THE INSULIN LEVEL AND ABNORMAL GLUCOSE PATTERN IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

THESIS

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بسم الله الرحمن الرحيم

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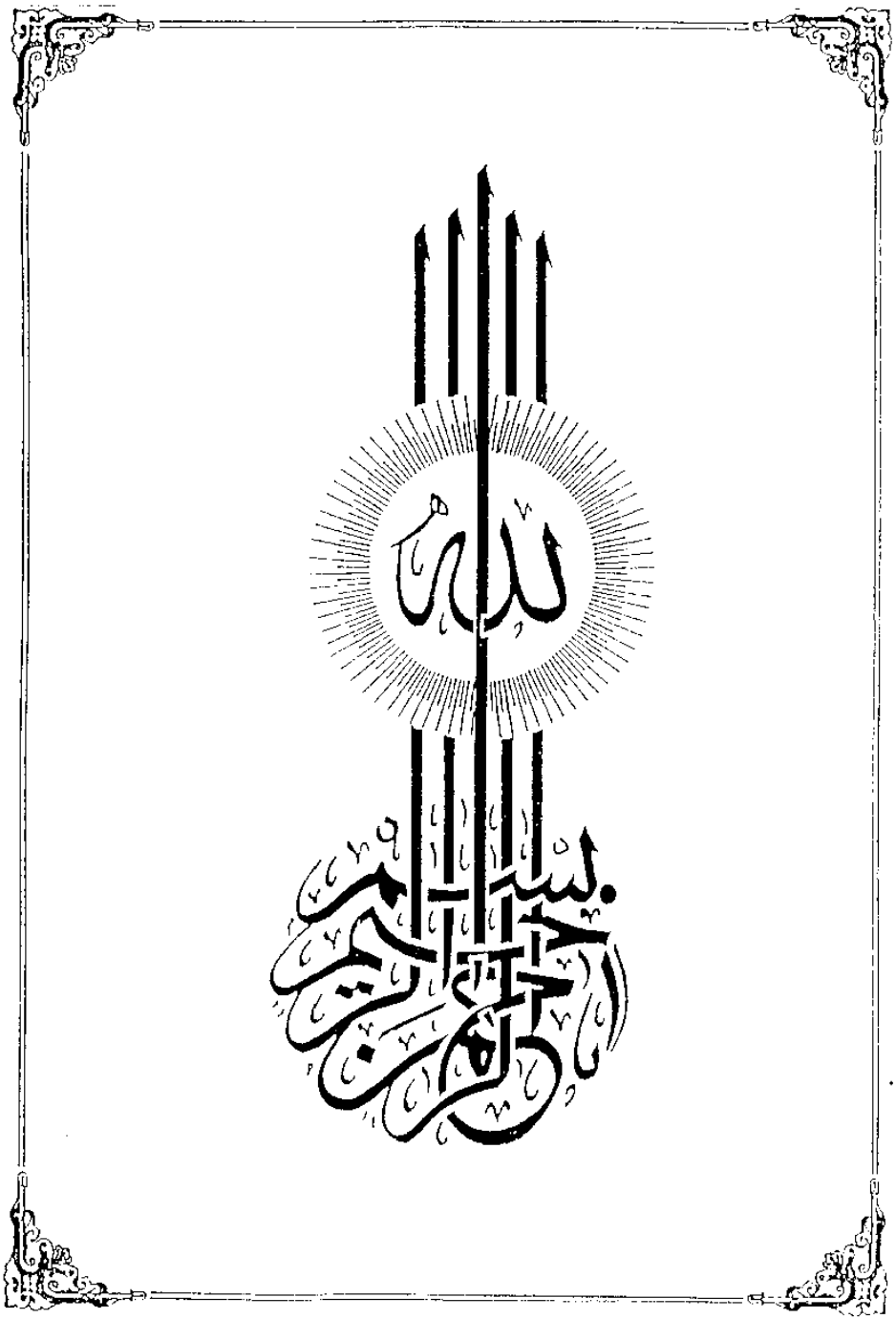

INTRODUCTION AIM OF THE WORK

are varied and include defects in the insulin-receptor system, and anti-insulin receptor antibodies (Taylor et al., 1982). The ovaries of many of these patients are enlarged, and pathologic examination often reveals marked stromal hyperthecosis. In patients with the hyperandrogenism, insulin resistance and acanthosis migricans syndrome, bilateral oophorectomy results in a decrease in circulating androgens, but does not usually ameliorate the insulin resistance (Flier, 1982).

Hence to determine the effect of different methods of management of polycystic ovarian syndrome on the hormonal profile, and the effect of diabetes mellitus and insulin level on polycystic ovarian syndrome, we determined the hormonal profile before and after treatment.

AIM OF THE WORK

Our aim of this work includes:

1. Finding a relationship between polycystic ovarian syndrome and abnormal carbohydrate metabolism, and insulin level, and the prognosis of these cases after insulin therapy.

