Review

The management of infertility associated with polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome [PCOS] is the commonest cause of anovulatory infertility. Treatment modes available are numerous mainly relying on ovarian stimulation with FSH, a reduction in insulin concentrations and a decrease in LH levels as the basis of the therapeutic principles. Clomiphene citrate is still the first line treatment and if unsuccessful is usually followed by direct FSH stimulation. This should be given in a low dose protocol, essential to avoid the otherwise prevalent complications of ovarian hyperstimulation syndrome and multiple pregnancies. The addition of a GnRH agonists, while very useful during IVF/ET, adds little to ovulation induction success whereas the position of GnRH antagonists is not yet clear. Hyperinsulinemia is the commonest contributor to the state of anovulation and its reduction, by weight loss or insulin sensitizing agents such as metformin, will alone often restore ovulation or will improve results when used in combination with other agents. Laparoscopic ovarian drilling is proving equally as successful as FSH for the induction of ovulation, particularly in thin patients with high LH concentrations. Aromatase inhibitors are presently being examined and may replace clomiphene in the future. When all else has failed, IVF/ET produces excellent results. In conclusion, there are very few women suffering from anovulatory infertility associated with PCOS who cannot be successfully treated today.

Review

Polycystic ovary syndrome [PCOS] is associated with approximately 75% of women who suffer from infertility due to anovulation [1,2]. It is a very heterogeneous syndrome both in its clinical presentation and laboratory manifestations. The majority of women with anovulation due to PCOS have menstrual irregularities, usually oligomenorrhea or amenorrhea, associated with clinical and/or biochemical evidence of hyperandrogenism. The main disturbances in this syndrome are:

1. Abnormal morphology of the ovary, detected by a characteristic hyperechogenic enlarged central stroma and >9 small follicles of 2–9 mm diameter on transvaginal ultrasound examination of the ovaries [3].

2. Abnormal steroidogenesis, mainly increased ovarian production of androgens but also increased progesterone and estradiol production.

3. Hyperinsulinemia, present in about 80% of obese women and 30–40% of women of normal weight with PCOS [4] and more strongly associated with anovulation than any other feature of the syndrome.

4. Abnormal gonadotrophin secretion, most commonly manifested as increased serum LH concentrations in 40% of women with ultrasonically detected PCO [5]. A functional deficiency of the endogenous action of FSH also seems to be present in women with anovulatory PCOS.

Several modes of inducing ovulation for these patients will now be described. It will be seen that they basically depend on either a reduction of insulin concentrations, FSH stimulation or a reduction of LH concentrations or a combination of these.

Weight loss

Excess body weight is a common problem of modern society, reaching epidemic proportions in some countries. For women with PCOS, an excess of body fat accentuates insulin resistance and its associated clinical sequelae. Central obesity and BMI are major determinants of insulin resistance, hyperinsulinemia and hyperandrogenemia. The rate of insulin resistance in women with PCOS is 50–80% and a large majority of these women are obese [6,7].

They almost inevitably have the stigmata of hyperandrogenism and irregular or absent ovulation. Insulin stimulates LH and ovarian androgen secretion and decreases sex hormone binding globulin concentrations [8].

The successful treatment of obesity and hyperinsulinemia is capable of reversing their deleterious effects, of which there are several, on the outcome of treatment. More gonadotrophins are required to achieve ovulation in insulin resistant women [9,10]. Obese women being treated with low dose gonadotrophin therapy have inferior pregnancy and miscarriage rates [11]. Both obese [12] and insulin resistant [10] women with PCOS, even on low dose FSH stimulation, have a much greater tendency to a multifollicular response and thus a relatively high cycle cancellation rate in order to avoid hyperstimulation.

Just as obesity expresses and exaggerates the signs and symptoms of insulin resistance, then loss of weight can reverse this process by improving ovarian function and the associated hormonal abnormalities [13–15]. Loss of weight induces a reduction of insulin and androgen concentrations and an increase in sex hormone binding hormone concentrations. Curiously, in obese women with PCOS, a loss of just 5–10% of body weight is enough to restore reproductive function in 55–100% within 6 months of weight reduction [13–15]. Weight loss has the undoubted advantages of being effective and cheap with no side effects and should be the first line of treatment in obese women with anovulatory infertility associated with PCOS.

Clomiphene citrate

The introduction of even small amounts of FSH into the circulation either directly with FSH injections or indirectly with with pulsatile GnRH or clomiphene citrate, is capable of inducing ovulation and pregnancy in a large number of anovulatory women with PCOS. Clomiphene citrate has long been the first line of treatment for those with absent or irregular ovulation. It is given in a dose of 50–250 mg per day for 5 days starting from day 2–5 of spontaneous or induced bleeding starting with the lowest dose and raising the dose in increments of 50 mg/day each cycle until an ovulatory cycle is achieved. In practice, I almost inevitably use a starting dose of 100 mg per day from day 4 or 5 and have found no advantage in using a daily dose of more than 150 mg which seems neither to significantly increase the ovulation rate nor follicular recruitment. This sort of regimen will cut down the number of 'superfluous' cycles of treatment until ovulation is achieved and until those resistant to clomiphene are identified. A course of 3–6 ovulatory cycles is usually sufficient to know whether pregnancy will be achieved using clomiphene citrate before moving on to more complex treatment as approximately 75% of the pregnancies achieved with clomiphene occur within the first three cycles of treatment [16].

