
Cycle Phase					
Ave.	2.187	2.237	2.218	0.042	53
S.D.	0.368	0.476	0.747		
Premenstrual Phase					
Ave.	3.056	3.318	3.177	0.376	53
S.D.	0.802	1.041	0.995		
10. Negative Affect-MDQ-T (α =.005):					
Cycle Phase					
Ave.	2.354	2.328	2.225	0.189	53
S.D.	0.693	0.594	0.662		
Premenstrual Phase					
Ave.	2.583	2.591	2.604	0.003	53
S.D.	0.845	0.766	0.935		
11. Positive Affect-MDQ-T (α =.005):					
Cycle Phase					
Ave.	2.501	2.349	1.978	2.752	53
S.D.	0.653	0.650	0.699		
Premenstrual Phase					
Ave.	2.343	2.227	1.719	3.137	53
S.D.	0.942	0.703	0.632		
12. Lack of Control-MDQ-T (α =.005):					
Cycle Phase					
Ave.	1.297	1.183	1.189	0.615	53
S.D.	0.495	0.267	0.240		
Premenstrual Phase					
Ave.	1.380	1.250	1.313	0.231	53
S.D.	0.832	0.370	0.544		

Table 2

Mean Values of Demographic Variables Compared Between Groups I, II, and III, including Mean Values for Study Drop-Outs.

	Completers			Drop-Outs		
	Group I (n=18)	Group II (n-21)	Group III (n-16)	Group I (n=6)	Group II (n=7)	Group III (n=6)
Age	28.9	26.7	28.5	29.0	30.0	32.0
Yrs. of Education	16.1	14.9	14.8	16.0	16.0	15.6
Income	6,200	7,388	9,800	5,600	9.500	8.833
No. of Children	.5	.4	.9	.8	.8	1.3
Employed/Students+	10 EM 8 ST	11 EM 7 ST	13 EM 2 ST	3 EM 3 ST	4 EM 2 ST	5 EM 1 ST
Caffeine Intake (cups)	2.2	4.0	2.9	3.0	4.0	3.2
Alcohol Intake*	1.7	1.4	1.4	1.0	.6	1.2
Placebo (PL) / B6 (TX)	9 PL 9 TX	8 PL 13 TX	9 PL 7 TX	3 PL 3 TX	6 PL 1 TX	3 PL 3 TX
Onset of symptoms (days prior to menses)	6.5	8.3	6.9	5.0	7.0	5.8
Length of menses	5.9	4.6	5.4	5.5	5.0	5.5

*1=Low, 2=Moderate, 3=Moderate +, 4=Excessive
+ EM = employed; ST = student

Carroll, 1980) and to further differentiate between premenstrual symptom typology (see Appendix A).

Initial assessment included the Premenstrual Assessment Form (PAF) developed by Halbreich et al. (1981). The PAF asks a woman to rate her last three cycles overall, to rage only the premenstrual phase of those cycles, and to rate the degree of symptom change from normal levels. The PAF contains 94 items which enable it to make fine distinctions between symptoms. This form was used for initial assessment, subtyping, and for matching subjects in this study.

An initial interview designed for the purposes of this study was also administered. This interview was conducted by research assistants and asked that each woman describe a typical day's food intake, the onset, duration, severity and type of menstrual symptoms they regularly experienced. They were asked if these symptoms peaked at any point, and when symptoms ended (see Appendix A).

During the three months of the study, each woman rated her mood on a daily basis and her menstrual symptoms every other day. The Moos Menstrual Distress Questionnaire, form T (Moos, 1969) was used to measure change in menstrual symptoms. It allows a women to describe the menstrual symptoms she experiences on a daily basis. A list of 47 symptoms commonly experienced menstrually and premenstrually are each rated in severity on a 1-6 scale. This scale provides a measure of absoluate degree of symptoms in contrast to the PAF, which attempts to measure degree of symptom change from normal baseline levels. The MDQ-T items have been factor analyzed and fall into eight symptom subgroups: pain, water retention, concentration, behavior change, negative affect, arousal (positive affect), autonomic reactions, and

control. The symptom subgroups of major interest in this study were negative affect, arousal, pain, and water retention. The pain scale reflects symptoms usually associated with dysmenorrhea, whereas the negative affect scale reflects symptoms generally associated with the PMS (see Appendix A).

A semantic differential form designed to rate levels of anxiety, depression and stress was administered daily to each woman. This checklist contains ten items selected to reflect depressive moods, five items to reflect anxiety, and one item which rated how stressful the day was perceived to have been. Adjectives which are polar opposites of each other were separated by a 10cm line (Osgood, Suci, Tannenbaum, 1957). Women were asked to indicate how they felt on that day by marking along the line in the place that best described their mood for the day. Adjectives reflecting depressive mood were selected from the Zung Self-Rating Depression Scale (Zung, 1965) and the Radloff Depression Scale (Radloff, 1977). Items reflecting anxiety were selected from the State-Trait Anxiety Inventory (STAI, Form X1) designed by Speilberger, Gorsuch and Lushane (1968). To avoid a halo affect in the daily mood measure, five separate alternating forms were used, each containing the same items, but counterbalanced and scrambled in order. Subjects were told that each form was not identical to the other and that care should be taken in filling them out (see Appendix A).

Women were asked to return all unused pills at the end of each month's cycle, so that compliance could be assesses by pill counts.

Postcards were mailed to remind subjects to return forms by mail on a bi-weekly basis, and telephone reminders were made before each scheduled office appointment. Exact rate of compliance could not be obtained, since pill counts were not completed on every subject. Estimates of compliance were based on completed pill counts only. These estimates are fairly consistent across groups (Group I = 86.8%; Group II = 87.5%; and Group III = 74.5%) with Group III appearing to be the least compliant.

Women were asked to fill out a post-study questionnaire and received a follow-up letter (see Appendix B).

CHAPTER III

RESULTS

Many authors assess the significance of changes in symptoms by subdividing the menstrual cycle into phases and adding symptom scores for each phase together. Comparisons are then made between scores (Sampson and Prescott, 1981). Phase definition, however, differs often from study to study, varying in number from four to seven. Rossi and Rossi (1980), after an extensive review of the literature and an analysis of their own preliminary data, chose to divide a cycle into five phases. They assumed a 28-day cycle and made appropriate adjustments for data analysis when cycles exceeded or did not reach this standard length. The criteria for phase definition, as outlined by Rossi and Rossi, includes every day of the menstrual cycle, and separates these days into a menstrual, follicular, ovulatory, luteal, and premenstrual phases. These divisions resulted from their findings that mood patterns unique to the luteal phase existed and that premenstrual and menstrual phase mood profiles were less consistent than expected. Their protocol for phase definition was used to analyze data generated from this study.

Group Equivalence

In order to assess whether there were any significant differences between Groups I, II, and III at baseline, paired t-test comparisons were made on each construct of interest. These constructs included a

semantic differential measure of Anxiety, Depression, overall Negative Affect, and Perceived Stress, as well as MDQ-T measures of Menstrual Pain, Poor Concentration, Behavior Change, Autonomic Symptoms, Water Retention, Negative Affect, Positive Affect, and Perceived Lack of Control. No significant differences in these measures were found at baseline between Groups I, II, and III (see Table 1). Comparison of demographic variables between groups did not show marked differences (see Table 2), nor were there marked differences in compliance rates between groups as noted in the Method section. These data indicate that Groups I, II, and III were equivalent in composition, compliance, and in degree and duration of premenstrual symptoms.

Effect of Vitamin B6

In order to assess the effectiveness of vitamin B6 on ameliorating premenstrual symptoms, an analysis was conducted on each individual group. In Group I, there was a significant effect of vitamin B6 on Poor Concentration during the premenstrual phase of cycle three ($F=19.90$; $p < .005$). In Group I, effects which approached significance were seen premenstrually in cycle number three in Negative Affect ($F=14.40$; $p < .01$), Behavior Change ($F=13.40$; $p < .01$), and Autonomic Symptoms ($F=11.27$; $p < .01$). In Group II, there was a significant effect of B6 on Poor Concentration during the follicular phase of cycle number two ($F=41.65$; $p < .001$). A covariance analysis adjusting for baseline values was conducted using a significance level of $p < .005$ ($F_{1,8}=14.69$) in order to control for variations that might exist across groups in

baseline levels of menstrual symptoms. When data from Groups I, II, and III were combined (n=56), there were no significant effects revealed by the analysis of covariance.

