Hyperandrogenic anovulation (the polycystic ovary syndrome)—back to the ovary?

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Hyperandrogenic anovulation is characterized by polycystic appearance of the ovaries, elevated free serum testosterone with decreased concentrations of serum sex hormone binding globulin, an increased ratio of luteinizing hormone to follicle stimulating hormone and varying degrees of insulin resistance. We hypothesize that this is the result of variably increased ‘ovarian androgenic insulin responsiveness’ acting in combination with body mass. Women who develop hyperandrogenism and anovulation when lean (having normal serum insulin concentrations) represent the more severely affected individuals, whereas those who can resume ovulation by losing weight (and lowering their elevated serum insulin) represent a milder form. The tendency of these women to develop ovarian hyperstimulation syndrome despite hypophyseal desensitization suggests a primary ovarian defect which is apparently more pronounced in lean subjects. The unique ability of surgical damage to the ovary to induce ovulation, raises the possibility that inflammatory-like tissue remodelling has a major role in rescuing follicles from androgen-induced atresia. Approaches that may facilitate the study of this possible mechanism may include examination of in-vitro perfused, post-surgery mammalian ovaries and the elucidation of signal transduction mechanism(s) of insulin in the ovary, with special reference to cells eminating from affected women.

Introduction
The association of hirsutism with acne, anovulation and a polycystic appearance of the ovaries were originally combined into the definition of a syndrome by Stein and Leventhal (1935). Although many more facets of this endocrinopathy have since been unravelled, its underlying causative factor(s) remain enigmatic (Donesky and Adashi, 1995). Moreover, and as if to add confusion, several subgroups, such as ‘lean’ versus ‘obese’ polycystic ovary syndrome patients, have been described and studied (Kiddy et al., 1992; Dunaif et al., 1995) and attention has been also devoted to a possible role of the adrenal in yet another subgroup of patients. As a general unifying concept, it has been suggested that the final clinical picture represents some form of a vicious cycle (Insler and Lunenfeld, 1991), to which several ‘entry points’ are possible, such as: obesity, adrenal hyperandrogenism, insulin resistance, hypothalamic–ovarian axis dysregulation, and a role for intra-ovarian androgen in suppressing ovulation (Sca ramuzzi et al., 1977), possibly by inducing granulosa cell apoptosis (Billig et al., 1993, 1996). Nevertheless, when one attempts to explain the pathophysiology of the various types of women who eventually are hyperandrogenic and do not ovulate, many gaps remain unexplained (Homburg, 1996).

In this article we review in a critical manner some key publications on hyperandrogenic anovulation (also entitled the polycystic ovary syndrome; PCOS) and suggest a con-
cept that rearranges the understanding of findings reported on the relative roles of insulin, ovarian androgen production and body mass in the ovulatory dysfunction seen in PCOS patients. This hypothesis points towards a primary ovarian defect which underlies this enigmatic entity, and suggests future directions for its study.

**Non-interventional observations**

Many studies which simply documented findings in women with hyperandrogenic anovulation revealed the following features (Kiddy et al., 1992; Buyalos et al., 1992): elevated free serum testosterone with decreased concentrations of serum sex hormone binding globulin; tonic elevation of serum luteinizing hormone (LH), with an increased ratio of luteinizing hormone to follicle stimulating hormone (FSH) (2:1 often serving as a cut-off value); varying degrees of insulin resistance and associated hyperinsulinaemia; polycystic appearance of the ovaries, with the classical necklace-like arrangement of small peripheral follicles around hyperechogenic stroma (Adams et al., 1986; Conway et al., 1989).

It is of note that while early reports defined patients by clinical findings associated with the syndrome, later evolution of its understanding led to wider inclusion criteria, of which laboratory findings predominate. Nevertheless, there is a view which regards ovulatory women whose ovaries have the typical polycystic appearance, as a transitional form from the purely ovulatory women to the overtly anovulatory PCOS patients (Adams et al., 1986; Polson et al., 1988).

