A meta-analysis of outcomes of conventional IVF in women with polycystic ovary syndrome

E.M.E.W. Heijnen1,2,5, M.J.C. Eijkemans3, E.G. Hughes4, J.S.E. Laven2, N.S. Macklon1 and B.C.J.M. Fauser1

1Department of Reproductive Medicine, University Medical Center, Utrecht, 2Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, 3Department of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands and 4Department of Obstetrics and Gynaecology, McMaster University, Hamilton, Ontario, Canada

5To whom correspondence should be addressed at: Department of Reproductive Medicine, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. E-mail: e.heijnen@erasmusmc.nl

This meta-analysis was conducted to compare outcomes of conventional IVF in women presenting with polycystic ovary syndrome (PCOS) and non-PCOS patients. Studies in which PCOS patients undergoing IVF were compared with a matched—no male factor—control group were considered for this review. A definition consistent with the Rotterdam consensus criteria of PCOS was required, and all patients within a given study had to be treated with the same ovarian stimulation protocol. Information regarding patient characteristics and pregnancy outcome was also required. Nine out of 290 identified studies reporting data on 458 PCOS patients (793 cycles) and 694 matched controls (1116 cycles) fulfilled these inclusion criteria. PCOS patients demonstrated a significantly reduced chance of oocyte retrieval per started cycle, odds ratio (OR) = 0.5 [95% confidence interval (CI) = 0.2–1.0]. However, no difference was observed in chance of embryo transfer per oocyte retrieval between the groups (OR = 0.7, 95% CI = 0.4–1.3). Significantly more oocytes per retrieval were obtained in PCOS patients compared with controls [random effects estimate 3.4 (95% CI = 1.7–5.1)]. The number of oocytes fertilized did not differ significantly between PCOS patients and controls, weighted mean difference (WMD) 0.1 oocytes (95% CI = −1.4–1.6). No significant difference was observed in the clinical pregnancy rates per started cycle, OR = 1.0 (95% CI = 0.8–1.3). The incidence of ovarian hyperstimulation syndrome (OHSS) after oocyte retrieval was rarely reported. This meta-analysis demonstrates an increased cancellation rate, but more oocytes retrieved per retrieval and a lower fertilization rate in PCOS undergoing IVF. Overall, PCOS and control patients achieved similar pregnancy and live birth rates per cycle.

Key words: IVF outcome/meta-analysis/PCOS

Introduction

Anovulation is a common cause of infertility. About 70% of infertile women presenting with oligomenorrhea or amenorrhea exhibit normal FSH and estradiol (E2) concentrations (World Health Organization [WHO], Type-2 anovulation) (The ESHRE Capri Workshop Group, 1995; Rowe et al., 2000). Normogonadotropic anovulatory infertility can be identified in 18–25% of the couples presenting with infertility (Hull et al., 1985). Polycystic ovary syndrome (PCOS) represents the most common diagnosis within this patient group (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004).

Pharmacological ovulation induction constitutes the first line treatment of choice in these women, aiming at mono-ovulation. Conventional strategies include the anti-estrogen clomiphene citrate as first line (Beck et al., 2005) and exogenous gonadotrophins as a second line intervention (Nugent et al., 2000). Although overall cumulative singleton live birth rates of 71% have been described after conventional ovulation induction, the multiple pregnancy rate (especially with exogenous gonadotrophins) is considerable (10%) (Eijkemans et al., 2003). The development of multiple dominant follicles resulting in multiple pregnancies cannot always be prevented. Therefore, the widespread use of gonadotrophin ovulation induction may be questioned (van Santbrink and Fauser, 2003; Fauser et al., 2005). Prospective cohort follow-up studies have identified patient characteristics upon initial screening capable of predicting clinical outcome like mono-ovulation and pregnancy (Imani et al., 1998; Imani et al., 1999). Moreover, different strategies generating mono-ovulatory cycles have recently been emphasized, including weight reduction and life style changes, insulin sensitizers (Lord et al., 2003), aromatase inhibitors (Mitwally and Casper, 2001) and laparoscopic electrocautery of ovaries (Farquhar et al., 2001).
E.M.E.W. Heijnen et al.

