ORIGINAL CONTRIBUTION

Missing Links: Adolescent Depression, Menarche, and Premenstrual Syndrome - *A Pilot Study*

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Hormonal factors have long been thought to play a significant role in the etiology of depression. The emergence of a 2:1 female excess of depressive illness during adolescence, the onset of menarche, and the depressive symptomatology associated with premenstrual syndrome (PMS) are potentially synergistic variables that require consideration. A review of the current literature, as well as an independent pilot study, were undertaken in order to explore this hypothesis. The pilot study examined the interrelationships between depressive disorder in female adolescents, age at onset of menarche, and the modulating effects of PMS. The Teenage Premenstrual Mood Questionnaire (TPMQ) was administered to three groups of women: 1) 18 depressed adolescents, 2) 16 age-controlled non-depressed adolescents, and 3) 20 first-year medical students. Results demonstrated a significantly earlier age at onset of menarche in depressed adolescents relative to controls (11.77 vs. 12.76, 13.01 respectively, $p<0.007$). Depressed adolescents reported experiencing PMS symptoms 100% of the time, compared to 33% in the adolescent control group and 60% in the medical student control group. Depressed adolescents also reported an increase in depressive symptoms (including more thoughts of self-harm) during the premenstrual period. Earlier onset of menses and PMS symptoms may reflect greater overall fluctuations or exposure to estrogen levels, which may then affect neurotransmitter systems implicated in depression. Although results are preliminary due to small sample sizes, menstrual factors may serve as hormonal probes in depressed teenagers.

INTRODUCTION

On the path toward elucidating the etiology of unipolar depression, a significant finding is the emergence of a 2:1 female excess of depressive illness that develops during adolescence and persists throughout the lifespan (1,2). In childhood, rates of depression are approximately equal, or are slightly elevated in boys. In the National Comorbidity Survey, it was demonstrated that female respondents reported an elevated risk of first onset of depression in comparison to males, as early as age 10 (1). It has not been firmly established whether the increase in depressed teenage girls is due solely to rising rates among females or is amplified by declining rates among teenage boys (3). However, the change in rates of depression would seem to coincide with the onset of the physical and hormonal changes of puberty. The implication that these changes play a role in the development of a major depressive disorder are further supported by studies examining the links between a history of depression and perimenstrual distress (4,5). Such studies have shown that there are two potentially interactive processes at work: a premenstrual factor that increases vulnerability to the appearance or exacerbation of a depressive episode, and a history of depression, which manifests itself as a propensity for developing depressive perimenstrual mood. These tendencies may appear at the onset of puberty.

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PUBERTAL CHANGES AND DEPRESSION

Endocrinological onset of puberty is marked by increased levels and frequency of pulsatile release of gonadotropins (6). There are distinct differences in the type and amount of hormones released in both males and females. While both sexes experience pulsatile gonadotropin releasing hormone (GnRH) release, females exhibit fluctuating estradiol and

progesterone levels, beginning before menarche and extending several months or years until regularization of the cycle occurs (6,7). These neuroendocrinological changes are reflected outwardly by growth and the development of secondary sex characteristics. Morphological stage has been shown to reflect internal endocrine levels, but is an imprecise measure, particularly in females (2). Additional research has shown that it is endocrine status, in terms of levels of hormones present, rather than visible pubertal changes, that has proven to be a predictor of depressive affect at puberty (9,10).

If circulating hormone levels play a role in the development of depression in adolescence, one might expect to see an earlier onset of depression or an increased risk for developing depression among adolescent women who experience early menarche. Studies have not directly measured the effects of pubertal timing on depression, but certain trends have been reported: in general, early puberty has been associated with positive pyscho-social correlations in boys, and negative effects in girls (11). A Swedish study found more psychosomatic, depressive and suicidal symptoms in early-developing females, and both late and early maturers had more use of psychiatric services than women who developed at the average age (11). It then becomes difficult to separate the psychosocial effects of late or early development from neuroendocrine influences. However, it can be argued that early and late onset of puberty due to fluctuating gonadotropin levels are the primary event which then lead to psychosocial sequelae.