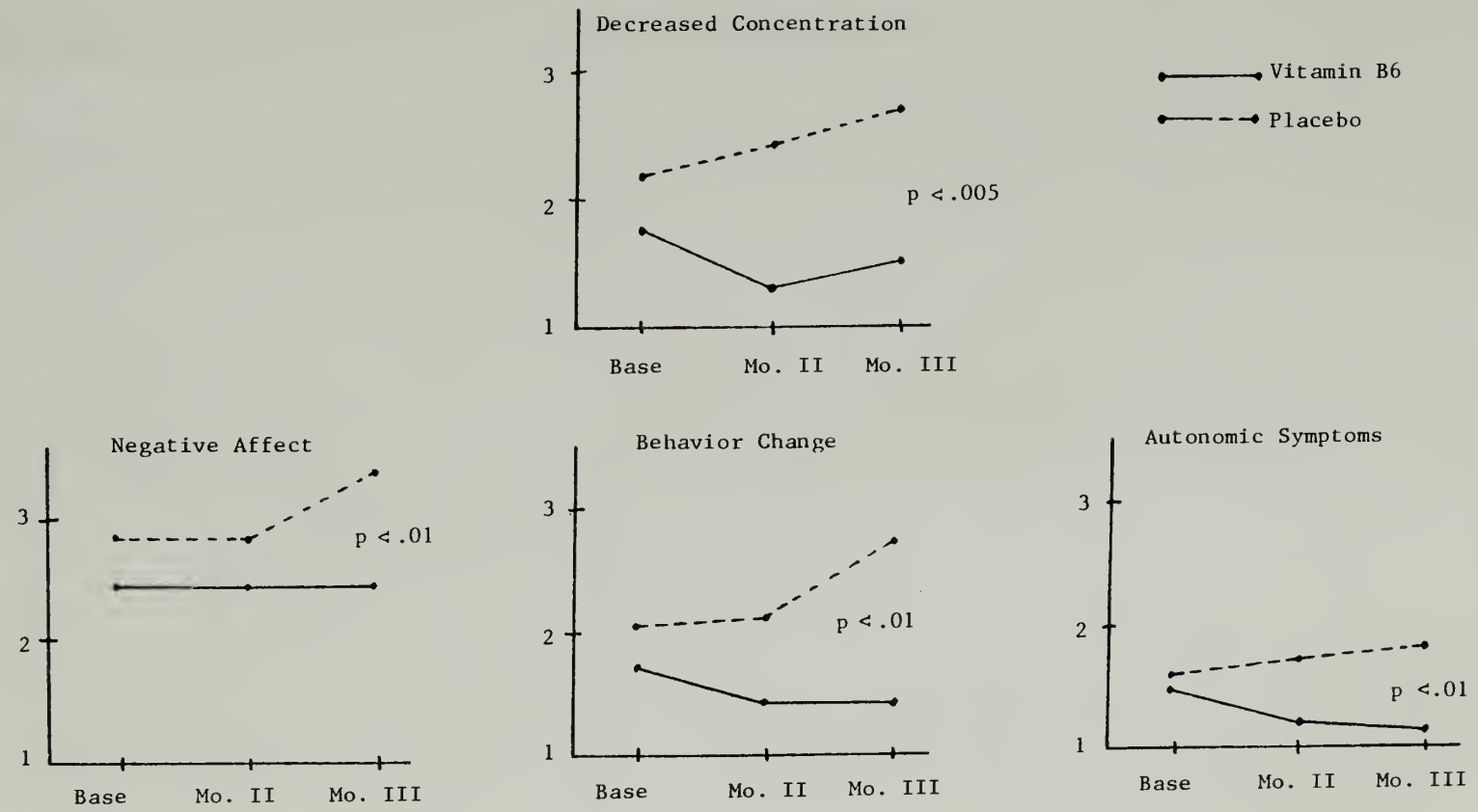
Three significant results ($p < .005$) and three results nearing signifiance ($p < .01$) were obtained out of 72 tests (2 cycles x 3 groups x 12 measures). At the $p < .01$ level, one would expect .7 significant results by chance and .35 significant results by chance at the $p < .005$ level; therefore, it is unlikely that the six results mentioned above were obtained by chance. Four of the six results were seen in the premenstrual phase of cycle number three in Group I. In three of these four cases, the vitamin B6 condition remained constant in measures across time. In all four cases, the placebo condition scores increased (or worsened) in value over time. It is also interesting to note that in three out of the six findings, the measure which was affected was Poor Concentration as measured by the MOOS menstrual distress questionnaire. The size of the effects in Group I were relatively large. Based on a six-point scale, the mean level of Behavior Change noted in Group I during the premenstrual phase of cycle three was 2.7 in the placebo versus 1.4 in the B6 condition. Similar size differences were seen for Autonomic Symptoms ($\bar{X}_{placebo} = 1.8$ versus $\bar{X}_{B6} = 1.1$); Negative Affect ($\bar{X}_{placebo} = 3.3$ versus $\bar{X}_{B6} = 2.4$); and Poor Concentration ($\bar{X}_{placebo} = 2.7$ versus $\bar{X}_{B6} = 1.5$) in Group I. These findings are summarized in Table 3 and Figure 2 . Figure 2 suggests that vitamin B6 was more effective in improving Poor Concentration, Autonomic Symptoms, Water Retention, Perceived Stress Levels, Behavior Change, and in increasing

Table 3

Summary of Paired F-Tests with Baseline Covariate

Group	Cycle	Phase	Category	F-Test d.f.	F-Test Ratio	F-Test Prob.
I	3	Premenstrual Phase	1. Behavior Change	1,8	13.40	.01
			2. Autonomic Symp.	1,8	11.27	.01
			3. Negative Affect.	1,8	14.40	.01
			4. Poor Concentration	1,8	19.90	.005
II	2	Luteal Phase	1. Poor Concentration	1,8	57.71	.001
III	2	Follicular Phase	1. Poor Concentration	1,7	41.65	.001

FIGURE 2. Paired t-tests which were significant or approached significance in Group I. This figure illustrates that the effect of vitamin B6 in Group I was to hold premenstrual symptoms at an even level while symptoms worsened under the placebo condition. It also illustrates that this effect occurred in the third month.



Group I. Premenstrual Phase Averages

Figure 2

Positive Affect than the placebo in Group I when Mean Change Scores are compared. Mean Change Scores [Baseline -(Mo 2 + Mo 3)/2] illustrate the direction and size of change in scores between the baseline and treatment phases of the study. A pattern for direction and size of change in symptoms can be discerned from a visual inspection of Mean Change Scores. Again, in this case, Mean Change Scores show that B6 was more effective than placebo as a treatment in Group I. Figure 2 illustrates that the effect of B6 on Poor Concentration during the premenstrual phase of cycle three in Group I is the result of placebo scores having increased dramatically, while B6 scores remained fairly constant during the third cycle. This trend suggests that B6 perhaps played a "protective role" by preventing a rise in Poor Concentration which otherwise might have occurred. Cycle three of Group I corresponded with a potentially stressful time of the year for both female students and employed women, winter finals and holiday season (see Figure 1). In Group I, 50% of the subjects were in cycle three of the study during winter exams and holiday season. Subjects reported a higher Perceived Stress Level during this period when scores were compared to theoretically less stressful periods of time. In Group I, the mean Perceived Stress Level score for the period between 12/15/82-12/26/82 was 5.47 as compared to 4.89 for the period between 11/30-12/15 (an 0.6 point difference on a 1-10 point scale). In Group II, the mean Perceived Stress Level score for the period between 12/15-12/26 was 5.35 as compared to 4.5 for the period between 1/15/83-1/26/83 (an 0.85 point difference on a 1-10 point scale). These averages are consistent with the suggestion that

FIGURE 3. *Mean change scores between baseline and treatment phase of the B6 condition in Group I and placebo conditions of Groups II and III (Premenstrual Phase). This figure illustrates that the placebo in Groups II and III had a larger effect on premenstrual symptoms than vitamin B6 had on premenstrual symptoms in Group I subjects.

$$\overline{X}_{change} = \text{Baseline} - [(\text{Month 2} + \text{Month 3}) \div 2]$$

*A change in the negative direction indicates improvement in intensity of premenstrual symptoms in all measures except positive affect.

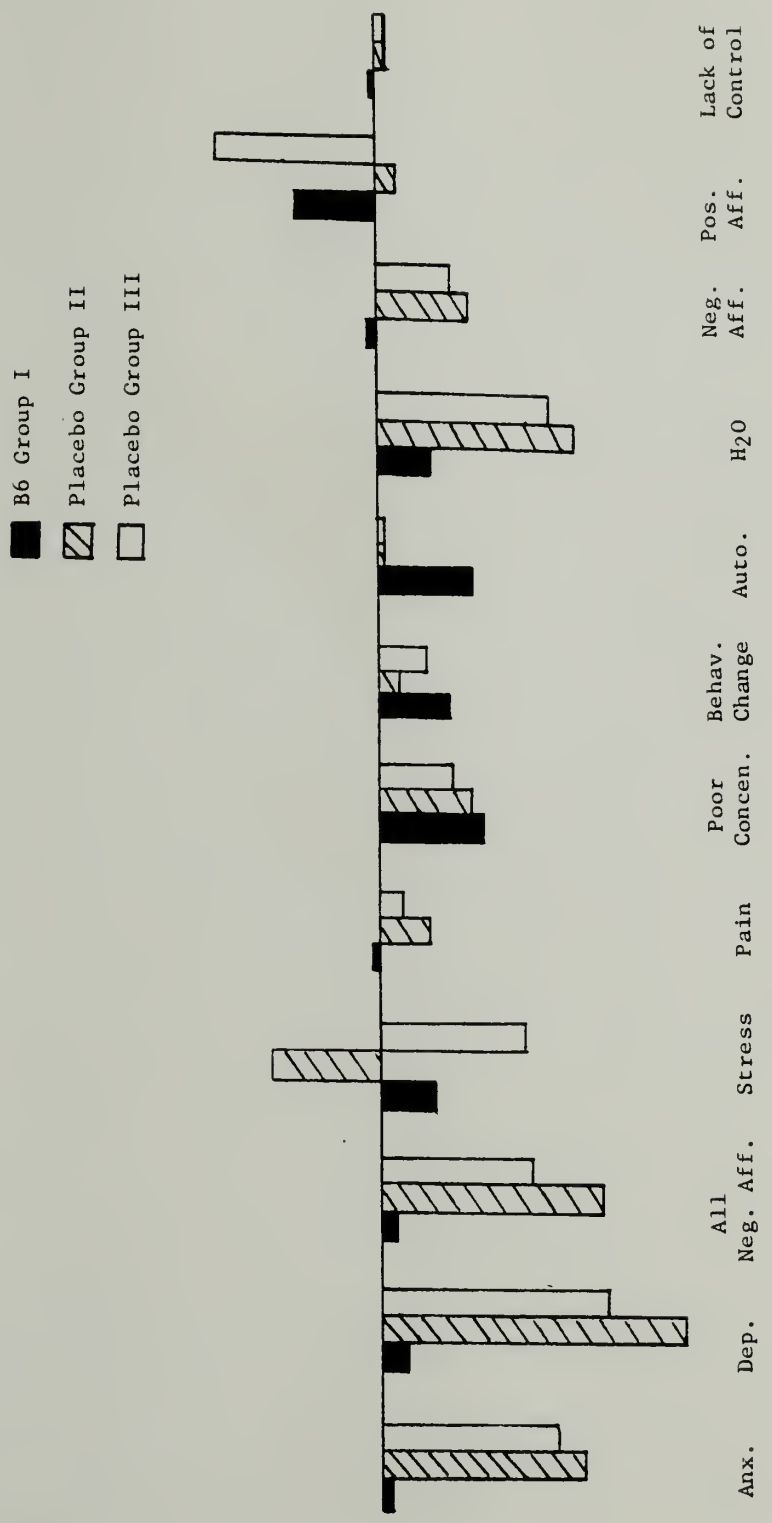

B6 Group I
Placebo Group II
Placebo Group III
Anx.
Dep.
All Neg. Aff.
Stress
Pain
Poor Concen.
Behav. Change
Auto.
H2O
Neg. Aff.
Pos. Aff.
Lack of Control

Figure 3

subjects in both Groups I and II perceived themselves to be under more stress during the winter exam and holiday season than other periods of the year.

Effect of Placebo

Paired t-test comparisons were made to determine whether there were significant differences between Group I, II and III in the effectiveness of the placebo. This was an important question, particularly because the perceptual characteristics of the placebo (and vitamin) varied between Groups I, and Groups II and III. Group I received the placebo and vitamin in matching tablet form. Groups II and III received placebo and vitamin in matching capsule form. Paired t-tests revealed no significant differences in the effect of placebo among Groups I, II and III. Nevertheless, the placebo effect in Groups II and III is greater than the effect of vitamin B6 in Group I on lessening the intensity of premenstrual symptoms in 10 out of 12 measures when Mean Change Scores are compared ($p = .00013$; for the chance of Group I scoring worst on 10 out of 12 measures*). Mean Change scores in Figure 3 suggest that the placebo in Groups II and III was more effective in improving Anxiety, Depression, Negative Affect, Perceived Stress Levels, Water Retention, and Positive Affect than vitamin B6 in Group I. This trend is consistent with the hypothesis that differential placebo effects occurred in this study. The capsule form of placebo delivery used in Groups II and III achieved a greater effect than the tablet form of vitamin B6

---

*Chance of 10 + chance of 11 + chance of 12 = $\frac{55}{3^{12}} + \frac{12}{3^{12}} + \frac{1}{3^{12}} = .00013$)

administration in Group I. It is also consistent with the hypothesis that vitamin B6 is less effective in ameliorating premenstrual symptoms than placebo in capsule form.

