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REVIEW

Mono-ovulation in women with polycystic ovary syndrome: a clinical review on ovulation induction

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Abstract Polycystic ovary syndrome (PCOS) affects 5–10% of women of reproductive age and is the most common cause of anovulatory infertility. The treatment approaches to ovulation induction vary in efficacy, treatment duration and patient friendliness. The aim was to determine the most efficient, evidence-based method to achieve mono-ovulation in women diagnosed with PCOS. Publications in English providing information on treatment, efficacy and complication rates were included until September 2015. Systematic reviews, meta-analyses and randomized controlled trials were favoured over cohort and retrospective studies. Clomiphene citrate is recommended as primary treatment for PCOS-related infertility. It induces ovulation in three out of four patients, the risk of multiple pregnancies is modest and the treatment is simple and inexpensive. Gonadotrophins are highly efficient in a low-dose step-up regimen. Ovulation rates are improved by lifestyle interventions in overweight women. Metformin may improve the menstrual cycle within 1–3 months, but does not improve the live birth rate. Letrozole is effective for ovulation induction, but is an off-label drug in many countries. Ovulation induction in women with PCOS should be individualized with regard to weight, treatment efficacy and patient preferences with the aim of achieving mono-ovulation and subsequently the birth of a singleton baby.

KEYWORDS: assisted reproduction, BMI, clomiphene citrate, infertility, PCOS

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Introduction

Polycystic ovary syndrome (PCOS) affects 5–10% of women of reproductive age and is the most common cause of anovulatory infertility (ESHRE Capri Workshop Group, 2012). The prevalence of PCOS depends on the diagnostic criteria used. According to the Rotterdam criteria, PCOS is characterized by at least two of the following three features: oligo- or anovulation (clinical); biochemical hyperandrogenism, or both; and polycystic ovarian morphology (PCOM) (ESHRE REA-SPCWG, 2004). In recent years, the Rotterdam criteria have been challenged by reports of a high prevalence of PCOM among young ovulatory women, partly due to the improvement in ultrasound technology (Duijkers and Klipping, 2010). It has been discussed whether the antral follicle threshold for the definition of PCOM should be changed or whether anti-Müllerian hormone could be used as an alternative marker of PCOM (Dewailly et al., 2011; Kristensen et al., 2010; Lauritsen et al., 2015).

Polycystic ovary syndrome is a heterogeneous disorder, ranging from anovulatory women with polycystic ovaries without signs of hyperandrogenism to women with severe metabolic disturbance. The increased risk of type 2 diabetes and cardiovascular disease is associated with the increased prevalence of obesity in women with PCOS (Domecq et al., 2013; ESHRE Capri Workshop Group, 2012). Moreover, ethnic variations in the presentation of symptoms of PCOS also play a role in the decision of treatment strategy (Alebic et al., 2015; Wijeyaratne et al., 2011).

Several approaches to ovulation induction exist in women with PCOS. These approaches vary in efficacy, treatment duration and patient compliance. Moreover, new treatment strategies are continuously being introduced. A clinical update focusing on the current evidence-based practice is therefore highly warranted.

Materials and methods

Search methods, eligibility criteria and outcomes of interest were specified in advance. Outcomes of interest were chosen based on the following objectives of treatment efficacy: cycle regulation, ovulation, live birth rate, multiple births, patient friendliness and side-effects.

Sources

A systematic search of *MEDLINE*, *EMBASE*, and the *Cochrane Library* was conducted on all articles published up to September 2015. Additional records were identified by reference lists in retrieved articles.

Study selection

Eligible articles were published in peer-reviewed journals and written in English. Articles not reporting on ovulation induction in the title or abstract were not included. Full-text articles were screened and the final inclusion decisions were made according to the following criteria: original studies, systematic reviews or meta-analyses; primary or first-line treatment and, if necessary, secondary treatment described; and treatment success, complications and side-effects described.

In the selected publications, data on treatment modalities were collected by two authors (KBP and NCF) (**Tables 1** and **2**). The treatment modalities were divided into six main subjects: clomiphene citrate; exogenous gonadotrophins; metformin; lifestyle intervention; laparoscopic ovarian drilling (LOD); and letrozole.

Study quality assessment

Two authors (KBP and NCF) assessed the quality of the selected articles (**Tables 1** and **2**). The level of evidence was determined in accordance with the Oxford Centre for Evidence Based Medicine guidelines (Phillips et al., 2009).

Results

Details of the included meta-analyses are presented in **Table 1**. The cited randomized controlled trials (RCTs) are presented in **Table 2**.

Clomiphene citrate

Clomiphene citrate can be used as first-line treatment for women with PCOS. Clomiphene citrate is inexpensive and simple to use, and may lead to ovulation in about 75% of patients. Clomiphene citrate treatment includes only a low risk of multiple gestations.

Clomiphene citrate has been used for ovulation induction for more than 5 decades (Greenblatt et al., 1961). It is administered daily for 5 days after a spontaneous or a progestogen-induced menstrual bleeding. The treatment can be initiated on cycle day 2, 3, 4 or 5 (Wu and Winkel, 1989). About 15–40% of women with PCOS are clomiphene citrate resistant (CCR) with no follicle development after a dose of 150 mg clomiphene citrate per day for 5 days (Abu Hashim et al., 2015). The definition of clomiphene citrate failure varies but is frequently defined as no conception despite ovulation during six cycles (Homburg, 2005; ESHRE, 2008). The clomiphene citrate treatment recommendations are presented in **Figure 1**. The evaluation of clomiphene citrate for ovulation induction in relation to efficacy, advantages and disadvantages is presented in **Figure 2**.

Clomiphene citrate dosing

A meta-analysis reported the following ovulation rates after 5 days of treatment for the following different doses: 46% (50 mg), 70% (100 mg), 76% (150 mg) and 85–90% > 150 mg (Rostami-Hodjegan et al., 2004). Another study showed an ovulation rate of 73% and a pregnancy rate of 36% in a collection of data from 5268 patients (Homburg, 2005). The ovulation rates and the probability of pregnancy are reported to be similar with treatment start on day 2, 3, 4 or 5 of the cycle (Wu and Winkel, 1989). The side-effects are dose-dependent. Doses lower than 50 mg/day may be considered for women

Table 1 Details of the included meta-analyses.

Reference	*Study design, sample size (n)*	*Patients*	*Comparison*	*End point(s)*	*Results*	*P-value/95% CI*	*Comments*	*Conclusion of the present study*	*Level of evidence (1)*	*Country of origin*
Clomiphene citrate										
Rostami-Hodjegan et al. (2004)	Meta-analysis including 13 studies ($n = 1762$)	Not described in detail	Dose–response relationship of clomiphene	Ovulation rate	Ovulation rate of: 46% (50 mg*1), 70% (50 mg*2), 76% (50 mg*3) 85–90% after >150 mg* 5	$P < 0.0001$	Old studies, but based on a large cohort ($n = 1760$)	Case reports indicated that dosage based on plasma drug concentration monitoring could improve patient management, and an algorithm is proposed to facilitate treatment	1a	UK
Gonadotrophins										
Abu Hashim et al. (2015)	Meta-analysis including eight studies ($n = 1373$)	Women with PCOS and CC resistance	Metformin + CC vs. gonadotrophins: ovulation rate: three studies metformin + CC ($n = 160$) vs. gonadotrophins ($n = 163$); pregnancy rate: three studies metformin + CC ($n = 160$) vs. gonadotrophins ($n = 163$) ;	Ovulation rate; clinical pregnancy rate	Metformin + CC caused fewer ovulations (OR 0.25) and pregnancies (OR 0.45)	Ovulation rate: $P < 0.00001$ 95% CI (0.15 to 0.41); pregnancy rate: $P < 0.002$ 95% CI (0.27 to 0.75)	Most trials were conducted in North Africa (Egypt) and Asia. Subgroup analysis according to PCOS phenotype was not possible. The dose of metformin administered varied.	There is evidence for the superiority of gonadotrophins, but the metformin + CC combination is mainly relevant for clomiphene-resistant PCOS patients and, if not effective, a next step could be gonadotrophins. More attempts with metformin + CC are only relevant if there is limited access to gonadotrophins.	1a	Egypt
			Metformin + CC vs. LOD: ovulation rate: two studies metformin + LOD ($n = 163$) vs. gonadotrophins ($n = 169$); pregnancy rate: two studies metformin + CC ($n = 163$) vs. LOD ($n = 169$)		No difference in ovulations (OR 0.88) or pregnancies (OR 0.96)	Ovulation rate: $P =$ NS; 95% CI (0.53 to 1.47); pregnancy rate: $P =$ NS; 95% CI (0.60 to 1.54)				
			Metformin + CC vs. aromatase inhibitors: ovulation rate: three studies metformin + CC vs. aromatase inhibitors ($n = 409$ total); pregnancy rate: two studies metformin + CC vs. aromatase inhibitors ($n = 309$ total)		No difference in ovulations (OR 0.88) or pregnancies (OR 0.96)	Ovulation rate: $P =$ NS 95% CI (0.58 to 1.34); pregnancy rate: $P =$ NS; 95% CI (0.53 to 1.36)				
Nahuis et al. (2010)	Meta-analysis including six studies ($n = 862$)	Infertile women with PCOS (WHO group II) and CC resistance or CC failure	Recombinant gonadotrophins with urinary gonadotrophins	Ovulation rate; LBR rate; ongoing pregnancy rate; clinical pregnancy rate	Ovulation rate (OR 1.40); LBR (OR 1.12); ongoing pregnancy rate (OR 1.27); clinical pregnancy rate (OR 1.13)	Ovulation rate: 95% CI (1.03 to 1.92); LBR: 95% CI (0.75 to 1.66); ongoing pregnancy rate: 95% CI (0.78 to 2.07); clinical pregancy rate: 95% CI (0.67 to 1.89)	Ovulation rate was reported in all six studies; LBR in four; ongoing and clinical pregnancy rate in three studies.	No difference in effectiveness, safety and tolerability between recombinant and urinary follitropins.	1a	The Netherlands
Weiss et al. (2015)	Meta-analysis including 14 studies ($n = 1726$)	Infertile women with PCOS (WHO group II) and CC resistance	Recombinant FSH vs. urinary gonadotropins (10 RCTs) purified FSH vs. human menopausal gonadotrophin (four RCTs)	LBR pregnancy rate OHSS	Recombinant FSH vs. urinary gonadotrophins: LBR: OR 1.26; pregnancy rate: 1.08; OHSS 1.52	LBR: 95% CI (0.80 to 1.99); pregnancy rate: 95% CI (0.83 to 1.39); OHSS: 95% CI (0.81 to 2.84);	LBR: $I^2 = 65\%$ OHSS: $I^2 = 65\%$; low rated quality of evidence.	No evidence of a difference in live birth and OHSS rates between urinary-derived gonadotrophins and recombinant FSH or human menopausal gonadotrophin and highly purified human menopausal gonadotrophin. Evidence for all outcomes was of low or very low quality	1a	The Netherlands
					Purified FSH vs. human menopausal gonadotrophin: LBR: OR 1.36; pregnancy rate: OR 1.44; OHSS: OR 9.95	LBR: 95% CI (0.58 to 3.18); pregnancy rate: 95% CI (0.55 to 3.77); OHSS: 95% CI (0.47 to 210)	LBR: $I^2 = 0\%$ Low to very low rated quality of evidence			

