Abnormal Bleeding

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The complaint of abnormal bleeding is one of the most frequent the gynecologist has to deal with. Patients with this problem cover the spectrum from absent bleeding (amenorrhea) to excessive bleeding in the form of either heavy prolonged periods (menorrhagia) or irregular frequent bleeding (metrorrhagia). In general, dysfunctional uterine bleeding (DUB) denotes bleeding in the absence of ovulation and it constitutes one of the most frequent diagnoses for those patients who have excessive abnormal bleeding. An infrequent form of DUB does involve ovulation but there is a prolonged function of the corpus luteum and irregular prolonged shedding of the endometrium.[1] Since this is uncommon, the term DUB in this report will refer to anovulatory cycles. While this topic has been extensively reviewed in many chapters in the past,[2] it is so common and our knowledge about it is improving so rapidly that an update seems appropriate. In order for appropriate management to be instituted, the physician must obtain an adequate menstrual history so that he or she may document that bleeding is abnormal. If the bleeding is truly abnormal, then the physician must perform a careful physical and pelvic examination and obtain appropriate laboratory tests so that he or she may make the diagnosis and begin appropriate therapy. Each of these areas will be dealt with in some detail.

Menstrual History

The complete menstrual history requires at least eight individual items of information:

1. Menarche
2. Frequency
3. Duration
4. Last menstrual period
5. Amount
6. Molimen
7. Other bleeding
8. Menopause

For each of these, one needs to know the mean and two standard deviations for the normal population so that responses beyond these confidence limits can be accurately defined as "abnormal." The data base to be obtained are as follows:

1. *Menarch*—The age of menarche ranges from 8 to 16 years, with an average of approximately 12 years. Puberty is a continuum of change over the 2-year time period, and the sequence of changes involves breast budding, the growth of pubic and axillary hair, breast growth, the production of cervical mucus, a spurt in total height growth, and eventual uterine bleed-

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ing. The menarche deals specifically with the onset of uterine bleeding, but disorders of menarche may also involve other aspects of pubertal development. Important controls of this developmental process include the nutritional state of the woman and her exposure to light. It appears as though women need to have a large caloric storage of fat in place before they initiate their reproductive cycles. This allows them to carry a pregnancy with minimal nutritional intake. Normograms have been developed that show that, for example, a woman whose height is 5 ft. 3 in., has to achieve a weight of approximately 91 lb. before menses begin.[3] Later in life, if marked deviations in weight occur, the cycles may be interrupted, as is seen in starvation weight loss or with marked obesity.[4] As countries become developed and their nutritional intake improves, the age at which a woman achieves her fat stores decreases, as does the age of menarche. Light also has its effect on the reproductive process. It enters through the retina and is processed through the optic nerves to the superior cervical ganglion and then up to the pineal gland. From that area, melatonin is released into the hypothalamic areas and it controls the outpouring of gonadotropin-releasing factor.[5]

