ABSTRACT

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Hoa T. Vo, M.A., 2007

Directed By: Professor, Barry D. Smith, Department of Psychology

This study extends current understanding of caffeine intake on the menstrual and premenstrual syndrome; in particular, the association between PMS and caffeine consumption in 83 undergraduate female students—34 PMS and 49 controls. Participants between the ages of 18 and 26 were recruited from psychology courses at the University of Maryland. Diagnoses of PMS were assigned based on a 30% increase across two consecutive cycles of prospective symptom ratings online. Participants were screened using the PHQ for the following exclusion criteria: pregnancy, caffeine sensitivity, and any diagnosis of psychiatric disorder within the past 6 months. It was hypothesized that PMS sufferers would consume more caffeine across the entire menstrual cycle. The result of the present study showed that caffeine intake was higher during the follicular phase than during the luteal phase for both diagnostic groups. However, there was no significant difference between the two groups in caffeine intake.

THE EFFECTS OF CAFFEINE ON PREMENSTRUAL SYNDROME

By

Hoa T. Vo

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Advisory Committee:
Professor Barry D. Smith, Chair
Dr. David R. Rubinow, Member 2
Professor Carl Lejuez, Member 3

Dedication

For my family members who provided encouragement and support. For my older brother, Thinh D. Vo, who's passing in 2005 left a monumental chasm in all our lives.

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Chapter 1: Introduction

Section 1: Study Purpose

The purpose of the present study was to examine the relationship between the physiology of the menstrual cycle and the consumption and processing of caffeine, as well as the possible role of caffeine in premenstrual syndrome (PMS).

Section 2: Background

PMS is a frequent and often debilitating disorder in women. Within the United States, approximately 1 in 6 women 15% of the female population experiences functional impairment as a result of Premenstrual Syndrome (The National Women's Health Information Center [NWHIC], 2004). While it remains unclear, some estimates suggest that 30-40% of women experience PMS (with or without functional impairment) at some time in their lives (ACOG, 2000; The National Women's Health Information Center [HHS], 2004). Premenstrual syndrome consists of an array of physical, behavioral, and emotional symptoms, including abdominal bloating, fatigue, physical discomfort, food craving, headaches, muscle and joint pain, breast tenderness (Bloch, Schmidt & Rubinow, 1997; Gotthell, Steinberg & Granger, 1999), depression, poor concentration, mood lability, irritability, low self-esteem, and sadness (Bloch et al., 1997; Dickerson, Mazyck, Hunter, 2003). Other symptoms that are presented frequently in research literatures include irritability, anger, and short-temper (Endicott 2000). Some symptoms that are often indicative of severe forms of PMS can include depression, hot flashes, and sleep disturbances (Sullivan, 2003). A

related, but more severe, luteal disorder is premenstrual dsyphoric disorder (PMDD). The PMDD diagnosis requires that the patient experience at least 5 symptoms associated with PMS, and one of those symptoms must be dysphoric mood (American Psychological Association [APA], 1994; World Health Organization [WHO], 1992).

Formal definitions of PMS remained ambiguous until the workshop at the National Institutes of Mental Health (Institutes of Mental Health [NIMH] 1983; Rubinow & Roy-Byrne, 1984). It was then that the scientific community established the diagnostic criterion for PMS as a 30 percent increase in the score on either The Daily Rating Form (DRF; Endicott, Schacht, & Halbreich, 1981) or The Self-Rating Scale for Premenstrual Tension Syndrome (PMTS-SR; Steiner et al., 1980) during the luteal, as compared with the follicular, phase of the menstrual cycle. An alternative definition is found in the International Classification of Diseases (ICD). Therefore, PMS is diagnosed if one of the following symptoms is experienced during the luteal phase and ends beginning with menses: minor psychological discomfort, bloating or weight gain, breast tenderness, muscular tension, aches and pain (include headaches), poor concentration, or changes in appetite (Severino & Moline, 1988; WHO, 1992).

Premenstrual syndrome has been predominantly seen as a disorder of the menstrual cycle (Bancroft, 1993). Even though the current understanding of menstrual cycle physiology is incomplete, the fundamentals deserve some attention. The length of the cycle is typically 28 days, where the first day of menstruation is regarded as the first day of the cycle and also the start of the follicular phase (Walker, 1997). At this time, a new follicle is selected to develop, thereby producing increasing amounts of estrogen (including estradiol). The rising levels of estradiol in

turn initiate the formation of a new layer of endometrium in the uterus (Ferin, Jewelewicz, & Warren, 1993). When the follicle has matured, it secretes enough estradiol to trigger acute release of luteinizing hormone (LH). The surge of LH is known as a "positive feedback response," regulated by the hypothalamic-pituary-gonadal axis (Bancroft, 1993). After ovulation, the residual follicle transforms into the corpus luteum—facilitated by the pituitary hormones. The corpus luteum then produces a massive amount of progesterone, as well as estradiol, during the second phase of the cycle, the luteal phase (Ferin et al., 1993). The progesterone has a significant role in the development of the endometrium to increase the likelihood of conception. In the absence of conception, progesterone and estradiol will fall, causing the shedding of endometrial tissue and the onset of menstrual bleeding (Bancroft, 1993).

Premenstrual syndrome appears to be a multifaceted disorder. Bancroft (1993) proposed a three-factor model in order to explain the etiology of PMS: (1) timing factor, (2) menstruation factor, and (3) vulnerability factor. First of all, the timing factor assumes that the hormonal cycle is mediated by varying levels of neurotransmitter activity that mediates mild changes that some women may experience premenstrually. Secondly, the timely variations of the hormonal cycle are affected by the increased levels of prostaglandins (precursor of progesterone) during the luteal phase, which lowers pain thresholds, increases fatigue and induces negative mood states. Lastly, women with PMS also have a predisposition toward neurotic and depressive traits, which is not directly related to the menstrual cycle, but may be

exacerbated by luteal hormonal physiology, increasing the probability of maladaptive responses to stress.

Numerous attempts have been made to identify abnormalities associated with the menstrual cycle which distinguish women with and without PMS. A persistent theme has been to search for differences in circulating levels of progesterone or the progesterone/estradiol ratio during the luteal phase (Bancroft & Backstrom, 1985; Eriksson et al., 2006; Rubinow & Schmidt, 1992). However given the limited understanding of the complex physiology of the normal menstrual cycle, it is not surprising that findings have been inconsistent (Bancroft, 1993). One hypothesis is that changes in the production of ovarian steroids affect certain brain chemicals, which, in turn, bring about the mood changes typically seen in women with PMS (Parry & Rausch, 1995; Walker 1995). Along the same rationale, Severino & Moline (1988) suggest that the ovarian steroids lead to alterations in the neuroendocrine systems that can in turn facilitate premenstrual mood changes. The temporal association of the symptoms of PMS with the luteal phase of the menstrual cycle, along with the discovery of the anesthetic effects of progesterone, led early investigators to theorize that the symptoms of the syndrome (e.g. irritability, anxiety, tension, and mood swings) are caused by a relative deficiency of progesterone (Munda, 1997). Interest in this research area has focused on the role of deficiency of the anesthetic progesterone metabolites, especially allopregnanolone, in PMS.

In order to study the effects of progesterone deficiency, Rapkin and colleagues (1997) examined the level of allopregnanolone (a neuroactive steroid) in 36 PMS patients and controls. The authors found that the serum is lowered in the PMS group

compared to the control group during the luteal phase (Rapkin et al., 1997). Furthermore, the authors hypothesize that diminished concentration of allopregnanolone may lead to an inability to enhance gamma aminobutyric acid-mediated inhibition during states of altered central nervous system excitability, such as those accompanying ovulation and stress. The lowered metabolite levels may be the origin of the various mood symptoms of PMS.

However, these findings are contrary to those suggested by Wyatt and colleagues (2001), in a meta-analysis, suggesting that allopregnanolone levels are similar in PMS and control subjects. Wyatt and colleagues (2001) yields limited support for the use of progesterone or progestogens in the management of PMS. The authors did not detect group differences between progesterone and placebo in any of 14 randomized trails (Wyatt et al., 2001). Given the overall finding that progesterone does not alleviate PMS, we can postulate that perhaps progesterone deficiencies may not be the sole cause of PMS. On the other hand, perhaps women with PMS are more vulnerable to experiences of heightened reactivity to normal hormonal changes that take place during the luteal phase (Schmidt, 2000). In other words, increased sensitivity to normal hormonal changes during the luteal phase contributes to PMS experiences. It is also suspected that rapid shifts in these two hormones facilitate the abnormal emotional and physical responses seen in women with PMS (Bancroft, 1993; Schmidt, 2000).

Psychological vulnerability factors of the premenstrual syndrome include the heightened propensity for depressive experiences and increased association with neuroticism. With regard to personality disposition, research has consistently found

evidence confirming that higher scores on neuroticism are positively correlated with higher rates of PMS (Berlin, et al., 2001; Coppen & Kessel, 1963; Slade & Jenner, 1980). Coppen and Kessel (1963) also suggested a positive correlation between neuroticism and severe PMS in 500 patients randomly sampled. Moreover, Slade and Jenner (1980) suggest that high neuroticism scores are associated with premenstrual and menstrual symptoms. High rates of co-morbidity are also noted between depression and luteal disorders. For example, Subhash & Shashi (2002) suggested that 30 to 76 percent of women diagnosed with Premenstrual Dysphoric Disorder (PMDD) have a lifetime history of depression compared to 15% of women without PMDD. The association between psychopathology and PMS is not fully understood. However, evidence consistently reveals that affective disorders such as depression and anxiety are common co-occurring conditions (Halbreich & Endicott, 1985; Hart, Coleman, Russell, 1987; Rubinow & Roy-Byrne, 1984; Schuckit, Daly, Herrman, & Hineman, 1975; Wetzel, Reich, McClure, & Wald, 1975). Haskett and colleagues (1984) hypothesized that perhaps the higher rate of co-occurrence of PMS and other psychiatric affective disorders is in part a reflection of the lack of diagnostic differentiation. In sum, researchers have detected heighten neuroticism scores in the population of women with PMS compared to the general population. Moreover, it appears that women with PMS are also at an increased risk for having had a history of or current episodes of other psychiatric disorders such as anxiety and or depression.

Even though social learning theories are seen as the stepchild of this research field, many researchers acknowledge that there is something to be said about its role in the experiences of PMS (Bancroft, 1993). The focus of this perspective on

stereotypical beliefs and reporting biases may be important. For instance, theorists attributed reporting of PMS experiences to retrospective measures of premenstrual symptoms; suggesting that reports reflect a woman's stereotyped beliefs about menstruation (Paige, 1971; Parlee, 1973; 1974) rather than actual experiences. Additionally, Ruble (1977) demonstrated that women who believed they were in the premenstrual phase reported more symptoms than women who believed otherwise. This finding was pervasive regardless of which actual cycle phase they were in. Although this social learning perspective cannot completely explain PMS experiences, it does point to the need to examine the role of society and culture in the patient's experience of the disorder.

Accordingly, some investigators have evaluated the role of cultural factors in PMS. Because many cultures convey very negative views of menstruation and in particular of premenstrual syndrome (Chrisler & Levy, 1990; Coutts & Berg, 1993; Walker, 1995), investigators believe that sociocultural expectations may direct a woman to attribute irritable moods to PMS even when the reported symptoms might not have any relationship to the menstrual cycle (Sullivan, 2003). In addition, Parlee (1974) suggested that the Menstrual Distress Questionnaire (MDQ) measures stereotypical beliefs about psychological concomitants of menstrual changes. He also concluded that menarche brings with it a socialization process that leads the woman to expect negative premenstrual emotional experiences. Other researchers, however, have shown that mood reports are unrelated to culturally biased preconceptions (Gallant, Hamilton, Popiel, Morokoff, & Chakraborty, 1991). Addressing this seeming dilemma, Miller (2002) provided an evolutionary perspective to suggest that

environmental contexts determine what behaviors are adaptive that then dictates how premenstrual experiences should be perceived. For example, premenstrual appetite increases carbohydrate cravings, which would be highly adaptive in a resource-poor environment because extra fuel is needed to build the uterine lining and thereby increases the probability of reproduction and species survival. On the contrary, an affluent society might interpret this change in appetite as a symptom (Miller, 2002). Reid (1985) also suggested that nutrition can bring forth changes that occur during premenstrual phase and experiences of PMS, which then elicit cravings for certain types of foods.

Section 3: Study Rationale

Dietary deficiencies or excesses of certain foods (Abraham & Rumley, 1987; Bendich, 2000; Miller, 2002; Thys-Jacobs et al., 1998; Tobin et al., 1994; Wyatt et al., 1999) such as caffeine may be associated with premenstrual dysfunction (see Appendix A: Literature Review). Caffeine consumption has been reported to exacerbate PMS (Abraham & Rumley, 1987; Piesse, 1984; Rossignol, 1985; Rossignol & Bonnlander, 1990; Rossignol, Bonnlander, & Phillis, 1991; Rossignol, Zhang, Chen, & Xiang, 1989), so caffeine restriction is frequently suggested (Abraham & Rumley, 1987; Harrison, 1982; Lark, 1984), despite limited empirical support.

Several studies have reported a relationship between caffeine and PMS, but, these studies were all conducted using self-administered questionnaires (Rossignol, 1985; Rossignol & Bonnlander, 1990; Rossignol et al., 1991; 1989). The first of these studies, showed that college women who consumed more than four drinks per day

had an increased risk of experiencing moderate or severe PMS symptoms (Rossignol & Bonnlander, 1991). A second study suggested that women who consume 8-10 caffeinated drinks per day were seven times more likely to experience PMS (Rossignol, 1985). A third study by Rossignol and colleagues suggested that students drinking moderate amounts of tea (up to 4 cups per day) were 4.5 times more likely to have PMS. The authors further indicated that those who drink from 4.5-8 cups per day were eight times more likely to have PMS (Rossignol et al., 1989).

While the Rossignol studies suggested that caffeine intake is associated with PMS experience (Rossignol, 1985; Rossignol & Bonnlander, 1990; Rossignol et al., 1991; 1989), findings from Caan and colleagues failed to support this association (Caan et al., 1993). Caan and colleagues diagnosed PMS retrospectively using the Menstrual Symptoms Questionnaire (MSQ). The authors collected data regarding level of caffeine intake for three consecutive days during both the premenstrual and postmenstrual periods via telephone interviews. The authors suggested that women with PMS were less likely to consume caffeinated coffee or tea, but were more likely to drink decaffeinated beverages (Caan et al., 1993).