Ovulation is restored in approximately 80% but will result in pregnancy in only about 35–40% of patients who are given clomiphene [16–18]. Additionally, around 20–25% of anovulatory women with PCOS will not respond at all to clomiphene citrate and are considered to be 'clomiphene resistant' [19,20]. Patients who do not respond to clomiphene are likely to be more obese, insulin resistant and hyperandrogenic than those who do respond [20]. As clomiphene citrate induces a discharge of LH as well as FSH and elevated LH concentrations are believed to impede conception, those with high basal LH levels are also less likely to respond to clomiphene treatment [21]. The most probable factor involved in this large discrepancy between ovulation and pregnancy rates in patients treated with clomiphene is the anti-estrogenic effects of clomiphene at the level of the endometrium and cervical mucus. While the depression of the cervical mucus, occurring in about 15% of patients, may be overcome by performing intra-uterine insemination [IUI], suppression of endometrial proliferation, unrelated to dose or duration of treatment but apparently idiosyncratic, indicates a poor prognosis for conception in my experience when endometrial thickness never reaches 8 mm. Monitoring of the clomiphene treated cycle by ultrasound evaluation of follicular growth, endometrial thickness and even estradiol and progesterone concentrations on day 12–14 of the cycle is justified by the identification of those who are not responding or have depressed endometrial thickness and is helpful in the timing of natural intercourse or IUI.

Although this monitoring implies added expense, this is neutralized by the prevention of protracted periods of possibly inappropriate therapy and delay in the inception of more efficient treatment.

The results of clomiphene treatment may be improved by co-treatment with several proposed adjuvants. The addition of an ovulatory dose of hCG, 5,000–10,000 IU is only theoretically warranted when the reason for a non-ovulatory response is that the LH surge is delayed or absent despite the presence of a well developed follicle. Although the routine addition of hCG at mid-cycle seems to add little to the improvement of conception rates [22]. I have found it very useful, given when an ultrasonically demonstrated leading follicle attains a diameter of 18–24 mm, for the timing of intercourse or IUI.

Daily doses of dexamethasone, 0.5 mg at bedtime, as an adjunct to clomiphene therapy, suppress the adrenal androgen secretion and may induce responsiveness to clomiphene in previous non-responders, mostly hyperandrogenic women with PCOS with elevated concentrations of dehydroepiandrosterone sulphate [DHEAS] [23,24]. Although this method meets with some success, medium to long term glucocorticoid steroid therapy often induces side effects including increased appetite and weight gain which is not an appealing proposition for women with PCOS.

The combined treatment of clomiphene with metformin is dealt with in the section on metformin.

Aromatase inhibitors

Aromatase inhibitors have been suggested as an alternative treatment to clomiphene as the discrepancy between ovulation and pregnancy rates with clomiphene citrate has been attributed to its anti-estrogenic action and estrogen receptor depletion. The aromatase inhibitors do not possess the adverse anti-estrogenic effects of clomiphene but, by suppressing estrogen production, mimic the central reduction of negative feedback through which clomiphene works. Letrozole, the most prevalently used anti-aromatase for this indication, has been shown to be effective, in early trials, in inducing ovulation and pregnancy in women with anovulatory PCOS and inadequate clomiphene response [25] and improving ovarian response to FSH in poor responders [26]. Evidence from larger trials is still awaited but some encouragement may be taken from the solidity of the working hypothesis and the success of the preliminary results.

Gonadotrophin therapy

Gonadotrophin [FSH] therapy is usually the next step following failure with clomiphene, i.e. there has been no

response to clomiphene in a daily dose of 150 mg or 4–6 ovulatory cycles have not resulted in a pregnancy.

The main complications of gonadotrophin therapy, ovarian hyperstimulation syndrome [OHSS] and multiple pregnancies, are both caused by multiple follicular development. Anovulatory women with PCOS are particularly prone to multiple follicular development when receiving gonadotrophins.

Acceptable cumulative conception rates have been achieved using conventional step-up treatment with gonadotrophins for women with PCOS. However, because of the peculiarly high sensitivity of polycystic ovaries to gonadotrophin stimulation, this form of treatment, employing incremental dose rises of 75 IU every 5–7 days, characteristically induces multiple follicular development, resulting in a high frequency of multiple pregnancies and ovarian hyperstimulation syndrome [OHSS]. A review by Hamilton-Fairley & Franks [27] reported a mean multiple pregnancy rate of 34% and severe OHSS of 4.6%. In a further study, although this traditional protocol produced a cumulative conception rate of 82% after six cycles, it was plagued by an unacceptable rate of multiple pregnancies and OHSS [28]. The supraphysiological doses of FSH used in the conventional protocol provoke an initial development of a large cohort, stimulate additional follicles, and even rescue those follicles destined for atresia [29]. Levels of FSH well above the threshold induce a multiple follicular development. While this can be utilized for the induction of superovulation for in-vitro fertilization and embryo transfer, for the induction of ovulation in women with PCOS the problem of achieving the desired monofollicular ovulation is particularly difficult and acute due to the extreme sensitivity of the polycystic ovary to gonadotrophic stimulation. This is not due to a difference of FSH threshold levels of the polycystic ovaries but probably to the fact that they contain twice the number of available FSH-sensitive antral follicles in their cohort compared with the normal ovary [30]. Any dose of FSH overstepping the threshold of the polycystic ovary will, therefore, produce multifollicular development and impending danger of multiple pregnancy and OHSS.

