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Menstruation : with especial reference to its occurrence during pregnancy

Clarence R. Heidenreich
University of Nebraska Medical Center

MENSTRUATION--WITH
ESPECIAL REFERENCE TO ITS OCCURRENCE
DURING PREGNANCY

CLARENCE R. HEIDENREICH

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INTRODUCTION

Menstruation, regarded as a normal process because of its practically universal occurrence among primates, still requires a complete answer as to its cause and purpose. Loss of blood from organic tissues, everywhere else in the animal kingdom a sign of injury, even danger, is in the uterus of certain primates evidence of healthy function. It is a paradox, indeed, that this curious phenomenon of periodic breakdown, seemingly an imperfection, a physiological flaw, is characteristic solely of those very animals we are pleased to think the highest of earth's creatures.

Considered from the point of pathology, menstruation is a disease. With the exception of labor and delivery, no other apparently normal function involves edema, leucocytic infiltration, ischemia from arteriolar spasm, capillary and arterial rupture and sloughing of tissue. The pathological physiology of no other normal process except termination of pregnancy involves such rapid shifts in water metabolism, increatinine excretion and in serum diastase and changes in systemic vascular physiology slightly suggestive of shock. Other pathological phenomena associated with this normal process are personality disturbances, skin eruptions, sore breasts, headaches, cramps, nasal congestion, dizziness, chilly sensation, abdominal discomfort, and change in activity of bowel and bladder.

THE SIGNIFICANCE OF MENSTRUATION

Among the primitive races it frequently led to superstious practices which affected the social status of women in many ways. It was also the object of much speculation as to its origin and significance, and from time to time, gods, evil spirits, snakes, lizards, crocodiles and birds were arranged as responsible for this mysterious event. To be sure we know that the periodic breakdown and hemorrhage has its origin in the endometrium, but up to the present no one has been able to demonstrate the significance of this seemingly wasteful and destructive process. Until early in the nineteenth century one of the most dominating concepts as to the purpose of menstruation was that the menses are a form of purification. Menstruation, from the Greek word catharsis, was held to be a form of purgation by which women were relieved of impurities and excess blood. The idea of purification was firmly upheld by Hippocrates and Aristotle, and to the early monks a woman was impure and unclean at time of menses, so that communion was forbidden to menstruating women in the early Christian churches.

One of the theories of folklore origin and without any scientific support was that the rhythm of menstruation was under the influence of the moon. The fact that the length of the menstrual cycle corresponds to one lunar month led many of the older writers to attribute to the moon a powerful causative influence on the process. Altho the ridiculousness of a statement

implying that all women menstruate at the same time was mentioned as early as the second century, this superstition has constantly reappeared.

Because animals like the sow and mare have in their cycles one prominent event, namely estrus, and humans display also one definite cyclic change, namely menstruation, the two phenomena were thought to be the same. The estrous theory proposed that menstruation is the same thing as a period of bleeding that occurs in female dogs when they are going into heat, that is the week preceding ovulation, or the proestrous bleeding in cows. Such bleeding does not resemble menstruation since microscopically it is seen to ooze from the engorged superficial blood vessels. It is thought that the engorgement results from the action of the estrogenic hormone, but unlike menstruation there is little or no breakdown of tissues. According to this theory, ovulation in primates would be expected to occur during menstruation, or immediately after the flow, just as in the bitch and cow ovulation occurs about the end of the proestrous bleeding. We believe now that ovulation takes place about fourteen days before menstruation. It is also difficult to reconcile this theory with the fact that unlike menstruation-like bleeding, which can be produced in monkeys and women by withdrawing estrogenic hormone, the proestrous bleeding of dogs is produced by building up the level of estrogenic hormone. Hartman has observed a slight bleeding from the uterus in mon-

keys and in women at the time of ovulation. Histologic examinations of the uterus at this time reveal findings equivalent of the proestrous bleeding. This proves clearly that menstruation is something else than proestrous bleeding.

Hartman (29) has called attention to the universality of leakage of blood into the brood chamber of viviparous and ovoviviparous vertebrates from the cartilagenous fishes on up. Such an event prevails even in the pregnant male sea horse and pipefish, and its function is possibly the delivery of vitally useful hemoglobin to the embryo. The awkward term "embryotrophe theory of menstruation" has reference to the nutritional value of the process. This is a very interesting conjecture, but the parallelism of this phenomena with menstrual bleeding is, of course, only an anology and not an explanation of menstruation, as it is only a statement of certain facts of natural history. Furthermore, we know that many other mammals succeed in implanting their embryos without any such provision of free blood or hemoglobin in the endometrium. We also know that sometimes in women and often in Rhesus monkeys, menstruation occurs in anovulatory cycles, when there can be no embryos to profit by it. This hints that perhaps the process of menstruation evolved without reference to the embryo.

Since only primates menstruate, must we conclude that this phenomenon is a mistake in the process of evolution? The investigations of Smith and Smith provide the most logical answer to this question. They have considerable evidence to suggest

that the pre-menstrual regression of the endometrium involves the formation or liberation of a highly toxic protein which is lethal to laboratory animals when injected in small amounts. The function postulated for this menstrual toxin, or menotoxin, is that of a pituitary stimulant.(62)(59) The toxic (euglobin) fraction of the menstrual discharge has been shown to produce persistent functional corporea lutea in rats, (61) similiar to the effect of many damaging agents acting on the pituitary.(4) Selye found enlargement of the adrenal to be a consistent reaction to noxious stimuli, and this likewise was mediated thru the hypophysis. (57) Adrenal enlargement in rats has been regularly observed from menstrual toxin, and recently pituitary hypertrophy has been demonstrated also with increased release of gonadotrophic as well as adrenotrophic hormones. In reviewing the literature, Tepperman (72) and others have emphasized one point of similarity among the various conditions producing this effect, namely protein catabolism, and they have theorized that protein breakdown products stimulate adrenotrophic activity in the anterior pituitary. It is thought that gonadotrophins are also released. Menstrual toxin may, therefore, be an important factor in pituitary-ovarian and other interactions. This idea corresponds with the repeated clinical observations of an earlier onset of the climacteric in women who have undergone hysterectomy without removal of their ovaries. But of what purpose could a cyclic toxemia be in the female primate in those instances in which the animal or women ovulates without a pre-

