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ORIGINAL ARTICLE *Reproductive endocrinology*

Do women with ovaries of polycystic morphology without any other features of PCOS benefit from short-term metformin co-treatment during IVF? A double-blind, placebo-controlled, randomized trial

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BACKGROUND: Women with ovaries of polycystic morphology (PCO), without any other features of polycystic ovary syndrome (PCOS), respond similarly to women with PCOS when stimulated with exogenous gonadotrophins, and both groups share various endocrinological disturbances underlying their pathology. In women with PCOS, metformin co-treatment during IVF has been shown to increase pregnancy rates and reduce the risk of ovarian hyperstimulation syndrome (OHSS). The aim of this study was to investigate whether metformin co-treatment before and during IVF can also increase the live birth rate (LBR) and lower severe OHSS rates for women with PCO, but no other manifestations of PCOS.

METHODS: This study was a double-blind, multi-centre, randomized, placebo-controlled trial. The study population included 134 women with ovulatory PCO (and no evidence of clinical or biochemical hyperandrogenism) undergoing IVF treatment at three tertiary referral IVF units. The primary outcome was LBR.

RESULTS: In total, 134 women were randomized, 69 to metformin and 65 to placebo. There were no statistically significant differences between the two groups in baseline characteristics. With regard to IVF outcome, no significant improvements were found in the metformin group when compared with the placebo group. In particular, there was no difference between the groups in rates of live birth [metformin $n = 27$ (39.1%), placebo $n = 30$ (46.2), (95% confidence interval 0.38, 1.49, odds ratio = 0.75)], clinical pregnancy [metformin $n = 29$ (42.0%), placebo $n = 33$ (50.8%)] or severe OHSS [metformin $n = 6$ (8.7%), placebo $n = 5$ (7.7%)].

CONCLUSIONS: There appears to be no benefit in metformin co-treatment before and during IVF in women with PCO without any other features of PCOS.

Clinical Trials.gov: NCT01046032.

Key words: polycystic ovaries / metformin / IVF / OHSS / PCOS

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder, affecting 6–10% of women of childbearing age (Franks, 1995; Balen and Michelmore, 2002). Ultrasound evidence of polycystic ovaries (PCOs) affects ~20–30% of the female population (Balen *et al.*, 1995; Michelmore *et al.*, 2001; Balen and Michelmore, 2002). However, only a proportion of these women are symptomatic,

and although it may be considered a normal variant, up to 34% of women attending fertility clinics have PCO (Balen *et al.*, 1993). Women with PCO alone, without any other features of PCOS, commonly respond in a way similar to those with PCOS when stimulated with gonadotrophins and are at an increased risk of ovarian hyperstimulation syndrome (OHSS) (MacDougall *et al.*, 1992; Swanton *et al.*, 2009).

This may be because women with PCO alone share some common metabolic characteristics with women who have PCOS, such as increased insulin resistance (IR), when compared with well-matched controls (Cenk Sayin *et al.*, 2003; Adams *et al.*, 2004). Adams *et al.* (2004) also demonstrated that women with PCO alone have elevated androgen levels and lower sex hormone-binding globulin (SHBG) levels compared with women with normal ovarian morphology.

Insulin-sensitizing agents, such as metformin, have been used alone to try and promote ovulation and conception in women with PCOS, though the effects appear limited (Palomba *et al.*, 2009; Tang *et al.*, 2009). However, metformin has also been examined as a co-treatment during IVF in women with PCOS. Kjotrod *et al.* (2004) demonstrated an increase in pregnancy rate (PR) from 23 to 71% ($P < 0.05$) in a subgroup of women with PCOS and a normal BMI, who were treated with metformin before and during IVF treatment (Kjotrod *et al.*, 2004). These findings were confirmed and extended by Tang *et al.* (2006), where a significant increase in clinical PR (CPR) (metformin = 38.5%, placebo = 16.3%, $P = 0.023$) was seen along with a significant reduction in rates of OHSS (metformin = 3.8%, placebo = 20.4%, $P = 0.023$). However, a recent meta-analysis suggested no increase in live birth rate (LBR) with metformin during IVF despite a significant reduction in the rate of severe OHSS (Tso *et al.*, 2009).

