بسم الله الرحمن الرحيم

وقل رب زدني علماً

"صدق الله العظيم"

THE ENDOMETRIUM HISTOLOGY IN POLYCYSTIC OVARIAN DISEASE

THESIS

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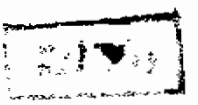

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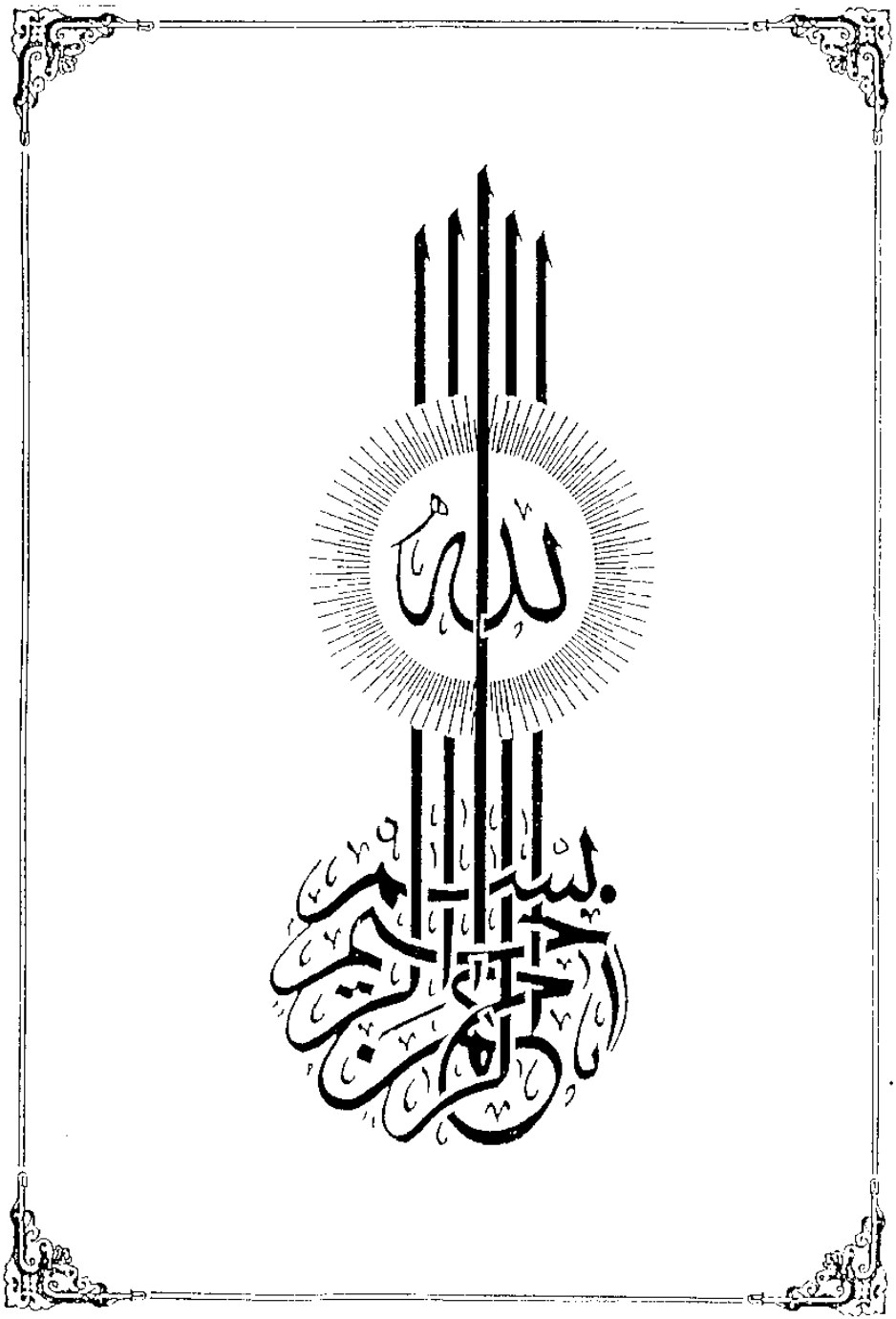

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INTRODUCTION

I

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In 1928 Dr Irving Stein foused gynecological attention on a certain group of patients who characterized by infertility,oligo-menorrhea,occasionally interspersed with menorrhagia and less commonly hirsutism,an enlarged clitoris ,and obesity.

Stein has always been careful to emphasize that the validity of this syndrome is dependent upon a charateristic pathological appearance of the ovaries,and this is important if successful diagnosis and treatment be achieved.

Bilateral enlargment of the ovaries is the rule,although possibly it may not be noted in incipient stages of the disease.

