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Thomas G. Guilliams Ph.D.

FEMALE CYCLE DIFFICULTIES

Non-invasive Diagnosis and Natural Treatment Options

The menstrual cycle is one of the most exquisite displays of biological rhythm. It is a fascinating combination of positive and negative feedback controls involving the hypothalamus, pituitary, thyroid, adrenals, ovaries and uterus. Unfortunately, for various reasons, the rhythm is often disrupted and difficulties arise. This review will look at some of the more common disruptions and difficulties with the menstrual cycle such as amenorrhea, anovulation, luteal phase deficiencies, abnormal uterine bleeding and PMS. This review focuses on several trends and diagnostic techniques used to distinguish if the patient can be treated with natural remedies, what those remedies are, and the research supporting those remedies. It will be clear that with the proper diagnosis and treatment, natural medicine is well suited to set the rhythm back in motion.

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The normal menstrual cycle is a cascade of hormonal events. Signals received and sent by both the brain and the uterus orchestrate the presentation of a fully functional egg and the preparation of the endometrial lining of the uterus to implant the egg, if and when it is fertilized. The cycle is typically broken into three phases: the follicular, the ovulatory, and the luteal phase. Let us briefly look at what occurs at each of these phases (Fig 1).

Follicular phase

The follicular phase begins with the first day of menses when estradiol and progesterone levels are very low. The reduced levels of ovarian hormones stimulate the pituitary secretion of follicle stimulating hormone (FSH), while at the same time allow for menstruation. FSH levels then stimulate a cohort of follicles in one of the ovaries to develop, leading to the maturation of one follicle containing a mature egg. The maturing follicle begins to secrete estradiol, stimulating the growth of the endometrium. As estradiol levels rise, FSH levels begin to drop preparing for the ovulatory spikes in the next phase. In a typical 28-30 day cycle, the follicular phase is 12-14 days (menstruation occurring on the first 4-7 days of this phase)

Ovulation

Ovulation occurs 24-48 hours after a sudden release of leutinizing hormone (LH), FSH from the pituitary gland, triggered by rising estradiol

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levels. This is often called the pre-ovulatory spike. The result is the rupture of the mature follicle and the release of the mature egg into the reproductive tract. LH, FSH and estradiol level decrease rapidly after the ovulation phase, typically 2-4 days.

Luteal Phase

The egg-less follicle is now called the corpus luteum (yellow body) and begins to secrete increasing levels of progesterone in response to pituitary LH secretion. This progesterone continues to stimulate and prepare the endometrial lining for the implantation of the fertilized egg. Estrogen levels also begin to rise, although the luteal phase is dominated by progesterone secretion. If fertilization and implantation do not occur, the corpus luteum ceases to produce progesterone and estradiol. The resulting drop in these hormones at the end of the luteal phase will initiate the rise in FSH levels, which will begin a new cycle. At the same time, the decreased levels of estradiol and progesterone will no longer support the endometrium and these tissues are shed gradually resulting in menstruation. The luteal phase typically lasts 14 or more days depending on the length of the cycle. Luteal phase deficiencies often result in infertility, difficult menstruation, irregular cycle lengths, PMS and other cyclical disturbances.