In addition, assisted reproduction technologies (ART) like intrauterine insemination (IUI) or IVF are increasingly applied (Fauser et al., 2005), although well-designed studies documenting efficacy and safety in PCOS are lacking in this patient group. Certainly, with improved outcome and the more frequent use of single-embryo transfer, eliminating chances for multiple pregnancies, IVF has become a serious alternative to ovulation induction. In addition, favourable IVF outcomes have been reported applying in vitro oocyte maturation in PCOS (Tan and Child, 2002). Despite this trend, uncertainty remains with regard to risk of ovarian hyperstimulation syndrome (OHSS), cycle cancellation rate, oocyte quality and fertilization rates in PCOS women undergoing IVF. Furthermore, it remains unclear whether pregnancy rates differ between PCOS and non-PCOS women. Most published data are derived from uncontrolled, observational studies with small study populations. The aim of this meta-analysis is to compare IVF outcome in women with and without PCOS, using the best available data.

Materials and methods

Criteria for considering studies for this review

Studies in which PCOS patients undergoing IVF were compared with a matched control group were considered for this review. The characteristics of the control group are given in Table I. No IVF/ICSI cycles may be performed in both groups. PCOS diagnosis had to be in line with the Rotterdam consensus criteria (two out of three of the following criteria: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries) (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004). Patients within a study had to be treated with the same ovarian stimulation protocol. Information regarding patient and cycle characteristics like age and number of oocytes retrieved and pregnancy outcome was also required.

Search strategy for the identification of studies

A search strategy was carried out based on the following Medical Subject Headings (MeSH): ‘Polycystic Ovary Syndrome’ major (MAJR) and ‘Fertilization in Vitro’ (MAJR) or ‘Reproductive Medicine’ (MAJR) OR ‘Reproductive Techniques, Assisted’ (MAJR)). In addition, a handsearch of Human Reproduction, 1991–2004 and Fertility Sterility, 1988–2004 was conducted. In addition, the pharmaceutical companies Ferring, Organon and Serono were invited to provide data from unpublished or ongoing studies relating to this topic. Finally, the bibliographies of identified studies were hand searched.

Identification

The MESH headings strategy yielded 290 publications. No additional publications were identified after the handsearch of Human Reproduction and Fertility Sterility, and no additional data was obtained from the pharmaceutical companies. One hundred and twenty-nine publications were excluded because it was clear from the title that they did not fulfil the selection criteria. Five of the 129 excluded publications were read in full (EH) to check the validity of this selection procedure. From the remaining 161 articles, 101 were excluded on the basis of the abstract (EH). Seven of the remaining 60 publications were considered by two independent readers (EH, NM) to fulfil the selection criteria for inclusion. Two more publications were included after the first author had retrospectively provided additional necessary information. All the bibliographies of the included publications were checked, and no additional articles were identified.

Methods of the review

No prospective randomized controlled trials were identified addressing our research question. We therefore searched for studies which compared IVF outcomes in PCOS patients with matched controls. The following information was extracted from potentially relevant studies: study characteristics, specified as matched control (retrospective/prospective), cohort study (retrospective/prospective) and crossover, patient population characteristics, identifying study groups and outcome measures. From the nine relevant studies ultimately selected for further analysis, the following data was extracted (Table I): definition of PCOS, previous treatment before IVF, constitution of the control group, treatment protocol and number of patients in the study and control group. The primary endpoints were number of oocytes retrieved, number of oocytes fertilized, number of patients with OHSS and number of clinical pregnancies. Secondary endpoints are summarized in Table II.

