HISTOPATHOLOGY OF ENDOMETRIUM UNDER THE EFFECT OF TRIPHASIC PILLS

THESIS

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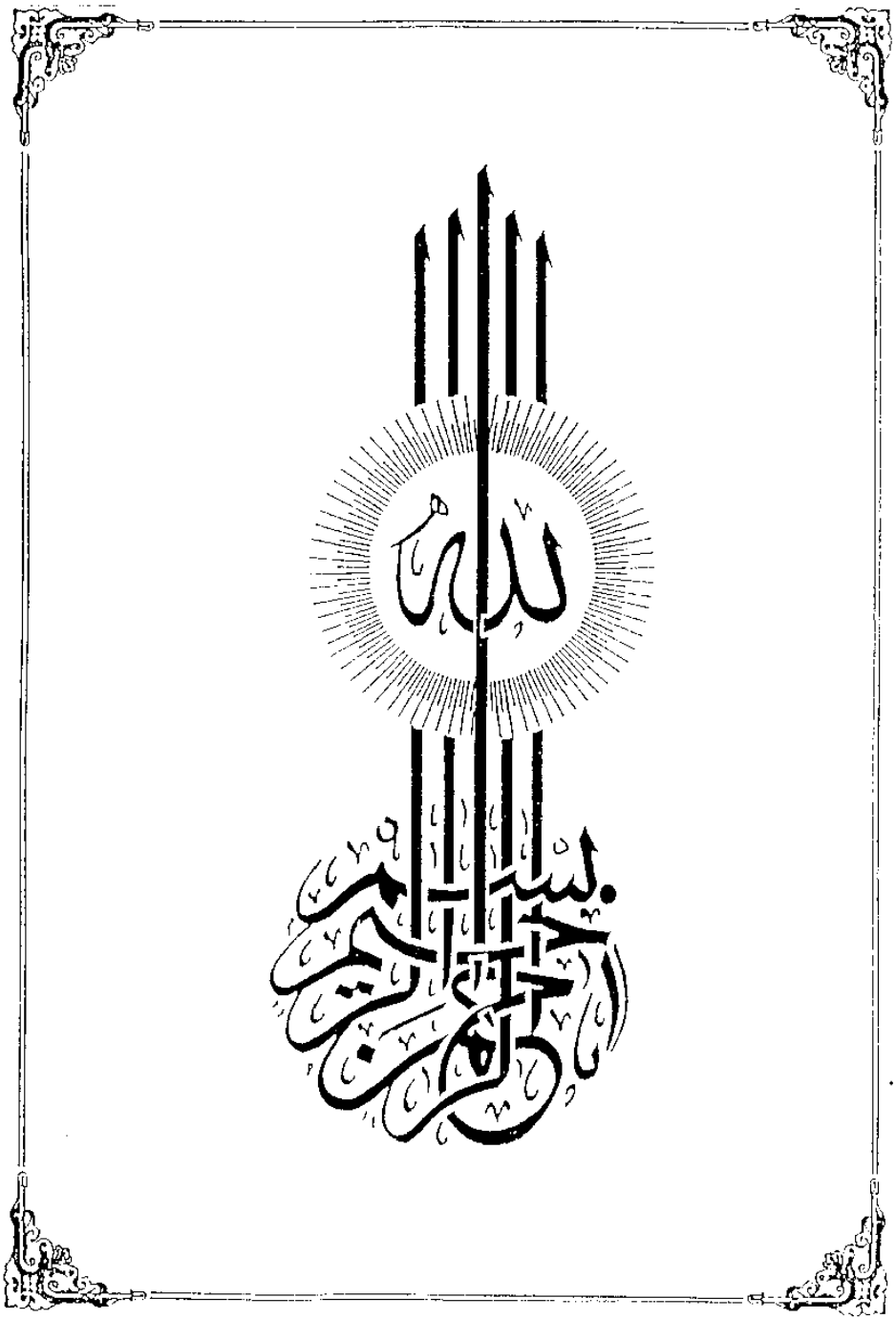

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INTRODUCTION

The contraceptive effictiveness of combined oral contraceptive has never been great problem and failure can mainly be attributed to errors in tablet intake. For several reasons research has been directed to the reduction of hormonal content. Subjective side effects reported by the users first promoted efforts to reduce the ingested doses. These side effects generally subsides after discontinuation of medication and mainly classified as trivial. great deal of attention has been drawn to some serious but fortunately rare side effects. These include above all thrombo-embolic diseases. From the begining the estrogen component was considered to be responsible for most of the adverse effects and appropriate reduction was made in many steps until the lowest dose was reached that was able to cause ovulation inhibition and give good cycle control. Recent research has drawn attention to the fact that the progestogen also could be of importance with regard to serious side effects with oral contraceptive. An increasing incidence of hypertension with increasing dose of progestogen has been reported. (Bergstein, 1976).

