Chapter | *3*

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

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Introduction

Anovulation is a common cause of infertility. About 70% of infertile women presenting with oligomenorrhoea or amenorrhoea exhibit normal follicle stimulating hormone (FSH) and oestradiol concentrations (World Health Organization [WHO], Type 2 anovulation) (77,78). Normogonadotropic anovulatory infertility can be identified in 18-25% of the couples presenting with infertility (79). Polycystic ovary syndrome (PCOS) represents the most common diagnosis within this patient group (80).

Pharmacological ovulation induction constitutes the first line treatment of choice in these women, aiming at mono-ovulation. Conventional strategies include the anti-oestrogen clomiphene citrate as first line (118) and exogenous gonadotropins as a second line intervention (119). Although overall cumulative singleton live birth rates of 71% have been described after conventional ovulation induction, the multiple pregnancy rate (especially with exogenous gonadotropins) is considerable (10%) (120). The development of multiple dominant follicles resulting in multiple pregnancies cannot always be prevented. Therefore the widespread use of gonadotropin ovulation induction may be questioned (121,6). Prospective cohort follow-up studies have identified patient characteristics upon initial screening capable of predicting clinical outcome like mono-ovulation and pregnancy (122,123). Moreover, different strategies generating mono-ovulatory cycles have recently been emphasized, including *weight* reduction and life style changes, insulin sensitizers (124), aromatase inhibitors (125) and laparoscopic electrocautery of ovaries (126).

In addition, assisted reproductive technologies (ART) like intra-uterine insemination (IUI) or in vitro fertilization (IVF) are increasingly applied (6) 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 (127). 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 PCO 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 1. No IVF/intra cytoplasmatic sperm injection (ICSI) cycles may be performed in both groups. PCOS diagnosed in line with the Rotterdam consensus criteria was required (2 out of 3 of the following criteria: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries) (80). 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 MESH headings: "Polycystic Ovary Syndrome"[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 hand-search 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 respective first author had 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 randomised 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 cross-over, patient population characteristics, identifying study groups and outcome measures. From the 9 relevant studies ultimately selected for further analysis the following data were extracted (Table 1): 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 2.

Statistical analysis

Data from the studies in Table 2 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 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 and random effects estimates were calculated using the likelihood method described by Hardy and Thompson, when at least 3 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 are presented for the WMD and pooled odds ratio 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 gonadotropins used, duration of stimulation, number of oocytes, number of oocytes fertilized and number of clinical pregnancies.

Results

Nine relevant studies were identified (128,81,129,82,130,131,132,83,133), reporting data on a total of 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 1. The sample size varied across the trials (19-392 patients; 19-518 cycles).

Table 1. Characteristics of studies regarding PCOS and a matched controlled group who were included in the study

Article	Definition PCOS	Previous Treatment	Control-group	Treatment Protocol	Study Population
Dor et al, Hum Rep, 1990	Anovulation/ Oligoanovulation AND Physical characteristics (obesity, hirsutism) AND LH/FSHratio>3 AND polycystic ovarian appearance on ultrasound	Failed to conceive after at least 6 ovulatory treatment cycles clomiphene citrate (CC) AND 4 treatment cycles HMG	Pure tubal factor patients Retrospective	CC + Human Menopausal Gonadotropin (HMG) OR HMG	16 PCOS (26 cycles) 37control (37 cycles)
Urman et al Fert Steril, 1992	Anovulation/ Oligoanovulation AND Hyperandrogenism (total T>2,43nmol/l)	CC resistant OR Failed to conceive after 6 treatment cycles CC 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 Fertil Steril, 1993	Anovulation/ Oligoanovulation AND/OR Hirsutism AND polycystic ovarian appearance on ultrasound	Failed to conceive after CC AND 6 ovulatory treatment cycles of gonadotropins	Pure tubal factor patients Retrospective Age matched	follicle stimulating hormone (FSH) + HMG GnRH agonist + FSH + HMG	68 PCOS (208 cycles) 68 controls (143 cycles)
Kodama et al Hum Rep, 1995	Anovulation/ Oligoanovulation AND Hormone disorders (elevated LH/FSH ratio>1,5) and/or elevated conc of ovarian androgens in serum (T>50ng/ml, and/or androstenedione>2ng/ml) AND polycystic ovarian appearance on ultrasound	Failed to conceive after at least 2 years of ovulation induction therapy with CC AND Ovulation induction therapy with gonadotropins	Not male factor patients Retrospective Age range matched	GnRH agonist + FSH + HMG	26 PCOS (78 cycles) 202 Control (423 cycles)
Hardy et al Hum Rep, 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 Hum Rep, 1997	Anovulation/ Oligoanovulation AND LF :FSH ratio > 1.5 AND polycystic ovarian appearance on ultrasound	Failed to conceive after at least 3 treatment cycles with gonadtrophins	Pure tubal factor patients Retrospective Age matched	GnRH agonist + HMG	26 PCOS (49 cycles) 26 control (46 cycles)
Doldi et al Hum Rep, 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 4 ovulatory treatment cycles with gonadotropins.	Pure tubal factor patients Retrospective	GnRH agonist + FSH	195 PCOS (271 cycles) 197 controls (247 cycles)
Mulders et al RBMonline, 2003	Anovulation/ Oligoanovulation AND normal serumFSH and E2 concentrations AND Free Androgen Index>4 AND polycystic ovarian appearance on ultrasound	Clomiphene resistant OR Failed to conceive after 6 ovulatory treatment cycles with CC AND 6 treatment cycles with gonadotropins	Pure tubal factor patients Retrospective Age matched	GnRH agonist + FSH	10 PCOS (10 cycles) 9 controls (9 cycles)
Urman et al RBMonline, 2004	Anovulation/ Oligoanovulation AND Clinical and/or biochemical evidence of hyperandrogenism	Failed to conceive after CC AND 4-6 treatment cycles with gonadotropins	Retrospective Age matched Duration of infertility matched	GnRH agonist + FSH	24 PCOS (28 cycles) 31 control (55 cycles)