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Table 1 (*continued*)

Reference	*Study design, sample size (n)*	*Patients*	*Comparison*	*End point(s)*	*Results*	*P-value/95% CI*	*Comments*	*Conclusion of the present study*	*Level of evidence (1)*	*Country of origin*
Metformin										
Tang et al. (2012)	Meta-analysis including 32 studies	Women with PCOS, oligo amenorrhoea and subfertility	Metformin vs. placebo: ovulation rate: 17 studies metformin ($n = 614$) vs. placebo ($n = 594$); pregnancy rate: eight studies: metformin ($n = 359$) vs. placebo ($n = 349$); LBR: three studies: metformin ($n = 57$) vs. placebo ($n = 58$)	Ovulation rate; clinical pregnancy rate; LBR	Ovulation rate: OR 1.8; pregnancy rate: OR 2.31; LBR: OR 1.8	Ovulation rate: $P < 0.01$; 95% CI (1.13 to 2.93); pregnancy rate: $P < 0.0001$; 95% CI (1.52 to 3.51); LBR: P = NS; 95% CI (0.52 to 6.16)	Ovulation rate: $I^2 = 48\%$; pregnancy rate: $I^2 = 45\%$; LBR: $I^2 = 0\%$	Metformin was associated with improved clinical pregnancy but there was no evidence that metformin improves live birth rates whether it is used alone or in combination with CC, or when compared with CC. Therefore, the role of metformin in improving reproductive outcomes in women with PCOS seems to be limited.	1a	UK
			Metformin + CC vs. CC: ovulation rate: 18 studies metformin + CC ($n = 1630$) vs. CC ($n = 1635$) pregnancy rate: 11 studies: metformin + CC ($n = 603$) vs. CC ($n = 605$); LBR: seven studies: Metformin + CC ($n = 451$) vs. CC ($n = 456$)		Ovulation rate: OR 1.73; pregnancy rate: OR 1.51; LBR: OR 1.16	Ovulation rate: $P < 0.0002$; 95% CI (1.50 to 2.00); pregnancy rate: $P < 0.04$; 95% CI (1.17 to 1.96); LBR: P = NS; 95% CI (0.85 to 1.56)	Ovulation rate: $I^2 = 62\%$; pregnancy rate: $I^2 = 49\%$; LBR: $I^2 = 35\%$			
Misso et al. (2013)	Meta-analysis including four studies ($n = 465$)	Infertile, non-obese women with PCOS (BMI < 32 kg/m^2)	Metformin vs CC: pregnancy rate: four studies; metformin ($n = 232$) vs. CC ($n = 233$) LBR: three studies; metformin ($n = 142$) vs. CC ($n = 143$)	PR LBR	Risk ratio: pregnancy rate: 0.98	Pregnancy rate: P = NS; 95% CI (0.49 to 1.96)	$I^2 = 80\%$	Owing to conflicting findings and heterogeneity across the included RCTs, there is insufficient evidence to establish a difference between metformin and clomiphene citrate in terms of ovulation, pregnancy, live birth, miscarriage and multiple pregnancy rates in women with PCOS and a BMI < 32 kg/m^2	1a	Australia
					LBR: 0.84	LBR: P = NS 95% CI (0.22 to 3.26)	$I^2 = 90\%$			
Xiao et al. (2012)	Meta-analysis including eight studies ($n = 1487$)	Women with PCOS <35 years	CC vs. metformin; ovulation rate: three studies: metformin (cycles = 1262) vs. CC (cycles = 1202); pregnancy rate: four studies ($n = 766$); spontaneous abortion: two studies ($n = 134$)	Ovulation rate; clinical pregnancy rate; spontaneous abortion rate	Ovulation rate: OR 0.48 in favour of CC vs. metformin pregnancy rate: OR 0.94; spontaneous abortion: OR 0.63	OR: $P < 0.01$ 95% CI (0.26 to 0.87); pregnancy rate: P = NS; 95% CI (0.26 to 3.43); P = NS 95% CI (0.06 to 6.47)	Large heterogeneity: random effects models used	Compared with CC, metformin used for ovulation induction treatment in women with PCOS can promote ovulation induction and pregnancy rate; the effect of the combination treatment is better than that of a single drug use.	1a	China
			CC + metformin vs. CC OR: six studies (cycles = 2295) pregnancy rate: six studies ($n = 969$ patients); spontaneous abortion: three studies ($n = 248$)		Ovulation rate: OR 1.52 in favour of CC + metformin vs. CC; pregnancy rate: OR 1.56 Spontaneous abortion: OR 1.40	OR: P = NS; 95% CI (0.95 to 2.45); pregnancy rate: $P < 0.003$ 95% CI (1.16 to 2.08) Miscellaneous: P = NS; 95% CI (0.79 to 2.48)	Ovulation rate: large heterogeneity: random effects models used; pregnancy rate: no heterogeneity (Ixl = 26%): fixed-effects model used; miscellaneous: fixed model used.			

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Table 1 (*continued*)

Reference	Study design, sample size (n)	Patients	Comparison	End point(s)	Results	P-value/95% CI	Comments	Conclusion of the present study	Level of evidence (1)	Country of origin
Siebert et al. (2012)	Meta-analysis including 14 studies (n = 2240)	Women with PCOS	Eight studies: CC + metformin vs. CC; ovulation rate: metformin + CC (n = 416) vs. CC (n = 481) four studies: LBR: metformin + CC (n = 393) vs. CC (n = 397) Two studies: ovulation rate: CC (n = 1163) vs. metformin (n = 1224); four studies: LBR: CC (n = 300) vs. metformin (n = 312) 10 studies: pregnancy rate: CC (n = 628) vs. CC + metformin (n = 622); four studies: pregnancy rate women with BMI >25 kg/m2: CC (n = 264) vs. CC + metformin (n = 260)	Ovulation rate; pregnancy rate; LBR	Ovulation rate: OR 1.60 in favour of CC + metformin vs CC; LBR: 1.09 Ovulation rate: OR 0.48 in favour of CC vs metformin LBR: 0.48 Pregnancy rate: OR 1.3; pregnancy rate: OR 1.22	OR: P < 0.00001; 95% CI (1.21 t o2.11) LBR: P = NS; 95% CI (0.78 to 1.51) Ovulation rate: P < 0.00001; 95% CI (0.41 to 0.57) LBR: P < 0.0006; 95% CI (0.31 to 0.73) Pregnancy rate: P < 0.05 95% CI (1.0 to 1.6); pregnancy rate: P = NS 95% CI (0.82 to 1.83)	Substantial difference in the number of patients in the included study groups. Trials including CC resistant women were excluded. Weakness: High heterogenity among included studies	CC alone is superior to M alone regarding live birth rate and ovulation. The combination (CC + M) is superior to CC alone as a primary method for ovulation induction and to achieve pregnancy in PCOS. However, when addressing live birth rate, no statistically significant difference could be demonstrated.	1a	South Africa
Naderpoor et al. (2015)	Meta-analysis including nine studies (n = 483)	Women with PCOS	Metformin + lifestyle intervention vs. placebo + lifestyle intervention: BMI: nine studies. Metformin + lifestyle intervention (n = 247) vs. placebo + lifestyle intervention (n = 246); menstrual cycle regulation: three studies. Metformin + lifestyle intervention (n = 35) versus placebo + lifestyle intervention (n = 35)	BMI; menstrual cycle regulation	Mean difference: BMI: −0.73 Mean difference: menstrual cycle/6 months: 1.06	BMI: P < 0.0005 95% CI (-1.14;-0.23) Menstrual cycle: P < 0.006 95% CI (0.30 to 1.82)	Heterogeneity across the studies was limited; however, most studies had small sample sizes (I^2 = 0%)	Lifestyle + metformin is associated with lower BMI and subcutaneous adipose tissue and improved menstruation in women with PCOS compared with lifestyle + placebo over 6 months. Metformin alone compared with lifestyle showed similar BMI at 6 months	1a	Australia
Palomba et al. (2014)	Meta-analysis including seven studies (n = 1023 cycles)	Infertile women with PCOS (WHO group II) and CC resistance or CC failure	Two studies: LBR: metformin + gonadotrophins (n = 298 cycles) vs. gonadotrophins (n = 363); seven studies: pregnancy rate: metformin + gonadotrophins (n = 438 cycles) vs. gonadotrophins (n = 504)	LBR PR	LBR: OR 1.94 Pregnancy rate: OR 2.25	LBR: P < 0.02; 95% CI (1.10 to 3.44) Pregnancy rate: P < 0.0001; 95% CI (1.50 to 3.38)	I^2 = 30%. Infertile PCOS populations with heterogeneous characteristics Different dose of metformin I^2 = 0%	Metformin administration increases the live birth and pregnancy rate in patient with PCOS who receive gonadotrophins for ovulation induction	1a	Italy
Cassina et al. (2014)	Meta-analysis including nine studies (n = 529)	Women with PCOS	To estimate the overall rate of major birth defects in women treated with metformin at least during the first trimester of their pregnancy. Nine studies. Metformin (n = 351) vs. controls (n = 178)	Major birth defects	OR: 0.86	Major birth defects: P = NS; 95% CI (0.18 to 4.08)	Small sample sizes. The quality of data is limited owing to extrapolation from studies which were not specifically designed to evaluate the rate of congenital defects. I^2 = 0%	There is currently no evidence that metformin is associated with an increased risk of major birth defects in women affected by PCOS and treated during the first trimester.	1a	Italy
Zhuo et al. (2014)	Meta-analysis including five studies	Women with PCOS	To determine the effect of metformin on gestational diabetes mellitus in PCOS. Five studies included: metformin (n = 143) vs. controls (n = 146)	Gestational diabetes mellitus in pregnancy	OR 1.07	95% CI (0.60 to 1.92); P = NS	Studies are very heterogeneous for protocols and doses of the drug administered and for characteristics of the studied populations. I^2 = 0%	Metformin did not significantly affect gestational diabetes mellitus with PCOS	1a	China