DEPRESSION AND THE MENSTRUAL CYCLE

A number of studies have attempted to link premenstrual syndrome (PMS), in particular mood changes, with depressive illness. Some have proprosed that PMS is actually a recurrent affective disorder in and of itself (14). While there is substantial evidence connecting PMS to psychiatric morbidity, in particular depressive illness (4), there are difficulties in both defining and assessing "PMS" and "depression," and thus comparing various findings. For the purposes of our discussion, the DSM-IV definition of depression will be used. PMS can be defined as "any mood, physical, or behavioural symptom ... that appears in the luteal phase of the menstrual cycle and disappears shortly after the onset of the next menstruation"(14).

It has been observed in both psychiatric and gynecological practices that premenstrual mood changes are the symptoms that most often cause women to seek treatment for PMS (15). Depression was the most commonly voiced complaint in studies of female subjects presenting at a premenstrual syndrome clinic, conducted by Freeman *et al.* (56%) (16) and Schinfeld and colleagues (55%) (17). Despite many apparent similarities between depressive disorder and PMS (mood fluctuations, appetite changes, sleep disturbances, fatigue) there are a number of characteristic symptoms of PMS, namely breast tenderness, the phenomenon of bloating, and the presence of hot flashes, that are not present in depression.

LONGITUDINAL EFFECTS

There have been multiple studies examining the relationship between a past history of depressive disorder and the presence of premenstrual dysphoric changes. Studies reveal an increased lifetime prevalence of depression in women confirmed as having PMS (15). Pearlstein *et al.* reported a 55% incidence of major depressive disorder (MDD) and a 75% presence of minor depression in 56 women presenting with PMS as their primary complaint (18). Further study revealed a 30% incidence of post-partum depression among the parous subjects. These incidences are twice the reported average for post-natal depression (10%-15%) (18), and almost three times the U.S. National Comorbidity Survey lifetime prevalence of MDD (21.3%) (1). Freeman *et al.* examined 168 women participating in a progesterone treatment study and found that 73% of patients had a past history of psychiatric illness, and 56% had a past history of major depressive disorder (19). Shuckit *et al.* studied premenstrual symptoms and depression in a population of college students and found both an increased lifetime history of depression and a greater likelihood of developing an affective disorder a year subsequent to the study among subjects reportedly suffering from PMS (20).

The potential for subject bias in a number of these studies is great: women who are likely to have received treatment for depression are more likely to present to clinics when experiencing depressive symptoms associated with PMS, and may misinterpret these symptoms as manifestations of underlying depressive pathology. However, the role of PMS as an exacerbating factor in depression, and the relationship between PMS and a past history of depressive disorder, cannot be dismissed.

In a study conducted by Warner *et al.* (4), an attempt to eliminate subject bias was made through the use of a questionnaire disseminated in a popular women's magazine. Of the 5457 respondents, a subgroup was selected to participate in a further study based on criteria such as age, marital status and contraceptive use. Two hundred and six women agreed to participate in further study. Of twenty possible premenstrual symptoms, only the item "feeling depressed" was selected for categorization. Women were grouped according to the presence or absence of depressive mood throughout the phases of their cycle. Findings showed that women reporting moderate to severe perimenstrual depression were more likely to have a history of treated depression as well as post-natal depression, possibly suggesting a common etiology among these syndromes. In addition, subjects who experienced persistent perimenstrual depression, often extending beyond the premenstrual week, were particularly likely to have had a history of treated depression.

These findings were confirmed in a study conducted by Bancroft and colleagues (5). In women with a clinical history of depression who were also prone to premenstrual symptoms, depressive symptoms were more likely to persist into the menstrual and post-menstrual phases, rather than being confined to the premenstrual phase. Bancroft postulates that

in women with a propensity for depressive illness, the recurrent exposure to perimenstrual mood change may lead to a more persistent affective disorder, with the mood change involving progressively more of the cycle as time goes on. Finally, in a study by Endicott, a relationship was found between the premenstrual phase of the cycle and increased suceptibility to the development or worsening of a period of depression (21).

