Polycystic ovary syndrome — from gynaecological curiosity to multisystem endocrinopathy

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Recent progress in the diagnosis, pathophysiology, long-term ramifications and treatment of polycystic ovary syndrome has been rapid but the pathogenesis remains a challenging enigma and the treatment symptomatic. Objective ultrasound criteria for diagnosis are being formulated and have enabled an appreciation of the true prevalence and the associated clinical and biochemical manifestations. Although a heterogeneous syndrome, the final common pathway seems to involve a dysregulation of enzymes responsible for ovarian androgen biosynthesis, possibly influenced by insulin, growth factors and luteinizing hormone. A single gene defect, inherited in an autosomal dominant pattern, has been proposed. The treatment is necessarily symptomatic, depending on the needs of the patient. Long-term deleterious sequelae now emerging may demand suppression of the syndrome earlier in life. As the most prevalent cause of anovulatory infertility, a further elucidation of the basic pathogenesis is needed to allow the application of more specific and successful modalities of treatment.

Keywords: GnRH/hyperandrogenism/insulin/ovulation induction/polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is probably the most prevalent endocrinopathy in women and by far the most common cause of anovulatory infertility, yet its pathogenesis still remains an enigma. This situation has produced an abundance of theories and a plethora of treatment regimes. The intellectual challenge which the solving of the puzzle presents has been taken up seriously of late and will hopefully produce more specific and successful treatment in the near future. The story is complicated by the complexity of the pathophysiological interactions, the heterogeneity of the clinical expression and even by the failure of investigators to agree on a common definition. This syndrome is no longer a mere rare gynaecological curiosity but an endocrinopathy with multisystem sequelae. This paper will attempt the well-nigh impossible task of crystallizing the state of the art without introducing too much personal opinion or bias.

History

As early as 1844, Chereau described sclerocystic changes in the human ovary (Chereau, 1844) some 90 years before the classic paper of Stein and Leventhal (1935). Elevated luteinizing hormone (LH) concentrations were first reported in 1958, creating a criterion for diagnosis, and the introduction of radioimmunoassays in 1971 stimulated reliance on a biochemical diagnosis. Although it was clear as early as 1962 that there was a wide variety of clinical presentation, it was only in 1976 that the concept of PCOS with normal LH concentrations was conceived (Rebar et al., 1976). A further milestone was the discovery of the association of PCOS and insulin resistance by Khan et al. (1976) and Burghen et al. (1980). Swanson et al. (1981) first described the ultrasound findings of women with PCOS in 1981 but only after Adams et al. (1985) refined and critically defined diagnostic criteria in their seminal paper did the ultrasound diagnosis of PCOS become accepted throughout the world.

Diagnosis

The progress in our ability to make an accurate diagnosis of PCOS has an historical perspective. For many years following the original description by Stein and Leventhal (1935), the diagnosis was purely clinical and relied on the presence of obesity, hirsutism, amenorrhoea and enlarged ovaries. It is clear today that this description represents extreme or advanced cases and if judgement was made purely on these clinical symptoms alone, many less blatant but nevertheless clinically significant cases would be missed. With the advent of radioimmunoassays, it was revealed that a large proportion of the women answering the clinical criteria had raised concentrations of LH. Since then, a raised concentration of LH or an LH:follicle stimulating hormone (FSH) ratio of 2:1 or more has become for some an essential criterion for diagnosis. The possibility of estimating testosterone in its total and free state, as well as many basic androgens, has added a further dimension to the diagnostic possibilities. The typical appearance of polycystic ovaries at laparoscopy, with or without confirmation by ovarian biopsy, is still regarded as a sine qua non for diagnosis by a number of clinicians.

It is my personal opinion that the advent of high resolution, transvaginal ultrasound examination of the ovaries has provided the biggest single contribution to the diagnosis of polycystic ovaries and that this examination, performed by an experienced operator, should be the basis of the diagnosis. It is a non-invasive technique for the characterization of ovarian morphology which has a high concordance rate with laparoscopic examination (Eden, 1988) and histological examination (Saxton et al., 1990). With ultrasound we are looking directly at the hub of the problem and at the one feature which is common to every case of polycystic ovaries (PCO) as opposed to...
clinical or endocrinological features which are notoriously variable, heterogeneous and inconsistent. Arguments that the ultrasonic features of PCO found in apparently normal women are merely a morphological variant and are of no clinical significance have been largely dispelled by several studies. In a series of apparently normal, eumenorhoeic women, Polson et al. (1988) found that >90% of the group with PCO had a clinical or biochemical feature consistent with the ultrasonic diagnosis. In similar groups of women, all ovulatory, those with PCO were more likely to be troubled by subfertility (Eden et al., 1989) and recurrent miscarriage (Sagle et al., 1988). In a very large series, Conway et al. (1989) demonstrated overall, the typical endocrinological and classical clinical findings of PCOS in women in whom the diagnosis was made solely on the basis of the ultrasound findings.

