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# Consensus on infertility treatment related to polycystic ovary syndrome

*The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group* March 2–3, 2007, Thessaloniki, Greece*

**The treatment of infertile women with polycystic ovary syndrome (PCOS) is surrounded by many controversies. This paper describes, on the basis of the currently available evidence, the consensus reached by a group of experts regarding the therapeutic challenges raised in these women. Before any intervention is initiated, preconceptional counselling should be provided emphasizing the importance of life style, especially weight reduction and exercise in overweight women, smoking and alcohol consumption. The recommended first-line treatment for ovulation induction remains the anti-estrogen clomiphene citrate (CC). Recommended second-line intervention, should CC fail to result in pregnancy, is either exogenous gonadotrophins or laparoscopic ovarian surgery (LOS). The use of exogenous gonadotrophins is associated with increased chances for multiple pregnancy and, therefore, intense monitoring of ovarian response is required. LOS alone is usually effective in <50% of women and additional ovulation induction medication is required under those circumstances. Overall, ovulation induction (representing the CC, gonadotrophin paradigm) is reported to be highly effective with a cumulative singleton live birth rate of 72%. Recommended third-line treatment is *in vitro* fertilization. More patient-tailored approaches should be developed for ovulation induction based on initial screening characteristics of women with PCOS. Such approaches may result in deviation from the above mentioned first-, second- or third-line ovulation strategies in well-defined subsets of patients. Metformin use in PCOS should be restricted to women with glucose intolerance. Based on recent data available in the literature, the routine use of this drug in ovulation induction is not recommended. Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction. Even singleton pregnancies in PCOS are associated with increased health risk for both the mother and the fetus.**

*Keywords:* polycystic ovary syndrome; infertility treatment; 2007 consensus

## Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies, affecting 5–10% of women of reproductive age. The syndrome is surrounded by controversies regarding both its diagnosis and treatment. The need to establish universally accepted diagnostic criteria led to the Rotterdam meeting in 2003, during which experts in PCOS from all over the world, arrived at a consensus regarding the diagnosis of the syndrome. The meeting was endorsed by both the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) and its proceedings were published in *Fertility and Sterility* (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004a) and in *Human Reproduction* (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004b).

Criteria proposed for the diagnosis of PCOS in the Rotterdam meeting were set in order to allow the performance of properly designed trials with good external validity in PCOS patients. These trials would assist in defining the various phenotypes of the syndrome, in discovering its genetic origins, in evaluating its long-term consequences and in describing its optimal treatment. Advantages and disadvantages of these criteria, and especially the various phenotypes, were discussed in subsequent publications (Azziz *et al*., 2006; Franks, 2006).

Although significant progress has been made towards the development of universally accepted diagnostic criteria for PCOS (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004a, b), the optimal treatment for infertile women with PCOS has not yet been defined.

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Various interventions have been proposed ranging from lifestyle modifications, administration of pharmaceutical agents [such as clomiphene citrate (CC), insulin sensitizing agents, gonadotrophins and gonadotrophin-releasing hormone (GnRH) analogues], the use of laparoscopic ovarian drilling and the application of assisted reproduction techniques (ART).

The recognition of the controversies surrounding the treatment of this enigmatic syndrome led to a second international workshop endorsed by ESHRE and ASRM, held in Thessaloniki, Greece in 2007, to address the therapeutic challenges raised in women with infertility and PCOS and to answer important questions regarding the value of various treatments available for these women, their efficacy as well as their safety. As with the Rotterdam meeting, a panel of international experts was invited to discuss the treatment of women with PCOS and infertility in order to arrive at a consensus regarding therapy. The reader should note that the vast majority of the available studies used variable criteria for PCOS definition. Nevertheless, the discussants overall felt that the reviewed and cited data were pertinent to the disorder of PCOS, independent of the specific criteria used.

## Lifestyle modifications

Preconceptional counselling in women with PCOS should identify risk factors for reproductive failure and correct them prior to treatment initiation. In this respect, it is imperative to recognize the presence of obesity and its centripetal distribution, which may vary according to ethnicity and geographical area, as well as to recommend folate supplementation in all women and smoking cessation where appropriate. It is well known that obesity is associated with anovulation (Pasquali *et al*., 2003), pregnancy loss (Froen *et al*., 2001) and late pregnancy complications (pre-eclampsia, gestational diabetes, etc) (Boomsma *et al*., 2006). Obesity is common in women with PCOS and is linked to failure or delayed response to the various treatments proposed, such as administration of CC (Imani *et al*., 1998, 1999), gonadotrophins (Mulders *et al*., 2003; Balen *et al*., 2006) (Fig. 1) and laparoscopic ovarian diathermy (Gjonnaess, 1994). Weight loss is recommended as first-line therapy in obese women with PCOS seeking pregnancy. This recommendation is based on extrapolation from the benefits of weight loss seen in multiple other conditions, such as diabetes and cardiovascular disease, as well as recognition of obesity's association with poor reproductive outcome.

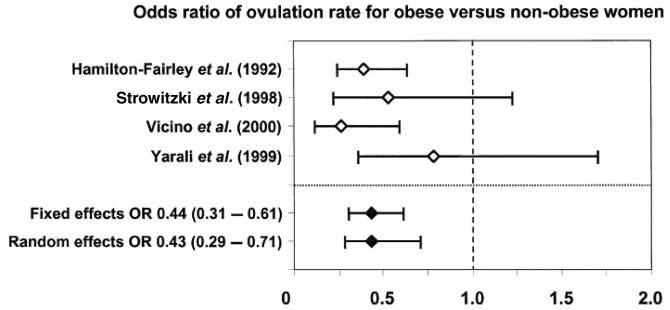



**Figure 1:** Association between obesity and ovulation rate in gonadotrophin ovulation induction, with a pooled odds ratio and 95% confidence interval (Mulders *et al*., 2003, with permission)

However, it should be noted that there is a paucity of studies suggesting that weight loss prior to conception improves live birth rate in obese women with or without PCOS (Moran *et al*., 2006). On the other hand, multiple observational studies have noted that weight loss is associated with improved spontaneous ovulation rates in women with PCOS (Pasquali *et al*., 2003; Moran *et al*., 2006), while pregnancies have been reported after losing as little as 5% of initial body weight (Kiddy *et al*., 1992). The treatment of obesity is multifaceted and involves behavioural counselling, lifestyle therapy (diet and exercise), pharmacological treatment and bariatric surgery (Yanovski and Yanovski, 2002). However, there are no properly designed studies to guide the choice of such interventions in overcoming infertility in women with PCOS. Generally, a combination of medical and behavioural therapies offers the greatest weight loss (Wadden *et al*., 2005), though long-term bariatric surgery is associated with the best weight maintenance after weight loss (Sjostrom *et al*., 2004). The effects of calorie restriction, increased physical activity and pharmacological and weight loss agents in the periconceptional period are unknown and potentially harmful on the goal of live birth (Morris *et al*., 2006; Tsagareli *et al*., 2006). These interventions should be conducted prior to pregnancy, not concurrently with infertility treatment, until the risk benefit ratio of these therapies on pregnancy are better understood. Table I shows randomized trials of lifestyle and pharmacologic weight loss therapy in women with PCOS.

