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ORIGINAL ARTICLE *Reproductive endocrinology*

Health-related quality of life in women with newly diagnosed polycystic ovary syndrome randomized between clomifene citrate plus metformin or clomifene citrate plus placebo

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STUDY QUESTION: What is the health-related quality of life (HRQoL) in women with polycystic ovary syndrome (PCOS) undergoing ovulation induction with clomifene citrate (CC) combined with metformin compared with those using CC combined with placebo?

SUMMARY ANSWER: Overall quality of life in women with PCOS treated with CC plus metformin was significantly lower than in women treated with CC plus placebo.

WHAT IS KNOWN ALREADY: There are no data on HRQoL in adult women who receive ovulation induction with the purpose of conceiving. Women with PCOS have higher scores on depression and anxiety scales and lower QoL scores than women without PCOS.

STUDY DESIGN, SIZE AND DURATION: This study was a secondary analysis of a multi-centre RCT completed between June 2001 and May 2004. The randomization was stratified per centre, and the centres received blinded, numbered containers with medication. There were172 women available for the HRQoL assessment: 85 were allocated to metformin and 87 were allocated to placebo.

PARTICIPANTS, SETTING AND METHODS: The Rotterdam Symptom Checklist (RSCL), a standard self-administered questionnaire, was used to assess physical symptoms, psychological distress, activity levels and overall HRQoL.

MAIN RESULTS AND THE ROLE OF CHANCE: In the intention to treat analysis, we found differences between the treatment groups with respect to physical symptoms and overall HRQoL. Physical well-being was significantly impaired in women allocated to metformin but not in women allocated to placebo. The increase in physical symptoms in the metformin group was caused by side-effects typical of metformin, and was most pronounced at Week 1 (mean difference 12 [95% confidence interval (CI): 8–16] and still apparent at Week 16 [mean difference 7 (95% CI 2–12]. Overall well-being was significantly impaired in the metformin group compared with the placebo group [mean difference 13 (95% CI 6–20)].

LIMITATIONS AND REASONS FOR CAUTION: RSCL measurements were available only for three quarters of the participants. Although the number of missing questionnaires and the baseline measurements, were comparable between the treatment groups, some form of selection bias cannot be ruled out.

WIDER IMPLICATIONS OF THE FINDINGS: Our finding that metformin was more burdensome than placebo, strengthens the recommendation that CC only and not CC plus metformin should be the drug of choice in this patient population.

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Key words: clomifene / health-related quality of life / metformin / polycystic ovary syndrome / randomized clinical trial

Introduction

Polycystic ovary syndrome (PCOS) is characterized by oligo-anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries (ESHRE/ASRM, 2004). The syndrome affects ~4–9% of women of childbearing age (Homburg, 2002). Infertility due to chronic anovulation is the most common reason for women to seek counselling or treatment. Clomifene citrate (CC) is the most commonly used drug for first-line treatment for ovulation induction in women with PCOS.

Another major biochemical feature of PCOS is insulin resistance accompanied by compensatory hyperinsulinemia, which leads to early LH-sensitivity of the follicle and to stimulation of both ovarian and adrenal androgen production (Dunaif *et al.*, 1989; O'Meara *et al.*, 1993; Barbieri, 1994; Dunaif, 1997; Nestler, 1997; Moran and Teede, 2009; Moran *et al.*, 2010).

Within the framework of hyperinsulinemia, use of metformin was introduced as a therapy for PCOS (Velazquez *et al.*, 1994). Metformin has been shown to result in ovulation in a significant proportion of women with PCOS, but not in higher live birth rates compared with CC (Moll *et al.*, 2006; Legro *et al.*, 2007; Tang *et al.*, 2012).

In deciding whether to treat a patient with metformin or not, the burden of treatment is also considered. So far, information on health-related quality of life (HRQoL) of women with PCOS treated by different modalities for ovulation induction is limited. One randomized study evaluated life style adjustment combined with either metformin or placebo (Ladson *et al.*, 2011). Women were advised to use barrier contraception and avoid pregnancy. That study had a significant number of drop-outs (60 versus 73%). No difference was seen in HRQoL between the two groups. A second randomized study evaluated the use of oral contraceptives combined with metformin or placebo in adolescents (12–18 years) (Harris-Glocker *et al.*, 2010). No difference in HRQoL between groups was observed. More recently, four large meta-analyses were published studying HRQoL in women with PCOS compared with normal controls (Barry *et al.*, 2011; Dokras *et al.*, 2011, 2012; Li *et al.*, 2011). These systematic reviews did not include patients treated with clomifene or metformin.