The mentioned studies are methodologically restricted in that (1) they did not diagnose PMS according to standards established by other researchers (NIMH 1983; Rubinow & Roy-Byrne, 1984). Specifically, data must be gathered for two complete cycles, during each of which there must be a 30 percent increase in symptoms during the luteal, as compared with the follicular, phase; (2) Rossginol's studies were cross-sectional and retrospective. While Caan and colleagues addressed the latter concern, their study was also cross-sectional. (3) The researchers did not report any screening

of their participants for preexisting psychiatric conditions. (4) The basis for determining the caffeine contents of foods and beverages was not specified.

The current study aimed to re-examine the effects of caffeine on premenstrual syndrome using more refined methodologies. In order to address the above limitations, the present study implemented the criteria suggested by the National Institutes of Mental Health (NIMH 1983; Rubinow & Roy-Byrne, 1984). Thus, daily diary data were collected for two cycles, and participants were diagnosed with PMS only if, during both cycles, they reported at least a 30 percent increase in scores on The Daily Rating Form (DRF; Endicott, Schacht, & Halbreich, 1981) or The Self-Rating Scale for Premenstrual Tension Syndrome (PMTS-SR; Steiner et al., 1980) from the follicular to the luteal phase. In addition, the Physician Health Questionnaire (PHQ) was used to screen for current and previous psychiatric conditions (participants who reported any psychiatric diagnoses within the past six months were excluded). Finally, caffeine values were adopted from Juliano & Griffiths (2005). Calculations were completed with the consideration of amount of intake per ounce of each type of food or drink. The present study is the first to address diagnostic limitations of prior studies examining the relationship between PMS and caffeine intake.

Section 4: Study Hypothesis

Since prior literature indicated a positive association between caffeine consumption and experiences of PMS, it is expected that women with PMS consume more caffeine than do controls across the entire menstrual cycle.

Chapter 2: Methods

Section 1: Participants

One hundred and ten undergraduate students at the University of Maryland enrolled in the study and completed the screening phase. Participants were primarily recruited through advertisements in a variety of psychology courses (e.g. introductory psychology, psychology of women, social psychology). The 110 participants who met criteria to participate in the diagnostic phase were screened for the following: caffeine sensitivity, pregnancy, diagnosed psychiatric condition within the past six months, and history of drug use These conditions were screened based on recommendations in the literature (Odber et al, 1998; Roca et al., 2003). Psychiatric history was assessed using the PHQ. Seven participants endorsed the following exclusion criteria: suicidal ideation (n = 3), previous or current diagnosis of depression (n = 3), and caffeine sensitivity (n = 1). In addition, twenty participants (18%) did not complete two months of daily diaries. The final sample (N = 83) ranged in age from 18 to 26 (M = 19, SD = 1.98) and was demographically similar to the population of women at the University of Maryland (see Table 1).

Section 2: Apparatus

The Participant Screening Form (see Appendix) is a demographic questionnaire created by the researcher that elicits the following information: age, racial and/or ethnic identity, medical history, current medications, caffeine and

alcohol/drug consumption level, previous history of psychiatric disorder, and pregnancy status.

The Physician Health Questionnaire (PHQ; Spiller, 1997; see Appendix) is a tool provided to help primary care practitioners quickly diagnose mental disorders. The full PHQ is a four-page questionnaire derived from the Primary Care Evaluation of Mental Disorders (PRIME-MD; Spiller, 1997). The first three pages assess for common mental disorders (somatoform, mood, anxiety, eating, and alcohol) and functional impairment. Many clinicians use only these first three pages, or only components, such as the 9-item depression module (PHQ-9; Spitzer et al., 1999). The fourth page includes questions about recent stressors and, for women, questions regarding menstruation, pregnancy and childbirth. The measure has excellent internal and test-retest reliability with Cronbach's alpha value of above 0.84 in three different studies (Kroenke et al., 2001). Additionally, internal validity was 0.86 and validity of 0.70 and around that range depending on disorder. The PHQ can detect major depression best (0.88) and is not as sensitive for detecting bodily pain (0.33). The current project included all four pages of the PHQ. The current study used PHQ instead of the Structured Clinical Interview for the DSM-IV (SCID-IV) in order to save time. The PHQ has been proven to be very effective when used for research purposes even though its usage in clinical settings might be limited (Spitzer et al., 1999).

The Caffeine Intake Form (see Appendix) was used in the study to record daily caffeine consumption. It assesses the amount of consumption for various

products containing caffeine. This form was used during the screening and also as a part of the daily diaries.

The Self-Rating Scale for Premenstrual Tension Syndrome (PMTS-SR; Steiner et al., 1980; see Appendix) was also used during the experiment. The correlation coefficients of the PMTS-SR compared with the Premenstrual Tension Scale for Others (PMTS-O) is 0.83 premenstrual and 0.84 postmenstrual as reported by Bergant and colleagues (2004). Reliability analysis for PMTS-O, was, pre- and postmenstrually 0.71 and .29, respectively, for PMTS-SR 0.77 and .078. Thus, the PMTS-SR has predictive validity and is a highly reliable questionnaire used widely in PMS research. It is also a good cross-sectional measure. The PMTS-SR was used during the experimental phases also as a part of the daily diaries. This measure has been shown to be a reliable tool (Rubinow, & Schimdt, 1992; 1995) for detecting differences pre- and postmenstrually (Wewers & Lowe, 1990).

Section 3: Procedures

The present study included two phases, Electronic Screening and Daily Diaries. Participants were required to attend an information session to receive instructions on how to proceed and also to sign informed consents.

Subsection 1: Electronic Screening

The screening session was online and available at a website provided on the Information Sheet for Participants (see Appendix). The screening session included a caffeine consumption survey, a demographic questionnaire, and the entire Physician Health Questionnaire (PHQ).

Subsection 2: Daily Dairies

Participants completed daily entries online at the same time every night for two consecutive menstrual cycles. Participants completed the questionnaire at the same time each night to account for possible confounding variables such as the time-of-day-effect. Because some women with PMS may experience exacerbated symptoms at night while others experience symptoms more during the day, no one specific time of day is without its merits. However, night-time recording was chosen as it was usually more convenient for participants. They were asked to begin the questionnaire as soon as possible and terminate all entries only when instructed. In order to increase the likelihood that participants complete the diaries on time, alerts were sent to the researchers as soon as entries were completed online. Data obtain from participants who missed more than five entries each month were excluded from the final analysis. Participants who missed one day of entry were able to make-up for them the following day by submitting two entries at the time they usual complete their entries. Data submitted more than 24 hours late were excluded from analysis. After debriefing, participants received an email asking whether they restricted caffeine consumption that states, "Did you purposely restrict the amount of caffeine you consumed during the course of this study? If yes, please indicate why." This question was intended to inquire whether participants who met criteria for PMS were more likely than asymptomatic participants to limit caffeine from dietary intake.

Chapter 3: Results

Section 1: Statistical Procedure

The average amount of caffeine intake was computed for each participant for each phase of the cycle. The final consumption figure for each phase was determined by calculating the average intake for that phase across the two menstrual cycles (caffeine values adopted from Juliano & Griffiths, 2005). Similar calculations were completed for symptom scores on The Self-Rating Scale for Premenstrual Tension Syndrome—a 5-point-likert scale (PMTS-SR). In order to meet criteria for PMS, participants had to endorse at least a 30% increase in symptom severity during the luteal phase, as compared to the follicular phase, for 2 consecutive months. The PMTS-SR assessed for symptoms such as mood swings (sudden sadness or tearfulness), depression, anxiety (tension, nervousness), irritability, avoidance of social activities, sensitivity, and loss of enjoyment or hopelessness. Percent increase was calculated using the difference between premenstrual and postmenstrual time periods. Premenstrual (luteal phase) was defined as the week immediately before menses. Similarly, postmenstrual (follicular) was the week immediately after menses. The final symptom scores for the luteal phase were obtained by averaging the premenstrual scores of the first and second menstrual cycles. Likewise, the follicular scores were calculated, for each participant, using the postmenstrual scores across the two cycles.

Two principal analyses were conducted. The first was a series of goodness-of-fit tests that examined differences among the groups on the relevant nominal variables. These included caffeine restriction, age, marital status, oral contraceptives,

routine pharmacological regime ("Do you take any medications on a regular basis?", and cigarette smoking. The second analysis was an analysis of variance that examined the present hypothesis that the PMS group ingests more caffeine than the control group. Post hoc analyses were completed to compare the PMS group with the modified, asymptomatic control group. Along with this, two additional correlations were completed to examine possible associations between level of caffeine intake and severity of symptom experience within members of the control group with higher follicular symptom ratings.

Section 2: Data Analysis

Goodness-of-fit tests revealed no significant differences among the groups (PMS and controls) on the variables noted above (see Table 2). The first variable examined was caffeine restriction. After debriefing, participants received an email asking whether they restricted caffeine consumption during the course of the study. A total of 46 participants out of 83 replied, and 24 of these indicated that they restricted caffeine consumption for various reasons (e.g., sleep deprivation, skin care, headaches, etc). Unfortunately, it is unclear whether participants were more likely to restrict consumption during the follicular or the luteal phase. It was then assumed that participants restricted intake throughout the entire experiment.

The series of goodness-of-fit analyses did not reveal group differences in caffeine restriction, χ^2 (1, N = 46) = 0.001, p = 0.98, suggesting that there were no relationships between diagnosis and restrictions in caffeine consumption. Similarly, no significant relationships were found for age, χ^2 (7, N = 83) = 5.63, p = 0.58; marital status, χ^2 (1, N = 83) = 2.99, p = 0.084; oral contraceptives χ^2 (1, N = 83) =

0.75, $p = 0.39$; regular use of medication (s) χ^2 (1, N = 83) = 0.48, $p = 0.49$; or cigarette smoking [χ^2 (2, N =83) = 1.52, $p = 0.47$].

Section 3: Hypothesis Testing

A mixed design Analysis of Variance (ANOVA) was conducted. The between-subjects variable was Group [PMS (N = 34) and Control (N = 49)], and menstrual cycle Phase (follicular vs. luteal) was the within-subjects factor. The analysis yielded a nonsignificant Group X Phase interaction, F (1, 81) = 1.82, $p = 0.18$ ($\sigma = 0.022$) and a nonsignificant main effect of Diagnosis, F (1, 81) = 1.59, $p = 0.21$ ($\sigma = 0.019$). However, the ANOVA detected significant differences in caffeine consumption between the two menstrual cycle phases, F (1, 81) = 5.42, $p = 0.02$ ($\sigma = 0.063$). Overall, the mean caffeine intake during the follicular phase for the control group was 134.52 mg/day, and for the PMS group was 121.92 mg/day. Additionally, the mean caffeine consumption for the luteal phase was 125.80 (mg/day) for the control group and 92.56 (mg/day) for the PMS group. The current data failed to provide support for the alternative hypothesis. Therefore, caffeine consumption did not inform whether or not a woman experienced PMS. These means suggested that caffeine intake was higher during the follicular phase for both diagnostic groups.

Section 4: Post Hoc

Post Hoc

Upon completing necessary calculations to determine group distribution [PMS (N = 34), control (N = 49)], it was found that within the control group, 16 participants were asymptomatic in both phases, and 33 reported higher follicular symptoms during

at least one of the two months. Of the latter group, 14 participants endorsed at least a 30% in symptom increase during the follicular phase, as compared with the luteal phase. However, only 4 of these 14 participants maintained this pattern over two consecutive months.

Since the 14 control participants with higher symptom counts during the follicular phase in one or both cycles may represent a different population, the analysis was repeated with these participants eliminated. Thus, the PMS group was compared with the modified, asymptomatic control group. The between-subjects variable was Group, PMS (N = 34) vs. asymptomatic controls (N = 35); the within-subject variable was menstrual cycle Phase. The analysis revealed a nonsignificant relationship for the Group X Phase interaction, [F (1, 67) = 0.93, p = 0.338 (σ = 0.014)] and also for the main effect of Diagnosis, [F (1, 67) = 0.39, p = 0.535 (σ = 0.006)]. Similar to the previous analysis, the ANOVA detected significant differences in caffeine consumption between the two menstrual cycle phases, [F (1, 67) = 7.86, p = 0.007 (σ = 0.105)]. Overall, the mean caffeine intake during the follicular phase for the asymptomatic control group was 134.03 mg/day, and for the PMS group was 121.92 mg/day. Additionally, the mean caffeine consumption for the luteal phase was 115.40 (mg/day) for the asymptomatic control group and 92.56 (mg/day) for the PMS group. The result of the initial analysis was supported even after the exclusion of the 14 women with clinically higher follicular symptoms from the control group.

Two additional correlations were conducted examining possible relationships between caffeine intake and PMS symptom experiences for participants who

endorsed higher follicular symptoms ($N = 33$). The first correlation, involving all the women in the current sample with higher follicular symptoms, did not suggest significant associations between PMS symptoms and caffeine intake during the follicular phase, [r (33) = -.080, $p = .477$]. The second correlation examined the same association among the women who endorsed at least a 30% increase in symptom during the follicular phase ($N = 14$). Acknowledging its limited sample size, the results also did not reveal a significant relationship between the level of caffeine intake during the follicular phase and symptom endorsement among this group, [r (14) = -.296, $p = .305$].

Chapter 4: Discussion

Women with PMS were no more likely to drink caffeine than non-PMS sufferers. Unexpectedly, the entire sample consumed more caffeine during the follicular than during the luteal phase. Results thus suggest that there was a menstrual cycle phase difference in level of consumption independent of diagnosis. The differences remained even after controlling for participants who experienced clinically significant PMS-like symptoms during the follicular phase.

It is important to note that correlational analyses within the group with higher follicular symptom ratings did not reveal significant associations between the intensity of follicular symptom ratings and the level of caffeine intake for this phase. In sum, the first correlational analysis conducted on the entire sample ($N = 33$) of women who endorsed higher follicular symptom ratings suggested that caffeine intake was not associated with follicular symptom endorsement. Of those, the second analysis examined the 14 participants who endorsed at least a 30% increase in PMS-like symptom during the follicular phase; this analysis also yield nonsignificant associations between caffeine intake and premenstrual symptom experiences. This suggests, with sample size limitations, that symptom severity is not related to the amount of caffeine intake for women who were symptomatic during the follicular phase. Overall, the present data suggested that caffeine consumption was independent of diagnosis. However, the results add to the existing (though limited) body of literature on the effect of caffeine on both the physiological and the psychological aspects of the menstrual cycle.