In the knowledge that: (i) there are metabolic similarities, including a degree of IR, between women with PCO and those with PCOS; (ii) women with PCO alone or PCOS are at significantly increased risk of developing OHSS during IVF compared with women with normal ovaries and (iii) metformin co-treatment has some beneficial effects on IVF clinical outcomes in women with PCOS, we decided to examine metformin during IVF for women with PCO alone. The aim of this study, therefore, was to investigate whether pretreatment with metformin before and during IVF increases the LBR compared with placebo in women with sonographic evidence of PCO but without any clinical manifestations of PCOS.

Materials and Methods

The primary outcome of the study was LBR. A number of secondary outcomes were analysed and included the following: severe OHSS requiring hospitalization (presence of clinical ascites and/or haematocrit >0.45) (Mathur and Jenkins, 2005; RCOG, 2006); duration of gonadotrophin stimulation, total dose of FSH (IU) administered; peak estradiol level (E_2) (pmol/l); number of oocytes collected; number of oocytes fertilized; number of embryos frozen; PR and CPR (clinical pregnancy defined as the presence of fetal heart activity at 6 weeks gestation). The secondary outcomes were mainly exploratory and the study was not powered to analyse these independently.

Ethical approval was obtained from the Oxfordshire Research Ethics Committee B (05/Q1605/87). The study design was a multicentre, double-blind, prospective, randomized, placebo-controlled study among women with sonographic evidence of PCO, but without any other manifestations of PCOS, and who were undergoing IVF treatment. The trial was registered at www.ClinicalTrials.gov with the identifier NCT01046032.

Three tertiary-level-assisted conception units in the UK participated: Oxford Fertility Unit, Oxford; IVF Hammersmith, London; Nurture, Nottingham. PCOs were diagnosed by the ultrasound presence of 12 or more follicles in at least one ovary measuring 2–9 mm in diameter, and/or increased ovarian volume ≥10 ml (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). This contemporary definition of PCO, as used in the recent metformin RCTs, was used in preference to the older Adams criteria.

Women were randomized to receive either metformin or placebo starting on day one of the menstrual cycle in which the IVF treatment was due to commence (8 weeks prior to oocyte collection). For the study, 70 identical packs of metformin and 70 identical packs of placebo were supplied by DHP Ltd., Crickhowell, Powys, a commercial clinical trial supplier. The randomization service was provided by DHP Ltd and used the PRISYM Clinical Trial Module to generate pseudo-random numbers to then produce sequentially numbered containers. Participants were recruited by the research doctors at each respective site and assigned intervention according to their sequential number. The method of concealment used was sealed envelopes, to be opened only if a serious adverse event occurred or after the trial had been completed for analysis of the results.

Sample size

We estimated a LBR (or ongoing PR) in the placebo group of 20%. With a study power of 0.80 and a significance level of 0.05, we calculated that 62 patients were required in each group to show an increase in LBR to 45% per cycle. This sample size calculation was based on the Kjotrod study in 2004 (Kjotrod *et al.*, 2004).

Protocol

One 500 mg capsule of metformin was taken every morning for 1 week, and then increased to two daily, and then three times daily until the day of oocyte collection. To reduce gastrointestinal adverse effects, capsules were consumed with meals. If troublesome gastrointestinal side effects occurred, dose reductions were allowed and recorded. Identical-looking capsules for the placebo were consumed the same way as metformin. Data were analysed on an intention-to-treat basis. No patient participated in the trial more than once.

The inclusion criteria were women ≤38 years of age, with PCO (without any other features of PCOS) attending their first or second IVF/ICSI treatment cycle. If women had previously been taking metformin, a minimum 1 month washout period was required. PCOs were diagnosed by ultrasound morphology with ≥12 follicles measuring 2–9 mm in diameter in at least one ovary and/or increased ovarian volume (≥10 ml) (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Written informed consent was taken from all participants.

The exclusion criteria were any clinical manifestations of PCOS, including oligo- or amenorrhoea with cycles ≥42 days apart; anovulation with mid-luteal progesterone <16 nmol/l; biochemical hyperandrogenism with serum testosterone ≥3.5 nmol/l and/or free androgen index >5 [FAI = (total testosterone/SHBG) × 100]; and clinical hyperandrogenism with hirsutism or acne requiring treatment at least weekly.