2. *Frequency*—By convention the first day of bleeding is called day 1 of the cycle, and the cycle frequency relates to the interval of time from the beginning of one menses to the beginning of the next. Generally, the average is 28 days, with the normal range of 21 to 35 days.
3. *Duration*—The mean duration of flow during the menses is 3 to 4 days, with a range of 2 to 7.
4. *Last menstrual period*—indicates the first day of the last normal menses.
5. *Amount*—The amount of menstrual flow can be quantitatively determined and has been found to average 35 ml, with a range of 20 to 80 ml. Of all the data about the menstrual cycle, the amount of blood loss is one of the most important pieces of information and yet it is the most difficult to precisely determine. While some women complain of heavy blood loss and use many tampons with menses, their actual determined loss may be normal.[2,6] If the historical information suggests a heavy flow, then laboratory confirmation is necessary. Since iron balance in a normal woman is only marginally adequate, an excess of menstrual bleeding usually depletes the iron stores and results in iron-deficiency anemia. The calculated iron loss is determined by this formula: ml blood loss × hemoglobin concentration of blood × 3.4 mg iron per gram of hemoglobin. Iron intake is fairly constant in most food sources and amounts to approximately 6 mg per 1000 calories. Since women usually consume about 2000 calories per day and have a gastrointestinal tract efficiency of iron absorption of 10 percent, they then are absorbing 1 to 1.5 mg of iron per day. If the blood loss of the menses exceeds 80 ml, they will usually develop iron deficiency anemia, unless they are taking extra sources of iron in their diet. Thus the complaint of abnormally heavy bleeding must be checked with a measurement of the patient's hemoglobin-hematocrit, and the presence of an iron deficiency anemia would substantiate the complaint. If the patient does not demonstrate anemia, then it may be due to her excessive production of red cells that allows her to compensate for the excessive loss. The second laboratory test in this area would therefore be a reticulocyte count to study the red cell production rate. If this is normal, the complaint is probably unfounded.
6. *Molimen*—The symptoms that accompany a normal ovulatory cycle are related to the production of estrogen and progesterone and their systemic effects, as well as their effect on the production of uterine prostaglandins. Women experiencing the luteal phase of their cycle have symptoms such as breast tenderness, bloating, mood changes, diarrhea, and uterine cramps. All of this indicates that ovulation has probably occurred.
7. *Other Bleeding*—The only other physiologic bleeding that occurs during the cycle is at the ovulation time. Whereas lower mammals routinely have their bleeding at ovulation, it is infrequently found in any significant amount in women. While cervical mucus microscopic examinations may detect some red cells at the time of ovula-

tion, true gross spotting occurs in less than 10% of women.

8. *Menopause*—Menopause is defined as the cessation of menses that accompanies the fall in ovarian steroid hormone production as a result of the loss of all ovarian follicles. The follicle loss may result artificially from surgical castration or naturally from attrition of these follicles with aging. The range for natural menopause is 35 to 55 years of age, with a mean of approximately 51 years. This age varies with factors such as parity, socioeconomic status, and smoking.

Differential Diagnosis of Bleeding

After the menstrual history is obtained, the physician must determine if the bleeding that is complained about falls into a normal or abnormal range. If the patient is describing abnormal bleeding, then it must be thoroughly evaluated, and a specific diagnosis is made and treatment started. The differential diagnosis of abnormal excessive bleeding falls into two categories: 1) organic lesions (benign or malignant); 2) dysfunctional uterine bleeding (physiologic or pathologic). The organic lesion category includes benign and malignant lesions that can occur anywhere in the genital tract, including the vulva, vagina, cervix, endometrium, tube, and peritoneal cavity. Because this group contains lesions that may eventually impair the health and life of the patient (cancers), it is the first category to be ruled out.

To determine whether or not an organic lesion exists, the patient must have a careful pelvic examination, followed by a tissue sampling throughout the reproductive tract and an assessment of whether she is ovulating. The chance of malignancy increases with age and, therefore, the older the patient with abnormal bleeding, the more important it is to perform the appropriate tissue samplings. The adolescent may not need tissue sampling for management, but the women of 40 years certainly would. In some settings the physical examination clearly defines the site of abnormal bleeding, for example, in a woman with a cervical polyp or cervical carcinoma. In most cases, however, the physical examination does not provide the precise evidence of the source of bleeding, and then the appropriate tissue samples are obtained by doing the dilatation and curettage (D and C).