The chronic low dose regimen of FSH was designed to reduce the rate of complications due to multiple follicular development [For review, see ref. [31], the reasoning being that the 'threshold theory', demanding the attainment and maintenance of follicular development with exogenous FSH without exceeding the threshold requirement of the ovary should be employed. The principle of the classic chronic low dose regimen is to employ a low starting dose for 14 days and then use small incremental dose rises when necessary, at intervals of not less than 7 days, until follicular development is initiated [32,33]. The

dose that initiates follicular development is continued until the criteria for giving hCG are attained. This form of therapy aims to achieve the development of a single dominant follicle rather than the development of many large follicles and thereby avoid the complications of OHSS and multiple pregnancies.

A comparative prospective study of the conventional regimen with chronic low dose administration of FSH for anovulation associated with PCOS [28] involved 50 participants treated with FSH, half of them using a conventional stepwise protocol [incremental dose rises of 75 IU every 5–7 days when necessary] and half with a regimen of chronic low dose as described above. Both methods of treatment had an initial dose of 75 IU FSH. Compared with the conventional dose protocol, the chronic low dose regimen yielded slightly improved pregnancy rates [40% versus 24%] while completely avoiding OHSS and multiple pregnancies, which were prevalent [11% OHSS and 33% multiple pregnancies] with conventional therapy. Uniovulation was induced in 74% versus 27% of cycles and the total number of follicles > 16 mm and estradiol concentrations were half those observed on conventional therapy. A large French multicentre study [34] with an identical objective and protocol design compared conventional and chronic low dose regimens in 103 anovulatory WHO Group II women. The comparison of low with conventional dose revealed pregnancy rates of 33.3% versus 20%, and with a multiple [twins] pregnancy rate of 14% and 22%, respectively. The total number of follicles > 10 mm and estradiol concentrations on the day of hCG in the low dose group were half those seen on conventional therapy. Additionally, the low dose regimen tended to produce a higher rate of mono- or bifollicular development in this study.

Reported results [31] using a chronic low dose protocol identical to that described above, show a remarkably consistent rate of uniovulatory cycles of around 70% and an acceptable pregnancy rate of 40% of the patients and 20% per cycle. However, the justification for the adoption of the chronic low dose protocol may be seen in the almost complete elimination of OHSS and a multiple pregnancy rate of <6%.

In the normal ovulatory cycle, decreasing FSH concentrations are seen throughout the follicular phase. In order to mimic more closely the events of the normal ovulatory cycle, the Rotterdam group examined a step-down dose regimen with a starting dose of 150 IU and decreasing the dose by 0.5 ampoules when a follicle of 10 mm ensues and by the same amount every 3 days if follicular growth continues [35,36]. A comparison of this regimen with the classic step-up regimen from the same group [37] demonstrated a monofollicular growth rate of 88% of cycles in the step-down regimen compared with 56% with the step-up protocol. In the step-down group, duration of treatment and gonadotrophin requirement were significantly reduced. However, a recently concluded randomized, French multicenter study comparing the step-up versus the step-down protocol demonstrated superiority of the step-up regimen as regards the rates of monofollicular development, overstimulation and ovulation. [38]

Assuming that the step-up protocol is superior to the step-down version, do the initial dose, the duration of its administration and the incremental dose rise influence results? From the largest published series of chronic low dose FSH therapy [12] it was possible to compare the results of a starting dose of 75 IU with that of 52.5 IU for an initial 14-day period with an incremental dose rise of 37.5 IU or 22.5 IU respectively. There were no significant differences between the two groups but pregnancy rate/ patient, uni-ovulatory cycle rate and miscarriage rate were all in favour of the smaller starting dose.

Although the majority of patients with PCOS will reach criteria for hCG administration within 14 days using 75 IU/day of urinary FSH [12] or 50 IU/day of recombinant FSH, some have attempted to cut down the initial period of 14 days without change of dose to 7 days. A comparison of 14 day versus 7 day starters [31] in 50 patients showed no significant differences other than a slightly higher rate of multiple pregnancies in the 7-day group. As we regarded a multiple pregnancy as a 'failure' of treatment, we reverted back to the 14 day initial period without any change of dose.

A recently completed multicenter study employing a step-up protocol starting with doses of 50 IU/day of 'Puregon' for a minimum of 7 days, compared two randomized groups using incremental dose rises of 25 IU or 50 IU when needed [H.J. Out, personal communication]. The use of the smaller incremental dose rises was significantly more beneficial in terms of monofollicular development, ovulation rates and cancellation rates.

To summarise, low dose, step-up gonadotrophin therapy should be preferred to the now outdated conventional therapy for patients with PCOS. Small starting doses in the first cycle for a 14-day initial period without a dose change and then a small incremental dose rise if required, seem on present evidence to give the best results.