Statistical analysis

Data from the studies in Table II were pooled if at least two studies reported a similar outcome characteristic. For each study, the difference in IVF-related outcome parameters between PCOS and control groups were computed from the reported data. When the outcome of interest was of a continuous nature (e.g. number of ampoules FSH), the difference in mean value between the two groups was calculated together with standard error. These differences were pooled across studies, resulting in a weighted mean difference (WMD). For binary outcome parameters (e.g. cancellation), the odds ratios (ORs) per study were calculated and pooled after logarithmic transformation. Pooling was performed using the inverse of the variance as weight. Heterogeneity between studies was tested for and random effects estimates were calculated using the likelihood method described by Hardy and Thompson (Hardy and Thompson, 1998), when at least three studies were available. It may occur that this calculation does not yield results, when the variation between studies is less than the random expected variation. In those cases, there is definitely no heterogeneity. The 95% confidence intervals (CIs) are presented for the WMD and pooled OR, respectively, using both the direct weighted method and the random effects (heterogeneity corrected) method. The random effects method is the preferred because it remains valid when true heterogeneity between studies is present. Statistical pooling was preformed for the following outcome parameters: number of cycles, oocyte retrieval and embryo transfer, number of ampoules gonadotrophins used, duration of stimulation, number of oocytes, number of oocytes fertilized and number of clinical pregnancies.

Results

Nine relevant studies were identified (Dor et al., 1990; Urman et al., 1992; Homburg et al., 1993a; Hardy et al., 1995; Kodama et al.,
Table I. Characteristics of studies regarding polycystic ovary syndrome (PCOS) and a matched control group who were included in the study

| Article Definition of PCOS Previous treatment Control group Treatment protocol Study population |
|--------------------------------------------------|--------------------------------------------------|
| Dor et al. (1990) Anovulation/oligoanovulation and physical characteristics (obesity, hirsutism) and LH/FSH ratio >3 and polycystic ovarian appearance on ultrasound Failed to conceive after at least six ovulatory treatment cycles clomiphene citrate and four treatment cycles HMG Pure tubal factor patients, retrospective clomiphene citrate + HMG or HMG 16 PCOS (26 cycles), 37 control (37 cycles) |
| Urman et al. (1992) Anovulation/oligoanovulation and hyper-androgenism (total T >2.43 nmol/l) Clomiphene citrate resistant or failed to conceive after six treatment cycles clomiphene citrate and 6–7 treatment cycles HMG Pure tubal factor patients, retrospective, age matched HMG or GnRH agonist + HMG 9 PCOS (19 ET cycles) 40 control (40 ET cycles) |
| Homburg et al. (1993a) Anovulation/oligoanovulation and/or hirsutism and polycystic ovarian appearance on ultrasound Failed to conceive after clomiphene citrate and six ovulatory treatment cycles of gonadotrophins Pure tubal factor patients, retrospective, age matched FSH + HMG, GnRH agonist + FSH + HMG 68 PCOS (208 cycles), 68 controls (143 cycles) |
| Kodama et al. (1995) Anovulation/oligoanovulation and hormone disorders (elevated LH/FSH ratio >1.5) and/or elevated concentration of ovarian androgens in serum (T >50 ng/ml, and/or androstenedione >2 ng/ml) and polycystic ovarian appearance on ultrasound Failed to conceive after at least 2 years of ovulation induction therapy with clomiphene citrate and ovulation induction therapy with gonadotrophins. Not male factor patients, retrospective, age range matched GnRH agonist + FSH + HMG 26 PCOS (78 cycles), 202 control (423 cycles) |
| Hardy et al. (1995) Anovulation/oligoanovulation and clinical and/or biochemical evidence of hyperandrogenism and polycystic ovarian appearance on ultrasound Less than three previous IVF cycles Prospective, pure tubal factor patients GnRH agonist + HMG 84 PCOS (104 cycles), 84 control (116 cycles) |
| Sengoku et al. (1997) Anovulation/oligoanovulation and LF : FSH ratio >1.5 and polycystic ovarian appearance on ultrasound Failed to conceive after at least three treatment cycles with gonadotrophins Pure tubal factor patients, retrospective, age matched GnRH agonist + HMG 26 PCOS (49 cycles), 26 control (46 cycles) |
| Doldi et al. (1999) Anovulation/oligoanovulation and Ferriman Gallwey score >7 for hirsutism and hyperandrogenaemia and elevating concentrations of LH or LH/FSH ratio >2 and polycystic ovarian appearance on ultrasound Failed to conceive after four ovulatory treatment cycles with gonadotrophins Pure tubal factor patients, retrospective GnRH agonist + FSH 195 PCOS (271 cycles), 197 controls (247 cycles) |
| Mulders et al. (2003) Anovulation/oligoanovulation and normal serum FSH and E2 concentrations and Free Androgen Index >4 and polycystic ovarian appearance on ultrasound Clomiphene resistant or failed to conceive after six ovulatory treatment cycles with clomiphene citrate and six treatment cycles with gonadotrophins Pure tubal factor patients, retrospective, age matched GnRH agonist + FSH 10 PCOS (10 cycles), 9 control (9 cycles) |
| Urman et al. (2004) Anovulation/oligoanovulation and clinical and/or biochemical evidence of hyperandrogenism Failed to conceive after clomiphene citrate and 4–6 treatment cycles with gonadotrophins Retrospective, age matched, duration of infertility matched GnRH agonist + FSH 24 PCOS (28 cycles), 31 control (55 cycles) |
1995; Sengoku et al., 1997; Doldi et al., 1999; Mulders et al., 2003; Urman et al., 2004), reporting data on 458 PCOS patients (793 cycles) and 694 matched controls (1116 cycles). Information about the studies including definition of PCOS and previous treatment is provided in Table I. The sample size varied across the trials (19–392 patients; 19–518 cycles). There was no difference in age between PCOS patients and controls (31.9 years versus 31.8 years), WMD – 0.1 years (95% CI = –0.6–0.3). No significant statistical heterogeneity was detected between studies. The random effects estimate for age between PCOS and non-PCOS women was –0.2 (95% CI = –1.1–0.5). Information about weight or body mass index was only provided in two studies and therefore could not be pooled.