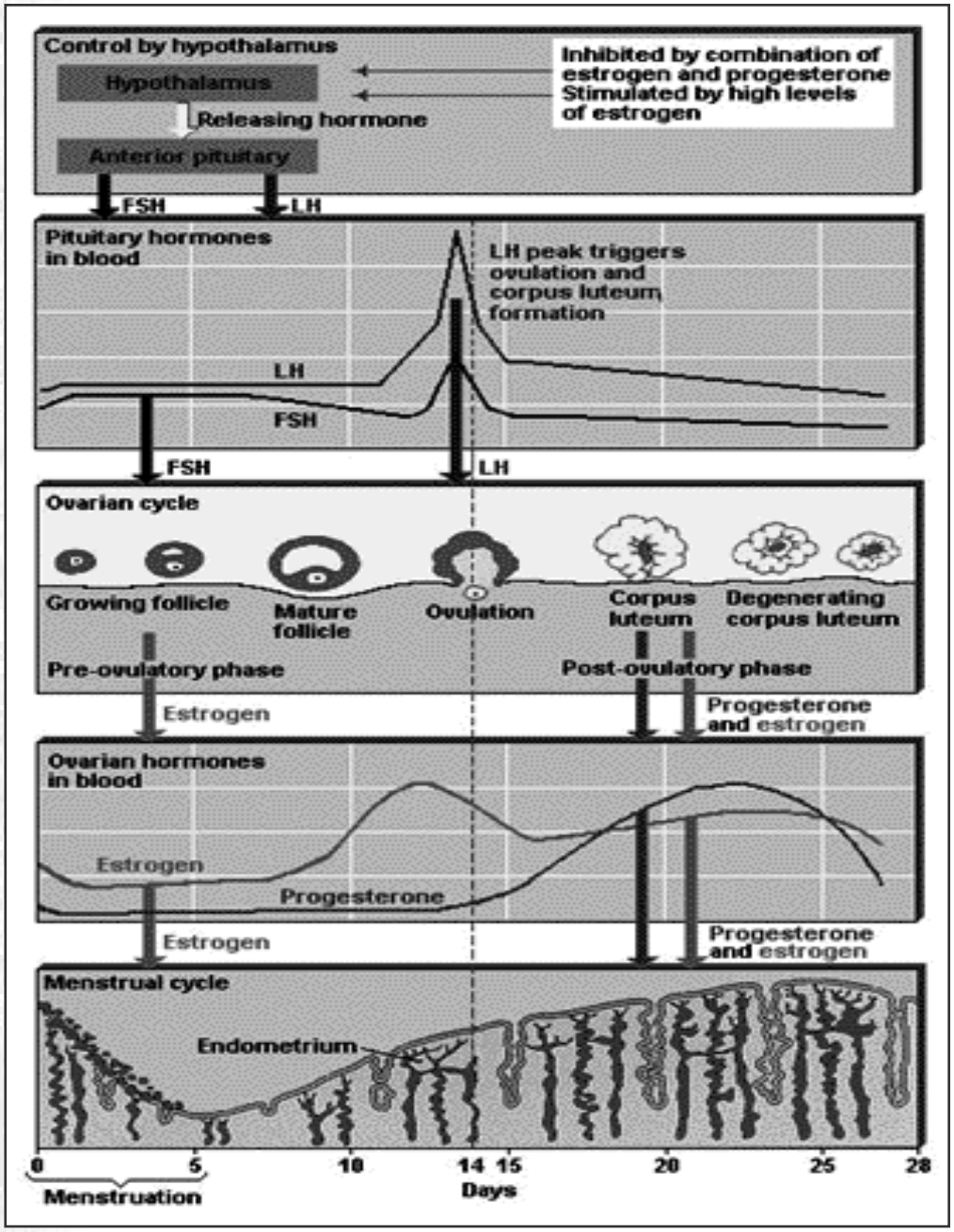

Figure 1

Diagnosing Irregularities in the Menstrual Cycle

The key to treating any aspect of menstrual irregularities or difficulties is proper diagnosis. This is especially true because the root cause may stem from areas not typically associated with the female reproductive organs. Specifically, two endocrine systems that must always be kept in mind are the adrenal and thyroid axis. Like the ovaries, each of these has positive and negative regulatory loops with the hypothalamus and pituitary. Each of these is defined as an axis, the hypothalamic-pituitary adrenal axis (HPA), HPO (ovarian), HPT thyroid. These axis not only overlap in their regulation within the hypothalamus and pituitary; but adrenal, thyroid and ovarian hormones have receptors on the other respective organ systems that directly influences their function. We will discuss some of these where they are applicable.

In the diagnoses of menstrual irregularities, the more information, the better. Historical patterns of the menstrual cycle, sleep patterns, stress, STDs, and any other information (some which may seem trivial and unrelated) are important clues to find the root cause or trigger for the irregularity. Mapping a women's cycle using basal body temperature charts (BBT) and cyclical salivary test for estradiol and progesterone are non-invasive and inexpensive tools that are helpful to determine ovulation and the abundance and timing of ovarian hormones. For instance, if progesterone levels are low or do not rise within 48-72 hours of ovulation, implantation of a fertilized egg is not likely. A spot check of hormone levels in the luteal phase is unlikely to reveal this, while a cycle map of 10-

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15 samples is very likely to reveal these types of timing issues. Measuring adrenal function, thyroid function and serum levels of the pituitary hormone prolactin would also be considered basic diagnostic tools in assessing irregularities of the menstrual cycle. With these clues in hand, various patterns usually emerge, pointing to one or more areas of weakness; leading either to further confirming tests, natural treatments, or advanced diagnostic protocols beyond the scope of this review.

Amenorrhea

The lack of menstruation can be divided into primary (no menses by the normal age of menstruation) or secondary amenorrhea (cease in menstruation for several months following regular cycles or 6 months following irregular cycles). Primary amenorrhea is due to a physical or end organ dysfunction 40% of the time; most other causes are related to hormone dysregulation similar to those causing secondary amenorrhea. Again, diagnosis is the key to treatment since amenorrhea is a symptom, not a diagnosis.