2. Finding the inter-relationship between the different hormones playing a role in the pathogenesis and prognosis of polycystic ovarian cases.(FSH, LH, testosterone, DHEA-S, prolactin and estradiol.

3. Correlation between cases treated by different three methods:
   * Diet regimen and insulin therapy.
   * Induction of ovulation by clomiphen citrate.
   * Bilateral wedge resection and its role in the induction of ovulation and the control of abnormal insulin level and carbohydrate metabolism.

4. A scoring between the different parameters in the management of the polycystic ovarian cases.

REVIEW OF LITERATURE

Polycystic ovarian syndrome:

Historical review and definition:

Gross sclerocystic changes in the human ovary were clearly described by Chereau, 1845 and partial resection of such ovaries was being practiced before 1897 in Europe by Gusserow, Martin, Wiedow, Zweifel, and others. In the American literature. Findley described wedge resection for "cystic degeneration of the ovary" as early as 1904. Although occasional reports about this condition continued to appear over the years. More interest was aroused in 1935 when this anatomical abnormality was related by Stein and Leventhal to a clinical syndrome consisting of "menstrual irregularity featuring amenorrhea, a history of sterility, masculine type hirsutism, and less consistently, retarded breast development and obesity". The delineation of a putative syndrome and especially the report of good results produced by wedge resection, made polycystic ovarian disease (PCOD) a happy hunting ground for theorists, whose field of speculation was not encumbered by too many facts, and for surgeons, who were understandably delighted with a functional disorder that was amenable to such a straightforward apprcach. (Goldzieher, 1981).

The triad of signs (amenorrhea, obesity and hirsutism) in the presence of bilateral polycystic ovaries is very important in the diagnosis of what was known as the Stein - Leventhal syndrome (Stein, 1964).

Subsequent morphological, biochemical and endocrinological investigations of the syndrome by numerous investigators revealed a heterogenous array of underlying defects and this resulted in a serious debate even in the existence of such a well defined syndrome. The term "Stencid type" was an accepted alternative to reflect the uncertainty of this clinical entity. Since the presence of bilateral enlarged multicystic ovaries was a prerequisite for the diagnosis, the term polycystic ovarian syndrome was introduced a few years later to emphasize its heterogenicity (Yen, 1980).

It must be emphasized that a polycystic ovary is a sign and not a specific diagnosis. A specific and precise definition of polycystic ovarian disease is impossible because the etiology and pathogenesis are not fully known. In general it may be defined as a nontumerous condition of the ovary characterized by theca-cell and stromal hyperplasia with LH - dependent hypersecretion of androgens (Givens, 1979).

The term PCOS is best reserved for describing a clinical but not a specific pathophysiologic syndrome, since the cause of the disorder encompasses several different abnormalities with similar clinical presentation (Yen, 1980 and Jaffee, and Vaitukaitis, 1982).

ETIOLOGY OF POLYCYSTIC OVARIAN SYNDROME

Heridetary factors in PCOS:

There have been sporadic reports of abnormal karyotypes in patients with PCOS, but they have not been confirmed in systematic studies of sizable groups of individuals. Cooper et al. (1968), Givens et al. (1971) and McDonough et al. (1972) have provided informations regarding familial patterns in PCOS. They found an autosomal dominant transmission in 18 families. Vaitukaitis (1983) stated that the syndrome may be an X-linked dominant inhirited disorder.

The increased menstrual and hair growth abnormalities found in female relatives of patients with PCO, and embryonic-like cells, in the ovaries of some patients support the concept of a genetic basis of PCO. It is interesting to speculate that some patients with PCO may share some features of pathogenesis with ovarian dysgenesis, particularly those PCO that have a reduced number of oocytes. Wilroy et al. (1975), encountered 4 individuals who possess PCO and some of the features of the phenotypic finding seen in the turner syndrome. The role of X chromosome in PCO including hyperthecosis is elucidated.

Zumoff et al. (1983) have believed that x-linked transmission could not be ruled out. The broad range of clinical findings-from a small cystic ovary on one side

and a streak ovary on the other, to turner phenotypes with PCO, and mosaicism, such as 46 XX/45 X or 46 XX/46XXq are consistent with the variability of x-linked disorders in general. The results indicated the relevance of the fact that the nymphomaniac cow syndrome is x-linked, and that a relationship between faulty-x chromosomes and increased follicular atresia is well- established. Twins with PCO and a normal sibling have been reported by McDonough et al. (1972). All three siblings had elevated urinary pregnanetriol levels. In two families in which there were women with PCOD, three of the men had low testosterone values and high luteinizing hormone/follicle stimulating hormone ratios (Givens et al., 1971).

