ENDOMETRIAL PATTERNS IN CASES OF FEMALE INFERTILITY

Thesis

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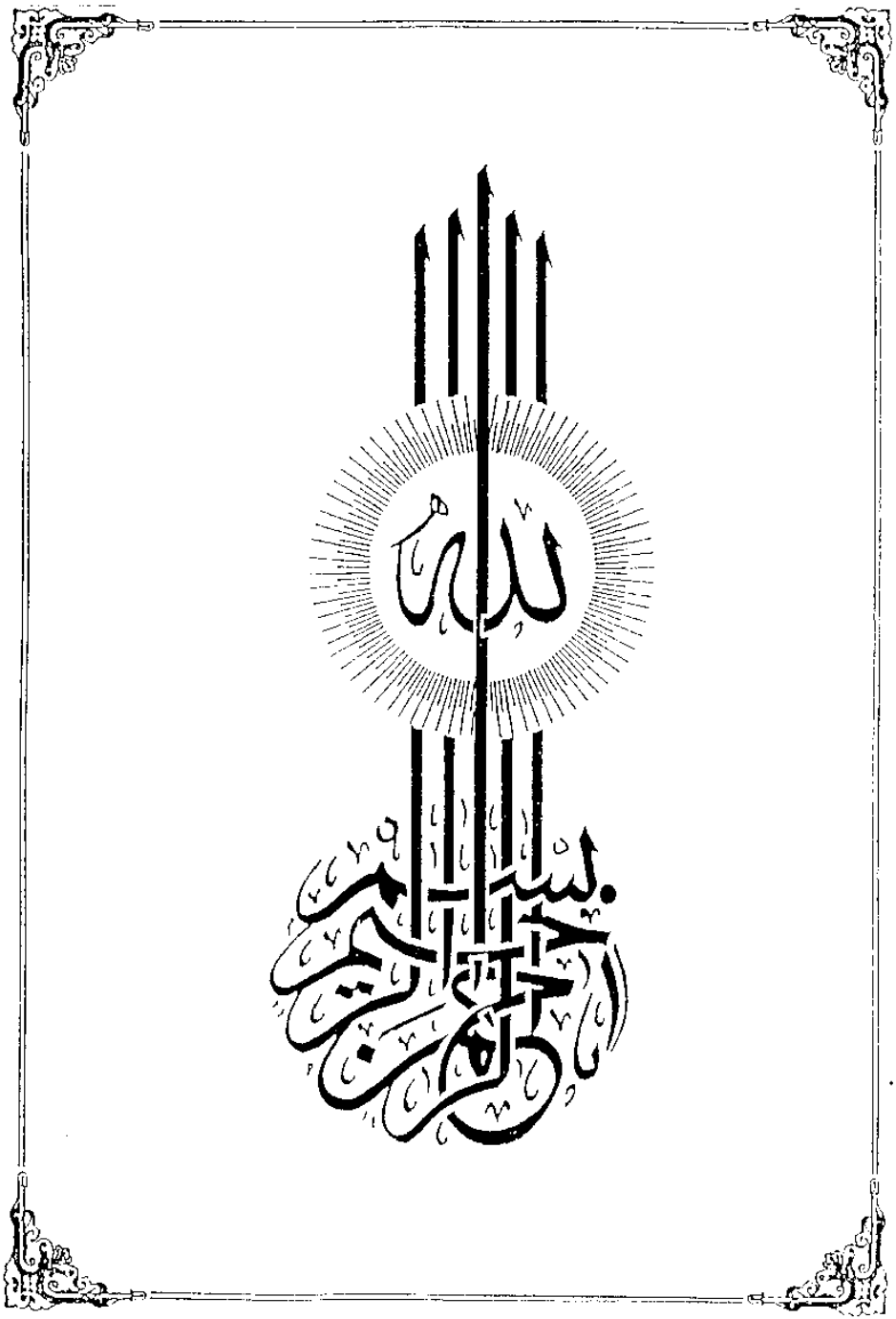

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INTRODUCTION

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When all the known causes of infertility in women are accounted for , there remains a residue in excess of 10% of subfertile or infertile women for whom there is no satisfactory explanation for their condition (Moghissi and Wallach , 1983) . It is not surprising therefore , that clinicians have importuned their histopathology colleagues, or taken steps themselves to look longer and harder at the endometrium, perhaps a reluctant or even inimical host to the blastocyst after a normal conception . Some have accepted the challenge and produced an impressive list of endometrial abnormalities associated with female infertility (Dallenbach-Hellweg ,1981a). Others , sceptical of the accuracy of assessment of endometrial morphology because of many uncontrollable factors, have questioned the relevance of such "para-abnormalities "(Robertson ,1981) .

