ANIMAL MODELS FOR STUDY OF POLYCYSTIC OVARIIES AND OVARIAN ATRESIA

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INTRODUCTION

In 1935, Stein and Leventhal described a syndrome in which there was an association between large, pale polycystic ovaries, menstrual irregularities, ovulatory failure, infertility, hirsutism and obesity. Isolated reports of polycystic ovaries in the human and the management of the associated infertility by partial wedge-resection of the ovaries had been reported in Europe almost a century earlier but a syndrome had not been described. Since 1935 extensive investigations have been undertaken to establish the pathophysiology of the polycystic ovary syndrome and several excellent reviews have been published on the subject (Mahesh et al., 1962; Goldzieher and Axelrod, 1963; Mahesh and Greenblatt, 1964; Shearman and Cox, 1966; Kirschner and Bardin, 1972; Greenblatt and Mahesh, 1976; Parker and Mahesh, 1976; Rebar et al., 1976; Mahesh, 1980, 1983, 1984; Yen, 1980, Goldzieher, 1981). In spite of the extensive research on the polycystic ovary syndrome, there is no consensus as to its pathophysiology because the so called syndrome is not a distinct entity in itself. An analysis of 1079 cases published in 1962 showed that 57% of the cases had amenorrhea, 69% hirsutism, 41% obesity, 74% infertility, 21% virilization, and 12% had cyclic menses (Goldzieher and Green, 1962). Variations were also found in the size of the ovary ranging from small to normal to large; in some cases, the tunica was thickened while in others it was not (Smith et al., 1965).

The concept of the polycystic ovary syndrome being a genetic disorder has been advanced based on the occurrence of the syndrome in sisters, identical twins and a mother and a daughter. In addition, isolated examples of the presence of chromosomal abnormalities, and X-chromosome linked or autosomal dominant mode of transmission of the disorder have been reported (reviewed by Mahesh, 1984). In spite of the well documented evidence of the genetic basis of inheritance of the polycystic ovary syndrome, a genetic link is found in a relatively small number of cases and is not a generalized finding.

The presence of elevated androgen secretion with or without an elevation in pregnanetriol and Δ5-pregnenetriol has been well documented in the polycystic ovary syndrome. In the early 1960s, the adrenal was considered the primary source of the disorder (Perlroff et al., 1957; Gallagher et al., 1958; Brooks and Prunty, 1960; Lipsett and Ritter, 1960). The concept of the adrenals as a source of excessive androgens was confirmed by the presence of polycystic ovaries in patients with virilizing adrenal tumors and congenital adrenal hyperplasia. By using
small doses of ACTH to stimulate steroidogenesis and measuring the ratios
of the secretory products, several investigators have reported the
presence of mild degrees of abnormality in the 21-hydroxylase, 11β-hydro-
xy1ase and 3β-hydroxysteroid dehydrogenase activities in patients with
polycystic ovaries (Given et al., 1975; Ikkos and Kellia-Sfikaki, 1975;

In 1953 Greenblatt observed a fall in urinary 17-ketosteroids after
wedge-resection of the ovary in untreated and cortisone treated women with
polycystic ovaries, and suggested that the ovary may be a source of
excessive androgens in the syndrome. The concept that polycystic ovaries
could secrete excessive androgens was confirmed by Mahesh and coworkers in
studies in which urinary steroids were measured before and after ovarian
wedge-resection and adrenal and ovarian suppression (Mahesh and
Greenblatt, 1961, 1964b; Mahesh et al., 1964). Large quantities of
dehydroepiandrosterone and Δ⁴-androstenedione have also been isolated from
ovarian tissue and ovarian venous blood of patients with the polycystic
ovary syndrome (Mahesh et al., 1962; Mahesh and Greenblatt, 1962, 1964a).
The isolation of dehydroepiandrosterone and Δ⁴-androstenedione from
ovarian tissue and follicular fluid from polycystic ovaries has
subsequently been confirmed by other investigators (Starka et al., 1962;
Baulieu et al., 1963; Short and London, 1961; Mahajan et al., 1963).

Early reports on the measurement of urinary gonadotropins by bioassay
in patients with the polycystic ovary syndrome indicated a hypersecretion
of LH (Ingersoll and McDermott, 1950; McArthur et al., 1958; Taymor and
Barnard, 1962). This was confirmed by radioimmunoassays of LH and FSH.
Although the serum LH levels were either normal or elevated, the FSH
levels were normal or depressed (Mahesh et al., 1970; Yen et al., 1970a;
Gambrell et al., 1971, 1973; Berger et al., 1975; Devane et al., 1975;
Duignan et al., 1975; Baird et al., 1977). The high LH concentrations
found in patients with the polycystic ovary appear to be the result of
increased frequency and/or increased amplitude of pulsatile LH release
(Rebar et al., 1976; Baird et al., 1977). Furthermore, when stimulated
with LHRH, patients with the polycystic ovary syndrome showed an
exaggerated response in the release of LH (Rebar et al., 1976; Berger et
al., 1975; Devane et al., 1975; Duignan et al., 1975; Baird et al., 1977;
Patton et al., 1975; Taymor et al., 1974; Oettinger et al., 1975; Moltz et
al., 1979). These observations have contributed to the concept of an
abnormal hypothalamic-pituitary axis in the polycystic ovary syndrome.
However, such an abnormal hypothalamic-pituitary axis in the polycystic
ovary syndrome is unlikely because a) the immediate lowering of LH after
estradiol administration in patients with polycystic ovaries appeared to
be comparable to that found in the normal cycle (Yen et al., 1970a; Rebar
et al., 1976; Baird et al., 1977), b) the estrogen induced positive LH
surge was similar in normal women and patients with polycystic ovaries
(Baird et al., 1977), c) treatment of patients having polycystic ovary
syndrome with clomiphene citrate resulted in an estradiol surge followed by
an ovulatory gonadotropin surge similar to that found in the normal
cycle (Mahesh and Greenblatt, 1964a; Yen et al., 1970b; Gambrell et
al., 1971; Baird et al., 1977). d) the augmentation of the anterior
pituitary gland's responsiveness to LHRH in the release of LH by estrogens
in the human is well documented (Jaffe and Keye, 1974; Yen et al., 1974,
1975). In the polycystic ovary syndrome there is a correlation between
the level of circulating estrogens and circulating LH (Devane et al.,
1975; Rebar et al., 1976; Baird et al., 1977; Kandeel et al., 1978). It
is therefore likely that the elevated circulating LH is due to high
circulating estrogens rather than an abnormal feedback. This was
confirmed by the finding that the fractional increase in LH after LHRH
administration correlates well with the level of circulating estrogens
(Rebar et al., 1976) and e) the administration of estrone benzoate to