

Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline

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Metformin alone compared with placebo increases the ovulation rate in women with polycystic ovary syndrome (PCOS) but should not be used as first-line therapy for anovulation because oral ovulation induction agents such as clomiphene citrate or letrozole alone are much more effective in increasing ovulation, pregnancy, and live-birth rates in women with PCOS. There is fair evidence that metformin alone does not increase rates of miscarriage when stopped at the initiation of pregnancy and insufficient evidence that metformin in combination with other agents used to induce ovulation increases live-birth rates. (*Fertil Steril*® 2017;108:426–41. ©2017 by American Society for Reproductive Medicine.)

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INTRODUCTION

The original description of polycystic ovary syndrome (PCOS), then termed the Stein-Leventhal syndrome, was based on a series of seven women presenting with amenorrhea (generally secondary) or occasional menometrorrhagia, hirsutism, “sterility,” and large, pale polycystic ovaries with thickened capsules (1).

Over time it became clear that the syndrome was quite heterogeneous with a wide clinical spectrum (2). Based on 1,079 cases collected from the literature, it was reported that hirsutism was present in 69% of affected women, infertility in 74%, amenorrhea in 51%, obesity in 41%, functional bleeding in 29%, and cyclic menses in 12%.

Subsequent endocrine studies documented elevated levels of circulating luteinizing hormone (LH) compared with those found in the normal early follicular phase (3) and elevated levels of virtually all androgens measured (4).

In the 1980s, a significant correlation was observed between testosterone and insulin levels in PCOS (5). Eventually, it became clear that insulin resistance is a common feature in the disorder and is not directly related to obesity (6).

Insulin resistance is generally defined as “a state (of a cell, tissue, or organism) in which a greater than normal amount of insulin is required to elicit a quantitatively normal response” and maintain glucose levels within the normal range (7). Individuals with insulin resistance may be overtly diabetic or merely have insulin resistance detected by testing. The clinical assessment of insulin resistance relies on any of several tests. The gold standard for identifying and quantifying insulin resistance is the euglycemic hyperinsulinemic clamp procedure that measures insulin-mediated glucose disposal in vivo (8). Other tests used to identify insulin resistance (in order of increasing complexity) include the (1)

determination of insulin levels in either the fasted state or after oral glucose tolerance testing with the results interpreted in light of plasma glucose levels (9); (2) calculation of the homeostasis (Homeostasis Model Assessment, HOMA) index (10); (3) assessment of sequential plasma glucose levels after the intravenous administration of insulin (insulin tolerance test) (9); and (4) estimation of an index of insulin sensitivity (S_i), by applying the minimal model technique to data obtained from the frequently sampled intravenous glucose-tolerance test (FSIVGTT) (8, 11).

This recognition led to many studies about the possible role of insulin-sensitizing agents, particularly metformin, in the treatment of PCOS. Metformin is a biguanide that lowers blood glucose levels in hyperglycemic individuals with type-2 diabetes mellitus but has no effect on glucose levels in normal subjects (12). The mechanism of action remains unclear, but it is known that metformin reduces absorption of glucose uptake from the gastrointestinal tract, inhibits hepatic glucose production, and increases insulin-stimulated glucose uptake in the periphery. Therapy with metformin does not lead to weight gain and may be

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associated with modest weight loss, largely because of a slight anorectic effect as well as gastrointestinal side effects, including abdominal discomfort, diarrhea, nausea, and vomiting. Importantly, metformin may be associated with the development of lactic acidosis, but almost all patients who develop acidosis have impaired renal function, and the incidence is rare when the drug is used appropriately.

Beginning in the 1990s, a series of studies involving relatively small numbers of women with PCOS, many uncontrolled and some controlled, indicated that metformin reduced insulin resistance in women with PCOS and increased the likelihood of ovulation and pregnancy without, or sometimes with, clomiphene citrate (CC) (13, 14). However, the exact role of metformin in the management of women with PCOS has been quite controversial.

The goal of this guideline is to provide recommendations for the use of metformin for ovulation induction in women with PCOS desiring pregnancy. For the purposes of this document, all patients had PCOS unless otherwise indicated.

LIMITATIONS OF THE LITERATURE

While a few large, well-designed randomized controlled trials (RCTs) have been conducted and are highlighted in this report, most of the literature consists of small observational studies. In addition, the populations studied are heterogeneous with varying characteristics including hirsutism, obesity, or anovulation. With respect to diagnosis, most of the recent studies have utilized the Rotterdam criteria (15) for diagnosing PCOS and patient inclusion. As noted by a National Institutes of Health (NIH) conference in 2012, those criteria have led to the inclusion of patients with widely differing phenotypes, so much so that one of the recommendations emanating from that conference was to strictly note the phenotype of patients included in any future study (16). That was not done in the studies included in this review, and, therefore, the PCOS phenotypes of the patients included in various studies are heterogeneous.

In addition, many of the studies utilizing metformin to treat women with PCOS included patients in whom the diagnosis of insulin resistance was never established at all, a strategy that generally is not recommended (17). Moreover, when insulin resistance was assessed, no consistent method has been used in this literature. The heterogeneous populations studied make it difficult to determine if any particular subgroup of patients would benefit from metformin therapy. Moreover, the doses of metformin differed among studies, and some studies only documented the occurrence of regular menses as opposed to ovulation (generally by the measurement of progesterone). In some studies, pregnancy and even live birth were confirmed, while in others these endpoints were not considered. In some studies, only the clinical pregnancy rate rather than the live-birth rate was considered. While ovulation also is an important outcome, it is not the most clinically relevant outcome as it may not lead to conception.

METHODS

This clinical practice guideline was based on a systematic review of the literature performed in the electronic database

MEDLINE through PubMed on December 7, 2016. No limit or filter was used for time period covered or language, but articles were subsequently culled for English language. This electronic search and examination of reference lists from primary and review articles yielded 1,017 studies, of which 73 studies were included.

A combination of the following medical subject headings or text words were used: aromatase inhibitors, clomiphene, dexamethasone, diathermy, diathermy/methods, female, fertility agents, follicle aspiration, follicle puncture, follicle stimulating hormone/therapeutic use, glucocorticoids, gonadotropin releasing hormone/therapeutic use, gonadotropins/therapeutic use, insulin sensitizer, intrauterine insemination, in vitro maturation, in vitro oocyte maturation techniques, IUI, IVF, laser therapy/methods, laser therapy/therapeutic use, letrozole, Leventhal, metformin, ovarian drilling, ovulation induction/adverse effects, ovulation induction/methods, PCO, PCOD, polycystic ovaries, polycystic ovarian syndrome/drug therapy, polycystic ovary syndrome/drug therapy, selective estrogen receptor modulators, Stein-Leventhal.

Initially, titles and abstracts of potentially relevant articles were screened and reviewed to develop inclusion/exclusion criteria (Table 1). Only studies that met the inclusion criteria were assessed in the final analysis. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a procedure correlated with an outcome measure (pregnancy, ovulation, or live-birth rates); meta-analyses; and relevant articles from bibliographies of identified articles.

Four members of an independent task force reviewed the full articles of all citations that potentially matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion among reviewers were discussed and resolved by consensus or arbitration after consultation with an independent reviewer/epidemiologist.

The level of the evidence was evaluated using the following grading system and is assigned for each reference in the bibliography:

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Descriptive studies, case series, case reports, letters, nonsystematic reviews, opinions based on clinical experience, and reports of expert committees.