In ovulation induction with metformin, three or four tablets a day need to be ingested until a pregnancy is achieved, far more than the 5–15 tablets a month with CC. There are also more side-effects. Although it is generally assumed that ovulation induction with metformin is therefore more burdensome than ovulation induction with CC, there are no data on HRQoL in adult women who receive ovulation induction with the purpose of conceiving.

The aim of this study was to examine HRQoL in a secondary analysis as part of a multi-centre trial in women with PCOS undergoing ovulation induction with either CC combined with metformin or CC combined with placebo.

Materials and Methods

The trial was conducted between June 2001 and April 2004 in 1 Belgian and 20 Dutch hospitals and is reported in detail elsewhere (Moll *et al.*, 2006). The study had been approved by the Institutional Review Boards of all hospitals.

PCOS was defined according to present guidelines (ESHRE/ASRM, 2004). Primary exclusion criteria were other causes of anovulation, age over 40 years and liver, kidney or heart disease/failure.

Informed and consenting patients were randomly allocated to either CC combined with metformin (metformin group) or to CC with placebo (placebo group). Randomization was done in the coordinating centre, using computer-generated blocks of four. Participants received a sealed container with medication and the randomization number written on the label. The medication dosage was increased from one to four tablets a day (i.e. 2000 mg) over a period of 7 days (Garber *et al.*, 1997). They followed this 'step-up' regimen to make sure that the side-effects were as little as possible. Patients continued to take the study medication until a positive pregnancy test, six ovulatory cycles or CC resistance occurred, whichever came first. Patients were on metformin or placebo for 1 month to give metformin enough time to have a sufficient insulin-sensitizing effect (Nestler *et al.*, 1998). If 1 month after starting the study medication, no spontaneous menstruation occurred and the pregnancy test was negative, we induced menstruation with dydrogesteron (Duphaston; Solvay Pharma, Weesp, The Netherlands), 10 mg three times a day for 10 days. From Day 3 or 5 till Day 7 or 9 after (spontaneous or induced) menstruation, patients took 50 mg CC per day. If ovulation did not occur with 50 mg CC, the dosage was increased to a maximum of 150 mg a day in the next cycle. Ovulation was defined by a biphasic basal temperature curve, a follicle with a diameter larger than 16 mm on transvaginal ultrasonography and/or progesterone higher than 14 nmol/l in the second half of a menstrual cycle. If a patient ovulated, she continued taking the same dose of CC until she became pregnant or until she had six ovulatory cycles. When a patient discontinued the study before one of the end-points was reached, she continued ovulation induction with CC.

The Rotterdam Symptom Checklist

HRQoL was defined as having a physical, psychological and social dimension. We used the Rotterdam Symptom Checklist (RSCL), a standard self-administered questionnaire with established validity and reliability (De Haes *et al.*, 1996). The RSCL is a tool that was developed to measure symptoms, and was originally developed to evaluate HRQoL in cancer patients. It comprises four sub-scales: physical symptoms, psychological distress, activity level and a single item measuring overall quality of life. Subscale scores were transformed into a 0–100 scale, with higher scores indicating more symptoms and a lower quality of life. Women were asked by their physicians to fill out the questionnaires at home. To compare short and long-term treatment effects, we assessed HRQoL at five time points. The first set of questionnaires was completed 1–2 weeks before randomization. Women subsequently completed the questionnaires at 1, 4, 8 and 16 weeks after randomization.

Analysis

Baseline values from women with PCOS included in the study were tabulated and compared with reference values from the general population, where available. HRQoL was first compared between treatment groups on an intention-to-treat basis. A mixed-model analysis of variance was used to detect changes in HRQoL over time (time effect), to compare HRQoL between treatment groups (treatment effect) and to examine differences in changes over time between treatment groups (time by treatment interaction effect).

