

# A Healthy Menstrual Cycle

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**ABSTRACT:** A healthy menstrual cycle involves the complex interaction of the hypothalamus, pituitary, ovaries, uterus, prostaglandins, and neuroendocrine factors. The ovarian hormones stimulate the target organs of the reproductive tract and exert feedback effects on the CNS-hypothalamic-pituitary unit to influence its hormone secretion. Disruptions can occur at any step in this multi-faceted process, resulting in hormonal imbalance and menstrual irregularities such as dysmenorrhea (painful periods), abnormal uterine bleeding (irregular, absent,

or heavy periods), premenstrual syndrome, and impaired fertility. This paper focuses on the etiology and nutritional management of dysmenorrhea and dysfunctional uterine bleeding. Nutritional factors that may play a role in these menstrual irregularities include vitamins B<sub>6</sub> and B<sub>12</sub>, magnesium, vitamins A, C, and E, iron, folic acid, and essential fatty acids. In addition, herbal therapies have a long history of use in the management of dysmenorrhea and dysfunctional uterine bleeding.

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## DYSMENORRHEA

Dysmenorrhea, or painful menstruation, is one of the most common gynecological complaints. It is estimated to affect almost half of all women at some time during their childbearing years, usually appearing during adolescence and tending to decrease with age and following pregnancy.<sup>1,2</sup> Lower abdominal cramping and pain that may radiate to the thighs and lower back is the most prevalent symptom.<sup>2,3</sup> Headache, nausea, constipation or diarrhea, and urinary frequency are often present, and vomiting may also occur.<sup>1,2,4</sup> It is characterized by pain occurring on the first day of menses, usually coinciding with the onset of flow, but may not be present until the second day.<sup>4</sup> The symptoms tend to peak after 24 hours and usually subside after 2 days.<sup>2</sup> While many women suffer mild discomfort during menstruation, dysmenorrhea is present if pain prevents normal activity and requires over-the-counter or prescription medication.<sup>4</sup>

There are three types of dysmenorrhea: primary, secondary, and membranous. *Primary dysmenorrhea* is characterized by the absence of an organic etiology, while *secondary dysmenorrhea* is associated with specific diseases or disorders, such as endometriosis, ovarian cysts, pelvic inflammatory disease, adenomyosis, cervical stenosis, fibroid polyps, and possibly uterine displacement with fixation. *Membranous dysmenorrhea* (uterine cast) is rare and causes intense cramping pain as a result of the passage of the intact endometrial cast through an undilated cervix.<sup>4</sup> The most common misdiagnosis of primary dysmenorrhea is secondary dysmenorrhea due to endometriosis. With endometriosis, the pain increases 1 to 2 weeks before the menses, reaches a peak 1 to 2 days before, and is relieved at the onset of flow or shortly thereafter.<sup>4</sup> The use of intrauterine devices (IUDs) may also cause severe cramping.

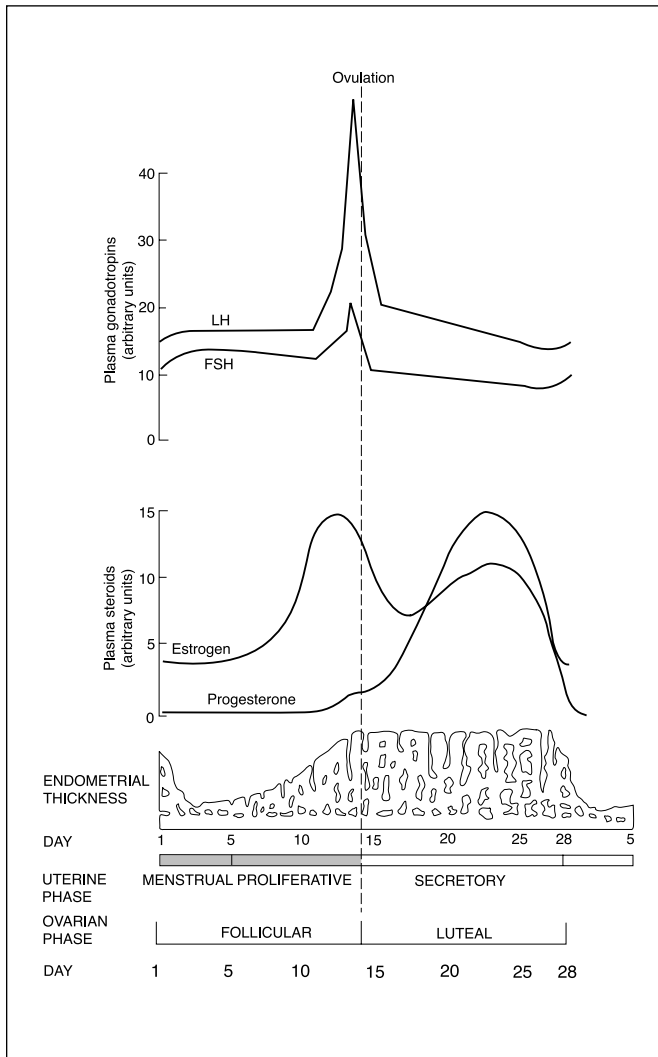
A majority of women suffering from dysmenorrhea are diagnosed with primary dysmenorrhea, the focus of this paper. While it is difficult to estimate the impact of primary dysmenorrhea on society, even by conservative estimates the social and economic costs of this syndrome are staggering.<sup>5</sup>

### • The Menstrual Cycle

In order to have a greater understanding of dysmenorrhea and dysfunctional uterine bleeding, and their potential etiologic factors, it is important to understand the menstrual cycle. The median menstrual cycle length is  $28 \pm 3$  days and the average duration of menstrual flow is  $5 \pm 2$  days with a blood loss averaging 130 ml.<sup>2</sup> The cycle, which can be divided into a follicular phase and a luteal phase, results from complex interactions between the hypothalamus, pituitary, and ovary.