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence.

TABLE 1**Summary of inclusion and exclusion criteria.****Inclusion criteria**

Level I, II-1, II-2 studies, systematic reviews, meta-analyses
 Human studies
 English
 Principally studies of metformin compared with placebo or other fertility treatments for ovulation induction (clomiphene citrate, letrozole, laparoscopic ovarian drilling, aromatase inhibitors, gonadotropins)
 Primary or secondary outcomes: pregnancy rate, live-birth rate, ovulation rate, miscarriage
 Side effects: discontinuation rate, multiple pregnancy, ovarian hyperstimulation syndrome (OHSS)
 Diagnosis of PCOS according to various published phenotypes

Exclusion criteria

Level II-3 and III studies: series, case reports, reviews, opinions, off topic
 Animal studies
 Non-English
 Stimulation (controlled ovarian stimulation, controlled ovarian hyperstimulation); in vitro fertilization (IVF)/assisted reproductive technology (ART)
 Studies without a comparison group
 Studies with a comparison group, but primary outcomes are metabolic
 Polycystic ovary syndrome (PCOS) patients of non-reproductive age
 Second-line or less commonly used therapies as primary focus
 Bromocriptine as focus
 Glucocorticoids, dexamethasone as focus
 Studies that report menstruation only with no other fertility outcome
 Acarbose as focus
 Glitazones as focus
 Weight loss/lifestyle modification as focus

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The strength of the recommendation was evaluated as follows:

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

DOES METFORMIN ALONE AS FIRST-LINE OVULATION INDUCTION THERAPY IMPROVE CLINICAL PREGNANCY AND LIVE-BIRTH RATES COMPARED WITH PLACEBO?

Ovulation

There are six randomized trials that assessed ovulation rate in patients with PCOS treated with metformin compared with placebo (18–23).

Several of these studies demonstrated that metformin is associated with a statistically significantly higher ovulation rate compared with placebo (18–20, 23). An RCT of 100 patients compared metformin to placebo in non-obese patients with PCOS and normal insulin sensitivity (18). The 6-month ovulation rate was 100% with metformin vs 37% with placebo ($P < .001$). In another trial of 92 patients, women with oligo-ovulation and polycystic ovaries (there were no inclusion/exclusion criteria related to obesity or insulin sensitivity) were recruited and ovulation frequency, as assessed by ratio of luteal weeks to observation weeks, was higher with metformin (23% vs 13%, $P < .01$) (20).

In a 2004 RCT, normo-androgenic women with anovulation ($n=24$) (there were no inclusion/exclusion criteria related

to obesity) treated with metformin were found to have a higher number of ovulatory cycles compared with placebo (16 vs 4 ovulations over the 3-month study period, $P < .05$) (19). The largest study randomized 116 (139 original participants before dropout and conceptions) women with PCOS, diagnosed if they had oligomenorrhea or amenorrhea and hyperandrogenism, and found a higher ovulation rate, defined as luteal weeks/observation weeks, in metformin vs placebo weeks (33% vs 12%, $P < .001$) (23). There is a limited group of smaller studies ($N=37$, $N=21$, respectively) showing no benefit (22) or only non-statistical improvement in ovulation (24).

Pregnancy Rates

The existing randomized trials examining clinical pregnancy rate in patients treated with metformin vs placebo are underpowered and fail to detect any improvement with metformin (20–22, 25–27). However, a meta-analysis was suggestive of a modest improvement in clinical pregnancy rate (odds ratio [OR] 2.31; 95% confidence interval [CI] 1.52–3.51) (28). Only one RCT in anovulatory women with PCOS and a body mass index (BMI) >32 kg/m² (received metformin or placebo) and ≤ 32 kg/m² (received CC, metformin, or both) reported live-birth rates (21). This trial found no statistically significant difference, reporting a live-birth rate of 16% (5/32) with metformin and 6% (2/33) with placebo in women with BMI >32 kg/m² (21).

Summary statements.

- There is good evidence that metformin alone vs placebo increases the ovulation rate in women with PCOS. (Grade A)
- There is insufficient evidence to suggest that metformin alone increases pregnancy rates or live-birth rates compared with placebo. (Grade C)

DOES METFORMIN ALONE AS FIRST-LINE OVULATION INDUCTION THERAPY IMPROVE CLINICAL PREGNANCY AND LIVE-BIRTH RATES COMPARED WITH CC?

Six randomized trials and two meta-analyses that assessed ovulation, clinical pregnancy rate, and/or live birth in patients treated with metformin vs CC were included (21, 26, 28–33).

Two well-designed RCTs demonstrated that CC is superior to metformin in the achievement of both ovulation and pregnancy (29, 32). The largest RCT to date (N=626) randomized an American population of infertile women with PCOS defined by oligomenorrhea and hyperandrogenism to CC, metformin, or both (29). This study demonstrated significantly higher rates of ovulation and live birth with CC alone compared with metformin (49% vs 29% and 22.5% vs 7.2%, respectively; $P < .001$ for metformin vs both CC and combination therapy; $P = .31$ for CC vs combination therapy). The population included in this study was notably obese (mean BMI > 34 kg/m²), androgenized ($> 75\%$ clinically hirsute), and insulin resistant (mean HOMA-IR > 5) (29). In another RCT of 115 Malay women with PCOS defined by Rotterdam criteria, the ovulation rate was better with CC compared with metformin (59% vs 23.7%, $P = .002$; OR 4.63 [1.73–12.37]), although live-birth rates were not statistically different in this trial (15.4% [6/39] vs 7.9% [3/38], $P = .306$; OR 2.64 [0.3–11]) (32).

There are several smaller RCTs that were unable to show a difference between CC and metformin in achievement of pregnancy, although the trials were likely underpowered and limited by sample size (21, 26, 30). One RCT with a subpopulation of 106 women with BMI ≤ 32 kg/m² showed no difference in live-birth rate: CC 36% (13/36) vs metformin 29% (10/35) vs CC plus metformin 43% (15/35), $P = .46$ (21). Two groups of women (n=180) in another RCT showed no difference in clinical pregnancy rate: 12.2% CC; 14.4% metformin (26). In a third RCT of 154 women who received CC, metformin, or both, ovulation rates were higher for metformin vs CC (n=113, 75.4% vs 50%, $P = .005$), although clinical pregnancy rates were the same (45.6% vs 35.7%, respectively, $P = \text{nonsignificant [NS]}$) (30).

Only one RCT indicated that metformin was associated with statistically improved outcomes compared with CC. In an RCT of 100 lean women with primary infertility and anovulatory PCOS, metformin was superior to CC in clinical pregnancy rate, but did not reach statistical significance for live-birth rates (clinical pregnancy rate: 15.1% vs 7.2%, $P = .009$; live-birth rate: 83.9% vs 56.3%, $P = .07$, respectively) (31).

Several meta-analyses on the topic demonstrate that CC is significantly better than metformin. A meta-analysis of 14 trials pooled 4 studies (21, 29, 31, 32) to demonstrate that metformin resulted in a significantly lower live-birth rate when compared with CC (OR 0.48; 95% CI 0.31–0.73, $P = .0006$) (33). A systematic review stratified its meta-analysis of metformin vs CC in participants with BMI < 30 kg/m² or ≤ 32 kg/m² in two studies (21, 31) and BMI ≥ 30 kg/m² in two studies (29, 32), but found the data in these four studies reporting on live birth inappropriate for pooling due to heterogeneity (28). The two studies of women with BMI < 30 kg/m² (N=100) or ≤ 32 kg/m²

(n=106) showed opposite results: in one study metformin was superior (31) while CC was superior in the other (21). The two studies analyzed for the obese group (BMI ≥ 30 kg/m²) (n=500) (29, 32) demonstrated that metformin was associated with a lower live-birth rate than CC alone (OR 0.3; 95% CI 0.17–0.52).