### *Diet*

It is generally agreed that energy restriction is required for weight loss. In fact, early improvements in reproductive function, in the absence of apparent weight loss, were probably due to energy restriction *per se*. However, there is little agreement on what constitutes the optimal diet for women with PCOS (Marsh and Brand-Miller, 2005). The resurgence of the Atkins' diet has generated considerable interest in very low calorie diets in recent years, and these can lead to significantly decreased body weight in PCOS (12% in 24 weeks) and improve reproductive outcome (Moran *et al*., 2004). A range of dietary approaches has been shown to be effective in weight loss and in improving reproductive function, but only two randomized controlled trials (RCTs) have compared the effect of different diets in women with PCOS (Moran *et al*., 2003; Stamets *et al*., 2004). However, these studies did not show that dietary patterns differentially affect weight loss and reproductive outcomes.

Increasing evidence in women without PCOS suggest that diets with reduced glycemic load may be beneficial in alleviating hyperinsulinemia and its metabolic consequences (Reaven, 2005). This is of particular relevance to women with PCOS, due to the close association between insulin resistance and reproductive health. In the absence of level I evidence, the recommended diet for obese women with PCOS is any hypocaloric diet (with a 500 Kcal/day deficit) with reduced glycemic load and, failing that, any calorie restricted diet with which patients can comply and achieve a 5% weight loss.

### *Exercise*

Insufficient physical activity might explain why women with PCOS have a tendency towards overweight/obesity. Baseline

**Table I.** Randomized trials of lifestyle and pharmacologic weight loss therapy in women with PCOS.

| Study | Number of patients | Duration | Intervention | Weight loss (kg) | Reproductive outcome |
|---|---|---|---|---|---|
| | | | Diet | | |
| Moran *et al*. (2003) | 28 | 16 w | Diet (RCT): 6000 KJ/day<br>HP: 40% C, 30% P, 30% F<br>LP: 55% C, 15% P, 30% F | 7.7 | 44% had improvement in ovulation |
| Moran *et al*. (2004) | 10 | 16 w | Diet (RCT): 6000 KJ/day<br>HP: 40% C, 30% P, 30% F<br>LP: 55% C, 15% P, 30% F | 7.1 | NA |
| Stamets *et al*. (2004) | 26 | 1 m | Diet (RCT): 4200 KJ deficit/day<br>HP: 40% C, 30% P, 30% F<br>LP: 55% C, 15% P, 30% F | 4.0 | Decreased T, increased menstrual bleeding |
| Moran *et al*. (2006) | 23 | 8 w 6 m | Diet (RCT): 5000 KJ/day 2 meal replacements plus low-fat dinner and snacks fat counting (<50 g/day) or carbohydrate counting (<120 g/day)<br>Exercise: 8000 steps/day | 4.7 | Decreased T, 57% had improved menstrual cyclicity |
| | | | Lifestyle | | |
| Hoeger *et al*. (2004) | 38 | 48 w | Combined therapy (RCT)<br>Diet: 2100-4200 KJ deficit/day. Individualised healthy meal plan: 50% C, 25% P, 25% F<br>Exercise: group sessions behaviour: group sessions | 6.8 | NS |
| Bruner *et al*. (2006) | 12 | 12 w | Diet (RCT): canadian Food Guide to Healthy Eating<br>Exercise: a combination of endurance and resistance activities 3 d/w | NS | NS |
| Tang *et al*. (2006a, b) | 143 | 6 m | Diet (RCT): 500 kcal deficit/d<br>Exercise: increase physical activity by 15 minutes a day (unmonitored) | 1.5 | Improved menstrual frequency (median 1 cycle / 6 m) |
| | | | Pharmacological | | |
| Sabuncu *et al*. (2003) | 40 | 6 m | Medication: sibutramine 10 mg/d | 5.8 | 37% decrease in T,<br>280% increase in SHBG |
| Jayagopal *et al*. (2005) | 21 | 3 m | Diet: 8 week run in of dietary modification Medication: orlistat 120 mg tid | 4.4 | 8% decrease in T |

SHBG, sex-hormone binding globulin; T, testosterone; w, week(s); m, month(s); C, carbohydrate; P, protein; F, fat; HP, high protein; LP, low protein; NA, not available; NS, no significant changes from baseline.

activity levels by self report were less in women with PCOS compared with control women (Wright *et al*., 2004). In the Nurses' Health Study, vigorous activity was associated with a reduced relative risk of anovulatory infertility (Rich-Edwards *et al*., 2002). Few studies have examined the role of exercise alone in improving reproductive function in PCOS. In a pilot trial examining exercise and nutritional counselling in PCOS, women were assigned to nutritional counselling alone or in combination with exercise. No differences were seen between groups with respect to weight loss or restoration of menstruation (Bruner *et al*., 2006).

Several studies have examined combination therapy of diet and exercise (Crosignani *et al*., 2003; Moran *et al*., 2006). Most of them, however, were not randomized trials and exercise was not supervised but rather consisted of lifestyle counselling. Although weight loss alone appears to improve menstrual frequency, the contribution of exercise alone could not be determined in these studies. It is clear that regular physical activity is an important component of weight loss programmes, because it is associated with better long-term weight loss maintenance (Knowler *et al*., 2002). However, its independent role in achieving weight reduction and improved reproductive outcome is less obvious. Increased physical activity is recommended for obese women with PCOS, but always while considering the possible orthopaedic and cardiovascular limitations (Moran *et al*., 2006).

### *Pharmacological treatment and bariatric surgery*

The available literature supports the adjuvant use of bariatric surgery and pharmacological weight loss for the treatment of obesity in PCOS, although large clinical trials are needed. In morbidly obese women, the PCOS phenotype appears to be very frequent (Alvarez-Blasco *et al*., 2006). Most importantly, this disorder has been found to improve markedly after sustained weight loss following bariatric surgery (Escobar-Morreale *et al*., 2005). Anti-obesity pharmacological agents have been used in obese women with PCOS, although few quality studies have been published (Sabuncu *et al*.,

2003; Jayagopal *et al*., 2005). Both orlistat, which blocks intestinal absorption of fat (Jayagopal *et al*., 2005), and sibutramine, an appetite suppressant (Sabuncu *et al*., 2003), have displayed a weight loss-independent effect on androgens and insulin resistance. Currently, there are no studies in women with PCOS regarding the use of rimonabant, which decreases food intake (Pi-Sunyer *et al*., 2006). This agent is not approved by the US Food and Drug Administration (FDA), although it is approved in Europe. It should be noted that these treatments should not be considered as first-line therapy for obesity in women with PCOS.

***Summary points***

(i) Obesity adversely affects reproduction and is associated with anovulation, pregnancy loss and late-pregnancy complications.
(ii) Obesity within PCOS is associated with failure of infertility treatment.
(iii) Weight loss prior to infertility treatment improves ovulation rates in women with PCOS, but there are limited data that it improves fecundity or lowers pregnancy complications.
(iv) Evidence-based schemas to guide the treatment of obesity in women with PCOS have not yet been developed.
(v) Experience from other areas of medicine suggests lifestyle modifications as the first-line treatment of obesity in PCOS.
(vi) The best diet and exercise regimens are unknown, but caloric restriction and increased physical activity are recommended.
(vii) Caution is recommended about conceiving during the use of hypocaloric diets, excessive physical exertion, pharmacological intervention or during the period of rapid weight loss after bariatric surgery, since the effects of these interventions on the evolution of early pregnancy are not yet known.
(viii) Treatment of adverse lifestyles, including obesity and physical inactivity, should precede ovulation induction.
(ix) The ideal amount of weight loss is unknown, but a 5% decrease of body weight might be clinically meaningful.