This cyclical process, which requires clear communication between the participating glands, is regulated in part by complex changes in the concentrations of five hormones: gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E), and progesterone (P) (Figure 1).<sup>2,6-9</sup> The interplay of these hormones is extremely complicated, with the steroid hormones (E, P) exerting both negative and positive feedback effects on gonadotropin secretion (LH, FSH). The release of LH and FSH from the pituitary is dependent on the secretion of GnRH from the hypothalamus, which is modulated by the feedback effects of E and P. LH and FSH, in turn, are important in stimulating secretion of E and P. Virtually all hormones are released in short bursts or pulses at intervals of 1 to 3 hours, so constant levels are not observed in the circulation. The frequency and amplitude of the pulses are modulated by steroid hormones and vary throughout the cycle.

**Figure 1. Hormone Levels and Endometrial Changes During the Normal Menstrual Cycle**



There are three distinct stages in the monthly endometrial cycle (Figure 1).<sup>2,9,10</sup> The *proliferative phase*, also referred to as the estrogen phase, begins approximately 5 days after menstruation and lasts for about 11 days. E secreted by the ovary stimulates the growth of the endometrium. The stroma cells and epithelial cells begin to proliferate rapidly, uterine glands begin to grow and elongate, and the spiral arteries begin to grow in order to supply the thickened endometrium. Rising E levels then trigger the midcycle LH surge, which induces ovulation. When ovulation occurs, the endometrium is approximately 3-4 mm thick. At this time the endometrial glands secrete a thin, stringy mucus, which protects and leads the sperm into the uterus.

The *secretory phase*, also called the progesterone phase, occurs after ovulation and lasts for about 12 days. The corpus luteum secretes high quantities of P and some E. The E causes slight cellular proliferation in the endometrium. P causes significant swelling of the endometrium and converts it to an actively secreting tissue. P also inhibits myometrial (uterine smooth muscle) contractions, in large part by opposing the stimulatory actions of E and prostaglandins. The endometrium reaches a thickness of

5-6 mm about one week after ovulation. The purpose of this process is to prepare the uterus for implantation of the ovum if fertilization occurs.

The desquamation of the endometrium, or menstruation, is caused by the sudden fall in blood P and E, which results from regression of the corpus luteum. This deprives the highly developed endometrial lining of its hormonal support. The immediate result is profound constriction of the uterine blood vessels, which leads to diminished supply of oxygen and nutrients. After the initial period of vascular constriction, the endometrial arterioles dilate, resulting in hemorrhage through the weakened capillary walls. The menstrual flow consists of this blood mixed with the functional layer of the endometrium. Prostaglandins are thought to mediate both the initial vasoconstriction as well as the uterine contractions accompanying menstrual flow.<sup>2,11</sup>

• **The Role of Prostaglandins in the Etiology of Primary Dysmenorrhea**

Prostaglandins (PGs) are hormone-like compounds that function as mediators of a variety of physiological responses such as inflammation, muscle contraction, vascular dilation, and platelet aggregation. They are modified forms of unsaturated fatty acids that are synthesized in virtually all cells of the body.<sup>12</sup> Studies have demonstrated that varying PG levels in the female reproductive tract affect the cyclic regression of the corpus luteum and the shedding of the endometrium. PGs may also mediate the effect of LH on ovulation.<sup>8</sup>

The association between the symptoms of dysmenorrhea and intrauterine production of PGs goes back 40 years to the report of Pickles,<sup>13</sup> who first identified a substance in menstrual fluid which stimulated contractions of human uterine smooth-muscle strips. This menstrual stimulant was subsequently found to contain  $\text{PGF}_{2\alpha}$  and  $\text{PGE}_2$ , with the  $\text{PGF}/\text{PGE}$  ratio higher in the endometrium and menstrual fluid of women with primary dysmenorrhea.<sup>14</sup>  $\text{PGF}_{2\alpha}$  and  $\text{PGE}_2$  have opposing vascular effects causing vasoconstriction and vasodilation, respectively.<sup>15</sup> While  $\text{PGF}_{2\alpha}$  administration stimulates uterine contractility during all phases of the menstrual cycle,  $\text{PGE}_2$  may inhibit myometrial contractility during menstruation and stimulate it during the proliferative and luteal phases.<sup>15</sup> Since they are both formed from a common precursor, arachidonic acid, the increase in  $\text{PGF}_{2\alpha}/\text{PGE}_2$  ratio indicates that synthesis can be directed preferentially towards the PG compounds.<sup>16</sup> Several studies suggest that women with primary dysmenorrhea have elevated concentrations of  $\text{PGF}_{2\alpha}$  and/or its metabolites in the endometrium, menstrual fluid, and peripheral circulation.<sup>15,17,18</sup>