The findings of this study do not support the theory posited by Rossignol & Bonnlander (1990; 1989), which suggested that caffeine is associated PMS symptoms. These authors suggested that caffeine was a stimulant often consumed precisely for the "lift" it provides (Rossignol et al., 1991). Among women with more severe symptoms in their study, there was a relationship between consumption of caffeine-containing beverages and premenstrual syndrome. Particularly, they suggested that the association between premenstrual symptoms and daily consumption of caffeine-containing beverages was dose-dependent (Rossignol et al., 1985). According to Rossignol and colleagues, the effect seems to be prevalent cross culturally (Rossignol et al., 1989). Some of the methodological flaws in the Rossignol studies were addressed above. In addition, Leviton's (1991) suggested that the authors assume that the caffeine content of one type of beverages is equal to the caffeine content of another. Specifically, the study asked participants to self-report number of caffeinated beverages without information on the type of amount of the drink (e.g. coffee, tea, etc). Secondly, the authors assumed "equivalency of symptoms" among participants; that is, they failed to operationalize PMS (Leviton, 1991). It is also important to add that the study examined PMS symptoms retrospectively and did not diagnose with prospective daily ratings. The authors assumed that there is an inherent association between caffeine intake and the prevalence of PMS, thus failed to consider possible confounding variables (Leviton, 1991).

The present study is the first to examine the association between PMS and caffeine intake using two months of prospective symptom ratings and caffeine

consumption. The database for this study contributes significantly to the literature in part because it captures the entire menstrual cycle. In addition, the present study screened for history of and current psychiatric conditions, where prior studies by Rossignol's group did not. The present methodology is superior because the internet data-collection methodology used provided careful daily monitoring of participants' completion of daily entries and therefore of their caffeine intake and symptoms.

The current data also lead to the intriguing possibility that some percentage of women may experience PMS-like symptoms during the follicular phase, rather than the luteal phase. However, although 14 participants reported such follicular symptoms, only four of these displayed the symptom during both menstrual cycles for which data were collected. Although, we certainly cannot reach any firm conclusion, but it would be worth pursuing this possibility in future studies with larger samples. A recent review may help explain why some women may experience PMS-like symptoms during the follicular phase. Teiner & Wit (2006) reported that caffeine intake during the follicular phase may "produce more pronounced mood-enhancing effects" (p. 8) compared to the luteal phase. Noting the limitations in their unpublished data, the authors suggested that this effect was similar to those seen in other stimulant drugs. Furthermore, the current data seem to support the hypothesis that perhaps caffeine plays a role in mimicking PMS symptoms in women who experienced more symptoms during the follicular phase.

Supporting the current findings, Caan and colleagues (1993) did not find significant differences between the pre-and postmenstrual period. They suggested perhaps that caffeine consumption was not a function of PMS, but rather of

environmental variables. Interestingly, Caan and colleagues found that though women with PMS consumed less caffeinated beverages, they consumed more decaffeinated coffee and herbal teas compared to controls. The authors then suggested that perhaps knowledge of the media played a role in determining consumption behavior of women who know or think they have PMS, but did not provide supporting evidence for this hypothesis. In the present study, 24 participants of 46 who responded indicate that they restrict their level of caffeine consumption for various reasons (i.e. sleep deprivation, skin care, headaches, etc), but none acknowledged the reason indicated by Caan and colleagues. In conclusion, the association between PMS and caffeine intake remains controversial. Despite its limitations, the current study does not provide support for the association between PMS and level of caffeine consumption.

Physiologically, researchers seem to agree that caffeine is metabolized 25% slower during the luteal phase than during the follicular phase (Balogh et al., 1987; Institute of Medicine, 2001), possibly due to differences in the level reproductive hormones (Teiner & Wit, 2006). More importantly, it has been postulated that this occurs as a result of a higher concentration of progesterone and estradiol during the luteal phase (Balogh et. al., 1987; Institute of Medicine, 2001). Additional support for the slower rate of elimination was provided by Lane and colleagues (1992). The authors found that the slower caffeine clearance during the luteal phase was associated with proximity to onset of menstruation and also to increased levels of progesterone.

In the past, it was thought that the temporal association of the symptoms of PMS with the luteal phase of the menstrual cycle was related to progesterone. Some investigators then hypothesized that PMS symptoms (such as irritability, anxiety, tension, and mood swings) originated due to a relative deficiency of progesterone during the luteal phase (Munda, 1997). Progressively, Rapkin and colleagues (1997) suggested lowered level of allopregnanolone in the PMS group compared to the control group during the luteal phase. The authors concluded that lowered metabolite levels could be the origin of the various mood symptoms of PMS such as anxiety, tension, and depression. Regardless of whether certain physiological changes produce slower metabolism of caffeine (Balogh et al., 1987; Institute of Medicine, 2001; James, 1997) and/or PMS symptoms (Rapkin et al., 1997) during the luteal phase, the evidence collectively helps explain the current finding by suggesting that perhaps less caffeine was needed to produce similar effects during the luteal phase compared to the follicular phase. Partially, this clarifies why the current sample consumed more caffeine during the follicular phase. In sum, the differences in physiological effects of caffeine on the menstrual cycle warrant future efforts.

As a guide to future research, it is important to begin to develop a theoretical model for understanding the effects of caffeine on the hormonal physiology of the menstrual cycle by understanding the effects of this powerful stimulant in the central nervous system. The central neurotransmitter adenosine is a purine nucleoside formed through the combination of adenine and D-ribose. One of the four major components of DNA and RNA, adenosine acts to inhibit a range of central synapses, thereby decreasing the rate of firing of central neurons and acting to inhibit

glutamateric transmission and dopamine release. One result is the downregulation of estrogen receptors. Caffeine is an adenosine antagonist, which binds to adenosine receptors, thereby reducing the inhibitory effects of the neurotransmitter and resulting in increased excitation of the affected neural systems. Since the central nervous system is responsible for the production of steroid hormones, the depressant action of adenosine may be influenced by the presence of estradiol and progesterone.

Research indicates that estradiol, like caffeine, antagonizes the inhibitory actions of adenosine, hence leading to possible emotional experiences—happiness, wellbeing (Phillis & O'Regan, 1988). The follicular phase is characterized by significant increases in estradiol, thereby explaining why, in general, women experience more positive emotions during the follicular compared to the luteal phase of the cycle. In addition, caffeine is a stimulant that also enhances positive affect. Hence, the presence of estradiol and caffeine during the follicular phase should lead to more positive mood experiences. If this were the case, women with higher PMS-like symptoms should report lower caffeine consumption during the follicular phase. However, correlational analyses between the severity of symptom endorsement in this group and caffeine intake yielded nonsignificant results. It is possible that the presence of caffeine during the follicular phase enhances both positive and negative affect in generally. Along the same lines, Terner & Wit (2006) suggested that stimulant drugs tended to produce enhanced mood effects during the follicular phase. Perhaps the presence of estradiol in collaboration with caffeine *over-stimulates* mood experiences.

During the luteal phase, progesterone production peaks. Since progesterone pontentiates the action of adenosine (Phillis, 1986), by inhibiting its reuptake into nerve and glial cells, it may lead to feelings of fatigue and depression associated with the initial luteal phase of the cycle (Phillis, 1989). Phillis suggested, in response to Rossingol's (1985) findings, that caffeine intake should depend highly on menstrual cycle phases. Specifically, caffeine consumption should increase during the luteal phase when progesterone production increases in order to counteract its effects on mood. In turn, it also makes intuitive sense to decrease consumption during the follicular phase to minimize the *over-stimulation* of mood experiences.

Given the above physiological interactions, it can be suggested that PMS sufferers are predisposed to experiences of premenstrual symptoms during the luteal phase while normal controls are liberated from such disposition. In sum, results indicate that women with PMS were less likely to consume caffeine during the luteal than the follicular phase, which in turn exacerbates their symptomatology during the luteal phase. In order to alleviate PMS experiences, women should consume more caffeine during the luteal phase and less during the follicular phase as opposed to prior recommendations—women with PMS should reduce caffeine intake overall (Harrison, 1982; Lark, 1984). Caffeine counteracts the effects of progesterone and facilitates the function of estradiol. It is then important to consume less caffeine during the follicular phase, when estradiol peaks, and more during the luteal phase, when progesterone levels increase.

Chapter 5: Study Limitations

The present findings should be interpreted with acknowledgment of the following limitations five limitations. (1) The current sample consisted of college students who may not be habitual caffeine consumers; the generalizability of the results to regular caffeine users may be limited. (2) Since symptoms of caffeine withdrawal were not accounted for and may overlap with symptoms of PMS, it is unclear whether symptoms endorsed were a result of PMS experiences or caffeine withdrawal or both. (3) Approximately 18% of the current sample had incomplete daily diaries. Of these, two of participants who did not report menstruation, 3 women terminated participation early due to family (death in the family) and medical (surgeries) emergencies, and 15 missed more than 5 consecutive entries in each cycle. Overall, the data did not indicate particular phases (follicular or luteal) in which participants were most likely to miss, thus it was speculated that the missing data was due to forgetting or time constraints. Missing data points were replaced by using the averages from the entire phase and data available from the other cycle. (4) There were approximately 33 participants endorsed higher symptom ratings during the follicular compared to the luteal phase. Of this group, 14 participants reported symptom severity of 30% or greater during the follicular phase. An analysis was conducted and no significant differences were found in the sample (N = 14 who reported at least 30% greater symptom severity during the follicular phase compared to N = 19 who reported less then 30% symptom severity; $p < .70$). Overall, the sample size for this group (N = 33) and the PMS group appeared sufficient (N = 34); however sample size was restricted in the pure control group (N=16). Although the

initial power analysis did reveal that the present sample was sufficient in order to detect moderate effects, additional data is being collected in order to increase the sample size for future analysis.

Chapter 6: Future Directions

Given the present findings, it is necessary that future studies of this sort use longitudinal methods of data collection, in order to facilitate the understanding of how the menstrual cycle interacts with caffeine consumption. It is also important, and a current limitation, to examine withdrawal symptoms in addition to PMS symptoms since they are highly correlated (Allen, Hatsukami, Christianson, & Nelson, 1996). One limitation of previous studies is the failure to screen for psychiatric conditions; even though the current study excluded women with current and or history of psychiatric diagnoses, future studies examining the effects of caffeine on mood should exclude or co-vary for PMS diagnoses, as they would for depression, anxiety, and other psychiatric conditions. Finally, future research should be more clearly guided by knowledge of underlying mechanisms and by theoretical models of caffeine-adenosine effects that integrate those mechanisms.

Chapter 5: Conclusion

Media and internet sites often suggest that caffeine exacerbates PMS symptoms (Harrison, 1982; Health Square, 2006; Internet Health Library, 2006; Lark, 1984), however, the present study did not support such claims. There were no significant differences found in the level of caffeine intake in women with and without PMS. However, it is important to consider the effects of caffeine on the menstrual cycle phases. In sum, results indicate that women with PMS were less likely to consume caffeine during the luteal than the follicular phase. However, it is possible that if PMS-sufferers consumed more caffeine, during the luteal phase to counteract the effects of progesterone, their mood may improve as a consequence. In general, it appears that women are more likely to experience enhanced mood effects during the follicular phase in response to caffeine intake. Therefore, it is suggested that consumption during this phase be lowered.

Appendices

Literature Review

Background on Menstrual Cycle

The prevailing tendency has been to see PMS as a disorder of the ovarian cycle. Historically, menstruation was merely a biological phenomenon. It was not until the 18th century that it became a social phenomenon (Walker, 1997) associated to the rise in the number of women seeking higher education. Empirical studies involving the menstrual cycle tended to suggest implications on different aspects of a woman's life. In particular, the area of research was marked by increased interests in the biological and in the psychological processes of the menstrual cycle (Walker, 1995). During its infancy, the field was primarily concerned with examining normative experiences of women across the menstrual cycle (Walker, 1997). In particular, many investigators focused on examining mood and behavioral changes associated with the menstrual cycle. Research in this area suggested that particular changes during the menstrual cycle were abnormal; so practitioners were seeking to "normalize" the menstrual experience. Around 1872 it became popular to perform ovariotomy in order to treat different forms of "menstrual insanity" (e.g. menstrual madness, neurasthenia, nymphomania) (Studd, 2006). However, it was later discovered that possible methodological flaws might have been inherent in the first wave of research (Endicott, 2000). Therefore, researchers begin to focus on formalizing methodology and examining processes associated with different phases of the menstrual cycle; this eventually lead to interest in a phenomenon called

Premenstrual Syndrome (PMS). At first, most studies conducted varied methodologically and were primarily questionnaire-based (e.g. Englander-Golden et al., 1978; Zimmerman & Parlee, 1973). Progressively, empirical studies on PMS were seen published in biomedical and psychosomatic journals primarily concerned with testing theories of the etiology of PMS (Walker, 1997). The link with depression was important to the development of future PMS research at this time, and the inclusion of Premenstrual Dysphoric Disorder in the DSM IV in the 1990's was the ultimate recognition of this field of research (Finfgeld, D.L., 2002).

Biologically, menstruation is the cyclic, orderly sloughing of the uterine lining, in response to the interaction of hormones produced by the hypothalamus, pituitary, and ovaries. The parts of the body that are involved in this process are: brain, pituitary gland, uterus and cervix, ovaries, fallopian tubes, and vagina (Norris & Sullivan, 1983). Each month from menarche on, the hypothalamus acts as an interpreter of the body's rhythms and transmits messages to the pituitary gland, which then sets the menstrual cycle in motion (Khan-Sabir et al., 2004; Norris & Sullivan, 1983). Throughout the menstrual cycle, the above body parts contribute to hormonal fluctuations that are also responsible for the regulation of pituitary hormones (e.g. follicle-stimulating hormone (FSH) and luteinizing hormone (LH)) (Khan-Sabir et al., 2004; Walker, 1997; The National Women's Health Information Center, 2004). Changes in the production of follicle-stimulating hormone and the luteinizing hormone then signal the shredding of the uterine linens to take place—menses.

Definitionally, the length of a menstrual cycle is divided into two phases that begins on the first-day of menstrual bleeding of one cycle to the onset of menses of the next cycle.

By convention, the day of menstruation clearly delineates the termination of an dndometrial cycle and the beginning of the new one. The beginning of menses marks the start of the follicular phase. In general, the follicular phase is approximately 14 days and is variable. The luteal phase, however, is 12-14 days long and is constant. Most women will have cycle lengths of approximately 23-25 days; however, irregularity may be expected around the extremes of reproductive life, menarche (beginning around age 12) and menopause (ending around the mid 50s) as a result of anovulation and inadequate follicular development. (Apter et al., 1987; The National Women's Health Information Center, 2004).