In a typical case , however , the examiner will note three size pelvic masses , a small uterus , and bilaterally enlarged " hen's egg "ovaries.

The enlargment of the ovaries is usually bilateral , although one side may predominate.

The polycystic ovary is found uniformly with Stein-Leventhal syndrome , however , it is by no means pathognomonic for essentially the ovarian pattern may be found in many cases of recurrent an-ovulation where bleeding is the presenting problem.

There are probably many closely related varieties of " polycystic-ovarian disease " which may produce a varity of endocrine dysfunction.

Judd et al.also indicate an indefinite border line between poly-cystic ovarian disease and hyperthecosis and suggest that may represent variations of the same basic disease process.

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The incidence of the syndrome differs greatly with different authors , depending on the criteria used to differentiate it from similar clinical syndromes.

According to early reports , it is rather rare.

Stein(I964) operated on only I08 cases within 34 years , and Leventhal (I958) observed only II4 women with the so- called Stein-Leventhal syndrome in 29 years.

Other authors report a considerably higher incidence (Taymor,I963 and Prunty,I967).

Polycystic ovaries are found quite frequently,normaly in I.4% of a random sample of I2I60 gynecological laparotomies (Vara,I95I), and in 3.5% of a consecutive series of 740 female autopsies. Polycystic ovaries are encountered more frequently in sterile patients as is to be expected 4.6% (Mc Googan,I954).

The originators postulated a mechanical cause for the symptomatology ,in that the thickned ovarian tunica and crowding of the cortex with cysts interfered with normal follicular development,thus producing amenorrhea and sterility.

The authors also believed that wedge resection completely restored physiological function but they admitted that surgery did not remove the abnormal stimulus which had produced the ovarian change.

They also stated that the histo-pathology of the wedges did not demonstrate features that were specifically related to the clinical picture.

In I937 K.V.Bailey of Manchester.England,treated a similar group of I7 patients by his technique of"extroversion" of the ovary.

He reported regular menstruation in I3 and a pregnancy in one.

His view was that a pituitary hormone deficiency caused a failure of normal follicle ripening and luteinisation resulting in the formation of polycystic ovaries.

In the last three decades has been written about the syndrome and some clinicians would doubt its existence.

It is commonly accepted that this clinical syndrome may be present in a variety of endocrine disorders pricipally involving the adrenal glands or the ovaries.

However,if the criteria that Stein and Leventhal outlined are adhered to ,and in particular an accurate evaluation of the size and appearance of the ovaries is made by laparoscopy,than a syndrome of what would appear to be primarily an ovarian disorder can be established.

There are many known causes of polycystic ovarian disease,such as androgen-secreting tumors,Cushing,s syndrome,and central nervous system tumors,although these represent only a small fraction of the total number of cases.

In the vast majority of patients,the etiologic factor(s) is still unknown.

Yen has recently provided an extensive discussion of polycystic ovarian disease.(84)

Many theories have been proposed to explain the failure of ovulation in polycystic ovarian disease.

Abnormalities in the ovarian , adrenal , pituitary , and hypothalamus have all been suggested as the primary cause of polycystic ovarian disease.

Early studies by Goldzieher and colleagues suggested that a defective or reduced ovarian aromatase was the primary cause.

The exaggerated pituitary LH response to LRF can also be explained by the elevated estrogens , although it is not known whether estrone is peculiar in this regard or not .

The primary effect of excessive androgen production may be at the level of the ovary in preventing follicular maturation due a higher than normal rate of atresia.

Studies of the hormonal changes in women undergoing ovarian wedge resection are consistent with this view.(40)

Wedge resection was followed by a prolonged decline in testosterone levels,and ovulation occured without significant changes in plasma LH or FSH prior to the ovulatory discharge.

Excessive production of adrenal androgens and their conversion to active compounds peripherally or within the ovary could interfere with normal follicular development during the onset of menarche.

Rising LH levels would stimulate further androgen production by the ovaries and the increased amounts of peripheral estrone would chronically elevate LH secretion,resulting in the abnormal cycle of events.

Inadequate follicular estrogen production as a result of deficient FSH secretion could also result in failure of follicular development and ovulation.

In patients with chronic anovulation,the average daily production of estrogen and androgens is increased.

This is reflected in higher circulating levels of testosterone and androstenedione,and higher levels of estrogen,largely estrone derived from the peripheral conversion of androstenedione.(I8)
The elevated LH levels are due to increased sensitivity of the pituitary gland to releasing hormone stimulation.(6I)
This increased sensitivity is probably the effect of the increased estrone levels since a correlation exists between the estrogen and the LH levels.
It is possible that the elevated androgens contribute to the increased LH in another fashion.