These findings have led to the hypothesis that painful menstruation may be due to hypertonicity of the myometrium with accompanying uterine ischemia caused by the local release of excessive amounts of PGs.<sup>18,19</sup> Furthermore, escape of PGs from the uterus into the systemic circulation could be responsible for other symptoms of dysmenorrhea such as GI disturbances, faintness, dizziness, and headaches.<sup>19</sup> This theory is supported by several research findings: 1) higher PG levels (especially  $\text{PGF}_{2\alpha}$ ) during the secretory phase than in the proliferative phase of the menstrual cycle;<sup>16,17,20,21</sup> 2) high PG levels and high  $\text{PGF}_{2\alpha}/\text{PGE}_2$  ratio found in the endometrium and menstrual fluid of women with dysmenorrhea;<sup>8,15,17,18</sup> 3) administration of PGs produces symptoms similar to dysmenorrhea;<sup>22</sup> and 4) PG inhibitors successfully relieve symptoms of dysmenorrhea.<sup>1,8,19</sup>

What regulates the intrauterine production of PGs at menstruation? Since ovulation is a prerequisite for primary dysmenorrhea, ovarian steroid hormones are likely to be involved. It has been suggested that high circulating estrogen levels in the luteal phase may cause the excessive PG production.<sup>19</sup> Subsequent research has determined that PG action on the uterus is dependent on progesterone levels, with high levels of progesterone rendering the uterus resistant to PG stimulation, and that excess PGs cause dysmenorrhea as progesterone falls prior to menses.<sup>8</sup>

- **Conventional Treatment Options for Primary Dysmenorrhea**

PG synthetase inhibitors (non-steroidal anti-inflammatory drugs), such as ibuprofen, mefenamic acid, naproxen, and indomethacin, have been used as analgesic treatment for dysmenorrhea since the early 1970s.<sup>1,19</sup> Prior to their discovery, women who had dysmenorrhea were dependent largely on narcotics or oral contraceptives for pain relief.<sup>8</sup> PG inhibitors block PG synthesis early in the inflammatory reaction by inhibiting the cyclooxygenase pathway. Once pain has become severe, relief is unlikely. However, these drugs should not be used prior to the onset of menses because of their teratogenic potential.<sup>4</sup>

In a comprehensive review of clinical trials of PG inhibitors in the treatment of primary dysmenorrhea, it was found that significant pain relief was reported for each of the PG inhibitors for the majority of women.<sup>1</sup> However, the authors concluded that 9% to 22% of dysmenorrheic women will not benefit from PG inhibitor treatment, possibly because some of these women may have secondary dysmenorrhea. While PG inhibitors are generally recognized as effective against pain, there are drawbacks. These drugs are not selective in their inhibition of PGs, translating to a reduction of all PGs, good or bad. In addition, possible side effects include dizziness, headache, nausea, vomiting, heartburn, and diarrhea, as well as GI damage with protracted use.<sup>3,23</sup>

Cyclic administration of oral contraceptives, usually in the lowest dosage but occasionally with increased estrogen, is also used to alleviate pain. The mechanism of pain relief may be related to absence of ovulation or to altered endometrium resulting in decreased prostaglandin production during the luteal phase.<sup>4,8</sup> Surgery is a rare form of intervention used in women who do not respond to medication.

- **Nutritional Management of Primary Dysmenorrhea**

#### **Essential Fatty Acids**

Essential fatty acids (EFAs), such as linoleic acid (LA) and gamma-linolenic acid (GLA), are vital precursors of prostaglandins. The anti-inflammatory series 1 PGs are derived from LA, which is converted to GLA by the enzyme delta-6-desaturase (D6D), and then to dihomo-gamma-linolenic acid (DGLA).<sup>12,24</sup> Nutrients known to increase the conversion of EFAs to the anti-inflammatory series 1 PGs include magnesium, vitamin B<sub>6</sub>, zinc, niacin, and vitamin C. Factors that interfere with the production of anti-inflammatory PGs include diets rich in saturated fats, alcohol consumption, and catecholamines released from the adrenal medulla during stress.<sup>7,8</sup>

Arachidonic acid (AA), found in animal fats, is the precursor of the pro-inflammatory series 2 PGs.<sup>8,25</sup> Much of the AA used for 2 series PG formation comes from dietary sources, notably meat and dairy products.<sup>7</sup> A deficiency of EFAs, either due to inadequate intake or failure of normal conversion of linoleic acid

to GLA, and a high consumption of saturated animal fats can result in overproduction of AA to the pro-inflammatory PGs.<sup>7</sup>

Because there is little GLA or DGLA in the usual human diet, supplementation with GLA-rich evening primrose oil or borage seed oil may effectively reduce the production of pro-inflammatory PGs in favor of anti-inflammatory PGs.

#### **Magnesium**

Magnesium's role in dysmenorrhea may be due to several factors: 1) magnesium has a direct effect on vascular tone and can act physiologically to control and regulate the entry of calcium into smooth muscle cells, acting as a naturally occurring calcium channel blocker.<sup>26,27</sup> Through controlling calcium, magnesium influences the contractility, tone, and relaxation of the uterine smooth muscle; 2) magnesium is required for the synthesis of second messenger cAMP (cyclic AMP) from adenosine triphosphate (ATP).<sup>24</sup> cAMP, a ubiquitous nucleotide derived from ATP through the action of the enzyme adenylate cyclase, plays a crucial role in the communication process between the gonadotropins (LH, FSH) and the ovaries;<sup>24</sup> 3) magnesium plays an important role in the conversion of LA to GLA, a rate limiting step in anti-inflammatory series 1 PG synthesis, and may inhibit the synthesis of PGF<sub>2α</sub>;<sup>28,29</sup> and 4) magnesium is involved in estrogen conjugation and the activation of the B vitamins, especially vitamin B<sub>6</sub>.<sup>30</sup>