GnRH agonists
The ability of GnRH agonists to suppress LH concentrations before and during ovarian stimulation has earned them an undisputed place in IVF treatment protocols. They confer the advantage of eliminating, almost completely, the annoying occurrence of premature luteiniza-

tion. In addition, some investigators have reported more pregnancies, possibly better quality eggs and less miscarriages [39]. Their possible application during ovulation induction should therefore be particularly relevant in the presence of the chronic, tonic, high serum concentrations of LH observed in a high proportion of women with PCOS. Theoretically, by suppressing LH concentrations, GnRH agonists should eliminate premature luteinization and alleviate the relatively low pregnancy rates and the high miscarriage rates witnessed in this group of patients [9]. In a large study [40] 239 women with PCOS received hMG with or without GnRH agonist for ovulation induction or superovulation for IVF/embryo transfer. Of pregnancies achieved with GnRH agonist, 17.6% miscarried compared with 39% of those achieved with gonadotrophins alone. Cumulative live birth rates after four cycles for GnRH agonist were 64% compared with 26% for gonadotrophins only.

The GnRH agonist has not become standard treatment for ovulation induction in PCOS despite the fact that our experience and that of others has shown an increased pregnancy rate and lower miscarriage rate in women receiving combination treatment of agonist and gonadotrophins when tonic LH concentrations are high [42]. There are several reasons for this apparent anachronism. Co-treatment with GnRH agonist and low dose gonadotrophin therapy is more cumbersome, longer, requires more gonadotrophins to achieve ovulation, has a greater prevalence of multiple follicle development and consequently more OHSS and multiple pregnancies. This combination therapy should be reserved for women with high serum concentrations of LH who have repeated premature luteinization, stubbornly do not conceive on gonadotrophin therapy alone or who have conceived and had early miscarriages on more than one occasion.

There is no doubt that GnRH agonists cannot help to reduce the incidence of OHSS and multiple pregnancies in PCOS ovulation induction. If anything, combining GnRH agonist with gonadotrophin stimulation will exacerbate the problem of multiple follicular development and therefore increase rates of cycle cancellation, OHSS and multiple pregnancy [41,42]. This may be due to several factors: loss of the endogenous feedback mechanism when using GnRH agonist, reduction of intra-follicular androgen levels following pituitary down regulation and consequently postponed atresia and, most probably, greater stimulation of follicles by the larger amounts of gonadotrophins needed when using GnRH agonist. A GnRH agonist is not the solution to the problem of multiple follicular development.

The two main complications of ovulation induction for PCOS are multifollicular development and the possible deleterious effects of high LH levels, low conception rates and high miscarriage rates. A combination of chronic low dose FSH stimulation with GnRH agonist therapy should theoretically therefore yield the best results. Scheele et al. [43] studied women with PCOS undergoing ovulation induction with chronic low dose FSH therapy, one group with and one without adjuvant GnRH agonist therapy. A very low rate of monofollicular ovulation was achieved [14%] in the agonist cycles compared with 44% of those treated with low dose FSH alone. Treatment with GnRH agonist abolished neither the inter- nor intra-individual variability of the FSH dose required to induce ongoing follicular growth but also seemed to induce an even further increase in the sensitivity of the PCO follicles to gonadotrophin stimulation once the threshold FSH dose had been reached.

GnRH antagonists

The antagonists have some advantages over the agonists and these may well become utilized in the treatment of anovulatory PCOS. Firstly, antagonists act by the mechanism of competitive binding and this allows a modulation of the degree of hormonal suppression by adjustment of the dose. Further, antagonists suppress gonadotrophin release within a few hours, have no flare-up effect and gonadal function resumes without a lag effect following their discontinuation. If we apply these advantages to an ovulation induction protocol for PCOS, one can visualize that, used in combination with low dose FSH administration, the antagonist could be given in single or repeated doses when a leading follicle of 13–14 mm is produced. This would theoretically prevent premature luteinization, protect the oocyte from deleterious effects of high LH concentrations and still allow the follicle to grow unhindered to ovulatory size. Compared to agonist treated cycles this would confer the, again, theoretical advantages of a much shorter cycle of treatment, promise more conceptions and less miscarriages, reduce the amount of gonadotrophin required and increase the incidence of monofollicular ovulation with a consequent reduction in the prevalence of OHSS and multiple pregnancies. Only one trial employing a GnRH antagonist with recombinant FSH, specifically for women with PCOS, has been published to date [44]. Following pre-treatment with oral contraceptives, a GnRH antagonist was started on in 20 patients on day 2 of the cycle. When LH concentrations were found to be suppressed, concurrent antagonist and recombinant FSH therapy was started and continued until the day of hCG. LH was effectively suppressed by one dose of antagonist and all patients ovulated. Overall clinical pregnancy rates were 44% and on-going pregnancy rates 28%. This is a preliminary trial but large RCT's are needed to confirm these results.