The two most common causes of secondary amenorrhea are pregnancy and menopause. These should be ruled out before proceeding further. Women who are extremely underweight (i.e. anorexia nervosa) or overweight have an increased risk of becoming amenorrheic. A complete history should evaluate the level of stress, weight-loss/dieting and strenuous exercise as all of these can lead to disturbances to the menstrual cycle through hypothalamic-pituitary adrenal stress (1,2,3). One study reported that women with hypothalamic amenorrhea had higher cortisol levels than normal menstruating women, but they had a blunted response from the hypothalamus (CRH). This led the authors to conclude that the hypothalamus was impaired in both the adrenal stress response as well as the gonadotropin hormone secretion in these women (4). Measuring salivary cortisol rhythm is highly recommended to help determine the status of the HPA. Challenge tests with dexamethasone, CRH or ACTH may also be helpful to distinguish the extent and nature of HPA insufficiencies. For a review on how stress affects the HPA and natural treatments for adrenal insufficiencies see *The Standard* volume 3 number 1. Thyroid function should also be monitored, as there is increasing evidence in both experimental and clinical studies linking the thyroid and ovarian axis. The effects of both hyperthyroidism and hypothyroidism can lead to menstrual irregularities, anovulation, amenorrhea, and infertility (5,6).

One of the most common endocrine disorders of the hypothalamus-pituitary is hyperprolactinemia, the over production of prolactin by the pituitary. The incidence in an unselected adult population is less than 0.5%, but is as high as 17% in women with reproductive disorders especially amenorrhea and infertility (8). The pituitary secretion of prolactin is controlled by a number of factors, most notably stimulated by thyrotropin releasing hormone (TRH) and inhibited by dopamine. Hypothyroidism, which increases TRH; or stress, which decrease dopamine, are therefore directly related to the increase in prolactin levels and therefore, menstrual irregularities. While pituitary adenomas may be responsible for increased prolactin levels, other factors may be addressed to decrease prolactin and improve menstrual regulation. Serum prolactin levels can easily be measured and compared to reference ranges to address this concern.

Treatment for secondary amenorrhea should initiate with diet and lifestyle changes. Normal body mass index (BMI), a healthy balanced diet, proper amounts of sleep and stress management may have a dramatic affect on hypothalamic-related amenorrhea. Increasing protein and healthy fatty acid (flax, fish, evening primrose) intake while decreasing carbohydrate intake will help with glycemic balance allowing proper endocrine function.

Once diet and lifestyle factors have been addressed, hormone level assessments and treatments can commence. To ensure that estrogen levels are adequate to establish the endometrium, salivary estradiol levels can be checked. If a progesterone challenge (400 mg of oral micronized progesterone for 10 days) is not followed by some amount of menstruation (even spotting), this points to an end-organ dysfunction or a hypothalamus deficiency. These can be distinguished by the use of estrogens followed by an estrogen/progesterone challenges. Often times, estrogen levels will be adequate, while progesterone levels will be low. This is typical of a luteal phase deficiency problem.

BASIC DIAGNOSTIC TOOLS

- Full Patient History
- Basal Body Temperature Chart
- Cyclical estradiol and progesterone (salivary) levels
- Salivary cortisol, DHEA (Adrenal Function)
- Thyroid Function Test (TSH, T3, T4, symptoms, temperature)
- Serum Prolactin levels
- Luteal melatonin levels
- Referrals to individuals who are able to complete advanced tests or biopsies if unable to perform these procedures or rule out conditions which require highly specific knowledge to attempt natural treatment protocols.

The most direct therapeutic approach would be to augment natural oral micronized progesterone (or equivalent sublingual dose) through the luteal-phase (for instance: gradually increasing from 50mg to 200 mg from day16-24, then decreasing back to 50 mg on day 30). While this will bring about a cyclicity, and may lead to ovulation; it will also help reduce long-term estrogen imbalance, which could lead to increased risk of breast and uterine cancer. The use of chaste tree extract (*Vitex agnus castus L.*) for amenorrhea, and other menstrual irregularities, has been established as the herb of choice in Europe where phytomedicine is common among physicians. See the related article on Vitex within this issue for a discussion of its mechanisms and clinical research. Other, phytoestrogenic herbs such as black cohosh, alfalfa, flax, licorice or red clover have been used to support the reproductive cycle in hypo-estrogenic cases. These would also be used in cases of menopause or premature ovarian failure (see T*he Standard* Vol. 4 no. 1). The use of two roots, peony (*Paeonia lactiflora*) and licorice (*Glycyrrhiza glabra*), have been used in combination for a number of female conditions. Studies, mostly in Japanese, have shown this combination to increase DHEA-S levels (51), decrease prostaglandin production (52), lower prolactin levels (50), and helpful for the treatment of polycystic ovarian disease (53).