Ultrasound assessment of the ovarian morphology should thus be the gold standard for the diagnosis of PCO. Based on the criteria of Adams et al. (1985), PCO should be diagnosed when more than eight discrete follicles of <10 mm diameter are seen in the ovary, usually peripherally arrayed around an enlarged, hyperchogenic, central stroma. Objective estimates of the size of the stroma are difficult but stroma occupying more than 25% of the ovarian volume has been suggested as the criterion. Polycystic ovaries are usually but not invariably enlarged and normal size ovaries with typical features do not preclude diagnosis. Recently, Dewailly et al. (1994) have described an objective quantitative method of ovarian stromal assessment by using a computerized ultrasonic technique to measure stromal and cyst areas. Reassuringly, they found that the stromal area in hyperandrogenaemic women was significantly larger than in those with normal androgen levels. In these women, the stromal area correlated with serum androstenedione and 17-hydroxyprogesterone concentrations but not with basal serum testosterone, LH or insulin concentrations. This suggests that by using this computerized ultrasonic technique, a much more objective, standardized diagnosis of PCO can be obtained.

Definitions

Based on the above and for the sake of clarity, the following definitions are suggested.

**Polycystic ovaries:** ovaries displaying the typical ultrasound features described above.

**Polycystic ovary syndrome:** the typical ultrasound features of the polycystic ovary in the presence of oligo/amenorrhea and/or clinical symptoms of hyperandrogenism such as hirsutism or acne.

Prevalence

Ultrasonic diagnosis of PCO has enabled us to appreciate the true prevalence of this phenomenon. An attempt was made by Polson et al. (1988) to assess the prevalence of PCO in the general, healthy female population of fertile age using 257 volunteers. Polycystic ovaries were found in 22%. In a similar study on 100 normal Arab women, Abdel Gadir et al. (1992) found a prevalence of 16%.

Polycystic ovaries have been associated with 75% of cases with anovulatory infertility (Adams et al., 1986; Hull, 1987). Using ultrasound criteria, PCO has been found in 87% of women with oligomenorrhoea and in a similar proportion of women with hirsutism and regular, ovulatory menstruation (Adams et al., 1986). These significant findings have helped explain many of the cases previously designated as ‘idiopathic’ and have facilitated specific treatment. Similarly, Adams et al. (1986) discovered PCO in 30–40% of women with amenorrhea.

The ultrasonic examination of the ovaries of 82 women presenting at a dermatology clinic complaining of acne revealed that 83% had PCO and this finding has revolutionized the treatment of this complaint (Bunker et al., 1989).

Clinical manifestations

Women with PCO may display a wide range of clinical symptoms. At the extreme ends of this range are the women who are phenotypically normal, have no signs of hyperandrogenism and who are eumenorhoeic but have PCO on ultrasound examination and the women who have the full blown expression of the classical Stein–Leventhal syndrome.

Several concepts are important in order to understand this heterogeneity of clinical presentation. Polycystic ovaries are there for life and only the clinical expression may change, while the typical ultrasonic findings will remain identifiable. If accepting that PCOS is basically a disorder of ovarian function, symptomatology is dictated by extra-ovarian factors. A typical illustrative example is that of an asymptomatic, eumenorhoeic and ovulatory woman with demonstrable PCO and of normal body weight who gradually becomes obese. She will almost invariably develop menstrual disturbances, anovulation and signs of hyperandrogenism such as hirsutism and acne. These symptoms may be reversibly by returning to her previous body weight probably by reducing her exposure to hyperinsulinaemia (Kiddy et al., 1992). Treatment with combined oral contraceptive pills or long-term gonadotrophin-releasing hormone agonists (GnRHa), by reducing exposure to endogenous gonadotrophins, is capable of severely decreasing symptoms of hyperandrogenism (Givens et al., 1976; Shaw, 1989).

Finally, hirsutism and menstrual cycle disturbances have been found to be significantly more frequent in obese than non-obese women with PCOS (Conway et al., 1989). Alopecia may occur in severe PCOS in untreated women and acanthosis nigricans is a rare but pathognomonic finding associated with obesity and insulin resistance.

Late sequelae

Untreated PCOS may be regarded as a progressive syndrome up to the time of the menopause. Much interest of late has centered the long-term sequelae of PCOS. In a seminal study, Dahlgren et al. (1992) examined 33 women aged 40–59 years who had undergone wedge resection 22–31 years previously. Compared with age-matched controls, they had a significantly greater incidence of hypertension and diabetes mellitus. Using
The exact aetiology of PCO remains unknown. While PCO by improving endocrine and lipid profiles and reducing hyperinsulinaemia is an adverse risk factor for coronary artery disease and is associated with reduced high density lipoprotein (HDL2) concentrations (Conway and Jacobs, 1993). Dahlgren et al. (1991) studied women with endometrial carcinoma in whom the incidence of hirsutism, obesity, infertility and hypertension was high compared with controls. While much more work is needed to clarify the association of PCOS with these possible late sequelae, it is highly likely that prolonged treatment with combined oral contraceptives or ethinyl oestradiol and cyproterone acetate may prove to be important in their prevention by improving endocrine and lipid profiles and reducing hyperandrogenaemia in women with PCOS.

**Laboratory manifestations**

In concert with the symptomatology, the biochemical findings in PCOS also lack uniformity. However, excessive ovarian androgen production is characteristic of most women with the typical ovarian morphology. Overall, comparisons of large groups of women with PCOS with healthy controls have demonstrated elevated concentrations of testosterone, free testosterone, androstenedione, LH, LH:FSH ratio, free oestradiol, oestrone and fasting insulin and reduced concentrations of sex hormone binding globulin (SHBG) (Conway et al., 1989; Franks, 1989).