## Clomiphene citrate

CC remains the treatment of first choice for induction of ovulation in anovulatory women with PCOS. Cost of medication is low, the oral route of administration is patient friendly, there are relatively few adverse effects, little ovarian response monitoring is required and abundant clinical data are available regarding safety of the drug. The mechanism of action in not entirely known, but it is thought to involve the blockade of the negative feedback mechanism that results in increased secretion of follicle-stimulating hormone (FSH). The main factors that predict outcome of treatment are obesity, hyperandrogenemia and age (Imani *et al*., 2002) (Fig. 2). Ovarian volume and menstrual status are additional factors that help to predict responsiveness to CC (Eijkemans *et al*., 2003).

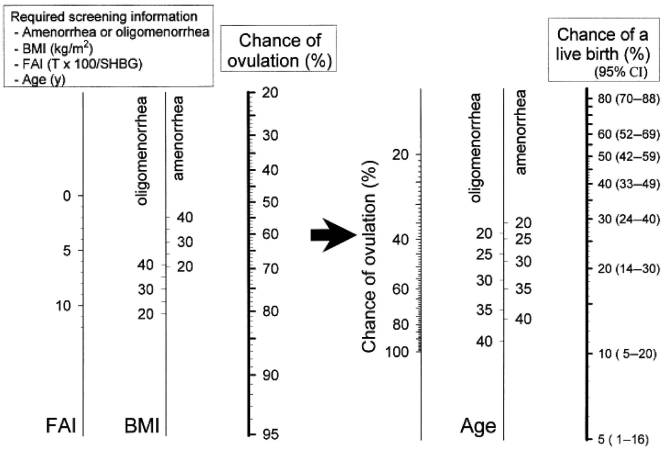



**Figure 2:** Nomogram designed to predict chances for live birth in CC induction of ovulation. Note the two different steps (Imani *et al*., 2002, with permission)

***Selection of patients***

There are no specific exclusion criteria for women with anovulatory PCOS, who have normal baseline FSH and estradiol ($E_2$) levels, but selection of patients for treatment should take account of body weight/body mass index (BMI), age [poorer outcome in older patients may justify consideration of alternative treatments such as exogenous gonadotrophins or *in vitro* fertilization (IVF)] and other infertility factors.

***Dose***

The starting dose of CC generally should be 50 mg/day (for five days, starting on Day 2–5 following a spontaneous or progestin-induced withdrawal bleeding). The recommended maximum dose is 150 mg/day, as there is no clear evidence of efficacy at higher doses and this is in accord with FDA recommendations of 750 mg/treatment cycle (Dickey *et al*., 1996).

***Monitoring***

Although results of large trials suggest that monitoring by ultrasound is not mandatory to ensure good outcome (Legro *et al*., 2007a), the practice in many centres is to monitor the first cycle to allow adjustment of the dose in subsequent cycles based to the observed response. In the absence of complete cycle monitoring, a pretreatment ultrasound is often performed to evaluate ovarian and endometrial morphology, which may be followed by serum progesterone measurements (typically one or two samples in the estimated luteal phase). There is no evidence that administration of human chorionic gonadotrophin (hCG) in mid-cycle improves the chances of conception (Kosmas *et al*., 2007).

***Efficacy***

Approximately 75–80% of patients with PCOS will ovulate after CC (Homburg, 2005; Messinis, 2005). Although there appears to be discrepancy between ovulation and pregnancy rates, life-table analysis of the largest and most reliable studies indicates a conception rate of up to 22% per cycle in those ovulating on CC (Hammond *et al*., 1983; Kousta *et al*., 1997; Eijkemans *et al*., 2003).

### *Duration of treatment*

Treatment generally should be limited to six (ovulatory) cycles (Eijkemans *et al*., 2003; Homburg, 2005). Further cycles (maximum 12 in total) may be considered on an individual basis after discussion with the patient. Normally, however, second-line therapy with FSH or laparoscopic ovarian surgery (LOS) should be considered at that time (Messinis and Milingos, 1997; Eijkemans *et al*., 2003). Cumulative live birth rates vary between 50–60% for up to six cycles (Kousta *et al*., 1997).

### *Adverse effects*

Hot flushes, headaches and visual complaints are well-recognized side effects during CC treatment, but the drug is generally well tolerated. The multiple pregnancy rate is $<10\%$, while hyperstimulation syndrome is rare (Eijkemans *et al*., 2003). Anti-estrogenic effects on endometrium and cervical mucus may occur but appear to represent an idiosyncratic response. There is no clear evidence that the chance of conception is adversely affected in ovulatory cycles (Kolibianakis *et al*., 2004).

### *Combination therapy*

There is now clear evidence that the addition of metformin (Moll *et al*., 2006; Legro *et al*., 2007a) or dexamethasone (Daly *et al*., 1984) to CC as primary therapy for induction of ovulation has no beneficial effect.

### *Alternative therapies*

Anti-estrogens other than CC: Tamoxifen appears to be as effective as CC for induction of ovulation, but is not licensed for that purpose (Messinis and Nillius, 1982; Steiner *et al*., 2005). It may be considered as an alternative to CC in women who suffer intolerable side effects such as hot flushes.

Aromatase inhibitors: Initial preliminary studies suggest that letrozole appears to be as effective as CC for induction of ovulation, but the drug is currently not approved for treatment of infertility. Prospective, sufficiently powered studies demonstrating efficacy and safety should be awaited before the widespread use of aromatase inhibitors can be recommended. It may, however, be considered as an 'off-label' option for some patients after appropriate discussion of risks and benefits.

### *Summary points*

(i) CC remains the treatment of first choice for induction of ovulation in most anovulatory women with PCOS.
(ii) Selection of patients for CC treatment should take account of body weight/BMI, female age and the presence of other infertility factors.
(iii) The starting dose of CC should be 50 mg/day (for 5 days) and the recommended maximum dose is 150 mg/day.
(iv) Results of large trials suggest monitoring by ultrasound or progesterone is not mandatory to ensure good outcome.
(v) Life-table analysis of the largest and most reliable studies indicates a conception rate of up to 22% per cycle in those women ovulating on CC.
(vi) Further studies should demonstrate efficacy and safety of aromatase inhibitors.

## Insulin sensitizing agents

Insulin sensitizing agents are currently being utilized to treat diabetes, and there is considerable interest for their use in the treatment of women with PCOS. Insulin sensitizers available include metformin, a biguanide, and the thiazolidinediones (pioglitazone and rosiglitazone). The primary risk with metformin is lactic acidosis, which is only seen in high risk patients with renal, liver or congestive heart failure (Alivanis *et al*., 2006). The major risk with the thiazolidinediones is liver toxicity, and recently there has been concern about increased cardiovascular morbidity with rosiglitazone (Nissen and Wolski, 2007). With regard to their use during pregnancy, metformin is a category B drug according to FDA, which means that either animal-reproduction studies have not shown a fetal risk but there are no controlled studies in women, or animal studies have shown an adverse effect not confirmed by controlled studies in women. Pioglitazone and rosiglitazone are category C drugs, which means that either studies in animals have shown adverse effects on the fetus and there are no controlled studies in women, or studies in women and animals are not available.