Irregular or Abnormal Uterine Bleeding

This review will only discuss benign dysfunctions treatable with natural remedies. Malignant conditions or extremely heavy bleeding should be handled by those specializing in such conditions. Practitioners

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who are unsure how to rule out fibroids, endometriosis, pre-cancerous conditions or non-gynecological blood disorders, should refer patients to someone who can make these determinations before proceeding with further diagnosis. That said, there are many conditions that can be treated with natural ingredients with excellent results.

Irregular uterine bleeding can be categorized as menorrhagia (heavy or prolonged menses), polymenorrhea (frequent menses), oligomenorrhea (light or infrequent menses) and even metrorrhagia (irregular and intermenstrual bleeding). Menorrhagia is often the result of anovulation, which may have its root cause in excessive estrogen production, low or no midcycle LH surge, hypothyroidism, hyperprolactemia or polycystic ovarian disease. The goal is to slow down the rate of the bleeding while also addressing the root cause.

Beside hormone augmentation (which may be warranted if other options are not successful) several astringent herbs may be quite helpful in easing the flow of menstruation. Herbalist in both the U.S. and Europe recommend herbs such as yarrow (*Achillea millifolium*), lady's mantle (*Alchemilla vulgaris*), shepherd's purse (*Capsella bursa-pastoris*) and motherwort (*Leonorus cardiaca*). Shepherd's purse, however, is the only approved herbal monograph for menorrhagia listed in the German Commission E (7). The use of the Chinese herb sanchi (Panax notoginseng) is also used to correct bleeding disorders and has been used for menorrhagia. Chaste berry (Vitex agnus castus) is often used to help regulate the underlying causes (see Chaste berry mini-monograph).

There is an interesting relationship between menstrual blood loss and prostaglandin production. Not only are various prostaglandins related to increased blood loss, women suffering from menorrhagia have increased levels of arachidonic acid in uterine tissues (49). Reducing dietary animal fats and replacing them with fish oils (containing EPA) and GLA-rich oils like borage and evening primrose should lower the amount of type 2 prostaglandins that are formed from arachidonic acid. As with all health concerns, diet and lifestyle factors should be always be addressed. Vitamin and mineral intake should be assessed to insure that levels of iron, magnesium, Vitamin C, B12, B6, and all essential fatty acids are adequate. Therapeutic levels of vitamin C with additional bioflavonoids are often recommended to help maintain vascular integrity.

Premenstrual Syndrome (PMS)

While there are nearly 150 symptoms that have been related to PMS, it is the regular cyclical pattern that is most characteristic. These symptoms begin in the mid-to-late luteal phase and almost disappear after the first day of menstruation. A typical list of symptoms would include mood swings, depression/sadness, anger/short temper, crying spells, swelling of extremities, breast pain/tenderness, abdominal bloating, lower abdominal cramping, low backache, headache, fatigue, craving for sweets or salt and insomnia. Depending on which symptoms and their relative severity, PMS may range from hardly noticeable to dramatically life-altering. It is reported that up to 80% of women experience some PMS symptoms, less than half of who describe these symptoms as contributing to "difficulties". In a recent study, 42% of women suffering from PMS regularly took medication, of which 80% was over-the-counter (9). This shows the high level of awareness, self-diagnosis and self-medication in this population.

Many of the issues described for luteal phase deficiency, apply to PMS sufferers. Very often, adrenal stress, thyroid dysregulation, hyperprolactinemia and estrogen/progesterone imbalance will be found. One interesting finding was that the HPA axis in PMS sufferers is under-active (lower cortisol levels), similar to the findings in patients with seasonal affective disorder (SAD). This differs from typical depressive disorders, characterized by an overactive HPA axis (10). A direct correlation with hypothyroidism and PMS has not been established, but several reports define a subset of patients whose PMS may be related to thyroid dysregulation (11,12).

From a chiropractic perspective, a group of 54 women diagnosed with PMS were compared with 30 women with no diagnosable PMS symptoms and found that the PMS sufferers had a higher incidence of spinal dysfunction. Most significant were positive cervical, thoracic, and low back tenderness, low back orthopedic testing, low back muscle weakness and neck stability index (13).

