THE MENSTRUAL CYCLE IN THE NORMAL HUMAN FEMALE

ROBERT FARRUGIA RANDON

GENERAL

The menstrual cycle is a sequence of morphologic changes in the reproductive system, particularly of the endometrium, that culminate in an episode of uterine bleeding. The cycle may be regarded as consisting of three phases: (a) proliferative (b) secretory (c) decidual or desquamative, but desquamation is more generally included in the proliferative phase. Typical length is twenty-eight days. Clinically, cycle ranges from twenty-five to thirty-one days and this is accepted as normal. It has, however, been found that only 53% of cycles may be expected to fall within this range. The question when exactly in the cycle ovulation does take place is an important one, and will be reviewed briefly after the description of the cyclic changes occuring in genital sites have been fully dealt with.

CYCLIC CHANGES IN THE FEMALE REPRODUCTIVE SYSTEM

The Uterus: It is the uterus which undergoes the most important changes during the menstrual cycle. The changes involve the myometrium, endometrium and the blood-vessels supplying the uterus. These changes will be described in turn:-

(a) Changes in myometrium:- During the last ten years or so, myometrial activity in the human has been much studied by the aid of intrauterine balloons (1). At the University of Georgia this question has been thoroughly investigated with the aid of pressure tracings and electro-uterograms. Balloons fastened to short sections of urethral catheters were placed in the uterus and cervix and then connected to Hamilton optical manometers (2, 3). The manometers and balloons were fluid-filled so that transmission of uterine pressure changes to manometers was accomplished by displacement of less than 0.01 cc. of fluid even when pressure-changes as large as 400mm Hg. occurred. Accurate tracings could be obtained with less than 0.1 cc. in balloon though usually 0.2-0.5 cc. was placed in cervical balloons and 0.5-0.1 cc., in uterine balloons. Pressure tracings obtained with small intra-uterine balloons seem superior to the electrouterograms. It has been found that during the proliferative phase contractions of the uterus are frequent and of small amplitude, whereas during the secretory phase the frequency diminishes and the amplitude increases. Downward from the dome of the uterus the contractions and relaxations of the muscle fibers become progressively more frequent and this presence of different pressures in different parts of the uterus allows during menses the downward propulsion of the menstrual debris towards and out of the cervical canal. During the relaxation phase there is a large pressure gradient between the lower uterine segment and the cervix and this propels the debris into the cervix and ultimately into the vagina. Therefore during the relaxation period the menstual debris is pushed down towards the lower uterine segment and during the contraction phase the debris is pushed down through the lower uterine segment into the cervix and lastly into the vagina. It has been found that Pitressin, and Neosynephrine increase uterine activity on injection. In some patients small doses of adrenaline have decreased the uterine activity. It has to be borne in mind also, that during the pre-ovulatory phase the myometrium becomes soft and spongy.

(b) Changes in endometrium and its blood supply (4):- In the early estrogenic phase there is proliferation of stroma and endometrium. Mitotic figures can be seen in the gland and stromal cells. The spiral arteries reach the surface. The outer and inner coats of the arteries are very thin and the middle coat consists of two to three layers of smooth muscle cells. The capillaries run parallel with the surface and the new capillaries are simple endothelial tubes. The veins also run parallel to the surface. These unite with the venous stems which run at right angles to the surface. These venous stems are thick walled. It has to be noted that the veins also undergo cyclic changes during the menstrual cycle.

In the late estrogenic phase the endometrium is some 2-3mm. thick. The cells lining the surface and glands are mostly columnar and contain a little glycogen. Most of the cells are mucus secreting. During the phase of endometrial proliferation the epithelial cells exhibit marked phosphatase activity, particularly at their free borders and in the cytoplasm apical to the nuclei. The secretions in the lumina contain much phosphatase. The spiral arteries during this phase increase in length. The adventitia is thick and the inner elastic lamina is better defined. Externally elastin fibrils are formed. Some of the spiral arteries may actually, on reaching the surface epithelium, continue in a course parallel to the surface. There is an increase and thickening of the venous stems and collagen and elastin can be demonstrated in their outer coat.

