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Irregular bleeding caused by anovulatory cycles

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IRREGULAR BLEEDING CAUSED BY ANOVULATORY CYCLES

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I. Introduction

The terms "dysfunctional uterine bleeding" and "functional uterine bleeding" mean so many different things to so many different people, that confusion is the rule rather than the exception in the interpretation of what is actually trying to be conveyed. Either term means literally, that an endocrine disturbance is the cause of the bleeding, and that the abnormal bleeding occurs in the absence of any demonstrable findings. Therefore, the implication is that the abnormal bleeding is due to some change in the normal hormonal control over menstruation, but not to a change in the uterus itself, since demonstrable disease in the uterus would immediately make the diagnosis of functional bleeding untenable. This then leads one to the conclusion that functional uterine bleeding means irregular menstruation which results from failure of ovulation. (1)

The above terms would then be satisfactory if they were used for this particular type of bleeding only, but the terms are used by the majority of individuals indiscriminately to describe any and all types of bleeding which does not follow a cyclic menstrual pattern. A more descriptive title for this thesis has been chosen which in itself describes both the cause, (anovulation) and the most outstanding clinical manifestation (irregularity) of the condition.

II. Hormonal Relationships of the Normal Menstrual Cycle

It is appropriate that before a discussion of abnormal bleeding of an anovulatory nature is undertaken and understanding of the normal menstrual cycle and the hormonal relationships associated with this cycle should be obtained. The following is a generally accepted concept of the physiologic processes involved with female generative organs and the interrelationship of the pituitary.

The ovaries have both a cytogenic function in their production of ova and an endocrine secretory function. Both the cytogenic and the endocrine function are under the control of the anterior lobe of the pituitary which secretes at least six and possibly more trophic hormones. (2) Three of these trophic hormones, (1) the follicle-stimulating hormone (FSH), (2) the luteinizing hormone (LH), and (3) the luteotropin hormone (prolactin) (LTH), are directly concerned with gonadal function and as such they are classified as gonadotrophic hormones. (3) These trophic hormones are recoverable from the urine after puberty in a somewhat changed form, but by analysis, the amount of these various hormones produced by the pituitary can be ascertained. (4) As a result various disease syndromes can be diagnosed on the basis of the amount of hormone recovered from the urine. The instigating factor which prompts the elaboration of these three hormones at puberty is not definitely established but it is thought to be on the basis of an intracranial neurohumoral mechanism that suppress the pituitary prior to pubescence. (5)

Up to puberty, and including fetal life, ovarian follicles develop to the point of antrum formation but then regress to become atretic follicles. Why then at puberty the follicles mature to the point of ovulation is not clearly understood unless it is on the basis of the increased output of FSH which we know occurs. It could also result from the fact that the ovarian follicles themselves have obtained sufficient maturity and have become sensitive to the relatively low level of FSH which first accompanies puberty. In either case the follicle reaches a degree of maturity in which it is capable of producing estrogen and thus cause a proliferation of the endometrium. It is questionable and doubtful whether the maturity of these follicles is sufficient to actually result in ovulation or not. More than likely theestrogen production reaches a point in which it inhibits the pituitaries production of FSH and and, as such, the stimulus for estrogen production is lost. (6) Without the estrogen stimulation, the proliferative phase of the endometrium breaks down with resulting shedding and this then is the anovulatory bleeding of the menarche which will be discussed later.

The first day of the adult menstrual bleeding is customarily considered as the first day of the menstrual cycle but in reality it is the beginning of the end of the complete cycle. Because of presidence we will use the first day of blood flow as the first day of the cycle. At this time the level of estrogen produced by the

ovary is low but the level of FSH is at its maximum. As a result of the strong stimulus of FSH upon the ovary, a number of follicles respond with growth and a subsequent increase in estrogen which usually occurs within four or five days. By this time the uterus has shed the endometrium produced by the previous cycle and bleeding ceases. The shedding becomes complete once the denuded surface has been resurfaced by epithelial growth from the broken ends of the endometrial glands under the influence of the estrogen being produced. Most of the follicles which were initially stimulated to grow regress and leave atretic follicles. A few continue to enlarge but in general only one will result in a mature Graafian follicle which is capable of ovulating around the fourteenth day of the cycle. In cycles approaching the average length of 25-29 days, there is definite correlation between the preovulatory and postovulatory phases. For example, if ovulation occurs on day 8 of a 28-day cycle then the postovulatory phase lasts 20 days. If ovulation takes place on day 18 then the preovulatory phase is 18 and the postovulatory phase is only 10 days. (7)

During the first 14 days of the cycle the FSH production gradually decreases as the estrogen level increases. This reciprocal relationship reaches its maximum at about the 14th day when the level of secreted estrogen is sufficient to inhibit further production of FSH by the pituitary. It is now believed that the follicle that is destined to become a mature Graafian follicle

requires FSH stimulation only for the first eight days of the cycle and the development after this date appears to be autonomous. (8) The endometrium reflects the increased estrogen output in a rapid growth of all elements - stroma, glands, and arterioles. An augmented output of LH also reflects this increased amount of estrogen and it is assumed that the LH provides the endocrine trigger mechanism for ovulation of the mature follicle in the middle of the cycle. We know that LH is not produced solely at or just prior to ovulation because, from animal experiments, it was determined that estrogen alone failed to bring about the characteristic changes reflected in target organs during the first two weeks of the cycle in the absence of some amount of LH. (9) Considerable evidence is also available to indicate that there is a small amount of progesterone being produced during this phase particularly for a day or two prior to ovulation. (9,10)