Metformin

The basic etiology behind the anovulation associated with PCOS is mainly insulin resistance and hyperinsulinemia [45,46]. This strong association between hyperinsulinemia and anovulation would suggest that a reduction of insulin concentrations could be of great importance. Weight loss for the obese can reverse this situation as mentioned above but for those who fail to lose weight or are of normal weight but hyperinsulinaemic, an insulin sensitizing agent such as metformin is indicated. However, the indications for the administration of metformin to anovulatory women with PCOS in an ovulation induction program have widened as it seems to be difficult to predict which individuals will respond well with this medication [46]. Metformin is an oral biguanide, well established for the treatment of hyperglycaemia, that does not cause hypoglycaemia in normoglycaemic patients. The sum total of its actions is a decrease in insulin levels and, as a consequence, a lowering of circulating total and free androgen levels with a resulting improvement of the clinical sequelae of hyperandrogenism.

There are now a large number of studies published on the effect of metformin in a dose of 1500–2550 mg/day in women with PCOS. The vast majority of these studies have demonstrated a significant improvement in insulin concentrations, insulin sensitivity, and serum androgen concentrations accompanied by decreased LH and increased SHBG concentrations [48]. The restoration of regular menstrual cycles by metformin has been reported in the large majority of published series and the reinstatement of ovulation occurred in 78%-96% of patients [45–50]. Fleming et al [46], in the largest randomized controlled trial published to date, demonstrated a significantly increased frequency of ovulation with metformin as compared to placebo in a group of 92 oligomenorrheic women with PCOS. This was achieved without any significant changes in the insulin response to glucose challenge after 14 weeks of metformin treatment in a dose of 850 mg, twice a day.

In a randomised controlled trial [RCT] performed on clomiphene resistant infertile patients with PCOS, compared with placebo, metformin markedly improved ovulation and pregnancy rates with clomiphene treatment [51]. In a large study, 46 anovulatory obese women with PCOS who did not ovulate on metformin or placebo for 35 days were given 50 mg of clomiphene daily for 5 days while continuing metformin or placebo. Of those on metformin, 19 of 21 ovulated compared with 2 of 25 on placebo [47].

When women with clomiphene resistant PCOS were administered FSH with or without pretreatment with metformin for one month in an RCT, those receiving metformin developed significantly less large follicles, produced less estradiol and had fewer cycles cancelled due to excessive follicular development. The reduction of insulin concentrations induced by metformin seemed to favour a more orderly follicular growth in response to exogenous gonadotrophins for ovulation induction [52]. In the one published study on the effects of metformin on clomiphene resistant patients undergoing IVF/ICSI, the results of cycles preceded by treatment with metformin were compared retrospectively to those in which metformin was not given. Those receiving metformin had a decreased total number of follicles but no difference in the mean number of oocytes retrieved. There were more mature oocytes, embryos cleaved, increased fertilisation and clinical pregnancy rates [70% vs 30%] in the metformin group [53]. These latter two studies would seem to confirm that both obese [12] and insulin resistant [10] women with PCOS have a much greater tendency to a multifollicular response and thus a relatively high cycle cancellation rate on low dose FSH stimulation.

The evidence so far is encouraging concerning the efficiency and safety of metformin as a single agent or in combination with clomiphene citrate or gonadotrophins for induction of ovulation in women with hyperinsulinaemic PCOS [54]. It remains to be seen whether metformin, which probably also has a direct androgen lowering action on the ovary, will be of help to all women with PCOS wishing to conceive. Not only does metformin seem to be safe when continued throughout pregnancy but preliminary data strongly suggest that this strategy can severely decrease the high miscarriage rate usually associated with PCOS [55,56]. It is hoped that the apparent lack of terratogenicity and beneficial effect of metformin on miscarriage rates will be confirmed by future studies.

Other compounds with the property of lowering insulin concentrations, the glitazones rosiglitazone and pioglitazone, and d-chiro-inositol, are under investigation and may also prove useful for women with anovulatory PCOS.

Laparoscopic ovarian drilling

Laparoscopic ovarian drilling [LOD] by diathermy or laser now presents a further treatment option for women with anovulatory infertility associated with polycystic ovary syndrome. This laparoscopic version of ovarian wedge resection employs a unipolar coagulating current or puncture of the ovarian surface with a laser in 4–10 places to a depth of 4–10 mm on each ovary. An analysis [57] of the first 35 reports, mostly uncontrolled series, showed that 82% of 947 patients ovulated following the operation and 63% conceived either spontaneously or after treatment with medications to which they had previously been resistant. A Cochrane data base analysis of six randomized controlled trials [58] mostly comparing laparoscopic ovarian drilling with gonadotrophin therapy, showed

similar cumulative ongoing pregnancy rates 6–12 months after LOD and after 3–6 cycles of gonadotrophin therapy [58]. A large, recently completed, multicenter study in The Netherlands, showed parity in the results of LOD and low-dose FSH therapy [Bayram et al., submitted for publication]. The Cochrane analysis [58] highlighted the main advantage of ovarian drilling – a very high prevalence of monofollicular ovulation and therefore a significant reduction in multiple pregnancy rates compared with gonadotrophin therapy. Further possible advantages of LOD are a reported reduction in miscarriage rates [59], the fact that it is an often successful "one-off" procedure which may avoid the use of expensive medical therapy and the exclusion of ovarian hyperstimulation syndrome. If ovulation is not forthcoming within 2–3 months following LOD, then ovulation induction can often be more successfully employed than preceeding the operation. However, in a large number of cases spontaneous ovulation has been induced even for several years following LOD in a similar fashion to ovarian wedge resection, the "predecessor" of LOD [60]. As LOD is less invasive and causes less pelvic adhesions then ovarian wedge resection, there is every reason to expect similar or even more impressive results from LOD than present evidence suggests. Those who are slim and have high LH concentrations seem to have the most favourable prognosis [61]. However, the mechanism involved in the restoration of ovulation is quite unknown although the principle endocrine change is a dramatic decrease in LH concentrations about two days after the operation.