There is conflicting research demonstrating that women who have experienced at least one episode of major depression are at no greater risk than their male counterparts for developing additional episodes (22-24). Since women as a group are not apparently at increased risk for developing subsequent episodes of depression, a subpopulation of women was then described for whom changes associated with the menstrual cycle were related to the progression of their depressive illness (15).

The concept of increased psychiatric morbidity in depression as related to the menstrual cycle, is reflected in hospital admissions records as well as in studies of suicide attempts and completions. Suicide attempts are more likely to occur during the premenstrual phase, with completions most often occuring in conjunction with the late luteal phase (25-27). The days surrounding the onset of menstruation show increased admissions for depression, in contrast to other diseases, such as schizophrenia, which showed no increase (28,29). The risk for relapse after recovering from a postpartum depression is also shown to increase during the premenstrual phase of the cycle (15).

Despite these interesting and compelling findings, more research is needed before the links between depression and PMS can be elucidated. The implications for both diagnosis and treatment of patients presenting with either or both of these disorders is substantial. While causation of depression is undoubtedly a complex process, the opportunity to examine adolescent women with depressive disorder may clarify the interrelationship between onset of puberty, perimenstrual distress, and depression. In an attempt to answer some of these questions, and to gain a broad perspective as to the observable trends in the adolescent and young adult population, as well as to highlight areas for further study, a preliminary research project was undertaken.

In order to put study results into perspective, the reported prevalence of PMS in the general population should be noted. Reports of PMS range from 5 to virtually 100 % (31). Although PMS may be present at all ages throughout the fertile period of a woman's life, certain age groups report PMS with greater frequency (31). In a study conducted by Hallman (31), PMS was highest among the 25-38 year age group, while the 17-24 year age group reported a low frequency (20.9%). The reason for this distribution was attributed to the fact that younger women are less aware of the connection between mood fluctuations and changing physiological states. A further contributing factor was the irregularity and infrequency in ovulation in young women (31). Adolescents below the age of 17 were not considered in the Hallman study, and respondents were not selected for on the basis of depression.

Our hypotheses regarding adolescent depression, onset of menarche, and frequency of premenstrual syndrome compared to a cohort control group were as follows:
1) adolescents with clinical evidence of depression will show earlier age at onset of menarche and increased frequency of premenstrual symptoms compared to age-matched peers.
2) these adolescents will also show increased psychiatric symptomatology during the premenstrual phase, compared to age-matched peers.

METHODS

Dr. Normand Carrey developed the Teenage Premenstrual Mood Questionnaire that was administered to three subgroups of women: 1) 19 depressed females who met DSM-IV criteria for major depressive disorder (mean age = 16.31); 2) 18 non-depressed normal controls (mean age = 14.53); 3) a reference group of 20 first-year female medical students (mean age = 23.1). Depressed adolescents were obtained by treating clinicians, over a period of nine months; all subjects met DSM-IV criteria for major depressive disorder. Normal adolescents were selected from a local high school, as a cohort control group. First-year medical students, ranging in age from 22-25 were selected by responding to an email request for research participants to serve as a biological reference group. The rationale for selecting the medical student control group is as follows: during adolescence, the menstrual cycle may be irregular due to variations in hormone levels; over the course of puberty, women show fluctuating GnRH release, along with varying levels of estradiol and progesterone. These fluctuations may persist for months or years before regular ovulatory and luteal patterns are established (10). This irregularity may be a contributing factor in the development of depression, or in the manifestation of premenstrual syndrome. Between the ages of 20 and 45, women showed the greatest regularity in cycle length (30); thus, the potential confounding factor of changing cycles was eliminated by the use of a medical student control group consisting of older females with more regular menstrual cycles. Previously or currently treated clinical depression were exclusion criteria for both control groups.

The questionnaire included questions dealing with the presence of PMS, regularity of menstrual cycle, onset of menstruation, presence of depressive disorder, thoughts of self-harm, and current medications. A subset of questions was administered only to adolescents suffering from depression. These included questions regarding worsening of PMS during depressive episodes, worsening of depression during PMS, onset of depression in relation to menarche and effectiveness of medication during PMS.