The function of LTH, or prolactin, in the ovarian cycle and its relationship to the other hormones has as yet not been clearly defined. We do know now that LH does not maintain the luteal phase of the cycle unless prolactin is also present. Experimentally, a fraction of pituitary extracts can be obtained which is free of both FSH and LH and this fraction will sustain or prolong the luteal phase of the follicle in animals. This hormone is also necessary for the production of milk by the postpartum female. (11)

After ovulation the estrogen level drops slightly. In those women who bleed a little at the time of ovulation this drop in estrogen is believed to be the reason for the bleeding and this is an instance of estrogen withdrawal bleeding. Another explanation of the bleeding at this time could be strictly on a mechanical basis with rbc's being carried into the uterus through the fallopian tubes having been picked up from the ruptured Graafian follicle. (12)

After ovulation the follicle undergoes rapid changes with the production of a yellowish lipochrome substance luteen. At this time the production of progesterone is greatly enhanced and this increased production can be detected within 48 hours by changes in the endometrium. In addition to its effect on the endometrium, progesterone also causes stimulation of the thermal center in the brain stem which is reflected in a slight rise in basal body temperature. (13) This temperature elevation is usually maintained as long as the corpus luteum is producing progesterone at its fullest capacity. This stimulus remains active until at approximately the twentieth day of the cycle the level of estrogen reaches the same peak that it had attained just prior to ovulation and the level of progesterone is close to its maximum. The secretions rise gradually in quantity for the next four days. There also appears to be a reciprocal relationship between LH and progesterone as was seen with FSH and estrogen. As the maximum level

of progesterone is reached it inhibits the pituitaries release of LH and therefore the stimulus to the corpus luteum is removed. Subsequently, in approximately four days, or the 28th day of the cycle, the endometrium has no stimulus for further growth and menstruation ensues.

A description of the actual anatomic changes of the endometrium which precedes menstrual flow follows. The arteries of the endometrium are derived from the uterine arteries and consist of tne following branches in decreasing order of magnitude. Immediately off of the uterine artery the arcuate arteries arise which circle the uterus and give off radial branches which penetrate directly inward. Prior to entering the endometrium the radial branches divide into straight arteries supplying the deeper third of the endometrium and the spiral arteriols which reach the surface of the endometrium. The straight arteries are not affected by cyclic hormonal changes and maintain a continuous circulation from which regrowth of the endometrium occurs between shedding episodes. The spiral arteriols are markedly influenced by hormonal changes. The terminal branches of these arteriols anastomose with venous branches and form a diffuse arteriovenous capillary network terminating in venous lakes or sinusoids. The spiral arterials undergo marked lengthening during the proliferative phase of the cycle and outgrow the proliferating stroma. As a consequence of this differential rate growth the spiral arteries become kinked

and coiled. Because of the accumulation of interstitial fluid the spiral arteries become somewhat stretched. When the levels of estrogen and progesterone fall the interstitial fluid becomes absorbed and the endometrium shrinks and forces the spiral arteries to kink and buckle leading to a decrease in the circulation and stasis. A few hours preceding the onset of menstrual bleeding an intense vasoconstriction occurs which may be induced by accumulation of cellular metabolites resulting from ischemia or anoxia. The vasoconstriction and buckling leads to severe ischemia and necrosis of the superficial parts of the endometrium resulting in actual desquamation. (14,15)

With the lack of production of both estrogen and progesterone by the ovary there is now no further inhibition to the pituitary and it begins the formation of a new cycle by producing FSH. Theoretically and practically therefore, a defect in any one of the stages of this cycle, either ovarian, pituitary, or endometrial, could result in menstrual irregularities, ovulatory failure, and/or amenorrhea.

III. Irregularity of Anovulatory Bleeding

The most important single feature which characterizes the bleeding of an anovulatory cycle from most other types of abnormal bleeding is the extreme irregularity of the onset of flow while the bleeding associated with other causes in the presence of ovulation is just as often regular. (1) Organic reproductive tract disease of the kind which causes bleeding will, in the presence of ovulation, lead to an abnormality of menstrual flow, but this abnormality will have a regular pattern. Likewise, pathologic conditions outside the reproductive tract, if they cause abnormal bleeding, will result in bleeding which will also follow a regular pattern if the condition exists together with ovulation. An example would be one of thyroid dysfunction in which ovulation has not been impaired. The one exception to the above statements is when a malignancy of the reproductive tract exists. With this condition, whether ovulation is occurring or not, the abnormal bleeding associated with the malignant neoplasm can show any pattern. The writer stresses that every diagnostic means available must be utilized to rule out the existence of a malignancy before a diagnosis of anovulatory bleeding can be made.

