THE HISTOPATHOLOGY OF THE CORPUS UTERI IN ASSOCIATION WITH CYSTIC OVARIAN LESIONS

THESIS

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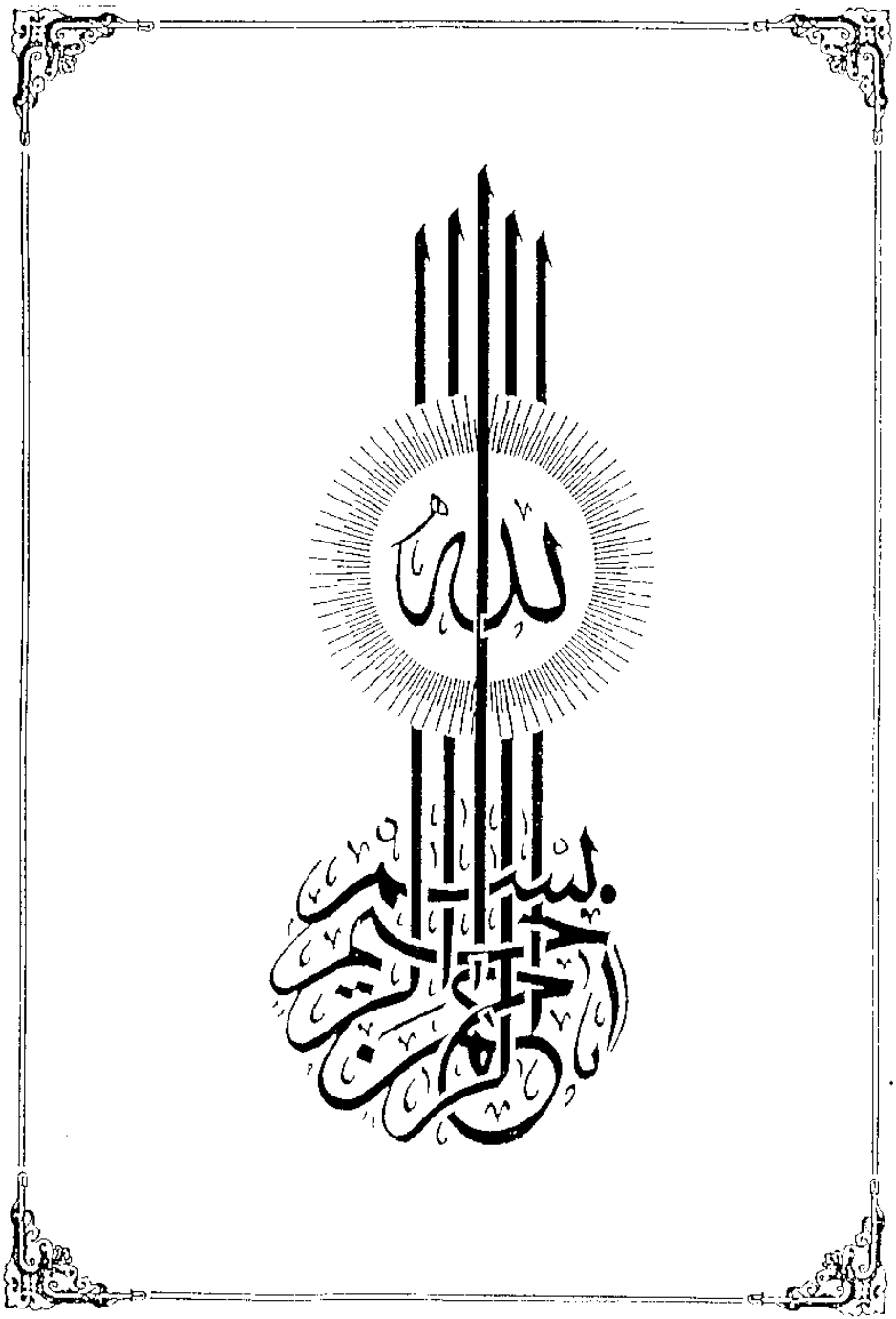

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INTRODUCTION AND AIM OF THE WORK

The female genital tract works as an organized unit. The ovary, as an endocrine gland gives hormonal orders to different target tissues including the body of the uterus (Ganong, 1983). Thus it is expected that ovarian pathology might reflect an abnormal hormonal function and this could probably have a role in pathogenesis of different uterine lesions. It is not uncommon in clinical practice particularly in females above the age of 40 to remove their uterus as well as adenxae for a primary disease in either of them. Among the commonest ovarian lesions seen in hysterectomy specimens are cysts of the ovary either neoplastic or non-neoplastic. These latter could be associated with ovarian morphological changes reflecting the abnormal function (Fechner and Kaufman, 1974).

The aim of this work is to study both endometrial and myometrial pathology in association with neoplastic and non-neoplastic cysts of the ovary to record the association between the ovarian and uterine pathology.

DEVELOPMENT OF THE OVARY

Ham and Cormack (1979) explained that the ovaries develop from the gonadal or genital ridges, which bulge from the surface of the intraembryonic coelomic cavity. The two ridges are located one on either sides of the midline of the embryo between the dorsal mesentery and mesonephros. Eventually the two ridges evolves into the two almond-shaped bodies that are present later in life.