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Table 1 (*continued*)

Reference	*Study design, sample size (n)*	*Patients*	*Comparison*	*End point(s)*	*Results*	*P-value/95% CI*	*Comments*	*Conclusion of the present study*	*Level of evidence (1)*	*Country of origin*
Palomba et al. (2009)	Meta-analysis including 17 RCTs	Women with PCOS receiving pregestational metformin	Pregestational metformin treatment vs. no metformin treatment (combined with other treatments for ovulation induction or ovarian stimulation and IVF/intracytoplasmic sperm injection)	Spontaneous abortion rate (before week 20) (total number of spontaneous abortions per total number of pregnancies during treatment)	OR: 0.89	95% CI (0.65 to 1.21) P = NS	No statistically significant heterogeneity	Metformin has no effect on the spontaneous abortion risk in women with PCOS when administered before pregnancy	1a	Italy
Lifestyle interventions										
Moran et al. (2011)	Meta-analysis including six RCTs (n = 164)	Females of reproductive age with PCOS (and overweight or obese)	Lifestyle treatment (diet, exercise, behavioural or combined treatments) vs. minimal or no treatment; lifestyle vs. minimal treatment: total testosterone (five RCTs; 144 participants) Hirsutism or excess hair growth (four RCTs, 132 participants) Weight (two RCTs, 108 participants); waist circumference (two RCTs, 108 participants); fasting insulin (five RCTs, 144 participants)	Primary outcomes: pregnancy, live birth, spontaneous abortion, ovulation and menstrual regularity (no data); secondary outcomes: total testosterone, hirsutism or excess hair growth (Ferriman–Gallwey score), weight, waist circumference, fasting insulin	BIOLifestyle vs. minimal treatment: total testosterone mean difference −0.27 nmol/L levels. Hirsutism or excess hair growth: mean difference −1.19 Weight: mean difference −3.47 kg Waist circumference: mean difference −1.95 cm Fasting insulin: mean difference −2.02 μU/mL No evidence of effect of lifestyle for BMI, free androgen index, sex hormone binding globulin, glucose or cholesterol	Total testosterone: 95% CI (−0.46 to −0.09); $P < 0.004$ Hirsutism: 95% CI (−2.35 to −0.03); $P < 0.04$ 95% CI (−4.94 to −2.00); $P < 0.00001$ 95% CI (−3.34 to −0.57); $P < 0.006$ 95% CI (−3.28 to −0.77); $P < 0.002$. n/a	No studies found assessing fertility treatment primary outcomes and ovulation or menstrual regularity or quality of life and treatment satisfaction.	Lifestyle intervention improves body composition, hyperandrogenism, and insulin resistance in women with PCOS. No evidence of effect on improved glucose intolerance, lipid profiles and no literature assessing clinical reproductive outcomes, quality of life and treatment satisfaction.	1a	Australia
Haqq et al. (2015)	Meta-analysis including 12 RCTs (n = 668)	Women with PCOS	Lifestyle interventions (exercise and diet) vs. usual care. BMI: eight RCTs, 232 women; body weight: four trials, 82 women. Waist–hip ratio: two trials, 102 women	BMI, body weight, waist–hip ratio	BMI: mean difference −0.12 kg/m^2 Body weight: mean difference −3.42 Waist–hip ratio: mean difference −0.03	BMI: 95% CI (−0.22 to −0.03); $P < 0.009$ Body weight: 95% CI (−4.86 to −1.99); $P < 0.00001$ Waist–hip ratio: 95% CI (−0.05 to −0.01); $P < 0.002$	High heterogeneity in some of the analyses. Dietary interventions, metformin and oral contraceptives were used in some of the included trials.	Lifestyle intervention improves body composition, insulin, total and low-density lipoprotein-cholesterol, C-reactive protein and cardio-respiratory fitness in women with PCOS.	1a	Australia
Laparoscopic ovarian drilling										
Farquhar et al. (2012)	Meta-analysis including 25 RCTs (n = 1933)	Subfertile women with clomiphene-resistant PCOS	LOD vs. ovulation induction; LBR per couple (eight RCTs, 1034 women); clinical pregnancy (18 RCTs, 1930 women); multiple pregnancy (12 RCTs, 1129 women); spontaneous abortion rates (15 RCTs, 1592 women)	Primary outcome: LBR per couple; secondary outcomes: clinical pregnancy rate, multiple pregnancy, spontaneous abortion rates.	LBR per couple: 34% of women after LOD vs. 40% after other medical treatment groups (CC + tamoxifen, gonado-trophins, aromatase inhibitors); OR 0.77 Clinical pregnancy: OR 0.94 Multiple pregnancy: OR 0.21 Spontaneous abortion rates: OR 1.10	95% CI (0.59 to 1.01) Clinical pregnancy: 95% CI (0.78 to 1.14); P = NS 95% CI (0.08 to 0.58); $P < 0.002$ (in favour of LOD) 95% CI (0.74 to 1.61); P = NS	Limited number of studies. No blinding of the participants. Randomization was only described in 16/25 studies	No evidence of a significant difference in rates of clinical pregnancy, live birth or miscarriage. Reduction in multiple pregnancy rates after LOD but ongoing concerns about the long term effects of LOD on ovarian function.	1a	Australia

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Table 1 (*continued*)

Reference	*Study design, sample size (n)*	*Patients*	*Comparison*	*End point(s)*	*Results*	*P-value/95% CI*	*Comments*	*Conclusion of the present study*	*Level of evidence (1)*	*Country of origin*
Moazami Goudarzi et al. (2014)	Meta-analysis including six RCTs (n = 499)	Infertile women with PCOS (WHO group II) and CC resistance	LOD vs. gonadotrophins; Pregnancy rate: six RCTs; LBR: three RCTs; multiple pregnancies: three RCTs; spontaneous abortion: four RCTs	Pregnancy rate (primary outcome); LBR; multiple pregnancies; spontaneous abortion rate	Pregnancy rate: OR 0.53; pregnancy rate after LOD = 33% vs. pregnancy rate after gonadotrophin = 55%. LBR: OR 0.44 Multiple pregnancies: OR 0.12 Spontaneous abortion: OR 0.59	Pregnancy rate: 95% CI (0.24 to 1.18); P = NS LBR: 95% CI (0.26 to 0.74) Multiple pregnancies: 95% CI (0.03 to 0.57) Spontaneous abortion: 95% CI (0.27 to 1.29)	I^2 = 73.2% (pregnancy rate); random effects model used; LBR: I^2 = 3.35; multiple pregnancies: I^2 = 0%. Spontaneous abortion: I^2 = 0%.	No significant difference in clinical pregnancy rate and miscarriage rate between LOD and gonadotropin. Higher live birth rate after gonadotropin. Less multiple pregnancies following LOD. Suggest focus on long term effects of LOD on ovarian function.	1a	Iran
Aromatase inhibitors										
Franik et al. (2015)	Meta-analysis including 26 RCTs (n = 5560 women)	Anovulatory subfertile women with PCOS	Letrozole vs. placebo, CC and LOD LBR: Letrozole vs. placebo (one RCT, 36 CCR women); pregnancy rate: Letrozole vs. placebo (one RCT, 36 CCR women); LBR: letrozole vs. CC (nine RCTs, 1783 women); pregnancy rate: letrozole vs. CC and timed intercourse (15 RCTs, 2816 women); pregnancy rate: letrozole vs. CC and intrauterine insemination (three RCTs, 1597 women); LBR: letrozole vs. LOD (two RCTs, 407 women); pregnancy rate: letrozole (+metformin) vs. LOD (three RCTs, 553 women)	LBR; OHSS; Pregnancy rate	Letrozole vs. Placebo LBR: OR 3.17; clinical pregnancy: OR 3.17 Letrozole vs. CC; LBR: OR 1.64 Letrozole vs. CC and timed intercourse: clinical pregnancy: OR 1.40; letrozole vs. CC and IUI: clinical pregnancy: OR 1.71 Letrozole vs. LOD; LBR: OR 1.19 Letrozole (+metformin) vs. LOD CP: OR 1.14	LBR: 95% CI (0.12 to 83.17); clinical pregnancy: 95% CI (0.12 to 83.17) LBR: 95% CI (1.32 to 2.04); P = NS in favour of letrozole Clinical pregnancy (timed intercourse): 95% CI (1.18 to 1.65); clinical pregnancy (intrauterine insemination): 95% CI (1.30 to 2.25) LBR: 95% CI (0.76 to 1.86); P = NS; clinical pregnancy: 95% CI (0.80 to 1.65)	Low rated quality of evidence. Adjuncts were added in some of the trials.	Letrozole seems to improve live birth and pregnancy rates compared with CC. Seems to be no difference between letrozole and LOD. OHSS was rare.	1a	Netherlands/ New Zealand