To elaborate on the above, we know that the most common causes of abnormal bleeding of an organic nature outside of a pregnancy episode and a malignancy are submucous fibroids, endometrial polyps, and cervical polyps. These growths are

undoubtedly influenced by the hormones produced by the ovaries. Since these growths can either bleed by themselves or produce endometrial bleeding, and since they are influenced by ovarian hormones, it follows that the bleeding they produce has to be somewhat cyclic in nature if the ovaries are producing both estrogen and progesterone. On the other hand, in irregular bleeding associated with anovulation, the absence of ovulation and of the corpus luteum deprives the patient of the important pituitary regulating effects of progesterone. The growth of the follicles then tends to be both prolonged and irregular and they alternate with or are combined with irregular cycles of follicular atresia. Estrogen secretion is thus prolonged and irregular and produces a sustained stimulus to endometrial growth. This results in endometrial hyperplasia in many of these patients and the hyperplastic endometrium is more sensitive to fluctuating estrogen stimulation. The combination then of failure of ovulation, irregular cycles of follicular growth and atresia, irregular but prolonged secretions of estrogens, and a hyperstimulated endometrium result in the totally irregular bleeding of an anovulatory type.

IV. Diagnosis of Anovulatory Bleeding

The diagnosis of irregular bleeding due to anovulation is always somewhat tentative because of the hazy borderline between pathologic bleeding, the outer limits of normal endometrial bleeding of various kinds, and the difficulty of exclusion of anatomical causes of abnormal bleeding. Among the various diagnostic methods used, the history, physical examination, and blood count are basic and are applicable in any bleeding problem. The following methods will be discussed as diagnostic helps only so far as they relate to bleeding presumed to be on an anovulatory basis having ruled out organic pathologic lesions.

(a) Uterine Curettage

Uterine curettage is helpful in analysis of dysfunctional bleeding, especially of the irregular anovulatory variety. The timing of the diagnostic curettage is important and varies with the type of abnormal bleeding. If anovulatory bleeding is suspected the curettage is best performed on the first day of the menstrual flow. As the endometrium mirrors steroidal activity, the phase of the cycle can usually be determined microscopically and the level of ovarian function can be determined for this particular episode. If ovulation has not occurred and bleeding ensues the typical proliferative endometrium with or without hyperplasia will be evident. Curettage has the disadvantage of requiring

hospitalization and anesthesia and as a result repeated use of this method is not practical for following therapy.

(b) Endometrial Biopsy

The same information which is derived from uterine curettage can be obtained by endometrial biopsy. This method has the advantage of being relatively inoxuous to the patient and can be repeated at frequent intervals to follow prognosis. (15)

(c) Cytology

The cytologic method employed as an aid in the diagnosis of abnormal uterine bleeding is based upon the fact that epithelial cells lining the cavities of various organs are shedding constantly. Vaginal smears are useful in this regard as they afford a rough measure of estrogen level as the type of cells shed varies with the amount of estrogen being produced by the ovary. (17)

(d) Basal Temperature

The body temperature of a normal woman follows a somewhat fixed pattern during the menstrual cycles if the temperature is taken under basal conditions. The curve is biphasic in nature and the temperature elevation is believed to be a reflection of the production of progesterone by the ovary. (18,17) It is difficult to relate the thermal shift to ovulation accurately but when present it does establish a presumption of its occurrence and as such one can infer that the patients cycles have or do not have an ovulatory pattern. If the patient retains a persistent corpus

luteum function the temperature remains elevated for more than the usual period of time, contrarywise, if ovulation occurs but is followed by a deficient corpus luteum the temperature remains elevated only for a brief period of time.

(e) Fern Test

The fern test, which is a relatively new diagnostic method, is based upon the observation that cervical mucus obtained during the estrogen phase and allowed to dry crystallizes into a characteristic ferning pattern. Under low power magnification the smear shows arborization resembling that of a fern leaf. This process is inhibited by progesterone so that a positive test during the last part of the menstrual cycle denotes continuous effect of estrogen upon cervical mucus uninterrupted by the postovulatory hormone, progesterone. If the fern test is then negative during the premenstrual phase it can be assumed that ovulation has occurred. (18)

(f) Hormone Assays

The last study to be discussed in diagnosing anovulatory bleeding will be the use of hormone assays. These assays have a limited application in this regard. Estimation of urinary pregnandiol is not as practical and available as basal body temperature determinations and a study of the endometrium. Single estimations of urinary estrogens are not as informative as vaginal cytology and the fern test. If the estrogen level is low as seen

by cytology and poor ferning then urinary assay of FSH helps to determine the source of the deficiency. If ovarian failure is secondary to pituitary insufficiency FSH excretion will be absent or low. Excessively high FSH excretion indicates primary ovarian failure. A test for the determination of the time of ovulation is not as important in bleeding problems as is the knowledge of whether or not ovulation is customarily occurring.

V. Anovulatory Bleeding at Menarche

Anovulatory bleeding occurs most frequently in the adolescent period just after the menarche and during the period just before the menopause. (19) It is statistically less common during the reproductive years. Therefore, this type abnormal bleeding will be discussed as it relates to the menarche, the premenopausal period, and the reproductive period.

