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. On the basis of the currently available evidence, a group of experts reached a consensus regarding the therapeutic challenges raised in these women. Before any intervention is initiated, preconceptional counseling should be provided emphasizing the importance of lifestyle, 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 gonadotropins or laparoscopic ovarian surgery (LOS). The use of exogenous gonadotropins is associated with increased chances for multiple pregnancy, and, therefore, intense monitoring of ovarian response is required. Laparoscopic ovarian surgery alone is usually effective in less than 50% of women, and additional ovulation induction medication is required under those circumstances. Overall, ovulation induction (representing the CC–gonadotropin paradigm) is reported to be highly effective with a cumulative singleton live-birth rate of 72%. Recommended third-line treatment is in vitro fertilization (IVF). 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-line, second-line, 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. (Fertil Steril® 2008;89:505–22. ©2008 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, infertility treatment, 2007 consensus

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies, affecting 5% to 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. That 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* and in *Human Reproduction* (1, 2).

Criteria proposed for the diagnosis of PCOS in the Rotterdam meeting were set 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 (3, 4).

Although significant progress has been made toward the development of universally accepted diagnostic criteria for PCOS (1, 2), the optimal treatment for infertile women with PCOS has not yet been defined. Various interventions have been proposed ranging from lifestyle modifications

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and administration of pharmaceutical agents such as clomiphene citrate (CC), insulin-sensitizing agents, gonadotropins, and gonadotropin-releasing hormone (GnRH) analogues to 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 and 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 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 counseling in women with PCOS should identify risk factors for reproductive failure and correct them before 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 (5), pregnancy loss (6), and late pregnancy complications (preeclampsia, gestational diabetes, etc.) (7). 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 (8, 9), gonadotropins (10, 11) (Fig. 1), and laparoscopic ovarian diathermy (12). Weight loss is recommended as the 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.

However, it should be noted that there is a paucity of studies suggesting that weight loss before conception improves the live-birth rate in obese women with or without PCOS (13). On the other hand, multiple observational studies have noted that weight loss is associated with improved spontaneous ovulation rates in women with PCOS (5, 13), and pregnancies have been reported after losing as little as 5% of initial body weight (14). The treatment of obesity is multifaceted and involves behavioral counseling, lifestyle therapy (diet and exercise), pharmacologic treatment, and bariatric surgery (15). 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 behavioral therapies offers the greatest weight loss (16) though long-term bariatric surgery is associated with the best weight maintenance after weight loss (17). The effects of calorie restriction, increased physical activity, and pharmacologic and weight loss agents in the periconceptional period are unknown and are potentially harmful to the goal of live birth (18, 19). These interventions should be conducted before pregnancy, not concurrently with infertility treatment, until the risk–benefit ratio of these therapies on pregnancy is better understood. Table 1 shows randomized trials of lifestyle and pharmacologic weight loss therapy in women with PCOS.

FIGURE 1

Association between obesity and ovulation rate in gonadotropin ovulation induction, with a pooled odds ratio and 95% confidence interval. (Mulders et al., Hum Reprod Update 2003;9:429–49. Used with permission.) Cited Studies: Hamilton-Fairley et al. (154), Strowitzky et al. (155), Vicino et al. (156), Yarali et al. (157).

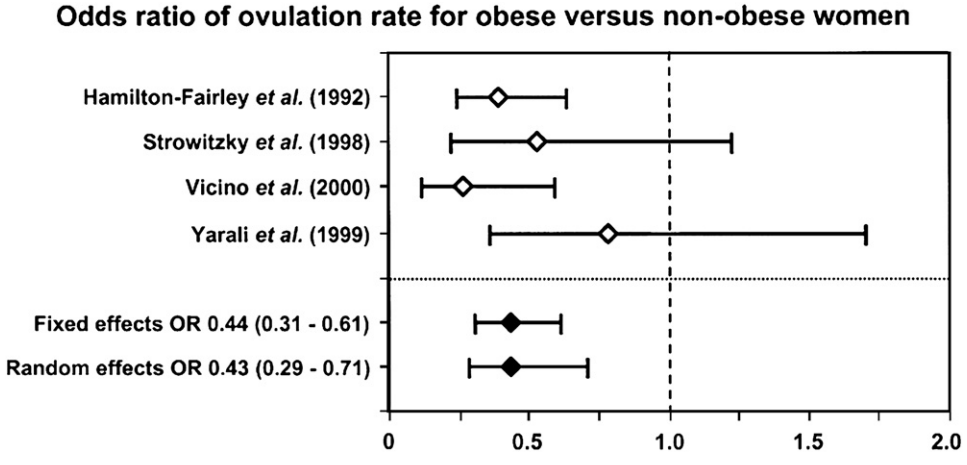

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TABLE 1

Randomized trials of lifestyle and pharmacologic weight-loss therapy in women with polycystic ovary syndrome.

Study	Number of patients	Duration	Intervention	Weight loss (kg)	Reproductive outcome
			Diet		
Moran et al., 2003 (13)	28	16 w	**Diet (RCT):** 6000 KJ/day HP: 40% C, 30% P, 30% F LP: 55% C, 15% P, 30% F	7.7	44% had improvement in ovulation
Moran et al., 2004 (21)	10	16 w	**Diet (RCT):** 6000 KJ/day HP: 40% C, 30% P, 30% F LP: 55% C, 15% P, 30% F	7.1	NA
Stamets et al., 2004 (22)	26	1 m	**Diet (RCT):** 4200 KJ deficit/day HP: 40% C, 30% P, 30% F LP: 55% C, 15% P, 30% F	4.0	Decreased T, increased menstrual bleeding
Moran et al., 2006 (28)	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) **Exercise:** 8000 steps/day	4.7	Decreased T, 57% had improved menstrual cyclicity
			Lifestyle		
Hoeger et al., 2004 (163)	38	48 w	**Combined therapy (RCT)** **Diet**: 2100–4200 KJ deficit/day. Individualized healthy meal plan: 50% C, 25% P, 25% F **Exercise:** Group sessions **Behavior:** Group sessions	6.8	NS
Bruner et al., 2006 (26)	12	12 w	**Diet (RCT):** Canadian Food Guide to Healthy Eating **Exercise:** A combination of endurance and resistance activities 3 days/week	NS	NS

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TABLE 1

Continued.

Study	Number of patients	Duration	Intervention	Weight loss (kg)	Reproductive outcome
Tang et al., 2006 (53)	143	6 m	**Diet (RCT):** 500 kcal deficit/day **Exercise:** increase physical activity by 15 minutes a day (unmonitored) Pharmacological	1.5	Improved menstrual frequency (median 1 cycle/6 m)
Sabuncu et al., 2003 (32)	40	6 m	**Medication:** Sibutramine 10 mg/day	5.8	37% decrease in T, 280% increase in SHBG
Jayagopal et al., 2005 (33)	21	3 m	**Diet:** 8-week run in of dietary modification **Medication:** Orlistat 120 mg tid	4.4	8% decrease in T

Note: C: carbohydrate; P: protein; F: fat; HP: high protein; LP: low protein; NA: not available; NS: no statistically significant change from baseline; RCT: randomized, controlled trial; SHBG: sex-hormone–binding globulin; T: testosterone; w: week(s); m: month(s).

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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 (20). 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 can improve reproductive outcome (21). 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 (13, 22). However, these studies did not show that dietary patterns differentially affect weight loss and reproductive outcomes.

Increasing evidence in women without PCOS suggests that diets with reduced glycemic load may be beneficial in alleviating hyperinsulinemia and its metabolic consequences (23). This is of particular relevance to women with PCOS because of 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 toward being overweight/obese. Baseline activity levels by self-report were lower in women with PCOS compared with control women (24). In the Nurses' Health Study, vigorous activity was associated with a reduced relative risk of anovulatory infertility (25). Few studies have examined the role of exercise alone in improving reproductive function in PCOS. In a pilot trial examining exercise and nutritional counseling in PCOS, women were assigned to nutritional counseling alone or in combination with exercise. No differences were seen between groups with respect to weight loss or restoration of menstruation (26).

Several studies have examined combination therapy of diet and exercise (27, 28). Most of them, however, were not randomized trials, and exercise was not supervised but rather consisted of lifestyle counseling. Although weight loss alone appeared 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 programs because it is associated with better long-term weight loss maintenance (29). 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 (28).