Large numbers of women may be at risk for magnesium deficiency. Dietary intake studies consistently show intakes of magnesium to be below the RDA in many age groups, with teenage girls and adult women among those most at risk of low intakes.<sup>31</sup> Magnesium depletion can be compounded by the use of diuretics, increased alcohol and dietary fat intakes, a high intake of dairy products, stress, and malabsorption syndromes.<sup>27,32</sup>

#### **Vitamin B<sub>6</sub>**

Vitamin B<sub>6</sub> (pyridoxine hydrochloride) is an important cofactor for the conversion of LA to DGLA in the production of anti-inflammatory PGs; for enzymes involved in estrogen conjugation in the liver; and for the synthesis of several neurotransmitters.<sup>33</sup> With decreased levels of B<sub>6</sub> in the body, the liver cannot conjugate estrogens, thus causing an increased blood level of estrogens. Vitamin B<sub>6</sub> also stimulates cell membrane transfer of magnesium and increases intracellular magnesium, which plays a role in muscle relaxation.

- **The Use of Selected Herbs in the Treatment of Dysmenorrhea**

Botanical medicines have been used for centuries throughout the world to treat the symptoms of dysmenorrhea and other menstrual irregularities (Table 1)<sup>34-44</sup> Herbs with a long history of use in treating women's problems include cramp bark (*Viburnum opulus*) and blue cohosh (*Caulophyllum thalictroides*), which relax the uterine muscle by acting as antispasmodics and are used to relieve cramping, along with pain in the lower back and thighs;<sup>43,45,46</sup> ginger root (*Zingiber officinale*), an inhibitor of prostaglandin synthesis, has been used for thousands of years for its anti-inflammatory properties;<sup>47,48</sup> wild lettuce leaf (*Lactuca elongata*) has been used since ancient times for its pain-relieving and calming effects;<sup>36</sup> and black cohosh (*Cimicifuga racemosa*) has antispasmodic and analgesic properties, easing cramping and muscle tension.<sup>46</sup> Dong quai (*Angelica sinensis*) demonstrates uterine tonic activity, causing an initial increase in uterine contraction followed by relaxation.

**Table 1. Selected Herbs for the Treatment of Menstrual Irregularities**

Common Name ( <i>Botanical name</i> )	Country of Origin	Traditional Use	Some Active Constituents
Agrimony Leaf ( <i>Agrimonia pilosa</i> )	China, North America	Hemostatic (controls bleeding), antiparasitic	Agrimophol, vitamins C, K, tannins
Anise Seed ( <i>Pimpinella anisum</i> )	Europe, Mediterranean	Carminative, fertility	Volatile oil: anethol; iron, quercetin-glucosides, rutin
Black Cohosh Root ( <i>Cimicifuga racemosa</i> )	North America	Female complaints associated with menopause and menses	Triterpenoid glycosides, isoflavones, formononetin
Blue Cohosh Root ( <i>Caulophyllum thalictroides</i> )	North America	Menstrual flow stimulant, antispasmodic, uterine tonic, promotes childbirth	Alkaloid: methylcytisine; glycoside: caulosaponin
Cramp Bark Root ( <i>Viburnum opulus</i> )	Europe, naturalized in North America 17th century	Uterine sedative, smooth muscle relaxant, diuretic antispasmodic, cardiogenic	*USP 1894; **NF 191660 Arbutin, valeric acid, tannins: anthocyanins, catechins, flavonoid
Dong Quai Root ( <i>Angelica sinensis</i> )	China	Antianemic, regulates menses, smooth muscle relaxant	Vitamin B <sub>12</sub> , ferulic acid, ligustilide, folic acid, choline, iron
Ginger Rhizome ( <i>Zingiber officinale</i> )	China, Pacific Rim, India	Stimulant, carminative, digestant, antiinflammatory	Terpenoid: zingiberene; gingerols
Shepherd's Purse Herb ( <i>Capsella bursapastoris</i> )	EurAsia	Hemostatic (controls bleeding)	Flavonoids: luteolin, quercetin, 7-rutinosides, vitamin C, hemostyptic peptide
Wild Lettuce Leaf ( <i>Lactuca elongata</i> )	North America, Europe	Relaxant, anodyne, diuretic	*USP 1820-1926 Lactucin, lactucopicrin, inulin

\*United States Pharmacopoeia

\*\*National Formulary

**DYSFUNCTIONAL UTERINE BLEEDING**

Abnormal uterine bleeding includes excessive bleeding, irregular bleeding, and absence of bleeding.<sup>11</sup> In about 25% of patients, these menstrual irregularities are due to organic causes such as systemic disease, pregnancy, or cancer.<sup>2</sup> For the remainder of patients, there is absolutely no organic pathologic condition but rather a functional abnormality in the hypothalamic-pituitary-ovarian axis, defined as *dysfunctional uterine bleeding* (DUB).<sup>2,11</sup> Before reaching a diagnosis of true DUB, the clinician must rule out any underlying pathologic conditions. Patterns of abnormal uterine bleeding and possible underlying medical causes are described below:<sup>2,4,11</sup>

**Menorrhagia** is heavy or prolonged menstrual bleeding that may occur as a single episode or on a chronic basis. Normal menstrual flow lasts about 5 days and produces a total blood loss of 60 to 250 ml. In menorrhagia, the menstrual period is extended and total blood loss can range from 80 ml to overt hemorrhage.