Baseline values were included in the analysis as covariates. Women with missing measurements were included in the analysis whenever data were available at baseline and for at least one time point during the trial (Zwinderman, 1992). Mean estimates with corresponding 95% confidence intervals (95% CIs) were calculated for each time point.

The power calculation was based on the ovulation rate. Expecting an ovulation rate of 75% in the placebo group (Eijkemans *et al.*, 2003; Imani *et al.*, 2002), 200 patients were required to demonstrate an absolute increase in ovulation rate of 15%, with a power of at least 80%

using a two-sided chi-square test with a 5% significance level. Our hypothesis for the HRQoL study was that metformin and CC treatment would be more burdensome to women than ovulation induction with CC alone. We expected that 10% of the women would not participate in the HRQoL study. Using a two-sided significance level of 0.05, including 180 participants would allow us to detect an effect size of 0.42 with a power of at least 80% in an unconditional analysis of variance. This amounts to changes in effect size of 5–11 on the four items of the RSCL scale. Data analysis was conducted using of the IBM SPSS for the Windows 19.0 statistical software (SPSS Inc. Chicago, IL, USA).

Results

A total of 225 women were included in the randomized trial (Moll *et al.*, 2006), of which 111 were allocated to metformin and 114 to placebo. For this analysis, 26 women in the metformin group and 27 women in the placebo group did not return a baseline and follow-up questionnaire and could not be included. In total, HRQoL data from 172 women were available: 85 allocated to metformin and 87 allocated to placebo. The baseline characteristics of all the included women are listed in Table I.

Table I The baseline characteristics of the women who participated in the HRQoL study.

Characteristics	Metformin (n = 85)	Placebo (n = 87)
Mean age (years) (SD)	28 (3.8)	29 (3.7)
Mean body mass index (SD)	28 (6.8)	28 (6.7)
Mean waist hip ratio (SD)	0.82 (0.09)	0.82 (0.09)
Mean duration of infertility (years) (SD)	1.5 (1.06)	1.3 (0.87)
Menarche (years) (SD)	13 (1.7)	13 (1.7)
Parity *N* (%)		
Nulliparous	77 (84)	83 (87)
Uni/multiparous	15 (16)	12 (13)

SD, standard deviation.

The patient flow during the trial is presented in Fig. 1. Within 16 weeks of randomization, 22 of the 85 women (26%) in the metformin group had a clinical pregnancy that resulted in an ongoing pregnancy, compared with 26 of 87 women (30%) in the placebo group.

Results of the HRQoL comparisons are presented in Table 2 and graphically in Fig. 2. Women allocated to metformin had significantly more physical symptoms than women allocated to placebo. The effect was most pronounced at Week 1 [mean difference 12 (95% CI: 8–16)], but persisted at Week 16 [mean difference 7 (95% CI: 2–12)]. The most frequent side-effects were abdominal aches, flatulence, nausea, lack of appetite and tiredness.

Psychological distress and activity level, as measured by the RSCL (De Haes *et al.*, 1996), were comparable between the two groups. However overall quality of life was lower in the metformin group than in the placebo group. This effect was most marked at Week 1 [mean difference 13 (95% CI: 6–20)]. The mixed model analysis found no time effect and no interaction with treatment for any of the four subscales. A time effect was found only for physical symptoms. Pregnancy had a negative effect on physical symptoms only: pregnant women had higher symptom scores. CC use had no effect on any of the subscales.

Discussion

This study compared the HRQoL in women with PCOS undergoing ovulation induction with either CC and metformin or CC and placebo. In the intention-to-treat analysis, we observed differences between study groups on physical well-being, which we attribute to the side-effects of metformin. Physical well-being was lowest 1 week after the metformin treatment and slowly recovered thereafter, although the effect was still apparent at 16 weeks after randomization. The overall quality of life was also lower in women treated with metformin at all time points.