Progesterone

One of the factors thought to contribute to PMS symptoms is a sudden drop in progesterone levels in the late luteal phase (not necessarily the absolute amount of progesterone made in the luteal phase). This dramatic decline results in late luteal estrogen dominance and imbalances that lead to PMS symptoms, it is speculated. While it would seem logical that progesterone therapy throughout the month or specifically during the late luteal phase would benefit PMS sufferers, clinical trials focused on this have yet to show conclusive positive results when vaginal suppositories or oral doses were given (14,15,16). It is probably best to measure progesterone and estradiol throughout the cycle (salivary test) in order to determine if this approach may have potential benefits before temporary augmentation of hormones are used.

Diet

Diet and nutrition play a major role in the treatment of PMS. One report listed PMS patients as consuming 62% more refined carbohydrates, 275% more refined sugar, 79% more dairy products, 78% more sodium, 53% less iron, 77% less manganese and 52% less zinc than women not suffering from PMS (17). The role of dairy products and animal fat may contribute to increased arachidonic acid levels, which subsequently are converted into prostaglandin PgE2. This prostaglandin is thought to increase in the luteal phase of PMS sufferers and those with frequent menstrual cramps. Consuming both omega-3 rich oils like flaxseed oil and fish oils, as well as GLA-containing oils like evening primrose or borage oil will help balance the prostaglandin levels (See The Standard Vol 3 no 2).

Last year, researchers at Georgetown University tested the role of a low-fat, vegetarian diet on PMS and dysmenorrhea (painful menstruation/cramps), postulating a role for sex-hormone binding globulin (SHBG) and estrogen levels (18). They found a significant increase in SHBG and a significant decrease in body weight, dysmenorrhea symptoms and PMS symptoms during months of low-fat and vegetarian diets compared to months on a control diet. While it is difficult to assess all the ramifications diet plays in PMS, it is clear that increasing fresh fruits and vegetables and decreasing processed foods, dairy, and animal fats would be beneficial.

Vitamin B6

The role of nutritional supplements supplying vitamins, minerals and herbs has long been postulated to benefit women suffering from PMS. Laboratory tests have shown that women suffering from PMS have nutritional deficiencies, most significantly vitamin B6 and magnesium (19). There have been at least 25 different clinical trials in which vitamin B6 has been used for the treatment of PMS. Of these, 9 of the best-controlled trials were used to conduct a meta-analysis (20). This study pointed out the need for a large, properly controlled clinical trial, but reported that there does seem to be a therapeutic benefit to using vitamin B6 for the treatment of PMS. While many of these trials used 100mg or even 200mg per day without noticeable side effects, the authors believe that 50mg per day is likely to be beneficial in the treatment of PMS. Consider all the sources of B6 (multivitamin, B-complex, PMS products etc) prior to adding additional B6 to the regimen.

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Magnesium

Not only is magnesium one of the minerals most often ingested in sub-optimal amount in women consuming a typical Western diet, intracellular magnesium is the most consistent physiological abnormality found among PMS sufferers compared with normal controls. Few clinical trials have been performed using magnesium for the treatment of PMS. A small trial, in which data was collected from 38 women, compared placebo to 200 mg of magnesium per day as magnesium oxide (21). They found that the magnesium group had significantly reduced fluid retention when compared with the placebo group but only after the second month of magnesium supplementation. The same group also reported a study where PMS sufferers were given 200 mg of magnesium (MgO), 50 mg of vitamin B6, both, or placebo (22). Even though this study had some major flaws, they still report a slight synergistic effect by combining magnesium and B6 in the treatment of PMS. In their conclusion they state that magnesium oxide was so poorly absorbed that several months would be required to see the full benefits of using this form and suggested the use of longer periods or other magnesium forms. The use of magnesium as an amino acid chelate, citrate, aspartate, or ascorbate would all be of superior therapeutic benefit when compared to MgO, frequently used for its high magnesium content and low cost. Hopefully, a better clinical trial will be done to assess the role of magnesium as a therapeutic agent for PMS, for now it seems more than reasonable to increase intake of magnesium for all individuals especially those being managed for menstrual irregularities and PMS.

Calcium

Recent evidence has postulated a role for calcium regulation disturbances in symptoms associated with PMS. From that, calcium supplementation is postulated to have a positive therapeutic benefit for PMS sufferers. In order to investigate this possibility, 466 women were randomized to receive either 1200 mg of elemental calcium (as calcium carbonate) or placebo for 3 menstrual cycles (23). While the results showed an extremely high reduction in PMS scores for the placebo group (30%), there was a significant drop in PMS scores in women taking calcium (48%). Since no dose-response information has reported, and most other studies use 1000-1350 mg of calcium per day with variable results, it is difficult to assess whether this represents a deficiency correction or a therapeutic effect. It should be noted also that this study, like others, was supported by a large manufacturer of commercial calcium carbonate products. They did not measure calcium absorption in this study.