IVF/ET

If all else fails for the infertile PCOS patient then in-vitro fertilization is a last resort providing excellent results. Although a smaller percentage of recovered oocytes are fertilized, the larger number of oocytes recovered from PCOS patients balances out the pregnancy rate in comparison with, for example, women with a mechanical factor [39]. In-vitro maturation of oocytes from women with PCOS may become a possible option [62]. However, it is proving technically difficult at present and concerns over the well being of pregnancies achieved from IVM have not yet been fully answered.

Conclusions

Following weight loss if warranted, clomiphene citrate is the usual first-line treatment. If clomiphene fails to induce ovulation and pregnancy, several therapeutic paths are open depending on the individual case: low dose FSH therapy, addition of metformin to clomiphene or FSH treatment, laparoscopic ovarian drilling and finally, IVF. Alternative possibilities for treatment in the near future include aromatase inhibitors and in-vitro maturation of oocytes. Whatever the treatment option used, there are very few women today who suffer from pure anovulatory

infertility due to PCOS who will remain involuntarily childless.

References

1. Adams J, Polson DW and Franks S: **Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism.** *Br Med J* 1986, **293**:355-359.
2. Hull MG: **Epidemiology of infertility and polycystic ovarian disease: endocrinological and demographic studies.** *Gynaecol Endocrinol* 1987, **1**:235-245.
3. Adams J, Franks S, Polson DW, Mason HD, Abdulwahid N, Tucker M, Morris DV, Price J and Jacobs HS: **Multifollicular ovaries: clinical and endocrine features and response to pulsatile gonadotrophin releasing hormone.** *Lancet* 1985, **2**:1375-1379.
4. Dunaif A, Segal K, Futterweit W and Dobrjansky A: **Profound peripheral resistance independent of obesity in polycystic ovary syndrome.** *Diabetes* 1989, **38**:1165-1174.
5. Balen AH, Conway GS, Kaltsas G, Techatrasak K, Manning PJ, West C and Jacobs HS: **Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients.** *Hum Reprod* 1995, **10**:2107-2111.
6. Legro RS, Finegood D and Dunaif A: **A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome.** *J Clin Endocrinol Metab* 1998, **83**:2694-2698.
7. Carmina E and Lobo RA: **Polycystic ovary syndrome: arguably the most common endocrinopathy is associated with significant morbidity in women.** *J Clin Endocrinol Metab* 1999, **84**:1897-1899.
8. Poretsky L, Cataldo NA, Rosenwaks Z and Giudice LA: **The insulin-related ovarian regulatory system in health and disease.** *Endocr Rev* 1999, **20**:535-582.
9. Homburg R: **Adverse effect of luteinizing hormone on fertility: fact or fantasy.** *Baillieres Clin Obstet Gynaecol* 1998, **12**:555-563.
10. Dale O, Tanbo T, Haug E and Abyholm T: **The impact of insulin resistance on the outcome of ovulation induction with low-dose FSH in women with polycystic ovary syndrome.** *Hum Reprod* 1998, **13**:567-570.
11. Hamilton-Fairley D, Kiddy D, Watson H, Paterson C and Franks S: **Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary treated with low dose gonadotrophin.** *Br J Obstet Gynaecol* 1992, **99**:128-131.
12. White DM, Polson DW, Kiddy D, Sagle P, Watson H, Gilling-Smith C, Hamilton-Fairley D and Franks S: **Induction of ovulation with low-dose gonadotrophins in polycystic ovary syndrome: an analysis of 109 pregnancies in 225 women.** *J Clin Endocrinol Metab* 1996, **81**:3821-3824.
13. Kiddy DS, Hamilton-Fairley D, Bush A, Anyaoku V, Reed MJ and Franks S: **Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome.** *Clin Endocrinol* 1992, **36**:1105-1111.
14. Pasquali R, Antenucci D, Casmirri F, Venturoli S, Paradisi R, Fabbri R, Balestra V, Melchionda N and Barbara L: **Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss.** *J Clin Endocrinol Metab* 1989, **68**:173-179.
15. Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X and Norman RJ: **Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women.** *Hum Reprod* 1995, **10**:2705-2712.
16. Gysler M, March CM, Mishell DR and Bailey EJ: **A decade's experience with an individualized clomiphene treatment regimen including its effects on the postcoital test.** *Fertil Steril* 1982, **37**:161-167.
17. MacGregor AH, Johnson JE and Bunde CA: **Further clinical experience with clomiphene citrate.** *Fertil Steril* 1968, **19**:616-622.
18. Imani B, Eijkemans MJ and te Velde ER: **A nomogram to predict the probability of live birth after clomiphene citrate induction of ovulation in normogonadotropic oligomenorrheic infertility.** *Fertil Steril* 2002, **77**:91-97.
19. Franks S and Hamilton-Fairley D: **Ovulation Induction:Gonadotrophins.** *In:Reproductive Endocrinology, Surgery and Technology* Edited by: *Adashi EY, Rock JA, Rosenwaks Z. Philadelphia, Lippincott-Raven*; 1996.
20. Imani B, Eijkemans MJ, te Velde ER, Habbema JD and Fauser BC: **Predictors of patients remaining anovulatory during clomiphene citrate induction of ovulation in normogonadotropic**

oligomenorrheic infertility. *J Clin Endocrinol Metab* 1998, **83:**2361-2365.