CC, clomiphene citrate; CCR, clomiphene citrate resistant; IUI, intrauterine insemination; LBR, live birth rate; LOD, laparoscopic ovarian drilling; NS, not statistically significant; OHSS, ovarian hyperstiulation syndrome; PCOS, polycystic ovary syndrome.

Table 2 Details of the included randomized controlled trials.

Reference	*Study design, sample size (n)*	*Patients*	*Comparison*	*End point(s)*	*Results*	*P- value/95% CI*	*Comments*	*Conclusion of the present study*	*Level of evidence (1)*	*Country of origin*	*Published in Journal*
Clomiphene citrate											
Lopez et al. (2004)	RCT ($n = 76$)	Infertile women with anovulatory PCOS, age <40 years; first treatment cycle	CC (50–150 mg/day for 5 days) ($n = 38$) Recombinant FSH in a low-dose, step-up protocol (starting dose 75 IU/day) for up to three cycles ($n = 38$)	Women who ovulated at least once	RR 1.17 30/38 (79%) vs. 35/38 (92%)	P = NS; 95% CI 0.97 to 1.46	The trial was discontinued after 76 patients and 21 months because it was not possible to include the planned 152 women per treatment group in a reasonable time period	No significant difference in the ovulation rates	4	Spain	Reproductive Biomedicine Online
Leader (2006)	RCT ($n = 158$)	Anovulatory or oligo-ovulatory infertile women	In the absence of follicles ≥12 mm after 7 days, the daily dosage was increased by 25 IU vs. 50 IU/week	Ovulation rate Monofollicular development	81.3% (25 IU) vs. 60.3% (50 IU) 41.3% (25 IU) vs. 21.8% (50 IU)	Absolute difference: 18.6%, 95% CI (4.6 to 32.7); $P < 0.009$ Absolute difference: 19.3%, 95% CI (4.7 to 34.0); $P < 0.010$	Multicentre study ($n = 18$); absolute difference adjusted for centre. One treatment cycle (maximum 35 days).	Weekly increments of 25 IU in the daily dose were more effective and efficient than 50 IU increments	1b	Canada	Fertility and Sterility
Gonadotrophins											
Christin-Maitre and Hugues, 2003	RCT ($n = 83$)	Women with anovulatory infertility due to PCOS (WHO type II), CC resistance or CC failure	Low dose step-up protocol (44 patients, 85 cycles), starting dose: 50 IU recombinant FSH/day up to 14 days of the first cycle Step-down protocol (39 patients, 72 cycles); starting dose: 100 IU recombinant FSH daily until follicular development (>9 mm) or until day 6 of stimulation in the absence of follicular development. Hereafter the dose was decreased or increased.	Monofollicular development (one follicle >16 mm at the time of HCG administration)	68.2 vs. 32% Ovulation was observed in 70.3% of the cycles using the step-up procedure as compared with 51.3% using the step-down procedure ($P < 0.01$)	$P < 0.0001$	Multi-centre study ($n = 11$); up to three consecutive treatment cycles	The step-up protocol using recombinant FSH (Puregon), is more efficient in obtaining a monofollicular development and ovulation than the step-down protocol, in women with CC-resistant polycystic ovaries	1b	France	Human Reproduction
Homburg et al. (2012)	RCT ($n = 302$)	Infertile women with PCOS, age <40 years, first treatment cycle	CC (50–150 mg/day for 5 days) Recombinant FSH (starting dose 50 IU/day in a step up protocol	Pregnancy rate (per cycle and cumulative) LBR	All results were in favour of recombinant FSH: pregnancy rate per first cycle 30% vs. 14.6%; pregnancy rate per woman (58% vs. 44% of women); LBR per woman (52 vs. 39%); cumulative pregnancy rate (52.1 vs. 41.2%); cumulative LBR (47.4 vs. 36.9%) within three cycles of ovulation induction	Pregnancy rate first cycle: $P < 0.003$; 95% CI 5.3 to 25.8; pregnancy rate per woman: $P < 0.03$; 95% CI 1.5 to 25.8; LBR per woman: $P < 0.04$; 95% CI 0.4 to 24.6; cumulative pregnancy rate: $P < 0.021$; 95% CI 0.4 to 24.6; cumulative LBR: $P <$ 0.031	Up to three cycles per patient If no response: CC dose was increased in subsequent cycles. FSH was increased weekly with increments of 25 IU. Results listed are according to intention-to-treat analysis. Per protocol analysis revealed results that were more in favour of recombinant FSH	Pregnancies and live births are achieved more effectively and faster after OI with low-dose FSH than with CC. This result has to be balanced by convenience and cost in favour of CC. FSH may be an appropriate first-line treatment for some women with PCOS and anovulatory infertility.	1b	The Netherlands	Human Reproduction

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Table 2 (*continued*)

Reference	*Study design, sample size (n)*	*Patients*	*Comparison*	*End point(s)*	*Results*	*P- value/95% CI*	*Comments*	*Conclusion of the present study*	*Level of evidence (1)*	*Country of origin*	*Published in Journal*
Metformin											
Curi et al. (2012)	RCT ($n = 40$)	Women with PCOS, age 18–34 years; BMI >25; sedentary lifestyle (no exercise routine)	Six months of: Metformin 850 mg twice daily or lifestyle changes, including a nutritious diet where the daily intake was reduced by 500 kcal and a daily 40-min training programme	Menstrual pattern	Menstrual frequency: metformin group at baseline and after 6 months: 0.273 ± 1.6 and 0.675 ± 1.02 Lifestyle changes group at baseline and after six months: 0.330 ± 0.194 and 0.706 ± 0.097	$P < 0.001$	High drop out rate. Per protocol analysis only ($n = 27$).	Our data suggest that a 6-month treatment with either metformin or lifestyle changes improves the menstrual cycle pattern in PCOS.	4	Brazil	Gynecological Endocrinology
Legro et al. (2007)	RCT ($n = 626$)	Infertile women with PCOS	CC (100 mg for 5 days) Metformin 2000 mg CC + metformin	Ovulation rate; pregnancy rate; LBR	Ovulation rate: 462/942 (49.0%) vs. 296/1019 (29.0%) vs. 582/964 (60.4%) pregnancy rate: 50/209 (23.9%) vs. 18/208 (8.7%) vs. 65/209 (31.1%) LBR: 47/209 (22.5%) vs. 15/208 (7.2%) vs. 56/209 (26.8%)	Absolute difference between combination therapy and metformin: ovulation rate: 31.4% (24.7 to 38.0); pregnancy rate: 22.4% (15.0 to 29.8); LBR: 19.6% (12.6 to 26.6); absolute difference between CC and metformin: ovulation rate: 20.0% (9.1 to 30.9); pregnancy rate: 17.7% (10.1 to 25.3); LBR: 15.2% (8.3 to 22.1)	Woman were treated for up to six cycles, or 30 weeks. All study medication was discontinued if a pregnancy test was positive	Clomiphene is superior to metformin in achieving live birth in infertile women with the PCOS, although multiple birth is a complication	1b	USA	New England Journal of Medicine
Palomba et al. (2005)	RCT (n = 100)	Anovulatory women with PCOS, age 20–34, BMI ≤30 kg/m^2, primary infertile.	Metformin (850 mg x 2/day) + placebo CC (150 mg cd 3–5) + placebo	Ovulation rate PR	Ovulation rate: 205 cycles in 45 women (62.9%) vs. 221 cycles in 47 women (67.0%); pregnancy rate: 15.1 vs. 7.2%;	OvR: p = NS PR: p < 0.009	Up to six months treatment	Six month metformin administration is significantly more effective than six cycle CC treatment in improving fertility in anovulatory non-obese PCOS women	1b	Italy	Journal of Clinical Endocrinology and Metabolism
Johnson et al. (2010)	RCT ($n = 171$)	Women with anovulatory or oligo-ovulatory PCOS	BMI >32 kg/m^2 received metformin or placebo ("standard care") BMI ≤32 kg/m^2 received metformin, CC ("standard care") or both. Treatment continued for 6 months or until pregnancy was confirmed	Clinical pregnancy rate; LBR	pregnancy rate: 22% (7/32) vs. 15% (5/33); LBR: 16% (5/32) vs. 6% (2/33) PR: 40% (14/35) vs. 39% (14/36) vs 54% (19/35); LBR: 29% (10/35) vs. 36% (13/36) vs. 43% (15/35)	P = NS P = NS P = NS P = NS	Multicentre study; insufficiently powered	There is no evidence that adding metformin to "standard care" is beneficial. Pregnancy and live birth rates are low in women with BMI >32 kg/m^2 whatever treatment is used, with no evidence of benefit of metformin over placebo. For women with BMI ≤32 kg/m^2 there is no evidence of significant differences in outcomes whether treated with metformin, CC or both	1b	New Zealand	Human Reproduction