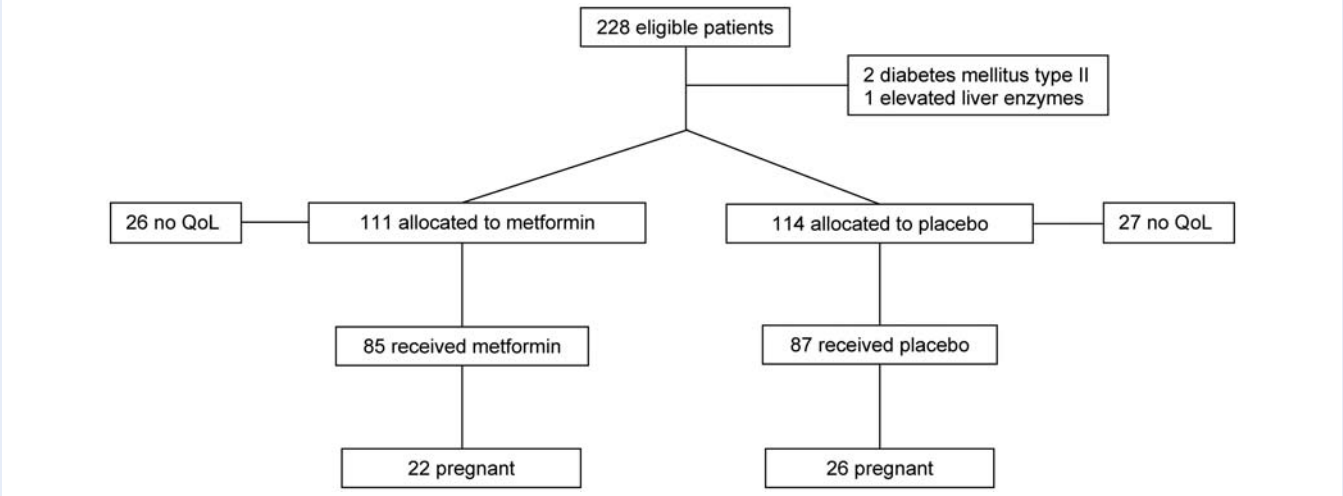

Figure 1 An overview of the clinical trial.

Table 2 Specification of the results from the RSCL.

Treatment	Time after randomization								
	Baseline	1 week	4 weeks	8 weeks	16 weeks	Reference	Treatment-effect	Time-effect	Pregnancy
RSCL									
Physical symptoms									
Metformin	13 (11)	26 (16)	22 (14)	18 (11)	19 (12)	10 (9)	**$P < 0.001$**	$P = 0.045$	**$P < 0.01$**
Placebo	13 (10)	14 (10)	15 (12)	13 (10)	11 (7)				
Psychological distress									
Metformin	16 (18)	14 (17)	11 (19)	13 (14)	11 (16)	17 (18)	$P = 0.32$	$P = 0.42$	$P = 0.19$
Placebo	16 (18)	11 (13)	16 (16)	15 (20)	11 (11)				
Activity level									
Metformin	1 (3)	3 (7)	2 (6)	1 (1)	1 (1)		$P = 0.45$	$P = 0.17$	$P = 0.48$
Placebo	1 (4)	1 (3)	1 (3)	1 (1)	1 (1)				
Overall quality of life									
Metformin	24 (17)	39 (19)	34 (22)	27 (16)	27 (19)	21 (84)	**$P < 0.001$**	$P = 0.08$	$P = 0.18$
Placebo	25 (18)	25 (17)	26 (19)	21 (17)	25 (13)				

Results are expressed as mean (SD); significant scores with $P < 0.01$ are bolded. The score at baseline was taken as a covariate in the analysis.
There was no interaction between changes in health-related quality of life over time and treatment group.
There was no significant effect of the use of CC.
The RSCL subscale scores were transformed into a 0–100 scale, with higher scores indicating a lower quality of life.

At baseline, the scores in both study groups for psychological distress, physical symptoms and overall quality of life were largely comparable with those of a normal healthy reference population of women (data not shown). There are no reference values available for the RSCL activity item, but as mean activity scores were all between 1 and 8 on a scale of 0–100 with higher scores indicating more problems, these women appeared to have a healthy activity level at treatment initiation.

This was the first study to evaluate the effect of metformin on quality of life in women with PCOS who are trying to conceive. The strength of this study was that it was done in a randomized setting. Women were blinded for the metformin treatment, as the metformin and placebo pills looked the same. Another strength was the number of patients included: 172 women returned the RSCL questionnaires. Two prior HRQoL studies in women with PCOS included 36 and 114 patients, respectively (Harris-Glocker *et al.*, 2010; Ladson *et al.*, 2011).