Results were analysed for all three study groups by the paired t-test and chi-squared methods, where applicable. However, owing to the small sample sizes and inadequate cell numbers, results often did not meet the requirements for statistical analysis. Trends were observed among the study groups in the areas of age at onset of menstruation, frequency and severity of PMS, and thoughts of self-harm during the

premenstrual period. Ratings regarding severity and frequency of PMS encompassed the following range: Never; Almost Never; Sometimes; Definitely; Most Definitely.

RESULTS

Age at onset of menstruation in the depressed adolescent group was significantly earlier, by paired t-test analysis, compared to both medical students and cohort controls (ANOVA $F = 8.37$, $p < 0.007$) as shown in **Figure 1**. Self-reported responses regarding regular menstrual cycles (**Figure 2**) showed greatest cycle regularity among medical students, followed by depressed adolescents and age-controlled peers. Up to 84% of depressed adolescents reported a worsening of their depressive symptoms during the premenstrual period (**Table 1**). Eighty-eight percent of depressed adolescents reported a worsening of PMS symptoms when feeling depressed (**Table 2**).

Figure 1 Mean age of menarche.

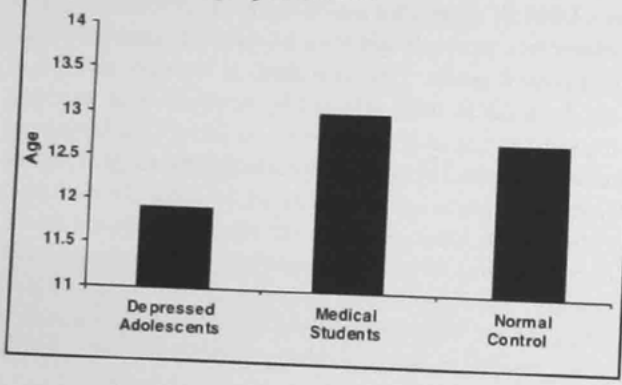
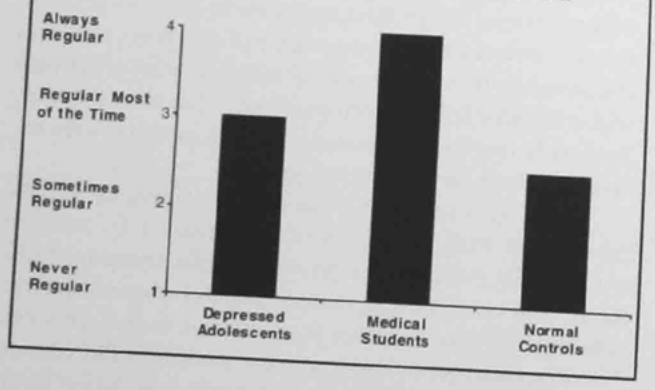


Figure 2 Mean self-report of regular menstruation.



Seventy percent of depressed adolescents reported onset of depression either prior to or within 1-2 years of onset of menses, while up to 29% reported depression occurring before the onset of menses. Of the 12 depressed adolescents taking antidepressant medication, 42 % reported some improvement of PMS symptoms with medication, while 58% reported no effect of medication on PMS. An increase in the incidence of thoughts of self-harm during the premenstrual phase was observed in the depressed group relative to controls (**Table 3**).

Table 1. Percentage of depressed adolescents reporting worsening of depression during PMS (n=18)

Depression Most Definitely Worse	**22.2%**
Depression Definitely Worse	**16.7%**
Depression Sometimes Worse	**44.4%**
Depression Never Worse	**16.7%**

Of interest was the incidence of PMS reported among the three study groups (**Table 3**, $p = 0.74$ for all three groups): 100% of depressed adolescents reported symptoms of PMS with each menstrual cycle, varying in frequency from "Sometimes" to "Most Definitely"; 33% of adolescent controls mentioned PMS "Sometimes";60% of female medical students reported PMS symptoms occuring with a frequency of "Sometimes" to "Definitely"with each menstrual cycle, a higher than expected incidence for this age group.