Nonetheless, most patients with PCOS have a normal 46 XX karyotype. Thus the possibility that patients with x-chromosome abnormalities may represent a subgroup of PCOS is highly likely. Of additional interest is the occurance of hypertension, hyperlipidaemia, hyperuricaemia, insulin resistant diabetes mellitus and acanthosis nigricans in families with ovarian hyperthecosis (Yen, 1980).

In order to determine whether the familial occurance of PCOS is related to the major histocompatibility complex (HLA). Mandel et al. (1983) examined four families in whom at least two siblings had clinical evidence of the

disease. The diagnosis of the PCOS was confirmed by increased serum testosterone, androstenedione, and LH levels compared to those in normal women. Elevated concentrations of dehydroepiandrosterone - sulfate indicated excess adrenal androgen secretion. The result of HLA genotyping in the families studied demonstrated that PCOS does not exhibit linkage to the HLA system.

Ovarian endocrine abnormality:

Yen (1980) had observed the thickened capsule of polycystic ovaries and had suggested that this may act as a physical barrier to ovulation. Stein and Leventhal (1935) postulated that an ovarian endocrine imbalance may lead to the disorder. Ginsburg and Havard (1976) reported that as ovarian wedge resection could restore regular menses and firtility in women with enlarged polycystic ovaries suggested a primary ovarian cause.

There were some reports which suggested that primary ovarian abnormality may be the origin of the polycystic ovarian syndrome in some patients. Polycystic ovaries contain many normal looking follicles at various stages of maturation. (Thompson and Taymor, 1980), but this

appears to be a failure of the normal intraovarian control mechanisms in the polycystic ovaries in that a dominant follicle appears. The remaining follicles are not suppressed. This is in contrast to the appearance in the normal or multicystic ovary (Adams et al., 1985b). Further evidence of an ovarian cause, is the presence of a unilateral polycystic ovaries in some women (Polson et al., 1985a).

Lachelin (1984) reported that the lack of aromatisation in polycystic ovaries was not due to an inherent enzyme defect or to lack of FSH receptors but to relative lack of effective FSH stimulation which is due to: a) reduced local FSH concentration, b) decreased FSH bioactivity, c) increased local androgen concentration, d) disturbance in LH/FSH ratio or e) the presence of an FSH binding inhibitor (Reichert et al., 1979).

Keettel, et. al., (1957) used the response of the immature rat ovary as a physiological indicator, demonstrated a qualitative effect which suggested to them an excess of LH in 10 of 11 patients with polycystic ovaries. Furthermore, a remarkable response of the polycystic ovaries to an FSH type, gonadotropin was regarded as a reflection of an FSH deficiency. DuToit (1951) felt that derangement of the theca cone prevented normal follicle maturation and ovulation. Shippel (1955) attributed the

ovarian changes to ovarian dysfunction resulting in anovulatory cycles with progression to theca cell dominance.

Evans and Riley (1960) suggested that any condition associated with recurrent anovulatory cycles may lead to the development of polycystic ovaries. Such recurrent follicular phases without ovulation and corpus luteum formation are most common during puberty, menopause and post partum periods.

Adrenal abnormality:

The role of the adrenal gland in the genesis of polycystic ovarian syndrome is controversial. It has been postulated for many years that adrenal hyperfunction may play a role. Polycystic ovaries had been found in some cases of adrenogenital syndrome, in Cushing disease and in women with virilizing adrenal tumors (Yen, 1978). DeVane et al. (1975) have demonstrated elevated plasma dehydroepiandrosterone sulfate levels, an androgen of predominantly adrenal origin. Steinberger et al., (1981) described resumption of menstrual cycles during treatment with glucocorticoids.

There are three etiological factors that may be considered concerning the role of the adrenal gland as a cause of polycystic ovarian syndrome. (1) A primary

adrenal enzymatic defect may exist which becomes manifest at the time of the adrenarche to account for the peripubertal onset of PCOS, by causing persistent anovulatory cycles without a persistent adrenal abnormality (Yen, 1980). (2) An exagerated adrenarche occasioned by excess of an adrenal stimulatory factor other than ACTH, the existence of such a factor has been suggested because the spurt in adrenal growth and the increase in size of the zona reticularis at the time of the adrenarche are independent of an increase in cortisol secretion, but correlate with the increase in plasma dehydroepiandrosterone sulfate levels (Grumback et al., 1978). (3) Cortisol and adrenal androgen secretion vary independently with age, and ACTH is not the trophic agent which controls the change in adrenal androgen secretion during the period of sexual maturation (Forest, 1978). In either case, the elevated androgen levels associated with the exaggerated adrenarche could result in increased extraglandular estrogen production which inturn would induce an elevated LH/FSH ratio and the associated ovarian androgen secretion. Thus the androgenic basis of this syndrome is shifted eventually from the adrenal to the ovary.

Mckenna et al., (1984) and Loughlin et al., (1985) tested the hypothesis that an abnormality of adrenal androgens is primary to estrone excess, which may in turn cause the gonadotrophin and ovarian abnormalities in