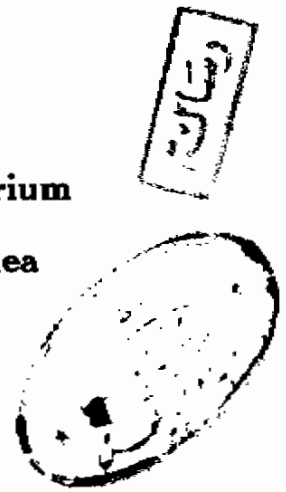
Histological Study of the Endometrium in Cases of Secondary Amenorrhea



THESIS SUBMITTED

FOR PRACTICAL FULLFILMENT

FOR THE DEGREE OF

MASTER OF GYNAECOLOGY & OBSTETRIC

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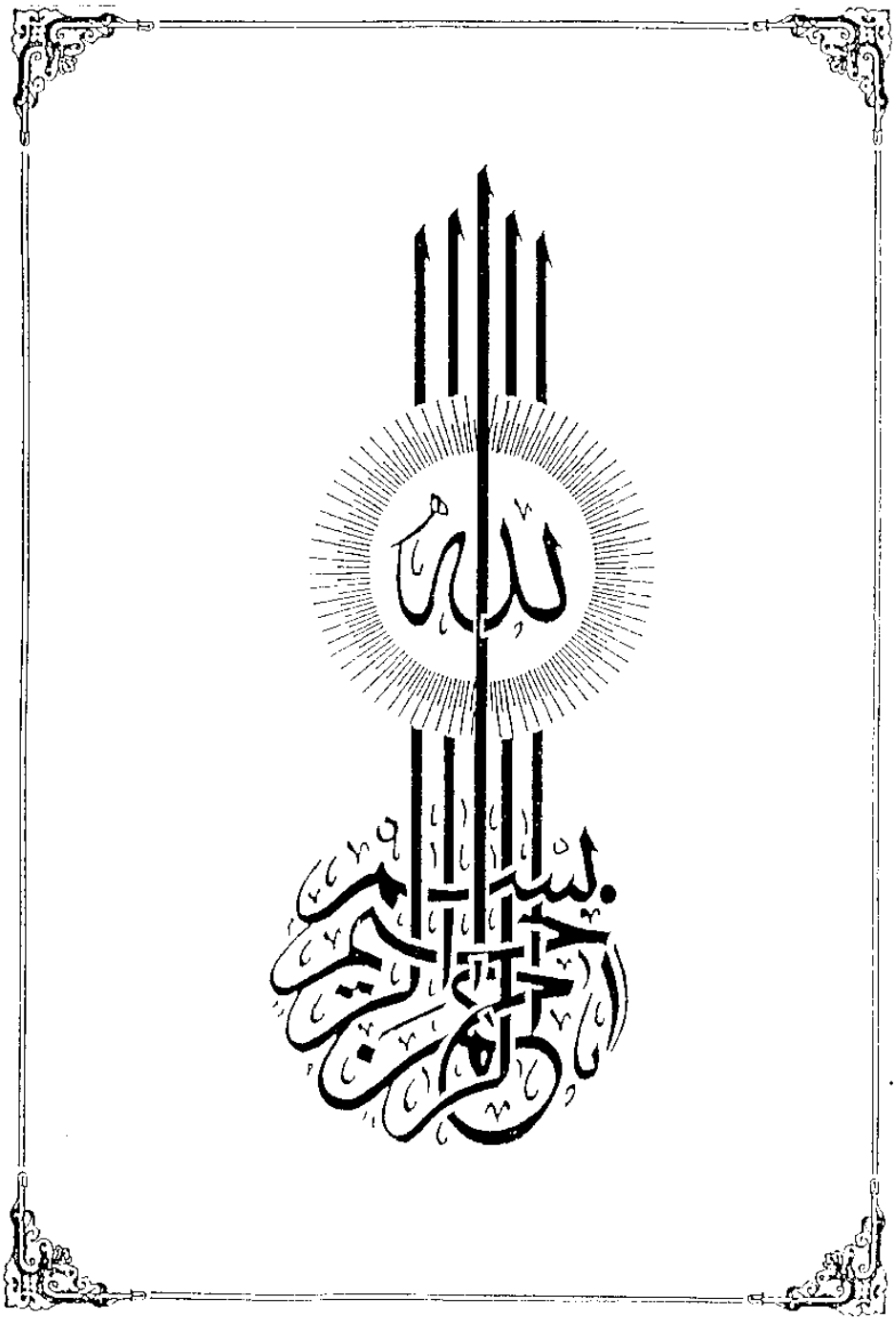
1982

Acknowledgment

I wish to express my deep gratitude to professor Dr. Mohamed Farouk Fikry for his valuable advice and guidence. He gave me generously of his time, help and encouragement throughout the period of this work.