Cancellation rate

PCOS patients demonstrated a significantly increased chance of cycle cancellation (12.8% versus 4.1%), OR = 0.5 (95% CI = 0.2–1.0) (Figure 1). However, no significant difference was observed in the likelihood of embryo transfer per oocyte retrieval between the groups, OR = 0.7 (95% CI = 0.4–1.3). Heterogeneity between studies and random effects estimate could not be calculated for both outcomes.

Gonadotrophins used

No significant difference was observed in the amount of gonadotrophins used in PCOS patients compared with controls, WMD –1.8 ampoules (95% CI = –4.2–0.5) (Figure 2a). No significant heterogeneity was detected between studies. The random effects estimate between PCOS and non-PCOS women was –1.2 (95% CI = –6.3–4.6).

Duration of stimulation

The duration of stimulation was significantly longer in the PCOS group. The WMD was 1.2 days (95% CI = 0.9–1.5) (Figure 2b). No significant statistical heterogeneity was detected between studies.
A meta-analysis of outcomes of conventional IVF in women with PCOS

The random effects estimate between PCOS and non-PCOS women was 0.9 (95%CI = −0.6; 2.1).

**Number of oocytes obtained and number of oocytes fertilized**

Significantly more oocytes per oocyte retrieval were obtained in PCOS patients compared with controls, WMD 2.9 oocytes (95% CI = 2.2–3.6) (Figure 3a). However, significant heterogeneity was detected between studies (P = 0.005). The random effects estimate between PCOS and non-PCOS women was 3.4 (95% CI = 1.7–5.1). In this case, the WMD is definitely a too small estimate of the true variability of the number of oocytes per oocyte retrieval.

The number of oocytes fertilized did not significantly differ between PCOS patients and controls, WMD 0.1 oocytes (95% CI = −1.4–1.6) (Figure 3b). Heterogeneity between studies and random effects estimate could not be calculated.