Botanicals

By far the most beneficial herb for treatment of luteal phase deficiencies and PMS is Vitex agnus castus (Chaste tree extracts). See the vitex monograph in this volume for more details on the benefits of using this herb. Other botanicals used are St. John's wort, Ginkgo, licorice, evening primrose, wild yam, dong quai, black cohosh and many more.

A pilot study of St. John's wort extract (900 mg/day standardized extract) for treating PMS was recently published (24). After two complete cycles they reported a significant reduction in all outcomes measured with a 51% improvement in overall PMS scores between baseline and the end of the trial. This was an open, uncontrolled trial; and considered preliminary. It should be noted that while safety of St. John's wort is excellent, it is speculated to cause oral contraceptives to be less effective due to its stimulation of the p450 enzyme system.

One study, published in French, reported that extracts of Ginkgo (dose unavailable) were capable of reducing congestive symptoms (primarily breast fullness and tenderness) compared with placebo (25). Numerous studies have been published using various Chinese herbs within the traditional Chinese medicine (TCM) model of diagnosis and treatment, their effectiveness is difficult to assess especially with the different diagnostic and social concepts that separate Western medicine from TCM.

Other Alternative Approaches

Menstrual cycle irregularities have engendered a myriad of treatment options. We have discussed those that involve natural medicinal supplements, but in the field of complementary and alternative medicine there are other treatments addressing female cycle management; some of which have been published as clinical trials. The largest field in this category would be traditional Chinese medicine (TCM). Not only numerous papers on Chinese herbal remedies for the treatment of irregularities of the luteal phase (26), but also the use of acupuncture and electro-acupuncture to stimulate ovulation, particularly in the case of polycystic ovarian syndrome (27).

Chiropractic manipulation was evaluated in a placebo-controlled trial as a therapy for PMS. The findings showed that high-velocity, low amplitude spinal manipulation with soft tissue therapy 2 to 3 times in the week prior to menses statistically reduced PMS symptoms scores over placebo (spring-loaded adjusting instrument wound down for minimum force)(28). The crossover design of the study led to some confusion in data interpretation, and more studies need to be conducted to investigate the role of chiropractic adjustments in the treatment of PMS or other cycle irregularities.

Additionally, reflexology of the ear, hand, and foot (29); relaxation and guided imagery (30); and circadian/light therapy work (31) are among a number of therapies with published reports in the literature.

NATURAL THERAPEUTIC TOOLS

- Chaste Tree Extract (Vitex agnus castus) 20 mg per day
- Natural Progesterone (sublingual tablet, liquid, micronized oral)
- Herbal combination for treating menorrhagia (astringents and uterine tonics)
- High quality essential fatty acids
- High quality multi-vitamin/mineral formula
- Combination formula to address luteal phase deficiencies including PMS (vitamins, herbs, minerals)
- Vitamin C with Bioflavonoids

Conclusion

With the growing desire for natural remedies, particularly among women 30-50, understanding the role of medicinal supplements for female cycle irregularities is vital to serving these patients. And, while they may feel that their symptoms point to a self-diagnosable condition, many have been disappointed with over-the-counter remedies or prescription medication. It is evident from this review that, with a logical and less-invasive diagnostic protocol, a natural treatment regimen can be selected that will be safe and highly effective.

VITEX MONOGRAPH - Female cycle emphasis

NAME AND HISTORY

Vitex agnus castus L. is also known as chasteberry, chaste tree, vitex or monk's pepper. The names are derived from the fact that in medieval times monks used it as a cooking spice for its taste and, it is said, for its abilities to suppress libido. It has a long recorded history of medicinal use, being mentioned by Hippocrates in the 4th century BC and both Pliny and Dioscorides in the 1st century A.D.

VITEX THE MEDICINE

The portion used for medicinal purposes is the dried ripe fruits (peppers) of the plant. Foremost among its constituents are flavonoid components like vitexin, orientin, and the abundant casticin; terpene compounds like the often measured agnuside and aucubin; and volatile oils. Tinctures, powders and dried extracts are most often how vitex is delivered.