Recent systematic reviews concerning depression, anxiety and HRQoL in women with PCOS did not include women with PCOS treated with metformin (Barry *et al.*, 2011; Dokras *et al.*, 2011, 2012; Li *et al.*, 2011). The overall conclusion of these reviews is that women with PCOS have higher scores on depression and anxiety scales and lower scores for QoL than women without PCOS. In our study, there was no difference at baseline between the women with PCOS and the general population. An explanation might be the smaller number of patients in our study, leaving non-clinical distress undetected. Apart from that, our group of patients had a short interval between diagnosis and start of treatment. They might have experienced less stress because they did not have disappointments with treatment failures yet. Since most women in our study were not obese, differences in BMI may have also been an explanation. However, a higher BMI does not seem to have an association with higher scores on the depression and anxiety scales (Moll *et al.*, 2006; Jedel *et al.*, 2010; Dokras *et al.*, 2011, 2012; Li *et al.*, 2011).

A potential weakness of this study was that RSCL measurements were available only for three quarters of the participants. Though the number of missing questionnaires was comparable between the treatment groups and baseline values were comparable as well, some form of selection bias cannot be ruled out. In HRQoL studies missing values especially pose problems when the absence of a value at a certain point in time is related to the severity of disease of the patient (Fielding *et al.*, 2009).

We used the RSCL to measure HRQoL. Many instruments are available to measure HRQoL. In recent studies that measured HRQoL in women with PCOS, a PCOS-specific QoL questionnaire was used (PCOSQ) (Cronin *et al.*, 1998; Guyatt *et al.*, 2004). Since the women included in our study were initially healthy and given that CC and metformin are relatively innocent drugs, we did not expect large differences in general HRQoL domains, such as social functioning. Since side-effects such as nausea and diarrhoea are commonly described following metformin use, we chose to use the RSCL, because this questionnaire focuses more on symptoms than some of the other questionnaires, such as the PCOSQ or the FertiQoL (Lord *et al.*, 2003; Jones *et al.*, 2004; Boivin *et al.*, 2011). Neither the PCOSQ nor the FertiQoL contains specific questions about the side-effects of treatment. The effects of treatment on daily activities and work and physical effects of treatment are only optional questions in the FertiQoL.

As ovulation induction with metformin requires three to four tablets to be ingested daily and since many women experience side-effects, we did expect that ovulation induction with metformin would be physically more burdensome to women. These side-effects lasted a long