Pharmacologic Treatment and Bariatric Surgery

The available literature supports the adjuvant use of bariatric surgery and pharmacologic 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 (30). Most importantly, this disorder has been

found to improve markedly after sustained weight loss after bariatric surgery (31). Anti-obesity pharmacologic agents have been used in obese women with PCOS although few quality studies have been published (32, 33). Both orlistat, which blocks intestinal absorption of fat (33), and sibutramine, an appetite suppressant (32), 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 (34). This agent is not approved by the U.S. Food and Drug Administration (FDA), but 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

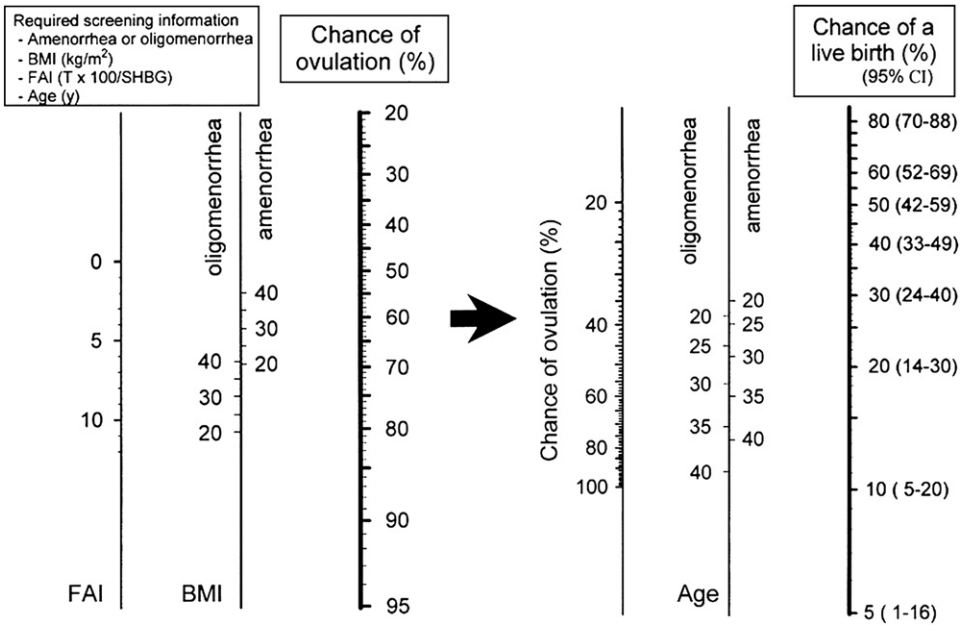
- Obesity adversely affects reproduction and is associated with anovulation, pregnancy loss, and late-pregnancy complications.
- Obesity within PCOS is associated with failure of infertility treatment.
- Weight loss before infertility treatment improves ovulation rates in women with PCOS, but there are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

CLOMIPHENE CITRATE

Clomiphene citrate (CC) remains the treatment of first choice for induction of ovulation in anovulatory women with PCOS. The cost of the 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 (35) (Fig. 2). Ovarian volume and menstrual status are additional factors that help to predict responsiveness to CC (36).

FIGURE 2

Nomogram designed to predict chances for live birth in clomiphene citrate induction of ovulation. Note the two different steps. (Imani et al., Fertil Steril 2002;77:91–7. Used with permission.)



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Selection of Patients

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

Dose

The starting dose of CC generally should be 50 mg/day (for 5 days, starting on days 2 to 5 after 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 per treatment cycle (37).

Monitoring

Although the results of large trials suggest that monitoring by ultrasound is not mandatory to ensure good outcome (38), the practice in many centers is to monitor the first cycle to allow adjustment of the dose in subsequent cycles based on 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 gonadotropin (hCG) in midcycle improves the chances of conception (39).

Efficacy

Approximately 75% to 80% of patients with PCOS will ovulate after CC administration (40, 41). 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 (36, 42, 43).

Duration of Treatment

Treatment generally should be limited to six (ovulatory) cycles (36, 40). 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 should be considered at that time (36, 44). Cumulative live-birth rates vary between 50% to 60% for up to six cycles (43).

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 less than 10%, and ovarian hyperstimulation syndrome (OHSS) is rare (36). 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 (45).

Combination Therapy

There is now clear evidence that the addition of metformin (38, 46) or dexamethasone (47) to CC as primary therapy for induction of ovulation has no beneficial effect.

Alternative Therapies

Anti-estrogens other than clomiphene citrate Tamoxifen appears to be as effective as CC for induction of ovulation but is not licensed for that purpose (48, 49). 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

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

INSULIN-SENSITIZING AGENTS

Insulin-sensitizing agents are currently being used 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 (50). The major risk with the thiazolidinediones is liver toxicity, and recently there has been concern about increased cardiovascular morbidity with rosiglitazone (51). With regard to the use of these agents use during pregnancy, metformin is a category B drug according to the 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 it does not appear to result in consistent significant changes in BMI or waist-to-hip ratio (52). Although oligomenorrhea 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 lifestyle modification, with no difference between metformin and placebo in this regard (53), and has been estimated to represent one extra ovulation every five woman-months (54).

With regard to the use of metformin for induction of ovulation, two RCTs have indicated that metformin does not increase live-birth rates above those observed with CC alone in either obese or normal weight women with PCOS (38, 46). The larger of these two trials (38) 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, but the combination of both drugs did not result in a significant benefit (Table 2). 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 (46). Thus, insulin sensitizers should not be used as first-choice agents for induction of ovulation in women with 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 (55, 56).

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 has been taking the medication (38). Although there have been suggestions that metformin treatment during pregnancy may be protective against complications (57), currently such use should take place only in a research context (58).

TABLE 2

Randomized trial from the National Institutes of Health Reproductive Medicine Network.

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

Source: Legro et al., N Engl J Med 2007;356:551–66. Used with permission.

[a] $P<.001$.

[b] $P<.001$ (combination vs. clomiphene citrate [CC]).

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Summary Points

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

GONADOTROPINS 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 gonadotropin therapy is based on the physiologic 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 (59, 60).

Regimens

The original description of gonadotropin administration for anovulation used 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 OHSS (61–63). Subsequent efforts to reduce the frequency of ovarian hyperstimulation have resulted in the development of low-dose protocols (37.5–75 IU/day), which have essentially replaced the original conventional protocol (64–67).

Starting doses of daily 150 IU FSH are no longer recommended in women with PCOS (68, 69) and have been replaced by low-dose FSH protocols. Currently, two low-dose regimens are used:

1. *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. After commencement of gonadotropin administration, if follicle development is not observed on ultrasound after 1 week, an increase in the dose is recommended. Once follicle growth is observed, the same FSH dose is maintained until follicular selection is achieved. To further reduce the risk of ovarian hyperresponsiveness, 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 (70–73).

2. *Step-down regimens:* 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 (74–76). Preliminary studies report that both step-up and step-down regimens achieve similar high rates of monofollicular development (77, 78). However, the largest study published so far has shown that the step-up regimen is safer in terms of monofollicular development (79). 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 (80). Alternatively, a combined approach of sequential step-up and step-down regimens has been shown to help reduce the risk of overresponse (81, 82).

Combination of GnRH Analogues and Gonadotropins

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 (83) and deleterious LH effect on granulosa cell steroidogenesis (84, 85). In addition, elevated LH levels may be associated with an increased pregnancy loss (86–89), although more recent data are not consistent with this assumption (10, 90, 91).

The concomitant use of a GnRH agonist with gonadotropin administration to improve pregnancy rates in patients undergoing ovulation induction has not been firmly established (92–94). Moreover, combined therapy was associated with an increased risk of OHSS (95–99), but there are insufficient data to draw solid conclusions on miscarriage and multiple pregnancy rates (100–102). 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 gonadotropins in PCOS patients. The question of whether LH suppression by a GnRH antagonist during gonadotropin-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 before the initiation of each cycle. Serial ovarian ultrasound is an excellent method of determining follicle growth and development in response to gonadotropin stimulation. In particular, documentation of all follicles greater than 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 gonadotropins, it is mandatory to counsel the patient about the risks associated with higher-order multiple pregnancies after polyovulation.