During the early secretory phase, the spiral arteries increase in length. Their terminal branches are coiled and their lower parts are even more so. The media has now become impregnated with elastin fibrils. The veins are even more distended than the arteries. The

larger venous stems dominate the picture. There is reduction of the glandular plexus and a number of sinus-like expansions may be found. The height of the endometrium has been considerably augmented and the stroma is oedematous at this stage. The phosphatase distribution in the surface and glandular epithelium remains unchanged during this phase.

In the late secretory phase, the stromal oedema is even more extensive. The coiling of the arteries decreases and they undergo degenerative changes. The intima and adventitia of the arteries are weak. The media contains only a few elastin tissue and have the appearance of being subject to a diffuse pre-hyalinisation. Some of the capillary endothelial cells appear to be swollen and exudation of fibrin is observed around the veins and capillary tubes. Infiltrations by numerous leucocytes and plenty of blood-extravasates are in evidence everywhere in the superficial layers. The venous lakes are still further developed and the venous stems are coiled in appearance. The walls of these stems are comparatively thick. Towards the end of the late secretory phase they begin to shrink. It has to be noted that by the late secretory phase there is a sharp reduction in the phosphatase content of both surface and glandular epithelium. It has also to be noted that from studies with mice uteri it has been found that the phosphatase in the endometrium is under control of steroid sex hormones (5). Atkinson and Engle (6) have stated that in the human female this enzyme system may play an active part in such hormone-regulated processes as endometrial growth and fat and glycogen metabolism. The assertion that alkaline phosphatase is associated with glycogen metabolism is denied by Hertig, and Gomori states that the relationship is not a strict one. Corner on the other hand, associates it with phospholipid and not with carbohydrate metabolism.

During menstruation in the desquamated parts of the endometrium the spiral arteries jut out from the lacerated surface but remain closed by a small clot. In the non-desquamative regions the arteries are less coiled. During menstruation the capillaries show extreme distension in the entire superficial region as well as in the adjacent parts of the spongy layer. Analogous features are exhibited by the venous plexus. Menstruation serves as a link in a chain of events necessary for reproduction and it permits of subsequent ovulation. The cause of menstruation according to Allen (8) is estrogen deprivation but this theory does not account for abnormal menstrual bleeding. Menstruation starts in the human female at about the age of twelve to fourteen years with a range of nine to eighteen years. Menstruation lasts for one to seven days; in over 90% of females it lasts from three to six days. The weight of the discharge is from 20 - 500gms.

Macht reported that circulatory blood, sweat and saliva at the time of menstruation contained a substance toxictoplant growth (9, 10). Smith and Smith demonstrated that menstrual blood contains a toxin which is derived from the secretory endometrium and is closely related with an atypical euglobulin (11). The toxin is similar to necrosin, which is obtained from pleural effusion in animals from irritation due to local turpentine infections (12, 13). It is produced possibly by a defective progesterone secretion and by other unknown factors. The toxin is believed to stimulate the pituitary, causing release of gonadotrophins and adrenotrophins. Un-extracted mentrual blood is lethal when injected into immature male rats. Fibrinolysin is found in pseudo-globulin fraction of menstrual discharge. The protective pseudo-globulin is present at catamenia to neutralise the menstrual toxin. It has been isolated from pleural and ascitic fluid of cancer patients. George Van S. Smith postulates that all the symptoms and signs associated with menstruation are due to activity of the menstrual toxin with possible exception of soreness and engorgement of breasts. According to the same authority the amount and duration of menstruation depends on the amount and rate of formation of the toxin and whether it is formed locally or diffusely (14). What mechanism is behind menstruation is a question which many have asked and only incompletely answered. Schlegel and Dalgard have found A-V passages in the human endometrium, an assertion denied by Bartelemez. Schlegel's theory of menstruation hinges mainly on the existence of these A - V anastomoses. Menstruation is preceeded by a sudden anaemic condition of the superficial endometrial tissue and this, according to Schlegel's theory may be ascribed to the opening of the numerous A - V channels at the pre-menstrual stage. Such an opening is said to be due to a substance of the Ach group. It has to be noted that in between the functional and basal parts of the endometrium are found nerves along the intensely-coiled first parts of the spiral arteries. In the endometrium the nerves are of the Ramak type. A periarterial nerve plexus has been found to extend from the myometrium and follow the spiral arteries for a distance up in the functional layer. When Ach conc. in the endometrium is high enough, it is postulated that the A - V channels open and result in a decreased blood flow combined with congestion peripherally. See figure back page. Markee (15) claims that the spiral arteries are not permanently differentiated from the straight ones and a certain amount of inter-conversion occurs. Before the onset of menstruation the spiral