The hypothalamus aromatizes androgens to estrogens,and this local change may sufficiently to raise estrogen levels in the anterior hypothalamus to stimulate the positive feedback mechanism(57)

It is daubtful that the hyperthecosis represents a seperate syndrome. Hyperthecosis refers to patches of luteinized theca-like cells scattered throughout the ovarian stroma,and it is characterized by the same clinical,histologic,and endocrine findings as seen with polycystic ovaries.(4I)
It is likely that both are morphologic manifestation of the same process,anovulation.

One group of investigations has indicated that high LH levels in anovulatory patients are associated with big ovaries,while low LH levels are found in association with small ovaries.(9)
Another group has failed to find a relationship between the size of polycystic ovaries and levels of LH.
The polycystic ovary may be associated with a variety of disorders in the hypothalamic-pituitary-ovarian axis,as well as extragonadal sources of androgens or with ovarian androgen producing tumors.(42,89)

The adrenal gland is involved in this syndrome.
Higher circulating levels of dehydroepiandrosterone sulfate almost exclusively an adrenal product,testify to adrenal participation.

Also hereditary factors have a role in the aetiology of polycystic ovarian disease.
In recent,many authors have suggested that polycystic ovary disease is genetically determined.
Some authors suspect that it may be transmitted by autosomal inheritance, wherease others have shown that the condition may be X-linked dominantly inheirted through the father (I6,25)
Wherease karyotypes of some patients with polycystic ovary disease showed various sex-chromosome anomalies(23)
The majority of patients with polycystic ovary disease who were studied cytogenetically did not show a demonstrable chromosomal abnormality.

The diversity of karyotypic aberrations found by other investigators leads to the conclusion that atypical and consistent chromosomal abnormality is not associated with polycystic ovary disease.

Polycystic ovarian disease may be the phenotypic expression of different chromosome constitutions.
The influence of the chromosome constitution may explain the heterogeneous symptomatology of the syndrome.
Chromosomal abnormalities were not found in some studies of women with Stein-Leventhal syndrome.
These chromosomal changes have not been typical on consistent,but include mosaics of 46Xx / 46XX,46XX / 47XXX,45XO / 46/X,45/O / 46XX 47/XX and 46/X / 47/XX.

Because some patients with the stigmata of Turner's syndrome and polycystic ovaries have identified, Givens and his co-workers have thought that some such individuals may have a defect in X-chromosome function.

The literature of the Stein-Leventhal syndrome contains a number of reports in which more than one number of a family was affected(13,78). Evans and Riley reported 2 affected sisters with almost identical findings and therapeutic results (20). An interesting features of the reports of Goldzieher and Green and of Jeffcoate was the occurance of concondantly affected identical twin sisters (26).

Suzar and Fallaux reported a family in which an affected mother had given birth,prior to having developed amenorrhea and sterility, to a daughter who was later found to be affected (73). However, in Stein's report of 70 women who had become pregnant one or more times following wedge resection of the ovaries,non of the daughters had shown any evidence of having inherited the ovarian disease (72).

Netter and associates reported chromosomal anomalies in 3 patients exhibiting the syndrome: one case was a mosaic of normal karyotype and of triple X (XX /XXX),another was a mosaic of the type XO/XY/XX, and the last,a case with mosaicis of normal karyotype and of XX with a partial deletion of one X (XX/XX) (55). In another publication, De Granchy and associates described 2 of these cases (17).

In the 1963 publication of Leon and associates,one patient was reported to have a normal XX karyotype and the other patient to have XX/XXY karyotype (45). As can be seen from these reports, no consistent finding has been demonstrated in the abnormal karyotypes ,and the presence of a normal karyotype in one patient shows that the Stein-Leventhal condition may be present without apparent chromosomal abnormalities.

Bishan and Marton cytologically examined 3 cases of the Stein-Leventhal syndrome. Two of these cases showed normal female karyotype. The other was found to exhibit an XO/XX mosaicism (II).

Byrd , Mahesh and Greenblatt reported 9 cases of the syndrome in which chromosomal analyses revealed the normal female complement(I2). In those cells analyzed,all deviations from acount of 46 were consistent with an interpretation of radom loss or gain of chromosomes other than the sex chromosomes.

The absence of chromosomal abnormalities in IO patients with the Stein-Leventhal syndrome was also observed by Van Campenhant and associates (8I). Vague and associates (80) found a male sex chromatin pattern in one out of four patients with the Stein-Leventhal syndrome.

However,there are two factors would suggest autosomal dominant inheritance. These factors are :-

I- The autosomes contain at least 90% of the chromatin in man.

2- An extremely hirsute father had an extremely hirsute son.

The effect of the hereditary potential for the disease in males is not known at the present time. However,if a tendency toward excessive hair in the male may be assumed to be the effect of the hereditary potential for the disease,the transmission from this father to his son is clearly autosomal.