In most previous studies, cycle cancellation has been advised when more than three follicles of 16 mm or larger were observed (65, 67, 103) to prevent OHSS and multiple pregnancies. In some studies, the limit was four or more follicles >14 mm (82, 104). Recently, more stringent criteria have been recommended for ovarian stimulation in unexplained infertility: no more than two follicles >14 mm (105) or no more than three or four follicles >10 mm (106, 107). 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 $\geq$16 mm without any information on the number of smaller follicles, except in the study by Leader (108), which defined a cycle as monoovulatory when a single follicle of $\geq$16 mm was present with no other follicle $\geq$12 mm. Measurements of circulating estradiol levels have been used to cancel ovulation induction cycles using gonadotropins (due to overresponse or underresponse) or to adjust the dose of gonadotropins used either upward or, more frequently, downward to minimize the risk of multiple pregnancies or OHSS. Although specific normative cut-offs vary, in 2006 the Practice Committee of the ASRM suggested that caution was indicated when a rapidly rising serum estradiol levels or an estradiol concentration in excess of 2500 pg/mL was present during gonadotropin ovulation induction (109). However, in other studies (106, 107), the cut-off estradiol concentration was much lower, below 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 $\geq$16 mm or more than one follicle $\geq$16 mm and two additional follicles $\geq$14 mm, 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 approximately 70%, a pregnancy rate of 20%, and a multiple live birth rate of 5.7% (103). Correspondingly, there is a low incidence of multiple pregnancies (<6%) and OHSS (<1%) (67, 80, 110, 111). These results compare favorably to the unacceptable high risk of multiple follicular development, multiple pregnancies (36%), and severe OHSS (4.6%) reported for conventional dose protocols (112). For a summary of clinical outcomes, see Table 3 (113).

TABLE 3

Comparison of ovarian response and clinical outcomes in low-dose step-up and step-down protocols for gonadotropin ovulation induction.

	Low-dose step-up			Step-down
	Hamilton-Fairley et al., 1991	Hull et al., 1991	Balen et al., 1994	van Santbrink et al., 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 cycle	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

Note: NR, not recorded. Cited Studies: Hamilton-Fairley et al. (111), Hull et al. (164), Balen et al. (165), Van Santbrink et al. (80).
Source: Fauser and Macklon, in Strauss JF, Barbieri RL, eds. Yen and Jaffe's reproductive endocrinology. Philadelphia: Elsevier Saunders, 2004:965–1012. Used with permission.

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A prospective follow-up study involving 240 women showed a favorable cumulative singleton live-birth rate of 72% after the combined analysis of ovulation induction using CC medication as first-line and exogenous gonadotropins as second-line treatment (36) (Fig. 3).

Summary Points

- The recommended starting dose of gonadotropin is 37.5–50.0 IU/day.
- Adherence to a 14-day starting period at least for the first cycle is less likely to result in excessive stimulation.
- Small FSH dose increments of 50% of the initial or previous FSH dose are less likely to result in excessive stimulation.
- The duration of gonadotropin therapy generally should not exceed six ovulatory cycles.
- 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.
- Intense ovarian response monitoring is required to reduce complications and secure efficiency.
- Strict cycle cancellation criteria should be agreed upon with the patient before therapy is started.
- Preventing all multiple pregnancies and OHSS is not possible at this time.
- 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 gonadotropins in women with PCOS.

LAPAROSCOPIC OVARIAN SURGERY

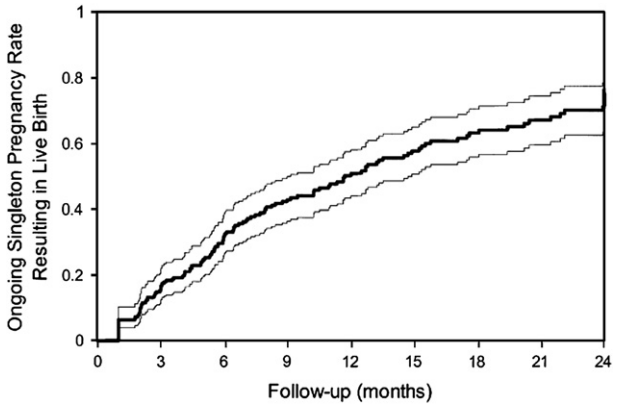
Surgical approaches to ovulation induction have developed from the traditional wedge resection to modern day minimal access techniques, usually employing laparoscopic ovarian diathermy or laser. Multiple ovarian puncture performed either by diathermy or by laser is known as "ovarian drilling" (114).

Indications for Laparoscopic Ovarian Surgery

The main indication for performing laparoscopic ovarian surgery (LOS) is CC resistance in women with anovulatory PCOS. The surgery 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

FIGURE 3

Cumulative pregnancy rate resulting in singleton live birth of a consecutive series of 240 normogonadotrophic anovulatory infertile women undergoing classic ovulation induction (clomiphene citrate as first-line, followed by follicle-stimulating hormone as second-line therapy). (Eijkemans et al. Hum Reprod 2003;18:2357–62. Used with permission.)



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or who live too far away from the hospital for the intensive monitoring required during gonadotropin therapy.

Extensive ovarian diathermy is not indicated to prevent hyperresponsiveness to exogenous gonadotropins (115). In addition, ovarian surgery has been suggested for nonfertility indications such as 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 (116).

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 (117). Ovarian surgery may also be performed transvaginally by hydrolaparoscopy (118), but 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 (119).

There is no evidence that any surgical technique is superior, but as few as four punctures have been shown to be effective. Most investigators use between 4 and 10 punctures; more punctures have been associated with premature ovarian failure (120–122). 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 approximately 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 (123). The addition of FSH should be considered after 6 months (123). Five RCTs that compared the effectiveness of LOS with that of gonadotropins for women with CC-resistant PCOS did not show a difference in ongoing pregnancy rate or live-birth rate (117, 123–127) (Fig. 4a). In one of these trials (123), if ovulatory cycles were not established 8 weeks after surgery or the woman became anovulatory again, then CC was given in increasing doses. Multiple pregnancy rates were significantly higher in the gonadotropin 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 gonadotropin-treated women (OR 0.61; 95% CI, 0.17–2.16). No cases of OHSS were observed in either of the two most recent studies (123, 125).

Economic analyses of two RCTs suggest that LOS treatment of women with CC-resistant PCOS resulted in reduced direct and indirect costs. In the New Zealand study, the cost of a live-birth was one-third lower with surgery; in the Netherlands study, the cost of a term pregnancy was estimated to be 22% lower (128, 129). Predictors of success have included LH level >10 IU/L, normal BMI, and shorter duration of infertility (12, 130, 131).

Safety

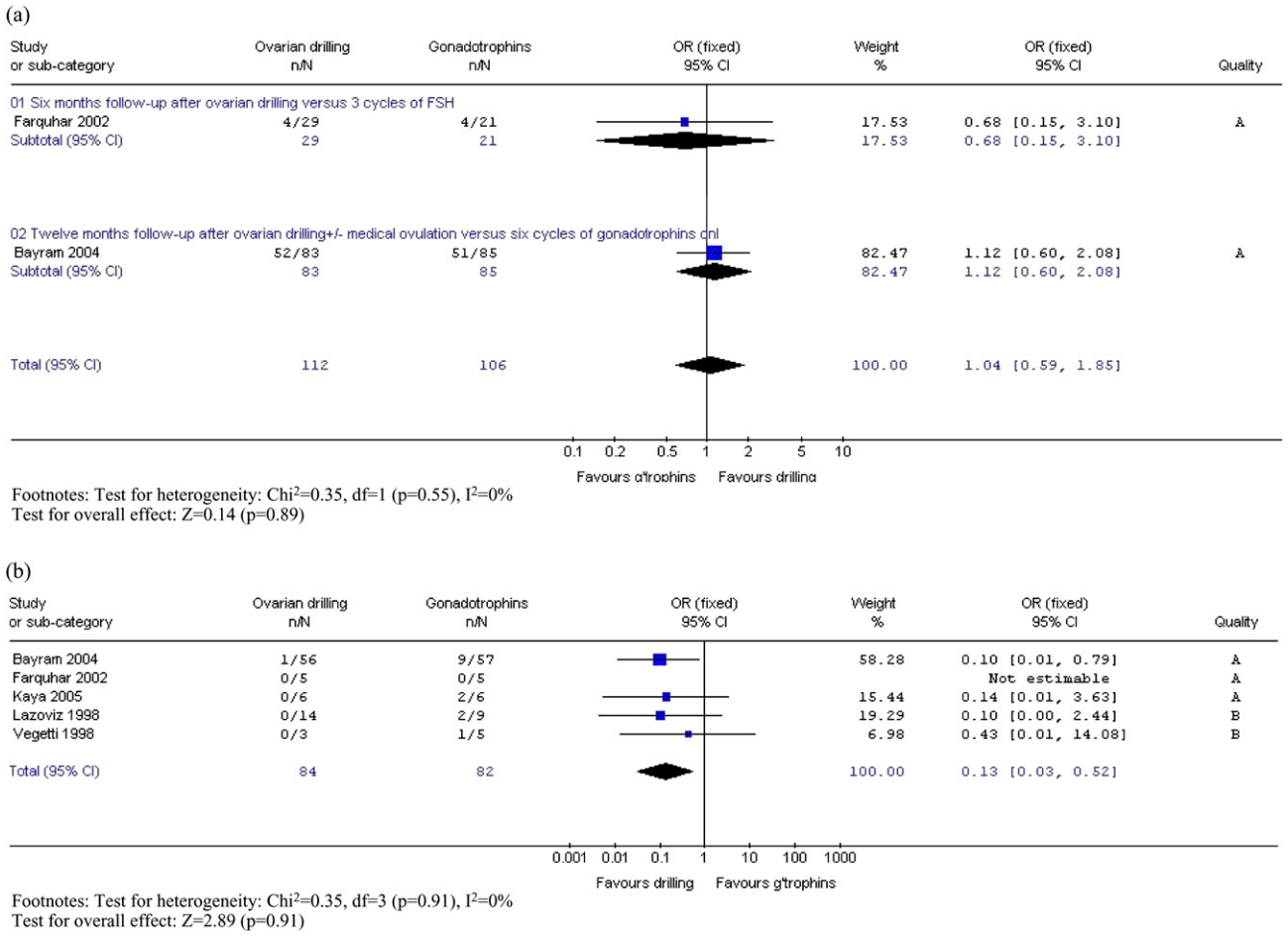
Immediate complications of the surgery are rare. Out of 778 cases of LOS, two cases with hemorrhage requiring laparotomy and one case with bowel perforation have been reported (132). Long-term adverse events potentially include adhesion formation and premature menopause. Only two second-look laparoscopy studies have been done. In one study, out of 17 cases there were two with severe adhesion formation (133). 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 (134). 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 has been reassuring in this respect (135, 136).