ceeding menstruation? One might think of menstruation as an evolutionary counter balance to the greater development of the cerebral cortex with its inhibiting and distorting influences on the vegetative systems, acting directly and thru the hypophysis as a supplement to hormonal interactions for keeping the pituitary in a proper state of reactivity during the reproductive period of life.

MENSTRUATION, ANOVULATORY MENSTRUATION OR PSEUDO-MENSTRUATION?

There have been numerous attemps to set forth just exactly what is meant by menstruation. In Dorland's Dictionary (19) menstruation is defined as "the monthly sanguineous discharge peculiar to the female, beginning at puberty and extending to the menopause. Curtis (16) states that "menstruation is a bloody uterine discharge associated with necrosis of the uterine mucosa, normally occuring through out the child bearing period, except in the event of pregnancy, at relatively regular intervals of from three and one half to five weeks." Another concept introduced by Robert Meyer is that "menstruation is the recurrent bleeding from the shedding of a proliferated endometrium." Or as Meyer originally proposed "Ohne Ovulation Keine Menstruation." Most of the German pathologists and gynecologists have refused to consider anovulatory periodic bleeding as menstruation because in their opinion there can be no menstruation without a corpus luteum. On the other hand, the American, British and French gynecologists do accept periodic anovular bleeding as menstruation. According to Seitz menstruation is "bleeding from the uterus occuring after a complete cycle in the absence of pregnancy." He places emphasis on "complete" in the definition, and by this he means that there must exist a corpus luteum and a premenstrual endometrium. No other type of cyclic bleeding constitutes true menstruation, but "pseudo-menstruation." It is the opinion of Mazer (41) and

his group that pseudo-menstruation is not synonomous with anovular menstruation. The latter term they believe should be reserved for those instances in which section of an ovary fails to reveal evidence of ovulation. An absence of the secretory phase does not necessarily mean failure of ovulation because there may be an inherent or acquired lack of uterine responsiveness.

The only true tests for ovulation are surgical disclosure of ovules or young embryos, pregnancy after a single coitus, or surgical, celioscopic or culdoscopic finding of a ruptured follicle or corpus luteum. While attemps are sometimes made to distinguish between the bleeding which occurs at the end of an ovulatory cycle and that which occurs in an anovulatory cycle, one should bear in mind that no qualitative differences have been shown. Markee (40) has made careful search for such differences in living endometrial transplants. He found that the amount of endometrial growth, rather than the occurrence of ovulation, explains the quantitative differences observed. Bartelmez (6) found that many intermediate stages occur between the typical ovulatory and anovulatory cycles in man, and that the endometrium removed during a known anovulatory cycle sometimes cannot be distinguished from that of an ovulatory cycle. Practically speaking, with particular reference to the patient, any cyclic bleeding presenting itself from the vagina is considered menstruation. Strictly speaking, those definitions

which exclude flowing during pregnancy are incorrect because as will be shown later menstruation can and does occur after conception.

THEORIES OF MENSTRUATION

Within the past few years a good deal has been learned about what actually happens to produce the menstrual breakdown. To make it clear we must understand the arterial blood circulation of the lining of the uterus. Blood is supplied to the endometrium by two types of arteries. The basal third of the endometrium receives its blood from small, straight, short arteries (Type II of Daron) and the superficial two-thirds from coiled arteries (Type I of Daron) which end in small groups or tufts or arterioles. (17) The function of the basal vessels is to "rescue" the functionalis so that it may be capable of supporting regeneration and endometrial growth during the next menstrual cycle. The coiled arteries make an extremely tortuous path toward the surface, where they break up into tiny capillary vessels that supply the inner one-third of the endometrium and also most of the middle third. The two types of arteries, are, however, not fixed, for Markee (40) has described the transformation of the straight arteries into the more spectacular coiled ones. Hartman has also shown that the entire double supply is capable of regeneration after wiping out, as thoroughly as possible with a sponge, all of the muscosa of the uterus.

The specific mechanism of menstruation as described by Markee from observations of grafts of endometrium in the anterior chamber of the monkey eye is a series of vascular changes which begins

with buckling of the coiled arteries supplying the functionalis, followed by stasis and necrosis, and then constriction of the part of these arteries located within or adjacent to the basalis with periodic relaxation of these producing hemorrhages from them or their branches. The coiled arteries begin to buckle when the endometrium can no longer keep pace with the more rapidly growing vessels. Additional coiling of the arteries appears before the onset of bleeding as endometrial regression sets in and the thickness of the mucosa decreases. The mechanical stasis thus produced is responsible for the necrosis of the endometrium and the extensive weakening of the vessels that inevitably leads to hemorrhage. The first sign of impending menstruation in the intra-ocular transplant is blanching of the tissues due to the vasoconstriction of an uninjured vessel located within the basalis or the adjacent myometrium. The constriction persists throughout the period of menstrual bleeding, being interupted in individual vessels only for short periods. It is during these periods of relaxation that menstrual bleeding occurs. The vasoconstriction of the arteries therefore controls the menstrual blood loss.