Furthermore progestogens belonging to the 19 nortestosterone type are reported to have adose-related negative effect on HDL. (Briggs, 1982). It therefore seems to be highly desirable for reduced progestogen dose in oral contraceptives. A further reason for striving to reduce

both estrogen and progestogen is the fact that the suppression of the hypothalamic-pitutary axis is reported to be dose dependent (Spellacy et al., 1980).

When the dose in oral contraceptives are reduced, the subjective side effects reported are diminished. Another problem is instead becoming paramount. Bleeding irrigularities especially in the first cycles, may be of such severity that some women abandon the pills. Some low-close oral contraceptives fail too often to give withdrawal bleeding in tablet free week. This is of great concern for the patient and will cause unnecessary pregnancy test.

A genial way to decrease the total dose per cycle is to divide the 21-day treatment period into three phases mimcking the endogenous hormonal levels. At least theoretically, this method whould reduce the bleeding irrigularities as it better conforms the endometrial dynamics. Although theortically these agents should be even safer than fixed dose formulation. It will be several years before sufficient epidemolgical data become available to evaluate their safety (Michell, 1985).

AIM OF THE WORK

The aim of this study is to evaluate the effect of triphasic pills on the histopathological picture of the endometrium in the different phases of the endometrial cycle.

HISTORICAL REVIEW OF ORAL CONTRACEPTION

The development of oral contraception represents one of the most significant scientific achievement of this century. This significance is attributed principally to the fact that its practical application has had such a pwerful impact on all aspects of society with far-reaching consequence (Greenblatt, 1980).

As early as 1897 Beard postulated that progestrone inhibited ovulation during pregnancy (Collaborative group 1975). Subsequent studies established the fact that progestrone did inhibit ovulation in the rabbit and in rats. These observations were also confirmed in humans. In 1921 Hebarlandt was the first scients to indicate that extracts from the ovaries of pregnant animal might be used as oral contraceptive. In 1934 Corner and Beard, isolated and established the structure of progestron. Then in 1937, Makepeace working with rabbits demonestrated that progestrone had the power to inhibit ovulation (Hatcher et al., 1987).

In 1937 Kurzrok noted that ovulation was inhibited during treatment of dysmenorrhea with ovarian oestrone and suggested that this hormone might be of value in fertility control.

It was only in 1950, when potent, orally active progestrone (first northyndrel and then norethisterone) became available, that an oral contraceptive pills became possible (Djerassi, 1979).

The first pills were thought to contain only progestrone and gave good cycle control. When purified preparations were tried, cycle control deteriorated. The impurity had been "mestranol", and when this oestrogen was restored to the tablets, the combined pills, "Enovid" "Norethinodrel" + mestranol" was created. (Macnaughton, 1985).

Successful trials with this preparations started in puertro-Rico in 1956 (Macnaughton, 1985).

Since 1960, when food and drug administration (F.D.A.) first approved these agents for contraceptive purposes, there had been adefinite trend towerd lower doses of both the oestrogen and progestin in the pills, for example, in early 1960, birth control pills contained 50-150 Ug of an oestrogen and 1-10 mg of progestin. Inlate 1960, it became clear that the most serious side effects and many minor side effects of the pills are oestrogen related. Today pills provided, commonly contain 30-50 Ug of an oestrogen and 1 mg or less progestin. Minipills available since 1973, contain no estrogen and also have less than 1 mg of progestational agent (Hatcher et al., 1987).

The sequential or "serial" oral contraceptive regimen was developped by Goldzieher and Coworkers (1963) and by Liggins 1964. The oestrogen generally mestrone or ethinyl oestrodiol is given as daily tablets for 15 or 16 days followed by a daily combination dose of oestrogen mixed with progestin for 5 days. During 1965, the first sequential oral contraceptive was marketed in Mixco by Syntex as "Secuntex" and in the united states by Elililly Company (Bennet, 1982).

The reduction of steroid dosage in oral contraceptive did occur by recognition of synergestic effect of progestrone with ethinyl oestrogen. Small amount of ethinyl oestrogen combined with small amount of progestagen have as much anovulatory activity as much larger amount of ethinyl oestrogen alone (Mann, Vessy, 1975).

The new triphasic approach introduces the combination steroid in step wise fashion as it is observed in normal menstrual cycle (Greenblatt, 1980).

NORMAL HISTOLOGY OF ENDOMETRIUM

The wall of uterine body consists of three layers. They are the endometrium, myometrium and perimetrium.