The reason for anovulatory cycles in the period just after the menarche is believed to be, not total failure of follicle production, but the inability of the follicle to produce enough estrogen to trigger the production of the luteinizing hormone by the anterior pituitary gland. (20,21) Without this, the follicle fails to rupture and to follow its normal course of development to a corpus luteum with the subsequent production of progesterone. During this period of lag in the development of the complete functional state of the ovary, the endometrium is exposed to unopposed stimulation by varying amounts of estrogen. It is fairly reasonable to assume that the bleeding disorders of adolescence are the manifestation of uncoordinated interrelationship between the pituitary and the ovary providing that organic pathology los been ruled out. (22)

The proliferative endometrium in anovulatory bleeding in late childhood is frequently associated with true hyperplasie of the endometrium but their association is not constent. (23) A certain

amount of hyperplasia undoubtedly accompanies every instance of anovulatory menstruation. This is due to the building up of a proliferative endometrium by estrogen without the production of progesterone as stated above. The endometrium in young girls with this condition usually shows a thick Swiss-cheese like proliferative hyperplasia. (24) At times a normoplastic proliferative endometrium is seen but the low hypoplastic type of proliferative endometrium seldom is present. In general, any stubborn or serious bleeding during adolescence may be suspected of being associated with anovulatory bleeding and/or hyperplasia. As indicated in the opening paragraphs anovulatory bleeding is characterized by its irregularity but in the early postmenarche period the bleeding may be almost or actually cyclic in character, so much so that it is confused with beginning true menstruation. (12) The relatively frequent incidence of anovulatory bleeding in the early teen-age group is attested to by the documented infrequency of pregnancy in many carefully studied groups of young girls who bleed but who do not become pregnant although they are exposed to regular cohabitation. (12) Anovulatory bleeding is frequent during adolescence as indicated by the absence of dysmenorrhea or other complaints commonly associated with normal menstruation. If the bleeding is sufficiently regular, temperature curves may reveal the characteristic monophasic curve of anovulatory bleeding. Diagnosis by vaginal smears and blood studies may show sustained high estrogen

levels and endometrial biopsy at the onset of bleeding may show characteristic proliferative or hyperplastic changes with the absence of a secretory change.

(a) Treatment

In the majority of adolescent patients having anovulatory uterine bleeding estrogen or progesterone need not be administered. It is of special importance to insist on an adequate intake of calories, protein, and vitamins, and to curtail the excessive physical and emotional stress common to this age group. (25) Likewise, obesity and the state of being markedly underweight have adverse effects on the function of the anterior lobe of the pituitary and the ovaries. Often counseling and the correction of the above conditions will be sufficient to bring the patient to normal menstrual function. The great majority of these patients, even though they may experience some dysfunctional bleeding, attain maturity in which normal menstruation takes place spontaneously. In a few patients bleeding may be severe and treatment be required.

Dilatation and curettage as a method of treatment in these cases is questionable as to effectiveness. It is obvious that this procedure will in no way alter the basic deficiency in which hormonal control of menstruation is not as yet complete. It is granted that this procedure is useful and sometimes necessary when patients do not respond to hormonal therapy or when the operation becomes necessary for hemostasis. (20) When hormonal

therapy is required it is not an attempt at the cure of the problem but it is substitutional and supportive therapy until the endogenous production by the patients ovaries is stabilized at a normal functioning level. The use of exogenous hormones as a means of temporarily regulating anovulatory bleeding is probably the method of choice in these young ladies. (26) Despite the fact that the bleeding encountered in this condition is due to a relative excess of estrogen unopposed by progesterone, the oral administration of estrogenic substances over a three-week period in each four weeks will often control bleeding. While the endogenous production of estrogen is unopposed by pituitary control the bodily level of estrogen may wax and wane and this results in withdrawal bleeding from the proliferative endometrium. The exogenous estrogens will consistently maintain the bodily concentrations above the bleeding level and thus abolish the process of intermittent withdrawal bleeding. Withdrawal bleeding will naturally occur because of the cyclic nature of therapy but it will be controlled bleeding. The oral route is preferable in most cases as it appears to ensure maintenance of a more constant blood level and it is more convenient and less expensive for the patient. If the administration of estrogens alone is not effective then progestational substances may be added to the estrogens in a cyclic fashion. The progesterone is started on the fourteenth day of the 21 days that the estrogens are given and is continued for

7-10 days. In this way the endometrium is primed with estrogen and the conversion of the proliferative phase produced under estrogen stimulation to a secretory phase by progesterone results in subsequent shedding of the entire endometrium. A "medical curettage" has thus been accomplished. (27) Another method of treatment is the cyclic administration of progestational steroids without the preliminary and coincident use of estrogens. This is effective to control bleeding if endogenous estrogen is available in sufficient amounts.

(b) Relationship of Thyroid Gland

No reference has as yet been made to the effect of the thyroid gland on the pituitary-ovary relationship. The exact mechanism has not as yet been explained, but clinically in a patient with a low BMR, the administration of exogenous thyroid extract in sufficient amounts to elevate the BMR to normal and to maintain it at a normal rate has proven effective in bringing an anovulatory type bleeding problem under control in a select group of patients. (28)

VI. Anovulatory Bleeding at the Climacteric

The second most common time in the female menstrual life in which anovulatory bleeding occurs is during the climacteric. "Climacteric" is a period of life during which the system undergoes marked changes, whereas "menopause" means actual cessation of menstruation. While probably the great majority of women ovulate until the end of menstrual life and occasionally beyond, there are many patients in whom the cycle becomes anovulatory for a variable time before its cessation. When anovulatory bleeding occurs in women over the age of 35 years, it is usually an indication of failing ovarian function. Although sporadic ovulatory cycles may occur for several additional years, these are frequently interspersed with anovulatory cycles and prolonged bleeding episodes which may actually be exsanguinating. It is important to stress again that a careful history, to rule out the use of exogenous hormones, and a detailed pelvic examination, including Papanicolaou smears, and/or endometrial and cervical biopsy and curettage if indicated, should be done to eliminate the possibility of a neoplasm as the cause of the bleeding, before a diagnosis of anovulatory bleeding is made. (29)