CHAPTER IV

DISCUSSION

In this dissertation, several goals were addressed: (1) to determine whether dietary supplements of vitamin B6 can exert a beneficial effect on premenstrual symptoms; (2) to develop a general methodology suitable for studying the menstrual cycle; (3) to begin the delineation of particular variables that warrant further research; and (4) to develop a vigorously controlled method for testing alternative treatments for premenstrual symptoms. A significant amount of progress has been made toward each of these goals.

Data from this study indicate that vitamin B6 may improve premenstrual symptoms under specific conditions which will be discussed below. The hypothesis that vitamin B6 may exert beneficial effects over time on physiological functioning and premenstrual dysphoria was not supported by combined analyses of data from all three groups studied. Nevertheless, a significant effect of vitamin B6 on improving Poor Concentration was seen premenstrually in Group I. Also seen in Group I were beneficial effects during the premenstrual phase of vitamin B6 approaching significance on measures of Behavior Change, Autonomic Symptoms, and Negative Affect. Similar effects on premenstrual symptoms were not replicated in Groups II and III; however, in Group II a significant effect of B6 on Poor Concentration was seen during the luteal phase of cycle number two. In Group III, a significant

effect of B6 was seen during the follicular phase of cycle number two on Poor Concentration. Differences in the premenstrual phase findings between Groups I, II and III cannot be explained by variations in compliance, demographics, or baseline measurement levels.

Differential placebo effects could account for Group I differing from Groups II and III. Perceptual characteristics of a placebo can lead to differential levels of effectiveness, as well as differential duration of placebo effectiveness. It is known that perceptual characteristics of drug preparation can lead to changes in expectancies regarding the efficacy of medications (Bukalew and Ross, 1981). Both color and size of preparation can affect the expected drug action and, therefore, its efficacy (Bukalew and Ross, 1981; Bukalew and Coffield, 1982a; Jacobs and Nordan, 1979). Capsule preparations were seen as more powerful than a tablet, and white tablets, which resemble the common aspirin (like that used in Group I), are perceived as less powerful than other colored tablets or capsules (Bukalew and Coffield, 1982a). This finding is more pronounced among whites than among blacks (Bukalew and Coffield, 1982b). The magnitude (and duration) of placebo affect may have been increased in Groups II and III, both of which received capsules rather than tablets, as in Group I. Data from Mean Change score comparisons support the hypothesis that there was a larger placebo effect in Groups II and III (see Figure 4), and in addition, that this effect was greater than the effect of vitamin B6 in Group 1 (see Figure 3). It is possible that a true effect of B6

FIGURE 4. *Mean change scores between baseline and treatment phases of the placebo condition. (Premenstrual phase comparisons only). This figure illustrates that in 10 cases out of 12, the placebo effect in Groups II and III was greater in reducing symptoms than that in Group I.

*A change in the negative direction indicates improvement in intensity of premenstrual symptoms in all measures, except positive affect.

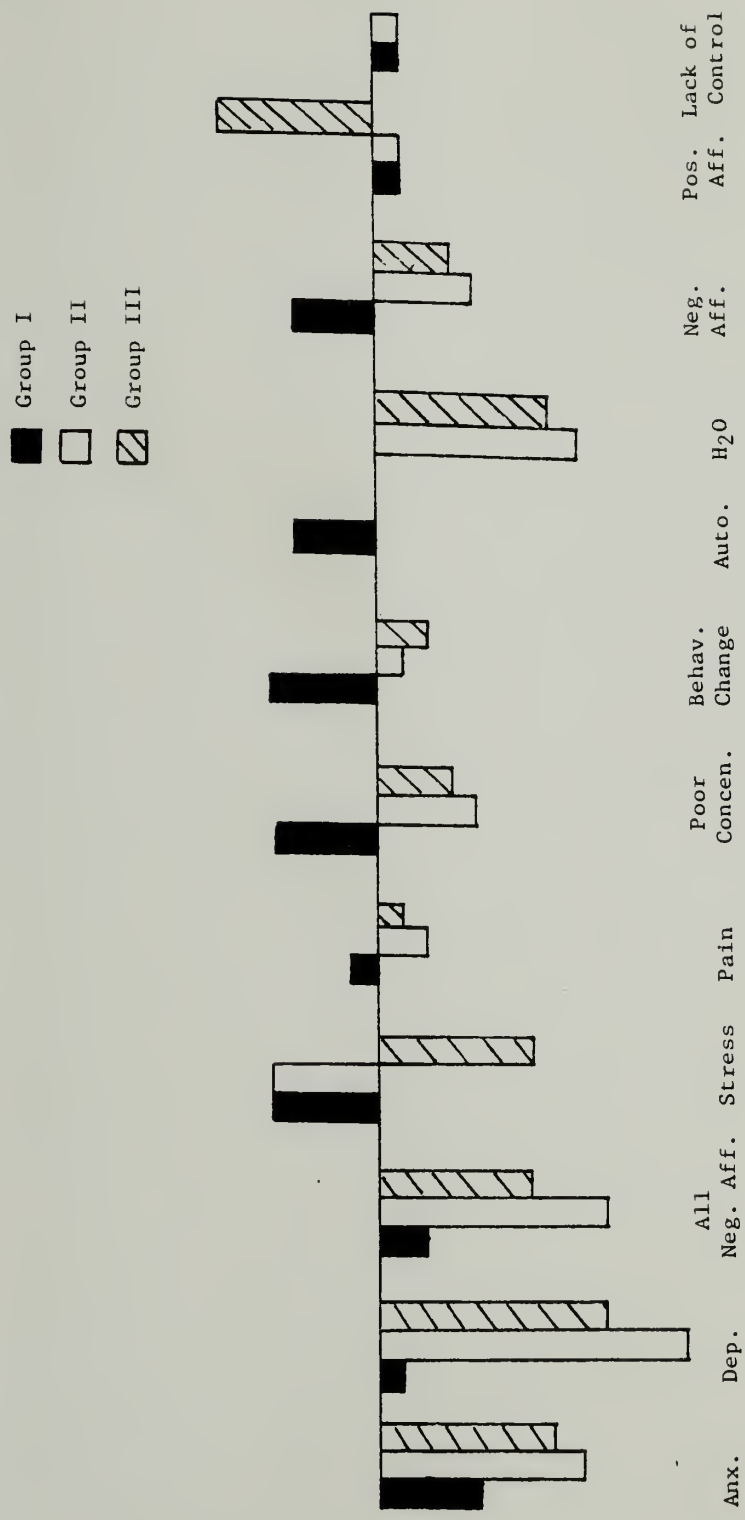

Group I
Group II
Group III
Anx.
Dep.
All Neg. Aff.
Stress
Pain
Poor Concen.
Behav. Change
Auto.
H_2O
Neg. Aff.
Pos. Aff.
Lack of Control

Figure 4

existed in all three groups, but was apparent only in Group I premenstrually (see Figure 5) when compared to a relatively less effective placebo due to its tablet form of preparation. A small true effect of B6 in Groups II and III could have been overshadowed by a larger magnitude placebo effect resulting from the use of capsules. Whatever the case, data from this study indicate that a placebo in capsule form is more effective than vitamin B6 in white tablet form. This finding does not, however, rule out the possibility that physiological variables play a role in the etiology of premenstrual symptoms. The high placebo response rate in premenstrual research (Day, 1979; Sampson, 1976; Steiner and Carroll, 1977) suggests that social-attitudinal factors may play an important role in the development and expression of premenstrual symptoms. It is also possible, however, based on the physiological literature, that somatic factors play an equally large role in influencing PMS. The most useful model for the study of PMS is one that conceptualizes a complex, and perhaps circular, pattern of interaction and feedback between psychological-social and physiological variables, as it is likely that psychological and somatic factors are inseparable and circular in their ability to influence one another. To this author's knowledge, there has been no systematic attempt to examime the true course and potential attenuation of placebo responses compared to active treatment (Rubinow and Roy-Byrne, 1984). Further research is warranted in order to assess the comparative usefulness of vitamin B6 over placebo in treating premenstrual symptoms, as a placebo in capsule form was more effective than vitamin

FIGURE 5. *Mean change scores compared between placebo and B6 conditions in Group I. (Premenstrual phase comparisons only.) This figure illustrates that in Group I, vitamin B6 was more effective than placebo in decreasing premenstrual symptoms in 6 out of 12 variables.

*A change in the negative direction indicates an improvement in intensity of premenstrual symptoms in all measures, except positive affect.

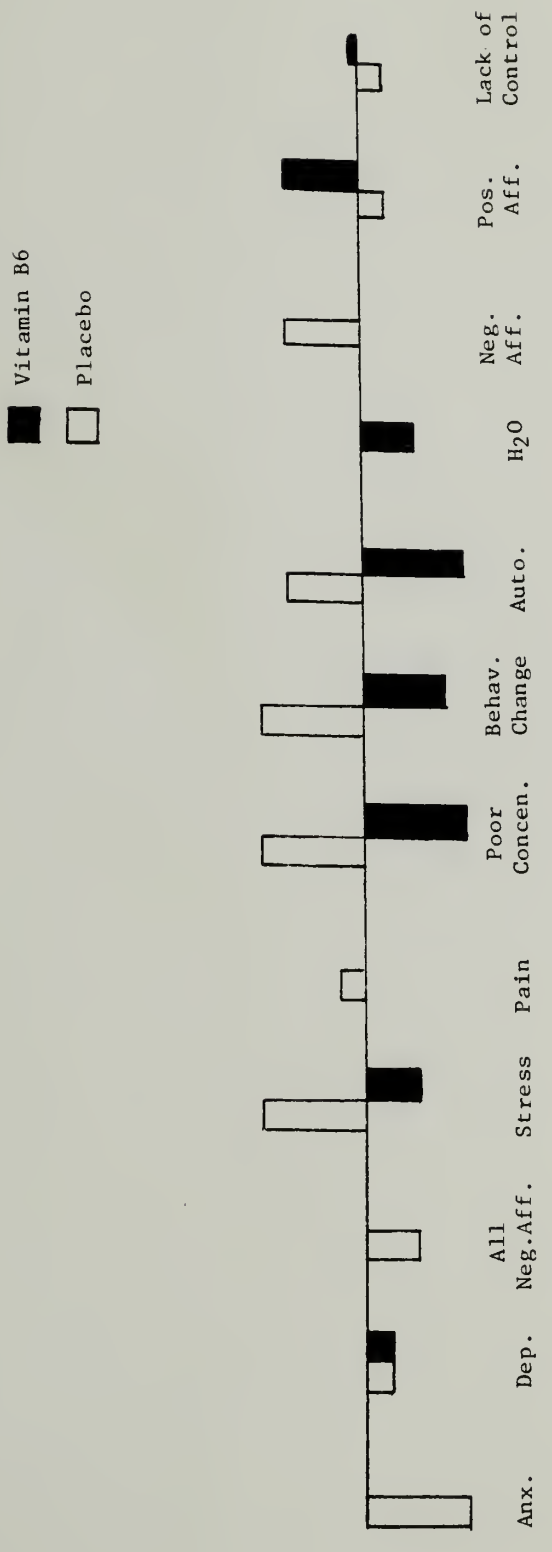

Vitamin B6
Placebo
Anx.
Dep.
All Neg.Aff.
Stress
Pain
Poor Concen.
Behav. Change
Auto.
H2O
Neg. Aff.
Pos. Aff.
Lack of Control

Figure 5

B6 in tablet form in this study.