Briefly, the endocrinology of the menstrual cycle involves the following hormonal changes. During days 1-6 of the menstrual cycle (early follicular phase), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels increase relative to baseline. Estrogen and progesterone levels remain low at this stage. About eight days into the follicular phase, FSH levels decrease due to negative feedback at the level of the pituitary gland and estradiol levels increase due to previous stimulation by FSH at the level of the ovary (Tsafriri et al., 1994). One day before ovulation, a surge in LH takes place while FSH levels also increase temporarily. LH and FSH production accelerate due to positive feedback by estrogen at the level of the pituitary gland. LH and FSH will then decrease back to baseline levels almost immediately. By the time ovulation occurs, LH and FSH would have declined.

Progesterone and, to a lesser extent, estrogen are productions of the corpus luteum, which is a result of the heighten LH during the pre-ovulatory. In the absence of fertilization, the corpus luteum degenerates and progesterone and estrogen levels subsequently fall. Estrogen and progesterone levels are lowest at the end of the menstrual cycle. At the termination of the current cycle, FSH secretion increases to initiate the beginning of the next cycle.

As mentioned, the menstrual cycle consists of two phases: the follicular and the luteal phases (with ovulation briefly in between). The follicular phase begins on the first day of menses and ends at ovulation (Severino & Moline, 1988). During the follicular phase, a process called Folliculogenesis ensues. It is a process "beginning with the recruitment of a primordial follicle into the pool of growing follicles and ends with either ovulation or death of atresia" (Khan-Sabir et al., 2004). Once menses begins, FSH levels will decline, due to the negative feedback of estrogen and the negative effects of inhibin produced by the developing follicle (Tsafriri et al., 1994). FSH activates the aromatase enzyme in granulosa cells, which converts androgens to estrogen (Khan-Sabir et al., 2003). A decline in FSH levels lead to the production of a more androgenic microenvironment within adjacent follicles that then contribute to the growth of a dominant follicle. Inversely, the granulosa cells of the growing follicle also secrete a variety of peptides that may play an autocrine/paracrine role in the inhibition of development of the adjacent follicles (Khan-Sabir et al., 2003). After ovulation, the corpus luteum (a transient endocrine organ) secretes progesterone. This is then followed by a secondary rise in estrogen levels during the midluteal phase and then declines at the end of the menstrual cycle.

The secondary rise in estradiol parallels with the rise of serum progesterone and 17-hydroxyprogesterone levels. Ovarian vein studies confirm that the corpus luteum is the site of steroid production during the luteal phase (Niswender, 1994).

Background Premenstrual Syndrome

Approximately 15% of menstruating women experience PMS (ACOG, 2000; NWHIC, 2004). Research further indicates that about 3 to 8 percent of those experience severe PMS or PMDD (as reported by APA in 2000; NWHIC, 2004) as diagnosed using prospective charting and verified with diagnostic criteria (Dye et al., 1995; Endicott, 2000; Wurtman, 1990). A recent study published in American Family Physician suggests that as many as 85 percent of menstruating women reported experiencing one or more premenstrual symptoms (Dickerson, Mazych, & Hunter, 2003). As a result of the widespread of the premenstrual syndrome phenomenon, researchers in many areas have attempted to examine it from different perspectives. Early waves of epidemiological studies had produced varied estimates of the prevalence of PMS and unscientific results due to the lack of efficient methodology (Moos, 1968; Parlee, 1973). In addition to trying to discover standard methods of measuring PMS and fine-tuning menstrual methodologies, social psychological research areas also begin to look into attitudes and expectations of menstrual experiences. Walker (1997) indicated that most of the research conducted in social psychology was done by psychologists who were keen to demonstrate that social factors as well as biological ones determine PMS experiences. Through common knowledge and social acceptance of the menstrual cycle and PMS, the number of women who endorsed that they have PMS raised during the 1970s (Walker, 1997).

Today, researchers in various areas of psychology and biomedicine continue to conduct etiological research.

Premenstrual syndrome appears to be a multifaceted disorder. Bancroft (1993) proposes a three-factor model in order to explain the etiology of PMS. First of all, the timing factor assumes that the hormonal cycle is mediated by varying levels of neurotransmitter activity that mediates mild changes that some women may experience premenstrually. Secondly, the timely variations of the hormonal cycle are affected by the increased levels of prostaglandins (precursor of progesterone) during the luteal phase, which lowers pain thresholds, increases fatigue and induces negative mood states. Lastly, women with PMS also have a predisposition toward neurotic and depressive traits, which are not directly related to the menstrual cycle, but may be exacerbated by luteal hormonal physiology, increasing the probability of maladaptive responses to stress. In addition to the three-factor theory, social theorists also suggest implications of cultural norms and expectations (Walker, 1995).

Etiological Perspectives

Biological. Genetic disposition facilitates the onset of most mood disorders including PMDD and PMS (Silberstein & Merriam, 2000). As early as the 1920's, Frank (1931) provided the basis for the present biomedical model of PMS. Furthermore, since the 1950s a wide range of etiologic theories have been advanced to explain the various manifestations of PMS (Khan-Sabir et al., 2003). This conceptualization posits that abnormal and intolerable moods occur when hormone levels are abnormal or excessive. Frank (1931) also suggests that (1) there is a progesterone efficiency, (2) excess estrogen, and (3) inappropriate ratios of the two

steroids. Later, Reid and Yen (1981) suggest that endogenous opioids form a link between ovarian hormones and PMS symptoms. Thus women with PMS have normal ovarian cycles but have a deficiency of opioids or a defective feedback sensitivity resulting in symptoms under normal hormonal conditions (Walker, 1995). In addition, McNatty and colleagues (1979) attributes the following etiology to PMS: altered levels or ratios of estrogen and progesterone, androgen excess, fluid retention, endogenous hormone allergy, vitamin and trace element deficiencies, prolactin excess, hypoglycemia, bacterial and yeast infections, thyroid dysfunction, endogenous opiate addiction and withdrawal, abnormal metabolism of essential fatty acids leading to prostaglandin E1 deficiency, and altered calcium metabolism, to mention a few (McNatty et al., 1979).

Psychological. Benedek and Rubenstein (1939) proposed, in a psychoanalytic framework, that changes in hormones across the menstrual cycle were correlated with changes in the focus of women's psychological conflicts. Generally, this view holds that physiological changes during the menstrual cycle were postulated to trigger particular conflicts resulting in cyclical anxiety and symptom formation in women (Severino & Moline, 1988). Others propose that psychological causes of PMS with (1) the correlation of PMS with personality profiles (e.g. especially neuroticism), (2) personality style—cognitive, coping and attribution, (3) rejection of female role, and lastly (4) adoption of the "sick role" (Walker, 1995).

Psychosocial. This perspective examines the role of emotions associated with PMS (Rodin, 1976; Ruble & Brooks-Gunn, 1979). Cyclical hormonal changes are acknowledged and are thought to correspond to changes in arousal. Note worthy,

arousal in itself is neutral, where labels for them are subjective. Attributions for arousal are in part affected by cultural beliefs and stereotypes of the individual and various environmental contexts (Walker, 1995). For example, Westerners tend to make more negative attributions regarding premenstrual experiences, where women of other cultural backgrounds are less likely to do so. A study conducted by Woods, Most & Dery (1982) concludes that when compared to a Bahrain sample, U.S and Italy women reported higher prevalence of premenstrual symptoms. The psychosocial model takes into account a combination of personal factors as well as external/environmental factors, and cultural expectations (Walker, 1995). Family environment may also play a role in that a high prevalence of a history of sexual abuse has been found in women seeking treatment for PMS (Kendler et al., 1998). In addition, women who experience high levels of stress may experience more severe PMS symptoms (Cox, 1977). Furthermore, Reid (1985) suggests that nutritional needs can bring forth changes premenstrually, making women more susceptible to food cravings (a symptom of PMS).

Supporting Evidence for each Perspectives

Biological. Research has yet specified how genetic predisposition affects experiences of PMS. Meanwhile, Severino & Moline (1988) report evidence that daughters of mothers with premenstrual tension are more likely to complain of premenstrual tension than daughters of mothers who are symptom free. They add, "If one monozygotic twin girl develops PMS, the other twin is extremely likely to be symptomatic as well". Biological disposition might play an important role in hormonal regulation, thereby affecting how the body functions (FitzGerald et al.,

1997; Lin & Thompson, 2001). As mentioned, some researchers suggest that there may be underlying biological vulnerabilities in women with PMS that might trigger changes in the production of hormones such as FSH and LH, ovarian steroids such as serotonin and progesterone, and perhaps also how these interact with normal bodily functions (Schmidt et al., 1994; 2002).

Khan-Sabir and colleagues (2003) suggested that during the luteal phase women with PMS were more likely to have decreased level of progesterone and FSH and increased levels of estradiol (Khan-Sabir et al., 2003). However, it remains questionable whether estrogen and progesterone is solely responsible for PMS. Further evidence suggests that estrogen and progesterone have a negative effect on the way nerve cells in the brain function, leading to premenstrual symptoms (FitzGerald et al., 1997). Premenstrual syndrome has been thought (since the 1930's) to be a result of decreased production of sex hormones by the ovaries after ovulation has taken place (in midcycle, or days 7-10 into the menstrual cycle) (Khan-Sabir et al., 2003). In other words, before menses (during the luteal phase), estrogen and progesterone levels start to drop, hence this period of time is referred to as "progesterone withdrawal" (Khan-Sabir et al., 2003). There is however, continual debate as to whether progesterone causes or relieves PMS symptoms. The common consensuses seem to be that progesterone and synthetic progestins can cause PMS types of mood symptoms (Jelovsek, 2004). Mortola at the Harvard Health institution suggests that the symptoms of excess progesterone are almost identical to the symptoms of its deficiency (as cited in Merck Source, 2004).

The changes in sex hormone levels affect certain brain chemicals which, in turn, bring about the mood changes that associate with PMS (Walker, 1995). Along the same rationale, Severino & Moline (1988) also believe that evidence suggest indirect effect of ovarian steroids in relation to other neurotransmitters and neuroendocrine systems that facilitate premenstrual mood changes rather than a simple explanation having to do only with fluctuations in the levels of steroid hormones. According to Steiner (1997), current researchers seem to agree that normal ovarian function, rather than hormone imbalance, is the cyclical trigger for PMDD-related biochemical events within the central nervous system and other target issues. Thus, it can be misleading to concentrate only on any one particular hormone (Rubinow et al, 1988).

Psychological. Psychological aspects of the menstrual cycle can be partly attributed to personality dispositions and psychopathology, social-learning, and psychosocial theories. Women with PMS consistently experience mood symptoms such as anxiety, irritability, and mood lability (Hurt et al., 1992). Bloch and colleagues (1997) also suggest that mood and not somatic symptoms account for most of the functional impairment in the group of women they examined. Similarly, Hurt and colleagues (1992) found that the highest prevalence among women presenting with PMS were anxiety, mood lability, anhedonia, depressed mood, decreased concentration, and sleep disturbance (Bloch et al., 1997). Evidence in these studies suggest that symptom in premenstrual disorder is a mood syndrome and not an epiphenomenon of premenstrual molimina.

In terms of personality disposition, heightened scores of neuroticism are commonly associated with women diagnosed of PMS (Berlin et al., 2001). Coppen and Kessel (1963) also suggest a positive correlation between neuroticism and severe PMS in a randomized sample of 500 patients. Slade and Jenner (1980) further suggest that high neuroticism scores were associated with premenstrual and menstrual symptoms. It appears that differences exist in PMS patients regarding personality characteristics as well as emotional functions. A high rate of comorbidity is present between depression and PMS. For example, Subhash and Shashi (2002) suggest that 30 to 76 percent of women diagnosed with PMDD have a lifetime history of depression compared to 15 percent of women without PMDD. The nature of psychopathology and PMS is still uncertain, but the following psychological disorders seem to co-occur with PMS: affective disorders (i.e. depression), anxiety (Halbreich & Endicott, 1985; Hart et al., 1987; Rubinow & Roy-Byrne, 1984; Schuckit el al., 1975; Wetzel et al., 1975). Recent research indicates that PMS may contribute to a decline in the ability to concentrate and a decrease in alertness and coordination (Lever & Brush, 1981; Rubinow & Roy-Byrne, 1984). An alternative explanation is provided by Haskett and colleagues (1984) suggesting that perhaps the co-occurrence of other psychiatric disorders and PMS, especially affective disorders, may in part reflect the lack of differentiation of these two disorders from each other.

Premenstrual dysfunction may also be a reflection of environmental variables (Day & Taylor, 1981). For instance, theorists think that bias in retrospective reporting may be responsible for the high rate of endorsement of PMS symptoms. In other words, they believe that self-reports are a reflection of woman's stereotyped

beliefs about menstruation (Paige, 1971; Parlee, 1973; 1974) rather than actual experiences. Additionally, Ruble (1977) showed that women who believe that they were in the premenstrual phase reported more symptoms than women who believe otherwise regardless of which actual cycle phase they were in. In sum, social learning theory alone can not sufficiently explain PMS experiences and a hindrance to this perspective is the limited empirical support. While literature in this area is primarily outdated, more recent research continues to evaluate the role of culture factors in PMS. These findings tend to convey that the negative views of menstruation are partly responsible for the experiences and reporting of premenstrual syndrome (Chrisler & Levy, 1990; Coutts & Berg, 1993; Walker, 1995; Sullivan, 2003). In addition, Parlee (1974) suggests that problems arise from measures such as the Menstrual Distress Questionnaire, whereby just reading the title is sufficient for providing stereotypical beliefs about psychological concomitants of menstrual changes. He also concludes that response to menarche is in part a socialization process into expecting negative emotional experiences. Another study looking at the validity of the menstrual questionnaire in a sample consisting of females and males demonstrate that males do experience certain symptoms of PMS as well and therefore concludes that there is no difference between the reports of both gender groups (Clarke & Ruble, 1978). However, note that though the experiences might be similar, PMS is diagnosed only for symptoms that are experienced with certain timeframe during the cycle. Research lead Sabin and Slade (1999) to believe that external stress does not exacerbate PMS symptoms. However, they suggested that somatic symptoms can make women more vulnerable to experiencing negative moods. This

finding is further reinforced by Lohstroh and colleagues (2003), suggesting that stressors facilitate changes in reproductive hormones. Because the social context for scientific work influences the focus of research and how questions are asked, it is important to understand then how the dominant social reality constructs menstrual phenomena and also what alternate constructions are the manifestation of the actual experiences resulting from biological and psychological factors (Dan & Monagle, 1990 p. 475). In support of the multifactorial model, Gallant and colleagues show that regardless of prior knowledge and expectations, there is no relationship to the attribution of mood changes (Gallant et al., 1991). Miller (2002) also provides another alternative explanation. He thinks that actual social factors can lead to gradual changes in the experiences of women who are susceptible to PMS. Miller suggests that environmental contexts determine whether certain behavior is adaptive and dictates how premenstrual experiences should be perceived. For example, premenstrual appetite increases carbohydrate cravings, which would be highly adaptive in a resource-poor environment because extra fuel is needed to build the uterine lining. On the contrary, an affluent society might interpret this change in appetite as a symptom (Miller, 2000).