Coiled arteries of the type thus shown to be fundamentally involved in menstruation in the monkey are also present in the human uterus, but have never been found in non-menstruating animals. Menstruation, then, is primarily an affair of the coiled arteries, which control the blood supply of the inner layer of the endometrium and by their closure cause breakdown,

tissue damage and hemorrhage.

In the monkey, five types of bleeding have been observed and reported in detail (40). These types are: (1) arterial or capillary bleeding with the formation of a hematoma;(2) similar bleeding without the formation of a hematoma; (3) diapedesis; (4) venous hemorrhage; and (5) secondary hemorrhage from a previously ruptured vessel.

Hemorrhage from an arteriole or capillary occurs owing to rupture of the wall shortly after a constricted coiled artery relaxes. If a hematoma is formed, this subsequently ruptures through the uterine epithelium. If a hematoma is not formed, the blood flows directly out into the uterine cavity through a tear in the stroma and epithelium.

Diapedesis, occurring over a longer period of time, accounts for some blood loss, but is eventually interrupted by constriction of the coiled artery. It may be repetitive, involving further hemorrhage into an already blood-soaked endometrium.

Venous hemorrhage occurs from veins opened by shedding or tearing of tissue in a previous hemorrhage or desquamation, and although it lasts longer than does that of the arteriole or capillary, it is slower, and so accounts for only about twenty-five per cent of the blood loss.

Secondary hemorrhages from an existing defect in the vessel wall are observed after fright or the intravenous injection of epinephrine. It is of interest to note that the escaped blood in a secondary hemorrhage "clots" almost immediately, while

"clots" are seldom seen during the other types of menstrual hemorrhage.

A comparison of the exacting histological studies of human uteri by Bartelmez (6) with Markee's observations in vivo on the monkey should certainly demonstrate that the isolated facts known about human menstruation fit into the sequence described for the monkey.

There is no lack of theories as to the influence controlling the action of the coiled arteries of the endometrium, but the real explanation remains obscure. The relation of the ovarian hormones to menstruation was brought forth in 1928 by Edgar Allen. He found that removal of both ovaries from a mature Rhesus monkey will usually cause within a few days a single period of menstruation-like bleeding. Allen reasoned that the effects of removal of the ovaries of his monkeys were really due to the removal of the estrogenic hormone. He therefore gave a castrated female monkey a course of estrogenic hormone and when treatment was discontinued, bleeding ensued. On this basis Allen formulated the estrin-deprivation or estrin-withdrawal hypothesis of menstruation, which suggest that natural menstruation, like experimental bleeding, is due to a cyclic reduction of the amount of the estrogenic hormone available in the body. Subsequent experiments done with carefully graded doses of the hormone, have shown that not only total deprivation, but also mere lowering of estrogen dosage

below a certain level will produce the bleeding. (81) Nevertheless, there are, several objections to the withdrawal theory. First, the prolonged daily injection of estrogenic substances into human castrates or spayed monkeys is accompanied by uterine bleeding, which occurs during the period of administration of the hormone. (32). Second, the use of large dosages of estrogen in late postovulatory phase fails to prevent the onset of the normal menstrual periods. Third, menstruation normally may occur in the presence of large amounts of estrogenic hormones in the blood (23). Fourth, a rise and fall in the estrogen content of the blood may occur during long periods of amenorrhea. (24).

Administration of the corpus luteum hormone even in small doses prevents menstruation in experimental animals, abolishing the very first menstrual period after injections are begun, provided they are started a few days before the expected onset. Both Hisaw and Corner (32)(15) found that experimental estrin-deprivation bleeding, produced by removal of the ovaries or discontinuance of a course of treatment with estrogenic hormone, is prevented by small doses of progesterone. An exceedingly vigorous condition of estrin withdrawal was arranged by giving a course of gonadotrophic hormone from the pituitary gland to stimulate the output of estrogenic hormone from the ovaries in addition to generous doses of estrogens and withdrawing these hormones at the same time the ovaries were removed. (22). In spite of all these reasons for withdrawal bleeding, modest doses of progestin completely prevented hemorrhage. On the other hand,

progesterone withdrawal, like estrin withdrawal invariably causes menstruation-like bleeding.

From these facts a simple, modified form of the estrin withdrawal hypothesis has been formulated. It is assumed that progesterone in some way has the property of suppressing the menstruation-preventing power of estrogen, while itself holding off menstruation. In the normal cycle the animal does not bleed in the first half of the cycle, because the ovaries are furnishing estrogen. There is no bleeding during the second half because the corpus luteum is furnishing progesterone. Therefore, when the corpus luteum undergoes retrogression, the animals finds itself deprived of the action of both estrogen and progesterone, and the endometrium breaks down. Ovulatory menstruation is thus a special case of estrin-deprivation bleeding. Anovulatory menstruation is probably due to estrin-deprivation alone. A most recent suggestion with some experimental evidence is that anovulatory menstruation may result from cessation of secretion of progesterone by the Graafian follicles. (32)

Naturally, a number of writers have questioned the adequacy of the withdrawal theory. Hartman and Firor (30) have raised numerous objections based on observations in monkeys, and they feel that some extra-ovarian factor must be involved. They have suggested that the answer may be in the field of pharmacolgy rather than endocrinolgy because of "the potency of infinitesimally minute guantities of chemical substance in their vasomotor action." Engle (20) states that "it may be a

mistake to say that the withdrawal of one of the hormones causes menstruation; rather such a lack of hormone permits changes in the endometrium and blood vessels, which result in the bleeding."