The primary cause for failure of ovulation in the older age group is obscure. The ovum does not rupture as it should and with the persistence of the ovarian follicle, the corpus luteum does not form and the endometrium becomes highly hypertrophic under

estrogenic stimulation. Then, as there is no progesterone being produced by a corpus luteum, conversion of the endometrium to a secretory type does not occur with the small amount of progesterone available from the follicle. The proliferative hyperplastic endometrium is then shed due to the inability of the estrogen being produced to maintain the endometrium and bleeding of an anovulatory type occurs. Actually the amount of estrogen being produced may not be great but it is a relative excess accompanied by a relative deficiency of progesterone. (30)

The change in ovarian function usually occurs over a period of time varying from a few months to a considerable number of years. Often the pattern reverses the changes of adolescence with the cycles gradually diminishing in amplitude. They become more and more frequently anovulatory, then often irregular, and finally they cease. Ovarian function may continue for a period of time at an intensity too low to produce bleeding but still capable of occasional ovulation as attested to by instance of menopausal pregnancy.

(a) Treatment

If a timed diagnostic curettage has yielded an endometrium of a proliferative or hyperplastic type it is fair to conclude that the bleeding is on an anovulatory basis. Following thorough curettage, menstruation may be essentially normal and one may treat these patients by letting nature take its course to a normal

menopause. However, approximately 50% of these patients will have a recurrence of the bleeding so definitive therapy becomes necessary. (31) Until recent years treatment was aimed at abolition of menstrual function by either intrauterine radium or external x-ray irradiation and this treatment was quite successful. Corscodin and Landell and other authors (6) have reported that patients thus treated showed a three and one-half times normal incidence of endometrial adenocarcinoma at a later date. In addition, radiation castration is frequently followed by troublesome vasomotor menopausal symptoms. It is generally agreed that after sudden and complete cessation of ovarian function symptoms are usually more severe than after "natural" menopause with gradual diminution of ovarian function which may persist at a low level long after menses has ceased. Hysterectomy, rather than irradiation, is advocated by some authorities (6) for treatment of functional bleeding in this age group especially if the bleeding is of a recurrent type. One advantage of this approach is that it removes the possibility of later uterine cancer. Holmstrom (32) believes that hysterectomy is radical treatment for a benign condition which can be satisfactorily handled nonsurgically by cyclic use of progesterone. Therapy with progesterone in this group is aimed at avoiding the profuse bleeding periods until ovarian production of estrogen ceases. This is accomplished by the administration of 25 mg of progesterone at approximately 30-day intervals.

By this time the endometrium in the absence of ovulation will show some degree of proliferation and the exogenous progesterone then causes formation of a secretory endometrium with shedding usually within four days. As ovarian function diminishes eventually there will be no response to progesterone administration. If bleeding fails to occur after three injections at monthly intervals it is assumed that the patient has entered the menopause. Sporadic recurrences of ovarian activity may appear within the next one or two years but with the prompt use of progesterone the bleeding will be self-limited.

Steroid therapy is not limited to the use of progesterone in anovulatory bleeding during the climacteric. The use of the chorionic or A.P.L. hormones of pregnancy urine has proved effective. (33) Testosterone propionate has been used to inhibit the growing follicle by its inhibition of the release of FSH from the pituitary and thus inhibit estrogen production and lessen endometrial proliferation. (34) Thyroid extract is usually of little use in the treatment of this type bleeding in this age group. Estrogens also are effective in controlling anovulatory bleeding but they are potentially carcinogenic particularly in this age group. There use is based upon the concept that the bleeding phases occurred when the estrogen level dropped below a certain point and by raising the estrogen level the bleeding might be checked at least temporarily. Estrogen and progesterone are given

together in a cyclic fashion to prevent ovulation and thus prevent uncontrolled bleeding. (32) This regime is similar to that discussed previously. Generally measures of treatment are also used with special attention to the possibility that bleeding of an excessive amount may have resulted in a blood loss anemia.

VII. Anovulatory Bleeding During the Reproductive Years

Statistically anovulatory bleeding during the reproductive period of a woman's life is less common than at either end of this period. However, Novak (6) indicates that 30-35% of cases are distributed throughout the reproductive years with 50% at the climacteric and about 15% at or near the age of puberty or in early adolescence. Anovulatory bleeding during the reproductive years has more serious implications than at any other times as it is often an explanation of infertility.

In the following paragraphs will be discussed anovulatory bleeding during the reproductive period, the treatment of this condition, and the possibility of attaining normal ovulatory cycles as a result of this treatment.

What is the basic defect which is responsible for the lack of ovulation? It appears to have been definitely established that rupture of the follicle itself is not sufficient to ensure ovulation and subsequent luteinization. What are the factors which determine the release of LH from the pituitary? Various theories as to the interaction of the pituitary and ovarian sex hormones have been suggested but still the exact motivating force behind ovulation is an unknown entity. The anterior pituitary gland is sometimes spoken of as the initiator of the menstrual cycle but it does not have an inherent rythmicity in instigating this cycle. There is a reciprocating integration with the ovaries and the

uterus and any disturbance in this integration can manifest itself by changes in the menstrual cycle.