Other exclusion criteria included: BMI >35 kg/m^2; basal FSH >12 IU/l; liver disease or alanine transaminase >80 IU/l; renal disease, or creatinine >130 nmol/l; alcoholism or drug abuse; diabetes mellitus (evaluated by fasting glucose >6.7 mmol/l); per oral steroid treatment in last month; cimetidine, anticoagulation, erythromycin or other macrolides in last month; hyperprolactinaemia (prolactin >700 mIU/l); abnormal thyroid

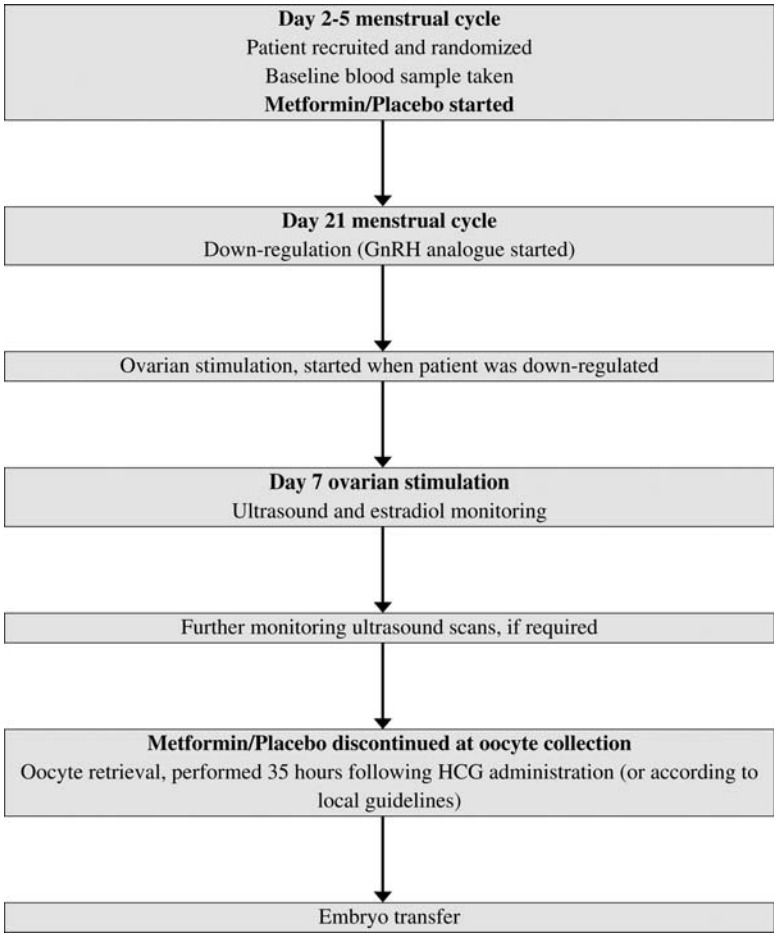

Figure 1 Study protocol.

function tests (thyroid-stimulating hormone outside of laboratory normal range); and congenital adrenal hyperplasia.

At recruitment, patients underwent a transvaginal ultrasound scan where the number of antral follicles was counted within each ovary and added together to give the antral follicle count (AFC). The ovarian volume of each ovary was measured, and combined to give the total ovarian volume. PCOS was excluded by ensuring that relevant exclusion criteria were not present. Morning fasting blood samples were taken on cycle day 2–5 and then patients were randomized to metformin or identical-looking placebo tablets (Fig. 1).

The IVF treatment regimen using a GnRH long agonist cycle was as follows:

- Patients were treated with metformin or identical placebo tablets starting at the beginning of the menstrual cycle in which the IVF treatment was due to commence.
- Patients then commenced pituitary suppression with Nafarelin (Syneral; Pharmacia Ltd., Milton Keynes, UK) 400 mcg twice daily intra-nasally starting on Day 21 of the menstrual cycle. Pituitary suppression was confirmed with a serum $E_2 < 150$ pmol/l after 3 weeks of Nafarelin.
- Once patients were down-regulated, a recombinant FSH (Gonal-F; Serono Pharmaceuticals Ltd., Feltham, UK, or Puregon; Organon Laboratories Ltd., UK) was administered sub-cutaneously. The dose was determined by the patient's age, basal serum FSH level and previous ovarian response to gonadotrophins (or according to local guidelines).
- Ultrasound and serum monitoring (E_2) of follicular response from Day 7 of gonadotrophin stimulation were then performed.
- Coasting was considered when the peak serum E_2 level was >15 000 pmol/l (or according to local guidelines).
- Ovitrelle 250 mg (Serono Pharmaceuticals Ltd., Feltham, UK) was then administered sub-cutaneously, when at least three leading follicles were >18 mm diameter (or according to local guidelines).
- Oocyte retrieval was performed 35 h following HCG administration (or according to local guidelines).
- IVF or ICSI was performed, as dictated by semen quality and local guidelines.
- A maximum of two embryos were transferred to the uterus transcervically 2 or 3 days later.
- Luteal phase progesterone 400 mg Cyclogest (Shire Pharmaceuticals Ltd., Basingstoke, UK) was then self-administered vaginally (or local guidelines followed) from the day before embryo transfer until the day of pregnancy test.
- A urinary-HCG pregnancy test was then performed on Day 16 post oocyte-recovery (or according to local guidelines).
- If pregnant, a transvaginal ultrasound was arranged for 2 weeks later to confirm clinical pregnancy (presence of fetal heart activity).