There was no difference in age between PCOS patients and controls (31.9 years versus 31.8 years), weighted mean difference (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 2 studies and therefore could not be pooled.

Table 2. Available information in selected studies

	Dor 1990	Urman 1992	Homburg 1993	Kodama 1995	Hardy 1995	Sengoku 1997	Doldi 1999	Mulders 2003	Urman 2004
no of patients	X	X	X	X	X	X	X	X	X
no of cycles	X	X	X	X	X	X	X	X	X
no of oocyte retrievals	X	X		X				X	
no of embryo transfers (ET)	X	X	X	X	X		X	X	X
age	X	X	X	X	X	X	X	X	X
BMI							X	X	
duration infertility		X		X		X			X
no of ampoules		X			X		X	X	X
duration stimulation					X			X	X
oestradiol on day HCG									
cancellations cycles (poor)				X				X	
cancellations cycles (hyper)				X				X	
OHSS severe		X		X					
no of oocytes	X	X	X	X	X	X	X	X	X
percentage fertilization	X	X	X	X	X	X	X	X	
no of oocytes fertilized	X			X	X	X		X	
no of embryos per ET		X	X		X	X	X	X	X
no of clinical pregnancies	X	X	X	X	X	X	X	X	X
no of livebirths	X	X					X		
no of miscarriages	X	X	X	X			X	X	X
no of multiple pregn rates			X					X	
implantation rate					X			X	X

Cancellation Rate

PCOS patients demonstrated a significantly increased chance of cycle cancellation (12.8% versus 4.1%), odds ratio (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.

Gonadotropins used

No significant difference was observed in the amount of gonadotropins 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).

Figure 1. Odds ratio for cancellation rate comparing PCOS patients and matched control

Study	N PCOS	N Control	OR	(95% CI)
Dor et al 1990	26	16	0.3	(0.03-3.9)
Urman et al 1992	19	40	0.08	(0-1.8)
Kodama et al 1995	78	423	0.4	(0.2-1.2)
Mulders et al 2003	49	46	0.2	(0.1-0.8)
Fixed effects OR	172	525	0.5	(0.2-0.9)