arteries do not shorten while the endometrium is decreasing in thickness. The spiral arteries however at this time become much twisted and buckled. Markee has found that there is a time relation between the merosis of the endometrium and the stasis in the spiral arteries. It has also been found by Bartelemez (16, 17) that it is contraction in the spiral arteries found in the basalis or at the junction between the basalis and the myometrium that controls the amount of blood lost at menstruation. Markee attributes the cause of menstruation to the decrease in number of capillaries supplying blood to the stroma, to the decreased rate of flow in the capillaries and to the decrease in pressure in endometrial capillaries brought about by a fall in the blood level of estrogen and progresterone.

Cervix: Under the influence of estrogen the epithelium of the cervix tends to revert to the stratified squamous type and the glandular secretion increases and becomes highly alkaline. The mucus when dried on a clean slide crystallises in a fern-like pattern and can be stretched into threads. During the progesterone phase of the menstrual cycle the cervical mucus is less alkaline, more scanty and viscid in character. It also loses its fern-like pattern and the property of being easily stretched into threads.

Vagina: Vaginal smears present a characteristic appearance according to when the smear was obtained. If a post-menstrual smear is obtained and suitably stained, many cyanophilic cells with vesicular nuclei can be seen. The proportion of cells showing eosinophilic staining is high. The percentage of superficial cells with pyknotic nuclei is also high (karyopyknotic index). In three or four days before ovulation the percentage of large eosinophilic cells increases and this is followed by a rise in the karyopyknotic index. A smear taken just before ovulation shows squamous cells already separated from each other and most of the cells have a pyknotic nucleus. A post-ovulatory smear shows a decrease in the eosinophilic and karyopyknotic indices. The cells appear in clusters and show some curling. As the luteal phase approaches the cells become more cyanophilic and folded. The nuclei are nearly all pyknotic. Degenerative changes in cells can be seen and so the smear looks "dirty".

Fallopian Tube: During the proliferative phase there is a uniform growth of the columnar cells and the rate and amplitude of the peristaltic contractions gradually increase. During the secretory phase the tall columnar cells regress and the non-ciliated cells begin to secrete and their height becomes greater than those of the degenerating columnar cells. The rate and amplitude of the peristaltic waves gradually decrease.

Breast: Breast changes are dependent on the cyclic hormonal secretions of estrogen, which is chiefly responsible for the development of the ducts and progesterone which is chiefly responsible for the growth of the lobular alveoli. In the mid-period stage the ducts expand to form new ductules and the acini enlarge. During menstruation there is a round-cell infiltration of stroma, and regression of proliferating epithelial ducts. In the post-menstrual phase the stroma is compact and the round cells disappear and the acini are small.