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Table 2 (*continued*)

Reference	*Study design, sample size (n)*	*Patients*	*Comparison*	*End point(s)*	*Results*	*P- value/95% CI*	*Comments*	*Conclusion of the present study*	*Level of evidence (1)*	*Country of origin*	*Published in Journal*
Morin-Papunen et al. (2012)	RCT ($n = 320$)	Infertile anovulatory women with PCOS, age 18–39 years; BMI >19 kg/m^2	Metformin vs. placebo for up to 9 months. Metformin dose: 500 mg + 1000 mg daily in non-obese women and 1000 mg + 1000 mg in obese women. After at least 3 months infertility treatment was combined if necessary	Spontaneous abortion rate Whole study population: pregnancy rate: LBR Pregnancy rate and LBR in non-obese and obese patients	Spontaneous abortion rate: 15.2% vs. 17.8% Pregnancy rate: 53.6 vs. 40.4%; LBR: 41.9 vs. 28.8% Non-obese women: pregnancy rate: 58.6 vs. 47.6%; LBR: 46.7 vs. 34.5%; obese women: pregnancy rate: 49.0 vs. 31.4%; LBR: 35.7 vs. 21.9%	P = NS $P < 0.006$ $P < 0.014$ Non-obese: pregnancy rate: P = NS; LBR: P = NS; obese: pregnancy rate: $P < 0.04$; LBR: P = NS	The population was divided into obese (BMI ≥27 kg/m2) and non-obese participants. If pregnancy occurred metformin was continued up to gestational week 12.	Obese women especially seem to benefit from 3 months' pre-treatment with metformin and its combination thereafter with routine ovulation induction in anovulatory infertility	1b	Finland	Journal of Clinical Endocrinolgy and Metabolism
Vanky et al. (2010)	RCT ($n = 257$)	Women with PCOS in the first trimester of pregnancy, aged 18–42 years	Metformin 2000 mg or placebo from first trimester to delivery	Preeclampsia; gestational diabetes mellitus; preterm delivery	Preeclampsia: 7.4 vs. 3.7%; gestational diabetes mellitus: 16.9 vs. 17.6%; preterm delivery: 8.2 vs. 3.7%	95% CI (−1.7 to 9.2); P = NS; 95% CI (−8.6 to 10.2); P = NS; 95% CI (−10.1 to 1.2); P = NS	Multicentre study. No subgroup analyses	Metformin treatment from first trimester to delivery did not reduce pregnancy complications in PCOS	1b	Norway	Journal of Clinical Endocrinology and Metabolism
Lifestyle interventions											
Nybacka et al. (2011)	RCT ($n = 54$)	Overweight/ obese women with PCOS, age 18 – 40 years	Dietary management Physical exercise Diet and exercise for 4 months and follow-up after at least 1year	Ovarian function, endocrinologic, and metabolic status and body composition	BMI (kg/m^2): dietary group: −1.74 (−2.66 to −0.81); BMI decrease: 6% Exercise group: −0.85 (−1.69 to −0.02) BMI decrease: 3% Diet and exercise group: −1.90 (−2.90 to −0.90) BMI decrease: 5%	$P < 0.001$	Similar improvement in the three groups of menstrual pattern; 14 patients dropped out	Dietary management and exercise, alone, or in combination, are equally effective in improving reproductive function in overweight/obese women with PCOS. The underlying mechanisms seem to involve enhanced insulin sensitivity. Supportive individualized programmes for lifestyle change could exert long-term beneficial effects	1b	Sweden	Fertility and Sterility
Palomba et al. (2010)	RCT (n = 96)	Overweight and obese CC-resistant PCOS patients, age 18 – 35 years	(A) Structured exercise training + hypocaloric diet for 6 weeks (B) 2 weeks of observation + one CC cycle (C) Structured exercise training + hypocaloric diet for 6 weeks + one CC cycle after the first 2 weeks	Ovulation rate after 6 weeks	(A) 4/32 (12.5%) (B) 3/32 (9.4%) (C) 12/32 (37.5%)	Relative risk (RR) for group C versus A: 3.9 (95% CI 1.1 to 8.3); $P <$ 0.035; pregnancy rate for group C versus B: 4.0; (95% CI 1.2 to 12.8); $P <$ 0.020)	Three-arm trial Short-term observation of the patients (6 weeks)	In overweight and obese CC-resistant PCOS patients, a 6-week intervention of structured exercise training and a hypocaloric diet was effective in increasing the probability of ovulation under CC treatment	1b	Italy	Human Reproduction

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Table 2 (*continued*)

Reference	*Study design, sample size (n)*	*Patients*	*Comparison*	*End point(s)*	*Results*	*P- value/95% CI*	*Comments*	*Conclusion of the present study*	*Level of evidence (1)*	*Country of origin*	*Published in Journal*
Legro et al. (2015)	RCT ($n = 149$)	Women with infertility owing to PCOS, age 18–40 years and body mass index 27–42 kg/m^2	16 weeks of preconception intervention and standardized ovulation induction with clomiphene citrate and timed intercourse for four cycles: (1) continuous oral contraceptive pills ($n = 49$);	Weight; ovulation rate LBR	Cumulative ovulation rate: 46%; LBR: 12%		The study was underpowered to detect a difference in live birth between the two lifestyle modification groups	A preconception weight loss intervention eliminates the adverse metabolic oral contraceptive effects and, compared with oral contraceptive pretreatment, leads to higher ovulation rates	1b	USA	Journal of Clinical Endocrinology and Metabolism
			(2) lifestyle modification consisting of caloric restriction with meal replacements, weight loss medication (either sibutramine, or orlistat), and increased physical activity to promote a 7% weight loss ($n = 50$) (lifestyle);		Lifestyle: mean weight loss −6.2% compared with continuous oral contraceptive pills: cumulative ovulation rate: 60%; LBR: 26%	Weight loss: 95% CI (−7.4 to −5.0); $P < 0.001$; lifestyle vs. combined: ovulation rate: RR 1.5 95% CI (1.1 to 1.9); $P < 0.002$					
			(3) combined treatment with both oral contraceptive pills and lifestyle modification ($n = 50$) (combined)		Combined: mean weight loss: −6.4% compared with continuous oral contraceptive pills; cumulative ovulation rate: 67%; LBR: 24%	Weight loss: 95% CI (−7.6 to −5.2); $P < 0.001$					
Laparoscopic ovarian drilling											
Nahuis et al. (2011)	RCT ($n = 168$)	CC resistant women with PCOS	LOD + rFSH – long term follow up after 8–12 years	LBR	Cumulative LBR 86%	LBR: RR 1.1; (95% CI 0.92 to 1.2); $P = NS$	The LOD group received further treatment with CC, recombinant FSH, intrauterine insemination or IVF if anovulation persisted after 6 months	In women with clomiphene-resistant PCOS, laparoscopic electrocautery of the ovaries is as effective as ovulation induction with FSH treatment in terms of live births, but reduces the need for ovulation induction or assisted reproduction techniques in a significantly higher proportion of women and increases the chance for a second child.	1b	The Netherlands	Human Reproduction
			Immediate recombinant FSH; long term follow up after 8–12 years		Cumulative LBR 81%						

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Table 2 (*continued*)

Reference	*Study design, sample size (n)*	*Patients*	*Comparison*	*End point(s)*	*Results*	*P- value/95% CI*	*Comments*	*Conclusion of the present study*	*Level of evidence (1)*	*Country of origin*	*Published in Journal*
Bayram et al. (2004)	RCT ($n = 168$)	CC resistant women with PCOS, age ≤40 years.	Laparoscopic electrocautery of the ovaries followed by CC and recombinant FSH if anovulation persisted Recombinant FSH	Ongoing viable pregnancy (at least 12 weeks pregnancy) within 12 months	56/83 (67%) 57/85 (67%)	Rate ratio 1.01; 95% CI (0.81 to 1.24) $P < 0.05$	Non-inferiority trial	The ongoing pregnancy rate from ovulation induction with laparoscopic electrocautery followed by clomiphene citrate and recombinant follicle stimulating hormone if anovulation persisted, or recombinant follicle stimulating hormone, seems equivalent to ovulation induction with recombinant follicle stimulating hormone, but the former procedure carries a lower risk of multiple pregnancy	1b	The Netherlands	BMJ
Aromatase inhibitors											
Ramezanzadeh et al. (2011)	RCT ($n = 67$)	Infertile patients with PCOS, age <35 years	Letrozole 5 mg 7.5 mg day 3 – 7 of a menstrual cycle	Total mean number of growing follicles ≥14 mm on days 12–14	1.97 ± 1.10 vs. 1.84 ± 1.01	P = NS	First cycle patients. No intention-to-treat analysis (67 patients were randomized)	The results of this study did not show any advantage to the use of 7.5 mg/day over 5 mg/day dose of letrozole as the first line treatment for induction of ovulation in women with PCOS	1b	Iran	Archives of Gynecology and Obstetrics

CC, clomiphene citrate; LFB: live birth rate; LOD, laparoscopic ovarian drilling; NS, not statistically significant; PCOS, polycystic ovary syndrome.