Summary Points

- Laparoscopic ovarian surgery can achieve unifollicular ovulation with no risk of OHSS or high-order multiples.
- Intensive monitoring of follicular development is not required after LOS.
- Laparoscopic ovarian surgery is an alternative to gonadotropin therapy for CC-resistant anovulatory PCOS.
- The treatment is best suited to those for whom frequent ultrasound monitoring is impractical.

FIGURE 4

Results from the meta-analysis of the randomized, controlled trials of laparoscopic ovarian surgery versus gonadotropins for (**a**) live-birth rate and (**b**) multiple pregnancy rate. Notes: Test for heterogeneity: chi-square = 0.35, df = 1 (*P*=.55), I^2 = 0%. Test for overall effect: Z = 0.14 (*P*=.89). (Farquhar et al., Cochrane Database Syst Rev 2007;3:CD001122. Copyright Cochrane Collaboration, reproduced with permission.)



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- Laparoscopic ovarian surgery is a single treatment using existing equipment.
- The risks of surgery are minimal and include the risks 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.
- Laparoscopic ovarian surgery should not be offered for nonfertility indications.

ASSISTED REPRODUCTION TECHNIQUES: IN VITRO FERTILIZATION

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 gonadotropin therapy. The major complication of ovulation induction is the 10% multiple pregnancy rate, especially after the use of gonadotropin therapy. For this reason use of gonadotropins may be questioned (137).

After failure of weight reduction, anti-estrogen therapy, or LOS, it may be argued that induction of ovulation with exogenous gonadotropin therapy should be omitted and replaced by ovarian stimulation and IVF (138). By using IVF with single embryo transfer, the risk of multiple pregnancies is markedly reduced (139, 140). In women with PCOS who do have associated pathologies, IVF is indicated, such as in cases 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 gonadotropins

(hMG) (141), hMG alone (142), recombinant FSH alone, GnRH-agonist associated with hMG or recombinant FSH (143), and GnRH-antagonist associated with hMG or recombinant FSH (143). Currently, the most standard protocol is a long desensitization protocol associated with FSH.

Efficacy

In a recent meta-analysis (144), 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 the 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. Specific data on the success rates of single-embryo transfer 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 (145).

Complications

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

Summary Points

- In vitro fertilization is a reasonable option because the number of multiple pregnancies can be kept to a minimum by transferring fewer embryos.
- The optimal stimulation protocol is still under debate.
- There is a need to perform further RCTs comparing FSH stimulation protocols with use of GnRH agonists versus GnRH antagonists.
- 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.
- 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.

ASSISTED REPRODUCTION TECHNIQUES: OVULATION INDUCTION AND HOMOLOGOUS ARTIFICIAL INSEMINATION

Indications

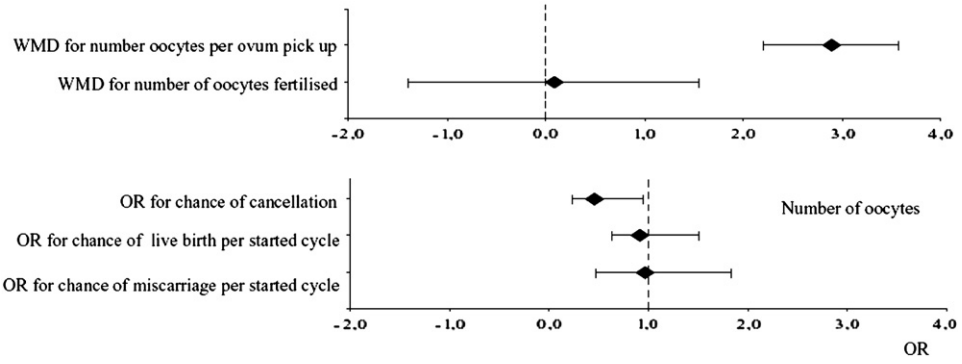
Currently, there are no RCTs conducted in women with PCOS comparing the pregnancy rates of intrauterine insemination (IUI) versus timed intercourse during ovulation induction. Because subfertility in women with PCOS is mainly due to anovulation, induction of ovulation is the main treatment for women 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 infertility (146), 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

Because 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 multiple pregnancies (147), also in combination with IUI. An additional approach

FIGURE 5

Main findings of clinical IVF outcomes in women with polycystic ovary syndrome compared with matched controls. (Heijnen et al., Hum Reprod Update 2006;12:13–21. Used with permission.)



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is to perform transvaginal ultrasound-guided aspiration of the supernumerary follicles (148).

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 (149).

Efficacy

Only limited studies on the results of ovarian stimulation and IUI in women with PCOS are available (150–152). 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

- Induction of ovulation in combination with IUI is indicated in women with PCOS and associated male factor infertility and may be proposed in women with PCOS who fail to conceive despite successful induction of ovulation.
- 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 after CC (35) and chances for success and complications from use of gonadotropins (10, 153) 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 after CC medication. Likewise, it may be possible to identify women more suitable for gonadotropins 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-embryo transfer is performed.

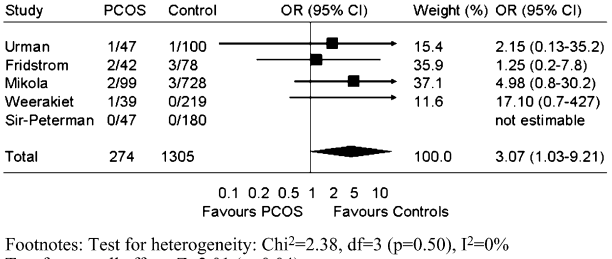
Even singleton pregnancies after ovulation induction in women with PCOS are characterized by more frequent pregnancy complications (such as gestational diabetes, pregnancy-induced hypertension, and preeclampsia) and neonatal complications (such as preterm births and admission to neonatal intensive care units) (7) (Fig. 6). Women should be counseled accordingly.

OVERALL CONCLUSIONS

- Evaluation of women with presumed PCOS desiring pregnancy should exclude any other health issues in the woman or infertility problems in the couple.
- Before any intervention is initiated, preconceptional counseling should be provided emphasizing the importance of lifestyle, especially weight reduction and exercise in overweight women, smoking, and alcohol consumption.
- The recommended first-line treatment for ovulation induction remains the anti-estrogen CC.
- Recommended second-line intervention should CC fail to result in pregnancy is either exogenous gonadotropins or LOS. Both have distinct advantages and drawbacks. The choice should be made on an individual basis. The use of exogenous gonadotropins is associated with increased chances for multiple pregnancy, so intense monitoring of ovarian response is required. Laparoscopic ovarian surgery is usually effective in less than 50% of women, and additional ovulation induction is required under those circumstances.
- Overall, ovulation induction (representing the CC–gonadotropin paradigm) is reported to be highly effective, with a cumulative singleton live-birth rate of 72%.
- Recommended third-line treatment is IVF because this treatment is effective in women with PCOS. Data concerning the use of single-embryo transfer in (young) women with PCOS undergoing IVF, which significantly reduces the chance of multiple pregnancies, are awaited.