I am also grateful to Assistant Professor Dr. Abd El Kader Saad El Din.

I am also deeply indebted to Dr. Ahmed Abd El Halim El Tawil lecturer of pathology for his kind help.



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INTRODUCTION

Amenorrhea is a symptom and not a disease. It may occur in a variety of disorders especially in the endometrium. It should demande our attention because of its association with infertility and emotional hazards. Menstruation is the result of a complicated sequence of endocrine events, the prime mover of which is the pituitary gland which starts this sequence, although menstruation depends on the proper function of a chain made up of the hypothalamus - anterior pituitary - ovary and the uterus, amenorrhea occurs due to breakage in one or more of these links.

NORMAL ENDOMETRIUM

The endometrium is the mucous membrane that lines the uterine cavity above the level of internal os. It is composed of surface epithelium, endometrial glands and stroma which is penetrated by blood vessels and lymphatics. The endometrium is fairly bound to the myometrium without an intervening submucosa. Teacher (1935), and Hertig (1946), mentioned that the thickness of the endometrium varies according to the part to which it belongs. It is usually thickest towards the middle of the anterior and posterior walls. It is thinner at the fundus and edges of the cavity and becomes to a very thin layer at the internal os.

Normal Components:

The histological interpretation of endometrial tissue demands careful assessment of three components epithelium, cytogenic stroma and blood vessels.

1- Surface Epithelium:

Continuous with that of the glands and responds in similar manner but to a lesser degree. It is basically columnar although varying in hight, ciliated areas are often seen particularly in hyperplasia.

2- Stroma:

Specialized mesenchyme where cells are oval, stellate or spindled and separated by fluctuating amounts of ground substance.

Mast cells are found in the stroma during reparative phase and early proliferative, as well as during the late secretary phase. Lymphocytes are normal finding in the stroma in the late secretary phase. Lymphoid follicles without other stigmata of inflammation may be found deep inthe endometrium.

3- Blood Supply:

The deep part of endometrium is supplied by short horizontal basal arteries from the underlying myometrial radial arteries. The inner part of the endometrium is supplied by sensitive coiled arteries.

Reactive Zones:

1- Zona basalis:

Thin strip of unripe endometrium resting on the myometrium. It responds to ovarian hormones particularly progesterone incompletely. The stroma is compact and stains darkly, the glands are irregular in shape.

2- Zona Spongiosa:

The glands are predominant, stroma is less prominent, loose and vascular.

3- Zona Compacta:

Consisting of compact stroma surrounding the necks of the glands. It is best recognized as a zone in the late luteal phase and early stages of pregnancy.

Zona compacta and most of the zona spongiosa respond in a cyclic fashion to ovarian hormonal stimulation and thus referred to as a functional zone. In menstruation all of the zona compacta and varying amount of the zona spongiosa are shed.

ENDOMETRIAL PHASES

According to the classic description of Noyes et al (1950), the normal cycle for diagnostic purposes is considered to be 28 days with ovulation occuring on or about the 14th day. However, there is considerable variation in response in different women and even in different cycles in the same women.

We recognize three phases to the normal cycle:

1- A menstrual phase which includes early repair.
2- A follicular phase or proliferative phase.
3- A luteal or secretory phase.

1) Menstrual phase:

When fertilization and implantation fail to take place a series of vascular and retrogressive changes occur in the endometrium and lead to menstruation. This phase occupies the first four days of the menstrual cycle, during which most of the functioning endometrium is shed.

Repair of the endometrium occurs immediatly, preceding in some areas while menstruation continues in others. The menstrual endometrium is characterized by shrinkage of epithelium and stroma, fragmentation, haemorrhage and varying degrees of leucocytic infiltration.

2) Proliferative phase:

This phase is governed by maturating ovarian follicles that produce oestrogen. Three subphases represented by early, mid and late proliferative endometrium can usually be recognized. Early endometrium is thin with sparse narrow and straight tubular glands and limited stroma formed by stellate and spindled cells with prominant nuclei. Division figures are infrequent, blood vessels are inconspicuous. As the cycle progresses there is a thickening of endometrium due to proliferation of

both glands and stroma. Division figures are found in both elements. The glands are larger, gently curved and the epithelial cells are columnar. Although the stroma is increased in amount, the cells have little cytoplasm and nuclei are prominent. Intercellular oedema or ground substance is generally increased.