21. Homburg R, Armar NA, Eshel A, Adams J and Jacobs HS: **Influence of serum luteinizing hormone concentrations on ovulation, conception and early pregnancy loss in polycystic ovary syndrome.** *Br Med J* 1988, **297:**1024-2106.

22. Agrawal SK and Buyalos RP: **Corpus luteum function and pregnancy rates with clomiphene citrate therapy: comparison of human chorionic gonadotrophin-induced versus spontaneous ovulation.** *Hum Reprod* 1995, **10:**328-331.

23. Diamant YZ and Evron S: **Induction of ovulation by combined clomiphene citrate and dexamethasone treatment in clomiphene citrate non-responders.** *Eur J Obstet Gynecol Biol* 1981, **11:**335-340.

24. Daly DC, Walters CA, Soto-Albors CE, Tohan N and Riddick DH: **A randomized study of dexamethasone in ovulation induction with clomiphene citrate.** *Fertil Steril* 1984, **41:**844-848.

25. Mitwally MF and Casper RF: **Use of aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate.** *Fertil Steril* 2001, **75:**305-309.

26. Mitwally MF and Casper RF: **Aromatase inhibition improves ovarian response to FSH: a potential option for low responders during ovarian stimulation.** *Fertil Steril* 2001, **75:**88-89.

27. Hamilton-Fairley D and Franks S: **Common problems in induction of ovulation.** *Ballieres Clin Obstet Gynaecol* 1990, **4:**609-625.

28. Homburg R, Levy T and Ben-Rafael Z: **A comparative prospective study of conventional regimen with chronic low-dose administration of follicle-stimulating hormone for anovulation associated with polycystic ovary syndrome.** *Fertil Steril* 1995, **63:**729-733.

29. Insler V: **Gonadotrophin therapy: new trends and insights.** *Int J Fertil* 1988, **33:**85-91.

30. Van der Meer M, Hompes P, de Boer J, Schats R and Schoemaker J: **Cohort size rather than follicle-stimulating hormone threshold levels determines ovarian sensitivity in polycystic ovary syndrome.** *J Clin Endocrinol Metab* 1988, **83:**423-426.

31. Homburg R and Howles CM: **Low dose FSH therapy for anovulatory infertility associated with polycystic ovary syndrome: rationale, reflections and refinements.** *Hum Reprod Update* 1999, **5:**493-499.

32. Seibel MM, Kamrava MM, McArdle C and Taymor ML: **Treatment of polycystic ovarian disease with chronic low dose follicle stimulating hormone: biochemical changes and ultrasound correlation.** *Int J Fertil* 1984, **29:**39-43.

33. Polson DW, Mason HD, Saldahna MBY and Franks S: **Ovulation of a single dominant follicle during treatment with low-dose pulsatile FSH in women with PCOS.** *Clin Endocrinol* 1987, **26:**205-212.

34. Hedon B, Hugues JN, Emperaire JC, Chabaud JJ, Barbereau D, Boujenah A, Howles CM and Truong F: **A comparative prospective study of a Chronic low dose versus a conventional ovulation stimulation regimen using recombinant human follicle-stimulating hormone in anovulatory infertile women.** *Hum Reprod* 1998, **13:**2688-2692.

35. Schoot BC, Hop WC, de Jong FH, van Dessel TJ and Fauser BC: **Initial oestradiol response predicts outcome of exogenous gonadotrophins using a step-down regimen for induction of ovulation in PCOS.** *Fertil Steril* 1995, **64:**1081-1087.

36. Van Dessel HJHM, Schoot BC, Schipper I, Dahl KD and Fauser BC: **Circulating immunoreactive and bioactive follicle-stimulating hormone concentrations in anovulatory infertile women during gonadotrophin induction of ovulation using a decremental dose regimen.** *Hum Reprod* 1995, **11:**101-108.

37. Van Santbrink EJP and Fauser BCJM: **Urinary follicle-stimulating hormone for normogonadotropic clomiphene resistant anovulatory infertility: prospective, randomized comparison between low dose step-up and step-down dose regimens.** *J Clin Endocrinol Metab* 1997, **82:**3597-3602.

38. Christin-Maitre S and Hugues JN: **A comparative randomized multricentric study comparing the step-up versus the step-down protocol in polycystic ovary syndrome.** *Hum Reprod* 2003, **18:**1626-1631.

39. Homburg R, Berkovitz D, Levy T, Feldberg D, Ashkenazi J and Ben-Raphael Z: **In-vitro fertilization and embryo transfer for the treatment of infertility associated with polycystic ovary syndrome.** *Fertil Steril* 1993, **60:**858-863.