These overall results, however, are more informative when the groups of women with PCOS are separated into subgroups of obese and non-obese. Comparisons of these groups reveal higher concentrations of insulin, free testosterone and oestrone but lower concentrations of SHBG, LH, insulin-like growth factor binding protein-1 (IGFBP-1) and growth hormone (GH) in the obese compared with the non-obese (Conway et al., 1990; Homburg et al., 1992; Insler et al., 1993).

The endocrine profile of women with PCOS tends to vary with the symptomatology. For example, those who are ovulating with regular menstrual cycles will have lower LH, FSH, testosterone, androstenedione and fasting insulin concentrations than those with menstrual irregularities (Franks, 1989). Insulin insensitivity in PCOS occurs when there is oligo/amenorrhoea but not when menses are regular (Robinson et al., 1993). Hirsute patients have higher androgen and lower SHBG levels than the non-hirsute (Franks, 1989) and LH concentrations are higher in infertile patients and in those who miscarry (Homburg et al., 1988a).

**Pathophysiology and pathogenesis**

The exact aetiology of PCO remains unknown. While PCO may be regarded as a multifactorial syndrome, the final common pathway of the typical changes in ovarian morphology (a *sine qua non* for diagnosis) and excessive ovarian androgen production are, in my opinion, the hub of the problem in the vast majority of cases. The key question in this premise is therefore the source of the excessive ovarian androgen production. The enzyme cytochrome P450c17α, which catalyses 17-hydroxylase and 17/20 lyase activities, the rate limiting step in androgen biosynthesis (Barnes et al., 1989), is disordered in PCOS (Rosenfield et al., 1990). In response to a single dose of GnRHa, women with PCOS have an increased response in both 17-hydroxyprogesterone and androstenedione, more typical of a male response (Rosenfield et al., 1990). This has been confirmed by the Franks group who, in addition, have evidence of an abnormal regulation of cytochrome P450c17α in ovulatory women with PCOS (Franks and White, 1993).

Several pathways which may cause increased activity of cytochrome P450c17α have been suggested. Luteinizing hormone is an obvious candidate, as this hormone is presumably the main regulator of androgen production from theca cells during a normal ovulatory cycle. It is therefore reasonable to suggest that consistently high concentrations of LH will produce excessive amounts of androstenedione by causing a hyperactivity of P450c17α. However, a proportion of women with typical features of PCOS do not have elevated concentrations of LH, particularly those who are obese (Homburg et al., 1992; Insler et al., 1993), so that an alternative mechanism must be sought to explain the source of the hyperandrogenism. One suggestion (Rosenfield et al., 1990) is that, whereas in the normal ovulatory cycle the surge of LH in mid-cycle downgrades its own receptors on theca cells and so limits androgen production, this does not happen for some reason in PCOS. A more thoroughly investigated suggestion is that a larger than usual number of LH receptors are maintained by a faulty fine tuning mechanism. Insulin-like growth factor-1 (IGF-1) potentiates the expression of LH receptors (Adashi et al., 1985) and stimulates LH-induced androgen production and the accumulation of androgens in the ovary (Barbieri et al., 1986; Cara and Rosenfield, 1988). Although circulating concentrations of IGF-1 have generally been reported to be not significantly higher compared with those in non-PCOS (Homburg et al., 1992), the biological activity of IGF-1 may be raised by a decrease in concentrations of IGFBP-1 which serves as an acute modulator of IGF-1 action (Suikkari et al., 1988). As IGFBP-1 has been shown to inhibit the action of IGF-1 in the ovary (Angervo et al., 1991), suppression of IGFBP-1 may increase the potential for IGF-1 to act synergistically with LH to stimulate the theca and interstitial cells of the ovary to produce androgens (Cara et al., 1990). Our group (Homburg et al., 1992) and others (Suikkari et al., 1988; Insler et al., 1993) have found that in obese PCOS patients (i.e. predominately hyperinsulinæmic with normal LH) serum IGFBP-1 concentrations were inversely correlated with insulin concentrations and were significantly lower than those found in non-obese PCOS. It is thus postulated that the synergism of free IGF-1 and LH is capable of increasing ovarian androgen output by inducing hyperactivity of cytochrome P450c17α.

Since the association of insulin resistance, the consequent hyperinsulinæmia and PCOS was first described (Khan et al., 1976; Burghen et al., 1980), it has become clear that hyperinsulinæmia plays a key role in the pathophysiology and probably the pathogenesis of PCOS. Several facts have prompted this statement. The type of insulin resistance associated with PCOS seems to be unique to this syndrome and is probably a decrease
in insulin sensitivity due to a defect in post-receptor signal transduction between the receptor kinase and the glucose transporter (Dunaif et al., 1993). The tyrosine kinase domain of the insulin receptor gene, however, appears to be normal (Conway et al., 1994). Insulin receptors are present in the human ovary (Poretsky et al., 1985) and insulin may also bind to IGF-1 receptors and acts as a gonadotrophic hormone, enhancing induction of ovarian LH receptors and LH binding capacity (Cara et al., 1990). Hyperandrogenaemia has been shown to be a consequence of hyperinsulinaemia and the reduction of insulin concentrations with diazoxide (Nestler et al., 1989) or weight loss (Kiddy et al., 1992) decreases ovarian androgen secretion. As already mentioned, the direct control and inverse relationship of insulin and IGFBP-1 may play a cardinal role in ovarian hyperandrogenism. In addition, hyperinsulinaemia is a probable cause of decreased levels of SHBG (Plymate et al., 1988) and so also plays a role in the disturbance of androgen transport and raised concentrations of free testosterone. A study of Lanzone et al. (1994) suggests that insulin affects the responsiveness of the adrenal glands to adrenocorticotrophic hormone (ACTH) so that hyperinsulinaemia may lead to a chronic adrenal hyperfunction. In obese women with PCOS, hyperinsulinaemia is extremely common (Franks, 1989) with an estimated incidence of about 75% (Conway et al., 1990). Although insulin resistance and hyperinsulinaemia correlate with body mass index, elevated concentrations of insulin can be found in >30% of non-obese patients with PCOS (Dunaif et al., 1989; Conway et al., 1990; Buyalos et al., 1992; Grulet et al., 1993) who overall, have higher insulin levels compared with normal ovulatory women.