In the late proliferative phase there is a further dilatation and tortuosity of the glands of the functional zone. With pseudostratification and sometimes prominent luminal folding of epithelial cells. Mitotic activity reaches its peak in both epithelial and stromal cells in this phase. The stroma is compact and the ground substance is reduced from the mid phase. Just prior or at the time of ovulation there is often hyperaemia of the stroma and sometimes a few haemorrhages with slight ovulatory bleeding for one or two days.

3) Luteal Phase:

The changes that are indicative of this phase appear 24-48 hours after ovulation. They are the result of the influence of progesterone from the corpus luteum on a properly primed endometrium.

Some workers believe that it is possible on endometrial biopsy to state the day of the cycle with fair accuracy. However, others are less confident of either their ability or that of the endometrium to act as a calendar and are content to recognize three subdivisions. These subdivisions are, the early luteal phase characterized by subnuclear vaculation. The mid luteal phase with stromal oedema and luminal secretions, predominate. The late luteal phase in which the decidual cells take on decidual character and the glandular epithelium is exhausted.

The development of sharply defined secretory vacules beneath the nuclei in the epithelial cells of the functional zone heralds the luteal phase and is an indication that ovulation has occured. At the same time there is increased dilatation and tortuosity of the glands. The stroma is compact and division figures are infrequent.

The subnuclear vacules persist approximately for three days, then pass around the nuclei to be discharged into the gland lumina. This is the mid-secretory phase. There is marked convolution of the dilated glands, so that knuckles of epithelium project into the lumen of the glands producing a

saw - toothed appearance. As the secretory vacules are discharged from the epithelial cells their inner margins are disrupted and frayed. The luminal secretions are abundant and pale pink. There is often a prominent increase in ground substance, so that the stroma seems oedematous. The spiral arteries are increased in prominence and appear as coiled clusters between the glands high in the zona compacta.

The glands of the late secretory phase are dilated, convaluted and lined by a low frayed epithelium that suggests secretory exhausion. The secretory coagulum in the gland lumina is retracted, inspissated and more deeply stained. Division figures are uncommon.

The main changes occur in the stromal cells. The cells beneath the surface epithelium and about the spiral arteries are now plump, with concid**erable** pale cytoplasm and resemble decidual cells. This predecidual change is at first patchy but soon forms a definite compact zone between the necks of the glands. A similar change but to a lesser extent occurs in the stratum spongiosum. The spiral arteries are very prominent with thick walls.

Small mononuclear cells, lymphocytes and neutrophils gather in the stroma near the end of this phase.

Just before menstruction the endometrium seems to shrink possibly because of constriction of the spiral arteries. Areas of degeneration and necrosis appear, followed by vascular dilatation, focal haemorrhage and finally fragmentation of the endometrium as it is cast off in menstruction initiating a new cycle.

Anovulatory Endometrium

Speroff et al (1978), mentioned that anovulation is a very common problem which presents itself in a variety of clinical manifestations, ranging from amenorrhea to irregular menses and hirsutism. Serious consequences of chronic anovulation include infertility and a greater risk for developing carcinoma of the endometrium and the breast. Normal ovulation requires coordination of the menstrual system at all levels: The central hypothalamic-pituitary axis, the feed-back signals, and the local responses within the ovary. The loss of ovulation may be due to any one of a variety of factors operating at each of these levels. The end result is a dysfunctional anovulation. Novak and Woodruff (1979), stated that normal menstrual periods in amount and rhythm may at times occur without ovulation. Frequently, however, there are disorders in duration, interval, and amount of bleeding. This was pointed out by Corner (1941), who suggested that the anovulatory type of cycle seen so often in monkeys might perhaps be at times encountered in human females. Opposed as this was to the then existing theory of menstruation, according to which ovulation is an absolutely essential part of the menstrual cycle. The correctness

of Corner's view has now been fully established. This is not the place to review all the evidence now available. Endometrial biopsy, when employed at the very onset of menstrual flow, has in many instances revealed an endometrium that shows not the slightest evidence of secretory changes commonly accepted as the criterion of corpus luteum activity and therefore of ovulation. It would be unsafe to give an estimate to the frequently anovulatory cycles in women. The majority of menstrual cycles are ovulatory. As a matter of fact, the problem has been studied chiefly in the relatively small group of women in whom a search is being made for the cause of existing sterility. Even, in this group widely differing figures regarding the incidence of anovulatory cycles have been reported. Anovulation can occur also in fertile women, in young girls or perimenopausal women. The recent widespread usage of basal temperature charts would suggest that certain women on occasions fail to ovulate alghough their general pattern is ovulatory. The menstrual phenomena with the anovulatory cycles are due to the functional activity of the follicle alone, instead of the sequential action of follicle and corpus luteum that characterizes the common biphasic type of cycle.