**Hypomenorrhea** is unusually light menstrual flow, sometimes only "spotting."

**Metrorrhagia** is uterine bleeding that occurs irregularly between menstrual periods. The bleeding is usually light, although it can range from staining to hemorrhage.

**Polymenorrhea** describes menstruation that occurs too frequently.

**Oligomenorrhea** is abnormally infrequent menstrual bleeding characterized by 3 to 6 menstrual cycles per year. When menstrual bleeding does occur, it can be profuse and prolonged or decreased in amount.

**Amenorrhea** (secondary) is the absence of a menstrual period for 3 or more months in women with past menses, precluding normal physiological causes such as pregnancy, lactation, and menopause.

Possible organic causes of abnormal uterine bleeding include, but are not limited to:<sup>2,3,11</sup> endometriosis, polycystic ovary syndrome, blood dyscrasias, thyroid dysfunction, pelvic inflammatory disease, anorexia nervosa, diabetes mellitus, pituitary disorders, uterine fibroids, cervical stenosis, cervicitis, endometrial polyps, gynecologic carcinoma, syphilis, vaginal adenosis, adrenal disorders, and corpus luteum cysts. The use of oral contraceptives (as well as their discontinuence), anticoagulants, corticosteroids, and IUDs can also cause abnormal uterine bleeding.

**ETIOLOGY OF DYSFUNCTIONAL UTERINE BLEEDING**

Dysfunctional uterine bleeding occurs most commonly at the extremes of reproductive age, with 20% of cases in adolescence and greater than 50% in patients over age 40.<sup>2,4</sup> Normal endometrial bleeding (menstruation) occurs as a result of stimulation of the endometrium by the physiologic levels and balance of estrogen and progesterone present in the normal ovulatory cycle and by the subsequent rapid withdrawal of these two hormones. This withdrawal results in complete and rapid shedding of the entire functional layer of the endometrium. Various disturbances in this balanced estrogen-progesterone relationship can result in four clinical etiologies of true DUB:<sup>4,11</sup>

**Nonovulatory DUB** – Greater than 70% of DUB cases are associated with anovulation. The bleeding in anovulatory women is generally the result of continued stimulation of the endometrium with unopposed estrogen, which occurs when there is a dysfunction of the hypothalamic-pituitary-ovarian axis. The endometrium, thickened by the estrogen, then sloughs incompletely and irregularly, and bleeding becomes

irregular, prolonged, and/or profuse. The absence of progesterone results in deficient endometrial prostaglandins so that appropriate spasm of the coiled arterioles is lacking. This also results in irregular and incomplete shedding of the endometrium.

**Irregular Ripening of the Endometrium (Luteal Phase Defect)** – This occurs in ovulatory cycles where the corpus luteum production of progesterone is inadequate to permit development of a receptive endometrium. Any disturbance of follicular growth and development can produce an inadequate follicle and a deficient corpus luteum. Patients with luteal phase defects can present primarily with DUB manifested as premenstrual bleeding, menorrhagia, or polymenorrhea.

**Irregular (or Prolonged) Shedding of the Endometrium** – Irregular shedding of the endometrium is apparently due to slow degeneration of the corpus luteum with prolonged exposure of the menstruating endometrium to the waning progesterone. Clinically, irregular shedding of the endometrium manifests itself by cyclic prolonged menstruation, which may be profuse.

**Endometrial Atrophy (or Threshold Bleeding)** – The normal amount of estrogen secreted during the proliferative phase of the cycle results in a stable endometrium that is intact and does not bleed. In the absence of estrogen, or with the minimal levels present premenarchally or postmenopausally, the endometrium is so unstimulated and atrophic that no bleeding occurs. However, with persistent intermediate levels of estrogen, irregular bleeding occurs. This is because there is enough estrogen to stimulate the endometrium but not enough to stabilize it, keep it intact, and maintain it.

### **Anemia**

An often overlooked factor that may contribute to menstrual irregularities is anemia.<sup>49,50</sup> Chronic anemia can be present at a sub-clinical level (not confirmed by laboratory findings), which is why it is not always considered as a contributing, or complicating, factor of DUB. The early stages of anemia present as vague symptoms of tiring easily, headaches, irritability, or depression.<sup>35,51,52</sup> Tachycardia, shortness of breath, angina pain, equilibrium disturbances, tinnitus, and a tendency to faint may develop later, but still in the absence of blood confirmation.<sup>51</sup> At any level of anemia, the impaired oxygen and nutrient carrying capacity can have a dramatic effect on tissues throughout the body, especially reproductive tissues. The reason reproductive tissues are susceptible to an even mild anemic state is the result of their function being dependent upon hormonal messages communicated from the neuroendocrine system through the blood to the target tissue.