The kinetics of growth hormone (GH) are also disturbed in PCOS. Despite initial disparate results, when GH concentrations are controlled for obese and non-obese PCOS and compared with weight matched controls, it has become apparent that they are significantly reduced in obese and significantly raised in non-obese PCOS (Prelevic et al., 1992; Insler et al., 1993). In obese PCOS, the low levels and reduced pituitary response on stimulation of GH release with L-dopa (Acar and Kadanli, 1993), arginine (Ovesen et al., 1992) or exercise (Jaatinen et al., 1993) may be accounted for by a negative feedback response to increased levels of biologically active IGF-1 (see above). The higher than normal concentrations of GH found in non-obese (predominately not hyperinsulinaemic) PCOS are harder to explain and have given rise to speculation that GH may be directly involved in the pathogenesis of these cases (Insler et al., 1993; Homburg, unpublished data). Our group has gone one step further and shown that GH administered to women with PCOS acutely decreases IGFBP-1 and SHBG and increases IGF-1 and insulin concentrations. The decrease in IGFBP-1 concentrations may well be a direct action of GH rather than mediated through insulin as Tapanainen et al. (1991) have shown that this response precedes any rise of insulin or IGF-1. Thus, the high concentrations of GH in non-obese PCOS may be partly responsible for ovarian hyperandrogenism.

Epidermal growth factor may also be involved in the pathological meshwork, as it has been reported to negatively influence the FSH-induced aromatase reaction and has been found in higher than normal amounts in the follicular fluid of women with PCOS (Mason et al., 1990).

There is a high prevalence of PCOS within families, suggesting a genetic component, but the demonstration of a clear mode of inheritance has proved difficult (Hague et al., 1988). However, Carey et al. (1993) have lately produced convincing evidence for a single gene defect by examining, in detail, the families of 10 probands with PCO and finding that each family showed autosomal dominant inheritance for PCO with >90% penetrance. Interestingly, they also described early onset male pattern baldness as an accurate phenotype for obligate male carriers. Men with premature male pattern baldness have an elevation of their serum androgens when compared to age and weight-matched controls (Stephens et al., 1993). The group of Carey et al. (1994) have gone a step further by identifying a new single base change in the 5′ promoter region of CYP17, the gene encoding for 17α-hydroxylase. However, the pathophysiological mechanism underlying this change is not yet clear. A congenital lack of dopamine has been suggested (Vaitukaitis, 1983) but it seems likely that decreases in dopamine levels in PCOS are secondary to hyperoestrogenism. Diminished opioid output is also a possibility (Quigley et al., 1981). Raised oestrogen levels, due to increased conversion of androgens in fatty tissue, have been purported to exert a positive feedback effect on the hypophysis, so increasing LH secretion. This is contradicted somewhat by the fact that non-obese women with PCOS have predominantly higher concentrations of LH than the obese (Homburg et al., 1992; Insler et al., 1993). Increased concentrations of free 17α-oestradiol are also evident (Franks, 1989) and may increase LH secretion through a similar mechanism. However, a significant increase in LH concentrations was observed before any increase in serum oestradiol could be detected during ovulation induction with pulsatile GnRH, suggesting that an ovarian steroid was not responsible for exaggerated secretion of LH (Schachter et al., 1995). In-vitro evidence that insulin facilitates LH secretion (Adashi et al., 1981) introduces a further possibility, supported by Prelevic et al. (1990). However, we and others (Homburg et al., 1992; Insler et al., 1993), found a negative correlation between these hormonal concentrations. An attractive, new theory proposes that the hypersecretion of LH in PCOS is mediated by a deficiency of the putative gonadotrophin surge attenuating factor which is produced by small and medium sized follicles and is thought to curtail the LH surge by reducing the sensitivity of the hypophysis to GnRH (Sopelak and Hodgen, 1984; Messinis and Templeton, 1990; Balen et al., 1993a).