DISCUSSION

Our hypothesis regarding earlier onset of menses in depressed adolescents was confirmed, with significant differences between the depressed adolescents and the two control groups. A trend towards increased psychiatric symptomatology in depressed adolescents during PMS compared to age-matched peers was also demonstrated. A surprising result was the absolute and relative incidences of PMS among the three test groups: 100% of depressed adolescents admitted to suffering from PMS, compared to 33% of adolescent controls and 60% of female medical students. These results may be explained as follows: medical students would certainly be aware of the occurrence of cyclical physiological changes, and may be quicker to attribute emotional stress to menstrual factors than the typical 17-24 year old. Adolescents suffering from depression may be more acutely aware of their mental state and may either attribute their depression to be partly due to menstrual changes, or they may suffer increased perimenstrual distress due to the presence of a depressive disorder. This finding has increased significance in light of the fact that the highest incidence of PMS is generally reported in the 25-38 age group (31).

Table 2. Percentage of depressed adolescents reporting worsening of PMS when feeling depressed (n=18)

PMS Most Definitely Worse	**11.1%**
PMS Definitely Worse	**16.7%**
PMS Sometimes Worse	**61.1%**
PMS Never Worse	**11.1%**

Table 3. Summary of results for all groups.

	Depressed Adolescents	Adolescent Control Group	First-Year Medical Students
Mean age at onset of menses	**11.77** 95% CI(11.2-12.2)	**12.76** 95% CI (12.5-13.5)	**13.01** 95% CI (12.3-13.2)
% Experiencing PMS ("Sometimes" or greater)	**100**	**33**	**60**
% Having thoughts of self-harm during premenstrual phase	**44**	**0**	**10**

Speculation as to how early onset of menstruation may be implicated in the development of a depressive disorder, points to the hypothalamic-pituitary-ovarian axis and the interrelationship between steroid hormones and neurotransmitter levels. Studies have shown that ovarian hormones have modulating effects on various neurotransmitters (dopamine, serotonin, GABA) as well as monoamine oxidases at the level of the hypothalamus (32). In addition, estrogen has been shown to influence the limbic system and affect during the premenstrual phase (33). This raises the possibility of an estrogen-progesterone imbalance with subsequent psychoneuroendocrine effects, either by direct action, or indirectly, via neurotransmitter mechanisms. If estrogen and progesterone are capable of altering neurotransmitter metabolism, degradation, and serum concentrations, it is possible that this hormonal imbalance may be responsible for the manifestation of adolescent depression and premenstrual syndrome. The fact that depressive symptoms have been shown to worsen during periods of PMS (5) supports the hypothesis that ovarian hormones may influence serotonin levels, resulting in a depressive episode among susceptible individuals.

Further evidence for the role of hormones in dysphoric disorders is displayed in the phenomenon of post-partum depression (4). Looking towards treatment, it has been proposed that pyridoxine (vitamin B_6) may be implicated in the etiology of premenstrual syndrome, owing to its role as a cofactor in the biosynthesis of serotonin and dopamine (34). Several studies have been undertaken in which favourable results were attributed to placebo effects rather than to the pharmacological action of pyridoxine (35). However, subjects in these studies were not selected for on the basis of depressive symptoms, and thus vitamin B_6 therapy may still prove to be of use in this subpopulation.

The mechanism by which hormonal levels trigger early onset of menstruation and possibly the development of depressive illness in adolescence, would seem to involve a complex interplay at the hypothalamic-pituitary level. In the recent literature, early onset of menses, reflecting greater exposure to estrogen, has been linked to a new breast cancer susceptibility gene, CYP17 (36). Therefore, women carrying the CYP17 gene may share a common diathesis with the subgroup of depressed women who have experienced early menarche.

The promising correlative nature of our findings in linking adolescent depression, the timing of menarche, and PMS, must be tempered by the reality of small sample sizes and the need for further research. Subsequent studies should involve larger sample sizes and more precise estimations of onset of menstruation than retrospective self-report. Menstrual factors may serve as indicators of a subtype of depression in which hormonal influences, specifically, increased exposure to estrogen, lead to an increased susceptibility to depressive illness. Treatment should then be focused on the effects of hormones on the antidepressant response. The search for potentially synergistic factors in the etiology of a wide range of neuroendocrine disorders remains a direction for future research.

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