In women with PCOS, metformin appears to lower the fasting insulin level, but does not appear to result in consistent significant changes in BMI or waist-to-hip ratio (Lord *et al*., 2003). Although oligomenorrhoea improves in some women with PCOS, significant numbers remain anovulatory and at risk for menorrhagia and endometrial hyperplasia. The degree of improvement in ovulation frequency is the same as is achieved with weight reduction through life-style modification with no difference between metformin and placebo in this regard (Tang *et al*., 2006a), and has been estimated to represent one extra ovulation every five woman-months (Harborne *et al*., 2003).

With regard to the use of metformin for induction of ovulation, two RCTs indicate that metformin does not increase live birth rates above those observed with CC alone, in either obese or normal weight women with PCOS (Moll *et al*., 2006; Legro *et al*., 2007a). The larger of these two trials (Legro *et al*., 2007a) demonstrated a selective disadvantage to metformin compared with CC and no apparent advantage to adding metformin to CC, except perhaps in women with BMI $>35\ kg/m^2$ and in those with CC resistance. Results in this trial were the same when subjected to either intention-to-treat analysis or analysis based on adherence: CC resulted in higher ovulation, conception, pregnancy and live birth rates compared with metformin, whereas the combination of both drugs did not result in a significant benefit (Table II). Addition of metformin did not decrease the incidence of miscarriage, which in fact was higher in the metformin group. Furthermore, metformin treatment conferred no additional advantage when administered to women newly diagnosed with PCOS (Moll *et al*., 2006). Thus, insulin sensitizers should not be used as first-choice agents for induction of ovulation in women with

**Table II.** Randomized Trial from the NIH Reproductive Medicine Network (Legro *et al*., 2007a, with permission).

| | CC | Metformin | Combination |
|---|---|---|---|
| N | 209 | 208 | 209 |
| Ovulation | 49[1] | 29 | 60[2] |
| Conception | 20[1] | 12 | 38[1] |
| Pregnancy | 24[1] | 9 | 31[1] |
| Live birth | 23[1] | 7 | 27[1] |
| Multiple | 6 | 0 | 3 |

[1]$P < 0.001$, [2]$P < 0.001$ (combination versus CC).

PCOS, and their administration does not appear to decrease the incidence of early pregnancy losses. In addition, there are insufficient data to document any advantage to the use of thiazolidinediones over metformin (Baillargeon *et al*., 2004; Legro *et al*., 2007b).

Although uncontrolled trials and case reports suggest that metformin is safe during pregnancy, it would be prudent to discontinue metformin when pregnancy is confirmed for any woman with PCOS and insulin resistance who was taking the medication (Legro *et al*., 2007a). While there have been suggestions that metformin treatment during pregnancy may be protective against complications (Vanky *et al*., 2004), currently such use should take place only in a research context (Vanky *et al*., 2006).

***Summary points***

(i) At present, use of metformin in PCOS should be restricted to those patients with glucose intolerance.
(ii) Decisions about continuing insulin sensitizers during pregnancy in women with glucose intolerance should be left to obstetricians providing care and based on a careful evaluation of risks and benefits.
(iii) Metformin alone is less effective than CC in inducing ovulation in women with PCOS.
(iv) There seems to be no advantage to adding metformin to CC in women with PCOS.

## Gonadotrophins and GnRH analogues

The aim of ovulation induction for women with anovulatory PCOS is to restore fertility and achieve a singleton live birth. The method of ovulation induction using gonadotrophin therapy is based on the physiological concept that initiation and maintenance of follicle growth may be achieved by a transient increase in FSH above a threshold dose for sufficient duration to generate a limited number of developing follicles. Application of this concept is essential when ovulation induction is conducted in women with PCOS, because they are specifically prone to excessive multiple follicle development (Brown, 1978; Baird, 1987).

### *Regimens*

The original description of gonadotrophin administration for anovulation utilized a high starting dose of 150 IU a day. In women with PCOS, as well as those with multiple follicle formation, this 'conventional protocol' was associated with an unacceptable rate of excessive follicle development and increased risk of ovarian stimulation syndrome (OHSS) (Thompson and Hansen, 1970; Dor *et al*., 1980; Wang and Gemzell, 1980). Subsequent efforts to reduce the frequency of ovarian stimulation have resulted in the development of low-dose protocols (37.5–75 IU/day), which have essentially replaced the original conventional protocol (White *et al*., 1996; Hayden *et al*., 1999; Balasch *et al*., 2000; Calaf *et al*., 2003b).

Starting doses of daily 150 IU FSH are no longer recommended in women with PCOS (Buvat *et al*., 1989; Brzyski *et al*., 1995) and have been replaced by low-dose FSH protocols. Currently two low-dose regimens are utilized:

(i) Step-up regimens: Step-up regimens are based upon the principle of a stepwise increase in FSH supply to determine the FSH threshold for follicular development. Following commencement of gonadotrophin administration, if follicle development is not observed on ultrasound after one week, an increase in the dose is recommended. Once follicle growth is observed, the same FSH dose is maintained until follicular selection is achieved. In order to further reduce the risk of ovarian hyper-responsiveness, the duration of the initial dose of FSH was extended (from 7 to 14 days) and the weekly dose increment was reduced (from 100 to 50% of the dose), leading to the so-called 'chronic low-dose regimen' (Seibel *et al*., 1984; Polson *et al*., 1987; Sagle *et al*., 1991; Dale *et al*., 1993).
(ii) Step-down regimen: This regimen is designed to achieve the FSH threshold through a loading dose of FSH with a subsequent stepwise reduction as soon as follicular development is observed on ultrasound (Schoot *et al*., 1992; van Dessel *et al*., 1996; Fauser and Van Heusden, 1997). Preliminary studies report that both step-up and step-down regimens achieve similar high rates of monofollicular development (van Santbrink and Fauser, 1997; Balasch *et al*., 2001). However, the largest study published so far has shown that the step-up regimen is safer in terms of monofollicular development (Christin-Maitre and Hugues, 2003). Moreover, it is widely accepted that monitoring of a step-down cycle may require more experience and skill compared with a low-dose step-up regimen (van Santbrink *et al*., 1995).
(iii) Alternatively, a combined approach of sequential step-up and step-down regimens has been shown to help reduce the risk of over-response (Hugues *et al*., 1996, 2006).

### *Combination of GnRH analogues and gonadotrophins*

It has been suggested that increased luteinizing hormone (LH) secretion in PCOS may interfere with fertility. The mechanisms include premature oocyte maturation, through inhibition of oocyte maturation inhibitor (Jacobs and Homburg, 1990) and deleterious LH effect on granulosa cell steroidogenesis (Willis *et al*., 1996, 1998). In addition, elevated LH levels may be associated with an increased pregnancy loss

(Homburg *et al*., 1988; Regan *et al*., 1990; Balen *et al*., 1993; Tarlatzis *et al*., 1995), although more recent data are not consistent with this assumption (Rai *et al*., 2000; Mulders *et al*., 2003; Oliveira *et al*., 2007).