ENDOCRINE FUNCTION

In the 1950's it was discovered that extracts of vitex were able to increase the size of the corpus luteum in animal models, although not as a result of direct hormone-like activity (32). Years later, two major endocrine modulations have been confirmed with extracts of vitex: 1) a decrease in prolactin levels and 2) an increase in luteinizing hormone (LH). The decrease in prolactin secretion has been confirmed in animal models (33) and was postulated to work by stimulating dopamine receptors on the pituitary. These findings were confirmed when *in vitro* experiments concluded that vitex extracts contained active principals that bind directly to dopamine D2 receptors, which mediate the inhibition of prolactin secretion from the pituitary (34,35).

CLINICAL USE OF VITEX

The clinical use of vitex includes the same list of conditions that can be attributed to hyperprolactemia: cyclic mastagia, PMS, abnormal cyclic ovarian function, amenorrhea, luteal phase deficiency, and infertility.

In a randomized, double-blind, placebo controlled study; women with latent hyperprolactinemia received either a vitex extract or placebo for 3 months. These women were characterized before the study as having shortened luteal phases, low luteal progesterone levels, and high levels of clinically stimulated prolactin (used to define latent hyperprolactinemia). After the three-month study, the vitex group had significantly reduced prolactin compared to placebo, normalized mid-luteal progesterone levels and their luteal phase lengthened by 5 days. In addition, women in the vitex group with previous PMS symptoms showed a significant reduction in those symptoms (36). A similar but smaller study of 13 women with hyperprolactinemia and cyclic disorders were treated with vitex. In every patient, prolactin levels were reduced, some to normal ranges, and the menstrual cycle normalized (37).

Infertility

While pregnancy may be recorded as an outcome of other clinical trials using vitex, several studies have looked directly at using vitex to treat infertility. In 1987, an open non-controlled study was done with a group of 18 infertile women of childbearing age with **normal** prolactin levels and **normal** thyroid function (38). All had abnormally low levels of progesterone in the mid-luteal phase (day 20). After only 3 months, progesterone levels rose in 11 of 18 patients, 7 of which returned to normal. All but 4 women had their basal body temperature phase shift normalize (a sign of normalizing ovulatory function) and 2 became pregnant within 3 months. A randomized, placebo controlled trial with 96 infertile women was carried out for 3 months in which the measured outcome was pregnancy, spontaneous menstruation in amenorrheic women, or improved luteal phase hormone profile. The vitex group had significantly more improvements in all outcomes measured against placebo. In women with luteal phase deficiencies or amenorrhea, pregnancy occurred more than twice as often in the vitex group than in the placebo group (39).

Cyclical mastalgia

As increased luteal-phase prolactin levels are thought to mediate much of the breast pain and tenderness experienced in the premenstrual phase, the use of vitex has been used clinically to treat such conditions (40). Two recent double-blind controlled studies were reported, one with 100 patients (41) and one with 120 patients (42). Each showed that the vitex group had significantly less pain and shortened duration of pain. The second study showed a drop in PMS symptoms, prolactin levels, and estradiol levels in the vitex group compared to placebo. Each of these studies lasted 3 months.

Menstrual irregularities

There are numerous clinical trials on a variety of menstrual irregularities and the treatment with extracts of vitex. Perhaps the largest of these reported trials was a collection of cases from physicians (Germany) reporting the use of vitex in their practice. 2,447 women with various menstrual complaints (1,016-PMS, 734-corpus luteal insufficiencies, 320-uterine myomas, 167-menopausal symptoms) who were given vitex as treatment were included in the report. After an average 5 months of vitex treatment, the efficacy was rated at 90% with 31% of women reporting complete absence of symptoms. Of these, nearly 3% became pregnant while on vitex and only 2.3% reported side effects (1% drop-out rate due to side-effects) (43).

A similar report of an open trial with 1,592 women (average age 32) with corpus luteum insufficiency presenting as menorrhagia (484), polymenorrhea (359), amenorrhea (202), dysmenorrhea (painful menstruation 186), anovulation (175), and infertility (145) was reported. Patients were assessed after an average of 6 months of treatment (44). The doctors reported a similar 90% satisfactory

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response with 33% of patients reporting completely free of symptoms after 6 months. Of the 145 women expressing the desire to become pregnant, 56 (39%) became pregnant during treatment.