FIGURE 6

Odds ratio for the incidence of perinatal mortality in babies from women with polycystic ovary syndrome versus controls. Notes: Test for heterogeneity: chi-square = 2.38, df = 3 (P=.50), I^2 = 0%. Test for overall effect: Z = 2.01 (P=.04). (Boomsma et al., Hum Reprod Update 2006;12:673–83. Used with permission.) Cited Studies: Urman et al. (158), Fridstrom et al. (159), Mikola et al. (160), Weerakiet et al. (161), Sir-Peterman et al. (162).



Footnotes: 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)

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- 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-line, second-line, 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.

REFERENCES

1. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19–25.
2. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7.
3. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab 2006;91:4237–45.
4. Franks S. Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: in defense of the Rotterdam criteria. J Clin Endocrinol Metab 2006;91:786–9.
5. Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. Hum Reprod Update 2003;9:359–72.
6. Froen JF, Arnestad M, Frey K, Vege A, Saugstad OD, Stray-Pedersen B. Risk factors for sudden intrauterine unexplained death: epidemiologic characteristics of singleton cases in Oslo, Norway, 1986–1995. Am J Obstet Gynecol 2001;184:694–702.
7. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update 2006;12:673–83.
8. Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. Predictors of patients remaining anovulatory during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. J Clin Endocrinol Metab 1998;83:2361–5.
9. Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. Predictors of chances to conceive in ovulatory patients during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. J Clin Endocrinol Metab 1999;84:1617–22.
10. Mulders AG, Laven JS, Eijkemans MJ, Hughes EG, Fauser BC. Patient predictors for outcome of gonadotrophin ovulation induction in women with normogonadotrophic anovulatory infertility: a meta-analysis. Hum Reprod Update 2003;9:429–49.
11. Balen AH, Platteau P, Andersen AN, Devroey P, Sorensen P, Helmgaard L, et al. The influence of body weight on response to ovulation induction with gonadotrophins in 335 women with World Health Organization group II anovulatory infertility. BJOG 2006;113:1195–202.
12. Gjonnaess H. Ovarian electrocautery in the treatment of women with polycystic ovary syndrome (PCOS). Factors affecting the results. Acta Obstet Gynecol Scand 1994;73:407–12.
13. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Galletly C, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88:812–9.
14. Kiddy DS, Hamilton-Fairley D, Bush A, Short F, Anyaoku V, Reed MJ, et al. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 1992;36:105–11.
15. Yanovski SZ, Yanovski JA. Obesity. N Engl J Med 2002;346:591–602.
16. Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, Cato RK, et al. Randomized trial of lifestyle modification and pharmacotherapy for obesity. N Engl J Med 2005;353:2111–20.
17. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683–93.
18. Morris SN, Missmer SA, Cramer DW, Powers RD, McShane PM, Hornstein MD. Effects of lifetime exercise on the outcome of in vitro fertilization. Obstet Gynecol 2006;108:938–45.
19. Tsagareli V, Noakes M, Norman RJ. Effect of a very-low-calorie diet on in vitro fertilization outcomes. Fertil Steril 2006;86:227–9.
20. Marsh K, Brand-Miller J. The optimal diet for women with polycystic ovary syndrome? Br J Nutr 2005;94:154–65.
21. Moran LJ, Noakes M, Clifton PM, Wittert GA, Tomlinson L, Galletly C, et al. Ghrelin and measures of satiety are altered in polycystic ovary syndrome but not differentially affected by diet composition. J Clin Endocrinol Metab 2004;89:3337–44.
22. Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkman CL, Legro RS. A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. Fertil Steril 2004;81:630–7.
23. Reaven GM. The insulin resistance syndrome: definition and dietary approaches to treatment. Annu Rev Nutr 2005;25:391–406.
24. Wright CE, Zborowski JV, Talbott EO, Hugh-Pemu K, Youk A. Dietary intake, physical activity, and obesity in women with polycystic ovary syndrome. Int J Obes Relat Metab Disord 2004;28:1026–32.
25. Rich-Edwards JW, Spiegelman D, Garland M, Hertzmark E, Hunter DJ, Colditz GA, et al. Physical activity, body mass index, and ovulatory disorder infertility. Epidemiology 2002;13:184–90.
26. Bruner B, Chad K, Chizen D. Effects of exercise and nutritional counseling in women with polycystic ovary syndrome. Appl Physiol Nutr Metab 2006;31:384–91.
27. Crosignani PG, Colombo M, Vegetti W, Somigliana E, Gessati A, Ragni G. Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. Hum Reprod 2003;18:1928–32.
28. Moran LJ, Brinkworth G, Noakes M, Norman RJ. Effects of lifestyle modification in polycystic ovarian syndrome. Reprod Biomed Online 2006;12:569–78.
29. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.
30. Alvarez-Blasco F, Botella-Carretero JI, San Millan JL, Escobar-Morreale HF. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. Arch Intern Med 2006;166:2081–6.
31. Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millán JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. J Clin Endocrinol Metab 2005;90:6364–9.
32. Sabuncu T, Harma M, Harma M, Nazligul Y, Kilic F. Sibutramine has a positive effect on clinical and metabolic parameters in obese patients with polycystic ovary syndrome. Fertil Steril 2003;80:1199–204.
33. Jayagopal V, Kilpatrick ES, Holding S, Jennings PE, Atkin SL. Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. J Clin Endocrinol Metab 2005;90:729–33.
34. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and

