# Women's Health: The Menstrual Cycle

## Women's Reproductive Health: Recent Advances in Therapies

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### Synopsis .....

Normal cyclic menstruation involves a delicate concert of hormonal events, characterized by midcycle ovulation and, if no pregnancy is achieved, menstrual flow. Women's health—and especially their reproductive health and fertility—may be affected by abnormalities in cyclicity or in menstruation. A number of valuable modes of therapy have recently become available.

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WISH TO DISCUSS THE PHYSIOLOGY and pathophysiology of normal cyclic menstruation. The latter will be divided into abnormal cyclicity, including causes and effects, decreased and increased estrogens, and abnormal menstruation because of an abnormal or even an absent uterus. Finally, ways in which new therapeutics are used to treat each of these abnormalities will be described.

The normal ovulatory cycle involves the complex development of a single dominant follicle with an oocyte (egg) in it, which ovulates around midcycle and subsequently forms a corpus luteum. This concert of events is driven by central hormones and modulated by the ovarian hormones, estrogens, and progesterone (1). GnRH or gonadotropin-releasing hormone, a hypothalamic hormone, helps drive the system. It does so in an intermittent pulsatile fashion. Luteinizing hormone, (LH), a pituitary hormone whose production is stimulated by the secretion of the pulsatile GnRH, is also released in a pulsatile fashion. It in turn stimulates the ovarian production disorders). Small ovulation induction pumps, which deliver minute physiologic concentrations of gonadotropin-releasing hormone(GnRH) around the clock, can be used for safe and successful treatment. Increased estrogen levels may also affect cyclicity, and may be suppressed with new GnRH antagonists or stimulated to cyclicity with pure follicle-stimulating hormone.

Abnormal menstruation may be caused by intrauterine scarring or fibroids. Outpatient hysteroscopic surgery may successfully and conservatively be used to treat these problems. Today, even women who have been born without a uterus or who have undergone hysterectomy may have a child through a host uterus program. This combines in vitro fertilization of the husband's sperm with his wife's egg with transfer of the embryo into a host who is capable of carrying the pregnancy.

Our potential to improve women's reproductive health continues to expand, as some of the recent developments described above for treating abnormalities of cyclicity or menstruation attest.

of estrogens and progesterone. Menstrual cyclicity is dependent on the normal production of these ovarian hormones. If no pregnancy occurs in the cycle, the uterine lining, built up as a result of estrogen and progesterone, sheds. Thus, in normal physiology, we have cyclicity and we have menstruation as an endpoint in a nonpregnancy cycle.

Abnormalities of ovulatory cyclicity may occur in response to decreased estrogens. Causes of decreased estrogens are common, such as excessive exercise, smoking, or eating disorders such as bulimia/anorexia (2). Regarding exercise, there is a correlation between amount of training, such as the number of miles run per week, and the incidence of anovulation (the complete lack of ovulation). The greater the training, the greater the frequency of ovulatory irregularity. Swimmers usually do not show the same pattern because of different body fatweight distributions, calorie intake, and eating habits.

Cigarette smoking can affect the reproductive



capabilities of both men and women (3). One mechanism of this impairment in females is decreased estrogen production and altered cylicity.

Eating disorders may emaciate an adolescent suffering from bulimia or anorexia and result in decreased estrogen production. The LH pattern in patients with decreased estrogens, unlike normal individuals with their pulsatile pattern, is flat and nonpulsatile. An important question is, what can we do for these individuals who have decreased estrogen levels that result in abnormal cylicity? First, one treats the primary disorder such as modifying smoking or running or eating habits. Today we also have the means by which we can help reinstitute the pulsatile physiology of GnRH using small portable programmable pumps (1, 4) that give a discrete pulse of GnRH through either a very small subcutaneous or intravenous needle and re-establish the pulsatile pattern of LH, which noncyclic females with decreased estrogens lack (4). This physiologically restores both the ovulatory cyclicity, and if the patient does not conceive, menstruation occurs in that cycle. This therapy has been successfully employed over the last few years in a number of medical centers, including our own.

Increased estrogen levels can also be a cause of abnormal cyclicity, Polycystic ovarian (PCO) syndrome is a ovarian disorder and is characterized in patients by obesity, excess hair growth, and large cystic ovaries, and because of the increased estrogens, heavy bleeding, menorrhagia, and even uterine cancer. These individuals typically have a very poor response to the most common ovulation induction agents (4). Characteristically, patients with PCO have an increase in LH and a decrease in folliclestimulating hormone (FSH). Medications that contain both LH and FSH, such as Pergonal, are not suited to these patients.

If the patient is infertile and wants to ovulate, we might prescribe FSH. We now have a new medication approved by the Food and Drug Administration for use for PCO, called pure FSH (4). Previously, LH and FSH combined were available, but not FSH alone. Pure FSH is a medication tailored to help a group of patients in whom our rate of success had not been optimal.

For PCO patients with excess estrogen causing abnormal bleeding and to whom ovulating is unimportant, GnRH antagonists may be a new option. GnRH antagonists are an alteration of the formula of GnRH that blocks GnRH action, as opposed to stimulating it (1). We discussed giving GnRH in a pulsatile fashion to induce LH and thus to induce ovulation. Here we are giving an altered or modified GnRH, which can lower LH, in order to lower estrogens in this group of patients in whom it is too high. Again, this is a new medication or formulation designed to succeed therapeutically where other therapies had not.