Summary of Perspectives

It appears that PMS is most likely to occur in a woman who is genetically predisposed toward this disorder. The genetic may be expressed in excess levels of estrogen, prolactin, and prostaglandins along with a deficiency in progesterone level. Given the presence of the predisposition, factors such as psychological and psychosocial also play an important part in the development of this syndrome.

Psychological distress might be a function of environmental stressors, and cultural perspectives or beliefs may trigger or exacerbate the expression of PMS symptoms.

Summary Definitions of PMS

Despite the various methods incorporated to study PMS in many different research areas, the diagnostic criteria remain standard for the most part. The progressive search for a diagnostic tool resulted in a plausible solution at a workshop at the National Institutes of Mental Health (NIMH) in 1983. It was this workshop that proposed that a difference of 30 percent between premenstrual and postmenstrual mood scores to be the criterion for PMS as a clinical diagnosis (Endicott, 2000; Rubinow & Roy-Byrne, 1984; Severino & Moline, 1988; Walker 1997). Psychiatric definitions of PMS are concerned with the type of experience reported as well as its timing.

The difficulty remains because more than two hundred symptoms have been associated with PMS (Dickerson et al., 2003; Gotthell et al. 1999), but irritability, tension, and dysphoria, bloating or weight gain, breast tenderness, muscular tension, aches and pain (include headaches), and changes in appetite are most common (Rubinow & Roy-Byrne, 1984; Steiner & Born, 2000). PMS brings to surface the question of nature vs. nurture, in that it is comprised of social, psychological and biological changes. The DSM does not include diagnostic criteria for PMS, but only for a more severe form of it, which is classified as PMDD. However, according to International Classification of Diseases (ICD) criteria, PMS is diagnosed if one of the following symptoms is experienced during the luteal phase and ends beginning with messes: minor psychological discomfort, bloating or weight gain, breast tenderness,

muscular tension, aches and pain (include headaches), poor concentration, and changes in appetite. Other symptoms that are present frequently in research literatures include: depression, irritability and anger or short-temper. Some symptoms that indicate severe forms of PMS can include: depression, hot flashes, and sleep disturbances (Sullivan, 2003). However Laura Miller (2002) states that PMS typically includes physical changes such as bloating and breast tenderness, but does not include mood changes.

Differentiating PMS from PMDD

The American Psychiatric Association has debated for years whether to include PMS in the Diagnostic and Statistical Manual (fourth edition) (APA, 1994). While PMS remains uncategorized, the American Psychological Association decided to only include in its appendix (meaning that the subject requires further study) a condition labeled Premenstrual Dysphoric Disorder (PMDD). This was done in order to alert psychiatrists to a combination of specific severe symptoms (mostly psychiatric in nature) that could mimic other psychiatric disorders with the exception that the symptoms recurred in the premenstrual phase of the menstrual cycle. In 2000 The American Psychological Association reports that approximately 3%-5% menstruating women have Premenstrual Disphoric Disfunction (PMDD) as diagnosed using prospective charting and verified with diagnostic criteria (Dye et al., 1995; Wurtman, 1990). Premenstrual Dysphoric Disorder is defined by the DSM-IV with greater severity in its delineation compared to PMS. It requires that the woman chart symptoms daily for two cycles, and their chief complaints must include one of the four core symptoms (irritability, tension, dysphoria—depression or anhedonia,

irritability, anxiety, lability/or feeling of being overwhelmed, changes in appetite and sleep disturbances are also considered, and liability of mood) and at least 5 of 11 total symptoms (Steiner, 1997). Furthermore, the symptoms should have occurred with most menstrual cycles during the last year and interfered with social or occupational roles (Endicott, 2000). In addition, charting of troublesome symptoms should demonstrate clear worsening premenstrually and remit within a few days after the onset of menstruation. According to the DSM definition, PMDD consists of dysphoric mood and related symptoms occurring during the late luteal phase of most menstrual cycles, beginning and remit at or shortly after the onset of menses, and completely resolving within a week of onset (Endicott, 2000). Much like PMS, PMDD is distinguished from other mood disorders by a characteristic pattern of symptoms. There must be a clear interval of at least 7-10 days during each menstrual cycle when the women feel well mentally and physically (Walker, 1997).

Possible Treatments for PMS

Since symptoms of PMS are heterogeneous and individually variable between cycles, it is difficult to clearly indicate which treatment is best for the disorder. However, even though there is no particular best treatment for premenstrual syndrome, a decent one is progesterone injection or suppositories (Rubinow & Roy-Byrne, 1984; Walker, 1997). Some other possible and well researched treatments include: psychological counseling to increase coping skills in conjunction with medical treatment, vitamin supplements, and dietary or lifestyle changes.

Medical Treatments. Since PMS is a milder form of PMDD, it is less likely that physicians will prescribe pharmacological treatments. However, means of

controlling symptoms can include: oral contraceptives, GnRH agonists, danazol, oestrogen implants, and ovarictomy. There is also evidence that selective reuptake inhibitor (SSRIs) antidepressants are effective for severe PMS (Bosarge, 2004; Freeman, Rickels, Sondheimer, & Polansky, 1999; Moline et al., 2001). Freeman and colleagues (1999) further suggest that serotonergic drug can reduce symptoms, improve functioning, and are generally tolerated by women with severe premenstrual syndrome. The authors demonstrate that in addition, a history of depression did not alter the treatment results. The literature presently provides evidence for the use of antidepressants (SSRIs) and clomipramine for treating PMDD symptoms (Bosarge, 2004; Freeman et al., 2001; Steiner & Pearlstein, 2000; Steiner, 2000). Miller (2002) suggests that fluoxentine can also be effective for treating PMDD. However, the drug is associated with many side effects such as tiredness, nausea, nervousness, and dizziness. One possible solution for reducing side effects is to prescribe the drug for the luteal phase alone. For example, in a study of sertraline (Zoloft), Freeman and colleagues (1999) found that luteal-phase dosing is more effective than continuous dosing—participants who only take the drug during the luteal-phase when they experience PMS symptoms benefit more (Lin & Thompson, 2001). A possible explanation is that limiting use of the drug might reduce side effects by limiting medication exposure (Miller, 2002). In addition, Prozac (fluoxetine) is a promising solution that can be administered throughout the cycle during the luteal phase (Mortola, 1994; Steiner et al., 1995; Lin & Thompson, 2001; Severino, 1994). Additionally, Miller shows that antidepressants that have little effect on serotonin are not particularly good at alleviating premenstrual symptoms compared to placebo.

Likewise, Rubinow and Schmidt (1995) reveal that approximately 40% of women with PMS do not respond to fluoxetine or other serotonergic drugs. Most recently, the FDA has approved intermittent dosage of Paxil Control Release pill for treatment of PMDD (Women's Health Weekly, Mar 2004)

Lastly, oral contraceptives have been widely prescribed as a treatment for PMS (Megivern, 2002; Sveindottir & Backstrom, 2000; Women's Health, 2004), but there is little data to support their effectiveness. The ACOG (2000) bulletin advises that oral contraceptives may be considered if a patient's PMS symptoms are mostly physical, but they may not be effective if mood symptoms are primary. More generally, oral contraceptives and danozol have not been shown to reduce PMS and are the least effective methods mentioned (Bancroft & Rennie, 1993; Joffe et al., 2003; Muse, 1992; Walker, 1997). Arbitrary findings have been reported on the effectiveness of birth-control pills on alleviating symptoms of PMS. Joffe and colleagues (2003) show that approximately 71% of the participants in their experiment reports that premenstrual mood symptoms neither improve nor deteriorated as a result of using the pill. As a result, authors attribute these differences to the lack of consistency in methodology and symptom definition and times of symptom assessment (Rubinow et al., 1984). Conclusively, the search for a universal medical treatment is far from over.

Psychological Interventions. Since psychosocial stressors are known to alter brain neurochemistry and stress-related hormonal activity, stress reduction techniques such as relaxation training can reduce symptoms of anxiety and tension (Blake et al., 1998 as cited in Pearlstein & Steiner, 2000; Christensen & Oei, 1995; Goodale et al.,

1900). Psychotherapy is a possible treatment of PMS and PMDD. Furthermore, Goodale and colleagues (1990) suggest that cognitive behavior therapy (CBT) can be used to help women cope with symptoms. Morse and colleagues (1991) also demonstrate that CBT is as effective in treating symptoms as hormone-based therapy. A recent study found that cognitive-behavioral therapy was as effective as fluoxetine (20 mg daily), in the treatment of women with PMDD (Blake, Salkovskis, Gath, Day, & Garrod, 1998; Lin & Thompson, 2001). Other studies show that cognitive therapy including reviewing dysfunctional attitudes and increasing coping strategies was found to be more effective in experimental compared to wait-list control condition (Blake et al., 1998, as cited in Pearlstein & Steiner, 2000). In summary, it seems for many women, PMS can be alleviated by using learned coping skills, increased social support—especially from other women, and increased perception of control over life events (Prior et al., 1987; Walton & Youngkin, 1987).

Daily Supplements. Daily supplements such as Vitamin B6, Vitamin E, Calcium carbonate, magnesium, and tryptophan have demonstrated their effectiveness for treating PMS (Parry, 1985). Some studies suggest that Vitamin B6 only slightly reduces PMS symptoms (Tobin et al., 1994; Wyatt et al., 1999). Calcium supplements are, on the other hand, more effective for reducing core premenstrual symptoms (Bendich, 2000; Miller 2002; Thys-Jacobs et al., 1998). Furthermore, large controlled clinical trials firmly demonstrate the beneficial effects of calcium supplements in reducing PMS symptoms. Bhatia and colleagues (2002) suggest that daily supplemental vitamins and minerals may relieve some PMS symptoms. A multivitamin with B6(100 mg), B complex, magnesium (300mg), Vitamin E (400 IU)

and vitamin C (1000 mg) may be recommended to alleviate irritability, fluid retention, joint aches, breast tenderness, anxiety, depression and fatigue. While research in this area is relatively unstable, herbal remedies and homeopathic treatments have not been systematically tested.

Alternative Supplements and Herbals. While herbal preparations are touted and used for PMS, there are few empirical evaluations reporting their efficacy. Evening Primrose Oil and Borage Seed Oil have been suggested as treatments for PMS, but formal study of these have been extremely limited and they are not recommended (Budeiri et al., 1996). Borage Oil may not be safe because the plant contains potentially toxic alkaloids, which could contaminate the oil. Controlled clinical trials are also needed to assess the effectiveness and safety of Black Cohosh, wild yam root, chaste tree fruit, and dong quai and these are not recommended for use in treating PMS at this time (Bhatia & Shashi, 2002).

Herbal remedies may have some role in the treatment of premenstrual symptoms. One recent double-blind, placebo-controlled trial concluded that agnus cactus fruit extract (1 tab a day), also known as chasteberry (Huddleston & Jackson, 2001), significantly decreased premenstrual symptoms of irritability, anger, headache and breast fullness when compared to placebo (Schellenberg, 2001). In another study, gingko biloba was found to improve PMS symptoms, particularly breast tenderness and fluid retention. Though early evidence suggested that evening primrose oil was a useful treatment of PMS, a recent review found that it was no more effective than placebo (Schellenberg, 2001). Other botanical remedies used clinically but which

require further investigation include black cohash, St. John's Wort and Kava Kava (Bhatia C.S., Shashi, K.B., 2002).

Lifestyle Changes. For treatment of PMS, the most recent practice bulletin issued by ACOG (Clinical Management Guidelines No. 15, April 2000) recommends lifestyle changes such as aerobic exercise (Aganoff & Boyle, 1994; Steege & Blumenthal, 1993), a complex carbohydrate diet, and/or nutritional supplements such as calcium, magnesium, and vitamin E. Some empirical evidence suggest that modifications of diet and exercise can alleviate PMS symptoms (Miller, 2002; Reid, 1985; Prior et al., 1987); however, there is no evidence to date suggesting that eating six small meals at regular three-hour intervals, high in complex carbohydrates and low in simple sugars, will help maintain a stead blood glucose level and avoid energy highs and lows. Along the same line, Women's Health Website and Rivera-Tovar and colleagues (1994) (as cited in Walker, 1997) suggest a dieting restricting caffeine, alcohol, salt, fats, and simple sugars in order to reduce bloating, fatigue, tension and depression. Caffeine is known to worsen any anxiety state, so it makes sense to recommend discontinuing all caffeine-containing beverages and products. Rossignol (1985) and Rossignol and colleagues (1990) suggested that caffeine is a major trigger for PMS symptoms.

One of the symptoms of PMS and what irritates some women is the bloating feeling, thus many women with PMS gain several pounds during the two weeks preceding their period, much of this in fluid weight. Farr (2000) suggests that avoiding salty foods can dramatically reduce bloating and water buildup, resulting in less breast and abdominal tenderness and less swelling in the hands and feet. Also

since brain cells also have a tendency to retain fluid, a salt-free diet might alleviate headaches and improve concentration.

Successful treatments of PMS include: daily supplements, such as calcium, incorporated with lifestyle changes, such as diet and exercise, can reduce symptoms. Note that evidence for this is currently limited. Some evidence suggests also that pharmacological treatments are effective for several PMS or PMDD symptoms. Psychotherapy is also an alternative. Herbal remedies may be used, but are not yet well tested. Lastly, patients should be aware that some treatments might be more effective than others and individual preferences should be taken into account.

Caffeine Affinity of Premenstrual Syndrome

Caffeine avoidance can be helpful in alleviating prominent anxiety symptoms, as Diana Dell (2004) stated. However, it is controversial because she thinks that some women with lethargy may find caffeine helpful. In addition, Rossignol & Bonnlander (1990) suggests that caffeine is a major trigger for PMS symptoms. They found in a variety of substances—coffee, tea, soft drinks, chocolate and some over-the-counter medications—caffeine is a stimulant that is often consumed precisely for the "lift" it provides. Among women with more severe symptoms in their study, there appears to be a relationship between consumption of caffeine-containing beverages and premenstrual syndrome. Particularly, they suggest that the association between premenstrual symptoms and daily consumption of caffeine-containing beverages is dose-dependent. In another study sampling of 295 college sophomores, Rossignol (1985) found that caffeine-containing beverages are related to the presence and severity of premenstrual syndrome.

