HISTOPATHOLOGICAL, ENZYMATIC AND GLYCOGEN CHANGES IN THE ENDOMETRIA OF WOMEN USERS OF CONTRACEPTIVE PILLS AND I.U.Ds.

THESIS

For M. Ch. (Obstetrics and Gynaecology)

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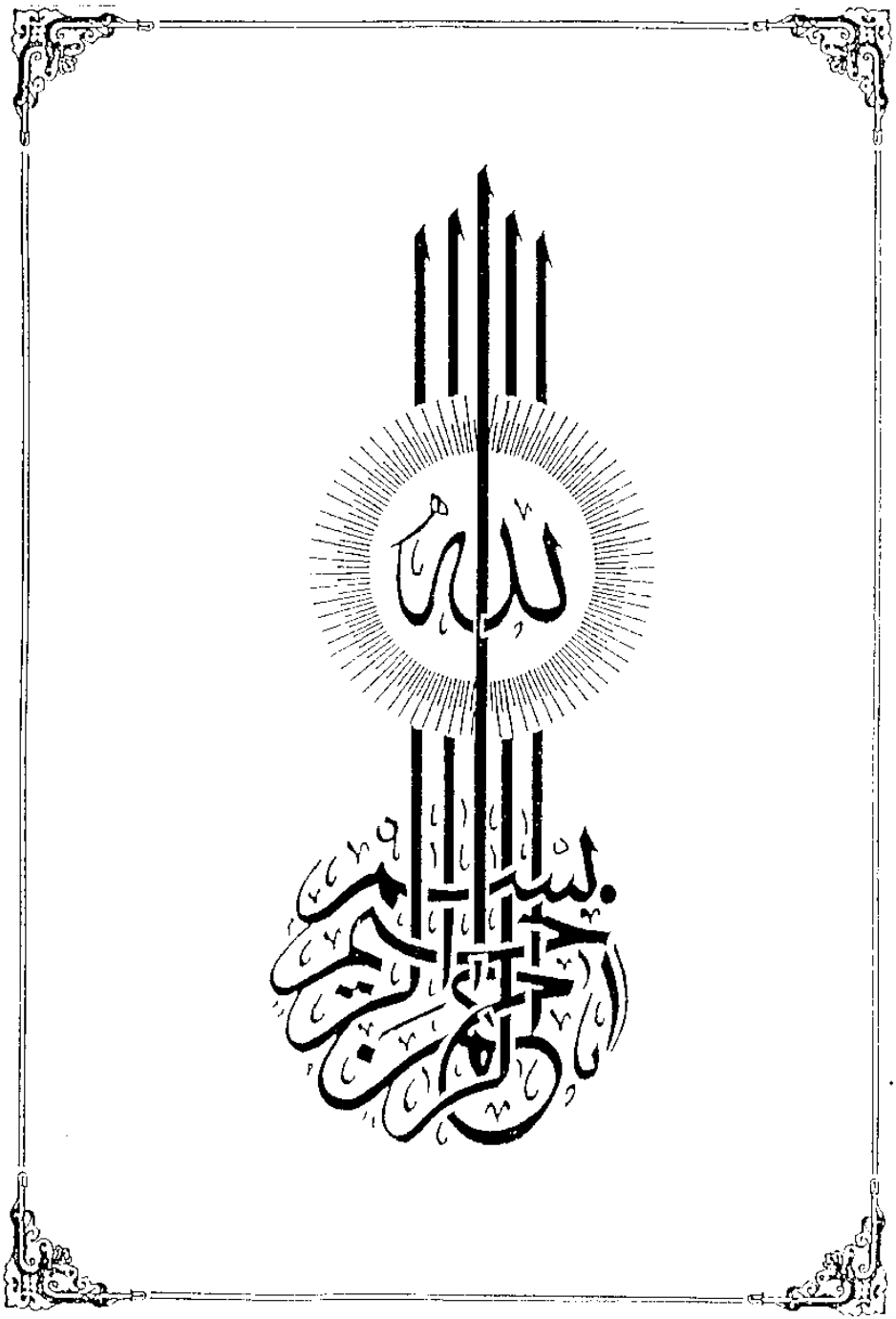

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INTRODUCTION

The dangers of population explosion are now universally recognised. In Egypt the annual birth rate is about 43/1000. The death rate had been reduced to 15/1000 due to reduction in infant mortality and increased longevity that resulted from improved health services. This means an increase rate of 28/1000 (2.8%), a high rate compared with that of 12/1000 or less in developed countries. This indicates the need of a family planning program, aiming to reduce the increase rate to 17/1000 in ten years.