The discrepancies between premenstrual phase findings in Group I and Groups II and III might also be the result of stressful seasonal events/holidays/final exams. Seasonal effects could account for cycle three differing from cycles one and two in Group I. As discussed in the Results section, in Group I, cycle three, an increase in Negative Affect, Poor Concentration, Behavior Change, and Autonomic Symptons were seen premenstrually in the placebo condition, but not in the vitamin B6 condition (see Figure 2). It is only during the third cycle that B6 is more effective than placebo. Since, for most subjects in Group I, the third cycle coincided with either academic finals or Christmas/holiday events (see Figure 1), it is possible that vitamin B6 may have acted in a protective fashion during stressful periods by preventing an increase in premenstrual dysphoria which otherwise would have occurred. Indeed, data from this study indicate that subjects in Group I were experiencing greater levels of stress during the third cycle (see Results section). Groups II and III may have differed from Group I because treatment phases did not coincide with stressful time periods. If vitamin B6 is only effective in a "protective" fashion during times of increases stress, effectiveness of vitamin B6 supplementation would not appear during less stressful time periods such as those during which Groups II and III were run, thus accounting for the discrepancies between Groups II and III and Group I in this study.

It is thought that greater amounts of vitamin B6 may be utilized by the body during stressful periods and it is a common recommendation among lay people to use vitamin B complex supplements during times of stress. However, to this author's knowledge, there have been no studies directly assessing the effects of environmental/psychological stressors on vitamin B6 status. It is known that psychological stress can result in faster transit times through the stomach and small intestine in humans (Cann, Read, Cammack, Childs, Holden, Kashman, Longmore, Nix, Simms, Swallow and Weller, 1983). Increased transit times might result in decreased absorption of nutrients. The requirement for B vitamins might be increased when metabolism is speeded up, as in muscular exercise, exposure to cold (Bourne, 1948-49), or possibly in response to environmental stressors. Gyorgy (1938) suggested that susceptibility to chilblains may be a function of pyridoxine reserves in the body, and that supplementation with vitamin B6 could aid in the prevention of chilblains. Changes in the status of other nutrients in response to stress have been documented. Stress is thought to alter the ratio of carnitines (a natural constituent of animal tissue involved in lipid metabolism), and it has been postulated that exogenous carnitines may provide protection against heart damage during periods of stress (Fanelli and Tenuta, 1981). Vitamin B6 status may eventually be linked to increased susceptibility to dysphoria during times of stress. Indeed, data from this study suggest that vitamin B6 may ameliorate premenstrual symptoms, specifically during times of stress.

A separate, but equally interesting finding in this study, was that vitamin B6 improved Poor Concentration levels in all three groups of subjects studied. Interestingly, these changes occurred in different menstrual cycle phases across groups. In Group I, vitamin B6 improved concentration levels premenstrually; in Group II, concentration was improved in the luteal phase; and in Group III, it was improved in the follicular phase of the cycle by vitamin B6 supplementation. It may be that concentration levels are more responsive to vitamin B6 supplementation than mood or other physiological parameters. Data from this study are consistent with the hypothesis that vitamin B6 may improve concentration levels regardless of menstrual cycle phase.

In summary, results from this study suggest that the beneficial effects of vitamin B6 on menstrual symptoms include: 1) a general overall ability to improve concentration levels regardless of menstrual cycle phase, and 2) an ability to improve some premenstrual symptoms (including dysphoria) during periods of increased stress. Ironically, data from this study also suggest that a placebo in capsule form can be more effective than vitamin B6 in tablet form in ameliorating premenstrual symptoms.

Progress was made toward the development of a general methodology suitable for studying the menstrual cycle and for testing alternative treatments for premenstrual symptoms in a vigorously controlled manner. Most research on PMS, including the pilot version of this dissertation, has suffered from variability introduced by inaccurate calculation of menstrual cycle phase, seasonal changes, random life events affecting

within subject variability, age differences, and perhaps differential responses from a variety of premenstrual symptom subtypes. This study effectively avoided miscalculation of menstrual phases due to irregularities in cycle length by shifting periodic record keeping to daily sampling through record keeping. The study also insured that miscalculations did not interfere with proper timing of vitamin intake by providing daily supplements to subjects throughout the entire treatment phase. The effects of seasonal weather changes were controlled by running separate groups of subjects which overlapped one month in participation over the academic year. Variation within subjects which can be introduced by random life events was addressed through increasing the number of subjects who were able to participate, by decreasing the length of time required for participation, and reducing office visits to a minimum (one visit/month). Subjects were matched for age and type of symptom using a diagnostic criteria developed by Steiner, Haskett and Carroll (1980). Indeed, these changes in methodology increased the number of women who participated in the study (the sample sizes in each group of this study were larger than others reported in the literature examining the effects of vitamin B6), avoided entirely the possibility of miscalculating menstrual cycle phases, and theoretically should have reduced any variability that might result from differential responses from various premenstrual symptom subtypes.

The process of delineating particular variables that warrant further research was begun. Serendipitously, the procedures used in this study highlighted the importance of avoiding differential placebo effects and controlling for the effects of emotionally stressful times of the year as other factors which can introduce unwanted variability. Changes in future research designs are indicated. Differential placebo effects could easily be avoided by matching placebo preparation form across conditions and groups. Use of a less effective form of placebo (tablet) would be recommended in order to determine whether vitamin B6 supplements have any effect, regardless of the strength of that effect and its clinical significance. The use of tablets would avoid the possibility that subtle effects of vitamin B6 might be overshadowed by larger placebo effects. Use of maximum strength form of placebo (capsule) would be recommended in order to determine the clinical significance of vitamin B6 treatment, or whether a placebo can be equally or more effective than vitamin B6. It would also be important to run a parallel control group which received placebo and vitamin B6.

Seasonal effects, or the effects of emotionally stressful time periods could be controlled by the use of a third No Treatment control group, and through the use of more comparable subjects, i.e., only students or only employed women. Replicating the study with systematic timing of data collection would allow for comparisons to be made between stressful periods and non-stressful time periods or seasons. It would be important to include more careful and direct measures of

stress levels. Ideally, subjects should be followed throughout the entire year. Data collected during January, February and March, as well as during June, July and August, would represent less stressful periods (avoiding exams and holidays). Data gathered during June, July and August would also avoid the potentially stressful winter months. If an effect of season were found, further research comparing the effectiveness of tablet versus capsule form of placebo and vitamin B6 would be needed.

In general, it would be important to increase the length of baseline measurements only if it were necessary to address variability between cycles in symptoms, since a longer study would reduce the number of subjects who would continue to completion, thus reducing the representativeness of any data gathered as it becomes more biased through self-selection, i.e., only representing those subjects who are willing to participate for longer periods of time.

This dissertation has determined that vitamin B6 may have a beneficial effect on premenstrual symptoms during stressful periods of time, and that vitamin B6 may improve concentration levels throughout the menstrual cycle. It has also determined that a capsule form of placebo may be more effective than vitamin B6 in tablet form in treating premenstrual symptoms. Several improvements in methodology introduced in this study have resulted in the ability to sample a larger number of subjects and to minimize the introduction of unwanted variability. A more rigorously controlled method for testing alternative treatments for premenstrual symptoms has been developed, and particular variables that warrant further research have been delineated.

REFERENCES

Abraham, G.E. and Hargrove, J.T. (1980) Effect of vitamin B6 on premenstrual symptomatology in women with premenstrual tension syndromes: A double-blind crossover study. Infertility, 3, 155-165.

Abramowitz, E.S., Baker, A.H. and Fleischer, S.F. (1982) Onset of depressive psychiatric cases and the menstrual cycle. American Journal of Psychiatry, 139 (4), 475-478.

Adamopoulos, D.A., Loraine, J.A., Lunn, S.F., Coppen, A.H. and Daly, R.J. (1972) Endocrine profiles in premenstrual tension. Clinical Endocrinology, 1, 283-292.

Adams, P.W., Wynn, V., Seed, M. and Folkard, J. (1974) Vitamin B6, depression, and oral contraception. The Lancet, 2, 516-517.

Adams, P.W., Wynn, V. Rose, D.P., Seed, M., Folkard, J., and Strong, R. (1973) Effect of pyridoxine hydrocholoride (vitamin B6) upon depression associated with oral contraception. The Lancet, 1, 897-904.

Backstrom, T. and Aakvaag, A. (1981) Plasma prolactin and testosterone during the luteal phase in women with premenstrual tension syndrome. Psychoneuroendocrinology, 6 (3), 245-251.

Backstrom, T. and Carstensen, H. (1974). Estrogen and progesterone in plasma in relation to premenstrual tension. Journal of Steroid Biochemistry, 5, 257-260.

Berlin, F.S., Bergey, G.K., and Money, J. (1982) Periodic psychosis of puberty: A case report. American Journal of Psychiatry, 139, 119-120.

Berstein, B.E. (1977) Effect of menstruation on academic performance among college women. Archives of Sexual Behavior, 6 (4), 289-296.

Biskind, M.S., Biskind, G.R., and Biskind, L.H. (1944) Nutritional deficiency in the etiology of menorrhagia, metrorrhage, cystic mastitis, and premenstural tension. Surgery, Gynecology and Obstetrics, 78, 49-57.

Blank, A.M., Goldstein, S.E., and Chatterjee, N. (1980) Premenstrual tension and mood change. Canadian Journal of Psychiatry, 25, 577-585.

Block, E. (1960) The use of vitamin A in premenstrual tension. Acta Obstetrica et Gynaecologica Scandinavica, 39, 586-592.

Bourne, G.H. (1948-49) Vitamins and muscular exercise. British Journal of Medicine, 2, 261-263.

Bukalew, L.W. and Ross, S. (1981) Relationship of perceptual characteristics to efficacy of placebos. Psychology Reports, 49, 955-961.

Bukalew, L.W. and Coffield, K.E. (1982a) An investigation of drug expectancy as a function of capsule color, size, and prepartion form. Journal of Clinical Psychopharmacology, 2, 245-248.

Bukalew, L.W. and Coffield, K.E. (1982b) Drug expectancies associated with perceptual characteristics: Ethnic factors. Perceptual and Motor Skills, 55, 915-918.