Anemia can not only be the cause of excessive uterine bleeding, but can also be the result.<sup>33,49</sup> The anemia can then aggravate menorrhagia by impairing the delivery of nutrients and oxygen required to repair and oxygenate the reproductive tissues. Additional causes of anemia can be iron-deficiency, which can be due to dietary deficiency and/or poor absorption.<sup>51,52</sup> Anemia can also be nutritional in origin and can result from insufficient dietary iron, vitamin B<sub>12</sub>, folic acid, vitamin C, vitamin B<sub>6</sub>, and vitamin E, which all play a role in the uptake and metabolism of iron and the formation of healthy red blood cells.<sup>33</sup>

### **Prostaglandins**

As in the case of dysmenorrhea, prostaglandins may play a role in dysfunctional uterine bleeding. This is supported by several findings: 1) large amounts of prostaglandins have been demonstrated in the premenstrual endometrium, and even greater concentrations (as much as 10 times higher) are present in the

menstrual fluid itself;<sup>11,14,20</sup> 2) elevated concentrations of PGE<sub>2</sub> and PGF<sub>2α</sub> in the endometrium were found in women with menorrhagia when compared to women with normal periods;<sup>15,17</sup> 3) the administration of PGF<sub>2α</sub> during the luteal phase of the cycle produces focal endometrial necrosis and sloughing with premature bleeding;<sup>11</sup> and 4) the administration of PG inhibitors is associated with a decrease in menstrual blood loss.<sup>15,53</sup> For a more thorough discussion of PGs, please refer to the PG section under dysmenorrhea.

### **Other Factors**

Obesity and excess adipose tissue in relation to lean body mass affect estrogen/progesterone ratios. Circulating androgens are metabolized by adipose tissue into active estrogens that influence the body balance of estrogens. Studies have shown that the extent of this conversion is significantly correlated with excessive body weight.<sup>54</sup> Menorrhagia in association with obesity may be the result of this increased peripheral conversion of androstenedione into estrogens.<sup>11</sup> In addition, aberrations in the menstrual cycle causing nonovulation, irregular ripening, or irregular shedding are often due to temporary causative factors, such as nutritional insufficiencies or high stress.

### **Conventional Treatment of DUB**

Treatment of DUB is usually in the form of hormonal therapy geared specifically to the hormone deficiency. For example, because the specific hormone lacking in nonovulatory DUB is progesterone, the treatment is to give a progestational agent daily for the last 10 to 14 days of the cycle.<sup>11</sup> Late luteal phase defect can also be treated in the same way, but because there is a corpus luteum producing some progesterone, the dosage can be reduced. The treatment for irregular shedding is estrogen, which causes regeneration of a new, intact endometrium and, by negative feedback suppression of LH (which is responsible for the maintenance of the corpus luteum), causes degeneration of the persistent corpus luteum.<sup>11</sup> For endometrial atrophy, both estrogen and progesterone are supplied. Instead of specific hormonal therapy for each type of DUB, an alternative method is the prescription of a combination birth control pill for 3 months.

### **A Nutritional Approach to DUB**

#### **Vitamin B<sub>6</sub>**

Vitamin B<sub>6</sub> plays a role in the manufacture of hemoglobin in red blood cells and increases its oxygen binding affinity.<sup>33</sup> Vitamin B<sub>6</sub> deficiency results in an anemia that resembles iron-deficiency anemia.<sup>51,55-58</sup> The blood levels of iron are adequate, but hemoglobin and red blood cells are not formed in the absence of vitamin B<sub>6</sub>.<sup>58</sup> Remission is totally dependent upon the administration of supplemental vitamin B<sub>6</sub>.<sup>55</sup>

Vitamin B<sub>6</sub> is also an important cofactor for the conversion of LA to DGLA in the production of anti-inflammatory PGs; for enzymes involved in estrogen conjugation in the liver; and for the synthesis of several neurotransmitters.<sup>33</sup> With decreased levels of B<sub>6</sub> in the body, the liver cannot conjugate estrogens, thus causing an increased blood level of estrogens. Vitamin B<sub>6</sub> also stimulates cell membrane transfer of magnesium and increases intracellular magnesium, which plays a role in muscle relaxation.

#### **Vitamins A and E**

Vitamin A affects the growth and development of reproductive tissues and helps to maintain healthy epithelial and secretory tissues associated with the vagina, uterus, cervix, corpus luteum,



and endometrium.<sup>33,58</sup> The development of the ovarian follicle is vitamin A dependent and insufficiencies may result in amenorrhea.<sup>59</sup> The antioxidant properties of vitamin A help to maintain tissue integrity and prevent tissues from becoming hyperproliferative. This is particularly useful where reproductive tissues are concerned, helping to maintain stability in an environment of fluctuating hormones.

Vitamin E helps to regulate the utilization and storage of vitamin A, and protects it from oxidation in the gut, liver, and other organs.<sup>33,58</sup> Impaired liver function can impact vitamin A metabolism and transport. Exposure to environmental pollutants results in enhanced degradation of vitamin A in the liver.

### **Magnesium**

Please refer to the discussion of magnesium under dysmenorrhea.

### **Phytoestrogens**

Phytoestrogens are a family of compounds found in plants, especially the soybean, which possess weak estrogenic effects.<sup>60</sup> By occupying estrogen binding sites, phytoestrogens can possess both estrogenic activity (agonist) and antiestrogenic (antagonist) activity by competing for estrogen-receptor sites with the more active endogenous estrogens. Women may be able to create a significant positive impact upon their hormone levels and ratios by the inclusion of soy protein and other phytoestrogens in their diets.<sup>43</sup>

### **Essential Fatty Acids**

Please refer to the discussion of EFAs under dysmenorrhea.