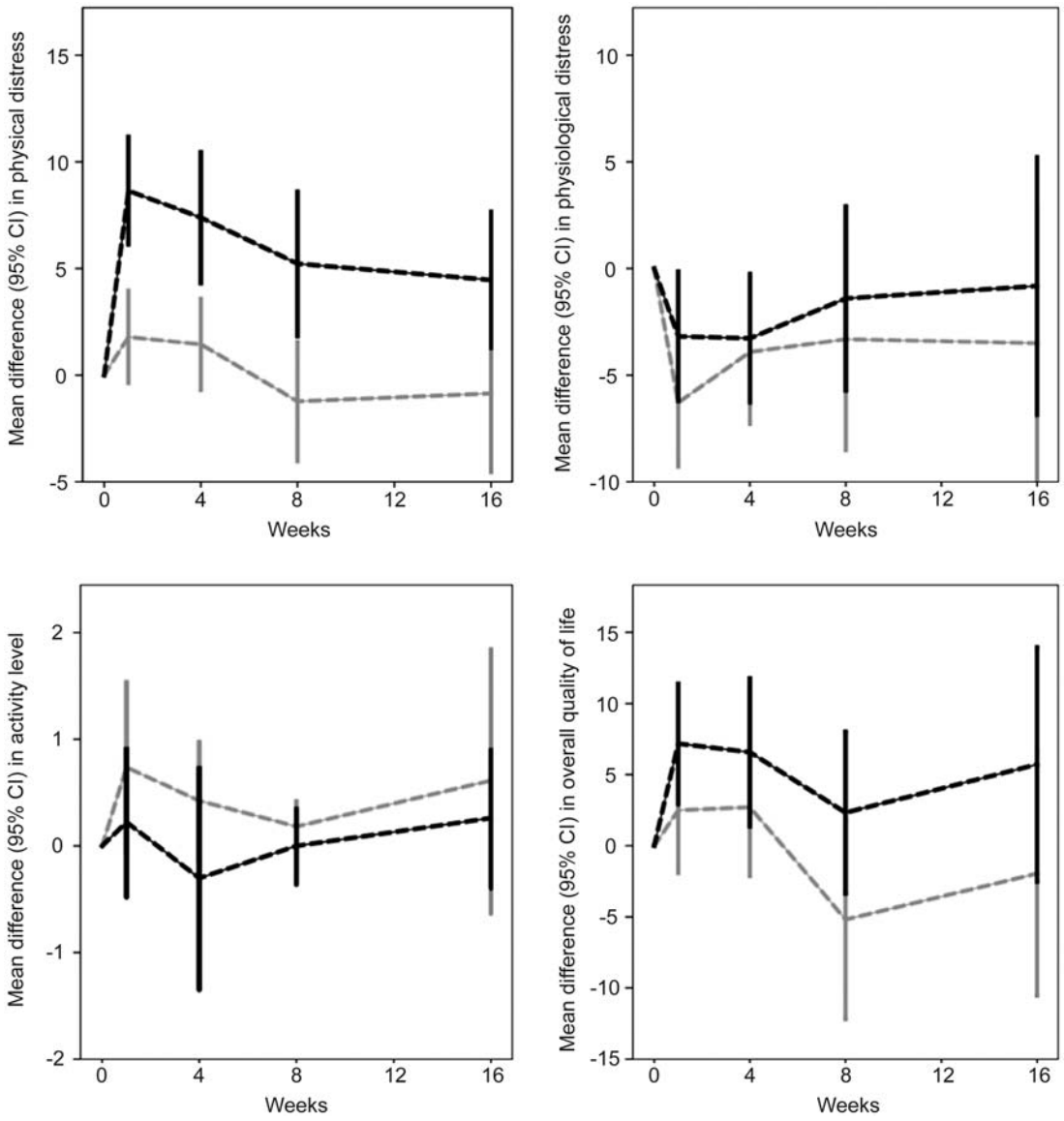

Figure 2 Mean differences in the four subscales of the RSCL with 95% CI, compared with the baseline measurements at the different time-points. Black dots represent women who were being treated with metformin, grey dots represent women who had been allocated to placebo.

time, even at 16 weeks the women in the metformin group had more physical symptoms than those in the placebo group.

For clinical practice, it requires explanation to the patients that metformin is likely to produce more side-effects. In some groups of patients (i.e. those who are clomifene resistant), metformin can offer better chances of ovulation (Moll *et al.*, 2007). These two potential effects should be taken into account when prescribing metformin to a patient. Nevertheless, besides our own randomized trial, another large clinical trial and a Cochrane review demonstrated that metformin does not increase live birth rate compared with CC treatment in women with PCOS (Legro *et al.*, 2007; Tang *et al.*, 2012). Hence, there are only limited reasons for using metformin in ovulation induction with clomifene.

Our finding that metformin was more burdensome for women's HRQoL than placebo only strengthens the recommendation that CC alone, and not CC plus metformin, should be the drug of choice in this patient population.

Authors' roles

E.M. conducted the trial and wrote the manuscript. M.W. was responsible for the statistical calculations and reviewed the manuscript. P.B. supervised the progression of the study and reviewed the manuscript. F.V. was involved in study design and set-up and reviewed the manuscript. He is also the guarantor of the trial.

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Conflict of interest

None declared.

References

Barbieri RL. Hyperandrogenism, insulin resistance and acanthosis nigricans. 10 years of progress. *J Reprod Med* 1994;**39**:327–336.

Barry JA, Kuczmierczyk AR, Hardiman PJ. Anxiety and depression in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod* 2011;**26**:2442–2451.

Boivin J, Takefman J, Braverman A. The fertility quality of life (FertiQoL) tool: development and general psychometric properties. *Hum Reprod* 2011;**26**:2084–2091.

Cronin L, Guyatt G, Griffith L, Wong E, Azziz R, Futterweit W, Cook D, Dunaif A. Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). *J Clin Endocrinol Metab* 1998;**83**:1976–1987.