Summary statement.

- There is fair evidence from one large, well-designed RCT that metformin alone is less effective than CC alone for the achievement of ovulation induction, clinical pregnancy, and live birth in women with PCOS. (Grade B)

DOES METFORMIN ALONE AS FIRST-LINE OVULATION INDUCTION THERAPY IMPROVE CLINICAL PREGNANCY AND LIVE-BIRTH RATES COMPARED WITH LETROZOLE ALONE?

There have been no head-to-head trials comparing the efficacy or safety of metformin to letrozole alone. While not the focus of this document, one large RCT comparing letrozole with CC for ovulation induction in women with PCOS demonstrated that letrozole was superior (higher cumulative live births 27.5% vs 19.1%, $P = .007$) (34). Since that time, the use of letrozole for ovulation induction has increased in this population and is a reasonable first-line agent for ovulation induction in women with PCOS.

Summary statements.

- There is insufficient evidence to suggest that metformin alone increases pregnancy or live-birth rates compared with letrozole alone. (Grade C)
- However, there is fair evidence based on one well-designed trial in support of letrozole for ovulation induction. (Grade B). Therefore, letrozole is a reasonable first-line agent for ovulation induction in PCOS patients.

WHEN USED IN COMBINATION WITH OTHER AGENTS AS FIRST-LINE THERAPY FOR OVULATION INDUCTION IN WOMEN WITH PCOS, DOES METFORMIN INCREASE PREGNANCY RATES AND LIVE-BIRTH RATES?

There are a number of RCTs assessing the use of metformin in combination with CC compared with CC alone for fertility in women with PCOS (21, 24, 26, 29, 32, 35–41). A few studies also investigated the combination compared with metformin alone (26, 29, 32, 42). There are also a number of systematic reviews and meta-analyses of primary studies (28, 33, 43–47), which investigate the role of metformin and other insulin-sensitizing agents in women with PCOS. Overall, it is clear that the combination of metformin with CC for ovulation induction is superior to metformin alone for all relevant outcomes including ovulation, clinical pregnancy rate, and live-birth rate. In comparing the combination to clomiphene alone, the findings are less clear.

Ovulation

Multiple RCTs demonstrate significant improvement in ovulation rates among women using the combination of metformin and CC compared with CC alone (29, 32, 35, 37, 38, 40), whereas a number of studies fail to find a significant difference (21, 24, 36, 39, 41). A meta-analysis of the combination compared with CC suggests improved ovulation with the combination therapy vs CC alone after combining data for 3,265 women from 18 trials (OR 1.74; 95% CI 1.50–2.00), although significant heterogeneity was noted among studies (28). Stratified analysis demonstrated no difference between obese and non-obese women. The heterogeneity among the primary studies may be attributed to a number of factors including the varying inclusion and exclusion criteria used to identify the study populations. For example, the two largest studies in the meta-analysis, a 2006 study with 225 participants (39) and a 2007 study by the Reproductive Medicine Network that included 626 participants (29) had different inclusion criteria and disparate outcomes. The study with 225 participants included women with cycles ≥ 35 days in length and polycystic ovaries on ultrasound and found no improvement in ovulation with the metformin-CC combination compared with CC alone (relative risk [RR] 0.89; 95% CI 0.7–1.1) (39), whereas the larger study (N=626) included women with ≤ 8 cycles per year and elevated serum testosterone levels and did find improved ovulation rates with combination therapy (2.2 ovulations per subject with CC alone vs 2.8 ovulations per subject with CC-metformin, $P < .001$) (29).

Clinical Pregnancy Rate

Multiple RCTs assessed clinical pregnancy rates among women using combination therapy compared with CC alone

(21, 24, 29, 32, 35, 37, 39, 40) (Table 2). Similar to the outcome of ovulation, a number of studies showed improved clinical pregnancy rates with the combination of metformin and CC over CC alone (35, 38, 48), whereas a number of others showed no significant difference (21, 24, 29, 30, 32, 37, 39). A 2006 study showed no benefit of metformin and CC over CC alone for achieving an ongoing pregnancy (RR 0.87; 95% CI 0.6–1.2) (39). On the other hand, a 2008 sub-analysis of the same data demonstrated that the combination may benefit women aged 28 years or older with visceral obesity, defined as a waist-to-hip ratio of ≥ 0.85 —a surrogate marker for insulin resistance (RR 1.6; 95% CI 0.98–3.8) (39, 49). Only 64 women were included in the sub-analysis and statistical significance was not achieved. A systematic review showed improved clinical pregnancy rate among 1,208 women in 11 trials using the combination therapy compared with CC alone (OR 1.51; 95% CI 1.17–1.96), although again with significant heterogeneity noted among studies (28).

Live-birth Rate

Only two studies included live-birth rate as an outcome (29, 32), the most clinically relevant outcome for fertility patients, particularly for those at higher risk for adverse pregnancy outcomes like stillbirth and miscarriage (50). Neither study required insulin resistance for inclusion. The larger of the two studies included 626 participants who were randomized to one of three treatment arms: combination of metformin and CC, metformin alone, and CC alone (29). The sample size was calculated to detect a 15% difference in live-birth rates between the combination arm and the single-agent arms after 6 months of treatment (50). In the 2007 study, live-birth rates were not significantly higher among women receiving the combination (n=209) compared with CC alone (n=209) (26.8% vs 22.5%, $P = .31$). Another small likely underpowered study reached similar conclusions with live-birth rates among women receiving the combination (n=38), with no difference noted compared to the rates seen among women using CC alone (n=39) (18.4% vs 15.4%, $P = .126$) (32). A systematic review reached similar conclusions, finding no significant benefit to the combination over CC alone (OR 1.16; 95% CI 0.85–1.56) (Fig. 1) (28). A sub-analysis (no power analysis) of available data for 70 obese women also failed to show any benefit of the combination over CC alone (OR 1.28; 95% CI 0.86–1.91) (Fig. 1) (28).

A number of studies have attempted to investigate the role of metformin as an adjuvant to other PCOS interventions like rosiglitazone or lifestyle changes, including diet and exercise, without any benefit to fertility outcomes (27, 51). There is one RCT of 320 women demonstrating significantly higher pregnancy and live-birth rates in women treated with metformin alone for 3 months followed by the addition of other ovulation induction agents compared to women not receiving metformin (53.6% vs 40.4%, $P = .006$; 41.9% vs 28.8%, $P = .014$, respectively). Clomiphene citrate was added first and if unsuccessful after four to six cycles, other medications were tried, including gonadotropins or aromatase inhibitors (52).

TABLE 2

Randomized controlled trials comparing probability of clinical pregnancy with metformin and clomiphene citrate vs clomiphene citrate alone.