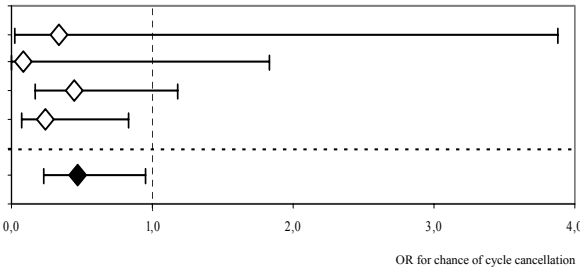
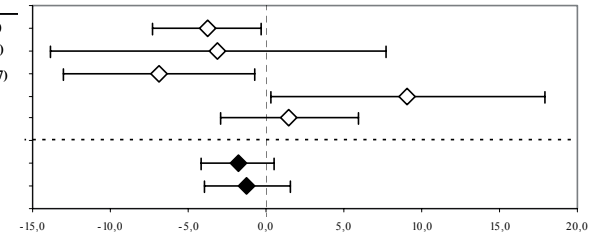
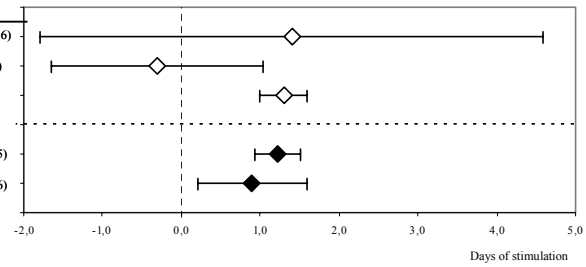


Figure 2. Difference in amount of gonadotropins used (a) and duration of stimulation (b) for ovarian stimulation for IVF comparing PCOS patients and matched controls

Study	N PCOS	N Control	WMD	(95% CI)
Urman et al 1992	19	40	-3.8	(-7.3--0.3)
Hardy et al 1995	10	9	-3.1	(-13.9-7.7)
Doldi et al 1999	104	116	-6.9	(-13.1--0.7)
Mulders et al 2003	49	46	9.1	(0.3-17.9)
Urman et al 2004	271	247	1.5	(-2.9-5.9)
Pooled WMD	453	458	-1.8	(-4.2-0.5)
Random effects	453	458	-1.2	(-4-1.6)



Study	N PCOS	N Control	WMD	(95% CI)
Hardy et al 1995	10	9	1.4	(-1.8-4.6)
Mulders et al 2003	49	46	-0.3	(-1.6-1)
Urman et al 2004	271	247	1.3	(1-1.6)
Pooled WMD	330	302	1..22	(0.9-1.5)
Random Effects	330	302	0.9	(0.2-1.6)



Duration of Stimulation

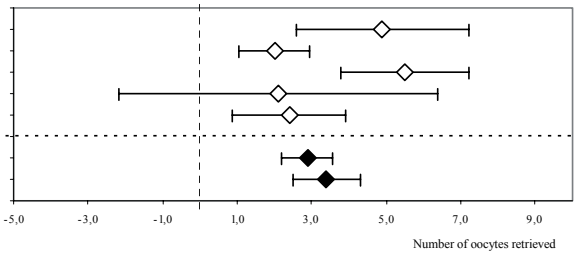
The duration of stimulation was significantly longer in the PCOS group. The WMD was 1.2 days (95% CI 0.9;1.5) (Figure 2b). No significant statistical heterogeneity was detected between studies. The random effects estimate between PCOS and non PCOS women was 0.9 (95%CI -0.6;2.1).

Number of Oocytes Obtained and Number of Oocytes Fertilized

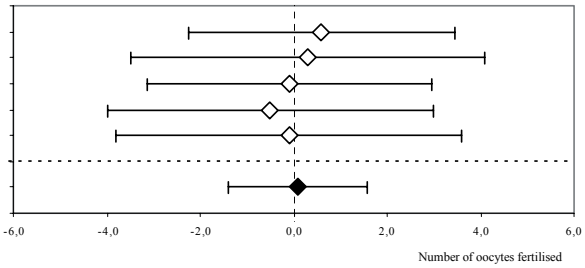
Significantly more oocytes per oocyte retrieval were obtained in PCOS patients compared with controls, WMD 2.9 oocytes (95% CI 2.2;3.6) (Figure 3a). However, significant heterogeneity was detected between studies (p = 0.005). The random effects estimate between

Figure 3. Difference in number of oocytes retrieved (a) and fertilised (b) during IVF comparing PCOS patients with matched controls

Study	N PCOS	N Control	WMD	(95% CI)
Dor et al 1992	26	37	4.9	(2.6-7.2)
Urman et al 1992	19	40	2	(1.1-2.9)
Kodama et al 1995	78	423	5.5	(3.8-7.2)
Mulders et al 2003	49	46	2.1	(-2.2-6.4)
Urman et al 2004	271	247	2.4	(0.9-3.9)
Pooled WMD	443	577	2.9	(2.2-3.6)
Random Effects	443	577	3.4	(2.5-4.3)



Study	N PCOS	N Control	WMD	(95% CI)
Dor et al 1992	26	37	0.6	(-2.2-3.4)
Kodama et al 1995	78	423	0.3	(-3.5-4.1)
Hardy et al 1995	10	9	-0.1	(-3.2-3)
Sengoku et al	28	55	-0.5	(-4--3)
Mulders et al 2003	49	46	-0.1	(-3.8-3.6)
Pooled WMD	163	515	0.08	(-1.4-1.6)



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.