In Egypt the family planning program have not achieved the expected results in spite of the great efforts including time and money spent. Better results would have been achieved if the contraceptives used were free from side effects. In this country, the use of the combined "Pills" and Intrauterine Contraceptive Device as the main contraceptive, has been faced with some difficulties, one of which is the many side effects like Bleeding, discharge, infection ... etc. The aim of the present work is to study the endometrial pattern in "pills" and IUCD users and compare it with the normal endometrium, to have the chance to get endometrial biopsies from women using hormonal contraception (IUCD)

and to follow these cases for 6 months and one year I worked in a big family planning centre in Zenhom aiming to find the histological, enzymatic and glycogen changes in the endometrium. In order to achieve this purpose I felt that a short outline of the histology of the endometrium with the changes in its arterioles and capillaries should be included in the literature together with the physiology of the menstrual cycle and the cyclic changes of alkaline phosphatase enzyme and glycogen in the endometrium. This is followed by a full account about the contraceptive pills and (IUCD) and their effect on the endometrium. One hundred and fourteen women studied and classified as follow:

- No. (40) IUCD
- No. (36) Pill users.
- No. (38) Control the findings are subjected to full analytical studies and the results are compared with those published in the literature.

HISTOLOGY OF THE ENDOMETRIUM

The endometrium is the uterine mucous membrane above the level of the internal os and below this is the endocervical epithelium. This sharp distinction is predicated on the remarkable ability of the endometrium to respond in cyclic fashion to the ovarian hormones with the resultant monthly phenomenon known as menstruation.

The endometrium is a specialized form of connective tissue characterized by a remarkable lability and sensitivity to the ovarian secretions and an amazing regenerative capacity towards restoration after a menstrual slough. The endometrium consists of a number of component parts, all responsive to the endocrine influence, and a knowledge of each of these is paramount to an ability to assess in accurate fashion the appropriate stage of the menstrual cycle. Most informative is the appearance of the endometrial glands with their lining epithelium. In the immediately post menstrual phase these glands are rather straight and tubular, but as the cycle progresses there is increasing convolution and tortuosity, especially when progesterone influence

is felt. Initially the lining epithelium is tall columnar, with a basal nucleus, but with beginning progesterone secretion the nucleus migrates towards the gland lumen producing a clear zone below it. This so called "subnuclear vacuole" is taken as the first evidence of ovulation; subsequently the gland lumen may contain increasing amounts of glycogen and mucin, which are detectable by special stains. With this secretory effect the epithelial cells become less distinct and exhibit a rather frayed and indistinct appearance. Much less helpful is the appearance of the epithelium lining the endometrial surface, although there is gradual increase in its height from a cuboidal to a "tall columnar" appearance. The stroma throughout the interval phase is composed of cells with little cytoplasm that feature a disproportionately large dark spindle or round nucleus. In the prevulatory phase the stroma area is rather dense and compact, but in the premenstrual phase there is increasing oedema and vascularity with actual hypertrophy of the cells. They become enlarged polyhydral and pale staining so that a true decidual reaction is suggested. This of course is an extreme response to progesterone, and it may occur in the absence of pregnancy. Obviously

chorionic ville of foetal origin, are pathognomonic of intrauterine pregnancy; a decidual reaction is merely suggestive, and may occur merely as an exaggeration of the normal progesterone response. If however fertilization has not taken place, transformation of the predicidual endometrium to actual decidual does not occur.

The endometrium may be divided into a superficial "Functional" zone consisting of an upper spongy zone below which is the so called compact area. Only this functional zone is responsive to a biphasic hormonal stimulus, and it alone participates in menstruation. The "non-functioning" basal layer is composed of young undifferentiated endometrium that has not achieved the capacity to full response to progesterone even in the premenstrual phase of the cycle, it shows only an estrogen effect, and it is not desquamated in toto at menstruation. Indeed it is from these basal buds that the endometrium grows and regenerates itself after menstrual bleeding. In fact regeneration of the surface endometrium begins before menstruation has completely ceased as a result of growth of this basal tissue.

In any case the teleological interpretation would be that every menstrual cycle is dedicated to getting the

endometrium into the best possible condition to maintain a fertilized egg in the event that this has occurred. The mucous surface of the endometrium is thick, vascular and contains abundant glycogen as a source of nutrition for any implanted conceptues. If however, pregnancy does not take place, menstruation occurs, and the whole process is repeated the next month. The foregoing then represents mearly a succinct sketch of the most important details of endometrial behaviour.

We believe that the classification of phases as originally suggested by Robert Meyer is still the most serviceable one, viz.:

1) Postmenstrual Phase:

This corresponds roughly to the week or so immediately following the cessation of a menstrual period. During this phase the endometrium is grossly quite thin, measuring usually only 1 or 2 mm in thickness. The surface epithelium is low and cuboidal, the glands are straight, with little or no tendency to convolution, and their epithelium is like that of the surface, with no suggestion of secretory activity. During the latter part of this phase, mitoses begin to be seen in the epithelial cells. The stroma is dense, compact, and nonvascular in appearance.