Most investigators have also reported an increased pulse frequency of LH in addition to the increased amplitude (Kazer,...
et al., 1987) and Crowley et al. (1993) argue that this increased frequency of GnRH pulsatility desensitizes pituitary FSH secretion and explains the finding that FSH concentrations in PCOS are some 30% below those in the early follicular phase of normal women. In their opinion, this may be the cause of the arrested folliculogenesis of PCOS. As serum inhibin concentrations are not elevated in PCOS compared with normal women (McLachlan et al., 1987), inhibin does not appear to be involved in this process. The discussion as to whether the neuroendocrinological manifestations in PCOS are the primary cause of the syndrome or whether these changes are secondary to abnormalities of secretion of ovarian steroids, growth factors or other substances is still unresolved. The fact that normalization of GnRH pulsatility by progesterone administration (Homburg et al., 1988b) or the imposition of 'physiological' doses and timing of GnRH (Christian et al., 1991), improves endocrinological and clinical parameters, does not contribute to the solution of the problem. It is my personal opinion that the abnormalities in the setting of the GnRH pulsatility clock are a secondary phenomenon and are not at the hub of the basic problem. This statement is prompted by the following reasons: PCO may be identified before menarche (Bridges et al., 1993) in women with hypogonadotrophic hypogonadism (Homburg and Jacobs, 1990; Shoham et al., 1992) and in a single ovary (Polson et al., 1986). In addition, the administration of long-term GnRHa or combined oral contraceptives does not alter the typical ovarian morphology of PCOS.

In summary, I would suggest that PCOS is basically a predominantly genetic disorder of ovarian androgen production induced by extraovarian factors, in particular, insulin resistance, hyperinsulinaemia and their biochemical sequelae. The clinical and endocrinological expression of the syndrome is determined by the extraovarian factors present.

Treatment

As the detailed basic cause of PCOS is still unknown, there is no single effective treatment regimen, merely a plethora of protocols which do not address the real cause but aim to break the vicious circle of pathological chain reactions. The treatment schedules outlined here are therefore symptomatic therapy, the choice of which is made according to the principal complaint of the patient.

However, there is one overriding principle for the treatment of obese women with PCOS, whether the main problem is cosmetically unacceptable signs of hyperandrogenism such as hirsutism or acne, infertility or prevention of long-term sequelae. Loss of 5% or more of total body weight is capable of reversing or severely reducing these symptoms and/or facilitating treatment of infertility (Kiddy et al., 1992). This is apparently achieved by reducing insulin and increasing SHBG and IGFBP-1 concentrations with a consequent reduction of ovarian androgen production and circulating free testosterone. It is safe to predict that a reduction in body mass index, maintained within normal range, may prevent the development of long-term sequelae such as diabetes mellitus, hypertension, cardiovascular and hyperlipidaemic disorders.

More sophisticated methods of reduction of insulin concentrations with diazoxide (Nestler et al., 1989), metformin (Velquez et al., 1994) or a somatostatin analogue (octreotide) (Prelevic et al., 1990) have proved to be effective in improving the endocrine milieu. Prelevic et al., 1995 utilized the property of octreotide to decrease insulin, LH and testosterone concentrations by administering 100 mg twice daily in parallel with HMG for 58 cycles in 28 anovulatory women with PCOS. Compared with a control group of 29 cycles using human menopausal gonadotrophin (HMG) alone, a more orderly follicular growth with a more appropriate endocrine milieu at the time of human chorionic gonadotrophin (HCG) administration and a significantly decreased incidence of ovarian hyperstimulation syndrome (OHSS) were recorded. More investigation is needed to examine the clinical feasibility of this mode of treatment.

For women with PCOS who are not interested in conceiving, the treatment of choice is a combination of cyproterone acetate and ethinyl oestradiol. Cyproterone acetate is a synthetic progesterone with both antagonodotropic and antiandrogenic effects, giving it an advantage for the treatment of PCOS over the majority of progestins in oral contraceptives. Its combination with ethinyl oestradiol has been successful in suppressing hyperandrogenism, resulting in improvement of clinical signs and normalization of the hormonal disturbances which characterize PCOS (Prelevic et al., 1989). The efficacy of this treatment is due to the antiandrogenic activity at androgen receptor level, suppression of serum LH and ovarian androgen concentrations, reduction in 5-reductase concentrations, increased metabolic clearance of testosterone and increase in SHBG concentration. The effect on acne and seborrhoea is usually rapid but due to the physiological cycle of the hair follicle, at least 6 months treatment are required before the reduction of hirsutism becomes clinically evident. As previously mentioned, untreated PCOS may be regarded as a progressive syndrome. It is therefore my opinion that early therapeutic intervention will not only temporarily alleviate symptoms but will place the progress of the syndrome 'on hold'. This would appear to be beneficial for future fertility prospects and possible delay or prevention of long-term sequelae.

The chronic anovulation and infertility associated with PCOS can often be successfully treated with clomiphene citrate (CC). Some 75% of those treated with CC in doses of 50–200 mg/day from day 4 or 5 of the cycle for 5 days will respond by ovulating. However, the overall pregnancy rate is only 30–40%. Several reasons have been forwarded to explain this apparent discrepancy. The main action of CC is through the hypothalamus, stimulating GnRH secretion and increasing FSH release from the hypophysis. This is often accompanied by a striking increase in serum LH concentrations (Van den Berg and Yen, 1973) and this may seriously compromise pregnancy rates in these patients (Shoham et al., 1990a). Pretreatment with progesterone is capable of modulating LH pulsatility, reducing LH concentrations and inducing more FSH synthesis and storage, so creating a more favourable environment for ovulation induction with CC (Homburg et al., 1988b). This treatment improved response to CC and consequent pregnancy
rates (Homburg et al., 1988b). An additional causative factor in those ovulating but not conceiving is the anti-oestrogenic effect of CC on the cervical mucus and, possibly, on the endometrium, hypothetically disturbing normal mechanisms of sperm transport and implantation. In some cases, the addition of ethinyl oestradiol to CC will enhance the pregnancy rate without interfering with the induction of ovulation.