PMS

Much of the recent therapeutic focus for vitex extracts is for the treatment of PMS. In 1997, a study was conducted to compare the use of vitex extracts with pyridoxine (B6) in the treatment of 175 women diagnosed with premenstrual tension syndrome (PMTS). Since there had been several studies demonstrating the effectiveness of pyridoxine in the treatment of PMTS, the authors felt it unnecessary and unethical to use a placebo arm for this three-month study (45). The results showed that, though both treatments were capable of reducing PMTS symptoms (breast tenderness, edema, inner tension, headache, constipation and headache), the vitex treatment was rated as excellent by twice as many physicians. In the patient assessment, 50% more said their symptoms were completely absent in the vitex group (36%) than the pyridoxine group (21%).

PMS symptom relief was also the outcome of a study reporting the results of an open-label multi-center trial (46). Forty-three patients were monitored for 8 months; 2 pre-treatment baseline months, 3 treatment months, and 3 post-treatment months. Using several questionnaires, including a menstrual distress questionnaire and both a visual analog scale and global impression scale for secondary assessment, they reported a 43% drop in PMS symptoms between the 3 treatment months versus baseline. Additionally, they found that at the end of the post-treatment months (month 8) a 20% reduction of symptoms remained, when compared with the baseline months. In this study, women who were concurrently taking oral contraceptives had similar results compared to women not taking oral contraceptives.

A large multicenter open trial conducted to monitor the effectiveness and safety of using vitex extracts for PMS was recently published (47). Of the 1634 patients monitored after 3 months of treatment, 81% rated their status as very much or much better. Physicians rated the treatment good or very good with 85% of their patients. A full 94% rated the tolerability of the treatment as good or very good and only 1.2% experienced adverse events (none rated serious). Because this was not an intervention or controlled study, these numbers prove only to support the safe and general effectiveness of vitex on a wide variety of patients.

The most recent study, published early this year in *The British Medical Journal*, discovered similar finding using a randomized, placebo-controlled study. They reported twice as many responders (52% vs. 24%) in the active vitex group compared with placebo. Responders included those with 50% or greater drop in symptoms including irritability, mood alteration, anger, headache, breast tenderness, bloating etc. The researchers conclude that the dry extract of vitex (used in this study) was an effective, safe, and well tolerated treatment for the relief of symptoms of premenstrual syndrome (48).

Dose

Almost all of the initial clinical trials performed with extract of *Vitex agnus castus* were using a liquid preparation. The dosage range was between 40-60 drops and given for at least 3 months. These dilute (1:5) extracts were also dried and used to make powders that were dosed at 175 mg per day.

More potent extracts are now being used and reported in the most recent clinical trials. These powdered extracts range from 9:1-12:1 in strength and are dosed either at 3-5 mg (equivalent to 175 mg of the 1:5 extract) (45,47) or 20mg per day (46,48). Both dosing regimens performed positively in the clinical trials tested, although the low dose regimen studies were designed poorly and had somewhat vague outcome measurements.

At this time, several extracts are being marketed which are standardized to agnuside, aucubin or casticin. While these are excellent marker constituents and likely represent some of the active components, it is unclear from a clinical perspective exactly what standardization marker or method best characterizes the therapeutic activity. Further studies into the active components may lead us to the extract of choice. Ideally, an extract of approximately 10:1, which maintains as much of the potential active components (agnuside, aucubin and active flavonoids like casticin), dosed at 20 mg per day should have characteristically effective and safe outcomes for the conditions listed above.

Contraindications/Adverse Effects

The safety profile of vitex and its extracts is excellent. No severe side effect or allergic reaction has ever been attributed to vitex use. Mild adverse reactions may include stomach upset, nausea, itching and headache. Use of vitex with birth control pills or other hormone therapies is not recommended, although no known interactions have been reported and one study reported that no differences were seen between patients on or off oral contraceptives when treated with vitex for PMS (46). Use of vitex concomitant with dopamine-antagonist is not recommended because of the dopaminergic actions of vitex constituents.

As there is no indication during pregnancy, vitex is not recommended during pregnancy. However, as it is often used during infertility treatment, it should be noted that no known harm has been reported during any stage of pregnancy. Although historical reports of vitex as a lactagogue (breast milk stimulant) are widely circulated, this affect may only be possible at very dilute concentration when vitex may act as a dopamine antagonist rather than a dopamine agonist. Unless recommended by someone experienced in the use of vitex as a lactagogue, other remedies should be sought to stimulate milk production. One possible negative side effect of using vitex as a postpartum lactagogue is the possibility of premature return of menses, as lactational amenorrhea is often considered as one of the beneficial side effects of breast-feeding.

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The following three monographs were extremely helpful in compiling the information about the use of Vitex agnus castus and the preparation of the mini-monograph in this review. A * beside the number in a cited reference signifies that the information from these references was translated and interpreted in one or more of these excellent monographs and subsequently reported here.

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