cardiometabolic risk factors in overweight or obese patients: RIO–North America: a randomized controlled trial. JAMA 2006;295:761–75.
35. Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. A nomogram to predict the probability of live birth after clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. Fertil Steril 2002;77:91–7.
36. Eijkemans MJ, Imani B, Mulders AG, Habbema JD, Fauser BC. High singleton live birth rate following classical ovulation induction in normogonadotrophic anovulatory infertility (WHO 2). Hum Reprod 2003;18:2357–62.
37. Dickey RP, Taylor SN, Curole DN, Rye PH, Pyrzak R. Incidence of spontaneous abortion in clomiphene pregnancies. Hum Reprod 1996;11:2623–8.
38. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med 2007;356:551–66.
39. Kosmas IP, Tatsioni A, Fatemi HM, Kolibianakis EM, Tournaye H, Devroey P. Human chorionic gonadotropin administration vs. luteinizing monitoring for intrauterine insemination timing, after administration of clomiphene citrate: a meta-analysis. Fertil Steril 2007;87:607–12.
40. Homburg R. Clomiphene citrate—end of an era? A mini-review. Hum Reprod 2005;20:2043–51.
41. Messinis IE. Ovulation induction: a mini review. Hum Reprod 2005;20:2688–97.
42. Hammond MG, Halme JK, Talbert LM. Factors affecting the pregnancy rate in clomiphene citrate induction of ovulation. Obstet Gynecol 1983;62:196–202.
43. Kousta E, White DM, Franks S. Modern use of clomiphene citrate in induction of ovulation. Hum Reprod Update 1997;3:359–65.
44. Messinis IE, Milingos SD. Current and future status of ovulation induction in polycystic ovary syndrome. Hum Reprod Update 1997;3:235–53.
45. Kolibianakis EM, Zikopoulos KA, Fatemi HM, Osmanagaoglu K, Evenpoel J, Van SA, et al. Endometrial thickness cannot predict ongoing pregnancy achievement in cycles stimulated with clomiphene citrate for intrauterine insemination. Reprod Biomed Online 2004;8:115–8.
46. Moll E, Bossuyt PM, Korevaar JC, Lambalk CB, van der Veen F. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. BMJ 2006;332:1485.
47. Daly DC, Walters CA, Soto-Albors CE, Tohan N, Riddick DH. A randomized study of dexamethasone in ovulation induction with clomiphene citrate. Fertil Steril 1984;41:844–8.
48. Messinis IE, Nillius SJ. Comparison between tamoxifen and clomiphene for induction of ovulation. Acta Obstet Gynecol Scand 1982;61:377–9.
49. Steiner AZ, Terplan M, Paulson RJ. Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis. Hum Reprod 2005;20:1511–5.
50. Alivanis P, Giannikouris I, Paliuras C, Arvanitis A, Volanaki M, Zervos A. Metformin-associated lactic acidosis treated with continuous renal replacement therapy. Clin Ther 2006;28:396–400.
51. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–71.
52. Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database Syst Rev 2003;3:CD003053.
53. Tang T, Glanville J, Hayden CJ, White D, Barth JH, Balen AH. Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. Hum Reprod 2006;21:80–9.
54. Harborne L, Fleming R, Lyall H, Norman J, Sattar N. Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. Lancet 2003;361:1894–901.
55. Baillargeon JP, Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Nestler JE. Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. Fertil Steril 2004;82:893–902.
56. Legro RS, Zaino RJ, Demers LM, Kunselman AR, Gnatuk CL, Williams NI, et al. The effects of metformin and rosiglitazone, alone and in combination, on the ovary and endometrium in polycystic ovary syndrome. Am J Obstet Gynecol 2007;196:402–10.
57. Vanky E, Salvesen KA, Heimstad R, Fougner KJ, Romundstad P, Carlsen SM. Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: results of a randomized study. Hum Reprod 2004;19:1734–40.
58. Vanky E, Hjorth-Hansen H, Carlsen SM. Metformin and early pregnancy? Fertil Steril 2006;86:1551–2.
59. Brown JB. Pituitary control of ovarian function—concepts derived from gonadotrophin therapy. Aust NZ J Obstet Gynaecol 1978;18:46–54.
60. Baird DT. A model for follicular selection and ovulation: lessons from superovulation. J Steroid Biochem 1987;27:15–23.
61. Dor J, Itzkowic DJ, Mashiach S, Lunenfeld B, Serr DM. Cumulative conception rates following gonadotropin therapy. Am J Obstet Gynecol 1980;136:102–5.
62. Thompson CR, Hansen LM. Pergonal (menotropins): a summary of clinical experience in the induction of ovulation and pregnancy. Fertil Steril 1970;21:844–53.
63. Wang CF, Gemzell C. The use of human gonadotropins for the induction of ovulation in women with polycystic ovarian disease. Fertil Steril 1980;33:479–86.
64. Balasch J, Fabregues F, Creus M, Casamitjana R, Puerto B, Vanrell JA. Recombinant human follicle-stimulating hormone for ovulation induction in polycystic ovary syndrome: a prospective, randomized trial of two starting doses in a chronic low-dose step-up protocol. J Assist Reprod Genet 2000;17:561–5.
65. Calaf Alsina J, Ruiz Balda JA, Romeu Sarrio A, Caballero Fernandez V, Cano Trigo I, Gomez Parga JL, et al. Ovulation induction with a starting dose of 50 IU of recombinant follicle stimulating hormone in WHO group II anovulatory women: the IO-50 study, a prospective, observational, multicentre, open trial. BJOG 2003;110:1072–7.
66. Hayden CJ, Rutherford AJ, Balen AH. Induction of ovulation with the use of a starting dose of 50 units of recombinant human follicle-stimulating hormone (Puregon). Fertil Steril 1999;71:106–8.
67. White DM, Polson DW, Kiddy D, Sagle P, Watson H, Gilling-Smith C, et al. Induction of ovulation with low-dose gonadotropins in polycystic ovary syndrome: an analysis of 109 pregnancies in 225 women. J Clin Endocrinol Metab 1996;81:3821–4.
68. Brzyski RG, Grow DR, Sims JA, Seltman HJ. Increase in androgen:estrogen ratio specifically during low-dose follicle-stimulating hormone therapy for polycystic ovary syndrome. Fertil Steril 1995;64:693–7.
69. Buvat J, Buvat-Herbaut M, Marcolin G, Dehaene JL, Verbecq P, Renouard O. Purified follicle-stimulating hormone in polycystic ovary syndrome: slow administration is safer and more effective. Fertil Steril 1989;52:553–9.
70. Dale O, Tanbo T, Lunde O, Abyholm T. Ovulation induction with low-dose follicle-stimulating hormone in women with the polycystic ovary syndrome. Acta Obstet Gynecol Scand 1993;72:43–6.
71. Polson DW, Mason HD, Saldahna MB, Franks S. Ovulation of a single dominant follicle during treatment with low-dose pulsatile follicle stimulating hormone in women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 1987;26:205–12.
72. Sagle MA, Hamilton-Fairley D, Kiddy DS, Franks S. A comparative, randomized study of low-dose human menopausal gonadotropin and follicle-stimulating hormone in women with polycystic ovarian syndrome. Fertil Steril 1991;55:56–60.
73. Seibel MM, Kamrava MM, McArdle C, Taymor ML. Treatment of polycystic ovary disease with chronic low-dose follicle stimulating hormone: biochemical changes and ultrasound correlation. Int J Fertil 1984;29:39–43.

74. Schoot DC, Pache TD, Hop WC, de Jong FH, Fauser BC. Growth patterns of ovarian follicles during induction of ovulation with decreasing doses of human menopausal gonadotropin following presumed selection in polycystic ovary syndrome. Fertil Steril 1992;57:1117–20.
75. van Dessel HJ, Schoot BC, Schipper I, Dahl KD, Fauser BC. Circulating immunoreactive and bioactive follicle stimulating hormone concentrations in anovulatory infertile women and during gonadotrophin induction of ovulation using a decremental dose regimen. Hum Reprod 1996;11:478–85.
76. Fauser BC, Van Heusden AM. Manipulation of human ovarian function: physiological concepts and clinical consequences. Endocr Rev 1997;18:71–106.
77. Balasch J, Fabregues F, Creus M, Puerto B, Penarrubia J, Vanrell JA. Follicular development and hormone concentrations following recombinant FSH administration for anovulation associated with polycystic ovarian syndrome: prospective, randomized comparison between low-dose step-up and modified step-down regimens. Hum Reprod 2001;16:652–6.
78. van Santbrink EJ, Fauser BC. 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: 3597–602.
79. Christin-Maitre S, Hugues JN. A comparative randomized multicentric study comparing the step-up versus step-down protocol in polycystic ovary syndrome. Hum Reprod 2003;18:1626–31.
80. van Santbrink EJ, Donderwinkel PF, van Dessel TJ, Fauser BC. Gonadotrophin induction of ovulation using a step-down dose regimen: single-centre clinical experience in 82 patients. Hum Reprod 1995;10: 1048–53.
81. Hugues JN, Cedrin-Durnerin I, Avril C, Bulwa S, Herve F, Uzan M. Sequential step-up and step-down dose regimen: an alternative method for ovulation induction with follicle-stimulating hormone in polycystic ovarian syndrome. Hum Reprod 1996;11:2581–4.
82. Hugues JN, Cedrin-Durnerin I, Howles CM, Amram M, Angelini A, Balen A, et al. The use of a decremental dose regimen in patients treated with a chronic low-dose step-up protocol for WHO Group II anovulation: a prospective randomized multicentre study. Hum Reprod 2006;21:2817–22.
83. Jacobs HS, Homburg RR. The endocrinology of conception. Baillieres Clin Endocrinol Metab 1990;4:195–205.
84. Willis D, Mason H, Gilling-Smith C, Franks S. Modulation by insulin of follicle-stimulating hormone and luteinizing hormone actions in human granulosa cells of normal and polycystic ovaries. J Clin Endocrinol Metab 1996;81:302–9.
85. Willis DS, Watson H, Mason HD, Galea R, Brincat M, Franks S. Premature response to luteinizing hormone of granulosa cells from anovulatory women with polycystic ovary syndrome: relevance to mechanism of anovulation. J Clin Endocrinol Metab 1998;83:3984–91.
86. Balen AH, Tan SL, Jacobs HS. Hypersecretion of luteinising hormone: a significant cause of infertility and miscarriage. Br J Obstet Gynaecol 1993;100:1082–9.
87. Homburg R, Armar NA, Eshel A, Adams J, Jacobs HS. Influence of serum luteinising hormone concentrations on ovulation, conception, and early pregnancy loss in polycystic ovary syndrome. BMJ 1988;297: 1024–6.
88. Regan L, Owen EJ, Jacobs HS. Hypersecretion of luteinising hormone, infertility, and miscarriage. Lancet 1990;336:1141–4.
89. Tarlatzis BC, Grimbizis G, Pournaropoulos F, Bontis J, Lagos S, Spanos E, et al. The prognostic value of basal luteinizing hormone:follicle-stimulating hormone ratio in the treatment of patients with polycystic ovarian syndrome by assisted reproduction techniques. Hum Reprod 1995;10:2545–9.
90. Rai R, Backos M, Rushworth F, Regan L. Polycystic ovaries and recurrent miscarriage—a reappraisal. Hum Reprod 2000;15:612–5.
91. Oliveira JB, Mauri AL, Petersen CG, Martins AM, Cornicelli J, Cavanha M, et al. Recombinant luteinizing hormone supplementation to recombinant follicle-stimulation hormone during induced ovarian stimulation in the GnRH-agonist protocol: a meta-analysis. J Assist Reprod Genet 2007;24:67–75.
92. Dodson WC, Hughes CL, Whitesides DB, Haney AF. The effect of leuprolide acetate on ovulation induction with human menopausal gonadotropins in polycystic ovary syndrome. J Clin Endocrinol Metab 1987;65:95–100.
93. Fleming R, Haxton MJ, Hamilton MP, McCune GS, Black WP, MacNaughton MC, et al. Successful treatment of infertile women with oligomenorrhoea using a combination of an LHRH agonist and exogenous gonadotrophins. Br J Obstet Gynaecol 1985;92: 369–73.
94. Fleming R, Haxton MJ, Hamilton MP, Conaghan CJ, Black WP, Yates RW, et al. Combined gonadotropin-releasing hormone analog and exogenous gonadotropins for ovulation induction in infertile women: efficacy related to ovarian function assessment. Am J Obstet Gynecol 1988;159:376–81.
95. Buckler HM, Critchley HO, Cantrill JA, Shalet SM, Anderson DC, Robertson WR. Efficacy of low dose purified FSH in ovulation induction following pituitary desensitization in polycystic ovarian syndrome. Clin Endocrinol (Oxf) 1993;38:209–17.
96. Charbonnel B, Krempf M, Blanchard P, Dano F, Delage C. Induction of ovulation in polycystic ovary syndrome with a combination of a luteinizing hormone-releasing hormone analog and exogenous gonadotropins. Fertil Steril 1987;47:920–4.
97. Homburg R, Eshel A, Kilborn J, Adams J, Jacobs HS. Combined luteinizing hormone releasing hormone analogue and exogenous gonadotrophins for the treatment of infertility associated with polycystic ovaries. Hum Reprod 1990;5:32–5.
98. Scheele F, Hompes PG, van der MM, Schoute E, 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.
99. van der Meer M, Hompes PG, Scheele F, Schoute E, Popp-Snijders C, Schoemaker J. The importance of endogenous feedback for monofollicular growth in low-dose step-up ovulation induction with follicle-stimulating hormone in polycystic ovary syndrome: a randomized study. Fertil Steril 1996;66:571–6.
100. Bachus KE, Hughes CL Jr, Haney AF, Dodson WC. The luteal phase in polycystic ovary syndrome during ovulation induction with human menopausal gonadotropin with and without leuprolide acetate. Fertil Steril 1990;54:27–31.
101. Clifford K, Rai R, Watson H, Franks S, Regan L. Does suppressing luteinising hormone secretion reduce the miscarriage rate? Results of a randomised controlled trial. BMJ 1996;312:1508–11.
102. Homburg R, Levy T, Berkovitz D, Farchi J, Feldberg D, Ashkenazi J, et al. Gonadotropin-releasing hormone agonist reduces the miscarriage rate for pregnancies achieved in women with polycystic ovarian syndrome. Fertil Steril 1993;59:527–31.
103. Homburg R, Howles CM. Low-dose FSH therapy for anovulatory infertility associated with polycystic ovary syndrome: rationale, results, reflections and refinements. Hum Reprod Update 1999;5:493–9.
104. Kamrava MM, Seibel MM, Berger MJ, Thompson I, Taymor ML. Reversal of persistent anovulation in polycystic ovarian disease by administration of chronic low-dose follicle-stimulating hormone. Fertil Steril 1982;37:520–3.
105. Farhi J, West C, Patel A, Jacobs HS. Treatment of anovulatory infertility: the problem of multiple pregnancy. Hum Reprod 1996;11: 429–34.
106. Dickey RP, Taylor SN, Lu PY, Sartor BM, Rye PH, Pyrzak R. Risk factors for high-order multiple pregnancy and multiple birth after controlled ovarian hyperstimulation: results of 4,062 intrauterine insemination cycles. Fertil Steril 2005;83:671–83.
107. Tur R, Barri PN, Coroleu B, Buxaderas R, Martinez F, Balasch J. Risk factors for high-order multiple implantation after ovarian stimulation with gonadotrophins: evidence from a large series of 1878 consecutive pregnancies in a single centre. Hum Reprod 2001;16:2124–9.
108. Leader A. Improved monofollicular ovulation in anovulatory or oligo-ovulatory women after a low-dose step-up protocol with weekly