The concomitant use of a GnRH agonist with gonadotrophin administration to improve pregnancy rates in patients undergoing ovulation induction has not been firmly established (Fleming *et al*., 1985, 1988; Dodson *et al*., 1987). Moreover, combined therapy was associated with an increased risk of OHSS (Charbonnel *et al*., 1987; Homburg *et al*., 1990; Scheele *et al*., 1993; Buckler *et al*., 1993; van der Meer *et al*., 1996), while there are insufficient data to draw solid conclusions on miscarriage and multiple pregnancy rates (Bachus *et al*., 1990; Homburg *et al*., 1993; Clifford *et al*., 1996). Therefore, the significantly higher hyperstimulation rate, the associated risk of multiple pregnancies and the additional inconvenience and cost of concomitant GnRH agonist administration, in the absence of documented increases in pregnancy success, do not justify the routine use of GnRH agonists during ovulation induction with gonadotrophins in PCOS patients. The question of whether LH suppression by a GnRH antagonist during gonadotrophin-based ovulation induction is of benefit to women with PCOS has not yet been addressed by RCTs.

### *Monitoring*

Ultrasound assessment of the ovary can be performed at baseline prior to the initiation of each cycle. Serial ovarian ultrasound is an excellent method of determining follicle growth and development in response to gonadotrophin stimulation. In particular, documentation of all follicles >10 mm may be helpful to predict the risk of multiple pregnancies. Adherence to the chronic low-dose regimen of FSH administration in women with PCOS should markedly reduce the likelihood of excessive ovarian stimulation and OHSS. However, before ovulation induction with gonadotrophins, it is mandatory to counsel the patient about the risks associated with higher-order multiple pregnancies following polyovulation.

In most previous studies, cycle cancellation has been advised when more than three follicles of 16 mm or larger were observed (White *et al*., 1996; Homburg and Howles, 1999; Calaf *et al*., 2003a) in order to prevent OHSS and multiple pregnancies. In some studies, the limit was four or more follicles >14 mm (Kamrava *et al*., 1982; Hugues *et al*., 2006). Recently, more stringent criteria have been recommended for ovarian stimulation in unexplained infertility: no more than two follicles >14 mm (Farhi *et al*., 1996) or no more than three or four follicles >10 mm (Tur *et al*., 2001; Dickey *et al*., 2005). In addition, recent data stress the need for taking into account the overall number of follicles and cycle cancellation may be considered in the presence of more than three follicles >14 mm. It should be noted that the definition of a monofollicular cycle has usually been a single follicle of 16 mm or higher without any information on the number of smaller follicles, except in the study by Leader (2006), which defined a cycle as monoovulatory when a single follicle of 16 mm or higher was present with no other follicle 12 mm or higher. Measurements of circulating $E_2$ levels have been used to cancel ovulation induction cycles using gonadotrophins (due to over- or under-response) or to adjust the dose of gonadotrophins used either upwards or, more frequently, downwards, in order to minimize the risk of multiple pregnancies or OHSS. While specific normative thresholds vary, in 2006 the Practice Committee of the ASRM suggested that caution was indicated when a rapidly rising serum $E_2$ level or an $E_2$ concentration in excess of 2500 pg/ml was present during gonadotrophin ovulation induction (Practice Committee of the American Society for Reproductive Medicine, 2006). However, in other studies (Tur *et al*., 2001; Dickey *et al*., 2005) the threshold $E_2$ concentration was much lower, <1000 pg/ml, which seems to be more realistic according to the number of growing follicles.

It would seem prudent to withhold hCG administration in the presence of more than two follicles ≥16 mm or more than one follicle ≥16 mm and two additional follicles ≥14 mm, in order to minimize the risk of multiple pregnancies in women with PCOS under the age of 38 without any other infertility factors.

### *Efficacy*

Overall, low-dose regimens result in a monofollicular ovulation rate of ~ 70%, a pregnancy rate of 20% and a multiple live birth rate of 5.7% (Homburg and Howles, 1999). Correspondingly, there is a low incidence of multiple pregnancies (<6%) and OHSS (<1%) (Hamilton-Fairley *et al*., 1991; van Santbrink *et al*., 1995; White *et al*., 1996; Balasch *et al*., 1996). These results compare favourably to the unacceptable high risk of multiple follicular development, multiple pregnancies (36%) and severe OHSS (4.6%) reported for conventional dose protocols (Hamilton-Fairley and

**Table III.** Comparison of ovarian response and clinical outcomes in low-dose step-up and step-down protocols for gonadotrophin ovulation induction (Fauser and Macklon, 2004, with permission).

| | Low-dose step-up | | | Step-down |
|---|---|---|---|---|
| | Hamilton-Fairley *et al.* (1991) | Hull (1991) | Balen *et al.* (1994) | Van Santbrink (1995) |
| Number of patients | 100 | 144 | 103 | 82 |
| Number of cycles | 401 | 459 | 603 | 234 |
| Duration treatment (days) | 14 | NR | NR | 11 |
| Ampules per cycle | 19 | NR | NR | 14 |
| Ovulation rate (%) | 72 | 74 | 68 | 91 |
| Monofollicular cycles: | | | | |
| % of ovulatory cycles | 73 | NR | NR | 62 |
| % of all started cycles | 55 | NR | NR | 56 |
| Pregnancy rate (%) | | | | |
| Per started cycles | 11 | 11 | 14 | 16 |
| Per ovulatory cycle | 16 | 15 | 20 | 17 |
| Cumulative pregnancy rate (%) | 55 | NR | 73 | 47 |
| Multiple pregnancy rate (%) | 4 | 11 | 18 | 8 |
| Ongoing singleton pregnancy rate (%) | 7 | 10 | 9 | 12 |
| OHSS rate (%) | 1 | NR | 1 | 2 |

NR, not recorded.

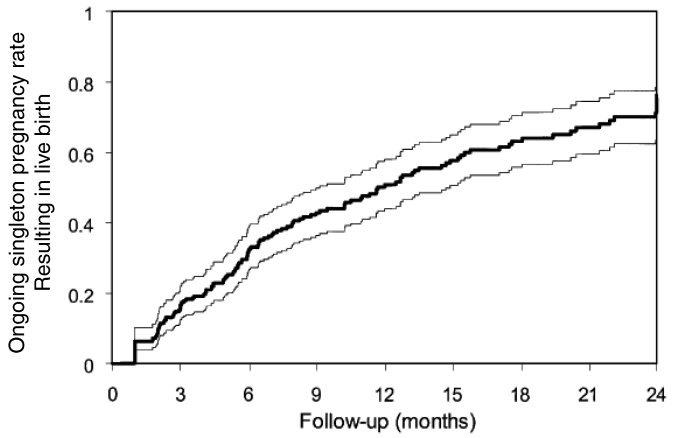



**Figure 3:** Cumulative pregnancy rate resulting in singleton live birth of a consecutive series of 240 normogonadotrophic anovulatory infertile women undergoing classical ovulation induction (CC as first-line, followed by FSH as second-line therapy) (Eijkemans *et al*., 2003, with permission)

Franks, 1990). For summary of clinical outcomes see Table III.

A prospective follow-up study involving 240 women showed a favourable cumulative singleton live birth rate of 72% following the combined analysis of ovulation induction using CC medication as first-line treatment and exogenous gonadotrophins as second-line treatment (Eijkemans *et al*., 2003) (Fig. 3).