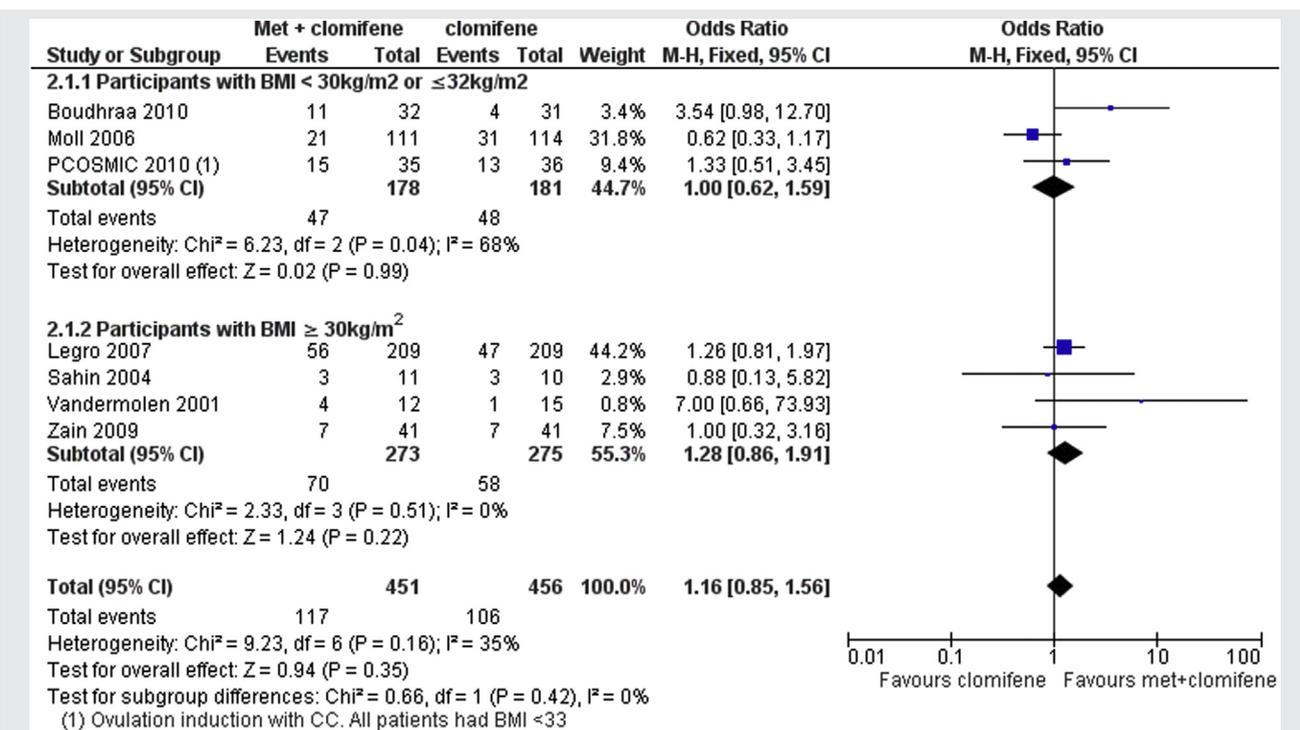
Study	N	Metformin-clomiphene (%)	Clomiphene alone (%)
Higher probability of clinical pregnancy with metformin-clomiphene citrate vs clomiphene citrate alone			
Ayaz 2013 (35)	42	66.6	28.6
Khorram 2006 (38)	31	44	0
Raja 2005 (48)	100	52.9	44
Tang 2012 ^a (28)	1,208	34	26
No significant difference in probability of clinical pregnancy			
Dasari 2009 (37)	40	25	8
Johnson 2010 ^a (21) (BMI ≤ 32)	171	54	39
Legro 2007 (29)	626	31.1	23.9
Moll 2006 (39)	225	40	46
Neveu 2007 (30)	154	31.7	35.7
Sahin 2004 (24)	21	45.5	30
Zain 2009 (32)	115	21.1	15.4

Note: BMI = body mass index.

^a Eleven randomized controlled trials; odds ratio 1.51 (95% confidence interval 1.17–1.96), although a moderate degree of heterogeneity was observed ($I^2 = 49\%$). Studies included: El-Biely 2001, Hwu 2005, Karimzadeh 2010, Khorram 2006, Legro 2007, Malkawi 2002, Moll 2006, Sahin 2004, Sturrock 2002, Vandermolen 2001, Zain 2009.

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FIGURE 1



Comparison of live-birth rates with clomifene citrate versus metformin with clomifene citrate (28). (Reprinted by permission of John Wiley & Sons, Inc. The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.)

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Summary statements.

- There is good evidence that metformin in combination with CC improves ovulation and clinical pregnancy rates but does not improve live-birth rates compared with CC alone in women with PCOS. (Grade A)
- There is fair evidence from one RCT that pretreatment with metformin for at least 3 months followed by the addition of another ovulation-inducing drug increases live-birth rate. (Grade B)

DOES THE COMBINATION OF METFORMIN AND CC OR OTHER OVULATION INDUCTION AGENTS IMPROVE OVULATION, CLINICAL PREGNANCY RATE, OR LIVE-BIRTH RATE IN THE SUBSET OF CC-RESISTANT PATIENTS WITH PCOS?

There have been several studies that have evaluated the use of metformin for ovulation induction in women with CC-resistant PCOS. Unfortunately, the existing studies are limited by a variety of methodologic issues including small samples sizes, varying time courses and doses of metformin treatment, as well as several different definitions of CC resistance ranging from failure of follicular development after treatment with CC 150 mg for two cycles to failure of conception after three cycles of an undefined dose of CC. These inconsistencies

among the available studies limit the ability to compare them and draw firm conclusions about the efficacy of metformin in this patient population. With these caveats in mind, studies to date have addressed the use of metformin alone or the addition of metformin to CC treatment (CC-metformin) for ovulation induction in women with CC-resistant PCOS compared with treatment with CC alone, laparoscopic ovarian drilling, aromatase inhibitors, and gonadotropins.

CC-Metformin versus CC Alone

There have been eight RCTs that have compared CC alone to CC-metformin for ovulation induction in women with PCOS who carried a diagnosis of CC resistance. CC resistance has been defined as failure to conceive after six cycles of CC 150 mg/day (37), failure of “follicular development” after two cycles of CC 150 mg/day (53), absence of “ovarian response” after three cycles of CC 150 mg/day (54), failure to ovulate or conceive after at least three consecutive cycles of CC 150 mg/day (55), and failure to ovulate in response to a 5-day course of CC 150 mg/day with no minimum number of cycles mentioned (56) (Table 3). While these definitions are similar in their focus on resistance to a maximum dose of CC 150 mg/day, the varying and, in some cases, vague outcome measures (“follicular development,” “ovarian response,” ovulation, and conception) and the lack of consistency in the number of failed cycles needed to meet the definition of resistance make comparing these patient populations

TABLE 3

Ovulation and clinical pregnancy rates with clomiphene citrate-metformin vs clomiphene citrate alone in clomiphene citrate-resistant patients.

Study	N	Metformin-clomiphene		Clomiphene alone	
		Ovulation (%)	Pregnancy (%)	Ovulation (%)	Pregnancy (%)
Improvement in ovulation and clinical pregnancy rate in clomiphene citrate-resistant patients					
Dasari 2009 (37)	9 (subgroup)	72	22.2	29	8
Hwu 2005 (53)	80	42.5	15	12.5	0
Kazerooni 2009 (54)	37	88.9	16.6	21.05	0
Kocak 2002 (57)	56	77.7	11	14.2	0
Malkawi 2002 (55)	28	68.8	56.3	25	16.6
Vandermolen 2001 (56)	26	75	55	27	7
Creanga 2008 ^a (44)	1,639 (17 studies)	NR	NR	NR	NR
Moll 2007 ^b (45)	210 (5 studies)	NR	27	NR	4
No significant difference in ovulation and clinical pregnancy rate in clomiphene citrate-resistant patients					
Ng 2001 (25)	20	0 (range 0–22)	1 (within 3 months of therapy)	6.9 (median; range 0–50)	2 (within 3 months of therapy)
Sturrock 2002 (59)	26	41.6	25	28.6	14.3

Note: NR = not reported.