Calorie and Selected Nutrient Values for Persons 1-74 Years of Age: First Health and Nutritional Examination Survey United States, 1971-1974. (1979, June) Vital Health and Statistics Servies, Series 11, Number 209. United States Department of Health, Education and Welfare. DHEW Publication Number (PHS) 79-1657. Public Health Service, Hyattsville, MD.

Cann, P.A., Read,N.W., Cammack,J., Childs, H., Holden, S., Kashman, R., Longmore, J., Nix, S., Simms, N., Swallow, K., and Weller, J. (1983) Psychological stress and the passage of a standard meal through the stomach and small intestine in man. Gut, 24, 236-240.

Carlson, N.R. (1977) Physiology of Behavior. Boston, MA: Allyn and Bacon.

Carney, M.W., Williams, D.G. and Sheffield, B.F. (1979) Thiamin and pyridoxine lack in newly-admitted psychiatric patients. British Journal of Psychiatry, 135, 249-253.

Coppen, A. and Kessel, N. (1963) Menstruation and personality. British Journal of Psychiatry, 109, 711-721.

Dalton, K. (1959) Menstruation and acute psychiatric illness. British Medical Journal, 1, 148-149.

Dalton, K. (1980) Cyclical criminal acts in premenstrual syndrome. The Lancet, November 15, 1070-1071.

Dalton, M.E. (1981) Sex hromone-binding globulin concentration in women with severe premenstrual syndrome. Postgraduate Medical Journal, 57, 560-561.

Day, J.B. (1979) Clinical trials in the premenstrual syndrome. Current Medical Research Opinion, 6, 40-45.

De La Fuente, J-R. and Rosenbaum, A.H. (1981) Prolactin in psychiatry. American Journal of Psychiatry, 138 (9), 1154- 1160.

Delitala, G., Masala, A., Alagna, S. and Devilla, L. (1976) Effect of pyridoxine on human hypophyseal tropic hormone release: A possible stimulation of hypothalmic dopaminergic pathway. Journal of Clinical Endocrinology and Metabolism, 42, 603-606.

Deutch, H. (1944) Psychology of Women (Ed. 1). London: Research Books, pg. 118.

DiNardo, P.G. (1975) Psychological correlates of the menstrual cycle. Dissertation Abstracts International, 37 (613), December, 3145-3146.

Endicott, J., Habreich, U., Schacht, S. and Nee, J. (1981) Premenstrual changes and affective disorders. Psychosomatic Disorders, 43, 519-528.

Fanelli, O. and Tenuta, F. (1981) Carnitive optical isomers' action on the epinephrine stress induced in the isolated perfused rabbit heart. Pharmacology, 22, 371-377.

Fortin, J.N., Wittkower, E.D. and Kalz, F. (1958) Psychosomatic approach to premenstrual tension syndrome: A preliminary report. Canadian Medical Association Journal, 79, 978.

Golub, S. (1976) The effect of premenstrual anxiety and depression on cognitive function. Journal of Personality and Social Psychology, 34 (1), 99-104.

Gonzalez, E.R. (1981) Even oral progesterone may be effective. Journal of American Medical Association, 245 (14), 1394-1396.

Gough, H.C. (1975) Personality factors related to reported severity of menstrual distress. Journal of Abnormal Psychology, 84, 59-65.

Gyorgy, R. (1938) Environmental temperature and "rat acrodynia." Journal of Nutrition, 16, 69-77.

Halbreich, M.D. and Endicott, J. (1981) Possible involvement of endorphin withdrawal on imbalance in specific premenstrual syndrome and postpartum depression. Medical Hypotheses, 7, 1045-1058.

Halbreich, U., Endicott, J. and Schacht, S. (1982) Premenstrual syndromes: a new instrument for their assessment. Journal of Psychiatric Treatment and Evaluation, 4, 161-164.

Halbreich, U., Endicott, J., Schacht, S. and Nee, J. (1982) The diversity of premenstrual changes as reflected in the premenstrual assessment form. Acta Psychiatrica et Scandinavia, 65, 46-65.

Haskett, R.F., Steiner, M., Osmun, J.N. and Carroll, B.J. (1980) Severe premenstrual tension: Delineation of the syndrome. Biological Psychiatry, 15, 121-139.

Herzberg, B.N., Draper, K.C., Johnson, A.L. and Nicol, G.C. (1971) Oral contraceptives, depression, and libido. British Medical Journal, iii, 495-500.

Hoes, M.J.A.J.M. (1980) The chronopathology of premenstrual psychopathology. Medical Hypothesis, 6, 1063-1075.

Horrobin, D.F. (1979) Cellular basis of prolactin action: Involvement of cyclic nucleotides, polyamines, prostaglandins, steroids, thyroid hormones, Na/K ATPase calcium: Relevance to breast cancer and the menstrual cycle. Medical Hypothesis, 5, 599-620.

Huapaya, L. and Ananth, J. (1980) Depression associated with hypertension: A review. Psychiatric Journal of the University of Ottawa, 5, 58-62.

Jacobs, K.W. and Nordan, F.M. (1979) Classification of placebo drugs: Effect of color. Perceptual and motor skills, 49, 367-372.

Jacobs, T.J. and Charles, E. (1970) Correlation of psychiatric symptomatology and the menstrual cycle in an outpatient population. American Journal of Psychiatry, 126, 1504-1508.

Jordheim, O. (1972) The Premenstrual Syndrome. Clinical trials of treatment with a progestogen combined with a diuretic, compared with a progestogen alone and with a placebo. Acta Obstetrica et Gynaecologica Scandinavica, 51, 77-80.

Kerr, G.D., Day, J.B., Munday, M.R., Brush, M.G., Watson, M. and Taylor, R.W. (1980) Dydrogesterone in the treatment of premenstrual syndrome. The Practitioner, 224, 852-885.

Kleinsasser, J.E. (1976) The premenstrual syndrome and its correlation to personality characteristics. Dissertation Abstracts International, 36 (8A), February, 5152.

Kutner, S.J. and Brown, W.L. (1972) Types of oral contraceptives, depression, and premenstrual syndromes. Journal of Nervous and Mental Diseases, 155, 153-157.

La Torre, R.A. (1974) Estradiol inhibition of catecholaminergic eating in the castrated female rat. Biological Psychiatry, 8, 337-341.

Mattes, J.A. and Martin, D. (1983) Pyridoxine in premenstrual depression. Human Nutrition: Applied Nutrition, 36A, 131- 133.

Mattsson, B. and Von Schoultz, B. (1974) A comparison between lithium, placebo, and a diuretic in premenstrual tension. Acta Scandinavia, 255, 75-84.

May, R.R. (1976) Mood shifts and the menstrual cycle. Journal of Psychosomatic Research, 20, 125-130.

McIntosh, E.N. (1976) Treatment of women with the galactorrhea-amenorrhia syndrome with pyridoxine (vitamin B6). Journal of Clinical Endocrinology and Metabolism, 42, 1191-1195.

Miller, B.F. and Keane,C.B. (1977) Encyclopedia and Dictionary of Medicine, Nursing and Allied Health (2nd Edition). Philadelphia, PA: W.B. Saunders Company.

Moos, R.H. (1968) The development of the menstrual distress questionnaire. Psychosomatic Medicine, 30, 853-867.

Moos, R.H. (1969) Fluctuations in symptoms and moods during the menstrual cycle. Journal of Psychosomatic Research, 13, 37-44.

Moos, R.H. (1977) Menstrual Distress Questionnaire Manual. Stanford, CA: Social Ecology Laboratory, Stanford University.

Munday, M., Brush, M.G. and Taylor, R.W. (1977) Progesterone and aldosterone levels in premenstrual tension syndrome. Journal of Endocrinology, 73, 21-26.

Munday, M.R., Brush, M.G. and Taylor, R.W. (1981) Correlations between progesterone, oestradiol, and aldosterone levels in the premenstrual syndrome. Clinical Endocrinology, 14, 1-9.

Muse, K.N., Cetel, N.S., Futterman, L.A., and Yen, S.S.C. (1984) The premenstural syndrome: Effects of "medical ovariectomy." New England Journal of Medicine, 311, 1345-1349.

Nobbs, B.T. (1974) Pyridoxal phosphate status in clinical depression. Lancet, 1, 405-406.

Osgood, C.E., Suci, G. and Tannenbaum, P.H. (1957) Measurement of Meaning. Urbana, IL: University of Illinois Press.

Parker, A.S. (1960) The premenstrual tension syndrome. Medical Clinics of North America, 44, 339-348.

Paulson, M.J. (1961) Psychological concommitants of premenstrual tension. American Journal of Obstetrics and Gynaecology, 81, 733-738.

Radloff, L.S. (1977) The CES-D Scale: A self-report depression scale for research in the general population. Applied Psychological Measurement, 1 (3), 385-401.

Reid R.L. and Yen, S.S. C. (1981) Premenstrual syndrome. American Journal of Obstetrics and Gynecology, 139, 85-104.

Rose, D.P. (1978) The interactions between vitamin B6 and hormones. Vitamins and Hormones, 36, 53-57.

Rossi, A.S. and Rossi, P.E. (1980) Body time and social time: Mood patterns by menstrual cycle phase and day of week. In Parsons, J. (Ed.), The Psychobiology of Sex Differences and Sex Roles. New York: McGraw-Hill, pp. 269-304.

Rubinow, D.R. and Roy-Byrne, P. (1984) Prmenstrual syndrome: Overview from a methodological perspective. American Journal of Psychiatry, 141, 163-172.

Russ, C.S., Hendricks, T.A., Chrisley, B.M., Kalin, N.H., and Driskell, J.A. (1983) Vitamin B6 status of depressed and obsessive-compulsive patients. Nutrition Reports International, 27, 867-873.

Sampson, G.A. (1979) Premenstrual syndrome: A double-blind controlled trial of progesterone and placebo. British Journal of Psychiatry, 135, 209-215.

Sampson, G.A. and Prescott, P. (1981) The assessment of symptoms of premenstrual syndrome and their response to therapy. British Journal of Psychiatry, 138, 399-405.

Schaumburg, H., Kaplan, J., Windenbank, A., Vick, N., Rasmus, S., Pleasure, D., and Brown, M.J. (1983) Sensory neuropathy from pyridoxine abuse. New England Journal of Medicine, 309, 445-448.

Seagull, E.A. (1974) An investigation of personality differences between women with high and low premenstrual tension. Dissertation Abstracts International, 34 (9B), March, 4695.

Shainess, N. (1961) A re-evaluation of some aspects of femininity through a study of menstruation: A preliminary report. Comprehensive Psychiatry, 2, 20-26.

Sherif, C.G. (1980) A social psychological perspective on the menstrual cycle. In Parsons, J. (Ed.), The Psychobiology of Sex Differences and Sex Roles. New York: McGraw-Hill, pp. 255-272.

Silverman, E.M. and Zimmer,C.H. (1976) Replication of "speech fluency fluctuations during the menstrual cycle." Perceptual and Motor Skills, 42 (3), 1004-1006.