### *Summary points*

(i) The recommended starting dose of gonadotrophin is 37.5–50 IU/day.
(ii) Adherence to a 14-day starting period at least for the first cycle is less likely to result in excessive stimulation.
(iii) Small FSH dose increment of 50% of the initial or previous FSH dose are less likely to result in excessive stimulation.
(iv) The duration of gonadotrophin therapy generally should not exceed six ovulatory cycles.
(v) Low-dose FSH protocols are effective in achieving ovulation in women with PCOS, but further refinement is needed to better control the safety of these regimens.
(vi) Intense ovarian response monitoring is required in order to reduce complications and secure efficiency.
(vii) Strict cycle cancellation criteria should be agreed upon with the patient before therapy is started.
(viii) Preventing all multiple pregnancies and OHSS is not possible at this time.
(ix) The significantly higher hyperstimulation rate, the associated risk of multiple pregnancies and the additional inconvenience and cost of concomitant GnRH agonist administration, in the absence of documented increases in pregnancy success, do not currently justify the routine use of GnRH agonists during ovulation induction with gonadotrophins in women with PCOS.

## Laparoscopic ovarian surgery

Surgical approaches to ovulation induction have developed from the traditional wedge resection to modern day minimal access techniques, usually employing laparoscopic ovarian diathermy or laser. Multiple ovarian puncture performed either by diathermy or by laser is known as 'ovarian drilling' (Gjonnaess, 1984).

### *Indications for LOS*

The main indication for LOS is CC resistance in women with anovulatory PCOS. LOS also may be recommended for patients who persistently hypersecrete LH, either during natural cycles or in response to CC, because it may reduce LH secretion. In addition, LOS may be useful in anovulatory women with PCOS who need laparoscopic assessment of their pelvis or who live too far away from the hospital for the intensive monitoring required during gonadotrophin therapy.

Extensive ovarian diathermy is not indicated to prevent hyperresponsiveness to exogenous gonadotrophins (Rimington *et al*., 1997). In addition, ovarian surgery has been suggested for non-fertility indications, for example, the management of menstrual irregularity or hyperandrogenism. Because of the inherent risks of surgery and the lack of long-term evidence from RCTs, surgery cannot be recommended in these circumstances (Balen, 2006).

### *Methods and dose*

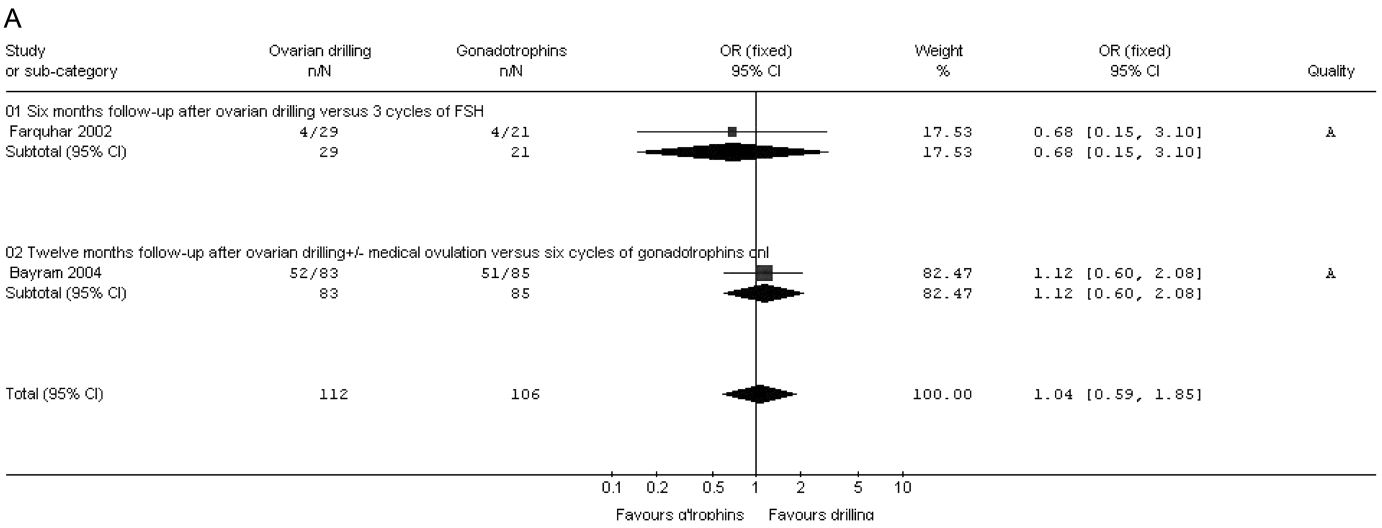
Commonly employed methods for LOS include monopolar electrocautery (diathermy) and laser. There does not appear to be a difference in outcomes between the two modalities (Farquhar *et al*., 2007). Ovarian surgery may also be performed transvaginally by hydrolaparoscopy (Fernandez *et al*., 2001). However, no large RCTs are yet available.

There are many variables in the potential for response after LOS, including the anthropometric characteristics of the patients and ovarian morphology. It has been proposed that the degree of thermal stromal damage should be determined by the size of the ovary (Naether *et al*., 1994).

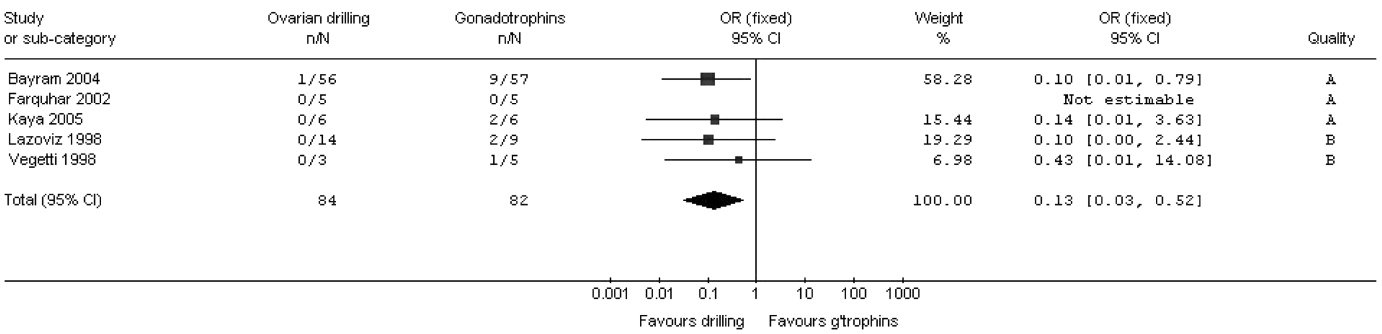
There is no evidence that any surgical technique is superior but as few as four punctures have been shown to be effective. Most authors use between four and ten punctures; however, more punctures have been associated with premature ovarian failure (Amer *et al*., 2002b, 2003; Malkawi *et al*., 2003). As in all surgical procedures, an important issue of successful outcome is the expertise of the surgeon. There are no data regarding repeated application of LOS and such use should not be encouraged.