increments of 25 international units of follicle-stimulating hormone. Fertil Steril 2006;85:1766–73.
109. Practice Committee of the American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome. Fertil Steril 2006;86(Suppl): S178–83.
110. Balasch J, Tur R, Alvarez P, Bajo JM, Bosch E, Bruna I, et al. The safety and effectiveness of stepwise and low-dose administration of follicle stimulating hormone in WHO group II anovulatory infertile women: evidence from a large multicenter study in Spain. J Assist Reprod Genet 1996;13:551–6.
111. Hamilton-Fairley D, Kiddy D, Watson H, Sagle M, Franks S. Low-dose gonadotrophin therapy for induction of ovulation in 100 women with polycystic ovary syndrome. Hum Reprod 1991;6:1095–9.
112. Hamilton-Fairley D, Franks S. Common problems in induction of ovulation. Baillieres Clin Obstet Gynaecol 1990;4:609–25.
113. Fauser BC, Macklon NS. Medical approaches to ovarian stimulation for infertility. In: Strauss JF, Barbieri RL, eds. Yen and Jaffe's reproductive endocrinology. Philadelphia: Elsevier Saunders, 2004: 965–1012.
114. Gjonnaess H. Polycystic ovarian syndrome treated by ovarian electrocautery through the laparoscope. Fertil Steril 1984;41:20–5.
115. Rimington MR, Walker SM, Shaw RW. The use of laparoscopic ovarian electrocautery in preventing cancellation of in-vitro fertilization treatment cycles due to risk of ovarian hyperstimulation syndrome in women with polycystic ovaries. Hum Reprod 1997;12:1443–7.
116. Balen A. Surgical management of PCOS. Best Pract Res Clin Endocrinol Metab 2006;20:271–80.
117. Farquhar C, Lilford RJ, Marjoribanks J, Vandekerckhove P. Laparoscopic "drilling" by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. Cochrane Database Syst Rev 2007;3:CD001122.
118. Fernandez H, Alby JD, Gervaise A, de Tayrac R, Frydman R. Operative transvaginal hydrolaparoscopy for treatment of polycystic ovary syndrome: a new minimally invasive surgery. Fertil Steril 2001;75: 607–11.
119. Naether OG, Baukloh V, Fischer R, Kowalczyk T. Long-term follow-up in 206 infertility patients with polycystic ovarian syndrome after laparoscopic electrocautery of the ovarian surface. Hum Reprod 1994;9: 2342–9.
120. Amer SA, Li TC, Cooke ID. Laparoscopic ovarian diathermy in women with polycystic ovarian syndrome: a retrospective study on the influence of the amount of energy used on the outcome. Hum Reprod 2002;17:1046–51.
121. Amer SA, Li TC, Cooke ID. A prospective dose-finding study of the amount of thermal energy required for laparoscopic ovarian diathermy. Hum Reprod 2003;18:1693–8.
122. Malkawi HY, Qublan HS, Hamaideh AH. Medical vs. surgical treatment for clomiphene citrate–resistant women with polycystic ovary syndrome. J Obstet Gynaecol 2003;23:289–93.
123. Bayram N, van Wely M, Kaaijk EM, Bossuyt PM, van der Veen F. Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation in polycystic ovary syndrome: randomised controlled trial. BMJ 2004;328:192.
124. Lazovic G, Milacic D, Terzic M, Spremovic S, Mitijasevic S. Medicaments or surgical therapy of PCOS. Fertil Steril 1998;70(Suppl):S472.
125. Farquhar CM, Williamson K, Gudex G, Johnson NP, Garland J, Sadler L. A randomized controlled trial of laparoscopic ovarian diathermy versus gonadotropin therapy for women with clomiphene citrate–resistant polycystic ovary syndrome. Fertil Steril 2002;78: 404–11.
126. Kaya H, Sezik M, Ozkaya O. Evaluation of a new surgical approach for the treatment of clomiphene citrate–resistant infertility in polycystic ovary syndrome: laparoscopic ovarian multi-needle intervention. J Minim Invasive Gynecol 2005;12:355–8.
127. Vegetti W, Ragni G, Baroni E, Testa G, Marsico S, Riccaboni A, et al. Laparoscopic ovarian versus low-dose pure FSH in anovulatory clomiphene-resistant patients with polycystic ovarian syndrome: randomized prospective study [abstract]. Hum Reprod 1998;13:120.
128. Farquhar CM, Williamson K, Brown PM, Garland J. An economic evaluation of laparoscopic ovarian diathermy versus gonadotrophin therapy for women with clomiphene citrate resistant polycystic ovary syndrome. Hum Reprod 2004;19:1110–5.
129. van Wely M, Bayram N, van der Veen F, Bossuyt PM. An economic comparison of a laparoscopic electrocautery strategy and ovulation induction with recombinant FSH in women with clomiphene citrate–resistant polycystic ovary syndrome. Hum Reprod 2004;19: 1741–5.
130. Abdel GA, Khatim MS, Alnaser HM, Mowafi RS, Shaw RW. Ovarian electrocautery: responders versus non-responders. Gynecol Endocrinol 1993;7:43–8.
131. Li TC, Saravelos H, Chow MS, Chisabingo R, Cooke ID. Factors affecting the outcome of laparoscopic ovarian drilling for polycystic ovarian syndrome in women with anovulatory infertility. Br J Obstet Gynaecol 1998;105:338–44.
132. Cohen J, Audebert A. De la "mecanique" au fonctionnel: place des traitements chirurgicaux in endoscopiques dans les dystrophies ovariennes. In: Dystrophies ovairennes. Paris: Masson, 1989:183–92.
133. Gurgan T, Urman B, Aksu T, Yarali H, Develioglu O, Kisnisci HA. The effect of short-interval laparoscopic lysis of adhesions on pregnancy rates following Nd-YAG laser photocoagulation of polycystic ovaries. Obstet Gynecol 1992;80:45–7.
134. Greenblatt EM, Casper RF. Adhesion formation after laparoscopic ovarian cautery for polycystic ovarian syndrome: lack of correlation with pregnancy rate. Fertil Steril 1993;60:766–70.
135. Amer SA, Banu Z, Li TC, Cooke ID. Long-term follow-up of patients with polycystic ovary syndrome after laparoscopic ovarian drilling: endocrine and ultrasonographic outcomes. Hum Reprod 2002;17: 2851–7.
136. Kaaijk EM, Hamerlynck JV, Beek JF, van der Veen F. Clinical outcome after unilateral oophorectomy in patients with polycystic ovary syndrome. Hum Reprod 1999;14:889–92.
137. van Santbrink EJ, Fauser BC. Is there a future for ovulation induction in the current era of assisted reproduction? Hum Reprod 2003;18: 2499–502.
138. Eijkemans MJ, Polinder S, Mulders AG, Laven JS, Habbema JD, Fauser BC. Individualized cost-effective conventional ovulation induction treatment in normogonadotrophic anovulatory infertility (WHO group 2). Hum Reprod 2005;20:2830–7.
139. Heijnen EM, Eijkemans MJ, De Klerk C, Polinder S, Beckers NG, Klinkert ER, et al. A mild treatment strategy for in-vitro fertilisation: a randomised non-inferiority trial. Lancet 2007;369:743–9.
140. Papanikolaou EG, Camus M, Kolibianakis EM, Van Landuyt L, Van Steirteghem A, Devroey P. In vitro fertilization with single blastocyst-stage versus single cleavage-stage embryos. N Engl J Med 2006;354:1139–46.
141. Dor J, Shulman A, Levran D, Ben-Rafael Z, Rudak E, Mashiach S. The treatment of patients with polycystic ovarian syndrome by in-vitro fertilization and embryo transfer: a comparison of results with those of patients with tubal infertility. Hum Reprod 1990;5:816–8.
142. Urman B, Fluker MR, Yuen BH, Fleige-Zahradka BG, Zouves CG, Moon YS. The outcome of in vitro fertilization and embryo transfer in women with polycystic ovary syndrome failing to conceive after ovulation induction with exogenous gonadotropins. Fertil Steril 1992;57: 1269–73.
143. Griesinger G, Diedrich K, Tarlatzis BC, Kolibianakis EM. GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis. Reprod Biomed Online 2006;13: 628–38.
144. Heijnen EM, Eijkemans MJ, Hughes EG, Laven JS, Macklon NS, Fauser BC. A meta-analysis of outcomes of conventional IVF in women with polycystic ovary syndrome. Hum Reprod Update 2006; 12:13–21.
145. Tang T, Glanville J, Orsi N, Barth JH, Balen AH. The use of metformin for women with PCOS undergoing IVF treatment. Hum Reprod 2006;21:1416–25.