Singer, K., Cheng, R. and Schou, M. (1974) A controlled evaluation of lithium in the premenstrual tension syndrome. British Journal of Psychiatry, 124, 50-51.

Smith, S.L. (1976) The menstrual cycle and mood disturbances. Clinical Obstetrics and Gynecology, 19, 391-397.

Speilberger, C.D., Gorsuch, R.L., and Lushene, R. (1968) Self- Evaluation Questionnaire. Palo Alto, CA: Consulting Psychologists Press.

Steiner, M. and Carroll, B.J. (1977) The psychobiology of premenstrual dysphoria: °Review of theories and treatments. Psychoneuroendocrinology, 2, 321-335.

Steiner, M., Haskett, R.F., and Carroll, B.J. (1980) Premenstrual tension syndrome: The development of research diagnostic criteria and new rating scales. Acta Psychiatrica et Scandinavia, 62, 177-190.

Stocker, J.M. (1974) Motor performance and state anxiety at selected stages of the menstrual cycle. Dissertation Abstracts International, 34 (7A), January, 3971-3972.

Stokes, J.W. and Mendels, J. (1972) Pyridoxine and premenstrual tension. Lancet, 1, 1177-1178.

Summer, B. (1972) Menstrual cycle changes and intellectual performance. Psychosomatic Medicine, 34, 263-269.

Swyer, G.I.M. (1955) Treatment of the premenstrual syndrome. Value of ethisterone, mephesin, and a placebo compared. British Medical Journal, i, 1410-1414.

Tarpin, J. (1976) The effect of the modification of sexual attitudes on premenstrual distress. Dissertation Abstracts International, 36 (9B), March, 4712.

Tasto, D.L. and Insel, P.M. (1977) The premenstrual and menstrual syndromes -- A Psychological approach. In Richman, S. (Ed.), Contributions to Medical Psychology. Elmsford, NY: Pergamon Press, pp. 153-165.

Ten-State Nutrition Survey, 1968-1970: Vol. 3, Clinical. Department of Health, Education and Welfare. Health Services and Mental Health Administration. DHEW Publication Number (HSM) 72-8131. Center for Disease Control, Atlanta, GA.

Watts, S., Dennerstein, L., and De La Horne, D.J. (1980) The premenstrual syndrome: A psychological evaulation. Journal of Affective Disorders, 2, 257-266.

Winston, F. (1973) Oral contraceptives, pyridoxine, and depression. American Journal of Psychiatry, 130, 1217-1221.

Wood, C. and Jakubowicz, D. (1980) The treatment of premenstrual symptoms with mefenamic acid. British Journal of Obstetrics and Gynaecology, 87, 627-630.

Yen, S.S.C. (1980) Neuroendocrine regulations of the menstrual cycle. In Kreiger, D.T. and Hughes, J.C. (Eds.), Neuroendocrinology. Sunderland, MA: Sinauer Associates, pp. 259-272.

Zimmerman,E. and Parlee, M.B. (1973) Behavioral changes associated with the menstrual cycle: An experimental investigation. Journal of Applied Social Psychology, 3 (4), 335-344.

Zondek, B. and Brzesinski, A. (1948) Inactivation of oestrogenic hormone by women with vitamin B deficiency. Journal of Obstetrics and Gynecology of the British Commonwealth, 55, 273-280.

Zuckerman, M. and Lubin, B. (1965) Manual for the Multiple Adjective Checklist. San Diego, CA: Educational and Industrial Testing Service.

Zung, W.W.K. (1965) A self-rating depression scale. Archives of General Psychology, 12, 63-70.

APPENDIX A

Samples of Forms and Questionnaires

TELEPHONE SCREENING FORMAT

Interviewer _____ Caller _____

Call Number _____ Caller's Age _____

Date _____ Address _____

_____

Where did she hear about this study?

_____ Phone _____

NECESSARY POINTS TO MAKE:

1. The study will last 3 months and will involve daily record keeping at home.
2. Moods and menstrual symptoms will be monitored over those months.
3. It will involve coming to Tobin Hall once a month to turn in the previous month's home records and receive additional home record forms.
4. They will be asked, after the first month, to take a dietary supplement 3 times/day, with each mean, that will contain either a supplement (such as a vitamin or mineral, not a drug) or a placebo.

****Does she feel her premenstrual mood changes are moderate to severe in nature????

INFORMATION TO COLLECT:

1. Age ____ Must be between 25 and 40 (enter above also).
2. Is she on oral contraceptives? _____
3. Does she cycle regularly? _____
4. Any serious health problems, or regular medication that she takes? _____

5a. Is she taking more than a multiple vitamin/mineral supplement regularly?

5b. Does she take Motrin or Ponstel? ____ Willing to go off it? ____

6. Is she planning a pregnancy or planning to leave the area? _____
7. Do Friends or relatives notice her PM mood changes? _____

****IF SHE ANSWERS NO TO ALL OF THE ABOVE (except cycling regularly), THEN PROCEED.....

SCHEDULE AN INITIAL INTERVIEW:

1. When is she expecting her next period to begin?
2. Schedule an appointment for her BEFORE it should begin.
3. Inform her that this appointment does not commit her or us, but that we will explain the study more fully and get more information from her at this time. She will be asked to fill out some questionnaires and will be given home records if she decides to participate.

Ask her for questions -- repeat appointment time and sign-off****

INFORMED CONSENT FORM

I understand that in this study I will be asked to keep a regular record of my menstrual symptoms and mood changes, and that I will come to Tobin Hall once a month to have my home record keeping checked and to receive additional record keeping forms. I understand that after a one month baseline period, I will be asked to take three capsules daily which may contain either a dietary supplement or a placebo (inert substance), which may or may not affect my menstrual cycle symptoms. I understand that all of my records and all other experimental data will be kept completely confidential and anonymous.

I understand that the dietary supplement and placebo represent no risk to my health. I also understand that if I participate for 3 months, I will receive $10 to $25 for my participation. I have been informed that I may withdraw my consent and withdraw from the study at any time without penalty. I understand that although during the study I will not be told what the dietary supplement is or whether I will be taking a supplement or a placebo, at the conclusion of the study I will be given all of this information as well as any other information I wish to have about the methods and hypotheses of the study.

_____ Signature _____

Date

Printed Name _____

If you have any questions or problems, please call Kim Kendall at 545-1559 (W) or 586-0570 (H).

INITIAL INTERVIEW QUESTIONNAIRE

Date _____ Name _____

Interviewer _____ Subject # _____

Age _____ Length of Cycle _____

Occupation _____ Length of Menses _____

Approx. Income _____ Educational level _____

General Dietary Habits

Please describe an average day's food intake in detail:

Breakfast:

Snack/tea/coffee:

Lunch:

Snack/tea/coffee:

Dinner:

Dessert/snack:

Alcohol (ave/day)

Total Caffeine (ave. # cups/day)

Vitamin/mineral Supplement (describe in detail, include amounts):

Medications/drugs (describe in detail, include dosages):

Cigarettes (ave. #/day)

Menstrual Symptom Typology

When in your cycle do you experience:

1. Menstrual symptoms (include length and onset):

2. Premenstrual symptoms (include length and onset), peaks? when? abrupt end?

continued....

How would you describe your menstrual symptoms?

Primarily mood changes ____

Mild/moderate/severe

Depression/anxious/irritable

Other _____

Primarily physical in nature:

Physical and Mood (BOTH):

How would you describe your premenstrual symptoms?

Primarily mood changes ____

Mild/moderate/severe

Depression/anxious/irritable

Other _____

Primarily physical in nature:

Physical and Mood (BOTH):

MOOS

Menstrual Questionnaire

Form A

Name _____ Married Status _____

Age _____ Number of Children _____

Today's Date _____ Occupation _____

Write the approximate dates of your most recent menstrual period (flow) in the space marked "A" below. Then write the dates of the menstrual period which preceded the most recent one in the space marked "D".

from _____ to _____	other times during most recent cycle	week before most recent flow	most recent flow from _____ to _____
D	C	B	A

On the next two pages is a list of symptoms which women sometimes experience. Please describe your experience of each of these symptoms during the three different time period listed below:

Col. 1 during your most recent menstrual flow (the dates delineated by area A on the diagram above),

Col. 2 during the one week before your most recent menstrual flow (area B on the diagram)

Col. 3 during the remainder of your most recent menstrual cycle (area C)

Note: The answers you put in columns 1, 2, and 3 should be accurage for your experience specificaly during your most recent menstrual cycle. Please do not simply report your general experience. Also, please report any experience of these symptoms whether or not they seem to you to be realted to your menstrual cycle.

For each answer choose the descriptive category listed which best describes your experience of that symptom during that time. Write the number of that description in the space provided. Even if none of the descriptions are exactly correct, choose the ones that best describe your experience. Do not leave any blank spaces.

Descriptive Categories:

1 - no experience of symptom
2 - barely noticeable
3 - present, mild
4 - present, moderate
5 - present, strong
6 - acute or partially disabling

		1. most recent flow (A)	2 week before (B)	3 remainder of cycle (C)
1.	Weight gain	___	___	___
2.	Insomnia	___	___	___
3.	Crying	___	___	___
4.	Lowered school/work performance	___	___	___
5.	Muscle stiffness	___	___	___
6.	Forgetfulness	___	___	___
7.	Confusion	___	___	___
8.	Take naps or stay in bed	___	___	___
9.	Headache	___	___	___
10.	Skin disorders	___	___	___
11.	Loneliness	___	___	___
12.	Feelings of suffocation	___	___	___
13.	Affectionate	___	___	___
14.	Orderliness	___	___	___
15.	Stay home from work/school	___	___	___
16.	Cramps (uterine or pelvic)	___	___	___
17.	Dizziness or faintness	___	___	___
18.	Excitement	___	___	___
19.	Chest pains	___	___	___
20.	Avoid social activities	___	___	___

	1 most recent flow (A)	2 week before (B)	3 remainder of cycle (C)
21. Anxiety	___	___	___
22. Backache	___	___	___
23. Cold sweats	___	___	___
24. Lowered judgment	___	___	___
25. Fatigue	___	___	___
26. Nausea or vomiting	___	___	___
27. Restlessness	___	___	___
28. Hot flashes	___	___	___
29. Difficulty in concentration	___	___	___
30. Painful or tender breasts	___	___	___
31. Feelings of well-being	___	___	___
32. Buzzing or ringing in ears	___	___	___
33. Distractable	___	___	___
34. Swelling (abdomen/breasts/ankles)	___	___	___
35. Accidents(cut finger/break dish)	___	___	___
36. Irritability	___	___	___
37. General aches and pains	___	___	___
38. Mood swings	___	___	___
39. Heart pounding	___	___	___
40. Depression (feeling sad/blue)	___	___	___
41. Decreased efficiency	___	___	___
42. Lowered motor coordination	___	___	___
43. Numbness or tingling in hands/feet	___	___	___
44. Change in eating habits	___	___	___
45. Tension	___	___	___
46. Blind spots or fuzzy vision	___	___	___
47. Bursts of energy or activity	___	___	___

In what ways, if any, was your most recent menstrual cycle unusual?