It was a similar line of thought that prompted Smith and Smith to revive the age old conviction that a violent poison was associated with menstruation. Some scientific basis for this idea was laid by Schick (53) and Macht (38) who observed its detrimental effect on certain forms of plant life. The Smiths have obtained a euglobulin-like material from the menstrual discharge which, in small amounts, is lethal to rats and rabbits. Late secretory endometrium, fresh from the operating room, ground and injected in saline suspension into rats has also been found to be toxic. Proliferative endometrium, even with hyperplasia, is not toxic. From this and other investigations Smith and Smith have deducted that this highly toxic protein material is either formed or liberated in the endometrium as a result of the premenstrual catabolism of this tissue which follows the withdrawal of hormone support, (estrogenic withdrawal being all that is necessary to initiate endometrial catabolism but the normal cycle depending on a balance of estrogen and progesterone). When injected, it caused pronounced generalized tissue and particularly vascular damage, and at the site of injection, a striking inflammatory reaction with edema, hemorrhage and necrosis similar to that observed in menstruating endometrium. Although not proven, one might logically assume

that this toxin is the immediate cause of menstruation. The vascular changes in the menstruation endometrium as described by Bartelmez and Markee are compatible with the idea that such a toxin is operative. Neighboring fields supplied by separate arterioles may blanch and bleed at rather extensive time intervals, as long as hours at times. If precipitation of bleeding were under general hormonal control, one would expect the endometrial mucosa to menstruate at all points at once, so that the whole process would be over in a matter of minutes; whereas, the process as actually observed suggests the local release of some vasoconstrictor material. The above considerations indicate that in addition to the hormonal component involved in the menstrual phenomenon, there is another component related to the change in endometrial metabolism.

Perhaps the first intimation that portions of the nervous system play a part in the reproductive cycle emanated from the attemps to locate the seat of disturbance in certain abnormalities of the cycle as seen in various pituitary disorders. It has been known for several years that continuous injections of sufficiently large doses of estrin brings about inhibition of the anterior pituitary sex hormone function. Hohlweg and Junkman (33) demonstrated that this inhibition of the anterior lobe is not a direct one upon the gland, but that it is mediated through the sex center in the midbrain. If they implanted a second hypophysis into the kidney, and the

animal was later castrated, only the normal hypophysis and not the implanted one showed the well known castration changes. The conclusion, therefore, reached was that the effect on the normal pituitary was not a direct one, but that it must be exerted thru the nervous pathways affecting the normal gland. These investigators concluded that there must be a sex center located in the floor of the third ventricle, as indeed had been previously suggested by Teel and Cushing (71) as a result of their study of the effects of tumors in this region.

There are a considerable number of facts to indicate that the regularity of the menses is controlled by a center or centers in the brain. The ultimate control of every other function, rhythmic or not, is vested in the central nervous system. Organic illnesses as peptic ulcer, colitis, cardiac disorders, hyperthyroidism and many others may arise as the result of derangements of the autonomic nervous system. The reproductive glands are subject to nervous control in a like manner. It is almost too common to mention that various menstrual disorders are etiologically related to emotional upsets. The facts that amenorrhea may be caused by mental strain, fear or merely immersing the feet in water at the time when the period is due offer evidence in favor of a menstrual center. Menstruation has been delayed by hypnosis. The periods in females addicted to morphine are absent although ovulation and conception are unaffected.

Although it has been assumed that denervation of the transplants in Markee's observations excludes the possibility of direct nervous control of the cycle, it does not exclude chemical transference of the nerve impulses. Basing his experiments upon the fact that denervated striated muscle has been proved sensitive to acetylcholine, Bender (7) assumes that acetylcholine injected intravenously in small quantities in the Macacus produced the same effects on the denervated extraocular and facial muscles as were produced by fright. At this point one should recall the secondary hemorrhages described by Markee as resulting from the fright or struggling of the animal.

Estrin administered to ovariectomized rabbits causes hyperemia (39) and atropine prevents this reaction. (49) Reynolds, therefore, argued that acetylcholine, the action of which is characteristically blocked by atropine must be responsible. He then demonstrated that the hyperemia produced in the uterus by estrin is accompanied by increased production of acetylcholine. Following up this reasoning Soskins and others (65) postulated that delayed menstruation, not caused by pregnancy and occurring in usually "regular" patients, may be due to an abnormally decreased vascular response rather than an endocrine dysfunction. They decided to potentiate the naturally occurring acetylcholine by inhibiting the cholinesterase action with prostigmine. Their results were successful,

and they also proved that prostigmine did not precipitate bleeding in the presence of pregnancy. Hirsch and Martin (31) have investigated the neurovascular relations in the uterus and were able to demonstrate a very close anatomical relationship between the uterine nerves and blood vessels, especially in the inner fourth of the myometrium. The nerve trunks contain non-myelinated or vasomotor fibers and myelinated or sensory fibers. They consider that the abundance and vascular distribution of nerves in the uterus suggest their participation in controlling the vascular phenomena associated with menstruation.

Therefore, although nervous regulation of the menstrual cycle has been ruled out by several authors, there appears to be abundant proof that the autonomic system does participate. The very fact that acetycholine is liberated in greater quantities as a result of estrin stimulation points to an involvement of the cholinergic autonomic impulses.

Experimental evidence points to an interchange between the hypothalamus and the hypophysis regulating the rate of secretion of anterior and posterior lobe hormones. (26) The gonadotrophic activity of the anterior pituitary is well established; thus, in turn, the hypothalamus must influence the flow of ovarian hormones. Since the hypothalamus has been recognized as the seat of emotions, it may be readily understood why emotional factors influence the rate of secretion of all these hormones. It has been postulated that afferent stimuli to the menstrual center in the hypothalamus are pro-

vided by the ovarian hormones and by nervous stimuli from the generative organs and the cerebral cortex, and that the efferent stimuli from the center operate thru the anterior pituitary gland and to a certain extent thru nervous impulses to the generative organs (73).