Monitoring, by ultrasound examination of the ovaries, of those who fail to ovulate on maximal doses of CC, will reveal that the majority of these women will show inadequate follicular development, demanding an ‘upgrade’ of treatment. However, a minority of the non-ovulators will develop large follicle(s) but have an isolated defect of oestrogen-mediated positive feedback and may respond to a well-timed injection of HCG. Finally, the addition of dexamethasone in the few who have high dihydroepiandrosterone sulphate concentrations has been reported to improve results (Daly et al., 1984).

In our practice, ‘clomiphene failure’ is regarded as a failure to ovulate on maximal doses of CC or a failure to conceive, despite apparent ovulation in six courses of treatment. In the latter case, male and mechanical factors are re-evaluated. Several treatment modes are now available to women with PCOS who are ‘clomiphene failures’, most of which are reasonably successful in breaking the vicious circle of chain reactions and inducing ovulation and pregnancy without the ability to attack the unknown source. The administration of native GnRH in a pulsatile fashion, either subcutaneously or i.v. in a suggested dose of 15 μg/pulse every 90 min using a pump apparatus, is apparently capable of superimposing the abnormal pattern of secretion with a more physiological pattern so producing a more balanced output of gonadotrophins. This form of treatment is, however, associated with low ovulation rates (50%/cycle) and pregnancy rates/ovulatory cycle of 29% (Shoham et al., 1990b). It is particularly unsuitable for obese, hyperandrogenaemic women and the high LH concentrations observed during induction present a further obstacle (Homburg et al., 1989). The advantages of this mode of treatment are that it will yield a monofollicular response in a large proportion and therefore ovarian hyperstimulation (OHSS) is not encountered and multiple pregnancies are rarely seen if HCG administration is avoided.

Stimulation of the ovaries with exogenous gonadotrophins is more acceptable treatment for CC-resistant patients. A conventional ‘step-up’, individually adjusted dose regimen employing HMG in our hands (Farhi et al., 1993) yields a cumulative conception rate of 82% after six cycles. However, due to the high sensitivity of the PCO to gonadotrophin stimulation and its propensity to multiple follicular development, this treatment regimen is plagued by a high frequency of multiple pregnancies and OHSS (Wang and Gemzell, 1980). The use of urinary human FSH has done little to remedy this situation (Garcea et al., 1985; Homburg et al., 1990; McFaul et al., 1990). Following the initial publication of Seibel et al. (1984), several investigators have examined the utility of a chronic low dose regimen of FSH in an attempt to reduce the complication rate (Polson et al., 1987; Hamilton-Fairley et al., 1991; Shoham et al., 1991; Dale et al., 1993; Scheele et al., 1993a; Homburg et al., 1995a). The basic thinking behind this regimen is the ‘threshold theory’ which demands the attainment and maintenance of follicular development with exogenous FSH, without exceeding the threshold requirement of the ovary (Brown, 1978) which, with supraphysiological doses of FSH, provokes an initial development of a large cohort, stimulates additional follicles and even rescues those destined for atresia (Insler and Lunenfeld, 1991). This is what tends to occur in PCOS with its peculiar hypersensitivity to gonadotrophins when concentrations of FSH well above the threshold are induced during conventional treatment. This threshold has a high inter-individual variability (5.7–12 IU/l) and higher FSH concentrations are associated with multifollicular, as opposed to monofollicular, growth (Van der Meer et al., 1994). The principle of the chronic low dose regimen is, therefore, to employ smaller incremental dose rises (e.g. 37.5 IU or less) at intervals of 7 days until follicular development is initiated. A compilation of reported results using this or similar regimens, reveals that 218 patients who completed 471 cycles achieved 83 pregnancies (18%/cycle). This rate compares favourably with that of more conventional regimens but has the advantage that it is accompanied by a very low prevalence of OHSS (one cycle) and multiple pregnancies (5%). A prospective study from our centre (Homburg et al., 1995a), comparing conventional with low-dose protocols employing 50 women with CC-resistant PCOS, revealed that the low-dose protocol slightly improved pregnancy rates (40 versus 24%) while completely avoiding OHSS and multiple pregnancies which were prevalent (11 and 33% respectively) using conventional incremental doses of FSH. We concluded that this treatment modality has distinct advantages and could well replace conventional gonadotrophin therapy for these patients.

The original report of Fleming et al. (1985) on cotreatment with GnRHa and HMG for anovulatory PCOS encouraged its use for this indication. While hopes that the state of near hypogonadotropic hypogonadism induced by GnRHa would produce results with HMG as successful as those of WHO group I cases have not been fulfilled, there is a definite place for the incorporation of GnRHa into stimulation protocols for women with PCOS. The main contribution is the reduction of LH concentrations throughout the follicular phase of the cycle. This almost completely eliminates the troublesome problem of premature luteinization and the need to abandon cycles for this reason, so increasing treatment efficiency. There is now mounting evidence that the ability of GnRHa to reduce the inordinately elevated concentrations of LH prevalent in PCOS, serves to increase ovulation and pregnancy rates and, most importantly, to reduce the prevalence of early spontaneous miscarriages, which are notoriously high in PCOS accompanied by raised LH concentrations.