40. Homburg R, Levy T and Berkovitz D: **GnRH agonist reduces the miscarriage rate for pregnancies conceived in women with polycystic ovary syndrome.** *Fertil Steril* 1993, **59:**527-531.

41. Van der Meer M, Hompes PGA and Scheele F: **The importance of endogenous feedback for monofollicular growth in low-dose step-up ovulation induction with FSH in PCOS, a randomized study.** *Fertil Steril* 1996, **66:**571-576.

42. Homburg R, Eshel A, Kilborn J, Adams J and Jacobs HS: **Combined luteinizing hormone releasing hormone analogue and exogenous gonadotrophins for the treatment of infertility associated with polycystic ovaries.** *Hum Reprod* 1990, **5:**32-37.

43. Scheele F, Hompes PGA, van der Meer M, Schoute E and Schoemaker J: **The effects of a gonadotrophin-releasing hormone agonist on treatment with low dose follicle stimulating hormone in polycystic ovary syndrome.** *Hum Reprod* 1993, **8:**699-704.

44. Elkind-Hirsch KE, Webster BW, Brown CP and Vernon MW: **Concurrent ganirelix and follitropin-beta therapy is an effective and safe regimen for ovulation induction in women with polycystic ovary syndrome.** *Fertil Steril* 2003, **79:**603-607.

45. Velazquez EM, Acosta A and Mendoza SG: **Menstrual cyclicity after metformin therapy in polycystic ovary syndrome.** *Obstet Gynecol* 1997, **90:**392-395.

46. Fleming R, Hopkinson ZE, Wallace AM, Greer IA and Sattar N: **Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial.** *J Clin Endocrinol Metab* 2002, **87:**569-74.

47. Nestler JE, Jakubowicz DJ, Evans WS and Pasquali R: **Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome.** *N Engl J Med* 1998, **338:**1876-80.

48. Nestler JE, Stovall D, Akhter N, Iuorno MJ and Jacubwicz DJ: **Strategies for the use of insulin-sensitizing drugs to treat infertility in women withpolycystic ovary syndrome.** *Fertil Steril* 2002, **77:**209-215.

49. Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, Zanolin E and Muggeo M: **Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation.** *J Clin Endocrinol Metab* 2000, **85:**139-146.

50. Ibanez L, Valls C, Ferrer A, Marcos MV, Rodrigues-Hierro F and de Zegher FI: **Sensitization to insulin induces ovulation in non-obese adolescents with anovulatory hyperandrogenism.** *J Clin Endocrinol Metab* 2001, **16:**3595-3598.

51. Vandermolen DT, Ratts VS, Evans WS, Stovall DW, Kauma SW and Nestler JE: **Metformin increases the ovulatory rate and pregnancy rate with clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone.** *Fertil Steril* 2001, **75:**310-315.

52. De Leo V, la Marca A, Ditto A, Ditto A, Morgante G and Cianci A: **Effects of metformin on gonadotropin-induced ovulation women with polycystic ovary syndrome.** *Fertil Steril* 1999, **72:**282-285.

53. Stadtmauer LA, Toma SK, Riehl RM and Talbert LM: **Metformin treatment of patients with polycystic ovary syndrome undergoing in vitro fertilization improves outcomes and is associated with modulation of the insulin-like growth factors.** *Fertil Steril* 2001, **75:**505-509.

54. Homburg R: **Should patients with polycystic ovary syndrome be treated with metformin?** *Hum Reprod* 2002, **17:**853-856.

55. Glueck CJ, Wang P, Goldenberg N and Sieve-Smith L: **Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin.** *Hum Reprod* 2002, **17:**2858-2864.

56. Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA and Nestler JE: **Effects of metformin on early pregnancy loss in the polycystic ovary syndrome.** *J Clin Endocrinol Metab* 2002, **87:**524-529.

57. Donesky BW and Adashi EY: **Surgical ovulation induction: the role of ovarian diathermy in polycystic ovary syndrome.** *Baillieres Clin Endocrinol Metab* 1996, **10:**293-310.

58. Farquhar C, Vandekerkhove P and Lilford R: **Laparoscopic "drilling" by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome.** *Cochrane Database Syst Rev* 2001, **4:**CD001122.

59. Abdel Gadir A, Mowafi RS, Alnaser HMI, Alonezi OM and Shaw RW: **Ovarian electrocautery versus human gondotrophins and pure follicle stimulating hormone therapy in the treatment**

　　　of patients with polycystic ovarian disease. *Clin Endocrinol* 1990, **33:**585-592.
60.　Lunde O, Djoseland O and Grottum P: **Polycystic ovary syndrome: a follow-up study on fertility and menstrual pattern in 149 patients 15–25 years after ovarian wedge resection.** *Hum Reprod* 2001, **16:**1479-1485.
61.　Gjonnaess H: **Ovarian electrocautery in the teatment of women with polycystic ovary syndrome. Factors affecting results.** *Acta Obstet Gynecol Scand* 1994, **73:**1-5.
62.　Child TJ, Phillips SJ, Abdul-Jalil AK, Gulekli B and Tan SL: **A comparison of in-vitro maturation and in-vitro fertilization for women with polycystic ovaries.** *Obstet Gynecol* 2002, **100:**665-670.