First, the mesodermal cells at the surface of the developing ovary differentiate into a layer of epithelial cells to form a covering for the ovary. Second, cords of cells (called the sex cords) that have an epithelial appearance appear beneath the covering epithelium and among the stromal cells. Third, primordial germ cells make their appearance in the cortex of the ovary along with the cells of the cords. Each primordial germ cell surrounded by a layer of epithelial cells is called a follicle. The primordial germ cells do not develop in the ovary. They probably develop in the endoderm of the yolk sac, from which they migrate to the developing ovary where they are called oogonia. Early in the development of the ovary, Ham and Cormack (1979), suggested that the germ cells increase greatly in number. However, most of them die and by the time of birth, there are only around two millions in the two ovaries. This number is further reduced in postnatal life so that at puberty a few hundred thousand from which only one will develop and be lost

from the surface of the ovary every 28 days as a result of ovulation.

HISTOLOGY OF THE NORMAL HUMAN OVARY

The ovary consists of a cortex and medulla. The surface of the cortex is covered with a single layer of epithelium. In young women this is cuboidal, but later in life it becomes flattened, though it remains cuboidal in the surface pits and cervices (Ham and Cormack, 1979).

The connective tissue substance of the cortex is called its stroma. It consists of spindle shaped cells and intercellular substance. Most of the stroma of the cortex contains a high proportion of cells to intercellular substance; hence it appears heavily nucleated. Moreover, the bundles of cells and fibres run in various directions showing a swirly appearance. The fibre bundles and cells beneath the surface epithelium are both arranged more or less parallel to the surface. The special layer is called the tunica albuginea, and the white appearance that its name suggests is due to its great content of intercellular substance and lack of vascularity (Ham and Cormack, 1979).

The medulla is small as compared to the cortex, and its connective tissue is loosely arranged. It contains more elastic fibres, some smooth muscle cells, spiral arteries and extensive convolutions of veins. Small blood vessels extend from the medulla into the cortex (Ham and Cormack, 1979).

The ovarian follicles are embedded in the stroma of the cortex mainly in the periphery, immediately beneath the tunica albuginea. Three types can be distinguished: primordial follicles, growing follicles, and mature or Graafian follicles.

A- Primordial follicles: The primordial follicles are the principle ones present before birth. Each consists of a primary oocyte enveloped by only one layer of flattened follicular cells (Jangueira and Carneiro, 1980).

B- Growing follicles: The earliest sign of the development of a follicle is given by the follicular cells. As the oocyte grows, the single layer of follicular cells becomes cuboidal and then, through mitotic division, increases into a stratified epithelium forming the granulosa cells. The oocyte also becomes large and an acidophilic, acellular layer -the zona pellucida- appears around it. The latter contains a PAS positive glycoprotein substance. While these modifications are taking place, the stroma immediately around the follicle modifies itself in order to form the theca folliculi. This layer subsequently differentiates

into the theca interna and theca externa (Janqueira and Carneiro, 1980).

The theca interna which is the inner layer, is composed of large spindle shaped, cuboidal or polyhedral cells with oval or elliptical nuclei and fine lipid droplets in their cytoplasm. They are enmeshed in a network of reticular fibres that are continuous with those of the theca externa and the rest of ovarian stroma. Like all organs of endocrine function, the theca interna is richly vascularized. Small blood vessels penetrate the theca externa and supply a rich capillary plexus in the secretory cells of the theca interna. In the granulosa cell layer there are no blood vessels during the stage of follicular growth. The theca externa consists of concentrically arranged fibres and fusiform cells that do not appear to have any secretory function. The line of demarcation between the two thecas is not usually very distinct, and the same is true of the boundary between the theca externa and the ovarian stroma. The boundary between the theca interna ad the granulosa layer is well defined and separated by thick lamina (Bloom and Fawcett, 1975 and Janqueira and Carneiro, 1980).

As the follicle grows, mainly because of the increase in number and size of the granulosa cells, fluid begins to accumulate in little pools between them. Later the little pools fuse with each other and forms a central pool of fluid rich in hyaluronic acid called follicular antrum. The cells of the

granulosa cells are more numerous at a certain point on the follicular wall, forming a dense cell mass, the cumulus oophorus, which contains the oocyte. The cumulus oophorus projects into the interior of the antrum rendering the latter not spherical in shape (Ham and Cormack, 1979).

C- Mature follicles (Graafian follicle): In the human, follicles require 10 to 14 days from the beginning of the cycle to reach maturity. As a result of the accumulation of liquid, the follicular cavity increases greatly and oocyte adheres to the wall of the follicle through a pedicle formed of granulosa cells. Since the granulosa cells do not multiply in proportion to the accumulation of liquid, the granulosa layer becomes thinner. The granulosa cells forming the first layer around the oocyte, and therefore in close contact with the zona pellucida become elongated and form the corona radiata, which accompanies the oocyte when it leaves the ovary (Janqueira and Carneiro, 1980).