**Observations on responses to drug challenges**

Since most anovulatory women seek medical advice for impaired fertility, the most common medical intervention consists of ovulation induction. Naturally, repeated measurements of principal hormones relevant to the latter provided additional depth to the understanding of PCOS. First clomiphene citrate, the non-steroidal anti-oestrogen, induces ovulation in a significant proportion of these women. This was explained by its ability to antagonize oestrogen in the hypothalamus, thus modulating the pattern of gonadotrophin releasing hormone secretion, which in turn increases the relative secretion of FSH (Van den Berg and Yen, 1973). Others have found an increase only in LH, but conceivably the eventual commencement of ovulation suggests a normalization of its ratio to FSH (Adashi, 1984). Interestingly enough, a significant percentage of PCOS patients fail to ovulate following the administration of this drug, revealing a possible continuum of severity (Garcia et al., 1977).

The next drug used for ovulation induction is human menopausal gonadotrophin, which is successful in some of the patients who are unresponsive to clomiphene citrate, thus further supporting the notion regarding a continuum of severity. In this connection, a unique feature of women suffering from PCOS is their tendency to develop ovarian hyperstimulation syndrome (Wang and Gemzell, 1980). This syndrome involves an exaggerated response to gonadotrophins by recruitment of an excessive number of follicles. It is notable that this adverse outcome of ovulation induction cannot be prevented by hypothalamic suppression, a phenomenon also often observed during assisted reproduction cycles (Homburg et al., 1990). This, in itself suggests that the hypothalamic principals are secondarily deranged, and a primary ovarian defect is the more likely cause of PCOS.

The above notwithstanding, many obese PCOS patients may resume ovulation when losing weight (Bilenka et al., 1995), and therefore weight loss has been advocated before any other intervention (Buyalos et al., 1992; Kiddy et al., 1992). This indeed causes resumption of ovulation in some, whereas it converts other patients from clomiphene citrate unresponsive to responsive (I.Ben-Shlomo, unpublished observations). Yet, there are more than a few patients who are not obese but who present all the features of PCOS.

The apparent effect of body weight on ovulation has propelled interest in carbohydrate metabolism as a cofactor in hyperandrogenic anovulation. This has led to the realization that the majority of PCOS patients have a deranged insulin sensitivity (Lanzon et al., 1990), with its most extreme form in the hyperandrogenic insulin resistance–acanthosis nigricans (HAIR-AN) syndrome (Khan et al., 1976). The exact relations between insulin and androgens, i.e. which of these excesses is primary, is not obvious, although hyperinsulinism has been suggested as primary in the work by Lanzon et al. (1990). In this perspective, weight loss which decreases the insulin load, was also noted to decrease serum androgen concentrations (Kiddy et al., 1992). Nevertheless, it has been well documented that lean women with PCOS do not have excessive insulin response, and were therefore suggested to constitute a separate subpopulation (Dale et al., 1992). A recent key experiment used the drug metformin to selectively suppress insulin in hyperandrogenic women (Nestler and Jakubowicz, 1996). The results were unequivocal in identifying insulin concentrations as primary and by inference causative to hyperandrogenism. Current knowledge favours the notion that the excess of insulin enhances stromal-thecal androgen production, possibly by causing ‘dysregulation’
of the enzyme P450c17α (Rosenfield et al., 1990). Nevertheless, this does not provide a satisfactory explanation of the mechanism leading to androgen overproduction and anovulation in lean women with normal insulin concentrations. (Dale et al., 1992).

Although it has been elegantly shown that insulin acts on granulosa cells through its own specific receptors (Willis and Franks, 1995), the insulin effect in the intact ovary has not been elucidated. In this regard, we have shown that in rat ovaries the major glucose transporters are numbers 1 and 3, and that they are cytokine regulatable (Kol et al., 1997). These, unlike glucose transporter protein 4, are not the classical insulin regulatable transporters, which raises the possibility that insulin acts in the ovary by mechanism(s) somewhat different than in the rest of the body, possibly at the level of signal transduction pathway, as hinted by findings in adipocytes from women with PCOS (Dunaif et al., 1995). It is also possible that insulin has a gonadotrophic-only effect in the ovary and is not concerned with ovarian metabolism (Willis et al., 1996).