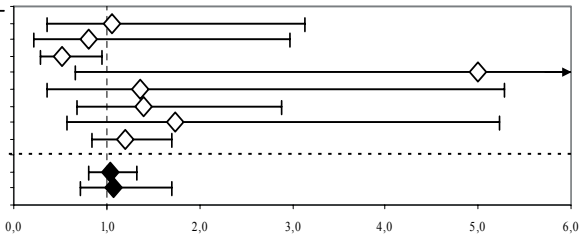
The number of oocytes fertilized did not significantly differ between PCOS patients and controls, WMD 0.1 oocytes (95% CI -1.4;1.6) (Figure 3b). Heterogeneity between studies and random effects estimate could not be calculated.

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 5 comparisons.

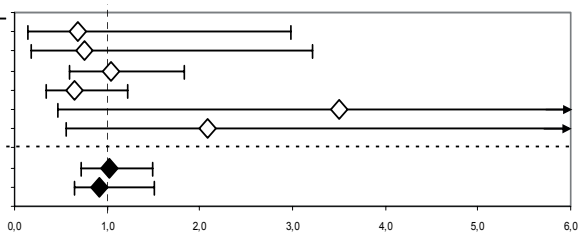
Figure 4. Odds ratio for number of clinical pregnancies (a) and live births (b) per started cycle comparing PCOS patients and matched controls undergoing IVF

Study	N PCOS	N Control	OR	(95% CI)
Dor et al 1990	26	16	1.1	(0.4-3.1)
Urman et al 1992	19	40	0.8	(0.2-3)
Kodama et al 1995	78	423	0.5	(0.3-1)
Hardy et al 1995	10	9	5	(0.7-38.2)
Sengoku et al 1997	28	55	1.4	(0.4-5.3)
Doldi et al 1999	104	116	1.4	(0.7-2.9)
Mulders et al 2003	49	46	1.7	(0.6-5.2)
Urman et al 2004	271	247	1.2	(0.9-1.7)
Fixed effects OR	585	952	1	(0.8-1.3)
Random effects	585	952	1.1	(0.7-1.7)



OR for chance of clinical pregnancies per strated cycle

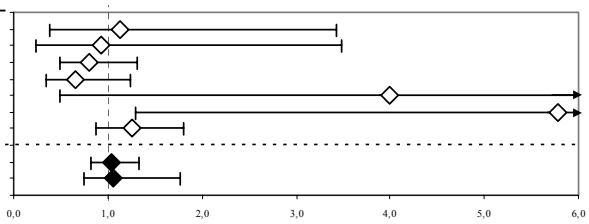
Study	N PCOS	N Control	OR	(95% CI)
Dor et al 1990	26	16	0.7	(0.2-3)
Urman et al 1992	19	40	08	(0.2-3.2)
Homburg et al 1993	208	143	1	(0.6-1.8)
Kodama et al 1995	78	423	0.7	(0.4-1.2)
Hardy et al 1995	10	9	3.5	(0.5-25.9)
Mulders et al 2003	49	46	2.1	(0.6-7.8)
Fixed effects OR	390	1067	1	(0.7-1.5)
Random effects	390	1067	0.9	(0.6-1.5)



OR for chance of live birth per started cycle

Figure 5. Odds ratio for number of clinical pregnancies per embryo transfer comparing PCOS patients and matched controls undergoing IVF

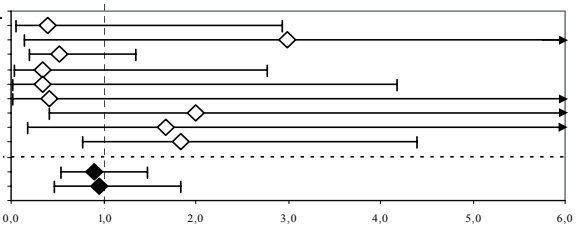
Study	N PCOS	N Control	OR	(95% CI)
Dor et al 1990	26	16	1.1	(0.4-3.4)
Urman et al 1992	19	40	0.9	(0.2-3.5)
Homburg et al 1993	208	143	0.8	(0.5-1.3)
Kodama et al 1995	78	423	0.7	(0.4-1.3)
Hardy et al 1995	10	9	4	(0.5-32)
Mulders et al 2003	49	46	5.8	(1.3-25.7)
Urman et al 2004	271	247	1.3	(0.9-1.8)
Fixed effects OR	661	924	1.1	(0.8-1.3)
Random effects	661	924	1.1	(0.8-1.8)