Recommendations:	**Consider:**			
1. Clomiphene citrate 50–100 mg*	**Lifestyle interventions** (in overweight women)	**letrozole*****	**Metformin******** (in overweight women)	**Ovarian drilling*********
2. Gonadotrophins. (Low-dose step-up protocol**)				
*A starting dose of 100 mg is recommended for obese women with BMI >30 kg/m^2, hyperandrogenism and/or amenorrhoea or women with a large ovarian volume. In case of response to treatment, six cycles are recommended.				
** Women with increased BMI and amenorrhoea often have a higher threshold value				
*** If Letrozole is approved as a labelled drug				
**** No effect on live birth rate. Treatment with metformin is controversial				
***** In women with clomiphene resistance and previous ovarian hyperstimulation syndrome or uncontrollable stimulations				

Figure 1 Treatment strategy for ovulation induction in women diagnosed with polycystic ovary syndrome. BMI, body mass index.

	Ovulation	Multiple pregnancies	Time to pregnancy	Ultrasound examinations	Side-effects	Patient compliance
Lifestyle interventions	↑					
Metformin	↑					
Clomiphene citrate	↑↑					
Letrozole	↑↑↑					
Gonadotrophins	↑↑↑					
Ovarian drilling	↑					

↑ Less likely to induce ovulation

↑↑ Likely to induce ovulation

↑↑↑ Most likely to induce ovulation

Green colour: The least discomfort / lowest risk for the patient

Yellow colour: Moderate discomfort / risk for the patient

Red colour: Inconvenience for the patient / highest risk

Figure 2 Evaluation of treatment modalities for ovulation induction in relation to efficacy, advantages and disadvantages.

who have experienced ovarian hyper response after a dose of 50 mg/day for 5 days (Dodge et al., 1986). The ovarian response is correlated to the body weight (Dickey et al., 2002; Lobo et al., 1982). High BMI, hyperandrogenaemia, amenorrhoea and a large ovarian volume predict a poor response to clomiphene citrate (Imani et al., 1998, 2000).

A Turkish pilot study included 60 patients with PCOS who did not respond to clomiphene citrate 50 mg/day for 5 days.

On cycle day 14, the patients were allocated to either clomiphene citrate 100 mg/day for 5 days ("stair-step protocol") or progestin-induced bleeding and a new clomiphene citrate cycle where the dose was increased to 100 mg/day for 5 days (Deveci et al., 2015). The ovulation and pregnancy rates per cycle did not differ significantly between the two groups (43.3 versus 33.3% and 16.7 versus 10.0%, but the duration of treatment was shorter in the stair-step group (20.5 ± 2.0 versus 48.6 ± 2.4 days; $P = 0.0001$).

The recommendation is currently six clomiphene citrate cycles, as the cumulative pregnancy rate among anovulatory women with PCOS is about 46% after four cycles and 65% after six clomiphene citrate cycles (Dickey et al., 2002).

Combination of clomiphene citrate and gonadotrophins

Veltman-Verhulst et al. (2012) reported a cumulative singleton live birth rate in patients with PCOS after treatment with conventional ovulation induction with clomiphene citrate followed by gonadotrophin stimulation in cases with CCR or clomiphene citrate failure within 2 years of 78% (Veltman-Verhulst et al., 2012). This corresponds well to the birth rate of 71% reported by Eijkemans et al. (2003) on the basis of the high pregnancy rate, a multiple pregnancy rate less than 3% and absence of ovarian hyperstimulation syndrome (OHSS), the authors concluded this treatment algorithm to be a relevant option for ovulation induction in patients with PCOS (Veltman-Verhulst et al., 2012).

Gonadotrophins

The low-dose, step-up protocol is recommended in the first gonadotrophin stimulation cycle in which the patient's FSH threshold value is unknown. The first step should last for a minimum of 7 days and subsequent dose increments should be small (25–37.5 IU).

Gonadotrophin stimulation is usually administered to women who are CCR as an effective second-line treatment, but can be used as first line (Abu Hashim et al., 2015; Lopez et al., 2004). As the polycystic ovary may be sensitive to gonadotrophin stimulation, careful dosage adjustment is recommended. Factors influencing the response are as follows: dose, stimulation regimen, number of stimulation days before dose adjustments and patient characteristics (**Figure 1**). Gonadotrophin stimulation is associated with a risk of OHSS and multiple gestations, which can be minimized by a low-dose step-up protocol (Calaf Alsina et al., 2003; Homburg and Howles, 1999).

The step-up protocol is characterized by a low starting dose of recombinant FSH or highly purified menotropin (37.5–50–75 IU/day), which can be increased if no response is detected after a minimum of 7 days (no increase in plasma oestradiol level/ no follicle ≥10 mm). The threshold dose, or a dose slightly below, can be used as the starting dose in subsequent cycles (Homburg and Howles, 1999). Patients with a higher body mass index (BMI) and amenorrhoea as opposed to oligomenorrhoea may have a higher threshold value (Imani et al., 2002).

In a cohort study including 945 treatment cycles in 343 women with a starting dose of 50 IU recombinant FSH/day, mono-ovulation was achieved in 61.3% of cycles (Calaf Alsina et al., 2003). Treatment was cancelled in 13.5% of cycles owing to either hyper response or spontaneous ovulation, and mild OHSS occurred in 6.8% of cases. The cumulative pregnancy rate after six treatment cycles was 53.1%, and 6.0% of the 136 clinical pregnancies were twins (Calaf Alsina et al., 2003). Another cohort study with a focus on BMI included 67 patients with PCOS in a low-dose step-up protocol with a starting dose of 50 IU recombinant FSH/day (Yildizhan et al., 2008). The median threshold recombinant FSH dose was 50 IU/day in non-obese (BMI <25 kg/m^2) patients compared with 75 IU/day in obese (BMI ≥25 kg/m^2) patients ($P < 0.01$).

In an RCT including 158 patents with POCOS and a BMI between 18–33 kg/m^2, the initial dose was 50 IU recombinant FSH per day for 7 days. The dose was then increased by either 25 or 50 IU every week (randomized) if no follicles 12 mm or wider were detected. In the 25 IU-increase group, mono-ovulation (one follicle ≥16 m, and no follicles ≥12 mm) was observed in 41.3% of patients compared with 21.8% in the 50 IU-increase group ($P < 0.010$) (Leader, 2006). Because of the risk of hyperstimulation, 21 patients had their cycles cancelled ($n = 16$ in 50 IU). Seven patients had their cycles converted to IVF ($n = 5$ in 50 IU). Other studies have shown that the administered dose of gonadotrophins is more important for the treatment outcome than the FSH or FSH and LH preparation used (Nahuis et al., 2010; Weiss et al., 2015).

Step-up versus step-down

In an RCT including 83 CCR patients, the step-up and step-down approaches were compared (Christin-Maitre and Hugues, 2003). The step-up approach was significantly more successful than the step-down approach in achieving mono-follicular development (68.2% versus 32.0%; $P < 0.0001$). Hyper stimulation (at least three follicles greater than 16 mm) was observed in 4.7% of the patients in the step-up protocol versus 36% in the step-down protocol. The two groups used the same amount of recombinant FSH, but the duration of stimulation was longer in the step-up group (Christin-Maitre and Hugues, 2003).

Clomiphene citrate versus gonadotrophins

An RCT reported the cumulative pregnancy rate and live birth rates (LBR) in first-cycle patients with PCOS (Homburg et al., 2012). Pregnancy rate and LBR were higher in low-dose recombinant FSH cycles compared with clomiphene citrate cycles. The cumulative pregnancy rate after three cycles was 41.2% for the clomiphene citrate group compared with 52.1% for the FSH group ($P < 0.021$). The cumulative LBR after three cycles was 36.9% for the clomiphene citrate group compared with 47.4% for the FSH group ($P = 0.031$).

Metformin

The effect of metformin on menstrual cycle regulation is seen within 1–3 months. Metformin may be beneficial as a supplement to lifestyle intervention in relation to weight loss. Metformin improves the ovulation rate compared with placebo. Evidence that metformin improves the live birth rate in women with PCOS is lacking.

Metformin is an insulin sensitizer used in the treatment of type 2 diabetes. Because of the metabolic features related

Table 3 An overview of the best efficacy of metformin alone or in combination with clomiphene citrate on ovulation, pregnancy and live birth rate.

	Ovulation rate	*Pregnancy rate*	*Live birth rate*
Metformin vs. Placebo	Metformin[a]	Metformin[a]	No sign. diff.[a]
Metformin vs. CC	CC[c,d]/No sign. diff. (BMI≤30 kg/m^2)[f]	No sign. diff.[c,b]/CC[e]	CC[d,e]
Metformin + CC vs. Metformin	Metformin + CC[e]	Metformin + CC[e]/No sign. diff.[g]	Metformin + CC[e]/No sign. diff[g]
Metformin + CC vs. CC	Metformin + CC[a,d] /No sign. diff.[c]	Metformin + CC[a,c]/No sign. diff. (BMI>25 kg/m^2)[d]	No sign. diff.[a,d]

CC, clomiphene citrate.
[a]Tang et al., 2012.
[b]Misso et al., 2013.
[c]Xiao et al., 2012.
[d]Siebert et al., 2012.
[e]Legro et al., 2007.
[f]Palomba et al., 2005.
[g]Johnson et al., 2010.

to PCOS, such as hyperinsulinaemia and insulin resistance, several clinical trials have tested the use of metformin for cycle regulation and ovulation induction in women with PCOS.