^a Ovulation: odds ratio 5.09 (95% confidence interval 1.44–17.98) compared with clomiphene citrate alone (subgroup analysis); early pregnancy: odds ratio 9.62 (95% confidence interval 2.95–31.45) compared with clomiphene citrate alone (subgroup analysis). Included studies: Baillargeon 2004, El-Biely 2001, Fleming 2002, Hoeger 2004, Hwu 2005, Khorram 2006, Kocak 2002, Legro 2007, Malkawi 2002, Moll 2006, Nestler 1996, Nestler 1998, Ng 2001, Onalan 2005, Refaie 2005, Sahin 2004, Vandermolen 2001.

^b Clomiphene citrate + metformin compared with clomiphene citrate alone: clinical pregnancy rate: risk ratio 5.6 (95% confidence interval 2.3–13); 5 trials, 110 women. Live-birth rate: risk ratio 6.4 (95% confidence interval 1.2–34); 2 trials, 107 women. Included studies: Hwu 2005, Kocak 2002, Malkawi 2002, Sturrock 2002, Vandermolen 2001.

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potentially problematic across studies. There have been four RCTs, a meta-analysis, and a systematic review that have all demonstrated a statistically significantly increased rate of ovulation and/or pregnancy rate with the addition of metformin with CC for ovulation induction compared with CC alone $P=.02$, clinical pregnancy rate $P=.02$ (56); ovulation OR 5.09 (95% CI 1.44–17.98), early pregnancy OR 9.62 (95% CI 2.95–31.45) (44); ovulation not reported, clinical pregnancy rate RR 5.58 (95% CI 2.34–12.32), live-birth rate RR 6.4 (95% CI 1.2–35) (45). In the four RCTs demonstrating a statistically significant benefit of metformin, CC resistance is defined in four distinct ways as detailed above. A fifth RCT of infertile PCOS patients treated with CC alone ($n=24$) or CC-metformin ($n=16$) evaluated the effect of adding metformin to a subgroup of “CC failures” ($n=9$), defined as failure to conceive with six cycles of CC up to 150 mg/day (37). After the CC failure group was treated with six cycles of CC-metformin, the cumulative ovulation rate was 72% compared to 29% with CC alone. In the CC-failure subgroup, two patients achieved pregnancy out of the nine treated (22.2%) (37). However, due to the limited sample size of the subgroup, the authors were unable to demonstrate that these differences were statistically significant (37).

The largest study addressing this question randomized 80 women with CC-resistant PCOS (defined as failure of follicular development after two cycles of CC 150 mg/day) to CC plus “ultra-short” metformin pretreatment or no metformin (53). The treatment group received 12 days of metformin 500 mg 3 times daily, CC 150 mg was added for 5 days, and metformin was continued until the lead follicle reached 20 mm at which time human chorionic gonadotropin (hCG) trigger was given with plans for timed intercourse. The control group did not receive metformin, but CC treatment and hCG trigger were the same between groups. The primary outcomes measured were ovulation rate and pregnancy rate. The authors found

that both ovulation (42.5% vs 12.5%; $P=.03$) and pregnancy rates (15% vs 0%; $P=.026$) were significantly higher in the metformin pretreatment group compared with controls.

The second largest randomized trial included 56 CC-resistant PCOS women comparing metformin or placebo pretreatment for 1 month prior to a CC ovulation induction cycle (57). CC resistance in this study was defined as no ovarian response for three consecutive cycles documented by ultrasound with concomitant failure of estradiol levels to increase after treatment with CC 150 mg/day. Main outcome measures included ovulation and pregnancy rates. Metformin pretreatment (850 mg twice daily) significantly increased the ovulation rate (77.7% vs 14.2%; $P<.001$). There was one pregnancy that occurred during the metformin pretreatment phase of the study and three pregnancies that resulted from the CC-metformin treatment cycle compared with no pregnancies in the placebo group in either phase of the study. While there was no significant difference in pregnancy rate for the CC-induced cycle ($P=.07$), the cumulative pregnancy rate was significantly higher in the metformin plus CC group overall when compared with placebo and CC ($P=.04$). The uniquely strict definition of CC resistance used in this study may have biased it toward an even more difficult-to-treat patient population, limiting the ability to compare or combine these results with other studies using a less strict definition of CC resistance (57).

One RCT of 20 Chinese CC-resistant PCOS patients (defined as failure to ovulate after three cycles of CC 100 mg/day) compared 3 months of pretreatment with metformin (500 mg 3 times daily) vs placebo followed by one cycle of CC (100 mg/day) in patients who were not already pregnant (25). The median ovulation rates were 0% (range 0%–50%) after placebo and 6.9% (range 0%–50%) after CC-placebo vs 0% (range 0%–22%) for both metformin alone and CC-metformin (25). The authors defend their use of

100 mg CC for both their definition of CC resistance and their administered treatment dose of CC citing prior reports (58) that patients failing to respond to 100 mg do not ovulate when given higher doses (25). The authors admit that it is uncertain if the ovulation rate in the metformin group could have been increased if the dose of CC had been increased as was the case in similar studies. It should also be noted that the average BMI of patients in this Chinese cohort was 24 which is on the low end of BMI compared to other studies evaluating this question (mean BMI of 29 across studies evaluated here). The authors noted this difference and discussed that it remains to be determined if metformin's proposed therapeutic effect to decrease insulin resistance and thereby improve ovulation rate can be expected in a population of lean women with PCOS. In a separate small RCT (N=26), no significant difference in ovulation or pregnancy rates between metformin and placebo was found in CC-resistant PCOS patients (defined as no ovulation after at least two courses of 50–100 mg CC) who were randomized to either 3-month pretreatment with metformin or placebo followed by 3-month CC treatment (up to 100 mg) for ovulation induction (59). In this case, the authors did not comment on the use or possible limitations of a maximum CC dose of 100 mg (Table 3).

Summary statement.

- There is fair evidence that CC-metformin improves ovulation and pregnancy rates compared with CC alone in CC-resistant PCOS women. (Grade B). However, more studies are needed to determine whether there may be subgroups of women (e.g., specific BMI, ethnicity, absence of insulin resistance, etc.) with PCOS and CC resistance for which CC-metformin provides the most benefit over CC alone.

Metformin versus Laparoscopic Ovarian Drilling (LOD)

There have been three large RCTs and two systematic reviews that assessed metformin compared with LOD in CC-resistant PCOS patients. The largest study was an RCT of 282 CC-resistant PCOS patients (defined as persistent anovulation after at least three cycles of CC 150 mg/day) comparing CC-metformin with LOD for ovulation induction. The patients in the metformin group received metformin 500 mg 3 times daily for 6–8 weeks followed by CC 100–150 mg daily for 5 days (60). The patients in the CC-metformin group received hCG triggers. In the LOD group, patients underwent LOD using a three-puncture technique for 4 seconds each using a monopolar needle set at 40 watts, and were followed to determine regularity of cycles, ovulation, and pregnancy rates. There was no significant difference between CC-metformin and LOD in terms of resumption of menses (68.8% vs 71.5%), ovulation rate (67% vs 68.2%), pregnancy rate (15.4% vs 17%), or miscarriage rate (20% vs 21%).