Biochemical analysis

Blood was taken from subjects in a fasted state. Plasma FSH, testosterone and SHBG levels were measured on the day of sampling and analysed in the local laboratory. Hormones were analysed by chemiluminescence immunoassay. Testosterone, FSH and LH were all measured using a Siemens ADVIA Centaur analyser (Frimley, UK). The method reproducibility, expressed as the inter-assay percentage coefficient of variation (CV%) were all $<10\%$ and were as follows: testosterone, 9.1% at 3.3 nmol/l, 5.5% at 20.0 nmol/l, 9.1% at 42.2 nmol/l; FSH, 6.5% at 3.9 IU/l, 3.4% at 14.1 IU/l, 3.3% at 51.8 IU/l; LH, 3.3% at 1.6 IU/l, 3.1% at 16.4 IU/l and 2.8% at 44.0 IU/l. SHBG was analysed on a Siemens Immulite 2000 analyser (Frimley, UK), with inter-assay CV% of 4.1% at 5.4 nmol/l, 5.3% at 82.7 nmol/l. Plasma glucose was measured with a standard hexokinase assay on an Siemens ADVIA 2400 analyser (Frimley, UK), with inter-assay CV% of 1.6% at 6.4 mmol/l and 1.0% at 16.0 mmol/l. All CVs were within acceptable limits.

Samples were then centrifuged no >30 min after sampling, and the resultant serum was then frozen at $-80^{\circ}C$ for later analysis. Fasting serum specific insulin was measured with a chemiluminescent assay performed on a DPC immulite 2500 machine (St Bartholomew's Hospital, London, UK).

Measures of insulin sensitivity were calculated as homeostasis model assessment of IR (HOMA2-IR) values using the Oxford Diabetes Trials Unit calculator (www.dtu.ox.ac.uk; University of Oxford, UK).

Statistical analysis

The Kolmogorov–Smirnov test was used to analyse normality in each variable. Means were compared using the independent sample *t*-test (two-tailed) or Mann–Whitney *U*-test as appropriate for skewed data. Variables that were not normally distributed underwent logarithmic (Log_{10}) transformation prior to statistical analysis. If these variables were still not normally distributed, they underwent non-parametric comparison. The Chi-square or Fisher exact tests were used for comparing proportions where appropriate. Binary logistic regression analysis was used for analysing IR and adverse outcome. All the tests were performed using the SPSS statistics package (version 14.0 for Windows; SPSS Inc., Chicago, IL, USA).