In a retrospective analysis from our centre (Homburg et al., 1993a), 239 women with PCOS received HMG with or without GnRHa for ovulation induction or superovulation for in-vitro fertilization (IVF)/embryo transfer. Of pregnancies achieved with GnRHa, 17.6% miscarried compared with 39.1% of those achieved with gonadotrophins alone. Cumulative live birth rates for GnRHa after four cycles were 64% compared with 26% for gonadotrophins only. Reduced miscarriage rates with GnRHa have also been reported by Balen et al. (1993b). While
a randomized, prospective study is sadly lacking to confirm these data, it is our policy to administer GnRHa to women with high LH concentrations in the follicular phase on the basis that there is little point in inducing a pregnancy which has a very high chance of being aborted. A further study from our centre (Homburg et al., 1993b) looked at the performance of women with PCOS undergoing IVF/embryo transfer who had high mean LH concentrations, compared with a control group of normally cycling women with mechanical infertility. Pregnancy rates were similar in the groups but whereas GnRHa reduced the miscarriage rate compared with gonadotrophins alone in the PCOS group, its administration to the control group had no such effect.

Administration of GnRHa to women with PCOS reduces LH and androgen concentrations. It has no effect on insulin resistance and hyperinsulinaemia, IGF-1 or IGFBP-1 concentrations (Dale et al., 1992; Homburg et al., 1995b). The reduction by GnRHa of intrafollicular concentrations of androgens which would normally induce atresia may be responsible for the increased number of follicles induced by consequent stimulation by GnRHa/HMG compared with HMG alone (Homburg et al., 1990). The increased number of developing follicles induced by cotreatment with GnRHa/HMG is accompanied by a raised incidence of OHSS and multiple pregnancies (Homburg et al., 1990).

Two interesting attempts have been made to utilize the beneficial effects of GnRHa, increase its efficiency and reduce its undesired influence on multiple follicular development. Filicori et al. (1988) followed pretreatment by GnRHa with pulsatile GnRH. While seemingly paradoxical, this combination produced good ovulation and acceptable pregnancy rates and no multiple pregnancies, but was limited by the long duration of each cycle and a relatively high incidence of abortion and luteal phase abnormalities. The logical idea of combining GnRHa with low dose FSH therapy was studied by Scheele et al. (1993b) but failed to reduce multiple folliculogenesis and its consequences. In the opinion of these investigators, the extreme sensitivity of the follicles to FSH once growth is initiated may be tempered by using even smaller incremental dose rises than those employed.

Surgical treatment by bilateral wedge resection, although relatively successful in restoring ovulation, has fallen from grace due to its propensity to adhesion formation. Laparoscopic ovarian diathermy was introduced by Gjonnaess (1984), working on the principle that similar results could be achieved while avoiding the introduction of a mechanical factor. In his small study and in larger studies since (Aakvaag, 1985; Kovacs et al., 1991; Naether et al., 1993), ovulation rates of 70–90% and pregnancy rates of 40–70% have been achieved. Postoperative laparoscopy has revealed the presence of intraperitoneal adhesions in about 20% of these cases but they are reported to be mild and unilateral (Dabirashrafi et al., 1991; Naether et al., 1993) and did not apparently affect the high pregnancy rate (Greenblatt and Casper, 1993). Significant falls of LH, androstenedione, dihydroepiandrosterone sulphate (DHEAS) and testosterone have been uniformly noted after ovarian diathermy. Laparoscopic argon laser capsule drilling has also been used with good results (Heylen et al., 1994). Laser photodiathermy may lessen adhesion formation and, following the operation, stimulation with HMG gives an enhanced ovarian response compared with the pre-diathermy response (Dabirashrafi et al., 1991; Kovacs et al., 1991). Although the majority of authors reported that the benefit of ovarian laparoscopic laser treatment is limited to approximately 6 months (reviewed by Gurgan et al., 1994), Naether et al. (1994) are of the opinion that the benefit of monopolar current is greater and that the effects may last for several years. The ideal protocol following this procedure to yield optimal results has yet to be firmly established. An excellent review by Donesky and Adashi (1995) on laparoscopic ovulation induction called for carefully constructed controlled trials before the procedure can be viewed as efficacious and safe.

For patients with PCOS who have failed to conceive during six ovulatory cycles of gonadotrophin therapy, we have found that IVF/embryo transfer is a very viable alternative. In a study from our centre (Homburg et al., 1993b), 68 such women underwent 208 cycles of IVF/embryo transfer with a cumulative conception rate of 82% at six cycles, almost identical to that of a control group of women with a pure mechanical factor undergoing similar treatment. MacDougall et al. (1993) reported very similar results. There are two possible explanations for the fact that these results were achieved with IVF/ET but not with gonadotrophin therapy. Either an overt mechanical factor was present or, more likely, this procedure allowed a more liberal approach to superovulation rather than concentrating on mono follicular development. Both of these comparative studies (Homburg et al., 1993b; MacDougall et al., 1993) reported that women with PCOS required less HMG, but produced more follicles and oocytes. However, fertilization rates were lower, probably a reflection of the number of oocytes retrieved from relatively immature follicles (<14 mm diameter) from women with PCOS. A fascinating recent development by Trounson et al. (1994) reports the successful recovery of immature oocytes from the ovaries of untreated PCOS patients and their maturation, fertilization and development in vitro. If this method can be successfully adopted, the problems of ovulation induction may well be bypassed.