Caffeine affects bodily function because it resembles adenosine—a byproduct of cell's energy usage. Adenosine functions as a type of cellular signaling molecule. Therefore, the presence of adenosine plays a role in the regulation of cellular processes (James, 1997; Institute of Medicine, 2001). Caffeine effects brain function by preventing adenosine's ability to bind to its receptor (Gupta & Gupta 1999; Smith et al., 1999; Smith et al., 2004; Institute of Medicine, (2001). Caffeine does not directly increase brain activity; instead it only prevents the brain from controlling its own activity. Adenosine receptors function in the kidneys as well. Adenosine is present in the kidney to control blood flow and the amount of urine excreted. When caffeine blocks the receptors, the blood vessels in the kidney dilate, and thus more urine is created. Hence, caffeine reduces level of water-retention.

In addition, experiences of PMS seems to be mediated by level of serotonin and gamma aminobutyric acid (GABA) (Merck Source, 2004). The premenstrual phase is characterized by a decrease in progesterone level (Khan-Sabir et al., 2004). Progesterone also affects levels of amino acids and lipid metabolism (Merck Source, 2004). One hypothesis is that hormonal fluctuations of estrogen and progresterone in women may be capable of altering the pharmacokinetics of certain agents (Kamimori et al., 1999). Kamimori and colleagues administered caffeine (300mg in 100ml of lemonade) to menstruating women during the follicular and luteal phase and found that the menstrual cycle does not significantly alter the pharmokinetics of caffeine. However, Fenster and colleagues demonstrated through urine sample collection and daily diary that women who consume more than 300mg of caffeine had a double risk for short cycle length. Thus it might be that menstrual cycle does not affect the

function of caffeine, but that caffeine has potential for altering the cycle. Furthermore, caffeine elimination rate is slower during the luteal phase when progesterone level is also low (Fenster et al., 1999; Institute of Medicine, 2001).

Both caffeine and PMS tend to either interfere or enhance performance on behavioral and time reaction tasks (Institute of Medicine, 2001; Walker, 1997). Walker (1997) further states that psychological literature studies the fluctuations in sensory processes or arousality, which perhaps indirectly links to the neuroendocrinology processes of the menstrual cycle, thereby effecting task performance or ability to think. However, it would be misleading to attribute changes in ability to concentrate to changes in hormonal levels themselves, but the belief is that menstruating women tend to experience mood changes that may cause the difference in performance levels (Walker, 1997). Since caffeine potentially leads to increases in alertness in women experiencing PMS, ingesting caffeine might reinforce positive mood states in women with PMS. The bottom line is that caffeine consumptions appear to have implications on PMS experiences. However, due to the lack of research in this area, it remains difficult to say definitely how caffeine can affect PMS experiences. Therefore, there is very little evidence for a causal model available. Presently, research suggests that caffeine elimination is approximately 25% slower during the luteal phase of the menstrual cycle when progesterone levels are highest, compared to the follicular phase (Balogh et al., 1987; James, 1997; Institute of Medicine, 2001). Furthermore, clearance rate may be slightly faster in women than in men.

Background on Caffeine

Caffeine is the world's most widely used stimulate drug (Karch, 1993; James, 1997; Smith et al., 2006). Of the numerous "substances" ingested, caffeine remains the most popular. More than 80% of the world's population, irrespective of age, gender, geography, and culture, consumes caffeine daily (Dews, 1984; James, 1997). Caffeine, also known as trimethylxanthine, is one of the families of methylated xanthines, often referred to as methylxanthines or simply xanthines (Gupta & Gupta 1999; James, 1997). In anhydrous form, caffeine is a white odorless powder with a bitter taste. The principal sources of the drug are overwhelmingly coffee and tea, which account for about 80% of dietary use (Smith et al., 1998 in Spiller, 1998).

Caffeine is a stimulant drug that increases cellular metabolism and also influences physiological and psychological functions (Burke, 1980). Furthermore, Smith and colleagues (1993) examined gender differences in effects of caffeine on physiology. Physiological effects of caffeine include cardiovascular, respiratory, renal, and smooth muscle effects. In addition, it affects mood, memory, alertness, and physical and cognitive performance (Institute of Medicine, 2001). Caffeine's effect on cognitive function appears to be mediated via many mechanisms: the antagonism of adenosine receptors, the inhibition of phosphodiesterases, the release of calcium from intracellular stores, and antagonism of benzodiazepine receptors (Myers et al, 1999; Institute of Medicine, 2001).

Caffeine distributes freely into intracellular water of all body tissues including gonadal tissues (Goldstein & Warren, 1962). While the exact mechanism of caffeine has not been determined, most evidence suggests that it increases cellular metabolism by inhibiting phosphodiesterase (Burke, 1980). Phosphodiesterase is an enzyme that inactivates cyclic AMP (adenosine monophosphate), which is an energy carrier nucleotide that acts as a biochemical regulator in the cell (Truitt, 1971). A large amount of AMP exists in the central nervous system compared to other body tissues, although caffeine seems to be distributed evenly throughout the body. Furthermore Grollman & Grollman (1970) and Truitt (1971) found that caffeine primarily stimulates the central nervous system.

Pharmacokinetics refers to the biological fate of a compound that has been ingested by a living organism, and it is a composite of the processes of absorption, distribution, metabolism, and excretion. Following oral ingestion, caffeine is rapidly absorbed from the gastrointestinal tract into the bloodstream (James, 1997). According to Karch (1993) approximately 90% of the caffeine contained in a cup of coffee is cleared from the stomach within 20-45 minutes (Institute of Medicine, 2001; Karch, 1993), and peak plasma concentration is reached at about 40 to 60 minutes (James, 1997).

The rate of absorption is affected by the presence of food in the intestine. If more food is present, caffeine metabolism will slow down (Institute of Medicine, 2001). The peak of plasma concentration is positively correlated with amount of consumption (James, 1997). In addition, caffeine concentration found in blood is also synonymous with caffeine found in saliva (James, 1997; Karch, 1993). Caffeine can

pass through all biological membranes and readily crosses the blood-brain barrier. There are also theories that suggest caffeine constricts blood vessels in the brain possibly causing headaches (Burke, 1980). Likewise, the absence of caffeine (withdraw effects) can also cause similar effects (Institute of Medicine, 2001). Other withdrawal symptoms of caffeine include: headache, depression, fatigue, lethargy, irritableness, increased muscle tension, nausea, and vomiting (Gupta & Gupta, 1999; Institute of Medicine, 2001).

In humans, the elimination half-life of caffeine generally varies between about 3 to 7 hours (James, 1997). Elimination averages about 5 hours and is not dependent on amount to any significant diurnal variation (Institute of Medicine, 2001). Rate of elimination varies depending on age, pregnancy, disease, and the use of other substances. For example as mentioned, caffeine elimination is approximately 25% slower during the luteal phase of the menstrual cycle when progesterone levels are highest, compared to the follicular phase (Balogh et al., 1987; Institute of Medicine, 2001; James 1997). Furthermore, the clearance rate may be slightly faster in women than in men. Cigarette smoking increases the rate of clearance by twice as much, contrarily, oral contraceptives decrease clearance by about the same order of magnitude (Kaminori et al., 1999; Patwardhan et al., 1980 as cited in James 1997).

The pharmacological effects of moderate caffeine consumption include: mild CNS stimulation and alertness, ability to sustain intellectual activity, and decreased reaction time (Institute of Medicine, 2001). Caffeine's physiological effects include decreased blood flow in the cerebral and increase systolic blood pressure (Cameron et al. 1990 as cited in Karch, 1993). The decrease in cerebral blood flow is a function of

adenosine receptors being blocked. Inhibition of numerous neurotransmitters such as benzodiazepines, neropinephrine, dopamine, serotonin, acetylcholine, glutamate, and GABA results from the mediating effect of adenosine receptors (Gupta & Gupta, 1999). Furthermore, adenosine inhibited the release of neurotransmitters from presynaptic neurons and modified the response to neurotransmitters postsynaptically (Gupta & Gupta 1999; Rall, 1990).

While dopamine is increased as a result of administration of caffeine, it decreases levels of serotonin, affecting sleep mechanisms, motor functions, and regulation of cerebral blood vessels (Gupta & Gupta 1999 pg.21). Adenosine concentrations are mainly regulated by ATP metabolism. So increasing the breakdown of ATP induces an increase in adenosine concentration (Latini et al., 2001). Davis and colleagues (2002) looked at the effects of caffeine on treadmill exercise in rats. Their findings supported the hypothesis that "intracerebroventricular CNS administration of the selective adenosine A1 and A2 receptor agonist NECA significantly reduced run time to fatigue, whereas intracerebroventricular caffeine increased run time to fatigue". This suggests that the effects of intracerebroventricular caffeine are mediated via blockade of the adenosine receptors in rats.

Ingestion of large amounts of caffeine (~10-14g) can result in aversive effects such as, convulsion, vomiting, restlessness, nervousness, and irritability. According to Karch (1993), consumption level of approximately 24 grams can result in death. The benefit of caffeine consumption is evidently dose-dependent, Smith and colleagues (2004) show that doses of approximately 300 mg will lead to positive effectives,

whereas higher levels of consumption might lead to experiences of negative affective mood.

Caffeine and Mood. Caffeine's effects on mood are often examined with respect to measures of arousal. Many studies have looked at alertness following caffeine consumption (Gupta & Gupta, 1999); however, the extent to which the effects of caffeine are perceived to be positive depends on not only the dose, but also the precaffeine arousal state of the individual. Smith and colleagues (2004) acknowledges that mood can be defined in many ways and using many different scales, but research has provided a fairly consistent picture of the effects of caffeine on mood state. Accordingly, psychological effect of caffeine is an increase in feelings of alertness produced by the arousing effects of the drug as it blocks adenosine receptor action, causing the physiological state of arousal that leads to the psychological state of alertness. Alertness is certainly one of the more consistent effects of caffeine (Kamimori et al., 2000). Overall, low dosage of caffeine tends to enhance positive mood states and that high doses are associated with negative affective changes (Smith et al., 2004). These changes in mood on either direction is a function of the individual's arousal state at the time of drug administration, with lower preexisting arousal levels yielding to larger drug effects (Smith et al., 2004).

Caffeine and Information Processing. In addition to mood, cognitive processes are also a function of caffeine consumption. Some research studies demonstrate that caffeine yields desirable increases in alertness and reduces reaction time on certain information processing tasks (Smith et al., 1992; Wilder et al., 1988). Studies also demonstrate that caffeine enhances problem-solving, improves logical

reasoning, and increases performance on arithmetic tasks (France et al., 1988; Lane et al., 1985). In addition, Krautz (1999) as cited Institute of Medicine (2001) used visual analogue scales to show that caffeine intake leads to reports of decreased sleepiness and increased concentration, alertness, confidence, talkativeness, and energy levels. Caffeine's function is dose-dependent such that an inverted U-curve can be applied to explain its dose-dependent functioning. For instance, several studies show that when high dosage is consumed information processes are hindered (Linde et al., 1994; Institute of Medicine, 2001). In particular, anxiety, jitteriness and nervousness are some side effects noted (Institute of Medicine, 2001). It can negatively affect scores on spatial processes. In addition to affecting information processing, memory, and vigilance performance, caffeine also affects the level of distractibility (Spiller, 1998). Caffeine has been shown to exacerbate the experience of stress on neuroendocrine responses (Lane et al., 1990).

Caffeine also affects mood states. Dosages greater than 300mg can lead to experiences of negative mood and higher levels of anxiety (Carrillo et al., 1996). A major contributing factor in anxiety is stress, thus a reasonable hypothesis might be that stress is an area of psychological functioning that is affected by caffeine (Smith, 1994). Since stress significantly affects the immune system by increasing the vulnerability of developing infectious disorders among other physical diseases. Caffeine increases physiological arousal, thus placing the body on stress-mode.

Caffeine's Potential for Abuse and Dependence. Caffeine is the most widely psychoactive drug consumed, thus it has considerable potential for abuse. The most noticeable behavioral effects after low or moderate doses of caffeine are increased in

alertness, energy, and ability to concentrate (Gupta & Gupta, 1999). Higher dosage can lead to more harmful effects such as caffeine intoxication or caffeinism, a state characterized by anxiety, restlessness, insomnia, and tachycardia. Griffdiths & Chausmer (2000) theorized that caffeine's effect on the central nervous system and behavioral reinforcing properties were addictive factors. Drug dependence can be defined as a pattern of behavior focused on the repetitive and compulsive seeking and taking of a psychoactive drug (Gupta & Gupta 1999; Smith et al., 2004). Drug dependence is differentiated from physical dependence in that it is not dependence on withdrawal or of intrinsic properties of the drug, but rather, it is a function of a combination of the properties of the drug, environmental factors, and the individual (Gupta & Gupta 1999). Caffeine is a drug that belongs in the middle or lower end of the continuum of the dependence-producing drugs. Furthermore, "Caffeine does not lead to the level of physical dependence comparable to nicotine, heroin or ethanol, but it does elicit some effects typical of dependence-producing drugs" (Gupta & Gupta, 1999). Caffeine enhances cognitive performance leading to experiences of positive reinforcement; in addition, it also alleviates withdrawal symptoms, which can be attributed as negative reinforcement (Smith et al., 2004). Caffeine partially meets the primary criteria of drug dependence according to Gupta & Gupta (1999) and Smith et al, (2004) because, (1) it is a psychoactive drug, (2) it is used by most individuals with minor problems, but a small number of people do have difficulties abstaining from consumption. (3) caffeine can also function as a reinforcer in animals, even though its reinforcing effects in humans are limited to certain conditions. As a result of the prevalence of caffeine consumption in the general

population, the International Classification of Diseases (ICD-10) includes a category of "Mental and behavioral disorders due to use of other stimulants, including caffeine" that can be used to diagnose caffeine dependence, caffeinism, harmful use, and withdrawal (ICD-10, 1992).

Withdrawal. As described in Gupta & Gupta (1999), the first controlled study that examines caffeine withdrawal was performed by Dreisbach and Pfeiffer (1943). The authors reported that after seven days of heavy caffeine consumption, subjects had severe withdrawal symptoms such as: throbbing headache, nausea, vomiting, and drowsiness, disinclination to work, mental depression, and yawning. Caffeine withdrawal symptoms included: headaches, tension, fatigue, decreased attention, increased anxiety, irritability, disturbed concentration, nausea/vomiting, depression, dysphoric mood, and symptoms of stress (Spiller, 1998). These symptoms are similar to nicotine withdrawal effects, and can impair behavior functioning. However, low-dose consumption does not lead to withdrawal symptoms when stopped (Rogers et al., 1995 as cited in Spiller, 1998), in addition, symptoms only occur at total abstinence.