Although castration experiments indicate the primacy of the ovarian hormones in the control of menstruation, there are facts that point to an involvement of extragondal factors. In this connection the hypophysis was suspected, but this theory was later settled to the contrary by hypophysectomy experiments of Smith, Tyndale and Engle (63). The anterior and posterior lobes and the pars intermedia are certainly not involved and the pars tuberalis (not removed by the authors cited) is perhaps not to be suspected.

A more likely gland is the adrenal cortex. To be sure, the role of the adrenals under normal conditions is obscure, but secondary effects of adrenal neoplasms point to a close relationship with the gonads. Anderson and Kennedy have shown that in the rat, the gland at estrus is larger than in the interval, while there is no such rhythm in the male (3). It has been maintained that during pregnancy and at the time of menstruation there are demonstrable anatomic changes consisting of a hyperplasia of the medullary and cortical cells and an increase of the lipoid content of the zona fasciculata. Castillo (12) found that castrated rats kept in constant estrus by daily injections of estrogen lapsed in a more nearly "interval"

on four or five day cycles. Episodes of bleeding during a course of estrogen injections in castrated monkeys have been observed repeatedly (21), and the phenomenon is also recorded for women (76). Some other organ must, therefore, be responsible for the rhythm that occurs in the absence of the ovaries.

That this organ may be the adrenal is a logical theory in view not only of the findings of Anderson and Kelly of cyclic swelling of the adrenal in the normal cycle, but also by the more remarkable discovery of Zuckerman, Bourne and Lewes (82) that this rhythm continues after castration. Further logic lies in the character of the secretions of the adrenal cortex, from which steroids have been extracted that affect the endometrium.

THE MAINTENANCE OF PREGNANCY

The maintenance of pregnancy is a truly complex affair. Inside a hollow chamber, the uterus, a living creature is growing at a tremendous rate, and this organ must not only tolerate but even support this parasite. All the other muscle-walled organs of the body are built to keep things moving--the heart, the intestines, the bladder, etc.--and so, ultimately, is the uterus. But, for nine months its lining must remain intact and its motility checked. Suddenly, the uterus begins to contract and the infant emerges from the narrow bony canal of the pelvis to be followed by the placenta and membranes. The changes which occur in the nonpregnant reproductive organs are bewildering enough, but a new source of confusion, the placenta, enters into the puzzle.

One to two days after ovulation the corpus luteum begins to produce progesterone and estrogens for ten to twelve days. At the end of this time, that is, twelve to fourteen days after ovulation, it usually ceases to function if pregnancy does not occur. Implantation of a fertilized egg takes place about ten days after ovulation or probably earlier, and almost immediately (within 24 to 48 hours) chorionic gonadotropin appears in the urine. The production of this substance by the trophoblast maintains the corpus luteum, causing it to continue to produce progesterone and estrogens. These maintain the endometrium in such a condition that

pregnancy continues. Evidence from animal experimental (52) and human hormonal (60) assay seems to indicate that the maintenance of a quantitative balance of the chorionic gonadotropins, estrogens, and progesterone plays an important role in maintaining gestation. Urinary excretion of these hormones, however, may imperfectly reflect the quantitative states of their metabolism and utilization, not only because of the inadequacy of our available methods of assay, but also because of the question of the sites and rate of their utilization, destruction, and conjugation.

It has been generally assumed that because of the known effects of the corpus luteum--initiation of progestational changes, maintenance of decidual nutrition and inhibition of uterine motility--it is indispensable to the maintenance of gestation. Nevertheless, accumulated evidence seems to indicate that the corpus luteum can be removed even as early as prior to the first missed period (51) without interference to pregnancy or to any significant changes in the urinary excretion of the chorionic gonadotropic hormone, total estrogen and pregnanediol. It seems that some other organ assumes the role of the corpus luteum in supplying the hormones necessary for the continuation of pregnancy, probably the placenta or the decidua.

MENSTRUATION DURING PREGNANCY

It is indeed surprising to find a function ordinarily performed by the lining membrane of the non-pregnant uterus taking place when the cavity of the uterus is lined by decidua, occupied by the ovum, and the mouth closed by a dense mucus. However, strange as it may appear, the cases on record are too numerous and too well authenticated to bear a doubt that a discharge resembling the catamenia in color, quantity and periodicity does not infrequently occur during gestation. That the ancients were well aware of the fact appears from a statement of Hippocrates that "the children of women who menstruate during pregnancy cannot be healthy."

Yet, the absence of discussion of menstruation during pregnancy in the literature is conspicuous. Consulting three of our most widely used textbooks of obstetrics, I found the first makes no mention of this topic, the second dismissed the subject with a statement that "menstruation may continue after conception.....the flow is otherwise abnormal," and the third states, "In not a few instances menstruation may appear once after the commencement of pregnancy, the the flow is usually less profuse than at other times....Only very rarely however, does the menstrual flow appear more than once..... One occassionally hears of women who menstruate regularly throughout pregnancy, but the majority of such accounts are apocryphal,....."

There are many who do not recognize periodic bleedin g during pregnancy as genuine menstruation, and among this group are those skeptics who doubt the periodicity of the flow because of the general indifference to menstrual discharge prevailing among the ordinary female. The opinions of the experts are divided. The one group admits the possibility while the other strongly denies it. In the mindsof the lay, who consider many uterine bleedings as the menses, the wide spread opinions is that true menstruation does occur.