Dilatation and Curettage

The dilatation and curettage (D and C) is often performed in the hospital, utilizing general anesthesia, and generally involves 10 steps:

1. Bladder catheterization
2. Pelvic examination under anesthesia
3. Cervical biopsies
3. Endocervical biopsy
5. Uterine sounding
6. Dilatation of the cervix to approximately 1 cm in diameter
7. Removal of gross polyps with a polyp forcep
8. Endometrial curettage
9. Removal of the curetted material from the endometrial cavity with a polyp forcep and
10. Resounding the uterus for evidence of perforation

The pathologist is only able to provide an accurate diagnosis of the cause of bleeding if he or she is provided with adequate tissue samples. The management of cancer of the endometrium depends upon its site of origin and its spread. If the lesion is only in the fundus, it can be treated appropriately with a simple hysterectomy, whereas an extension into the cervix requires a full-course of irradiation followed by surgery. Thus, it is important to find the source of the lesion, as well as its extent of involvement, and the diagnostic D and C is designed to selectively sample tissue from the outside inward so that lower sites will not be contaminated with cancer from higher sites by the surgeon and then misread by the pathologist as a natural spread of disease. The D and C will provide three to four different samples for

pathologic examination, namely the cervical biopsy, endocervical biopsy, endometrial polyp material, and endometrial curettings. The first diagnostic D and C is usually performed in a "blind" fashion. Studies with board certified obstetricians and gynecologists have demonstrated that, in 60 percent, less than half of the endometrial surface area is sampled in the routine D and C.[7] It is important for the physician to remember that if the therapy prescribed is not successful, then the diagnosis may be incorrect, because the lesion causing the bleeding may have been missed at the time of the D and C. In such cases, a second D and C is warranted, and that one should probably be visually directed with the assistance of a hysteroscope so that the specific lesion can be biopsied.

More recently, it has been demonstrated that office curettage with a variety of suction instruments provide a good tissue sampling and is as accurate for making a diagnosis of organic lesions as is the hospital-based D and C.[8] Obviously, the movement to an ambulatory diagnostic test greatly reduces the risk and cost of the procedure.[9] Because of the ease of application and low cost of the office suction curettage, more patients can be provided with the benefits of tissue diagnosis and, hopefully, more early neoplastic lesions will be discovered.

Detection of Ovulation

Because the problem of dysfunctional uterine bleeding relates to anovulatory cycles, except in the rare instance of irregular shedding, the confirmation of ovulation is extremely important in making the diagnosis and in evaluating management. Only two absolute indices of ovulation are available, namely, pregnancy and direct visualization of the follicle disruption. These are not practical in the clinical management of most patients, and indirect indices are usually used. They generally depend upon the detection of progesterone or its effects, which imply that ovulation occurred, with subsequent formation of a corpus luteum. On rare occasion, a woman will produce significant amounts of progesterone in the absence of ovulation, and thus these are only indirect indices.[10] The most frequently used indirect indices are the measurement of blood progesterone levels, the measurement of the progesterone metabolite pregnanediol in the urine, detecting secretory endometrium, and monitoring the basal body temperature to look for a biphasic thermal effect. The latter is very useful and inexpensive. It is generally helpful to begin all patients who have abnormal bleeding on a regimen of recording morning basal temperatures, in addition to recording their days of bleeding.[11]

Diagnosis and Management

The patient's management obviously depends upon the diagnosis that has been made after the complete evaluation of the patient by history, physical examination, ovulation detection, and tissue sampling. One of two diagnoses can be made at this time and different therapies would follow. The possible diagnoses are

Organic lesions

Each specific organic lesion has a management program that is well accepted. For example, submucus myomas require simple surgical removal, as do endocervical polyps, whereas invasive carcinoma of the cervix would require a more radical form of therapy. The two types of endometrium that could be seen are the proliferative or secretory types.

DUB

The endometrium in DUB would show either proliferative or endometrial hyperplasia patterns. Because the condition is by

definition anovulatory, secretory endometrium cannot be present unless exogenous progestins have been used or the patient has the rare DUB problem of irregular shedding of the endometrium. There are two forms of DUB that can occur in a woman during her reproductive years, namely the physiologic and the pathologic types.