**Number of clinical pregnancies**

No significant difference was observed for the clinical pregnancy rate per started cycle (37.4% versus 32.3%), OR = 1.0 (95% CI = 0.8–1.3) (Figure 4a), the number of live births per started cycle, OR = 1.0 (95% CI 0.7–1.5) (Figure 4b), the clinical pregnancy rate per oocyte retrieval, OR = 1.0 (95% CI = 0.7–1.7), the clinical pregnancy rate per embryo transfer, OR = 1.1 (95% CI 0.8–1.3) (Figure 5) and the number of miscarriages, OR = 0.9 (95% CI = 0.5–1.5) (Figure 6). No significant heterogeneity in clinical pregnancy per started cycle, number of live birth per started cycle, clinical pregnancy per oocyte retrieval, clinical pregnancy per embryo transfer and number of miscarriages was detected between studies. The random effects estimate between PCOS and non-PCOS women were respectively, 1.1 (95% CI = 0.7–1.7), 0.9 (95% CI = 0.6–1.5), 1.0 (95% CI = 0.5–2.8), 1.1 (95% CI = 0.8–1.8), 1.0 (95% CI = 0.5–1.8) for the five comparisons.

**OHSS after oocyte retrieval**

In most of the studies, the incidence of OHSS was not clearly reported. Data regarding this risk were therefore difficult to pool. In one study, there was a trend toward more cases of OHSS within the PCOS group. The development of ascites requiring hospital admission occurred in 2 of the 19 (11%) of the PCOS cycles. Another study reported a 16.6% incidence of mild to moderate OHSS and a 3.9% incidence of severe OHSS requiring hospitalization in patients with PCOS. No information regarding the non-PCOS patients was provided in either studies. One study reported three cases of OHSS in the PCOS group and one case of OHSS in the non-PCOS women.

**Implantation rate and multiple pregnancy rate**

Data regarding implantation rate were available but without standard error and therefore could not be pooled. Data regarding multiple pregnancy rate were reported in only two publications and could also not be pooled.

**Discussion**

Meta-analysis in general has several drawbacks, such as dependence on the quality of the reporting of primary analysis findings...
Figure 3. Difference in number of oocytes retrieved (a) and fertilized (b) during IVF comparing polycystic ovary syndrome (PCOS) patients with matched controls.

Figure 4. Odds ratio (OR) for number of clinical pregnancies (a) and live births (b) per started cycle comparing polycystic ovary syndrome (PCOS) patients and matched controls undergoing IVF.
A meta-analysis of outcomes of conventional IVF in women with PCOS

and dependence on sufficient numbers of eligible studies to justify statistical analysis. This meta-analysis has an additional disadvantage because of the use of matched control studies. Nevertheless, the findings of this meta-analysis contribute to systematizing the knowledge about outcomes of conventional IVF in women with PCOS.

The current meta-analysis demonstrates that despite the fact that more oocytes per cycle were obtained along with lower fertilization rates, PCOS and non-PCOS patients achieve similar pregnancy rates and live births per started IVF cycle (Figure 7).

The results showed a significant reduction in oocyte retrievals per started cycle in the PCOS group. Only two publications provided information regarding the reason for cancellation before retrieval. One study reported insufficient ovarian response to be significantly more frequent in PCOS women compared with non-PCOS controls (Mulders et al., 2003). These authors suggested that patient selection after preceding ovulation induction may explain the overrepresentation of poor responders in this group. The same study described a non-significant difference in the incidence of OHSS in the PCOS group compared with the control group. In contrast, another study found significantly more cycles cancelled in the PCOS group because of imminent severe OHSS (6% versus 1%) (Kodama et al., 1995). This is consistent with previous studies of

Figure 5. Odds ratio (OR) for number of clinical pregnancies per embryo transfer comparing polycystic ovary syndrome (PCOS) patients with controls.

Figure 6. Odds ratio (OR) for number of miscarriages per biochemical pregnancy comparing polycystic ovary syndrome (PCOS) patients with controls.