Such accurate observers as Mauriceau, Velpeau, and Baudelocque are among the more than twenty references cited by Churchill (13) who have known of one or more menstrual periods in pregnant women. In the works of Mauriceau, Dewees, Burton, Velpeau, and Blundell are recorded cases in which the discharge persisted for four, five and six months, even during the whole of the period of gestation. Still more remarkable and rare are those cases in which the flow appears for the first time during pregnancy as noted by Perfect, Reid, Velpeau, and others, or where it only appears during pregnancy according to Daventer, Baudelocque, and Dewees (13). Daventer recorded a case in which he had the opportunity of observing the occurrence of the catamenia during the time of gestation only in four successive pregnancies in the same woman.

There are many such single observations on menstrual-like bleeding in pregnancy, but the actual incidence is certainly

unknown. Spruck (66) observed it in nineteen of 9,000 pregnant women, giving an incidence of 0.2-0.3 per cent. In only 0.05 per cent, however, was the periodic flow of such amount or duration as to resemble a normal flow. In the 2,800 pregnancies studied by Willibald (78) there were twenty (0.7%) with menstrual-like bleeding. In three of these cases there was one heavy flow, while in five cases there were two periods of heavy flow. Of the remaining there were seven cases (0.25%) in which there were several episodes of reduced amount of flow and in five cases (0.18%) the bleeding was normal in amount and duration. Vignes (74) reports 180 cases in a series of 1,344 pregnancies (13%) but only seven of ninety-five cases studied showed regularity (7.3%).

While menstruation as a rule does not occur during pregnancy, cases are encountered in which periodic bleeding is observed. It is not rare for a single, usually slight bleeding associated with pain or abdominal cramps to appear at about the first menstrual date after supervention of pregnancy. In light of the work of Hartman (29) upon monkeys, this is quite possibly to be interpeted as the "placental sign", analogous to the bleeding noted in these animals at the corresponding period. This bleeding has been said to result from the syncytial cells of the trophoblast digesting into the endometrium causing a defect at the site of implantation of th e ovum. The blood so set free may find itself in the endometrial

glands with extravasation into the uterine cavity. This explanation for a first menstrual period has been doubted because the amount of blood set free is not likely to be sufficient to simulate a normal period.

Wintz (80) formulated two explanations for the first period after the beginning of pregnancy from observations of three cases during World War I. A single intercourse occurred on the 21st, 23rd and 24th days respectively as calculated from the previous menstrual flow. If the histories are as reliable as Wintz reports they are, then conception took place on the day of the intercourse. Nevertheless, in each case the menstrual flow started on the expected day. Wintz assumes that ovulation occurred on the 7th, 9th, and 10th days respectively preceding intercourse. Since conception was delayed, the uterine mucosa had begun to regress before the corpus luteum of menstruation had changed to the stabilizing corpus luteum of pregnancy. That the fertilized egg in the foregoing cases was not expelled is due to its very sheltered position in the fallopian tube. This proposal is insignificant in view of the fact that we recognize a shorter period of viability for the ovum. But, it is possible that the estrogens failed to condition th e tube to the proper peristaltic activity so that the blastocyst was delivered to the uterus after the lining had sloughed. The second suggestion made by Wintz assumes that the sperm does not fertilize the ovum liberated at the ovulation

previous to coitus, but that it lies in wait for the ovum of the next ovulation. If this were true, the menstruation would then precede fertilization of the ovum, but to the laity who would associate conception with this isolated intercourse, the menstruation would have occurred during the pregnant state.

Could the first and successive periodic bleedings appearing in early pregnancy be related in some way to inadequate function of the corpus luteum? The interpretation of the endocrine mechanisms involved following fertilization reveals a short overlap of about two to four days from the onset of chorionic gonadotropin action and the usual tim e for the corpus luteum of the menstruation to degenerate. Bleeding after fertilization of the ovum might occur if the corpus luteum activity were subnormal owing to inadequate stimulation by chorionic gonadotropin as a result of a defective trophoblast. The latter condition might result from improperly nourished cytotrophoblasts due to a disturbance of maternal endocrine activity. Or perhaps if excessive bleeding on a vitamin C or K deficiency basis occurred in the corpus luteum so that a corpus hemorrhagicum is produced, the production of progesterone and estrogen may be interfered with so that hormonal imbalance and uterine bleeding result.

According to the German concept the proof lies in the demonstration of: (1) sloughed proliferative mucosa, and (2)that, in addition, to the corpus luteum of pregnancy,

another corpus luteum of an age compatible with the discharged mucous membrane. The case reported by Wintz offers evidence for this occurrence. A gravida three patient undergoing an examination for an ovarian cyst was found to have a uterus corresponding in size to a three months pregnancy. She had not stopped menstruating, but had had two periods at the proper time. At each period there were shreds of mucous membrane which revealed typical secretory endometrium on microscopic examination. The patient underwent an exploratory laparotomy at which time a corpus luteum of pregnancy was observed in the left ovary, the uterus was soft and spongy and the size of a three months pregnancy. The right ovary containing a second corpus luteum and an ovarian cyst were removed. The surgical diagnosis of a corpus luteum of menstruation was confirmed by microscopic examination. The age was estimated at ten days, and since the operation was on the twentieth day after the last period, the author concluded that the woman would have had a third menstruation. She had menstruated twice during her first pregnancy and once during the second. Wintz had the opportunity to explore another woman who had menstruated regularly for five months. Again he found the corpus luteum ofpregnancy in the one ovary, but in the other he found a freshly ruptured follicle. In time relation this ovulation occurred eleven days after the last menses. The corpus luteum of the preceding period

could not be identified for certain.