Physiologic DUB

The physiologic dysfunctional uterine bleeding or cyclic bleeding without ovulation occurs normally at two times in a woman's life.[12] Detailed studies of the indirect indices for ovulation, namely basal body temperature records, have shown that during the first 2 or 3 years after menarche and during the last 2 or 3 years before menopause, a woman's cycles are frequently anovulatory as noted in Figure 1. This results in unopposed estrogen, which dilates the spiral arteries and causes a growth of the endometrium to a point of endometrial hyperplasia. Eventually, the estrogen will have a negative feedback in the hypothalamic area and result in a decrease in gonadotropin-releasing factor, follicle-stimulating hormone (FSH), and luteinizing (LH) hormone and a decrease in estrogen and therefore failure to maintain the vasodilatation. The resultant bleeding occurs from irregular ulcerations in the endometrial surface, which produces the symptoms of heavy and prolonged bleeding.

Because DUB and endometrial hyperplasia are physiologic at two times in a woman's life, almost all women experience it. It is therefore preposterous to suggest that all endometrial hyperplasia requires hysterectomy. With that type of reasoning, all women would need a hysterectomy and if not done during the menarchial years, it could be done in the premenopausal time period. Endometrial stimulation with unopposed estrogen results in a continuum of change, however, and there is concern that eventually it could lead to endometrial carcinoma. Thus, one could see the endometrium progress through the stages of proliferative, endometrial hyperplasia, adenomatous hyperplasia, atypical hyperplasia, carcinoma in situ, and invasive endometrial carcinoma. Most would agree that when it reaches the atypical stage, surgery is indicated.

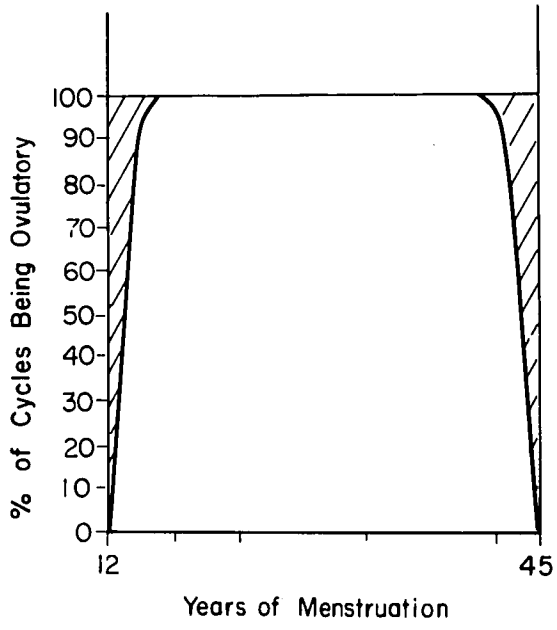

FIG. 1. *Graphic summary of the frequency of ovulation in a woman's reproductive years. Physiologic anovulation is common for 2–3 years after menarche and before menopause.*

The management of physiologic DUB requires certainty that no other organic lesion exists. Then the patient should be treated monthly with progesterone for at least 6 months. That will cause spiral artery constriction and result in normal progesterone-withdrawal menses. Since progesterone is not well absorbed orally, a more convenient therapy is with a progestinlike medroxyprogesterone in the form of Provera (Upjohn, Kalamazoo, Mich). Studies of the morphology of the endometrium under the influence of progestins suggest that a long duration of therapy (10-13 days) is needed to regress the proliferation.[13] Some authors report no adenocarcinoma developing when 10 days of treatment are given each cycle.[14] Thus, Provera 10 mg/day for 10-13 days per month is recommended. The progestogen needs to be administered at least six cycles, and during that time the young woman should reach a state of maturation of her neural endocrine pathway so that she would then be spontaneously ovulating and correcting her own problem by producing natural progesterone. The older woman hopefully would have reached her menopause and would no longer have estrogen being produced from follicles. If the problem recurs after 6 months of treatment, it can then be treated for another 6 months. During the progesterone treatment, the bleeding pattern should be perfectly normal, and if not, one must suspect that an organic lesion has been missed. Rarely one may need to treat acute bleeding with intravenous estrogen (Premarin [Ayerst, New York, NY] 25 mg intravenously).[15]