### **Vitamin C**

Vitamin C (ascorbic acid) has three biological actions of particular relevance to reproductive tissues: it is required for the synthesis of collagen, for the synthesis of steroid and peptide hormones, and it protects tissues from oxidative damage.<sup>33,61,62</sup> There is an abundance of ascorbic acid in the ovary, which is consistent with its known roles in hormone synthesis and synergism with neurotransmitters in stimulating hormone secretion.<sup>61</sup> The follicular-luteal cycle also requires high rates of tissue remodeling and collagen synthesis for follicle growth, for repair of the ovulated follicle, and the development of the corpus luteum.<sup>61</sup>

Vitamin C and rutin, a bioflavonoid, play roles in improving capillary and blood vessel integrity, which is important in the control of blood flow.<sup>41</sup> Vitamin C, through its essential role in the development of collagen, helps to strengthen arteries and blood vessels. Vitamin C and rutin play protectant roles in maintaining capillary integrity by functioning as antioxidants.<sup>62</sup> When taken orally, vitamin C enhances non-heme iron absorption by as much as 600% by keeping it in a biologically available form and protecting it from oxidation in the gastrointestinal tract.<sup>63-66</sup> Vitamin C is also thought to form a chelate with iron, acting as a vehicle for its entry into the intestinal wall.<sup>64</sup>

Bile acid synthesis is vitamin C dependent. Bile acids are required for absorption of the fat-soluble vitamins A, D, E, and K, beta-carotene, and EFAs, each of which plays an important role in menstrual regularity and hormone balance.<sup>24</sup>

### **Iron**

Iron is the oxygen-carrying component of the blood and is therefore the determinant of how much oxygen reaches and is used by all body tissues. The manufacture of red blood cells

decreases when the body does not have an adequate amount of iron, with anemia being the final stage of iron deficiency.<sup>58</sup>

Iron deficiency is the most prevalent nutrient deficiency, and is thought to be the most common form of anemia.<sup>51</sup> In studies of nutritional status, 35% to 58% of young, healthy women have been found to have some degree of iron deficiency.<sup>33</sup> Iron deficiency can be caused by inadequate dietary intake, impaired absorption, chronic blood loss, and pregnancy.<sup>33</sup> Dietary iron absorption is inhibited by certain high fiber foods,<sup>51,63,67</sup> such as green leafy vegetables and whole grains, as well as coffee.<sup>68</sup>

### **Vitamin B<sub>12</sub> and Folic Acid**

Other factors not associated with iron assimilation are necessary for the proper development and maintenance of red blood cells. Vitamin B<sub>12</sub> and folic acid are essential to proper growth and function of all the cells in the body.<sup>24,58</sup> Without proper amounts of B<sub>12</sub> and folic acid, the red blood cell producers in the bone marrow do not proliferate properly, becoming larger than normal (called megaloblasts).<sup>24</sup> They produce oversized red blood cells called macrocytes that are released into the peripheral blood. Because of the macrocyte's increased size and fewer numbers, their normal capacity to carry hemoglobin is impaired and the hemoglobin's normal oxygen transport function is reduced. Another problem is that their large, fragile, irregularly shaped membranes reduce the lifespan of the macrocytes markedly. This condition is known as pernicious anemia or megaloblastic anemia.<sup>24</sup>

### **• The Use of Selected Herbs in the Treatment of Dysfunctional Uterine Bleeding**

Traditional herbal strategies that help regulate the flow of excess menstrual blood combine plants observed to: 1) help reduce excessive bleeding quickly; 2) support the integrity of uterine tissue, blood vessels, and capillaries; 3) balance female hormones to ensure the normal maturation of the ovarian follicle, corpus luteum, and endometrium; 4) relax muscles; and 5) control inflammation. Please refer to Table 1 on page 4 for a listing of herbs traditionally used to treat menstrual irregularities.

The herbs shepherd's purse (*Capsella bursapastoris*) and agrimony (*Agrimonia pilosula*) are known for their ability to help control bleeding. In China and Europe, agrimony is a major herb used to help reduce bleeding and to treat profuse menstruation. Research indicates agrimony, which contains tannins, saponins, and bitter principles,<sup>41,46</sup> can increase coagulation of the blood by up to 50%.<sup>34</sup> Shepherd's purse is classified as an antihemorrhagic and urinary antiseptic containing flavonoids, rutin, potassium salts, and vitamin C.<sup>41</sup> In Europe and Germany, shepherd's purse is used in mild menorrhagia and metrorrhagia.<sup>44</sup> Rutin is a flavonoid isolated from a wide variety of herbs like buckwheat (*Fagopyrum esculentum*). The primary benefit is its role in decreasing capillary fragility, which controls bleeding tendencies.<sup>41</sup>

Blue cohosh root (*Caulophyllum thalictroides*) is classified as a uterine tonic whose constituents strengthen the uterus so it can perform its natural function. Native American women used blue cohosh for painful and profuse menstruation.<sup>37,43</sup> This is a plant that can promote or control menstrual flow depending on the circumstance. Cramp bark (*Viburnum opulus*) is a uterine sedative useful in managing abdominal and uterine cramping.<sup>43</sup>

Black cohosh root (*Cimicifuga racemosa*), dong quai root (*Angelica sinensis*) and anise seed (*Pimpinella anisum*) supply phytoestrogens useful in anovulatory disorders associated with

excessive or suppressed menses. Dong quai and anise also function to improve digestion and assimilation and build the blood. Anise is an herbal source of iron and has demonstrated an ability to improve the absorption of iron.<sup>35,36</sup> Dong quai contains a spectrum of B vitamins including folic acid and B<sub>12</sub>, as well as vitamin C and iron, which support its reputation as a blood replenisher.<sup>34,35,69</sup>