What are the possible sources and stimuli to account for periodic genital hemorrhage during gestation? The ideas prevalent in the late nineteenth century were that the discharge usually arises from the lower portion of the uterus or from the vessels of the cervix, but in some instances it may have its origin in the mucous membrane of the vagina. The mucous membrane of the cervix and the vagina are said to share the vicarious function, and this suggestion is supported by those cases in which the entire uterus is removed, and yet menstruation persists after operation. The reply to this phenomenon is that a strip of endometrium has been left in the genital tract, and this tissue responds as if it were lining the uterine cavity. It is with no greater ease to account for a monthly discharge of menstrual fluid from the cervical and vaginal mucosa than from the mucous membrane of the lungs, gums, eyes, or nose. Norton (45) reported an unusual case in which both uterine menstruation and a severe vicarious hemorrhage from the lungs persisted throughout the entire duration of pregnancy. The patient had suffered with vicarious hemoptysis for many years before pregnancy occurred. The uterine hemorrhage during pregnancy as before was slight in amount and persisted up to twelve days before delivery without producing any harmful effects.

There are a considerable number of facts to indicate

that the menstrual wave, ovulation and corpus luteum formation persist throughout the gestation period. While ovulation is commonly in abeyance during pregnancy, the menstrual wave, as manifested by slightly increased body metabolism, nervous irritability and sore breasts, may occur for several months after conception in certain individuals. For this reason measures are employed in threatened or habitual abortion to allay uterine irritability at the time of the expected menstrual period. Leopold and Ravano (36) found that follicles are continually and regularly undergoing ripening during pregnancy, and that ovulation occurs in about 5 per cent of all cases. In this, however, he is contradicted by Seitz (55), who denies such occurrence. Ovulation can be induced experimentally in the mouse without abortion following. It occurs spontaneously in the horse, while in the cow, follicles tend to enlarge with occassional estrus (64). After reviewing the literature on superfetation, Studdiford (68) concluded that no case reported presented sufficient evidence to prove that the difference in ages of two fetuses resulted from fertilization of ova on separate occasions. In this connection one should consider the case of superfetation described by Monech (44). This patient brought forth a seven months fetus which was followed in three days by a three months fresh fetus in its membranes. Monech offers this as a true

case of superfetation because the second fetus was fresh and not compressed or mumified as it would have been if both pregnancies had begun simultaneously. According to Seitz (54), Boerner and Klink, luteinization (10) of immatured follicles in the nonpregnant female is said to be found very rarely, while it is said to be found rather frequently during pregnancy. On the other hand, ovulation will hardly take place under normal conditions without being followed by luteinization. At this point let us not forget that Wintz demonstrated by anatomic examination of the ovary corpus luteum formation in addition to the corpus luteum of pregnancy. It is more than probable that ovulation may continue throughout pregnancy, and hence there is no reason why a true menstrual flow may not occur up to the fourth or fifth month at which time the decidua reflexa and decidua vera fuse.

Markee has been unable to show any qualitative difference between anovulatory and ovulatory menstruation. The quantitative differances he attributes to the amount of endometrial growth rather than the occurrence of ovulation. Wilson and Kurzrok (79) likewise suggest that the particular type of endometrium has no bearing on the process of menstruation. In two cases they observed menstruation from secretory endometrium on the sixth day of the cycle. They postulate a "bleeding factor", the potentially variable reaction of the vascular component of the endometrium to the ovarian hormones. Thus, the occurrence of the menstrual

bleeding depends not alone on the stimulus supplied by the ovary, but also on the reaction of the endometrial vessels to this stimulus. Employing estrogen-progesterone therapy, Greenblatt (27) could induce uterine bleeding at will in a yound female who had been surgically castrated one year previously. On thorough curettage before and after therapy he failed to obtain endometrium, indicating complete atrophy of the endometrial lining. The hormonal induction of bleeding to simulate a menstrual episode on three occasions in this patient would appear to emphasize the importance of the myometrium and its vascular supply and the minimal role played by the endometrium in this bleeding. It is not unreasonable to assume, then, that periodic bleeding could occur from a decidual type of endometrium irrespective of changes occurring in the ovary as in the non-pregnant female.

It has been shown that the nervous system is implicated in the control of the menstrual cycle as well as in cases of pseudocyesis. The subjective symptoms are easily explained, but not so the objective signs. Demonstration of marked alteration in excretion of gonadotrophins and estrogens in pseudocyesis presents evidence that the endocrine system is affected by the psyche (67). Further support of this hypothesis is given by the fact that when the patient was told that she was definitely not pregnant, prompt recession in the physical signs took place, attended by a

return to normal hormonal titers. The etiology of pseudo-cyesis is not clear, but it is associated with a desire for pregnancy. In a diametrically opposite manner regular uterine hemorrhage may result from pregnaphobia or a desire of not being pregnant. Undoubtedly, some case reports of menstruation during pregnancy are instances in which the patient attempted to deceive the physician by denying the cessation of menstruation.

Conditions in which menstruation during pregnancy is more likely are those related to congenital anomalies of the uterus. These are no longer rare anatomic curiosities. The incidence of duplication of the uterus is given as from 1:600 to 1:7,000 (34). In the absence of pregnancy, the menstrual discharge may come from both uteri simultaneously or alternately from one side at intervals of two weeks. Whether the non-gravid horn forms a decidua is debatable. A case of pregnancy complicated by a double uterus was reported by Taylor (70). In this instance the pathological report of the material passed from the nonpregnant horn was normal endometrium. Bainbridge (5) and Miller (43) cited other cases of menstrual flowing in pregnancy complicated by duplication of the uterus. Findley suggested an independence of function of the two horns, perhaps the one ovary exerting its effects on the uterus of the same side. Further support of this thought lies in the fact that in the case described by Corbet (14), uterine horns acted

independently in delivery their contents. Obenour (47) studied an analgous case of independent function of the uterine components. This woman menstruates regularly every twenty-eight days but has two periods, separated by one to three days. Each period is normal in length with an average flow proceeding from each uterus individually. The surgical demonstration of a ruptured follicle in a woman menstruating during pregnancy was the patient described by Wintz as having duplication of the uterus and vagina.