Abnormal menstruation—referring to the bleeding itself, not the cyclicity—may be caused by a number of problems. One of the problems could be an abnormal uterus. The uterine lining builds up in a sequential fashion from early in the cycle, to midcycle, to late in the cycle. Then menstruation occurs. This is partly controlled by a normal configuration and contour of the uterus. A common cause of an abnormal uterus and of irregular or heavy menstruation are leiomyomas (benign muscle tumors of the uterus often called fibroids). These can cause heavy bleeding and also infertility and miscarriage because of problems with implantation or the area in which the fetus can grow. The fibroids are often removed through a major operative procedure called a myomectomy, which requires an incision in the abdomen and uterus, leading to possible scarring and all of the coincident problems that major operative procedures can entail.

Hysteroscopy is a procedure of growing import (5). It has been available for a number of years but recently is being used much more widely. Hysteroscopy uses lens systems and fiber optic lighting to visualize directly inside the uterine cavity and permits performing certain operative procedures on an outpatient basis without major surgery, such as some myomectomies (6).

Another form of abnormal uterus can be caused by infection and repeated curettage, a syndrome called Asherman's syndrome, associated with uterine scarring. From inside the uterus, this scarring looks like stalagtite and stalagmite formation in a cave. This scarring can cause infertility, miscarriage, and abnormal menstruation—usually very light or absent flow. Now we can remove such scarring hysteroscopically under direct visualization with the direct application of miniature hysteroscope scissors or cautery, allowing outpatient treatment (5).

Finally, an absent uterus must qualify as abnormal menstruation. Women who had been born without a uterus or had a hysterectomy without oophorectomy had been considered sterile. The Host-Uterus Program, recently initiated at George Washington University, is a new technique applicable for these women (fig. 1). The plan is to take the husband's sperm and the wife's eggs from normal ovaries, fertilize them in vitro using currently applicable in vitro fertilization technologies, and transfer the resultant embryo into a synchronized host who has a uterus. The host carries the pregnancy and delivers the child. The resultant child would be the genetic complement of the husband and the wife. (This is very different from surrogacy, in which a surrogate is inseminated with the husband's sperm, conceives, carries, and delivers a child which is genetically her own. She then chooses to give up that child to the couple.) The Host Uterus Program is now applicable to a group of patients who were previously beyond therapeutic treatment and had been considered sterile even though their ovaries and eggs were perfectly normal (7).

#### Figure 2. Menstrual cycle



Other applications of the Host-Uterus Program may be for Asherman's syndrome or fibroids that may not be successfully treated through the hysteroscope, severe DES-related uterine abnormalities (8), or for high-risk obstetrical patients (such as those with severe diabetes or heart disease or those undergoing cancer chemotherapy), or fetuses at risk because of RH sensitization.

In summary (fig. 2), the physiology of the menstrual cycle and how newly developed therapies may help patients with alterations of that physiology have been reviewed. Normal cyclic menstruation, and specifically how pulsatile GnRH output drives the system, resulting in ovulation and ovarian output of estrogens and progesterones (1), has been discussed. Abnormal cyclicity and how this can be manifest by decreased or increased estrogens was noted. Decreased estrogens, caused by smoking, exercise, or anorexia, now may be treated by physiological restoration of absent GnRH pulsatility using miniaturized pumps (1, 2, 4). Increased estrogen, such as from PCO syndrome, may respond therapeutically by lowering estrogens with non-pulsatile GnRH antagonists to prevent endometrial cancer or abnormal bleeding or by inducing ovulation in infertile women with newly available pure FSH (4).

Abnormal menstruation may have its etiology in an abnormal or absent uterus. An abnormal uterus may demonstrate increased bleeding from leiomyoma (fibroids) or decreased bleeding due to uterine scarring (Asherman's syndrome). Both may safely and effectively be treated by expanded use of minor hysteroscopic surgery, replacing more extensive and less effective major surgeries (5, 6). Today's technologic advances applied to the clinical care of women's health may be exemplified by the last example of abnormal menstrual cyclicity—that of women without a uterus. In vitro fertilization techniques can, through a Host-Uterus Program, allow these women with irremediable sterility to have their own biologic child (7). It is the clinical applicability of advances such as those described in this paper that make basic and clinical research an important cornerstone of our health care system.

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# Climacteric Medicine: Cornerstone for Midlife Health and Wellness

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Synopsis .....

Midlife care should consider the whole woman, with preventive attention to osteoporosis and cardiovascular disease. A new delivery system, using a skin patch, is available for replacement or additive hormonal thereapy. Useful hormonal therapy may include both estrogen and progesterone.

**L**<sub>N</sub> 1983, THE LIFE EXPECTANCY for females at birth was 78.3 years, and it exceeded that for men by 7.3 years; for women who reach the age of 65, a further 18.8 years of longevity can be anticipated (1). These encouraging data are marred by the reality of a significant impairment in the quality of later life, with many women confined to institutions. For example, about 5–15 percent of elderly women are transiently incontinent (2), the prevalence increasing to 40 percent in hospital patients (3) and more than 50 percent in institutionalized persons (4). More than \$8 billion per year is spent on care for the incontinent, institutionalized elderly. Osteoporosis is another condition that impacts negatively on the health status of elderly women. More than 300,000

women fracture their hips due to osteoporosis each year and, of this number, about 12-20 percent die due to factors directly attributable to the fracture (5). Only one-third of the survivors will regain normal activity (6). The total cost of osteoporosis (including fractures of the vertebrae) was estimated to be \$6.1 billion in 1983 (7). Cardiovascular disease is another cause of significant morbidity; it accounted for 51 percent of all deaths in 1981 at an estimated cost in 1984 of \$64.4 billion (8). Death from heart disease affects women, too, resulting in 10 times more deaths than breast cancer.

This list of seemingly unrelated conditions are in fact linked by at least two life events: chronological aging and the senescence of ovarian function. The