Robertson (1984) , proposed the question that if the male and female partners are normal by current testable criteria, yet the union remains infertile, can the endometrium be blameless in all such circumstances ? He mentioned the fact that the loss of fertilized ova in the first two weeks of gestation probably exceeds 50% , usually attributed to failure of implantation . In a recent communication , Whittaker et al. (1983), said that 8% of such a loss was

detected in normal healthy women by assessment of plasma hCG levels during ovulatory cycles. Clearly , this finding must represent the tip of an iceberg , as it depends upon the early conceptus having developed to the stage of producing assayable levels of hCG. Making allowance for an approximate 30% incidence of abnormal conceptuses in this loss (Hertig et al., 1959) , it would seem that the endometrium must shoulder the blame for the rejection of an unknown percentage of the remainder .

On the other hand , if one considers the many prerequisites for the union of sperm with oocyte , the timed transport of the resultant zygote, morula and blastocyst to the uterine cavity and its secure nidation in the prepared endometrium , one may ask if the endometrium is not too often identified as the culprit. Perhaps the best argument against defective endometrium being a significant cause of infertility is the occurence of ectopic pregnancy. It is clear that the tubal mucosa for example , differing markedly from the uterine mucosa, is an acceptable milieu to the blastocyst , at least on occaisons. Therefore , it is difficult to accept that minor or even major deviations from the normal in the endometrium should be hostile to the blastocyst (Robertson ,1984) .

Robertson (1984) , concluded that most causes of infertility have little to do directly with endometrial

abnormalities. This does not mean , however , that an endometrial biopsy or curettage specimen has no place in the investigation of the infertile woman . It can be used as an adjunct to the monitoring of the efficacy of treatment for ovulatory failure and in the confirmation and typing of endometrial hyperplasia in the woman with persistent anovulatory cycles. It is virtually indispensable for the diagnosis of genital tuberculosis and as a means of culturing the Mycobacterium for antibiotic sensitivity testing. While there are better methods now available, such as laparoscopy, for the diagnosis of pelvic inflammatory disease , the finding of unsuspected endometritis in the infertile women can be used as an indicator of low-grade chronic genital tract infection that may not be otherwise apparent . There would seem to be no need for routine investigation of the endometrium in women afflicted with endometriosis or tubal disorders. The most controversial use of endometrial biopsy as an investigational technique is in the diagnosis of luteal deficiency and related disorders. If it is to be used in this circumstance , then it is essential that there should be the closest possible consultation between the clinician and the pathologist. It is too early yet to declare the endometrium always blameless in reproductive failure but there is little hope that purely morphological studies , even at the ultrostructural level , will supply answers to the unresolved questions . The investigation

of the complex biochemistry and biology of the endometrium is still very much in the developmental stage. Pathologists interested in reproductive biology must be prepared to adapt and to devise new techniques based on biochemical discoveries to supplement their traditional morphological assessment of this important and fascinating tissue .

REVIEW OF LITERATURE

CHAPTER I

THE NORMAL ENDOMETRIUM IN THE REPRODUCTIVE PERIOD OF LIFE

The endometrium of the corpus uteri is composed of two layers : the basalis, from which the endometrium regenerates after menstrual shedding , and the overlying functionalis which responds to circulating hormones . In the second half of the menstrual cycle , the functionalis is differentiated into the superficial compacta and the underlying spongiosa. During the menstrual cycle the endometrium varies in thickness from 1 mm postmenstrual to about 8 mm at the end of the third week . Every layer consists of two major components : the epithelial component, either as glands or as superficial epithelium, and the mesenchymal component of stromal cells with pluripotential properties (Dallenbach-Hellweg, 1981b) .

A) The individual structures :

(1) The glandular epithelium :

This is a single layer of columnar epithelial cells, the height of which varies from 6 μ postmenstrual to 20 μ at the end of the proliferative phase .