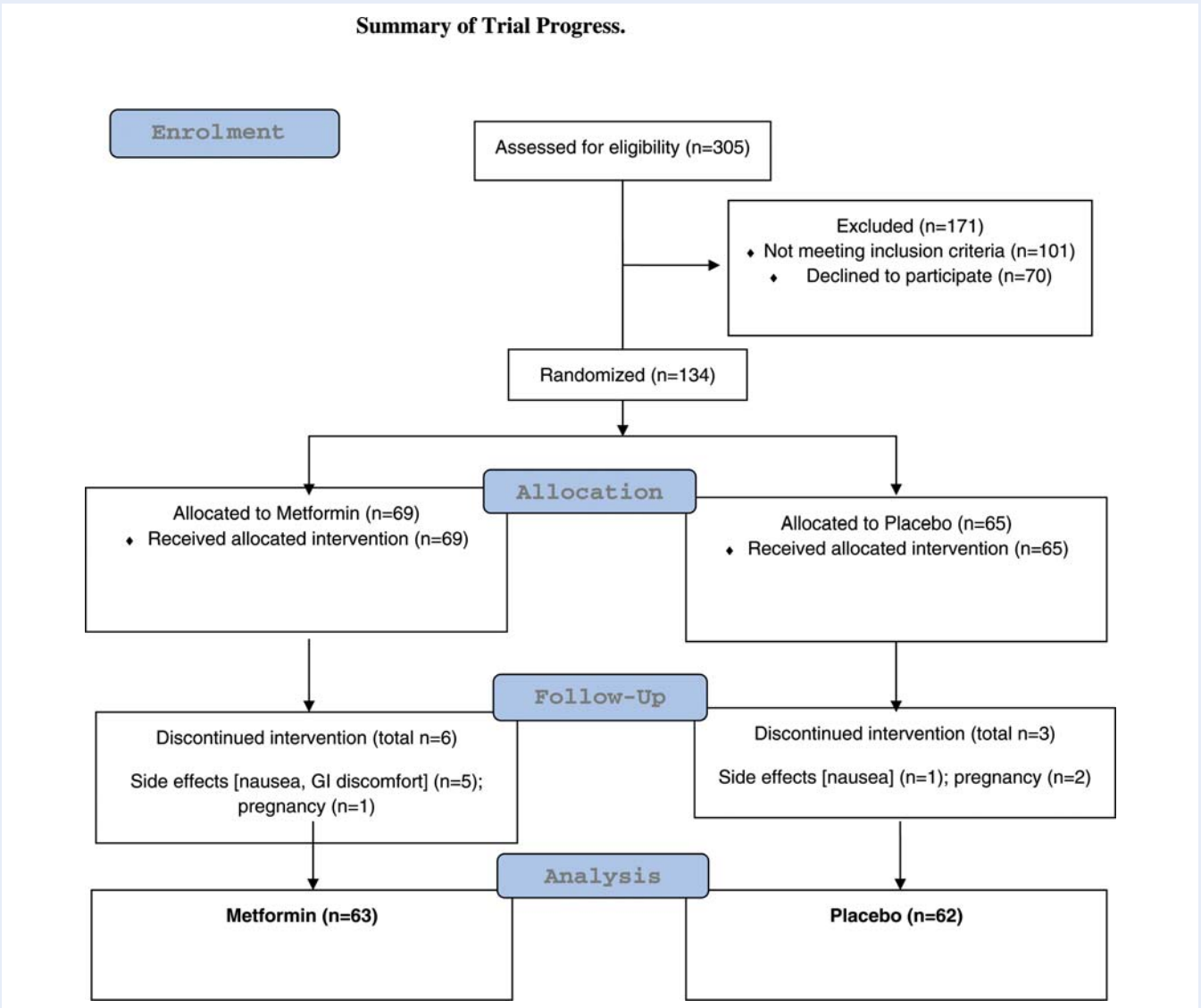

Figure 2 Summary of trial progress.

Table I Characteristics of women in trial.

Characteristics	Metformin ($n = 69$)	Placebo ($n = 65$)
Age (years)	32.0 (3.7)	32.9 (3.9)
BMI (kg/m^2)	24.6 (4.0)	24.4 (3.8)
Subfertility (months)	43.2 (20.0)	48.6 (24.5)
Previous fertility treatment *n* (%)	32 (46.4%)	31 (47.7%)
No. patients—live births ≥24 weeks *n* (%)	4 (5.8%)	10 (15.4%)
No. patients—previous pregnancies *n* (%)	23 (33.3%)	16 (24.6%)
Ovarian volume (cm^3)	15.8 (7.8)[a]	15.4 (6.5)[a]
Total antral follicle count	27.7 (7.3)	28.7 (7.1)
Testosterone (nmol/l)	1.5 (0.4)	1.6 (0.5)
SHBG (nmol/l)	52.6 (27.1)	55.4 (18.2)
Free androgen index	3.6 (2.1)	3.4 (2.1)
Fasting insulin (mIU/l)	6.0 (0.27)[b,c]	6.3 (0.30)[b,c]
HOMA2-IR	0.93 (0.23)[b,c]	0.87 (0.22)[b,c]

Results are means (SD) unless indicated. SD, standard deviation.
[a]Median (interquartile range).
[b]Geometric mean (SD).
[c]Log_{10} values used for statistical analysis.