*Corpus Luteum:

It is formed from the active Graafian follicle at the time of ovulation. The cells of the plicated granulosa layer and those of the theca interna enlarge, accumulate liquid and are transformed into pale-staining polygonal cells the lutein cells. Those derived from the granulosa cells are called granulosa lutein cells and those at the periphery, originating from the

cells of the theca interna, are smaller and more deeply stained and are called theca lutein cells (Bloom and Fawcett, 1975).

Grossly, it is characterised by a yellow colour due to carotene pigment and may be solid or cystic. The corpus luteum passes through different phases. At the stage of proliferation, it has the appearance of a collapsed follicle. The granulosa layer is not yet luteinized and the theca is markedly hyperplastic. The mitotic figures are still present. This stage lasts not over 24 hours. Within the 48 hours post ovulatory period, the membrana granulosa is penetrated by vascular channels arising from the vessels of the theca. Luteinization of the granulosa is beginning and is marked by an abundant acidophilic cytoplasm. The mitotic figures are decreased. The theca, formerly markedly luteinised is now less prominent and forms trabeculae with blood vessels and fibrous tissue. At the mature phase, 7-10 days after ovulation, the corpus luteum presents the characteristic convoluted appearance with a completely organised fibrous center. Several days prior to the onset of menstruation the retrogressive phase begins. There is increased lipid content in the granulosa lutein cells and increased fibrosis of the paralutein cells. The cells gradually become hyalinised. Over a period of months, the corpus luteum becomes a fibrous scar known as corpus albicans. If pregnancy occurs, the corpus luteum, instead of regressing, persists and is characterized by the prominent vascularisation around it and an increase amount of cytoplasm in the granulosa lutein cells (Jones and Wentz, 1976).

Follicular atresia:

Most ovarian follicles become atretic (about 99%) due to a degenerative process characterised by cessation of mitosis in the granulosa cells, separation of granulosa cells from the basal lamina and death of the oocyte. This process begins in intrauterine life, becomes prominent at birth and continues on a smaller scale throughout reproductive life. The process of atresia may take place during any stage in the development of a follicle. When atresia starts in a primordial follicle, the follicular cells become smaller and separated from one another. The oocyte and follicular cells start to autolyse and their space is occupied by cells of the ovarian stroma. In growing follicle, the same occurs. The zona pellucida becomes wavy and its material persists longer than the cells of the follicle. When a follicle in the late stage of growth undergoes atresia, large quantity of degenerative material is produced which elicits the formation of macrophage from monocytes carried in the blood by vessels that invade the area of atresia. While removal of the remnants of the follicle in atresia takes place, cells of the ovarian connective tissue that invade the area produce a small amount of collagenous matrix which later is reabsorbed and replaced by the ovarian stroma, but the theca cells persist as part of the ovarian stroma. These theca cells are active steroid-secretors and are called interstitial cells and actually constitute the interstitial glands which may be the source of ovarian testosterone (Janqueiro and Carneiro, 1980).

PHYSIOLOGY OF THE OVARY

The ovary secretes three general classes of steroid hormones: oestrogens, androgens and progestins. It achieves its hormonal secretion via functional subunits that must be considered as a heterogenous tissue with three separate but related steroid secreting organelles. These functional subunits are the follicle, the corpus luteum, and the stroma. Any of these ovarian compartments can synthesize oestrogens, progesterone, and androgens in the same way, although the follicle is specialized in oestrogens, the corpus luteum in progesterone (and oestrogen), and the stroma in androgen (Ryan, 1977).

All steroid hormones have a common carbon ring structure (cyclopentanophenanthrene ring) and the fundamental differences in the three steroids are in the number of carbon atoms present and substituents attached (Ryan, 1977).

1) Oestrogens:

The most potent natural oestrogen and the primary ovarian secretory product is 17-β-oestradiol. Oestrone is second in potency and oestriol is relatively weak. Oestriol is considered to be a metabolic product of the other oestrogens. There are two peaks of secretion of oestrogens: one just before ovulation and one during the mid luteal phase. The theca interna cells of the follicle are the primary source of oestrogens. However the

follicular fluid has a high oestrogen content, and much of this oestrogen appears to come from the granulosa cells (Ganong, 1983).

The corpus luteum secretes predominately progesterone, but in addition, oestradiol is produced (Ryan, 1977).

The total amount of oestrogens formed by the human corpus luteum during the luteal phase of the cycle is no less than that produced by the follicle during the follicular phase. It should be noted that stimulation of the corpus luteum by LH (Leutinizing hormone) increases not only the synthesis of progesterone but also the oestrogens (Gower and Fotherby, 1975).

Oestrogens are also formed by the stroma which is the only ovarian subunit remaining in the postmenopausal period that could be active in hormone secretion (Ryan, 1977). The biosynthetic capacity of the stromal tissue is much less than that of follicular or luteal tissue(Gower and Fotherby, 1975).

2) Androgens

The major androgen secreted by the ovarian stroma is the androstenedione. It is a biologically weak compound but can be peripherally converted to testosterone, the potent androgenic substance secreted by the testis. Testosterone is converted in peripheral target tissues to 5 α -dehydrotestosterone (DHT), an