The thickness of endometrium varies according to the phase of menstrual cycle in sexually matured female. The endometrium consists of:

1. External epithelial lining made of single layer of columner epithelium.
2. Uterine glands made of cells similar to those of the epithelium, interspersed with some ciliated cells.
3. The endometrial stroma or lamina propria composed of numerous stromal cells, an abundant mucoid matrix and fine collagenous and elastic fibers.

Functionally the endometrium can be divided into two layers:

1. The basol layer (Lamina basalis) which always remain part of uterine wall.
2. Functional or decidual layer (Lamina functionalis) which is partly sloughed off and partly regressed during menstruation (Verma, 1983).

1. The Glandular Epithelium:

It is a single layer of columnar epithelial cells. Their height varies depending on the functional "hormonal" state, from 6 U post menstrual to 20 U. at the end of the proliferative phase (Dellenbache-Hellweg, 1971). During the proliferative phase the endometrial glands have long columnar cells with average 24 Um in length and 5 Um width the intercellular spaces and the junctional complexes between the cells are similar to those of the epithelium. The apical parts of the cell is flattend or dome like and the lumen of the glands contain an amorphous material of low to moderate opacity. The ovoid nucleus in these cells measured from 5.5 to 8 Um in length 3 to 4 Um in width and centrally basal in position (Verma, 1983).

Between 10th to 16th day of the cycle the content of neuclei of D.N.A. reaches its maximum (Nordqvist, 1970). Mitotic figures may be found throught the proliferative phase, their occurence is maximal in mid proliferative phase (Verma, 1983). During the secretory phase the neuclei become round, vesicular and gradually lose DNA. Mitotic figure are most numerous just before ovulation (Dallenbache Hellweg, 1975).

Jahnnison and Hagenfeldt 1971 found an accumelation of neuclei in secretory phase between cycle day 14 and 22 and suggested therefore that the synthesis of D.N.A. in

the human endometrium was synchronized.

The neucleoli of the early proliferative phase are finally granular and compact. During the first week of the secretory phase the neucleoli contain a characteristic tubular or meshwork-like structure "the nucleolar channel system", which some investigators believe that it serves the exchange of substances between nucleolus and cytoplasm (Terzakis, 1965) for example the rapid transport of specific progestogen induced riboneucleoprotein (Armestrong et al., 1973).

The appearance of the structure seems to depend on adequate level of progestrone and may be induced in vitro or experimentally when enough progestogen is adminestered (Nakao et al., 1971).

The substances secreted by the glandular epithelial cells and found within the glandular lumon is chemically complex and its composition varies with the phase of menstrual cycle. During the proliferative phase it consists of mixture of desquamated superficial glandular cells, RNA, protein and acid mucopolysaccharids. During the secretory phase the secretion appears as globules which contain rounded aggregate of glycogen, acid and neutral mucopolysaccharids , protein, peptides, neutral lipids, phosphatids and neumerous enzymes. During the 4th week of

the cycle, the globules degenerates, at first they appear amorphous, but later they become homogenous (Dallenbach - Hellweg, 1975). The number of ciliated cells flactuate considerably from patient to patient, probably depending on the functional state of the endometrium (Dallenbach-Hellweg, 1975).

Dazo et al., 1970 reported this ciliated cells are more abundant close to the tubal cornua and endocervical mucosa. "clear cells" as possible precursor cells are commenest in proliferative phase and in glandular cystic hyperplastic endometria (Schuller, 1968).

In atrophic endometrium they are virtually nonexistent (Fleming et al., 1968). From these facts we could assume that estrogen stimulate the cilia to develop (Schuller, 1973).

During the late secretory phase, the dome like protrusions of epithelial cells may become detached and appear to float freely in the glandular lumen. This has been interpreted as apocrine secretion but is more likely an early sign of degeneration and cell death of the beginning of menstrual phase. (Verma, 1983).

11. The Superfecial Epithelium:

It closely resembles the glandular epithelium during the proliferative phase, although it contain greater number of ciliated cells than dose the glandular epithelium (Frenczy et al., 1972).

At onset of secretory phase however, it lacks the apical accumelation of acid mucopolysaccharids (Lewin, 1961).

Neutral mucopoly saccharids as well are very sparse. Yet glycogen appears in superficial epithelium earlier in larger amount, and remains longer than it does in the glandular epithelium. There is uniformly high content of RNA in its cytoplasm and nucleoli during the whole cycle (Bremer et al., 1951). Suggesting that synthesis of protein persists. Thus the superficial epithelium differs from glandular epithelium functionally. That difference is easy to understand when we consider how important its secretion might be for adherence, and implantation of the blastocyst. (Dallenbach-Hellweg, 1975).