The immediately postmenstrual phase is sometimes spoken of as the rest phase, but it is questionable whether in the normally menstruating woman the endometrium is ever completely at rest. In women with abnormally long cycles, however, there may be virtual quiescence for a good many days, and this may be properly spoken of as a rest period.

2) The Interval Phase:

This stage, beginning approximately one week after menstruation and extending to about one week before the next period, is therefore about two weeks in duration. The growth activity already evident toward the end of the postmenstrual phase becomes more and more pronounced, so that the surface epithelium usually becomes taller and definitely columnar, while the glands become more and more hypertrophic, with gradual widening of the lumina and steadily increasing convolution. The gland epithelium in the earlier, preovulation phase of the interval (early interval phase) shows no trace of secretory activity, but later one finds the nuclei pushed toward the lumina of the glands as a result of the formation of the so-called subnuclear vacuoles, already spoken of. These are commonly interpreted as

representing the earliest evidence of ovulation in the human female.

Later in the interval (late interval phase) the secretory activity of the epithelium becomes increasingly marked, so that there is seldom any doubt as to this point on histologic examination alone. Where any doubt exists, demonstration of glycogen by differential staining will usually clear up the uncertainity. In the late stages of the interval, the glycogen granules will be found not only in the epithelium, but at times even in the lumina of the glands. The stroma in this stage is more abundant and somewhat more hyperemic than in the preceding phase.

3) Premenstrual (Progestational, Predecidual, or Secretory) Phase:

In this phase the mucosa is thick, soft, and velvety, measuring from 3 or 4 to 7 or 8 m.m. in thickness. It is usually of rather pale, edematous appearance. The surface epithelium remains quite tall and nonsecretory. The glands exhibit a steadily increasing tortuosity, the necks being often rather straight and nontortuous, but the middle sections presenting marked scalloping and

often a "saw-tooth" appearance on longitudinal section. On the other hand, the very tips of the glands immediately adjacent to and often dipping into the interstices of the muscle layer, commonly show little or no tortuousity. The basal layer varies much in thickness, sometimes being well marked, in other areas almost absent.

Corresponding to this stratum difference in gland outline, the gland epithelium likewise shows differences in secretory response at the different levels. In the middle, labyrinthine layer, corresponding to the greatest tortuosity of the glands, the epithelium is low and pale-staining, with a frayed-looking lumen edge suggesting a melting-down of the cytoplasm. The nuclei have receded toward the basement membrane. The spiral twisting of the glands produces on section small tuft-like eminences of epithelium with an appearance of stratification. On the other hand, the epithelium of the basal layer often shows no secretory response at all, presumably because the immature epithelium near the growing tips of the glands, while responding to the estrogenic growth hormone, is not capable of responding to progesterone.

The stroma is most abundant in the superficial layer, between the necks of the glands. Here the cells

show varying degrees of hypertrophy. Whereas, in the earlier stages of the cycle, there is almost no cytoplasm surrounding the nucleus, in the premenstrual phase a definite and sometimes rather broad cytoplasmic zone is often evident, giving a decidual-like appearance to the cells. In the middle zone, the stroma is much less abundant, forming narrow septa between the glands, while in the basal layers the decidual-like change is apt to be absent.

The above described differences in the histologic response at different levels of the endometrium have led very naturally to a division into three strata, viz.: compacta, spongiosa, and basalis. While these are usually well differentiable in the premenstrual phase they are then sharply marked off in the decidua of early pregnancy.

The progestational phase above described is a period during which blood before the onset of menstruation, when the catabolic changes produced by the new hormone of the corpus luteum begin to be expressed histologically. A rather massive infiltration of leukocytes occurs, chiefly polymuclear, but with many

mononuclear cells. The superficial layers take on a granular appearance, with poor staining and imperfect cell differentiation. These degenerative changes are indicative of the impending death of the superficial layers. It is important to recognize the normality of the immediately premenstrual pseudo-inflammatory infiltration, as otherwise this phase might be readily mistaken for a genuine endometritis.

4) Bleeding Phase:

That the endometrial surface is actually desquamated at menstruation is now universally accepted, though there was much difference of opinion on this point up to the work of Schroder in 1915, followed later by that of Novak and Pelinde (1924) and others. It is only by a systematic chronologic study of endometria removed on the various days of the cycle that the progress of these retrogressive changes can be demonstrated and traced. Even before desquamation begins, its imminence is indicated by the degenerative changes in the upper layers, as suggested by the poor staining and granular appearance of both the epithelial and stromal elements. An interesting feature of this immediately premenstrual phase is the rather massive infiltration of the endometrium with polymorphonuclear