7/1/81

PREMENSTRUAL ASSESSMENT FORM

(PAF)

Uriel Halbreich, M.D., Jean Endicott, Ph.D., & Sybil Schacht, M.S.W.*

This form is used to describe changes which may occur during the premenstrual period.

Instructions are on page 2.

Card No: ____ ID No: __ __ __ __ __ __ __ __ Study No: __ __

Date: __ __ __ __ __ __ Name or Initials _____

Education: (1) 15+ yrs; (2) 15 yrs; (3) 12-14 yrs; (4) 12 yrs;
(5) 10-12 yrs; (6) 7-9 yrs; (7) 6 yrs or less

Degrees: _____

Occupation: _____
(specify title, type of work, size of business, etc.)

Education of husband/mate _____
(use education code above)

Occupation of husband/mate _____
(specify)

==========

Average number of days from one menstrual period to the next ___ days.
If irregular, ranges from ___ days to ___ days.
If less than 21 days, reason: _____. If more than 38 days, reason: _____.
Average duration of premenstrual period ___ days. Average duration of blood flow ___ days.
Still having menstrual periods: 1 - No 2 - Yes. If Yes, current phase: 1 - During premenstrual period, 2 - During blood flow, 3 - During week after end of blood flow, 4 - Any other week _____
_____.
Age at first menses: _____. Number of children: _____
Number of miscarriages/abortions: _____
Do you have mittelschmerz (ain in the middle of menstrual cycle)?
1 - No 2 - Yes

Special Conditions During Last Three Menstrual Cycles

Dysmenorrhea (pain when menstruating): 1-No 2-Yes (describe)_____

_____

Endometriosis (diagnosed by doctor): 1-No 2-Yes (describe)_____

_____

Take birth control pills: 1-No 2-Yes (specify type, how long taking) _____

_____

Have intra-uterine device: 1-No 2-Yes (specify type, how long using)

_____

_____

Use medication/home remedies to "treat" premenstrual changes: 1-No 2-Yes (specify type, reason) _____

_____

Use any other medications: 1-No 2-Yes (specify type, reason, how long using) _____

_____

*New York State Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons, Columbia University, 722 West 168th Street, New York, NY 10032

Supported in part by NIMH Grants No. MH-30907 and MH-23864 and New York Department of Mental Hygiene.

Currently pregnant: 1-No 2-Yes (specify) _____ months

Post menopausal: 1-No 2-Yes (how long) _____ years _____ months

Not menstruating for other reason: 1-No 2-Yes (specify reason) _____

_____

Any medical disorder(s) currently present: 1-No 2-Yes (specify) _____

_____

The physical, behavioral, and mood changes which take place during the premenstrual period may be either positive or negative.

Please focus on the usual changes which have taken place during your last three premenstrual periods, even if the changes did not last throughout the entire premenstrual period.*

The premenstrual period may range from one to fourteen days. Each woman should determine the duration of her premenstrual period using these factors as guides. Physical, behavioral, and mood changes are considered to be part of the premenstrual period if:

(a) they appear or change during the premenstrual period;
(b) they do not exist in the same form or severity immediately prior to the premenstrual period;
(c) they disappear or return to usual state during the full flow or menses

INSTRUCTIONS

Think about the changes which you experience premenstrually. Consider each item. Decide whether it describes a new condition or change which usually has occurred during your last three premenstrual periods. Circle the appropriate number to indicate the severity of change from your usual state

For example, you may be anxious OR, if you are mildly anxious most of the time, the anxiety may become more severe. Either type of change should be noted.

DEFINITIONS OF THE RATINGS OF SEVERITY OF CHANGE FROM USUAL NONPREMEN STRUAL STATE:

1 - Not applicable, not present at all, or no change from usual level.

_____

*Some studies may have special instructions which differ from these.

2 - Minimal Change (only slightly apparent to you, other would probably not be aware of change)

3 - Mild Change (definitely apparent to you and perhaps to others who know you well)

4 - Moderate Change (clearly apparent to you and/or others who know you well).

5 - Severe Change (very apparent to you and/or others who know you well).

6 - Extreme Change (the degree of change in severity is so different from your usual state that it is very apparent to you OR even people who do not know you well might notice).

1 - Not applicable, not present, no change, 2 - Minimal, 3 - Mild, 4 - Moderate, 5 - Severe, 6 - Extreme

Changes Present During Premenstrual Period	Usual Level of Change During Last 3 Premenstrual periods					
	1	2	3	4	5	6
Have rapid changes in mood (e.g., laughing, crying, happy, etc.) all within same day	1	2	3	4	5	6
Have decreased energy or tend to fatigue easily ..	1	2	3	4	5	6
Have decreased ability to coordinate fine movements, poor motor coordination or clumsiness	1	2	3	4	5	6
Feel anxious or more anxious	1	2	3	4	5	6
Sleep too much or have difficulty getting up in the morning or from naps	1	2	3	4	5	6
Have a feeling of malaise (i.e., general, non-specific bad feeling or vague sense of mental or physical ill-health)	1	2	3	4	5	6
Feel jittery or restless	1	2	3	4	5	6
Have loss of appetite	1	2	3	4	5	6
Have pain, tenderness, enlargement, or swelling of breasts	1	2	3	4	5	6
Have headaches or migraines	1	2	3	4	5	6
Be more easily distracted (i.e., attention shifts easily and rapidly)	1	2	3	4	5	6

1 - Not applicable, not present, no change, 2 - Minimal, 3 - Mild, 4 - Moderate, 5 - Severe, 6 - Extreme

Changes Present During Premenstrual Period	Usual Level of Change During Last 3 Premenstrual periods					
Tend to have accidents, fall, cut self, break things unintentionally	1	2	3	4	5	6
Have nausea or vomiting	1	2	3	4	5	6
Show physical agitation (e.g., fidgeting, hand wringing, pacing, can't sit still)	1	2	3	4	5	6
Have feelings of weakness	1	2	3	4	5	6
Feel that you just "can't cope" or are overwhelmed by ordinary demands	1	2	3	4	5	6
Feel insecure	1	2	3	4	5	6
Have "flare-ups" of allergy, breathing difficulties, stuffy feeling, or watery discharge from the nose	1	2	3	4	5	6
Feel depressed	1	2	3	4	5	6
Have periods of dizziness, faintness, vertigo, (room spinning), ringing in the ears, numbness, tinkling of skin, trembling, lightheadedness	1	2	3	4	5	6
Tend to "nag" or quarrel over unimportant issues	1	2	3	4	5	6
Think of what it would be like to do something to self, like crash the car, wish to go to sleep and not wake up, or have thoughts of death or suicide	1	2	3	4	5	6
Feel less desire to talk or more about (it takes an effort to do so)	1	2	3	4	5	6
Become more forgetful	1	2	3	4	5	6
Feel dissatisfied with personal appearance	1	2	3	4	5	6
Become more violent with people or things (e.g., deliberately break things, hit someone)	1	2	3	4	5	6
Take naps during the day or have an overwhelming desire to do so	1	2	3	4	5	6
Feel sense of unreality, like in a dream, unreal, etc	1	2	3	4	5	6
Feel pounding of heart or have rapid heartbeat	1	2	3	4	5	6
Get more enjoyment or excitement out of little things	1	2	3	4	5	6

1 - Not applicable, not present, no change, 2 - Minimal, 3 - Mild, 4 - Moderate, 5 - Severe, 6 - Extreme

Changes Present During Premenstrual Period	Usual Level of Change During Last 3 Premenstrual Periods					
Have difficulty concentrating	1	2	3	4	5	6
Feel confused	1	2	3	4	5	6
Have lowered judgment (i.e., realize judgment was less good than usual when looking back on decision made during premenstrual period	1	2	3	4	5	6
Feel passive, want others to make decisions, to take charge, etc	1	2	3	4	5	6
Have an increased feeling of well being	1	2	3	4	5	6
Have a lack of self control	1	2	3	4	5	6
Tend to become more childlike	1	2	3	4	5	6
Tend to feel or be tearful, weep, or cry	1	2	3	4	5	6
Feel need to urinate more frequently or have an increased amount of urine	1	2	3	4	5	6
Become constipated	1	2	3	4	5	6
Tend to be self-indulgent in use of time, spending money, eating, etc	1	2	3	4	5	6
Have episodes of impulsive behavior	1	2	3	4	5	6
Tend to smoke more, drink more alcohol or use "drugs of abuse" (e.g., "pot," "speed," etc)	1	2	3	4	5	6
Feel under stress	1	2	3	4	5	6
Pick at, bite or scratch skin, or bite fingernails	1	2	3	4	5	6
Have mood swings from high to low or low to high	1	2	3	4	5	6
Tend to become "hysterical" if something upsets you	1	2	3	4	5	6
Have guilt feelings	1	2	3	4	5	6
Feel "empty"	1	2	3	4	5	6
Have outbursts of "irritability" or bad temper	1	2	3	4	5	6
Feel sad or blue	1	2	3	4	5	6
Have tired legs (weak, sore, tremble)	1	2	3	4	5	6

1 - Not applicable, not present, no change, 2 - Minimal, 3 - Mild, 4 - Moderate, 5 - Severe, 6 - Extreme

Changes Present During Premenstrual Periods	Usual Level of Change During Last 3 Premenstrual periods.					
Tend to have backaches, joint and muscle pains or stiffness	1	2	3	4	5	6
Family or friends know "she is in one of her moods today"	1	2	3	4	5	6
Feel "at war" on awakening or have complaints or outbursts about old irritants	1	2	3	4	5	6
Act spiteful	1	2	3	4	5	6
Feel lonely	1	2	3	4	5	6
Urinate less frequently or in lesser amounts	1	2	3	4	5	6
Have weight gain	1	2	3	4	5	6
Tend to be intolerant or impatient or to lose the ability to respond to or understand the faults, needs or errors of others	1	2	3	4	5	6
Tend to be overtalkative	1	2	3	4	5	6
Have relatively steady abdominal heaviness, discomfort or pain	1	2	3	4	5	6
Have increased sexual activity or interest (fantasy, with self, with others)	1	2	3	4	5	6
Have trouble sleeping	1	2	3	4	5	6
Check, if wake early in morning and can't get back to sleep	____					
Have intermittent pain or cramps in the abdomen	1	2	3	4	5	6
Have a decrease in self-esteem (i.e., don't feel good about self or feel a failure)	1	2	3	4	5	6
Tend to blame others for problems (personal, at home, work, school, etc.)	1	2	3	4	5	6
Have increase in activity, organization, efficiency or involvement socially, at home or work	1	2	3	4	5	6
Tend to brood over unpleasant events	1	2	3	4	5	6
Have skin problems such as acne, pimples, etc	1	2	3	4	5	6

1 - Not applicable, not present, no change, 2 - Minimal, 3 - Mild, 4 - Moderate, 5 - Severe, 6 - Extreme