• **The Traditional Chinese Medicine Approach to Menstrual Irregularities**

In traditional Chinese medicine (TCM), the blood feeds nutrients and oxygen to all the tissues of the body, nourishing the mind and reproductive organs and facilitating communication between all body systems. Because monthly blood loss is associated with being a woman, the blood is considered intimately linked to female health and reproductive function. Disturbances in menstrual blood flow, volume, duration, regularity, or quality are considered to be a reflection of hormonal imbalances related to blood disharmonies. Some patterns of blood disharmonies that are common to the Western practitioner include cardiovascular and circulatory problems (*blood stasis/stagnation*), toxicity (*blood heat*), and anemias or hemopoietic disorders (*blood deficiency*). In TCM, herbal and dietary strategies for menstrual irregularities target improving the blood.

Interestingly, many Asian herbs traditionally used to regulate blood possess pharmacological properties that mediate communication between the neuroendocrine system and the associated glands and organs.<sup>70</sup> They also contain active constituents that behave like weak hormone mimics. Dong quai (*Angelica sinensis*), frequently referred to as “women’s ginseng,” is a multifaceted herb that regulates menses and acts as a hematinic, an analgesic, and sedative.<sup>71</sup> However, the roots of rehmannia (*Rehmannia glutinosa*), peony (*Paeonia lactiflora*) and ligusticum (*Ligusticum wallichii*) are equally profound in their ability to balance female hormones and are frequently combined, in varying ratios, to enhance each others action.

Women who have secondary amenorrhea, infrequent menstrual cycles (oligomenorrhea), irregular menstrual bleeding (metrorrhagia), or whose menstrual blood is pale red in color, thin, and “lacks

density” (hypomenorrhea), may benefit from a traditional Chinese herbal decoction (boiled in water) that not only builds the blood, but restores the vital energy (ch’i) required to increase stamina, strength, and improve absorption of food (Table 2).<sup>34-36,69,72</sup> Codonopsis root (*Codonopsis pilosula*) is frequently exchanged with ginseng root (*Panax ginseng*) because the ch’i stimulating properties are comparable.

• **Dietary and Lifestyle Recommendations**

A recommended diet centers around complex carbohydrates, including whole grains, legumes, vegetables, and fruits, and the avoidance of polyunsaturated vegetable oils, refined sugar, alcohol, and caffeine-containing foods and beverages. It is also recommended to limit intake of dairy products and animal fats. A weight management program may be very helpful in both reducing adipose aromatase activity and facilitating more desirable estrogen metabolism and excretion.

Stress can affect hormone production and stimulate the secretion of a range of other hormones that interfere with the sex hormones. The demands placed on women today may contribute to a prolonged “stress overload,” which can have an adverse impact on hormonal balance and lead to menstrual irregularities. An important part of stress reduction is regular exercise, which helps to improve blood circulation and increases endorphin and neurotransmitter levels.

• **A Healthy Menstrual Cycle Now for a Healthier Tomorrow**

A healthy menstrual cycle throughout a woman’s reproductive years is a sign of balanced ovarian hormones, as well as other endogenous substances. Menstrual difficulties such as primary dysmenorrhea and dysfunctional uterine bleeding can be indicative of potential hormonal imbalances, which can lead to impaired fertility and menopausal problems in the future. Interventions which can help to balance these factors may not only be helpful in treating menstrual difficulties, but could lower the risk of other hormone-related problems in the future.

**Table 2. TCM Herbal Approach to Dysfunctional Uterine Bleeding (with the exception of excessive blood flow)**

Common Name (Botanical name)	Country of Origin	Traditional Use	Some Active Constituents
Rehmannia Root, prepared ( <i>Rehmannia glutinosa</i> )	China	Nourishes the blood, generates fluids	Sterol, campesterol, catalpol, rehmannin, some alkaloids
Dong Quai Root ( <i>Angelica sinensis</i> )	China	Antianemic, regulates menses, smooth muscle relaxant	Vitamin B <sub>12</sub> , ferulic acid, ligustilide, folic acid, choline, iron
Peony Root ( <i>Paeonia lactiflora</i> )	China	Antimicrobial, astringent, antiinflammatory	Monoterpene glycosides: paeoniflorin, benzoylpaeoniflorin; sterols
Licorice Root ( <i>Glycyrrhiza uralensis</i> )	China	Moves and strengthens the ch’i, antiinflammatory, spasmolytic	Triterpenoid saponin: glycyrrhizin, Flavonoids: liquiritin, quercetin
Ligusticum Rhizome ( <i>Ligusticum wallichii</i> )	China	Circulates the blood and ch’i, increases uterine contractions	Ferulic acid, cnidilide, ligustilide, alkaloids: tetramethylpyrazine
Codonopsis Root ( <i>Codonopsis pilosula</i> )	China	Strengthens the ch’i, nourishes the fluids, improves digestion	Phytosterols, triterpenes, saponins, polysaccharides
Poria Fungus ( <i>Poria cocos</i> )		Builds ch’i by improving assimilation, nerve	Polysaccharide: pachymarose, organic acids: pachymic acid, etc.
Chasteberry Fruit ( <i>Vitex agnus castus</i> )	Europe	Control and regulation of the female reproductive system	Monoterpene: agnuside, eurosoid, aucubin; flavonoids: vitexin

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