Table II IVF cycle outcomes in the two groups (intention to treat analysis).

Outcome	Metformin ($n = 69$)	Placebo ($n = 65$)	*P*-value
LBR/cycle started *n* (%)	27 (39.1%)	30 (46.2%)	0.411[a]
CPR/cycle started *n* (%)	29 (42.0%)	33 (50.8%)	0.311[a]
PR/cycle started *n* (%)	36 (52.2%)	37 (56.9%)	0.581[a]
No. patients—severe OHSS *n* (%)	6 (8.7%)	5 (7.7%)	0.833[a]
Cancellation/FAE *n* (%)	2 (2.9%)	3 (4.6%)	0.485[a]
No. patients coasted *n* (%)	6 (8.7%)	11 (16.9%)	0.161[a]
Severe OHSS or avoidance technique *n* (%)	13 (18.8%)	12 (18.5%)	1.00[a]
Total dose of FSH (IU/l)	1650 (684)[b]	1650 (625)[b]	0.232[c]
No. days stimulation	10.9 (2.5)	11.0 (2.8)	0.930
Peak E_2 level (pmol/l)	4353 (4164)[b]	3367 (4292)[b]	0.798[c]
No. oocytes	15.7 (7.5)	14.6 (9.3)	0.56
No. oocytes fertilized	9.6 (5.2)	7.6 (4.8)	0.024
No. embryos transferred	2.0 (0)[b]	2.0 (0)[b]	0.06[c]
No. embryos frozen	4.0 (7.0)[b]	2.0 (5.0)[b]	0.102[c]
Implantation rate (%)	30.6%	38.9%	0.188[a]
No. patients withdrawn	6 (8.7%)	3 (4.6%)	0.494[a]

Results are means (SD) unless indicated. SD, standard deviation.
[a]Chi-square test/Fisher's exact test.
[b]Median (interquartile range).
[c]Mann–Whitney *U*-test.

Results

In total, 134 patients were randomized between December 2005 and July 2008 (Oxford $n = 90$, Hammersmith $n = 25$, Nottingham $n = 19$) (Fig. 2). There were nine patients who failed to complete the study as per protocol, either because of withdrawing due to side effects, or conceiving while down-regulating. In total, 63 patients in the metformin group and 62 in the placebo group underwent oocyte retrieval. Of these patients, 61 in the metformin group and 59 in the placebo group underwent embryo transfer.

There were no statistically significant differences between the two groups in baseline characteristics (Table I). When analysing LBR, there were no statistical differences between the two groups [metformin $n = 27$ (39.1%), placebo $n = 30$ (46.2%); odds ratio (OR) = 0.75, 95% confidence interval (CI) 0.38, 1.49]. No significant improvements in any other secondary IVF outcome measures were found in the metformin group when compared with the placebo group, other than the number of oocytes fertilized (Table II). In particular, no improvement in the clinical pregnancy [metformin $n = 29$ (42.0%), placebo $n = 33$ (50.8%)], or severe OHSS rates [metformin $n = 6$ (8.7%), placebo $n = 5$ (7.7%)] was observed. The lack of statistical difference persisted when the data were analysed per protocol. No statistical differences were noted in outcomes between centres.

Subgroup analyses of women with a BMI >30 kg/m^2 (metformin $n = 8$, placebo $n = 6$), an AFC ≥30 (metformin $n = 27$, placebo $n = 23$), AFC ≥40 (metformin $n = 4$, placebo $n = 5$) or those women who had an increased degree of IR (HOMA2-IR > 1.0; metformin $n = 15$, placebo $n = 12$) showed no statistical differences with regard to LBR, CPR or OHSS rates between metformin and placebo groups. In the group of women with an AFC ≥40, there were significantly higher numbers of oocytes fertilized ($n = 10.4$, $n = 2.5$) and embryos frozen ($n = 6.3$, $n = 0$) in the metformin group compared with placebo ($P = 0.020$ and $P = 0.048$, respectively), though the sample size was very small ($n = 9$). These outcomes are exploratory and this study was not powered to detect these differences.

There were no differences between the groups in the rate of development of severe OHSS or the number of patients undergoing an avoidance technique (cycle cancellation, elective cryopreservation, dose reduction or coasting). The total dose of FSH required for the cycle was no different between the two groups. Although not significant, there were almost twice as many patients coasted in the placebo group. Overall, 17 patients were coasted, and 6 (35%) of these women achieved a clinical pregnancy.