Changes Present During Premenstrual Periods	Usual Level of Change During Last 3 Premenstrual Periods					
Have edema, swelling, puffiness, or "water retention"	1	2	3	4	5	6
Stay at home more	1	2	3	4	5	6
Have less sexual interest or activity (fantasy, self, others)	1	2	3	4	5	6
Tend to avoid social activities	1	2	3	4	5	6
Feel bloated	1	2	3	4	5	6
Have lowered performance, output, efficiency or ease in tasks at work, at home, or with hobbies, etc	1	2	3	4	5	6
Miss time at work because of premenstrual changes	1	2	3	4	5	6
Want to be alone	1	2	3	4	5	6
Feel a lack of inspiration and creativity	1	2	3	4	5	6
Crave specific foods (sweets, bread, chocolate, pickles)	1	2	3	4	5	6
Have an increase in appetite or tend to eat more	1	2	3	4	5	6
Feel worse in the morning	1	2	3	4	5	6
Pay less attention to physical appearance	1	2	3	4	5	6
Feel cold and/or more sensitive to temperature change	1	2	3	4	5	6
Have bursts of energy or feel more energetic	1	2	3	4	5	6
Become more sensitive to, or intolerant of, personal rejection of self or one's work	1	2	3	4	5	6
Feel more affectionate	1	2	3	4	5	6
Tend to seek advice more often, or about simple matters	1	2	3	4	5	6
Have pessimistic outlook	1	2	3	4	5	6
Drink more coffee, tea, or cold drinks with caffeine (cola, rootbeer, etc)	1	2	3	4	5	6
Feel pain or discomfort during intercourse	1	2	3	4	5	6

1 - Not applicable, not present, no change, 2 - Minimal, 3 - Mild, 4 - Moderate, 5 - Severe, 6 - Extreme

Changes Present During Premenstrual Period	Usual Level of Change During Last 3 Premenstrual Periods.					
Do less housework (cleaning, care of clothes, etc)	1	2	3	4	5	6
Spend less time at leisure activities (hobbies, TV, reading)	1	2	3	4	5	6
Have "flare up" or appearance of cold sores, diarrhea, belching, spontaneous bruises, varicose veins, chest pain, hemorrhoids, numbing, tingling, epilepsy ("fits"), sensitivity of skin to sun (Specify _____) ...	1	2	3	4	5	6
Have an increase in eye problems or changes in vision (e.g., sty, redness, watering, mistiness, discomfort, sensitivity to light)	1	2	3	4	5	6

In order to obtain a good comparison of your premenstrual state, as compared to your usual state, it would be helpful to have a narrative description of the differences, if any, between these two times.

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

DAILY MOOD FORM
PMS 1982-83

Day of Cycle ___ Participant _____

Date _____

Indicate how you feel today by marking along the line in the place that best describes how you feel today. Do not spend too much time on each statement, but give an answer which seems to describe your feelings best. Be sure to mark all dimensions.

1.	Irritable	_____	Pleased
2.	Outgoing	_____	Withdrawn
3.	Not Lonely	_____	Lonely
4.	Decisive	_____	Indecisive
5.	Tired	_____	Energetic
6.	Distracted	_____	Focused
7.	Valuable	_____	Worthless
8.	Full	_____	Empty
9.	Helpless	_____	Powerful
10.	Sad	_____	Happy
11.	Downhearted	_____	Lighthearted
12.	Calm	_____	Tense
13.	Content	_____	Worried
14.	Nervous	_____	Confident
15.	Jittery	_____	Relaxed

Please rate how stressful your day has been:

16.	Not al all stressful	_____	Extremely stressful

MENSTRUAL DISTRESS QUESTIONNAIRE

Form T

Name _____

Today's Date _____

On the next 2 pages is a list of symptoms which women sometimes experience. For each symptom choose the descriptive category listed below which best describes your experience of that symptom today. Circle the number of the category which best describes your experience of the symptom today. Even if none of the categories is exactly correct, choose the one that best describes your experience. Please be sure to circle one number for each symptom. Please also remember to put your name and the date in the blank spaces at the top of this page.

Descriptive Categories:

1. No reaction at all
2. Barely noticeable
3. Present, mild
4. Present, moderate
5. Present, strong
6. Acute or partially disabling

---

1. Weight gain	1	2	3	4	5	6
2. Insomnia	1	2	3	4	5	6
3. Crying	1	2	3	4	5	6
4. Lowered school or work performance	1	2	3	4	5	6
5. Muscle stiffness	1	2	3	4	5	6
6. Forgetfulness	1	2	3	4	5	6
7. Confusion	1	2	3	4	5	6
8. Take naps or stay in bed	1	2	3	4	5	6
9. Headache	1	2	3	4	5	6
10. Skin disorders	1	2	3	4	5	6
11. Loneliness	1	2	3	4	5	6
12. Feelings of suffocation	1	2	3	4	5	6
13. Affectionate	1	2	3	4	5	6
14. Orderliness	1	2	3	4	5	6
15. Stay home from work or school	1	2	3	4	5	6
16. Cramps (uterine or pelvic)	1	2	3	4	5	6

1. No reaction at all
2. Barely noticeable
3. Present, mild
4. Present, moderate
5. Present, strong
6. Acute or partially disabling

17. Dizziness or faintness	1	2	3	4	5	6
18. Excitement	1	2	3	4	5	6
19. Chest pains	1	2	3	4	5	6
20. Avoid social activities	1	2	3	4	5	6
21. Anxiety	1	2	3	4	5	6
22. Backache	1	2	3	4	5	6
23. Cold sweats	1	2	3	4	5	6
24. Lowered judgment	1	2	3	4	5	6
25. Fatigue	1	2	3	4	5	6
26. Nausea or vomiting	1	2	3	4	5	6
27. Restlessness	1	2	3	4	5	6
28. Hot flashes	1	2	3	4	5	6
29. Difficulty in concentration	1	2	3	4	5	6
30. Painful or tender breasts	1	2	3	4	5	6
31. Feelings of well-being	1	2	3	4	5	6
32. Buzzing or ringing in ears	1	2	3	4	5	6
33. Distractable	1	2	3	4	5	6
34. Swelling (e.g., abdomen, breasts, ankles)	1	2	3	4	5	6
35. Accidents (e.g., cut finger, break dish)	1	2	3	4	5	6
36. Irritability	1	2	3	4	5	6
37. General aches and pains	1	2	3	4	5	6
38. Mood swings	1	2	3	4	5	6
39. Heart pounding	1	2	3	4	5	6
40. Depression (feeling sad or blue)	1	2	3	4	5	6
41. Decreased efficiency	1	2	3	4	5	6
42. Lowered motor coordination	1	2	3	4	5	6
43. Numbness or tingling in hands or feet	1	2	3	4	5	6
44. Change in eating habits	1	2	3	4	5	6
45. Tension	1	2	3	4	5	6
46. Blind spots or fuzzy vision	1	2	3	4	5	6
47. Bursts of energy or activity	1	2	3	4	5	6

APPENDIX B

Sample of Post-Study Questionnaire and Follow-up Letter Sent to Participants

POST-STUDY QUESTIONNAIRE

Participant _____

1. Keeping self-observation records often has an effect on people's feelings and behavior. What was your reaction to keeping records? Did it many any changes in your moods or activities?

2. Were your menstrual cycles, while you were participating in the study, typical for you, or different? How different? Which cycles were different?

3. Did you make any major changes during the study, or did anything major happen to you? (moved, married, separated, etc.)

4. Would you be willing to take part in a similar study again. If so, what suggestions for changes would you make for the study, in terms of questionnaires and other procedures.

5. Did you notice any changes in your feelings or behavior when you started taking the pills? What were the changes and when did you experience them?

FOLLOW-UP LETTER SENT TO PARTICIPANTS

Dear Participant:

The Premenstrual Study research team would like to thank you for your time and effort which have contributed so greatly to the success of our project. The confidential information which you have given us has been combined with information from other participants. The meaning of the results of our study is still unclear at this point. We studied three separate groups of women. Half of each group received B6 and half received a placebo supplement. Only in the first group of women did vitamin B6 show a significant effect in lowering premenstrual depression and increasing concentration. No effects were seen in the 2nd and 3rd groups of women we studied. It is possible that the women in our 2nd and 3rd groups received an expired or less potent vitamin B6 supplement than those in the 1st group. The vitamin B6 received by women in groups 2 and 3 is currently being reassayed for potency and these results are not yet in.

Unfortunately, all of this means that we cannot be sure that vitamin B6 did have a greater effect than placebo supplements on lowering premenstrual depression in our study. It seems to have done so in our 1st group and we are currently trying to understand why our results differed for the 2nd and 3rd groups of women who participated earlier this year.

Enclosed you will find a check for $12.00 as a small token of our appreciation for your participation in our project. Also enclosed is a graph of your individual data on a number of variables which we measured over 3 menstrual cycles. We have divided each of your 3 cycles into 5 phases and taken an average score for each phase and plotted this on the graphs which are enclosed. There are 15 points on each graph, representing 3 months divided into 5 phases each. On the graph these phases are represented with "M, 2, 3, 4, P":

M - menstrual phase
2 - luteal phase
3 = ovulatory phase
4 = follicular phase
5 = premenstrual phase

Each graph represents a different variable and the scale on each graph differs, so that it is <u>not</u> possible to make comparisons between two different measures. It is possible to note whether your level of any single measure (i.e., depression) varies over the month, or varied from the 1st month (or baseline period) to the 3rd month (or 2nd month on the vitamin or placebo). Remember that Month 1 (the 1st 5 points

on each graph) was baseline only. The placebo or vitamin was taken during months 2 and 3 (the 6th - 15th points on each graph). Also, remember that it is difficult to understand what your graphs may mean, since your scores were affected by many other things besides the vitamins or placebos, such as external events, stress, weather, and what have you.

Most of the labels on the graphs are self-explanatory, but some are unclear.

All Neg. Affect.	= a combined score of depression and anxiety
Percv. Stress	= the amount of stress you perceived in your life each day
Menstr. Pain	= menstrual pain, cramps, backache, etc.
Poor Concen.	= decreased concentration
Autonom. Symp.	= autonomic symptoms, such as dizziness, insomnia, nausea, etc.
H_2O Retent'n.	= water retention, swollen breasts, weight gain, etc.
Neg. Aff. Moos	= Negative affect on the every-other-day form; includes depression, irritability, and anxiety
Pos. Aff. Moos	= Positive affect on the every-other-day form; feeling of well-being, affectionate, excitement, etc.
Lack of Cont.	= Lack of control

Please write to me at the address below if you have further questions regarding the study. The final write-up will be available in the Psychology Department Library (Tobin Hall) later next spring if you are interested in seeing it. (Because of the bulk and cost of this write-up, it will not be sent to participants.)

Again, we want to thank you very much for your time and patience!

Sincerely,

Kim Kendall, M.S.
Director, PMS Research Project
and the PMS Research Team

KK/jb