Follicular and corpus luteum cysts often are associated with some degree of abnormality of the menstrual cycle and may result in palpable enlargement of the ovary. These are considered as "physiologic cysts" and are mentioned here only because of their physiologic basis. The ovary containing multiple follicular cysts is usually less than 5 cm in diameter and the physiologic results of this cyst can result in bleeding or amenorrhea. The ovary usually returns to normal within three or four months and the symptoms disappear. A corpus luteum cyst may also produce abnormal bleeding and like the follicular cyst it rarely exceeds 8 cm in diameter and usually regresses within three or four months. On occasion the normal regression of the corpus is deferred leading to maintenance of the progestational phase of the endometrium.

Psychosomatic factors play a predominent role in the cessation of menstruation in some individuals. The results of various psychic stimulating episodes may result in either complete lack of menstruation or an excessive flow. Environmental factors may consistently affect menstrual function in some. Menstruation abnormalities are common occurrences in women in boarding schools, nurses training, and in the Armed Forces. (35) The severity of local and constitutional symptoms related to abnormal uterine bleeding is often the direct result of the patient's psychic

reaction to the presenting problem. States of abnormal bleeding may be associated with severe constitutional symptom complexes which have as their ultimate basis the desire on the part of the patient for pregnancy, or the fear of pregnancy, or even the fear of the loss of sexual function.

In cases of hypopituitarism which leads to hypogonadism, there is usually a decreased amount of gonadotrophic hormone in the urine. With this occurring estrogen output is reduced and if there is a sufficient decline of the gonadotrophic hormones there may be a failure of ovulation. Ovulatory failure precludes the formation of a corpus luteum and there can be no progesterone formation of a sufficient degree to produce a secretory endometrium. Estrogen withdrawal bleeding then occurs from a proliferative endometrium. Effects similar to the above are also seen in cases of primary ovarian failure, but in this case the amount of gonadotrophic hormone excreted in the urine is high. Another concept proposed by the Biskinds (36) is that in a deficiency of the vitamins of the B Complex the liver loses its ability to inactivate estrogens. With the relative excess of estrogens thus resulting, the anterior pituitary gland is continually inhibited and the production of LH and LTH is inhibited. Failure of ovulation thus ensues and anovulatory bleeding may result. It is obvious that diet plays an important role in the menstrual cycle.

Schroder (6) in 1915 began his efforts on determining the mechanism of anovulatory bleeding. By correlating histologic study of the uterus and ovaries, he concluded that the bleeding disorder is produced by abnormal persistence of unruptured follicles with consequent absence of functioning corpora lutea and with the production of hyperplasia of the endometrium as a result of the abnormally persistent and excessive estrogenic stimulation. Statistics that are significant are lacking as regards the incidence of anovulatory cycles in the child-bearing years. Most of these figures have been derived from a select group of women who have undergone intensive study because of sterility of unknown etiology and would thus be meaningless in statistical analysis.

As regards the sterility question, Novak indicates that even though menstruation occurs in a normal amount, character, and rhythm, ovulation has not occurred and thus the patient cannot become pregnant. The latter half of this statement is agreed upon but the writer contends that if ovulation has not occurred, only in a very small percentage of these patients will the menstrual flow be of a normal amount, character, and rhythm. In the opening statements it was stressed that the one outstanding characteristic of anovulatory bleeding is its extreme irregularity. Even when absence of ovulation is established as the probable cause of sterility, no dynamic method of dealing with the problem can as yet be offered the patient. Patients of this group

characteristically exhibit no evidence of endocrinopathy and are usually in good general health. (12)

(a) Induction of Ovulation

The induction of ovulation is obviously the desirable end result to be attained in any method of treatment attempted. The closer the attainment of this end is reached by physiologic principles the greater the chances of success will be. Induction of ovulation is extremely difficult regardless of the methods used. The most physiologic approach has been the use of gonadotrophin therapy in two phases with the gonadotrophins being derived from pregnant mare serum, pituitary plus chorionic, and chorionic plus pregnant mare serum. (37) The essentials of this method lie in (1) the administration of pregnant mare serum to make the follicle mature, (2) the administration of chorionic gonadotrophin to replace pregnant mare serum as soon as the maturation of the follicle is reflected by changes in the amount of cervical mucus. The clinical results of this form of therapy vary, possibly because of the differences in the methods of administration of the serum. As yet no decisive conclusion has been reached as to the most rational and effective method for the induction of human ovulation by the administration of pregnant mare serum. When pregnant mare serum was administered alone, the ovulations induced were mostly delayed, while when pregnant mare serum was administered with chorionic gonadotrophins, ovulations were all prompt. (37)

To induce human ovulation by giving pregnant mare serum alone requires the production of the luteinizing hormone from the patient's own pituitary. When chorionic gonadotrophin is administered in addition, the secretion of luteinizing hormone may not always be necessary because of the luteinizing hormone like action of chorionic gonadotrophin. This action of chorionic gonadotrophin has been proven by Whalen (37) and others by the induction of ovulation in a mature follicle by the administration of chorionic gonadotrophin alone. It is possible to determine the degree of maturity of follicles by determining the fluctuations in the amount of cervical mucus. When the amount of mucus aspirated amounts to 300 c. mm. the follicle is almost mature, when it attains 400 c.mm. it is fully mature. When the maturity of a follicle is thus ascertained, pregnant mare serum is replaced by chorionic gonadotrophin so that ovulation occurs.