Another large randomized trial of 110 CC-resistant PCOS patients (no definition given) compared diagnostic laparoscopy plus metformin (850 mg metformin twice daily) to LOD alone with primary outcomes of ovulation rate, preg-

nancy rate, and miscarriage rate (61). Of note, authors state that LOD treatment consisted of four to eight punctures depending on size of the ovary for 4 seconds each using monopolar diathermy (40–60 watts). The patients were treated as allocated and then followed for six cycles. LOD resulted in significantly higher ovulation (50.8% vs 33.5%; $P=.001$) and pregnancy rates (pregnancy rate per cycle=8.1% vs 3.9%; $P=.03$; cumulative pregnancy rate=38.2% vs 20%; $P=.03$) compared with metformin. There was no significant difference in the miscarriage rate between LOD and metformin (19% vs 18.2%; $P=.9$). It should be noted that the design of this study was unique given the inclusion of diagnostic laparoscopy with the metformin treatment group to allow for blinding of the laparoscopic procedure performed and to control for the effects of surgery alone (61).

An earlier, large RCT with a similar study design found benefit with metformin compared with LOD. In this study, 120 CC-resistant PCOS patients (defined as anovulation after at least three consecutive cycles of CC 150 mg/day) were randomized to diagnostic laparoscopy plus metformin (850 mg twice daily) or LOD plus placebo for ovulation induction (62). These authors described LOD as three to six punctures depending on the size of the ovary for 2 to 3 seconds with monopolar coagulating current set at 40 watts. The duration of treatment was 6 months following laparoscopy. Ovulation rates were not different between groups. However, per-cycle pregnancy rate (18.6% vs 13.4%), cumulative pregnancy rate (72.6% vs 56.4%), and live-birth rate (82.1% vs 64.5%) were increased in the metformin group compared with LOD, respectively, but the results did not appear to meet statistical significance by repeat calculation. Miscarriage rates were found to be lower in the metformin group (15.4% vs 29%; $P<.05$). The same authors conducted a small follow-up study in women who didn't respond to either metformin or LOD (N=28), adding CC 150 mg for 5 days for six cycles with continued follow-up of ovulation, pregnancy rates, and live-birth rates (63). There was no significant difference between LOD-CC and metformin-CC in terms of ovulation, clinical pregnancy, or live-birth rate with the addition of CC to the prior treatments. These same authors also performed an RCT of 50 CC-resistant PCOS patients comparing CC used concurrently with metformin (up to 1700 mg/day) to LOD alone for ovulation induction (64). The duration of study was 15 months, and there were no significant differences in pregnancy or live-birth rates between LOD and CC-metformin. The authors concluded that both LOD and CC-metformin seem to be effective treatments for ovulation induction in CC-resistant PCOS patients, but this study was limited by the small sample size and analysis by cycle rather than by woman.

A meta-analysis and systematic review of 12 RCTs found no significant difference between ovulation and pregnancy rate for LOD compared to CC-metformin in CC-resistant PCOS women (65). A second systematic review of 27 RCTs found that CC-metformin resulted in a higher live-birth rate compared with LOD, but there was no difference in pregnancy rate between metformin alone and LOD plus metformin (45). (Fig. 2)

Summary statements.

- There is fair evidence that overall pregnancy rates are not different with CC-metformin, CC-LOD, or LOD alone in women with CC-resistant PCOS. (Grade B)
- There is insufficient evidence regarding pregnancy rate or live-birth rate with the use of metformin alone compared with LOD for ovulation induction in CC-resistant PCOS patients. (Grade C)

CC-Metformin versus Aromatase Inhibitors

One RCT compared CC-metformin compared with aromatase inhibitors in CC-resistant patients (66). This study included 250 CC-resistant PCOS patients (defined as persistent anovulation or ovulation with a very thin endometrium [<5 mm] at the time of hCG administration after three cycles of CC 150 mg/day) randomized to CC-metformin or letrozole for ovulation induction. The patients in the CC-metformin group received 500 mg metformin 3 times daily for 6–8 weeks followed by 150 mg CC for 5 days. The patients in the letrozole group received 2.5 mg daily for 5 days without any pretreatment. There was no significant difference in ovulation rate (69.6% vs 64.9%; $P=.82$) or clinical pregnancy rate (14.4% vs 14.7%; $P=.53$) between CC-metformin and letrozole, respectively (66).

Summary statement.

- There is insufficient evidence to compare metformin plus CC to aromatase inhibitors alone or metformin plus aromatase inhibitors for ovulation induction in CC-resistant women. (Grade C)

CC-Metformin versus Gonadotropins

There have been three RCTs that compared ovulation and pregnancy rates between CC-resistant PCOS patients using CC-metformin vs gonadotropins, and the results are conflicting, (67–69). One study, an RCT of 153 CC-resistant PCOS patients, compared a low-dose, step-up regimen of highly purified urinary follicle-stimulating hormone (HP-uFSH; starting dose of 75 IU with step-up of 37.5 IU every 7 days until follicular response) to CC-metformin (500 mg metformin for 6–8 weeks followed by CC 100 mg for 5 days, which was increased to 150 mg if there was no ovulatory response) for up to three cycles of ovulation induction (67). In this study, CC resistance was defined as persistent anovulation after at least three cycles of CC 150 mg/day. There was a significantly higher rate of ovulation (83.8% vs 62%, $P=.01$) and pregnancy rate (21.5% vs 11.2%, $P=.02$) in the gonadotropin group. The multiple pregnancy rate was higher in the HP-uFSH, but this difference was not statistically significant (18.7% vs 11%). Two women in the HP-uFSH group had mild ovarian hyperstimulation syndrome (OHSS) (67). Another randomized trial of 165 women comparing CC-metformin vs gonadotropin-metformin vs gonadotropin alone found that ovulation and pregnancy rates were significantly increased in women treated with gonadotropins (pregnancy rate 7/55 [13%] in

the CC-metformin arm vs 16/55 [29%] in the gonadotropin-only arm, $P<.05$) (69).

However, another study did not find a benefit to gonadotropins when compared with CC-metformin. This was an RCT of 60 CC-resistant PCOS patients (defined as anovulation after a “dose schedule” of CC 200 mg/day) comparing CC-metformin (6 months’ pretreatment with 500 mg metformin 3 times daily for 6 months followed by 150 mg CC for 5 days) to a low-dose, step-up human menopausal gonadotropin (hMG) regimen (starting dose 75 IU with step-up of 75 IU every 7–10 days until follicular response) for three cycles of ovulation induction (68). In this study, there was significant improvement ($P<.001$) in ovulation rate after treatment (46.7%) in the CC-metformin group. The authors reported an ovulation rate of 43.3% in the hMG group per cycle but did not compare the ovulation rate between groups. When comparing CC-metformin to hMG, there was no difference in pregnancy rates (16.7% vs 23.3%) between groups (68).

In PCOS patients pursuing gonadotropin therapy for ovulation induction, there is evidence that co-treatment with metformin in combination with gonadotropins improves live-birth rate (OR 2.31; 95% CI 1.23–4.34) and ongoing pregnancy rates (OR 2.46; 95% CI 1.36–4.46) compared with gonadotropins alone (70).