### *Efficacy*

In ~50% of LOS-treated women, adjuvant therapy will be required. In these women, the addition of CC can be considered after 12 weeks if no ovulation is detected (Bayram *et al*., 2004). The addition of FSH should be considered after six months (Bayram *et al*., 2004). Five RCTs compared the effectiveness




Footnotes: Test for heterogeneity: $Chi^2 = 0.35$, df = 1 (p = 0.55), $I^2 = 0\%$
Test for overall effect: Z = 0.14 (p = 0.89)




Footnotes: Test for heterogeneity: $Chi^2 = 0.35$, df = 3 (p = 0.91), $I^2 = 0\%$
Test for overall effect: Z = 2.89 (p = 0.91)

**Figure 4:** Results from the meta-analysis of the RCTs of LOS versus gonadotrophins for (**A**) live birth rate and (**B**) multiple pregnancy rate (Farquhar *et al*., 2007, with permission)

of LOS with that of gonadotrophins for women with CC-resistant PCOS and did not show a difference in ongoing pregnancy rate or live birth rate (Lazovic G *et al*., 1998; Vegetti W *et al*., 1998; Farquhar *et al*., 2002, 2007; Bayram *et al*., 2004; Kaya *et al*., 2005) (Fig. 4a). In one of these trials (Bayram *et al*., 2004), if ovulatory cycles were not established eight weeks after surgery or the woman became anovulatory again, then CC was given in increasing doses. Multiple pregnancy rates were significantly higher in the gonadotrophin arms of the five trials, compared with LOS [odds ratio (OR) 0.13, 95% confidence interval (CI) 0.03–0.98] (Fig. 4b). On the other hand, miscarriage rates did not differ between the LOS group and gonadotrophin-treated women (OR 0.61, 95% CI 0.17–2.16). No cases of ovarian stimulation were observed in either of the two most recent studies (Farquhar *et al*., 2002; Bayram *et al*., 2004).

Economic analyses of two RCTs suggest that treating women with CC-resistant PCOS by LOS resulted in reduced direct and indirect costs. In the New Zealand study, the costs of a live birth were one-third lower with surgery, and in the Netherlands study, the costs of a term pregnancy were estimated to be 22% lower (Farquhar *et al*., 2004; van Wely *et al*., 2004). Predictors of success have included LH level >10 IU/l, normal BMI and shorter duration of infertility (Abdel *et al*., 1993; Gjonnaess, 1994; Li *et al*., 1998).

### *Safety*

Immediate complications of the surgery are rare. Out of 778 cases of LOS, two cases with haemorrhage requiring laparotomy and one case with bowel perforation have been reported (Cohen and Audebert, 1989). Long-term adverse events potentially include adhesion formation and premature menopause. Only two second-look laparoscopy studies have been done. In one study, out of 17 cases there were two with severe adhesion formation (Gurgan *et al*., 1992). In a second study of eight patients, all of the women had ovarian adhesions on second look after LOS despite the application of an adhesion barrier to one ovary as part of a study protocol (Greenblatt and Casper, 1993). Premature ovarian failure is a concern with ovarian drilling, especially

when a large number of punctures is used. However, long-term follow-up of women with PCOS treated by LOS is reassuring in this respect (Kaaijk *et al*., 1999; Amer *et al*., 2002a).

***Summary points***

(i) LOS can achieve unifollicular ovulation with no risk of OHSS or high-order multiples.
(ii) Intensive monitoring of follicular development is not required after LOS.
(iii) LOS is an alternative to gonadotrophin therapy for CC-resistant anovulatory PCOS.
(iv) The treatment is best suited to those for whom frequent ultrasound monitoring is impractical.
(v) LOS is a single treatment using existing equipment.
(vi) The risks of surgery are minimal and include the risk of laparoscopy, adhesion formation and destruction of normal ovarian tissue. Minimal damage should be caused to the ovaries. Irrigation with an adhesion barrier may be useful, but there is no evidence of efficacy from prospective studies. Surgery should be performed by appropriately trained personnel.
(vii) LOS should not be offered for non-fertility indications.

## Assisted reproduction techniques: IVF

In principle, anovulation is not an indication for IVF. The logical therapy for women with PCOS is induction of ovulation, especially by CC administration, and in case of failure by using exogenous gonadotrophin therapy. The major complication of ovulation induction is the occurrence of a 10% multiple pregnancy rate, especially after the use of gonadotrophin therapy. For this reason, use of gonadotrophins may be questioned (van Santbrink and Fauser, 2003).

After failure of weight reduction, anti-oestrogen therapy or LOS, it may be argued that induction of ovulation with exogenous gonadotrophin therapy should be omitted and replaced by ovarian stimulation and IVF (Eijkemans *et al*., 2005). By utilizing IVF with single-embryo transfer, the risk of multiple pregnancies is markedly reduced (Papanikolaou *et al*., 2006; Heijnen *et al*., 2007). In women with PCOS who do have associated pathologies, IVF is indicated, such as in case of tubal damage, severe endometriosis, preimplantation genetic diagnosis and male factor infertility.

***Protocols***

Several stimulation protocols have been published for the treatment of patients with PCOS undergoing IVF, including CC associated with human menopausal gonadotrophins (hMG) (Dor *et al*., 1990), hMG alone (Urman *et al*., 1992), recombinant FSH (recFSH) alone, GnRH agonist associated with hMG or recFSH (Griesinger *et al*., 2006) and GnRH antagonist associated with hMG or recFSH (Griesinger *et al*., 2006). Currently the most standard protocol is a long desensitization protocol associated with FSH.

***Efficacy***

In a recent meta-analysis (Heijnen *et al*., 2006), it was shown that the cycle cancellation rate is significantly increased in patients with PCOS (12.8 versus 4.1%; OR 0.5, 95% CI 0.2–1.0). Duration of stimulation is significantly longer in patients with PCOS (1.2 days, 95% CI 0.9–1.5), even when the daily dose of FSH is similar to that of women without PCOS. Significantly more cumulus–oocyte complexes (2.9, 95% CI 2.2–3.6) were retrieved in women with PCOS, but fertilization rates were similar as compared with women without PCOS (Fig. 5).

Regarding the probability of pregnancy, the clinical pregnancy rate per started cycle was similar (≈35%) between PCOS and non-PCOS patients. The same was true for pregnancy rates per oocyte retrieval and embryo transfer (ET). Specific data on the success rates of single ET in women with PCOS are still lacking. There is some evidence that the adjuvant use of metformin may enhance ongoing pregnancy rates and reduce the incidence of OHSS (Tang *et al*., 2006b).

***Complications***

The most important complication of ovarian stimulation is the occurrence of OHSS. However, currently no solid data are present regarding the occurrence of OHSS in women with PCOS undergoing ovarian stimulation for IVF.

***Summary points***

(i) IVF is a reasonable option, because the number of multiple pregnancies can be kept to a minimum by transferring small numbers of embryos.
(ii) The optimal stimulation protocol is still under debate.
(iii) There is a need to perform further RCTs comparing FSH stimulation protocols with use of GnRH agonist versus GnRH antagonist.

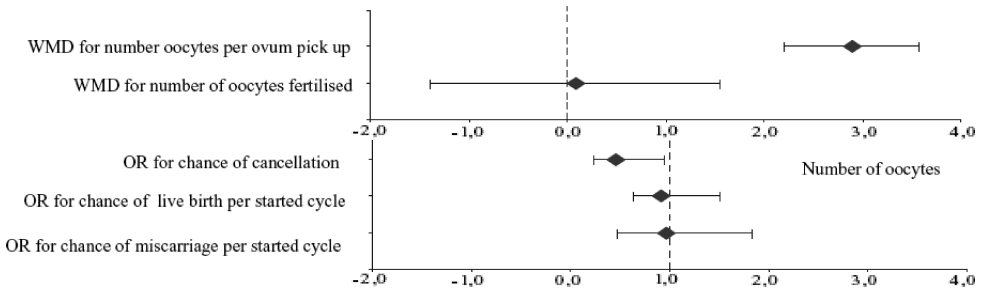



**Figure 5:** Main findings of clinical IVF outcomes in women with PCOS compared with matched controls (Heijnen *et al*., 2006, with permission).