Ill effects from administration of these substances occurred in some patients. Enlargement of ovaries with tension in the lower abdomen and the symptom of pressure on the bladder were encountered. Antihormone formation has been found to occur by Ostergaard and Leatten (38) with the gonadotrophins derived from animal sources. Since the pituitary gonadotrophins cause ovulation in a normal menstrual cycle it was assumed that a preparation of human pituitary gonadotrophins might be effective in some anovulatory cycles where animal pituitary gonadotrophins had

failed and it seemed possible to use human pituitary gonadotrophins for long-term therapy without the complication of antihormone formation. (38) Obviously human pituitaries were not available for extraction of the hormones so it was necessary to extract the gonadotrophins from human urine from postmenopausal or castrated women who produce large amounts of gonadotrophins. After purifying the extract and administering the material daily to a normally menstruating girl for a period of four months, no antihormones were detectable in her plasma. The results of these human hormones in producing ovulation are inconclusive.

The use of progesterone in the management of anovulatory bleeding problems has been derided by some authors. (39) One bluntly states that "to try to convert anovulatory into ovulatory cycles by the simple expedient of supplementary progesterone therapy is a rather fatuous ambition in the present state of our knowledge." (39) Swartz and Jones (10) feel that the reestablishment of regular menses, which does occasionally occur following several months of progesterone therapy, is a result of the natural history of the disease rather than a specific therapeutic effect. Holmstrom (9,19,32) has found the cyclic administration of progesterone to be an effective form of therapy. He believes, and has proven, that not only does regular cyclic bleeding occur during the course of treatment, but spontaneous ovulatory cycles usually follow when therapy is discontinued, except in women approaching the menopause.

When continual estrogen stimulation causes the formation of a hyperplastic or proliferative endometrium and no progesterone has been produced because ovulation has failed to occur, the exogenous use of a sufficiently large dose of progesterone will convert the endometrium to a secretory phase. Shedding of the converted endometrium follows in about four days. Therefore, the irregular and prolonged bleedings associated with anovulatory cycles can readily be controlled by such therapy. It is further believed that the progesterone initiates a chain reaction which results in subsequent spontaneous ovulatory cycles.

The best evidence indicates that no one hormone is responsible for the initiation of ovulation but that when an optimal ratio between the secretion of follicle-stimulating hormone and luteinizing hormone exists then ovulation occurs. It is reasonable to assume that if there is an imbalance between these two hormones then ovulation will fail. There is experimental evidence which indicates that progesterone can influence the secretion of gonadotrophins and subsequent ovulation. (32) It is also possible that progesterone may exert a direct effect on the ovary. This may be a direct sensitization so that the ovaries are able to respond with ovulation when properly stimulated by the gonadotrophins. We know that progesterone is present prior to ovulation and on this basis the progesterone treatment of anovulatory bleeding to produce ovulation appears to be theoretically possible but practically it is presently questionably effective.

The treatment followed by Holmstrom (32) in the age group under discussion is the administration of a single dose of 25 to 50 mg of progesterone parenterally. About four days after the progesterone administration the endometrium will be shed. Regular cyclic bleeding can then be induced by the administration of the progesterone on the twenty-fourth day of succeeding cycles. If bleeding fails to occur one of three things has occurred: (1) Ovulation has recently occurred and if so bleeding will occur in about fourteen days. (2) The endometrial proliferation has not been sufficient to respond to progesterone stimulation. (3) Pregnancy has intervened.

If bleeding occurs as expected the hormone is administered until evidence that ovulation is occurring spontaneously. This is indicated by failure of bleeding to follow the expected pattern. If bleeding occurs earlier or later than four days following the progesterone, therapy is withheld for the next cycle. Should the lengthened cycle be due to an early pregnancy the progesterone will have no harmful effect.

In order to scientifically prove whether or not progesterone actually does influence the output of gonadotrophins it would be necessary to measure the output of these pituitary hormones following the administration of the progestational material. This requires a bioassay method sensitive enough to measure small changes in the production of FSH and LH for it is assumed that even in

anovulatory cycles both hormones are being produced to some extent. This has been accomplished by using the known synergistic effect of FSH and chorionic gonadotrophins on the immature mouse ovary. A dose of human chorionic gonadotrophin sufficiently large to produce a maximal luteinizing effect is administered. Any subsequent increase in ovarian weight following administration of the sample to be tested is assumed to be due to FSH. (40)

VIII. Summary

The terms "dysfunctional uterine bleeding" and "functional uterine bleeding" are used by the majority of individuals to describe any and all types of bleeding which does not follow a cyclic menstrual pattern. Therefore, a title was chosen for this thesis which describes both the cause, anovulation, and the most outstanding clinical manifestation, irregularity of the condition.

The ovaries have both a cytogenic function in their production of ova and an endocrine secretory function. Both of these functions are under the control of the anterior lobe of the pituitary. The three trophic hormones of the pituitary associated with ovarian function are FSH, LH, and LTH. In discussing anovulatory bleeding a basic understanding of the hormonal interplay associated with normal menstrual cycles is necessary.

The relationship which exists between the pituitary, the ovaries, and the uterus is one of reciprocating influences and a defect in any one of the stages of the cycle could result in menstrual irregularities, ovulatory failure, and/or amenorrhea.