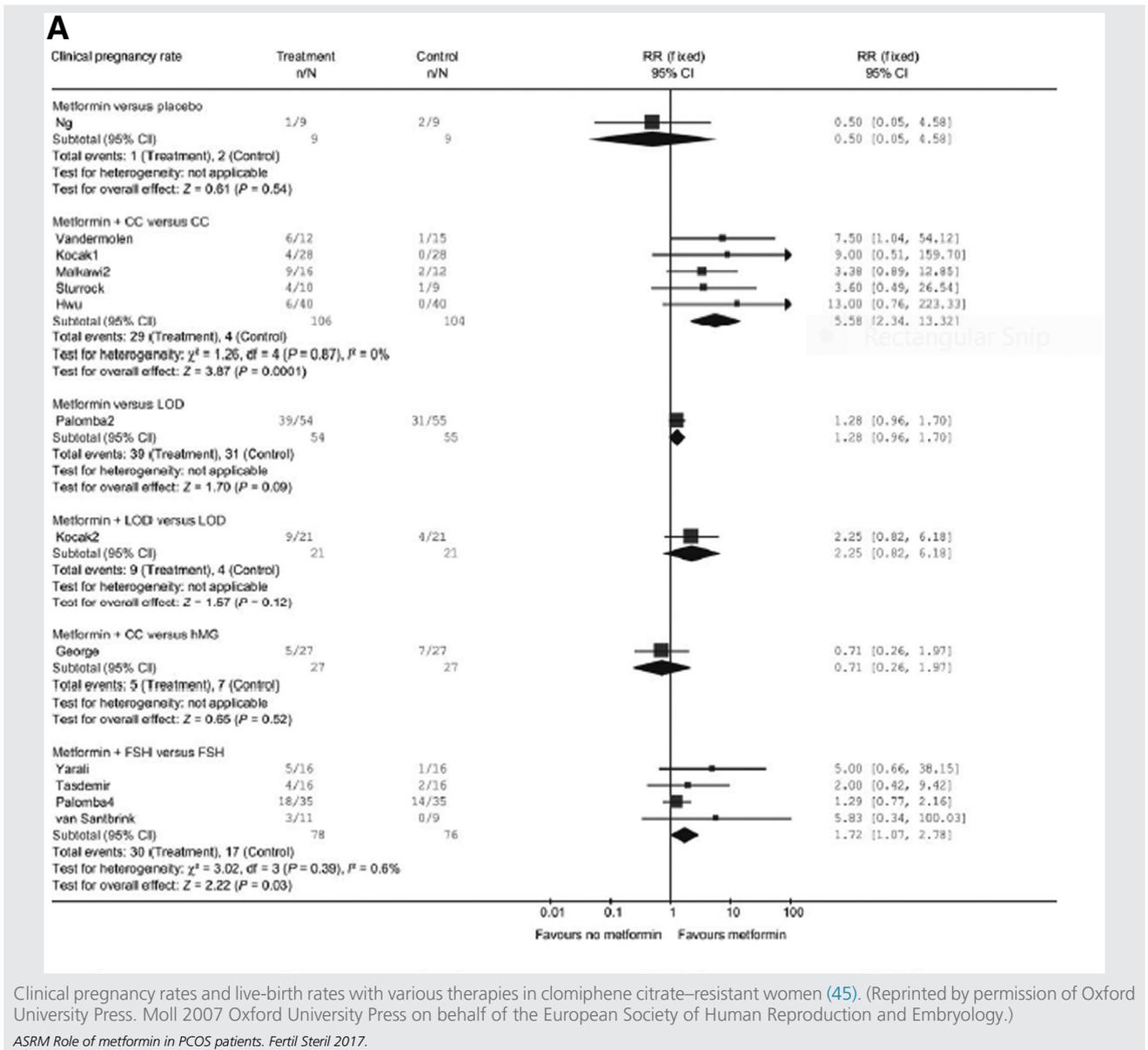
Summary statement.

- There is insufficient or conflicting evidence regarding metformin use combined with CC compared with gonadotropins for ovulation induction in women with CC-resistant PCOS. (Grade C)

DOES PRE-PREGNANCY USE OF METFORMIN REDUCE THE RISK OF MISCARRIAGE IN NON-ASSISTED REPRODUCTIVE TECHNOLOGY (NON-ART) PREGNANCIES?

There has been controversy about the potential impact of metformin to reduce miscarriage risks during pregnancy. It is important to recognize the limitations of the literature in this area given that miscarriage is typically a secondary outcome in the studies included in this guideline; thus, studies included would not have typically been powered to detect a difference on this topic. In addition, metformin was typically stopped at the time of a positive pregnancy test so any effect would occur at the time of implantation or very early pregnancy. Of 23 identified RCTs reporting miscarriage rates, only two found a significant reduction in miscarriage rate associated with pre-pregnancy metformin usage. One study was in non-obese PCOS patients with primary infertility and compared metformin plus placebo to those on CC plus placebo (9.7% vs 37.5, $P=.045$) (31). The other study compared metformin plus laparoscopy +/- CC if persistently anovulatory to those who had LOD plus multivitamins/placebo +/- CC if persistently anovulatory (15.4% vs 29.0%, $P<.05$) (62). The largest RCT to include this information showed no significant difference in miscarriage rate associated with metformin use (29).

FIGURE 2



Notably, metformin was discontinued with documentation of pregnancy. The authors of this study felt that the differences in miscarriage rate in the first trimester between the metformin-alone group (40%) and both the CC group (23%) and CC-plus-metformin (25%) group, although not statistically significant, warranted further study (29). There were six level-II studies that reported miscarriage rates, with only one finding a significant reduction in miscarriage rates (30, 71–75). That study compared miscarriage rates of 56 women who continued metformin throughout pregnancy with 50 who discontinued metformin with pregnancy initiation (8.9% vs 36%, $P < .001$) (71).