Evidence among low-to-moderate dose consumers is not well defined. In a detailed study looking at moderate caffeine consumers, researchers found that during the placebo period subjects report abnormally high Beck Depression Inventories than when on caffeine. Furthermore, subjects on placebo, or in caffeine withdrawal, rated higher anxiety level, high fatigue scores, and most strikingly, over half complained of headache (Silverman et al., 1992). Another study (cited in Gupta & Gupta, 1999) showed that short-term caffeine withdrawal was associated with reports of decreased

vigor, increased fatigue, sleepiness, and yawning. Withdrawal symptoms will appear approximately 12 to 24 hours after abstinence and gradually disappear (Gupta & Gupta, 1999).

Individual Variation. One of the most ubiquitous beliefs about caffeine is that its affects vary greatly from individual to individual in the normal population. However, studies cited in Dews (1984 pg. 94) conducted by (Goldstein et al., 1965 and Dews, 1982) demonstrate that factors such as dosage and absorption rate are the cause of apparent differences in behavior. They also added that tolerance level is also a factor in behavioral differences. Thus, characteristically, people who are low-consumers or non-consumers tended to be the ones who are also caffeine sensitive. In addition to environmental factors such as dietary intake, tolerance, and subjective experiences, and genetic disposition are important considerations (Smith et al., 2004; Gupta & Gupta 1999). Hence it is difficult to tease apart the effects of environmental and genetic influences in individual differences on physiology and behavior due to caffeine ingestion. It is very likely that both environmental and genetic factors serve to explain why certain individuals experience extreme arousing effects with a small dose, while others react minimally to larger doses. Personality dimensions in arousability or arousal potential will also yield to individual differences (Gupta & Gupta, 1999). Often extraversion, as measured by Eysenck, reveals less arousal as a result of caffeine ingestion. Introverts are more likely to experience higher heart rate reactivity, higher skin conductance levels (Smith, et al. 1986; Smith et al., 2004).

Summary of Literature Review

Women have been advised to reduce caffeine consumption to decrease premenstrual symptoms; however, little evidence seems to be available to validate this advice. The research available in this area is vague and suggestive. For instance, the Women's Health Website and Rivera-Tovar and colleagues (1994) (as cited in Walker, 1997) suggest that substantially reducing the use of caffeine, alcohol, salt, fats, and simple sugars to reduce bloating, fatigue, tension and depression. Rossignol and colleagues also suggested associations between caffeine intake and the prevalence of PMS (Rossignol et al, 1985; 1989; 1990; 1991).

Table 1: *Racial distribution of sample compared to the population of students at the University of Maryland in 2004.*

Race	*Sample (N)*	*Sample (%)*	*University (%)*
White American	72	65.4	60.2
Black American	15	13.7	8.7
Asian American	9	8.2	10.7
Latin American	14	12.7	20.4

N = Number of participants in each ethnic group

Table 2: *Chi-square Comparisons for the Control and PMS Groups*

Chi-Square Comparisons	Control		PMS	
Information	Total	Percent	Total	Percent
Caffeine Restriction (Yes)	13	54.2%	11	45.8%
Marital Status	4	100%	0	0%
Oral Contraceptives	17	53.1%	15	46.9%
Regular Medication	18	64.3%	10	35.7%
Cigarette Smoking	2	66.7%	1	33.3%

Caffeine Menstrual

35. Age:
36. What ethnicity do you consider yourself?
    a. Caucasian American
    b. African American
    c. Asian/Pacific American
    d. Hispanic American
    e. Other
37. Marital Status
    a. 1 = Single
    b. 2 = Married and living with spouse
    c. 3 = Separated married not living with spouse
    d. 4 = Divorced
38. Do you take oral contraceptives?
    YES NO
39. Are you pregnant?
    YES NO
40. Do you take any medication regularly?
    YES NO
41. If you do take medication regularly, state what kind and how much.
42. How much COFFEE (CUPS)do you drink daily?
43. How much TEA (CUPS) do you drink daily?
44. How many COLA DRINKS (CANS) do you drink daily?
45. Please indicate if you take NODOZ on a regular basis.
    YES NO
46. Please indicate if you take VIVARIN on a regular basis.
    YES NO

47. Please indicate if you take ANACIN on a regular basis.
    ☐ YES ☐ NO
48. Please indicate if you take A.S.A. COMPOUND on a regular basis.
    ☐ YES ☐ NO
49. Please indicate if you take BROMO SELTZER on a regular basis.
    ☐ YES ☐ NO
50. Please indicate if you take COPE on a regular basis.
    ☐ YES ☐ NO
51. Please indicate if you take COUNTERPAIN on a regular basis.
    ☐ YES ☐ NO
52. Please indicate if you take EXCEDRIN on a regular basis.
    ☐ YES ☐ NO
53. Please indicate if you take EMPIRIN COMPOUND on a regular basis.
    ☐ YES ☐ NO
54. Please indicate if you take FEMICIN on a regular basis.
    ☐ YES ☐ NO
55. Please indicate if you take MEDACHE on a regular basis.
    ☐ YES ☐ NO
56. Please indicate if you take MIDOL on a regular basis.
    ☐ YES ☐ NO
57. Please indicate if you take PAC on a regular basis.
    ☐ YES ☐ NO
58. Please indicate if you take SAL-FAYNE on a regular basis.
    ☐ YES ☐ NO
59. Please indicate if you take STANBACK on a regular basis.
    ☐ YES ☐ NO
60. Please indicate if you take TRIGESIC on a regular basis.
    ☐ YES ☐ NO
61. Do you smoke cigarettes?
    ☐ YES ☐ NO
62. If you do, how many cigarettes do you smoke daily? _____
63. What brand do you smoke? _____
64. Have you ever experience adverse (highly unpleasant or problematic) reactions to caffeine?
    ☐ YES ☐ NO
65. If yes, please indicate when. _____
66. If yes, please indicate how many times this has happened. _____

67. Describe your symptom(s).

68. What did you consume (e.g. chocalate bar, Starbucks coffee, caffeine pill, etc.)?

69. Have you or any member(s) of your family been diagnosed with depression?

☐ YES ☐ NO

70. If yes, please indicated who and the date of the diagnosed?

71. Are you lactose-intolerant?

☐ YES ☐ NO

Caffeine Menstrual

72. During the last 4 weeks, how much have you been bothered by STOMACH PAIN?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot
73. During the last 4 weeks, how much have you been bothered by BACK PAIN?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot
74. During the last 4 weeks, how much have you been bothered by PAIN IN YOUR ARMS, LEGS, OR JOINTS (KNEES, HIPS, ETC.)?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot
75. During the last 4 weeks, how much have you been bothered by MENSTRUAL CRAMPS OR OTHER PROBLEMS WITH YOUR PERIODS?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot
76. During the last 4 weeks, how much have you been bothered by PAIN OR PROBLEMS DURING SEXUAL INTERCOURSE?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot
77. During the last 4 weeks, how much have you been bothered by HEADACHES?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot

78. During the last 4 weeks, how much have you been bothered by CHEST PAIN?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot
79. During the last 4 weeks, how much have you been bothered by DIZZINESS?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot
80. During the last 4 weeks, how much have you been bothered by FAINTING SPELLS?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot
81. During the last 4 weeks, how much have you been bothered by FEELING YOUR HEART POUND OR RACE?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot
82. During the last 4 weeks, how much have you been bothered by SHORTNESS OF BREATH?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot
83. During the last 4 weeks, how much have you been bothered by CONSTIPATION, LOOSE BOWELS, OR DIARRHEA?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot
84. During the last 4 weeks, how much have you been bothered by NAUSEA, GAS, OR INDIGESTION?
    a. ☐ 1. Not bothered
    b. ☐ 2. Bothered a little
    c. ☐ 3. Bothered a lot
85. Over the last 2 weeks, how often have you been bothered by LITTLE INTEREST OR PLEASURE IN DOING THINGS?

a. ☐ 1. Not at all
b. ☐ 2. Several days
c. ☐ 3. More than half the days
d. ☐ 4. Nearly every day

86. Over the last 2 weeks, how often have you been bothered by FEELING DOWN, DEPRESSED, OR HOPELESS?
    a. ☐ 1. Not at all
    b. ☐ 2. Several days
    c. ☐ 3. More than half the days
    d. ☐ 4. Nearly every day
87. Over the last 2 weeks, how often have you been bothered by TROUBLE FALLING OR STAYING ASLEEP, OR SLEEPING TOO MUCH?
    a. ☐ 1. Not at all
    b. ☐ 2. Several days
    c. ☐ 3. More than half the days
    d. ☐ 4. Nearly every day
88. Over the last 2 weeks, how often have you been bothered by FEELING TIRED OR HAVING LITTLE ENERGY?
    a. ☐ 1. Not at all
    b. ☐ 2. Several days
    c. ☐ 3. More than half the days
    d. ☐ 4. Nearly every day
89. Over the last 2 weeks, how often have you been bothered by POOR APPETITE OR OVEREATING?
    a. ☐ 1. Not at all
    b. ☐ 2. Several days
    c. ☐ 3. More than half the days
    d. ☐ 4. Nearly every day
90. Over the last 2 weeks, how often have you been bothered by FEELING BAD ABOUT YOURSELF, OR THAT YOU ARE A FAILURE, OR HAVE LET YOURSELF OR YOUR FAMILY DOWN?
    a. ☐ 1. Not at all
    b. ☐ 2. Several days
    c. ☐ 3. More than half the days
    d. ☐ 4. Nearly every day

91. Over the last 2 weeks, how often have you been bothered by TROUBLE CONCENTRATING ON THINGS, SUCH AS READING THE NEWSPAPER OR WATCHING TELEVISION?
    a. ☐ 1. Not at all
    b. ☐ 2. Several days
    c. ☐ 3. More than half the days
    d. ☐ 4. Nearly every day
92. Over the last 2 weeks, how often have you been bothered by MOVING OR SPEAKING SO SLOWLY THAT OTHER PEOPLE COULD HAVE NOTICED; OR THE OPPOSITE - BEING SO FIDGETY OR RESTLESS THAT YOU HAVE BEEN MOVING AROUND A LOT MORE THAN USUAL?
    a. ☐ 1. Not at all
    b. ☐ 2. Several days
    c. ☐ 3. More than half the days
    d. ☐ 4. Nearly every day
93. Over the last 2 weeks, how often have you been bothered by THOUGHTS THAT YOU WOULD BE BETTER OFF DEAD, OR OF HURTING YOURSELF IN SOME WAY?
    a. ☐ 1. Not at all
    b. ☐ 2. Several days
    c. ☐ 3. More than half the days
    d. ☐ 4. Nearly every day
94. In the last 4 weeks, have you had an ANXIETY ATTACK - SUDDENLY FEELING FEAR OR PANIC? Note: if you checked NO please scroll down to the question beginning with a *
    a. ☐ 1. No
    b. ☐ 2. Yes
95. Have you ever HAD AN ANXIETY ATTACK BEFORE?
    a. ☐ 1. No
    b. ☐ 2. Yes
96. Do some of these ANXIETY ATTACKS come suddenly out of the blue - that is, in situations where you do not expect to be nervous or uncomfortable?
    a. ☐ 1. No
    b. ☐ 2. Yes
97. Do these ANXIETY ATTACKS bother you a lot or are you worried about having another attack?

a. ☐ 1. No

b. ☐ 2. Yes

98. Thinking about your last bad anxiety attack, WERE YOU SHORT OF BREATH?

a. ☐ 1. No

b. ☐ 2. Yes

99. Thinking about your last bad anxiety attack, DID YOUR HEART RACE, POUND, OR SKIP?

a. ☐ 1. No

b. ☐ 2. Yes

100. Did you have chest pain or pressure?

a. ☐ 1. No

b. ☐ 2. Yes

101. Did you sweat?

☐ YES ☐ NO

102. Did you feel as if you were choking?

☐ YES ☐ NO

103. Did you have hot flashes or chills?

☐ YES ☐ NO

104. Did you have nausea or an upset stomach, or the feeling that you were going to have diarrhea?

☐ YES ☐ NO

105. Did you feel dizzy, unsteady, or faint?

☐ YES ☐ NO

106. Did you have tingling or numbness in parts of your body?

☐ YES ☐ NO

107. Did your tremble or shake?

☐ YES ☐ NO

108. Were you afraid you were dying?

☐ YES ☐ NO

109. *Over the LAST 4 WEEKS, how often have you been bothered by feeling nervous, anxious, on edge, or worrying a lot about different things. Note: If you checked NOT AT ALL, scroll down to the next question beginning with a *

a. ☐ 1 = Not at all

b. ☐ 2 = Several days

c. ☐ 3 = More than half the days

110. Over the LAST 4 WEEKS, how often have you been bothered by feeling restless so that it is hard to sit still?

a. ☐ 1 = Not at all

b. ☐ 2 = Several days

c. ☐ 3 = More than half the days

111. Over the LAST 4 WEEKS, how often have you been bothered by getting tired very easily?

a. ☐ 1 = Not at all

b. ☐ 2 = Several days

c. ☐ 3 = More than half the days

112. Over the LAST 4 WEEKS, how often have you been bothered by muscle tension, aches, or soreness?

a. ☐ 1 = Not at all

b. ☐ 2 = Several days

c. ☐ 3 = More than half the days

113. Over the LAST 4 WEEKS, how often have you been bothered by having trouble falling asleep or staying asleep?

a. ☐ 1 = Not at all

b. ☐ 2 = Several days

c. ☐ 3 = More than half the days

114. Over the LAST 4 WEEKS, how often have you been bothered by havign trouble concentrating on thins, such as reading a book, watching TV, etc.?

a. ☐ 1 = Not at all

b. ☐ 2 = Several days

c. ☐ 3 = More than half the days

115. Over the LAST 4 WEEKS, how often have you been bothered by becoming easily annoyed or irritable?

a. ☐ 1 = Not at all

b. ☐ 2 = Several days

c. ☐ 3 = More than half the days

116. *Questions about eating: Do you often feel that you can't control WHAT or HOW MUCH you eat?

☐ YES ☐ NO

117. Questions about eating: Do you often eat, WITHIN ANY 2-HOUR PERIOD, what most people would regard as a unusually LARGE amount of food? Note: If you answered NO to etheir this or the previous question, please

scroll down to the next question beginning with the *

☐ YES ☐ NO

118. Questions about eating: has this been often, on average as twice a week for the last 3 months.

☐ YES ☐ NO

119. In the LAST 3 MONTHS have you OFTEN MADE YOURSELF VOMIT in order to avoid gaining weight?

☐ YES ☐ NO

120. In the LAST 3 MONTHS have you OFTEN TOOK MORE THAN TWICE THE RECOMMENDED DOSE OF LAXATIVES in order to avoid gaining weight?