(iv) It is reassuring that in the published data the pregnancy rates in women with and without PCOS are similar. This observation suggests that implantation is not compromised in PCOS.
(v) The increase in the cycle cancellation rate in women with PCOS appears to be due to absent or limited ovarian response or due to increased OHSS.

## ARTs: ovulation induction and homologous artificial insemination

### *Indications*

Currently there are no RCTs conducted in women with PCOS comparing the pregnancy rates of intrauterine insemination (IUI) versus timed intercourse during ovulation induction. Since subfertility in women with PCOS is mainly due to anovulation, induction of ovulation is the main treatment for women with PCOS. Due to the fact that IUI has been shown to significantly improve the probability of conception when compared with timed intercourse in couples with subfertility attributed to male factor (Cohlen *et al*., 2000), it appears reasonable to combine induction of ovulation with IUI in women with PCOS if there is an associated male factor. In women with PCOS who failed to conceive despite successful induction of ovulation, IUI may also be considered.

### *Protocol*

Since many women with PCOS are very sensitive to the use of ovulation induction agents, careful monitoring is essential to reduce the risk of OHSS and that of multiple pregnancies (ESHRE Capri Workshop Group, 2003), also in combination with IUI. An additional approach is to perform transvaginal ultrasound-guided aspiration of the supernumerary follicles (De Geyter *et al*., 1996).

Semen preparation is necessary before IUI, but there is insufficient evidence to recommend any specific preparation technique. Double insemination did not show any significant benefits in pregnancy rate over single IUI (Cantineau *et al*., 2003).

### *Efficacy*

Only limited studies on the results of ovarian stimulation and IUI in women with PCOS are available (Gerli *et al*., 2004; Mitwally and Casper, 2004; Palomba *et al*., 2005). The clinical pregnancy rates per cycle ranged from 11 to 20% and the multiple pregnancy rates ranged from 11 to 36%. However, there was inadequate information on the singleton live birth rates or high multiple pregnancy rates.

### *Complications and side effects*

The theoretic risk of pelvic infection has not been reported. In view of the paucity of data on the use of ovarian stimulation and IUI in women with PCOS, further studies are necessary in this category of patients.

### *Summary points*

(i) Induction of ovulation in combination with IUI is indicated in women with PCOS and an associated male factor and may be proposed in women with PCOS who failed to conceive despite successful induction of ovulation.
(ii) Currently, double insemination does not appear to enhance the probability of pregnancy as compared with single IUI.

## General comments

Initial studies have shown that many features associated with PCOS—such as obesity, hyperandrogenemia and polycystic ovaries predict poor outcome of ovulation induction. Multivariate models have been developed predicting ovulation and pregnancy following CC (Imani *et al*., 2002) and chances for success and complications from use of gonadotrophins (Mulders *et al*., 2003; van Santbrink *et al*., 2005) and LOS. These observations need to be confirmed in independent patient populations. These approaches may eventually result in more patient-tailored treatment algorithms in ovulation induction. For instance, CC may not be the drug of first choice in some women previously shown to have poor outcomes following CC medication. Likewise, it may be possible to identify women more suitable for gonadotrophins or LOS as second-line treatment. For some older women, IVF may represent the preferred treatment modality certainly under conditions of low chances for multiple pregnancy in case single ET is performed.

Even singleton pregnancies after ovulation induction in women with PCOS are characterized by more frequent pregnancy complications (such as gestational diabetes, pregnancy-induced hypertension and pre-eclampsia) and neonatal complications (such as preterm births and admission to neonatal intensive care units) (Boomsma *et al*., 2006) (Fig. 6). Women should be counselled accordingly.

## Overall conclusions

(i) Evaluation of women with presumed PCOS desiring pregnancy should exclude any other health issues in the woman or infertility problems in the couple.

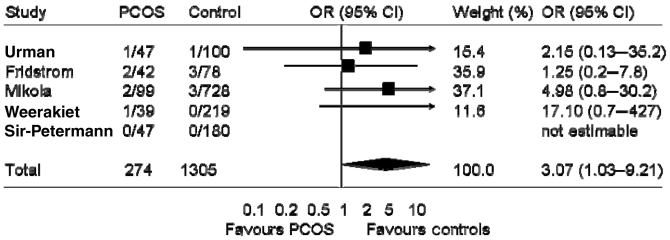



**Figure 6:** OR for the incidence of perinatal mortality in babies from women with PCOS versus controls (Boomsma *et al*., 2006, with permission)
Test for heterogeneity: $\chi^2 = 2.38$, df = 3 ($P$=0.50), $I^2 = 0\%$. Test for overall effect: $z = 2.01$ ($P = 0.04$).

(ii) Before any intervention is initiated, preconceptional counselling should be provided emphasizing the importance of life style, especially weight reduction and exercise in overweight women, smoking and alcohol consumption.

(iii) The recommended first-line treatment for ovulation induction remains the anti-estrogen CC.

(iv) Recommended second-line intervention should CC fail to result in pregnancy is either exogenous gonadotrophins or LOS. Both have distinct advantages and drawbacks. Choice should be made on an individual basis. The use of exogenous gonadotrophins is associated with increased chances for multiple pregnancy and intense monitoring of ovarian response is therefore required. LOS is usually effective in $<50\%$ of women and additional ovulation induction is required under those circumstances.

(v) Overall, ovulation induction (representing the CC, gonadotrophin paradigm) is reported to be highly effective with a cumulative singleton live birth rate of 72%.

(vi) Recommended third-line treatment is IVF, because this treatment is effective in women with PCOS. Data concerning the use of single ET in (young) women with PCOS undergoing IVF, significantly reducing chances of multiple pregnancies, are awaited.

(vii) More patient-tailored approaches should be developed for ovulation induction based on initial screening characteristics of women with PCOS. Such approaches may result in deviation from the above mentioned first-, second- or third-line ovulation strategies in well-defined subsets of patients.

(viii) Metformin use in PCOS should be restricted to women with glucose intolerance. Based on recent data available in the literature, the routine use of this drug in ovulation induction is not recommended.

(ix) Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction.

(x) Even singleton pregnancies in PCOS are associated with increased health risk for both the mother and the fetus.

## Appendix

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group March 2–3, 2007, Thessaloniki, Greece. Group members: B.C. Tarlatzis (Gr), B.C.J.M. Fauser (NL), R.S. Legro (USA), R.J. Norman (Aus), K. Hoeger (USA), R. Pasquali (It), S. Franks (UK), i.e. Messinis (Gr), R.F. Casper (Can), R. Homburg (Is), R. Lobo (USA), R.W. Rebar (USA), R. Fleming (UK), B.R. Carr (USA), Ph. Bouchard (Fr), J. Chang (USA), J.N. Hugues (Fr), R. Azziz (USA), E.M. Kolibianakis (Gr), G. Griesinger (Ger), K. Diedrich (G), A. Balen (UK), C. Farquhar (NZ), P. Devroey (B), P.C. Ho (HK), J. Collins (Can), D.G. Goulis (Gr), R. Eijkemans (NL), P.G. Crosignani (It), A. DeCherney (USA), A. Van Steirteghem (B).

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