146. Cohlen BJ, Vandekerckhove P, te Velde ER, Habbema JD. Timed intercourse versus intra-uterine insemination with or without ovarian hyperstimulation for subfertility in men. Cochrane Database Syst Rev 2000;2:CD000360.
147. ESHRE Capri Workshop Group. Mono-ovulatory cycles: a key goal in profertility programmes. Hum Reprod Update 2003;9:263–74.
148. De Geyter C, De Geyter M, Castro E, Bals-Pratsch M, Nieschlag E, Schneider HP. Experience with transvaginal ultrasound–guided aspiration of supernumerary follicles for the prevention of multiple pregnancies after ovulation induction and intrauterine insemination. Fertil Steril 1996;65:1163–8.
149. Cantineau AE, Heineman MJ, Cohlen BJ. Single versus double intrauterine insemination (IUI) in stimulated cycles for subfertile couples. Cochrane Database Syst Rev 2003;1:CD003854.
150. Gerli S, Casini ML, Unfer V, Costabile L, Bini V, Di Renzo GC. Recombinant versus urinary follicle-stimulating hormone in intrauterine insemination cycles: a prospective, randomized analysis of cost effectiveness. Fertil Steril 2004;82:573–8.
151. Mitwally MF, Casper RF. Aromatase inhibition reduces the dose of gonadotropin required for controlled ovarian hyperstimulation. J Soc Gynecol Investig 2004;11:406–15.
152. Palomba S, Falbo A, Orio F Jr, Manguso F, Russo T, Tolino A, et al. A randomized controlled trial evaluating metformin pre-treatment and co-administration in non-obese insulin-resistant women with polycystic ovary syndrome treated with controlled ovarian stimulation plus timed intercourse or intrauterine insemination. Hum Reprod 2005;20: 2879–86.
153. van Santbrink EJ, Eijkemans MJ, Laven JS, Fauser BC. Patient-tailored conventional ovulation induction algorithms in anovulatory infertility. Trends Endocrinol Metab 2005;16:381–9.
154. Hamilton-Fairley D, Kiddy D, Watson H, Paterson C, Franks S. Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low dose gonadotrophin. Br J Obstet Gynecol 1992;99:128–31.
155. Strowitzki T, Seehaus D, Korell M, Hepp H. Low-dose FSH stimulation in polycystic ovary syndrome: comparison of 3 FSH preparations. Exp Clin Endocrinol Diabetes 1998;106:435–9.
156. Vicino M, Loverro G, Bettocchi S, Simonetti S, Mei L, Selvaggi L. Predictive value of serum androstenedione basal levels on the choice of gonadotropin or laparoscopic ovarian electrocautery as ovulation induction in clomiphene citrate-resistant patients with polycystic ovary syndrome. Gynecol Endocrinol 2000;14:42–9.
157. Yarali H, Bukulmez O, Gurgan T. Urinary follicle-stimulating hormone (FSH) versus recombinant FSH in clomiphene citrate-resistant, normogonadotropic, chronic anovulation: a prospective randomized study. Fertil Steril 1999;72:276–81.
158. Urman B, Sarac E, Dogan L, Gurgan T. Pregnancy in infertile PCOD patients. Complications and outcome. J Reprod Med 1997;42:501–5.
159. Fridstrom M, Nisell H, Sjoblom P, Hillensjo T. Are women with polycystic ovary syndrome at an increased risk of pregnancy-induced hypertension and/or preeclampsia? Hypertens Pregnancy 1999;18:73–80.
160. Mikola M, Hiilesmaa V, Halttunen M, Suhonen L, Tiitinen A. Obstetric outcome in women with polycystic ovarian syndrome. Hum Reprod 2001;16:226–9.
161. Weerakiet S, Srisombut C, Rojanasakul A, Panburana P, Thakkinstian A, Herabutya Y. Prevalence of gestational diabetes mellitus and pregnancy outcomes in Asian women with polycystic ovary syndrome. Gynecol Endocrinol 2004;19:134–40.
162. Sir-Petermann T, Hitchsfeld C, Maliqueo M, Codner E, Echiburu B, Gazitua R, Recabarren S, Cassorla F. Birth weight in offspring of mothers with polycystic ovarian syndrome. Hum Reprod 2005;20: 2122–6.
163. Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. Fertil Steril 2004;82: 421–9.
164. Hull MG. Gonadotropin therapy in anovulatory infertility. In: Howies CM, ed. Gonadotrophins, GnRH analogues, and growth factors in infertility: future perspectives. Oxford: Alden Press, 1991:56–61.
165. Balen AH, Braat DD, West C, Patel A, Jacobs HS. Cumulative conception and live birth rates after the treatment of anovulatory infertility: safety and efficacy of ovulation induction in 200 patients. Hum Reprod 1994;9:1563–70.