In summarizing the treatment of infertility associated with PCOS, basically, the induction of ovulation may be achieved by boosting FSH stimulation of the ovaries either indirectly with clomiphene or native pulsatile GnRH, or directly with gonadotrophin preparations. The selection of treatment could not be guided by basal clinical or endocrine features in a series of 306 treatment cycles whose outcome was reported by Farhi et al. (1993). However, there seem to be two main determinants of the success of this treatment in achieving a live birth: the degree of hyperinsulinaemia and the concentrations of circulating LH. Either of these, when in excess, not only make induction of ovulation and conception relatively difficult but are associated with high rates of early miscarriage (Homburg et al., 1988a; Hamilton-Fairley et al., 1992). Their correction, particularly in obstinate cases, should be a major consideration in the attempt to achieve optimal results. With such a range of reasonably successful treatments for the induction of ovulation in PCOS, the emphasis in the selection of therapy should
now be placed on minimizing the prevalence of undesired side effects while retaining acceptable efficiency.

The LH hypothesis

Women with PCOS have a very high prevalence of high LH concentrations. A number of clinical reports have linked high concentrations of LH in the follicular phase to decreased reproductive function. When high concentrations were found in the first few days before oocytes were collected from women for IVF (Howles et al., 1986) or on the day of HCG administration (Stanger and Yovich, 1985), they were associated with impaired rates of fertilization and conception.

In a prospective study of almost 200 women with regular menstrual cycles receiving no treatment, Regan et al. (1990) reported a striking association of raised follicular phase concentrations of LH with infertility and miscarriage. When the mid-follicular phase concentrations of LH were >10 IU/L, the conception rate was 61% at 12 months compared with 80% in the women with normal LH concentrations. In those who did conceive, the miscarriage rate in the women with normal concentrations was 12% compared with 64% in those with elevated concentrations. These differences were very significant, both statistically and clinically.

The deleterious effect of raised LH concentrations has also been reported during treatment cycles. In women receiving CC, a reduced conception rate was found in those in whom serum LH concentrations were high in the follicular phase (Shoham et al., 1990a). In a large series of women with PCOS from our unit, treated with pulsatile, native GnRH, both failure to conceive despite ovulation and the occurrence of miscarriage rather than continuation of pregnancy were associated with elevated follicular phase concentrations of LH (Homburg et al., 1988a). There was no correlation between follicular phase concentrations of either androgens or progesterone and conception or miscarriage rates in these women.

Following laparoscopic ovulation induction, patients with the highest preoperative LH concentrations who experienced the fall of LH were the most likely to ovulate spontaneously following the operation (Abdel Gadir et al., 1993). Early resumption of the anovulatory state was associated with a return to pretreatment concentrations of LH.

In addition, it has been reported that 80% of women with recurrent spontaneous miscarriage had ultrasonically diagnosed PCO (Sagle et al., 1988). It may be argued that the very presence of PCOS in some way influences the rates of fertility and miscarriage. Both our series (Homburg et al., 1988a) and a study of more than 500 women with PCOS (Conway et al., 1989), in which those complaining of infertility had significantly higher LH concentrations than those with proven fertility, suggest that hypersecretion of LH is the true culprit rather than the mere presence of PCO.

Regarding the mechanism of these deleterious effects of LH, we have suggested (Homburg et al., 1988a) that, hypothetically, when concentrations of LH are high throughout the follicular phase rather than merely at the time of the physiological surge, the hormone penetrates the follicle and allows the oocyte to mature prematurely, resulting in the ovulation of an oocyte that is physiologically ‘aged’. Such oocytes are unlikely to be fertilized or will tend to produce embryos that survive poorly and therefore abort. In the normal ovulatory cycle, it is only with the appearance of the mid-cycle LH surge that the completion of the first meiotic division occurs and this timely maturation is a prerequisite for successful fertilization and development of the embryo.

There is still some discussion as to whether the effects of high LH concentrations are a direct influence on the oocyte or affect the endometrium. In an ongoing study, we have examined, in recipients, the performance of embryos derived from oocytes donated by women with PCOS who underwent ovarian stimulation with gonadotrophins with or without GnRHa. Thus, the endometrium of the recipients was a constant, while the donated oocytes were exposed (no GnRHa) or not exposed (with GnRHa) to high concentrations of LH during superovulation. In those not receiving GnRHa, the implantation rate/embryo in the recipients was 6.6% (14/212) compared to 11.7% (26/222) in those who received GnRHa (P < 0.05, Fisher’s exact test). This insinuates that the effect of high LH concentrations is directed at the oocyte and not the endometrium.

A possible partial solution to the problem, referred to above, is to administer GnRHa in order to block endogenous gonadotrophin excretion before and during gonadotrophin therapy. In this way, we succeeded in halving the miscarriage rate in women with PCOS treated for induction of ovulation and for superovulation for IVF (Homburg et al., 1993a). Other methods which lower raised LH follicular phase concentrations, such as progesterone pretreatment (Homburg et al., 1988b) and ovarian wedge resection or cauteterization (Abdel Gadir et al., 1993), facilitate ovulation and improve results of treatment.

Conclusions

This summary of the state of the art of our knowledge of PCOS has also served to indicate the gaps in this knowledge. When the jigsaw puzzle of the pathogenesis and pathophysiology is solved, the treatment modalities will become more specific and, presumably, more successful regarding the therapy of the cosmetic, fertility or long-term ramifications of this fascinating syndrome.

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