In at least a fraction of the cases with continued menses in pregnancy, examination of the genital canal during bleeding revealed a definite local cause not directly related to the pregnancy. For example, Willibald, Pok and others have shown that in some instances of this sort, erosions of the cervix, polypi or vaginitis are the source of bleeding, although it is not clear how such lesions could produce periodic hemorrhage, especially when in most cases there is no history of bleeding after coitus. Bleeding may originate from the cervix, and the most likely cause is carcinoma, though capillary oozing sometimes occurs from an erosion, the vascularity of which is exaggerated (8). An excessively swollen condition of the mucous membrane of the cervix may cause hemorrhage which may simulate that of the menses (18). Taussig (69) states that the presence of myomata in the uterus may lead to a persistence of a menstrual-like bleeding in the early pregnant uterus.

The only common pathological changes occurring in the placenta that may produce menstrual-like bleeding is that reported by Davis (18). He writes: "When a separation of the placenta nearest the cervix occurs, the separation may proceed no further than its original extent. The hemorrhage may cease, and the pregnancy continue to a successful termination. In such cases there is a slight vaginal hemorrhage which gradually subsides. The uterus is little if at all sensitive, and the patient may think that she has a slight return of menstruation."

Williams and Fralin (77) have shown that only two percent of all women partake of an adequate diet in pregnancy. They observed vitamin deficiencies in fifty per cent. In early pregnancy, morning sickness and vomiting may vitiate an adequate diet and thereby deplete the vitamin resources. As pregnancy advances, women are in need of a supplemental vitamin intake, especially A and the B complex, because of accelerated metabolism in such a condition, and because of transmission of vitamins to the growing fetus thru the placenta as evidenced by the finding of large amounts of vitamin C in that organ.

Plasma vitamin C decreases in normal pregnancy from non-pregnant values of 1.1 mg. per cent to 0.35 or 0.4 mg. per cent at term. Ley (37) and others recommend large doses of ascorbic acid for patients with threatened or habitual abortion to insure a maintenance level of vitamin C of at least 5 mg.

per cent. They maintain that a large amount of vitamin C stimulates the hormonal production of the corpus luteum and so maintains pregnancy

In recent years considerable work has been done in an effort to work out the function of the liver as related to the metabolic changes of female sex hormones. Gubner and Ungerleider (28) obtained good results in menstrual disorders in the presence of prothrombin deficiency by administration of vitamin K. Perfect conjugation of estrogen in the liver may be impossible with mild degrees of vitamin B deficiency, and it is possible that such a deficiency is responsible for abnormal bleeding from the uterus. Thus, periodic losses of blood indistinguishable from those of menstrual origin may arise from the decidua vera because of a menstrual proclivity aided by deficiency of one or more vitamins.

From a study of 180 cases of "metrorrhagia during pregnancy," Vignes suggests various causes for this bleeding. He states that mere congestion from coitus, automobile travel, toxic absorption of foods and medicaments may be responsible for the blood losses. In other cases the cause may be hypothyroidism, dysfunction of the pituitary or corpus luteum or overactivity of the follicular cells. Vignes also associates menstruation-like bleeding with "decidual endometritis" and "hydro-hematorrhea". Those who advocate endometritis as a cause of the decidual bleeding point out that the accidental hemorrhage is far commoner in multiparae than in primigravidae and that the

endometrium of the former is more likely to be in an unhealthy condition than that of the latter. As a final suggestion for menstrual-like bleeding one should bear in mind that endometriosis of the bladder and vagina may give rise to periodic hematuria or vaginal hemorrhage which the patient mistakes for menstruation.

One might question whether the pregnant state actually existed in these women who continue with the menses. Sufficient data is given by Willibald in his case reports confirm the approximate day of conception and to conclude that the pregnancies were full term and the babies of average length and weight and not premature according to our concept as to the duration of a normal pregnancy.

Supression of the menses is generally looked upon as the first reliable sign of pregnancy and because of its almost uniform occurrence is constantly used by women as the test of conception and provides the best means of calculating the date of parturition. This has less clinical significance than the statement of Allen (2) that the most important and frequent cause of death in ectopic pregnancy is due to delays in treatment.arising from misinterpretation of symptoms by either the patient or the physician. Vaginal bleeding from an extrauterine pregnancy frequently occurs at or near the time of the next expected menstrual period and goes unnoticed because women are extremely inaccurate concerning their menstrual function, and they are unaware that the bleeding is abnormal in

character. After reviewing 148 cases of abortion and finding only one patient who had had three slight vaginal hemorrhages, Willibald concluded that there was no positive correlation between abortion and menstruation during pregnancy as had been suggested by others.

Nature when building up the fetus has no excess of materials to be periodically discharged, and altho not factually demonstrated, a transient anoxia from menstrual bleeding in pregnancy may be the cause of fetal anomalies or monstrosities.

SUMMARY AND CONCLUSIONS

1. The significance and theories of menstruation have been reviewed in an attempt to learn the possible causes of menstruation in the non-pregnant and pregnant female.

2. Altho menstruation during pregnancy has been considered doubtful, a review of the literature, especially the foreign, has disclosed evidence to confirm its occurrence.

3. The incidence of menstruation during pregnancy is reported to be from 0.05 to 13 per cent.

4. Since very few of the reported cases have been studied objectively, the source of the bleeding is uncertain as is the cause. It is recommended that patients be examined at the time the bleeding occurs.

5. The case reports are inadequate as to number and data to correlate the occurrence of menstruation during pregnancy with the age, menstrual history and parity of the patient and the outcome of the pregnancy.

6. The clinical aspects of menstruation during pregnancy have been discussed.

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