Because the bleeding is resulting from an excess of unopposed estrogen, it is unnecessary to treat these patients with estrogen, either alone or in the form of oral contraceptives. Indeed, oral contraceptives may be contraindicated for both types of patients. The young patient with physiologic DUB would be at risk of developing the postpill amenorrhea syndrome because it has been shown that those who had it took the oral contraceptive at a time close to their menarche or were irregularly ovulating when placed on the oral contraceptives or both were in the high-risk group. The perimenopausal woman with physiologic DUB is at risk from oral contraceptive treatment because of her age and the association of myocardial infarctions in the older oral contraceptive users. Finally, the woman will probably also need iron replacement therapy so that she can replenish her red cell volume.

Pathologic DUB

When a woman becomes mildly ill with either an emotional or physical ailment, such as anxiety or a chronic infection, one of the first systemic effects is loss of the midcycle surge of gonadotropin-releasing factor (GN-RF), with the resultant loss of ovulation. The tonic center release of GN-RF remains present and the net result is follicle development and the production of unopposed estrogen, ending in endometrial hyperplasia and dysfunctional uterine bleeding. If the disease state progresses to a more severe form, for example, with severe depression or a disseminated malignancy, then no GN-RF will be produced by the hypothalamic center and, as a result, there will be a low gonadotropin secretion and a low production of ovarian steroids, resulting in atrophic endometrium and secondary amenorrhea. Thus, there is a continuum from the normal ovulatory cycles to secondary amenorrhea, with the intermediate area of irregular bleeding resulting from DUB. It is important to remember that the first recognizable symptoms of a disease in a woman may be a disruption of her normal menstrual cycle and she may then present with this early complaint to her obstetrician-gynecologist, who must always serve as her primary care physician, with the responsibility of carrying out a complete thorough evaluation of her health in order to be able to detect these early disturbances. In general, the therapy for this type of patient would be 1) to administer iron to replace blood loss; 2)

to control blood loss by the cyclic administration of progesterone, which will produce a medical curettage with regular bleeding; and 3) to correct the disease state that is the cause of the problem. The latter may need antibiotics for infection, hormones for deficiencies, tranquilizers for anxiety, or any of many specific therapies.

Secondary Problem—Infertility

Patients who have dysfunctional uterine bleeding may also be complaining of infertility. In these patients, following a complete evaluation, the therapy must involve induction of ovulation. This may result from correcting their disease state. If no disease is found, then it can most easily be accomplished medically with one of three types of treatment. Clomid, either alone or with human chorionic gonadotropin (hCG), can be administered to stimulate the hypothalamic area to release GN-RF. If the hypothalamic center cannot be stimulated with clomid, then GN-RF can now be infused in pulses with a pump system and can induce ovulation if the pituitary gonadotropin cells are normal. Finally, if there is an absence of pituitary gonadotropin function, LH and FSH can be exogenously replaced with Pergonal and hCG. Monitoring the success of these therapies is easily performed with the basal body temperature record, ultrasound, and blood hormone profiles. The major hazard of the treatments is hyperstimulation of the ovary and multiple ovulations, but monitoring follicle size with ultrasound can usually prevent this.

Summary

Dysfunctional uterine bleeding (DUB) is a common cause of abnormal uterine bleeding and its diagnosis depends upon excluding organic lesions of the reproductive tract. The workup of the patient requires a complete medical history, physical examination, studies for ovulation, and genital tissue sampling. Whereas DUB is a physiologic normal phenomenon in the early and late years of the reproductive cycle, it is a pathologic entity at other times and can result from mild emotional or physical diseases in the patient. Management requires periodic progesterone replacement, increased iron intake, and therapy for any disease that is detected. Generally, oral contraceptives are not indicated, and hysterectomy is rarely needed. If infertility is also a complaint, specific ovulation induction therapy may also be needed. Control of the bleeding abnormality is the expected therapeutic response, and failure to achieve this suggests that a specific genital organic lesion has been overlooked.

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