The extreme irregularity of the onset of flow is characteristic of anovulatory bleeding, while the bleeding associated with other causes in the presence of ovulation, is just as often regular. This statement is in general, true for all except malignant neoplasms of the female reproductive system.

The diagnosis of anovulatory bleeding is at best somewhat tentative but in addition to the history, physical, and blood count the following diagnostic procedures are useful in making the differential diagnosis: uterine curettage is excellent but has the disadvantage of requiring hospitalization; the same information derived from uterine curettage can be obtained from endometrial biopsy and does not require hospitalization; cytologic evaluation of vaginal smears give an indication of hormonal levels of estrogen during various phases of the cycle; basal body temperature fluctuations occurring at the expected time of ovulation gives presumptive evidence that ovulation is taking place; ferning of cervical mucus under estrogen-stimulation and absence of the ferning pattern under progesterone stimulation indicates the presence or absence of a corpus luteum; and lastly, hormonal assays of urinary excretory products are available and are of diagnostic aid but they have limited application in this regard as they are not as practical and available as the former procedures mentioned.

Anovulatory bleeding is a frequent occurrence during the menarche and results because of an uncoordinated interrelationship between the pituitary and the ovary. In the majority of adolescent patients with this condition, definitive treatment is rarely indicated as the treatment will in no way alter the basic deficiency in which hormonal control of menstruation is not as yet complete. Operative intervention is only necessary when the

procedure becomes necessary for hemostasis. When hormonal therapy is required it is not in an attempt at the cure of the problem but it is substitutional and supportive therapy until endogenous production by the patients ovaries is stabilized at a normal functioning level.

The second most common time in the female menstrual life in which anovulatory bleeding occurs is during the climacteric. The change in ovarian function usually occurs over a period of months to years. Cycles become more and more frequently anovulatory and finally they cease. Treatment of this group of patients has ranged from complete hysterectomy to abolition of ovarian function by the use of radiation. The method of choice, however, appears to be cyclic use of progesterone in an effort to avoid the profuse bleeding periods until ovarian production of estrogen ceases.

Anovulatory bleeding during the reproductive period of a woman's menstrual life is statistically less common then at either end of this period. Here the question of sterility is paramount in married women desiring children and treatment during this period is aimed at bringing about ovulation. This has been accomplished by the use of cyclic progesterone therapy according to some authorities. The use of chorionic gonadotrophins and pregnant mare serum has also been used in this regard with questionable results.

The question of why ovulation occurs and what individual hormone is responsible for its occurrence has not yet been answered.

Work in this field holds promise of more accurate knowledge of these events in the near future.

IX. Conclusion

In conclusion, the writer wishes to stress once more the importance of ruling out any organic pathology before a diagnosis of anovulatory bleeding is made. This is especially important in abnormal bleeding during the climacteric as it is around this age group that the incidence of malignant neoplasms appreciably increases. I would also like to point out that unless the physician has a thorough understanding of the hormonal relationships involved in the menstrual cycle, at least so far as we now understand the, he will be treating anovulatory bleeding problems haphazardly and by methods that are considered too drastic, by the writer, for the relief of the condition.

The problem of anovulatory bleeding at either end of a woman's reporductive life is one which requires only symptomatic treatment as the normal physiologic mechanisms will correct the condition if given sufficient time. In the beginning months of normal menstruation, the pituitary-ovary-uterus relationship is in its infancy and as such the coordination is not sufficiently developed to produce ovulatory cycles. As this coordination progressively becomes more mature anovulatory cycles cease and a regular ovulatory period takes over. During the climacteric the reverse is true. Either the ovaries have ceased producing ova or the pituitary-ovary-uterus relationship has reached a point in which there is no further coordination as had previously existed. Treatment directed toward

relief of excessive menstrual flow, alleviation of worry and anxiety, and explanation to the patient concerning the cause of the bleeding is usually sufficient in most cases of anovulatory bleeding of the menarche and climacteric. The writer does not believe that radical treatment by surgical intervention with removal of the uterus or x-ray therapy in any form is necessary or desirable in the majority of cases of anovulatory bleeding.

Anovulatory bleeding during the child-bearing years presents a distinctly different problem because of its relationship to infertility. It is in this age group that efforts have been directed toward producing ovulation by use of progesterone, pituitary extracts, and chorionic gonadotrophin hormones from both animals and humans. Holmstrom believes that it is possible to initiate ovulation by progesterone and Novak is just as convinced that this is wishful thinking. From the literature reviewed, it is impossible to arrive at a definite conclusion as to the possibility of inducing ovulation by the use of exogenous hormonal products but the writers beliefs lean towards thoseof Dr. Holmstrom.

Much has been written about various aspects of abnormal bleeding in the last few years, but the literature contains little or real value regarding the etiology beyond the accepted fact that the abnormal bleeding is due to ovarian, hypothalamic, or pituitary dysfunction. Because of the vast research programs carried on during this period in an attempt to determine the interrelations

of the pituitary gland and the gonads, the discovery, identification, and synthesis of the sex steroids, and the discovery and partial identification of the pituitary and chorionic gonadotrophins has been accomplished. The lack of understanding regarding the true cause of ovarian dysfunction is but an example of the complexity of woman. Future studies of bleeding disorders will have to be directed toward the more subtle causes of deranged pituitary-gonadal activity, and in so doing, it is entirely possible that a substance will be found which is primarily responsible for ovulation.

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