Figure 7. Main findings of clinical outcomes of IVF in polycystic ovary syndrome (PCOS) compared with matched controls.
OHSS incidence and cycle cancellation in women with PCOS (MacDougall et al., 1992; Delvigne et al., 1993a). Specific characteristics of PCOS considered to explain the higher incidence of OHSS include the presence of polycystic ovaries (Delvigne and Rozenberg, 2002; Aboulghar and Mansour, 2003; Delvigne and Rozenberg, 2003), an LH : FSH ratio > 2 (Delvigne et al., 1993b) and hyperandrogenism (Bodis et al., 1997). Furthermore, an increased expression of vascular endothelial growth factor (VEGF) mRNA within the hypertrophic stroma of polycystic ovaries has been associated with increased risk of OHSS (Kamat et al., 1995).

No significant difference was observed in the number of ampoules used for ovarian stimulation between the groups. However, the duration of ovarian stimulation was significantly extended in the PCOS group compared with the non-PCOS group. There was some inconsistency between the studies regarding these outcome parameters. This reflects the different stimulation protocols used because of the ongoing development of medication over the period in which the studies were published. The stimulation protocols and use of GnRH agonist co-treatment differed between studies, but they were applied consistently to PCOS and control groups within individual studies. The stimulation protocols used in the studies are summarized in Table 1.

An increased number of oocytes were retrieved following ovarian stimulation in the PCOS group compared with controls, but the fertilization rate was higher in the control group resulting in an equal total number of oocytes fertilized in both groups. A number of published studies have addressed possible reasons for this observation. One study concluded that the number of healthy non-atretic follicles is probably not increased in PCOS women because a normal inhibin B level, produced by pre-antral and small antral follicles, was found in PCOS patients (Laven and Fauser, 2004). Another study compared the oocyte quality before intracytoplasmic sperm injection after the removal of the cumulus cells in PCOS and non-PCOS patients (Ludwig et al., 1999). No significant difference in rate of metaphase II oocytes, rate of germinal vesicles oocytes and fertilization rate was showed between the two groups. This finding points to involvement of cytoplasmic factors instead of involvement of the nuclear maturity of oocytes. A further study (Sengoku et al., 1997) investigated the chromosomal normality of unfertilized oocytes from patients with PCOS and patients with tubal infertility. Although no significant differences in oocyte aneuploidy rates were found between the two groups, a reduced fertilization rate was observed. The authors concluded that the reduced fertilization rate is not attributable to chromosomal aberrations or immaturity of oocytes recruited from patients with PCOS.

LH concentrations in PCOS patients are higher compared with controls (Balen, 1993). It has been suggested that elevated LH levels in PCOS are associated with an increased rate of miscarriage (Balen et al., 1993), although this has been disputed more recently by others (Imani et al., 1999; Nardo et al., 2002). It has been proposed that using a GnRH agonist to suppress LH can reduce this risk (Homburg et al., 1993b). In our meta-analysis, one study compared stimulation protocols with or without GnRH agonist co-treatment (Homburg et al., 1993a). This study showed an improved cumulative conception rate, cumulative live birth rate and miscarriage rate in women treated with a GnRH agonist in combination with gonadotrophins compared with gonadotrophins alone in women with PCOS.

In conclusion, IVF seems an appropriate treatment option for PCOS patients. Many of the common beliefs concerning significantly reduced chances for success and increased complication rates in PCOS patients undergoing IVF could not be confirmed in the current meta-analysis. Our study shows that a woman with PCOS has a similar chance for pregnancy or live birth per started IVF cycle as a non-PCOS woman. Reducing the number of embryos transferred will probably reduce the risk of multiple pregnancy compared with ovulation induction. However, IVF remains a complex treatment with significant costs and risks. In particular, the risk of OHSS should be taken seriously. More research is necessary to define the optimal place of IVF and ovulation induction therapies for anovulatory infertile PCOS patients and to investigate the specific role of strategies like lifestyle changes, insulin sensitizers, aromatase inhibitors and laparoscopic electrocautery of ovaries in the treatment strategy. Outcomes from IVF and single-embryo transfer remains to be established for PCOS.
A meta-analysis of outcomes of conventional IVF in women with PCOS


Submitted on May 11, 2005; revised on July 15, 2005; accepted on July 27, 2005