☐ YES ☐ NO

121. In the LAST 3 MONTHS have you OFTEN FASTED-NOT EATEN ANYTHING FOR AT LEAST 24-HOURS in order to avoid gaining weight?

☐ YES ☐ NO

122. In the LAST 3 MONTHS have you OFTEN EXCERCISED FOR MORE THAN AN HOUR SPECIFICALLY TO AVOID GAINING WEIGHT AFTER BINGE EATING?

☐ YES ☐ NO

123. If you checked YES to any of the above methods to avoid gaining weight, were any as often, on average, as twice a weeks?

☐ YES ☐ NO

124. * Do you ever drink alcohol (including beer or wine)? Note: if you checked NO scroll down to the next question beginning with the *

☐ YES ☐ NO

125. Have any of the following happened to you MORE THAN ONCE IN THE LAST 6 MONTHS: YOU DRANK ALCOHOL EVEN THOUGH YOU DOCTOR SUGGESTED THAT YOU STOP DRINKING BECAUSE OF A PROBLEM WITH YOUR HEALTH?

☐ YES ☐ NO

126. Have any of the following happened to you MORE THAN ONCE IN THE LAST 6 MONTHS: YOU DRANK ALCOHOL, WERE HIGH FROM ALCOHOL, OR HUNG OVER WHILE YOU WERE WORKING, GOING TO SCHOOL, OR TAKING CARE OF CHILDREN OR OTEHR RESPONSIBILITIES?

☐ YES ☐ NO

127. Have any of the following happened to you MORE THAN ONCE IN THE LAST 6 MONTHS: YOU MISSED OR WERE LATE FOR WORK, SCHOOL, OR OTHER ACTIVITIES BECAUSE YOU WERE DRINKING OR HUNG OVER?

☐ YES ☐ NO

128. Have any of the following happened to you MORE THAN ONCE IN THE LAST 6 MONTHS: YOU HAD A PROBLEM GETTING ALONG WITH PEOPLE WHILE YOU WERE DRINKING?

☐ YES ☐ NO

129. Have any of the following happened to you MORE THAN ONCE IN THE LAST 6 MONTHS: YOU DROVE A CAR AFTER HAVING SEVERAL DRINKS OR AFTER DRINKING TOO MUCH?

☐ YES ☐ NO

130. * If you checked off ANY problems on this page, how DIFFICULT have these problems made it for you to do your work, take care of things at home, or get along with other people?

a. ☐ 1 = Not difficult at al
b. ☐ 2 = Somewhat difficult
c. ☐ 3 = Very difficult
d. ☐ 4 = Extremely difficult

131. During the LAST 4 WEEKS, how much have you been bothered by WORRYING ABOUT YOUR HEALTH?

a. ☐ 1 = Not bothered at all
b. ☐ 2 = Bothered a little
c. ☐ 3 = Bothered a lot

132. During the LAST 4 WEEKS, how much have you been bothered by YOUR WEIGHT OR HOW YOU LOOK?

a. ☐ 1 = Not bothered at all
b. ☐ 2 = Bothered a little
c. ☐ 3 = Bothered a lot

133. During the LAST 4 WEEKS, how much have you been bothered by LITTLE OR NO SEXUAL DESIRE OR PLEASURE DURING SEX?

a. ☐ 1 = Not bothered at all
b. ☐ 2 = Bothered a little
c. ☐ 3 = Bothered a lot

134. During the LAST 4 WEEKS, how much have you been bothered by DIFFICULTIES WITH HUSBAND/WIFE, PARTNER/LOVER OR BOYFRIEND/GIRLFRIEND?

a. ☐ 1 = Not bothered at all
b. ☐ 2 = Bothered a little
c. ☐ 3 = Bothered a lot

135. During the LAST 4 WEEKS, how much have you been bothered by THE STRESS OF TAKING CARE OF CHILDREN, PARENTS OR OTHER FAMILY MEMBERS?

a. ☐ 1 = Not bothered at all

b. ☐ 2 = Bothered a little

c. ☐ 3 = Bothered a lot

136. During the LAST 4 WEEKS, how much have you been bothered by STRESS AT WORK OR OUTSIDE OF THE HOME OR AT SCHOOL?

a. ☐ 1 = Not bothered at all

b. ☐ 2 = Bothered a little

c. ☐ 3 = Bothered a lot

137. During the LAST 4 WEEKS, how much have you been bothered by FINANCIAL PROBLEMS OR WORRIES?

a. ☐ 1 = Not bothered at all

b. ☐ 2 = Bothered a little

c. ☐ 3 = Bothered a lot

138. During the LAST 4 WEEKS, how much have you been bothered by HAVING NO ONE TO TURN TO WHEN YOU HAVE A PROBLEM?

a. ☐ 1 = Not bothered at all

b. ☐ 2 = Bothered a little

c. ☐ 3 = Bothered a lot

139. During the LAST 4 WEEKS, how much have you been bothered by SOMETHING BAD THAT HAPPENED RECENTLY?

a. ☐ 1 = Not bothered at all

b. ☐ 2 = Bothered a little

c. ☐ 3 = Bothered a lot

140. During the LAST 4 WEEKS, how much have you been bothered by: thinking or dreaming about something terrible that happened to you IN THE PAST (ie. your house being destroy, a severe accident, being hit or assaulted, or being forced to commit a sexual act?

a. ☐ 1 = Not bothered at all

b. ☐ 2 = Bothered a little

c. ☐ 3 = Bothered a lot

141. In the last year, have you been hit, slapped, kicked or otherwise physically hurt by someone, or has anyone forced you to have an unwanted sexual act?

☐ YES ☐ NO

142. What is the most stressful thing in your life right now?

143. Are you taking any medicine for anxiety, depression or stress?

☐ YES ☐ NO

144. THIS SECTION ON IS FOR WOMEN ONLY: Questions pertaining to menstruation, pregancy, and childbirth. Which best describes your menstrual periods?

a. ☐ 1 = Periods are unchanged

b. ☐ 2 = No periods because of pregnancy or recently gave birth

c. ☐ 3 = Periods have become irregular or changed in frequency, duration or amount

d. ☐ 4 = No periods for at least a year

e. ☐ 5 = Having periods because taking hormone replacement (estrogen) therapy or oral contraceptive

145. During the week before your period starts, do you have a SERIOUS problem with your mood (ie. depression, anxiety, irritability, or anger)?

☐ YES ☐ NO

146. If you answered YES to the previous question, do these problems go away by the end of your period?

☐ YES ☐ NO

147. Have you given birth within the last 6 months?

☐ YES ☐ NO

148. Have you had a miscarriage within the last 6 months?

☐ YES ☐ NO

149. Are you having difficulty getting pregnant?

☐ YES ☐ NO

Caffeine Menstrual

1. Please indicate the number of times TODAY that you consumed REGULAR COFFEE. If you had a large drink at a coffee shop, count it as 2 drinks.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
2. Please indicate the number of times TODAY that you consumed INSTANT COFFEE. If you had a large drink at a coffee shop, count it as 2 drinks
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
3. Please indicate the number of times TODAY that you consumed DECAFFEINATED COFFEE. If you had a large drink at a coffee shop, count it as 2 drinks.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
4. Please indicate the number of times TODAY that you consumed ESPRESSO (ONE SHOT). If you had a large drink at a coffee shop, count it as 2 drinks.
    a. ☐ 0
    b. ☐ 1

c. ☐ 2
d. ☐ 3
e. ☐ 4
f. ☐ 5

5. Please indicate the number of times TODAY that you consumed CAFFE MOCHA (2 SHOTS). If you had a large drink at a coffee shop, count it as 2 drinks.
   a. ☐ 0
   b. ☐ 1
   c. ☐ 2
   d. ☐ 3
   e. ☐ 4
   f. ☐ 5
6. Please indicate the number of times TODAY that you consumed CAFFE LATTE (2 SHOTS). If you had a large drink at a coffee shop, count it as 2 drinks.
   a. ☐ 0
   b. ☐ 1
   c. ☐ 2
   d. ☐ 3
   e. ☐ 4
   f. ☐ 5
7. Please indicate the number of times TODAY that you consumed ANY OTHER ESPRESSO DRINK. If you had a large drink at a coffee shop, count it as 2 drinks.
   a. ☐ 0
   b. ☐ 1
   c. ☐ 2
   d. ☐ 3
   e. ☐ 4
   f. ☐ 5
8. Please indicate the number of times TODAY that you consumed HOT CHOCOLATE (COCOA). If you had a large drink at a coffee shop, count it as 2 drinks.
   a. ☐ 0

b. ☐ 1
c. ☐ 2
d. ☐ 3
e. ☐ 4
f. ☐ 5

9. Please indicate the number of times TODAY that you consumed ANY OTHER COFFEE/COCOA TYPE DRINK. If you had a large drink at a coffee shop, count it as 2 drinks.
   a. ☐ 0
   b. ☐ 1
   c. ☐ 2
   d. ☐ 3
   e. ☐ 4
   f. ☐ 5
10. Please indicate the number of times TODAY that you consumed COCA-COLA.
   a. ☐ 0
   b. ☐ 1
   c. ☐ 2
   d. ☐ 3
   e. ☐ 4
   f. ☐ 5
11. Please indicate the number of times TODAY that you consumed DIET COKE.
   a. ☐ 0
   b. ☐ 1
   c. ☐ 2
   d. ☐ 3
   e. ☐ 4
   f. ☐ 5
12. Please indicate the number of times TODAY that you consumed PEPSI-COLA.
   a. ☐ 0
   b. ☐ 1

c. ☐ 2
d. ☐ 3
e. ☐ 4
f. ☐ 5

13. Please indicate the number of times TODAY that you consumed JOLT COLA.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
14. Please indicate the number of times TODAY that you consumed AFRI COLA.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
15. Please indicate the number of times TODAY that you consumed ANY OTHER COLA.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
16. Please indicate the number of times TODAY that you consumed MOUNTAIN DEW.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3

e. ☐ 4
f. ☐ 5

17. Please indicate the number of times TODAY that you consumed DR. PEPPER.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
18. Please indicate the number of times TODAY that you consumed BARQ'S ROOT BEER.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
19. Please indicate the number of times TODAY that you consumed ANY OTHER SODA.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
20. Please indicate the number of times TODAY that you consumed ANY OTHER DECAFFEINATED DRINKS.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5

21. Please indicate the number of times TODAY that you consumed GREEN TEA (MADE FROM A TEA BAG).
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
22. Please indicate the number of times TODAY that you consumed BLACK TEA (MADE FROM A TEA BAG).
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
23. Please indicate the number of times TODAY that you consumed ANY HERBAL TEA.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
24. Please indicate the number of times TODAY that you consumed BOTTLED ICED TEA.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
25. Please indicate the number of servings of COFFEE FLAVORED ICE CREAM you consumed TODAY.

a. ☐ 0
b. ☐ 1
c. ☐ 2
d. ☐ 3
e. ☐ 4
f. ☐ 5

26. Please indicate the number of times TODAY that you consumed COFFEE FLAVORED YOGURT.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
27. Please indicate the number of servings of CHOCALATE CANDY that you consumed. If you had a mini-size count as one serving.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
28. Please indicate the number of times TODAY that you consumed NODOZ, MAXIMUM STRENGTH.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
29. Please indicate the number of times TODAY that you consumed NODOZ, REGULAR STRENGTH.
    a. ☐ 0
    b. ☐ 1

c. ☐ 2
d. ☐ 3
e. ☐ 4
f. ☐ 5

30. Please indicate the number of times TODAY that you consumed EXCEDRIN, REGULAR.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
31. Please indicate the number of times TODAY that you consumed EXCEDRIN, PM.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
32. Please indicate the number of times TODAY that you consumed VIVARIN.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4
    f. ☐ 5
33. Please indicate the number of times TODAY that you consumed ANACIN.
    a. ☐ 0
    b. ☐ 1
    c. ☐ 2
    d. ☐ 3
    e. ☐ 4

f. ☐ 5

34. Please indicate the number of times TODAY that you consumed ANY OTHER DRUG WITH CAFFEINE.

a. ☐ 0
b. ☐ 1
c. ☐ 2
d. ☐ 3
e. ☐ 4
f. ☐ 5

Caffeine Menstrual

47. Please indicate the most appropriate score for the level of irritability/hostility you are experiencing (irritable, hostile, negative attitude, angry, short-fused, yelling, and screaming at others).
    a. ☐ 0 = Not irritable.
    b. ☐ 1 = Doubtful, trivial, not reported without direct question.
    c. ☐ 2 = Mild, occasional outbursts of anger and hostile behavior, spontaneously reported.
    d. ☐ 3 = Moderate, irritable behavior evident, frequent outbursts.
    e. ☐ 4 = Severe, affects most interactions between self and significant other.
48. Please indicate the most appropriate score for the level of tension you are experiencing (tense, restless, jittery, upset, highstrung, unable to relax).
    a. ☐ 0 = Not tense.
    b. ☐ 1 = Doubtful, trivial.
    c. ☐ 2 = Mild, occasional tension.
    d. ☐ 3 = Moderate, tense, jittery, unable to relax, restless behavior evident.
    e. ☐ 4 = Severe, constantly tense and upset.
49. Please indicate the most appropriate score for the level of efficiency you are experiencing (decreased efficiency, easily fatigued).
    a. ☐ 0 = No disturbance.
    b. ☐ 1 = Doubtful, trivial.
    c. ☐ 2 = Mild, somewhat reduced efficiency.
    d. ☐ 3 = Moderate, easily fatigued, gets much less done than usual.
    e. ☐ 4 = Severe, fatigue causes serious interference with functioning.
50. Please indicate the most appropriate score for the level of dysphoria that you are experiencing (dysphoric--a state of feeling unwell or unhappy mood, distinguish from depression).
    a. ☐ 0 = Not dysphoric
    b. ☐ 1 = Somewhat blue, sad, elicited only on direct questioning.

c. ☐ 2 = Mild dysphoric and labile mood, spontaneously reported.

d. ☐ 3 = Marked spontaneous emotional lability, occasional cyring, feelings of loneliness.

e. ☐ 4 = Severe, obvious and persistent.

51. Please indicate the most appropriate score for the level of motor coordination you are experiencing (clumsy, prone to accidents, lowered motor coordination).

a. ☐ 0 = No disturbance.

b. ☐ 1 = Doubtful, trivial.

c. ☐ 2 = Mild clumsiness, feel awkward.

d. ☐ 3 = Moderate, frequent.

e. ☐ 4 = Severe impairment in motor coordination, e.g. unable to write properly, sew, or unable to drive.

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