**Observations on responses to surgical challenges**

As early as their initial communication, Stein and Leventhal (1935) noted that when a wedge is resected from each of the polycystic ovaries of anovulatory women, they become ovulatory for at least several months. The early interpretation was mechanical, namely disruption of the ovarian sclerotic ‘capsule’ (tunica albuginea) was believed to enable escape of ovulated oocytes. Later observations on cauterization of the ovaries revealed that it is the physical damage to the ovaries that precipitates a new hormonal balance (Judd et al., 1976; Katz et al., 1978; Gjönnæss, 1984). This balance was believed by some to result from reduced ‘androgen load’, presumably of stromal origin, leading in turn to disruption of the previously described ‘vicious cycle’ (Insler and Lunenfeld, 1991). Regrettably, no systematic and quantitative attempt was made to relate the amount of ovarian tissue removed or damaged to the extent of the hormonal change. There was one study, however, that found resumption of ovulation following unilateral laparoscopic diathermy (Bal en and Jacobs, 1994). In our opinion the latter suggests that too little tissue is lost in all such surgical interventions to account for the dramatic changes in serum concentrations of testosterone and LH. This in turn points towards a possible role for local tissue remodelling response, the results of which influence hypothalamic–pituitary activity. In this regard, the list of growth factors capable of modifying gonadotrophin action in the ovary is increasing steadily (Adashi, 1995). Some of these are also vasoactive and angiogenic in nature, properties that may contribute to a fundamental change in local balance of blood supply.

**Hypothesis**

The eventual hormonal and clinical profile known as PCOS or hyperandrogenic anovulation is contingent upon a product of specific ‘ovarian androgenic insulin responsiveness’ and the insulin concentrations present in the woman’s serum at a given time. High insulin concentrations promote ovarian androgen output and when total androgen load increases above a certain threshold, the ovulatory mechanism collapses. Thus, a woman with relatively high ovarian androgenic responsiveness to insulin need not be obese (with the attendant high insulin concentrations) to become hyperandrogenic, whereas a woman with relatively low ovarian androgenic responsiveness to insulin becomes anovulatory only when she gains weight. Accordingly, for each woman there is a threshold of body mass, beyond which she stops ovulating and loses menstrual regularity. In some women this threshold is too low to be achieved by weight loss, whereas other women may never ascend beyond their threshold. In other words, some women can never be lean enough to ovulate whereas some women can never be fat enough to stop ovulating. Figure 1 gives a graphic representation of the above description and some representative individual ‘ovarian androgenic insulin responsiveness’ curves.

This graphic representation implies that lean women with PCOS are more severely afflicted, which indeed is reflected in the frequent observation that this specific subgroup of patients is more prone to develop the severe form of ovarian hyperstimulation syndrome (Navot et al., 1992). These women are hyperandrogenic and anovulatory despite normal insulin concentrations, which implies that their ovaries produce much androgen in response to little insulin. In this regard, the extreme form of hyperandrogenism known as the HAIR-AN syndrome is the combination of overweight, high ‘ovarian androgenic insulin responsiveness’, and extreme concentrations of insulin due to insulin resistance. As can be seen in the Figure 1, women with other sources of androgen load, including the adrenal, reach the threshold for anovulation with a lower body mass despite having normal insulin response pattern (as reflected in the slope of the individual curve).

A central issue which demands an explanation is the role of surgical wedge resection or its equivalent, ovarian cauterization. Unlike drug therapies which induce ovulation as long as the drug is present (bearing in mind the late effects of clomiphene citrate which have been shown to result
Figure 1. A schematic representation of several individual ‘andro- 
genic insulin responsiveness’ curves, as they pertain to development 
of the polycystic ovary syndrome. (A) Normal pattern of ovarian an-
drogen production in relation to body mass. (B) A curve representing 
patients who suffer from excessive production of androgen. It is ap-
parent that at a given weight ovulation disappears, and that with 
weight loss ovulation reappears. (C) A curve representing women 
who do not lose ovulation even when extremely overweight. (D) A 
curve representing women with extra-ovarian sources such as the 
adrenal. Wedge resection, as suggested in the text, shifts a woman 
from a steep to a more gradual slope.