OR for chance of clinical pregnancy per embryo transfer

Figure 6. Odds ratio for number of miscarriages per biochemical pregnancy comparing PCOS patients and controls undergoing IVF

Study	N PCOS	N Control	OR	(95% CI)
Dor et al 1990	26	16	0.4	(0.1-2.9)
Urman et al 1992	19	40	3	(0.1-64.3)
Homburg et al 1993	208	143	0.5	(0.2-1.3)
Kodama et al 1995	78	423	0.3	(0-2.8)
Hardy et al 1995	10	9	0.3	(0-4.2)
Sengoku et al 1997	28	55	0.4	(0-13.3)
Doldi et al 1999	104	116	2	(0.4-9.8)
Mulders et al 2003	49	46	1.7	(0.2-15.1)
Urman et al 2004	271	247	1.8	(0.8-4.4)
Fixed effects OR	793	1095	0.9	(0.5-1.5)
Random effects	793	1095	1	(0.5-1.8)



OR for chance of miscarriage per biochemical pregnancy

OHSS after Oocyte Pick Up

In the majority of 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 ovarian hyperstimulation syndrome 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 study. One study reported 3 cases of OHSS in the PCOS group and 1 case of OHSS in the non PCOS women.

Implantation Rate and Multiple Pregnancy Rate

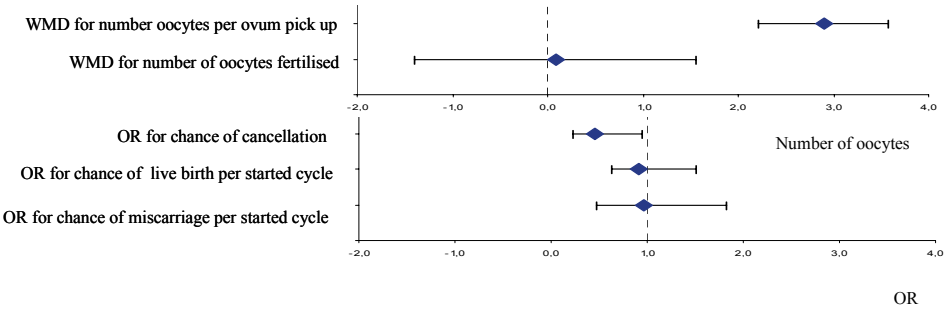
Data regarding implantation rate were available but without standard error and therefore could not be pooled. Data regarding multiple pregnancy rate were reported in only 2 publications, and could also not be pooled.

Discussion

Meta-analysis in general has several drawbacks, such as dependence on the quality of the reporting of primary analysis findings 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 contributes 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 birth rates per started IVF cycle (Figure 7).

Figure 7. Main findings of clinical outcomes of IVF in PCOS compared with matched controls



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 (131). These authors suggested that patient selection after preceding ovulation induction may explain the over representation 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%) (130). This is consistent with previous studies of OHSS incidence and cycle cancellation in women with PCOS (134,135). Specific characteristics of PCOS considered to explain the higher incidence of OHSS include the presence of polycystic ovaries (136,137,138), an LH:FSH ratio > 2 (139) and hyperandrogenism (140). 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 (141).

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 studied are showed 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 (142). Another study compared the oocyte quality before intracytoplasmic sperm injection after the removal of the cumulus cells in PCOS and non-PCOS patients (143). 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 cytoplasmatic factors instead of involvement of the nuclear maturity of oocytes. A further study (132) 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 (144). It has been suggested that elevated LH levels in PCOS are associated with an increased rate of miscarriage (145) although this has been disputed more recently by others (123,146). It has been proposed that using a GnRH agonist to suppress LH can reduce this risk (147). In our meta-analysis, one study compared stimulation protocols with or without GnRH agonist co-treatment (82). 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 gonadotropins compared with gonadotropins 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 is to that of non-PCOS women. 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 life style changes, insulin sensitizers, aromatase inhibitors and laparascopic electrocautery of ovaries in the treatment strategy. Outcomes from IVF and single ET remains to be established for PCOS.