Metformin may regulate the menstrual cycle within 1–3 months of treatment in anovulatory women with PCOS (Costello and Eden, 2003; Curi et al., 2012; Mathur et al., 2008; Sinawat et al., 2012). The daily dose is 1000–2000 mg administered in two to three daily doses in combination with a meal to minimize possible gastrointestinal side-effects.

The effect of metformin on ovulation, pregnancy and LBR may depend on the women's BMI and insulin resistance. An overview of the best efficacy of metformin alone or in combination with clomiphene citrate on the above mentioned parameters is presented in **Table 3** (Johnson et al., 2010; Legro et al., 2007; Misso et al., 2013; Palomba et al., 2005; Siebert et al., 2012; Tang et al., 2012; Xiao et al., 2012). Overall, clomiphene citrate is superior compared with metformin in achieving LBR.

A recent meta-analysis found a lower ovulation rate for metformin compared with clomiphene citrate (OR 0.48; $P < 0.01$) but no significant difference in ovulation rate was found for combined clomiphene citrate plus metformin compared with metformin (OR 1.52; 95% CI 0.95–2.45) (Xiao et al., 2012). Siebert et al. (2012) found a higher ovulation rate for the combination clomiphene citrate plus metformin compared with clompiphene citrate (OR 1.6, 95% CI 1.2 to 2.1; $P < 0.00001$).

The pregnancy rate is higher for metformin compared with placebo (pooled OR 2.31, 95% CI 1.52 to 3.51) (Tang et al., 2012). Xiao et al. (2012) found similar pregnancy rates for metformin compared with clomiphene citrate (OR 0.94; 95% CI 0.26–3.43) (Xiao et al., 2012). The pregnancy rate is increased when metformin is combined with clomiphene citrate versus metformin (OR 1.56; 95% CI 1.16–2.08; $P < 0.003$). Similar pregnancy rates data for metformin plus clomiphene citrate versus clomiphene citrate have been reported (OR 1.3; 95% CI 1.0 to 1.6; $P < 0.05$) (Siebert et al., 2012) (pooled OR 1.51, 95% CI 1.17 to 1.96) (Tang et al., 2012). No significant difference was found in the risk of spontaneous abortion neither for metformin versus clomiphene citrate (OR = 0.63; 0.06 to 6.47) nor for metformin plus clomiphene citrate versus metformin (OR 1.40; 95% CI 0.79 to 2.48) (Xiao et al., 2012).

Despite increased pregnancy rates for the combination of metformin plus clomiphene citrate, there is no significant effect on LBR (OR 1.16, 95% CI 0.85 to 1.56) (Tang et al., 2012). Additionally, Siebert et al. (2012) found a lower LBR for metformin compared with clomiphene (OR 0.48; 95% CI 0.31 to 0.73; $P < 0.001$) (Siebert et al., 2012). The same negative results applies for the combination of metformin plus clomiphene citrate versus clomiphene citrate (OR 1.16; 95% CI 0.85 to 1.56) (Tang et al., 2012).

Obese women

Subgroup analyses of BMI groups found a pooled odds ratios for LBR of 0.3 (95% CI 0.17 to 0.52) and 0.34 for pregnancy rate (95% CI 0.21 to 0.55) in favour of clomiphene citrate over metformin (Tang et al., 2012) in obese women (BMI ≥30 kg/m^2).

A recent meta-analysis found that metformin in combination with lifestyle intervention was associated with weight loss and improved menstrual cycle regularity compared with lifestyle intervention and placebo (any BMI) (Naderpoor et al., 2015).

Women with a BMI 27 kg/m^2 or over may benefit from metformin pretreatment (pregnancy rate 49.0 versus 31.4%; $P < 0.04$; and LBR 35.7 versus 21.9%; $P < 0.07$) (Morin-Papunen et al., 2012).

Metformin in combination with gonadotrophins

A systematic review of low-quality RCTs found that metformin increased the pregnancy rate (OR 2.25; 95% CI 1.50 to 3.38) and LBR (OR 1.94; 95% CI 1.10 to 3.44) in women treated with gonadotrophins for ovulation induction (Palomba et al., 2014).

Safety

Evidence that metformin has a teratogenic effect or prevents gestational diabetes when used in the first trimester of pregnancy is lacking (Cassina et al., 2014; Sivalingam et al., 2014; Zhuo et al., 2014). Currently, there is no indication for continuing metformin treatment during pregnancy in women with PCOS (Palomba et al., 2009; Vanky et al., 2010).

Recommendations

Pregnancy rates are higher for metformin compared with placebo, but there is no evidence that metformin improves

the LBR either when used alone, in combination with clomiphene citrate or when compared with clomiphene citrate (Misso et al., 2013; Tang et al., 2012). Recent meta-analyses suggest that metformin may have a positive effect on weight regulation and could therefore be considered in overweight or obese women with PCOS (Naderpoor et al., 2015).

Lifestyle interventions

Overweight women with PCOS should be informed of the beneficial effect of weight loss and exercise, which increases the probability of ovulation.

Lifestyle changes can improve menstrual irregularities and insulin resistance (Curi et al., 2012; Lass et al., 2011). Obesity is associated with increased risk of anovulation, increased androgen production and reduced ovarian responsiveness to FSH (Perales-Puchalt and Legro, 2013).

The primary consultation of overweight patients should focus on lifestyle interventions such as dietary advice, exercise and weight loss (Norman et al., 2004; Nybacka et al., 2011) (**Figure 1**).

A recent meta-analysis reported a beneficial effect of lifestyle intervention on body composition (BMI, body weight and waist-to-hip ratio), hyperandrogenism (clinical, biochemical, or both), and insulin resistance in women with PCOS (Moran et al., 2011). This conclusion was supported by two additional meta-analyses (Domecq et al., 2013; Haqq et al., 2015). Long-term follow-up studies with clinical end points such as LBR, however, are lacking.

A prospective cohort study of 69 anovulatory, infertile obese women (BMI ≥30) used diet and exercise as intervention. Within the study period of 6 months, 90% of the patients who completed the treatment achieved spontaneous ovulation. Ovulation generally occurred during the fifth month of treatment when the average weight loss was 6.5 kg, although the women still had a BMI >30 kg/m^2. None of the women who failed to complete the treatment achieved spontaneous ovulation within the 6-month period (Clark et al., 1998).

An RCT of 96 overweight women who were CCR studied the efficacy of structured training (Palomba et al., 2010). A 6-week intervention of structured exercise training and hypocaloric diet significantly increased the probability of ovulation under clomiphene citrate after only one treatment cycle. The ovulation rate was four out of 32 (12.5%) in the exercise and diet group compared with three out of 32 (9.4%) in the clomiphene citrate group versus 12 out of 32 (37.5%) in the exercise and diet plus clomiphene citrate group ($P < 0.035$).

A cohort study of 270 women with PCOS evaluated the ovulation rate in relation to BMI. After six clomiphene citrate or gonadotrophin treatment cycles, the ovulation rate was 79% among women with a BMI of 18–24 kg/m^2, 15.3% with a BMI of 30–34 kg/m^2 ($P < 0.001$) and 12% with a BMI ≥35 kg/m^2 ($P < 0.001$) (Al-Azemi et al., 2004).

Nybacka et al. (2011) conducted an RCT and found that dietary management and exercise, alone or in combination, are equally effective in improving reproductive function in overweight and obese women with PCOS.

A bodyweight loss of 5–10% can induce spontaneous ovulation or increase the response to clomiphene citrate (Legro et al., 2015). Even a limited weight loss can be a significant factor due to the loss of visceral fat (Ravn et al., 2013; Yildirim et al., 2003).

Laparoscopic ovarian drilling

Minimal invasive surgery with laparoscopic ovarian drilling (LOD) could be considered as an alternative treatment in infertile PCOS women characterized by CCR, excessive or uncontrollable reaction to gonadotrophins or previous OHSS.

The mechanism of LOD is uncertain, but may be linked to the destruction of the androgen-producing cells in both the follicles and the interstitial tissue of the ovaries (Li and Ng, 2012). The lower concentrations of androgens and inhibins may increase the FSH secretion and induce follicular growth through negative feedback mechanisms (Abu Hashim, 2015). Another explanation could be the injury-mediated increased blood flow of the ovaries, which may release a cascade of local growth factors, such as insulin-like growth factor 1, interacting with FSH and thus leading to follicular growth (Abu Hashim, 2015).

A meta-analysis of subfertile women with CCR PCOS (25 RCTs) found no significant difference in the clinical pregnancy rate, birth or spontaneous abortion rates for women treated with LOD compared with clomiphene citrate plus tamoxifen, gonadotrophin or letrozole (Farquhar et al., 2012). On the contrary, they found a significantly lower LBR after LOD compared with treatment with clomiphene citrate plus metformin (OR 0.44, 95% CI 0.24 to 0.82). The number of multiple pregnancies was lower after LOD compared with gonadotrophins (OR 0.13, 95% CI 0.03 to 0.52).

Nahuis et al. (2011) found no significant difference in the long-term outcome (8–12 years) of 168 women with CCR PCOS. The cumulative singleton LBR was 86% in the group treated with LOD compared with 81% in the gonadotrophin group.

Knowledge of the long term consequences of LOD on ovarian reserve, adhesion formation and secondary infertility are limited. Available research does not support an increased risk of reduced ovarian reserve or premature ovarian failure (Api, 2009). Fernandez et al. (2011), in their review, found the complications of LOD to be rare but may include a risk of general complications of laparoscopy, general anaesthesia, damage to the adjacent organs and ligaments, bleeding, haematoma and risk of adhesion formation to the adnexa.

Letrozole

Letrozole is still an off-label drug in many countries, but may be an efficient treatment for ovulation induction in women with PCOS.