De Haes JC, Olschewski M, Fayers P, Visser MR, Cull A, Hopwood P, Sanderman R. *Measuring the Quality of Life of Cancer Patients with the Rotterdam Symptom Checklist (RSCL): a Manual*. The Netherlands: Northern Center for Health Research, University of Groningen, Groningen, 1996.

Dokras A, Clifton S, Futterweit W, Wild R. Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Obstet Gynecol* 2011;**117**:145–152.

Dokras A, Clifton S, Futterweit W, Wild R. Increased prevalence of anxiety symptoms in women with polycystic ovary syndrome: systematic review and meta-analysis. *Fertil Steril* 2012;**97**:225–230.

Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev* 1997;**18**:774–800.

Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 1989;**38**:1165–1174.

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**:2357–2362.

ESHRE/ASRM. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;**19**:41–47.

Fielding S, Fayers PM, Ramsay CR. Investigating the missing data mechanism in quality of life outcomes: a comparison of approaches. *Health Qual Life Outcomes* 2009;**7**:57.

Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med* 1997;**103**:491–497.

Guyatt G, Weaver B, Cronin L, Dooley JA, Azziz R. Health-related quality of life in women with polycystic ovary syndrome, a self-administered questionnaire, was validated. *J Clin Epidemiol* 2004;**57**:1279–1287.

Harris-Glocker M, Davidson K, Kochman L, Guzick D, Hoeger K. Improvement in quality-of-life questionnaire measures in obese adolescent females with polycystic ovary syndrome treated with lifestyle changes and oral contraceptives, with or without metformin. *Fertil Steril* 2010;**93**:1016–1019.

Homburg R. What is polycystic ovarian syndrome? A proposal for a consensus on the definition and diagnosis of polycystic ovarian syndrome. *Hum Reprod* 2002;**17**:2495–2499.

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**:91–97.

Jedel E, Waern M, Gustafson D, Landen M, Eriksson E, Holm G, Nilsson L, Lind AK, Janson PO, Stener-Victorin E. Anxiety and depression symptoms in women with polycystic ovary syndrome compared with controls matched for body mass index. *Hum Reprod* 2010;**25**:450–456.

Jones GL, Benes K, Clark TL, Denham R, Holder MG, Haynes TJ, Mulgrew NC, Shepherd KE, Wilkinson VH, Singh M *et al*. The polycystic ovary syndrome health-related quality of life questionnaire (PCOSQ): a validation. *Hum Reprod* 2004;**19**:371–377.

Ladson G, Dodson WC, Sweet SD, Archibong AE, Kunselman AR, Demers LM, Williams NI, Coney P, Legro RS. The effects of metformin with lifestyle therapy in polycystic ovary syndrome: a randomized double-blind study. *Fertil Steril* 2011;**95**:1059–1066.

Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, Steinkampf MP, Coutifaris C, McGovern PG, Cataldo NA *et al*. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med* 2007;**356**:551–566.

Li Y, Li Y, Yu Ng EH, Stener-Victorin E, Hou L, Wu T, Han F, Wu X. Polycystic ovary syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from a meta-analysis. *Fertil Steril* 2011;**96**:452–458.

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; CD003053.

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. *Br Med J* 2006; **332**:1485.

Moll E, van der Veen F, van Wely M. The role of metformin in polycystic ovary syndrome: a systematic review. *Hum Reprod Update* 2007; **13**:527–537.

Moran L, Teede H. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. *Hum Reprod Update* 2009;**15**:477–488.

Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2010;**16**:347–363.

Nestler JE. Insulin regulation of human ovarian androgens. *Hum Reprod* 1997;**12**(Suppl 1):53–62.

Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med* 1998;**338**:1876–1880.

O'Meara NM, Blackman JD, Ehrmann DA, Barnes RB, Jaspan JB, Rosenfield RL, Polonsky KS. Defects in beta-cell function in functional ovarian hyperandrogenism. *J Clin Endocrinol Metab* 1993; **76**:1241–1247.

Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst Rev* 2012;**5**:CD003053.

Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. *Metabolism* 1994; **43**:647–654.

Zwinderman AH. Statistical analysis of longitudinal quality of life data with missing measurements. *Qual Life Res* 1992;**1**:219–224.