Using logistic regression analysis, there was a significant association ($P < 0.05$; OR 1.006; 95% CI 0.0–0.86) between IR (as measured using Log_{10} HOMA2-IR) and total adverse outcome (cycle cancellation before oocyte recovery over concerns of OHSS, all embryos frozen or severe OHSS requiring hospitalization). However, there is not a difference between the two study groups and as the CI indicates, there is a degree of uncertainty over the OR for this effect.

Discussion

To our knowledge, this is the only RCT to assess the use of metformin in women with PCO (with regular ovulatory cycles and absence of hyperandrogenism) undergoing IVF treatment. It was not possible to

demonstrate an improvement in the metformin group with regard to pregnancy outcome or rates of OHSS during IVF treatment. However, there may be a degree of uncertainty in interpreting these data, given the CIs.

Despite compelling evidence that women with PCO respond in a way similar to those with PCOS when stimulated with exogenous gonadotrophins and have similar rates of OHSS, there were no differences between the study groups regarding these outcomes. The mean number of oocytes retrieved and E_2 level on Day 9 of stimulation, surrogate markers of OHSS (Whelan and Vlahos, 2000; Aboulghar, 2003) were not different between the groups. In contrast to that observed in women with PCOS (Tang *et al.*, 2006), metformin did not have a beneficial effect in reducing OHSS rates.

Given that women with PCO and PCOS have similar rates of severe OHSS during IVF, the pathophysiology of hyperstimulation may not be related to IR and may be mediated through another mechanism such as increased vascular endothelial growth factor levels. However, there was a significant correlation between worsening IR and an adverse outcome, and this may exacerbate OHSS. Although statistically significant, the increase in odds of an adverse outcome occurring with worsening IR in our study was very small and further analysis of this would be warranted. Metformin had no effect on OHSS rates or cycle cancellation rates. This suggests that women with PCO only are not as IR as once thought compared with women with PCOS and this is something we are studying further.

Dickerson *et al.* (2010) analysed 49 women undergoing IVF treatment, all of whom had normal ovarian morphology. They showed that patients with a higher level of androgens and IR are more likely to develop OHSS (Dickerson *et al.*, 2010). These findings were in women with normal ovaries and therefore adverse outcome related to IR may not be limited to patients with PCO or PCOS.

The most likely explanation as to why there was no benefit in using metformin in this population is that women with PCO may be less IR compared with women with PCOS. While some studies have shown women with PCO to share some endocrinological disturbances with those with PCOS, the difference between these data and other studies may represent variations in categorizing patients and attributing the correct phenotype. Some studies were conducted prior to the Rotterdam criteria, and may have used different variables in diagnosing ovulatory PCO and PCOS.

For this study, the power calculation was based on previous studies (Kjotrod *et al.*, 2004). Patients recruited to this study had a relatively good prognosis for IVF treatment (<39 years of age, undergoing their first or second cycle) and the LBRs reflected not only this, but the fact that the protocol for this study was written in 2004 and LBRs have increased since then.

The duration of metformin in this study is thought to be adequate by the authors. In the study by Tang *et al.* (2006), patients took metformin or placebo form the day of down-regulation until oocyte collection and the differences were significant. Patients in our study started intervention ~3 weeks earlier, during the baseline menstrual cycle in which IVF treatment was to commence. Unfortunately, we do not have any data regarding ovarian morphology after metformin and before ovarian stimulation.

The Rotterdam criteria are vague with regard to what constitutes both clinical and biochemical hyperandrogenism. Only testosterone levels and FAI were analysed and this may have lead to bias within the study. However, although other androgens were not specifically measured, criteria were chosen for clinical hyperandrogenism, such as acne and hirsutism requiring treatment, based on advice from the Endocrinologists at Oxford. Stricter criteria may enable better comparison between study populations and allow for more robust statistical analysis. More data are required to analyse the degree of IR in women with ovulatory PCO compared with those with PCOS along with a normal control group.

In summary, this study suggests that short-term metformin co-treatment before and during IVF is not of benefit in women with PCO without any other features of PCOS.

Authors' roles

All authors were involved in conception, study design, protocol development (including development of multicentre trial), ethics application, site-specific ethics application, development of each recruitment site, site-specific data collection and analysis, patient recruitment, data analysis, manuscript drafting, revisions and final approval of the manuscript.

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