Letrozole is an aromatase inhibitor and has been introduced as an alternative treatment for ovulation induction in PCOS. It has recently been approved by the US Food and Drug Administration but is still an off-label drug in most European countries (Palomba, 2015). Letrozole inhibits the aromatase activity and the cytochrome P450 enzyme complex and induces an acute hypo oestrogenic state that stimulates the release of FSH (Palomba, 2015).

The largest meta-analysis to date included 26 RCTs (5560 women) and compared letrozole with placebo, clomiphene citrate with or without adjuncts, and LOD. The authors

concluded that letrozole was superior to clomiphene citrate (with or without adjuncts) in relation to LBR (OR 1.34, 95% CI 1.32 to 2.04) in women with CCR or as first-line treatment, both with timed intercourse (Franik et al., 2015). Similarly, letrozole had a higher clinical pregnancy rate compared with clomiphene citrate (with or without adjuncts) in both timed intercourse (OR 1.40 95% CI: 1.18 to 1.65) and IUI (OR 1.71, 95% CI 1.30 to 2.25) (Franik et al., 2015). Additionally, fewer multiple pregnancies occurred with letrozole compared with clomiphene citrate (OR 0.38, 95% CI 0.17 to 0.84) (Franik et al., 2015). As the quality of some of the included studies was low, the conclusions should be interpreted with caution.

To date, the clinical experience of the use of letrozole for ovulation induction in Europe is limited (Palomba, 2015). The efficacy of letrozole is dependent on the patient's BMI and weight with a higher efficiency in relation to ovulation induction observed in obese women (McKnight et al., 2011).

Letrozole dosing

An RCT included women with PCOS undergoing first-cycle ovulation induction and timed intercourse. The women were allocated to either 5 ($n = 30$) or 7.5 mg ($n = 37$) letrozole daily for 5 days (from day 3 of the menstrual cycle). Ovulation occurred in 90% and 89% of the patients in the two groups and the pregnancy rate per first ovulatory cycle was 25.8% (5 mg) versus 21.2% (7.5 mg). There was no advantage of using 7.5 versus 5 mg letrozole per day (Ramezanzadeh et al., 2011).

Safety

Letrozole has been shown to be teratogenic, embryo-toxic and fetotoxic in animal models (Palomba, 2015). On the other hand, previous studies in humans have demonstrated (absolute) safety for the treatment of letrozole in relation to the health of the offspring (Palomba, 2015). A 3-year follow-up from the Assessment of Multiple Intrauterine Gestations of Ovarian Stimulation (AMIGOS) and the PPPCOS-II is currently being conducted (Palomba, 2015).

Discussion

Different treatment options may all lead to ovulation in women with PCOS. In the present review, the most commonly used treatments strategies for ovulation induction are discussed.

Clomiphene citrate is an efficient, inexpensive and well-tolerated drug with a well-known safety profile when dosed correctly (Palomba, 2015). This review supports the use of clomiphene citrate as first-line treatment for ovulation induction in PCOS. Theoretically, continuation of treatment for another six cycles of clomiphene citrate before switching to, for example, gonadotrophins may be cost-effective (Moolenaar et al., 2014). This issue is currently being investigated in an ongoing Dutch RCT (Nahuis et al., 2013).

Planning ovulation induction in women with PCOS requires a clinical evaluation of the patients' BMI and, if possible, their PCOS phenotype. Four major PCOS phenotypes have now been identified: hyperandrogenism and chronic anovulation (classic PCOS); hyperandrogenism and polycystic ovaries but ovulatory cycles (ovulatory PCOS); chronic anovulation and polycystic ovaries without hyperandrogenism (mild PCOS); and hyperandrogenism, chronic anovulation and polycystic ovaries (severe PCOS) (Conway et al., 2014). The natural history of PCOS and the reproductive outcome vary between the different phenotypes (Moran et al., 2015). The phenotypes including hyperandrogenism and anovulation are associated with a more severe endocrine disturbance than the phenotype, including only polycystic ovaries and anovulation (Diamanti-Kandarakis and Panidis, 2007).

Several studies have underlined the association between obesity and PCOS (Lim et al., 2012; Moran et al., 2015). A recent review states that even though the degree of obesity varies across phenotypes, insulin resistance and reproductive and metabolic challenges are exacerbated by obesity (Moran et al., 2015). Furthermore, obesity is associated with an increased risk of adverse events for the mother and offspring during pregnancy, such as gestational diabetes, hypertension, cesarean section, macrosomia, and stillbirth (Muktabhant et al., 2015). Hence, prevention and treatment of obesity is important in the management of PCOS. Overweight and obese women should be advised to lose weight before initiating fertility treatment, as lifestyle intervention can induce spontaneous ovulation and increase the chance of pregnancy (Curi et al., 2012). It is, however, less clear if, or to what extent, clinics offer advice, support and follow-up, or whether an upper BMI, waist-to-hip ratio limit, or both, should be achieved before fertility treatment. Another important challenge is to maintain the patient's motivation during lifestyle intervention (Nybacka et al., 2011).

A meta-analysis by Naderpoor et al. (2015) suggests that metformin may improve success in weight management. Otherwise, the role of metformin in ovulation induction is controversial. Metformin regulates the menstrual cycle and improves the ovulation rate compared with placebo (Tang et al., 2012). So far, evidence that metformin improves the LBR in women with PCOS is lacking. Interestingly, metformin may have a role as pretreatment before standard assisted reproduction techniques. A recent Finnish RCT demonstrated improved pregnancy rates after 3–9 months of metformin before assisted reproduction techniques (Morin-Papunen et al., 2012). Unfortunately, the women only used metformin for a shorter period in most studies describing the efficacy of metformin in relation to ovulation induction. Therefore, an eventual effect of a longer metformin pretreatment remains to be shown.

In a selected group of women with a history of OHSS or uncontrollable stimulations, LOD should be treated as an alternative treatment, as this treatment modality is inferior to clomiphene citrate and gonadotrophins (as first-line treatments) (Abuelghar et al., 2014; Bayram et al., 2004; Farquhar et al., 2012; Moazami Goudarzi et al., 2014). Furthermore, data on the long-term consequences are insufficient (Fernandez et al., 2011).

Letrozole is still not registered for ovulation induction in Europe, and data on long term follow-up have not yet been published. An American study by Legro et al. (2014) included patients with a very high BMI, which is rarely seen in European studies, without any lifestyle interventions (Legro et al., 2014). This illustrates the influence of different country settings and populations on treatment strategies. In countries in which letrozole is registered for ovulation induction, it may be considered in (overweight) women who are CCR with PCOS. In countries in which letrozole is still an off-label drug, however, we advocate the use of gonadotrophins. Although gonadotrophin treatment is more expensive and requires

extensive monitoring (Farquhar et al., 2004), a careful step-up protocol with serial ultrasound scans provides a high chance of pregnancy and a low risk of multiple gestations (Christin-Maitre and Hugues, 2003; Homburg et al., 2012). Furthermore, strict cancellation criteria should be applied to minimize the risk of multiple gestations.

Access to treatment, willingness (Poder et al., 2014) or possibility to pay for ovulation induction, reimbursement policies, legal aspects and expectations for the duration of treatment may influence the choice of treatment strategy for ovulation induction. Furthermore, clinicians should consider the cost of a treatment. A recent retrospective study from Belgium, including 78 women with CCR PCOS showed that the societal cost before an ongoing pregnancy was less after menotropin treatment compared with LOD surgery (De Frene et al., 2015). In a Dutch RCT, van Wely et al. (2004) concluded that the costs until an ongoing pregnancy occurred were comparable with a strategy starting with LOD versus recombinant FSH. Contrarily, Farquhar et al. (2004) found that LOD was cost-effective compared with gonadotrophin stimulation (van Wely et al., 2004). In line with this, in a long-term follow-up study Nahuis et al. (2012) found a lower cost per live birth after LOD-only compared with gonadotrophins. In a Belgian study, the societal cost was mostly ascribed to productivity loss after LOD owing to a long recovery phase, which may explain the conflicting conclusions between some of the studies (De Frene et al., 2015).

Regarding treatment after six cycles with clompihene citrate failure, an ongoing Dutch trial is evaluating the cost-effectiveness of further six treatment cycles with either clomiphene citrate or gonadotrophin stimulation with or without intrauterine insemination (Nahuis et al., 2013).

Future treatment strategies for ovulation induction may include adjuncts such as the insulin-sensitizing agent myo-inositol. Recent studies found that myo-inositol improved the ovulation and pregnancy rate in insulin-resistant patients with PCOS when given alone or in combination with clomiphene citrate (Kamenov et al., 2015) or as a supplementation in a low-dose step-down protocol (Morgante et al., 2011). It may also improve oocyte and embryo quality in IVF of patients with PCOS (Pacchiarotti et al., 2016) and an animal study in rats demonstrated that myo-inositol was effective in preventing OHSS (Turan et al., 2015). The conclusion from a recent Consensus Conference indicated that Inositol nutritional supplementation (myo-inositol) improved the treatment outcomes in patients with PCOS (Bevilacqua et al., 2015). More large-scale studies are needed to finally establish the role of myo-inositol in ovulation induction treatment.

In conclusion, the understanding of the cause, definition and treatment of PCOS has evolved over time. Although clomiphene citrate as treatment modality has existed for more than 50 years, an increased awareness of the effect of obesity and different PCOS phenotypes has emerged. Accordingly, ovulation induction in women with PCOS has to be individualized according to weight, treatment efficacy and patient compliance, with the aim of achieving mono-ovulation and subsequently the birth of a singleton baby.

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