Ovary: As all these changes in the breast, uterus, vagina etc. are taking place the ovary is also undergoing very important developmental changes. F.S.H. does not only cause follicular development but causes also the ovary to secrete estrogen. The estrogen affects the reproductive tract in a manner outlined above and the estrogen level reaches its highest after two weeks of secretion. By then its blood concentration is great enough to stimulate the pituitary to secrete L.H. This last hormone causes ovulation and is responsible for the corpus-luteum formation. The mechanism of ovulation is still unknown. Some workers claim that it is due to an increase in intrafollicular pressure, while others vouch enzyme theories for it. Neither of these theories can on its own merits account for ovulation. For example, it has been found that in fish, amphibia and certain mammals there is no accumulation of antral fluid and so the intra-follicular pressure mechanism in these cases obviously cannot operate. As to the enzyme theory it is very difficult to explain how the various enzymes cause a break in the follicular wall in a relatively small and circumscribed are comprising the stigma. Ovulation appears to be due to morphologic changes in the follicular wall brought about by gonadotrophic and other hormones. It has been found thanks to the splendid work of many research workers in this field, that in a majority of females with a menstrual cycle of length between twenty-four to thirty-four days, ovulation takes place between the tenth and the fourteenth day from the onset of menstruation. In a minority ovulation takes place between the eight and the seventeenth day after bleeding starts. Ovulation timing is a procedure of the greatest importance. It can be timed by plotting basal body temperature-curves for the whole length of the cycle. Ovulation is marked by a fall followed by an immediate rise in temperature. Other methods (18) for timing ovulation include the examination of vaginal smears, Lanis-rat ovary hyperemia test, fern test, Birnberg glucose-stick, fertility testor of Doyle and Ewers and pregnanediol essay. The explanation of each of these tests is quite beyond the scope of this article. Ovulation having

taken place, the corpus luteum which is then formed secretes progesterone for about two weeks.

The purpose of the menstrual cycle is to cause ovulation and at the same time ovulation must take place for the cycle to be normal. Still there is much to be known on this subject but, as has been seen, much progress has been made since the days when it was thought that the cycle was under the control of the moon.

BIBLIOGRAPHY

(1) Adair and Davis: Ann. Obst. and Gynaec. 27: 383, 1934.

(2) Hamilton W.F., Brewer G & Brotman I: Am. J. Physical. 107:427: 1934.

(3) Hamilton W.F., Woodbury R.A. & Harper H. T. Jr: J.A.M.A. 107:853: 1936

(4) Hasner: The Vascular Cycle of the Human Endometrium. 1946.

(5) Atkinson W.B. & Elftman M: Effect of Steroid Sex Hormones on distribution of Alkaline Phosphatase in Uterus of Mouse: Proc. Soc. Exper. Biol & Med 62: 148-150. 1946.

(6) Atkinson & Engle: Studies on Endometrial Alkaline Phosphatase during Human Menstrual Cycle and Hormone-treated Monkey: Endocrinology 40:327-333, 1947; 36:270-295, 1946.

(7) Advances in the Treatment of Menstrual Dysfunction. Edited by Goldfarb pp. 19-20.

(8) Allen E. Menstrual Cycle of Monkey, Macacus Rhesus; Observations on Normal Animals, effects of Removal of Ovaries and effects of injections of Ovarian and Placental Extracts into Spayed Animals, Contrib. Embryol. 19: 1-44. 1927.

(9) Macht D. I: Chemical Nature of Menstrual Toxin: Am. J. M. Sc. 206: 281-305 (Sept) 1943.

(10) Macht D. I: Chemical Nature of Menstrual Toxin: Am. J. Obst. & Gynaec. 57:251-260 (Feb) 1949.

(11) Smith O. W: Menstrual Toxin; I. Experimental Studies. Am. J. Obst. & Gynaec. 54:201-211 (Aug) 1947.

(12) Smith O. W. & Smith G. V: Evidence that Menstrual "Toxin" and sanine "Necrosin" are Identical. Proc. Coc. Exper. Biol & Med. 59, 116-119 (June) 1945.

(13) Studies in Isolation of Factor Responsible for Tissue Injury in Inflammation: Science, 97: 165, 1943.

(14) Smith G. V: Menstrual Toxin; II. Clinical Significance, Am. J. Obst. & Gynaec. 54: 212-218 (Aug) 1947.

(15) Markee: Menstruation in Intraocular Endometrial Transplants in Rhesus Monkey. Contrib. Embryol. 177:219, 1940.

(16) Bartelemez. G. W: Histological Studies on the Menstruating Mucus-membrane of Human Uterus Contrib. Embryo. 124: 141. 1933.

(17) Bartelemez G. W: Menstruation: Physiological Review 17: 28, 1937.

(18) Cohen, M. R. & Hankin M. Detecting Ovulation, Fertil. Steril. II: 497, 1960.