The nuclei of the glandular cells during the proliferative

phase are elongated and have dense chromatin. Between the tenth and sixteenth day of the cycle their content of deoxyribonucleic acid (DNA)reaches its maximum. During the secretory phase the nuclei become round , vesicular and gradually lose DNA . Mitoses are most frequent just before ovulation (Nordqvist ,1970) . By electronmicroscopy (E.M.) the nuclear membrane contains multiple convolutions , the chromatin is relatively more coarsely aggregated along the nuclear envelope as well as in the nucleoplasm. This is consistent with the cessation of mitoses and the production of specialized proteins and secretory products (Demopoulos, 1982) . Just prior to the onset of menstruation , nuclear debris often appears at the base of the endometrial glands. This debris consists of fragmented bits of nuclear chromatin, often sequestered in vacuoles beneath the nucleus of the endometrial lining cell. The origin of this nuclear debris is not clear. It resembles degenerating polymorphnuclear leucocytes ; however intact leucocytes are not usually seen in this location (Demopoulos ,1982).

Johannisson and Hagenfeldt (1971) , found an accumulation of nuclei in the S-phase between cycle days 14 and 22 and suggested that DNA synthesis in the human endometrium is synchronized .

The nucleoli of the early proliferative phase are finely granular and compact. They enlarge as midcycle

is approached. In the first week of the secretory phase the nucleoli contain a characteristic tubular or meshwork-like structure , the nucleolar channel system, which is believed to serve the exchange of substance between the nucleolus and cytoplasm (Clyman ,1963 ; Ancla and DeBrux, 1965) . Kohern et al. (1970), stated that the appearance of this structure is dependant on adequate level of progesterone. Nakao et al. (1971), induced it experimentally by gestogen administration.

Gross (1964) , confirmed the previous observation that cellular ribonucleic acid (RNA) is increased in the proliferative phase and diminished in the progestational phase (McKay et al., 1956; Boutselis et al., 1963).

Wynn and Harris (1967) , indicated that the cytoplasm, especially in the basal part of the cells , contains abundant ribosomes , some are free and some are bound to endoplasmic reticulum. With the onset of the secretory phase the previously rough endoplasmic reticulum becomes smooth (Wynn and Woolley ,1967).

At the time of ovulation a distinctive ultrastructural feature involving the mitochondria is seen. A small proportion of them in almost all epithelial cells enlarge and become giant mitochondria. This is caused by a true

increase in the amount of material that comprises the outer and inner membranes and the number of cristae (Armstrong et al., 1973).

The apical surface of the epithelial cells in the proliferative phase has elongated delicate microvilli which contain alkaline phosphatase. During the secretory phase these microvilli draw back and disappear and the activity of alkaline phosphatase diminishes. The epithelial cells expel their products by apocrine secretion (Borell et al., 1959).

The substance secreted by the glandular epithelial cells varies with the phase of the menstrual cycle . Johannisson and Hagenfeldt (1971) , found minute amounts of glycogen in the glandular cells by the electron microscope several days before ovulation ; the maximum amount occured between the sixteenth and twentieth days. The secretion found in the glandular lumen in the proliferative phase consists of a mixture of desquamated glandular cells, RNA, proteins and acid mucopolysaccharides. During the secretory phase the secretion appears as globules that contain glycogen , acid and neutral mucopolysaccharides, proteins , peptides , neutral lipids , phosphatides and numerous enzymes (Salm ,1962).

Occasionally , ciliated cells are found among the glandular epithelial cells. Their number varies , probably depending on the functional state of the endometrium. In atrophic endometrium they are virtually non existent and it could be assumed that oestrogen stimulates the cilia to develop (Schüller 1968 , 1973). In a case report on Kartagener syndrome , Pederson (1983), speculated that the absence of dynein arms in endometrial cilia could be a cause of infertility. This still awaits final answer.

(2) The superficial epithelium :

During the proliferative phase it closely resembles the glandular epithelium , although it contains greater numbers of ciliated cells than does the glandular epithelium (Ferenczy et al.,1972). Ciliated cells are most numerous during the middle and late proliferative and early secretory phases , when they may account for 20% or more of the epithelial cells , according to Fleming et al. (1968) . At the onset of the secretory phase, the superficial epithelium lacks the apical accumulation of acid mucopoly-saccharides and neutral mucopolysaccharides are very sparse. Yet , glycogen appears in the superficial epithelium earlier, in larger amounts, and remains longer than it does in the glandular epithelium. Its activity of acid phosphatase is lower than in the glandular epithelium but its content of phosphatides is higher. Noteworthy is the uniformly high