from an exceptionally low clearance rate) (Ben-Shlomo 
and Zohar, 1989), surgical interventions seem to induce 
new properties in the ovary, which are expressed by a re-
sumption of ovulation for at least several months. We pro-
pose that this is indeed the case as long as local tissue 
remodelling processes are taking place, and disappears 
when these regress. Thus, the temporary presence of 
growth factors, of which several were shown to synergize 
the effect of FSH in ovarian tissue, may be instrumental in 
shifting the delicate balance of some follicles towards suc-
cessful development rather than atresia. It is also possible 
that the same growth factors, as part and parcel of the local 
healing response, fundamentally change local blood sup-
ply pattern, in turn exposing some follicles to higher con-
centrations of FSH and lower concentrations of androgens 
by promoting their clearance, thus preventing their poss-
able adverse local effect on developing follicles. With refer-
ence to the proposed individual curve of ‘ovarian andro-
genic insulin responsiveness’, one should view the 
results of these surgical interventions as shifting a given 
patient from her original curve to a new, less steep curve 
(see Figure 1). In this way she resumes ovulation despite 
maintaining the same body mass. As is well recognized, the 
change is only temporary, and the patient gradually ‘creeps 
back’ to her original curve. In support of the quantitative 
price of the change and the continuum of severity of the 
basic defect, it is notable that some patients who are orig-
inally unresponsive even to ovulation induction by gona-
dotrophins do not resume spontaneous ovulation but 
evertheless following the operation become responsive to 
gonadotrophins. A study by Balen and Jacobs (1994) dem-
onstrated that even one-sided surgical intervention was 
sufficient to cause a drop in serum androgen and LH with a 
resumption of ovulation in some patients, thus further sup-
porting the quantitative nature of both the defect and the 
treatment effect.

The issue of heredity of this syndrome is not yet re-
solved, but the variability of clinical presentations and de-
gres of severity suggest more than one factor. Admittedly, 
there is a report on familial cases which appears to portray 
an autosomal dominant pattern with complete penetration, 
but these are by no means the majority of cases (Carey et 
al., 1993). In our opinion and as suggested by Eden (1991), 
the coexistence of many severity levels of ‘ovarian andro-
genic insulin responsiveness’ had an evolutionary advan-
tage at certain points during the history of mankind. Thus, 
during times of starvation there still existed a subgroup of 
women capable of ovulating (‘lean’ PCOS), whereas during 
more affluent times a significant percentage of women 
ovidated less regularly. It is possible that even if a single 
gene encoding a regulatory protein is responsible for the 
clinical syndrome, there may exist several variations which 
may account for the differing levels of severity. Recent 
evidence, however, does not support a single gene as the 
central player in the generation of PCOS. Furthermore, 
Franks et al. (1997), who thoroughly reviewed this issue, 
suggested a combined role for environmental, possibly 
nutritional factors. Not surprisingly, the interplay with the 
intensively studied leptin, which is central to many aspects 
of nutrition, adds another facet of complexity to this issue 
(Conway and Jacobs, 1997).

Summary and directions for future studies
PCOS is the result of variably increased ‘ovarian andro-
genic insulin responsiveness’ acting in combination with 
body mass. The unique ability of surgical damage to the 
ovary to induce a temporary but prolonged new hormonal 
balance, which favours ovulation, raises the possibility that 
inflammatory-like tissue remodelling, with its attendant 
cytokines and growth factors, has a major role in rescuing 
appropriately staged ovarian follicles from androgen-in-
duced atresia.

An approach that may facilitate the study of this possible 
mechanism is the examination of in-vitro perfused, post-
surgery mammalian ovaries in models such as that per-
ected by Brännstrom et al. (1989). An additional line of 
evidence may be developed by the elucidation of the exact
signal transduction mechanism(s) of insulin in the ovary, with special reference to cells emanating from women with PCOS. This line of exploration may in the future suggest specific therapeutic strategies that can interfere with the potentially deranged signal transduction mechanism of insulin in the ovary.

References


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