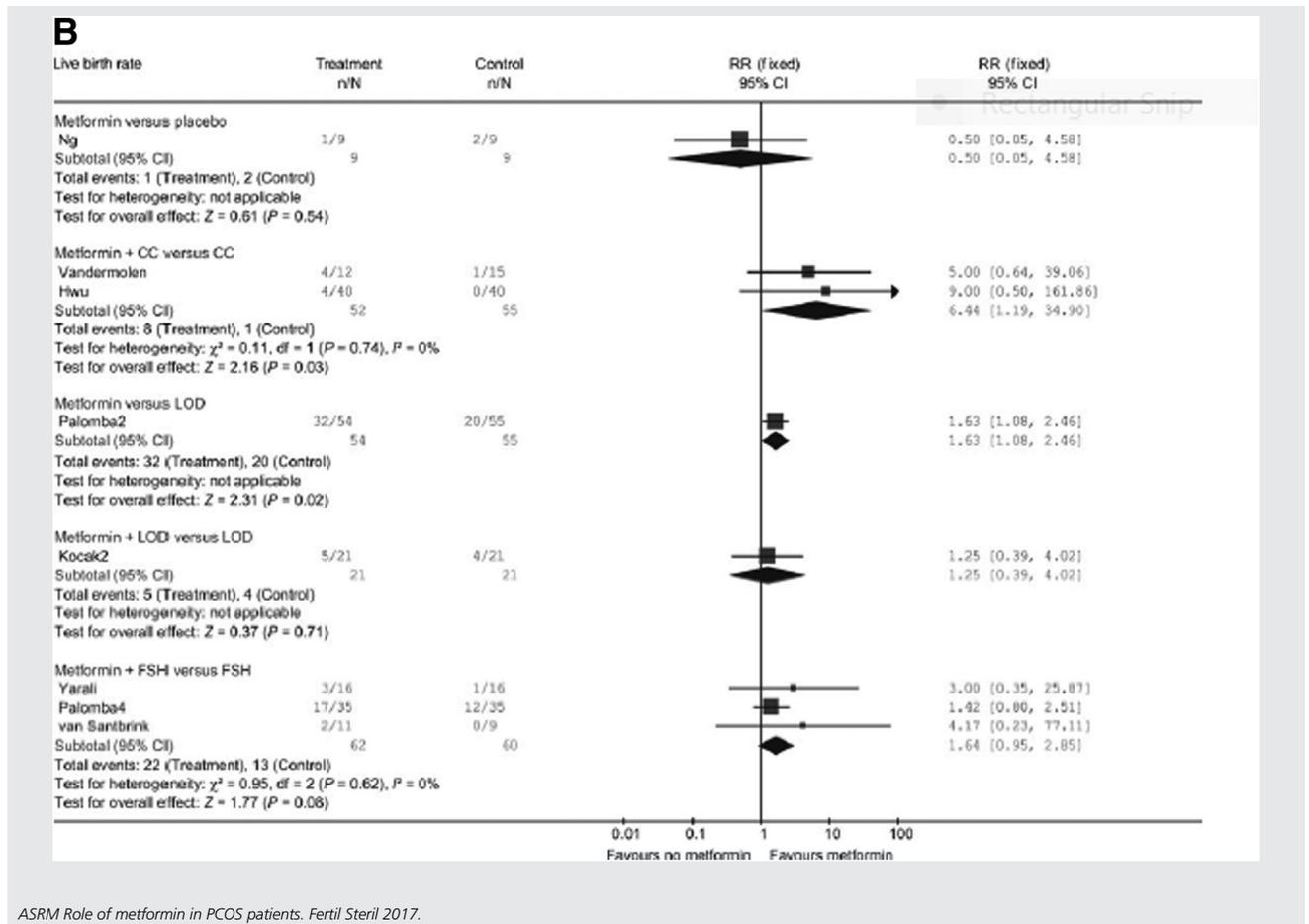
Five systematic reviews failed to identify a significant impact on miscarriage rates associated with metformin alone or in combination with CC (28, 46, 65, 76, 77). Four reviews found no effect on miscarriage rate. Two did not find

significant heterogeneity among included studies (28, 65), while the other two noted significant heterogeneity (46, 77). The fifth review looked specifically at lean patients and did not find a significant difference in miscarriage outcomes ($N=83$) (76).

This analysis is limited in that it specifically included studies involving the use of metformin for ovulation induction; thus, studies solely looking at the effect of metformin use on pregnancy outcomes, including miscarriage, would have been excluded with the exception of one study (71). Due to this limitation, this document cannot appropriately address the impact of continued metformin use throughout the first trimester on miscarriage risks as relevant studies could have been excluded.

While there are no well-controlled studies assessing fetal risks when metformin is taken during pregnancy, there are no

FIGURE 2 Continued



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data to suggest fetal risks to date. Therefore, metformin has been classified as US Food and Drug Administration (FDA) pregnancy category B.

Summary statements.

- There is fair evidence that metformin used while attempting pregnancy and stopped at the initiation of pregnancy does not affect the rate of miscarriage. (Grade B)
- There is insufficient evidence to recommend metformin during pregnancy to reduce the chance of miscarriage. (Grade C)

DOES METFORMIN AFFECT THE LIKELIHOOD OF MULTIPLE PREGNANCIES?

There were 15 randomized trials identified that reported multiple pregnancy rates in patients on metformin (21, 26, 29, 32, 37, 39, 42, 56, 60, 62–64, 66, 67, 78). There was a high degree of variability in the treatment utilized in the comparison arms of these studies. Seven studies had a metformin-alone arm. The other arm of these studies included either placebo, CC, CC plus metformin, or LOD. Nine studies that reported multi-

ple rate had a CC-plus-metformin arm vs either CC, aromatase inhibitors, LOD, or gonadotropins.

Several systematic reviews suggest no difference in multiple pregnancy rates between metformin alone and CC, or CC plus metformin (28, 45, 65, 76). A recent meta-analysis did not show a significant reduction in multiple pregnancy with metformin co-treatment in gonadotropin cycles compared with gonadotropins alone (OR 0.55; 95% CI 0.15–1.95) (70). However, the analysis is limited by sample size.

Consideration of the above data must include the overall caveat that while analyses showed no difference in the rate of multiple pregnancies among groups studied, most trials were insufficiently powered for comparisons regarding this outcome. There is no evidence to suggest that metformin alone induces multiple pregnancy. Studies comparing metformin with CC could not show a difference in multiple rate due to limited power of the studies. There is also no evidence of an effect (either increase or decrease) on multiple pregnancy rates in cycles using combination CC plus metformin vs CC alone. It should be noted that there are no studies that appear to have sufficient power for this analysis, so there remains insufficient evidence to exclude an impact with combination CC plus metformin (70).

Summary statements.

- There is good evidence that metformin alone does not increase the rate of multiple pregnancy. (Grade A)
- While there is no evidence of an effect (either increase or decrease) on multiple pregnancy rates in cycles using combination CC plus metformin vs CC alone, there remains insufficient data on this matter due to lack of adequate power to detect a difference. (Grade C)
- There is insufficient evidence of a reduced risk for multiple pregnancy with the addition of metformin to FSH compared with FSH alone. (Grade C)

IS METFORMIN MORE EFFECTIVE IN LEAN OR OBESE PCOS PATIENTS?

The specific question regarding the comparative efficacy of metformin in non-obese vs obese patients has not been assessed in RCTs designed to answer this question. However, there are 14 randomized trials that evaluated the role of BMI on the efficacy of metformin treatment to some degree (18, 19, 21, 23, 26, 27, 31, 38, 52, 56, 61, 63, 68, 79). Most studies categorized patients as obese with BMI ≥ 30 kg/m², with a few exceptions from non-US locations which used a BMI cut-off of 32 kg/m² for their studies due to a criterion within their specific health systems. Results of those studies are singled out below due to their inconsistency from the typical BMI definitions in the United States. Although there is significant heterogeneity, some limited data suggest that BMI may impact the efficacy of metformin. The small size of subgroups in addition to the heterogeneity of studies including different comparison groups significantly impede the ability to clearly answer this question.

Non-obese

Eight RCTs had subgroup analyses involving non-obese patients, typically defined as BMI < 30 kg/m². There was significant variability in the comparison groups, and numbers are small in most studies with mixed findings overall (18, 19, 21, 23, 31, 52, 68, 79). Three studies showed improved ovulation rates vs placebo suggesting that metformin is effective in lean patients (18, 19, 79). One study showed improved pregnancy rate, but not ovulation rate or live-birth rate in subjects receiving metformin compared with CC (31). There were two studies in CC-resistant patients with mixed results. One study showed no difference between pregnancy rate in CC plus metformin vs hMG (68), and another showed that both metformin and LOD both resulted in increased pregnancy rate when added to CC in non-obese CC-resistant patients (63). The latter had only 8 and 20 patients per group, respectively. Two systematic reviews showed no difference in pregnancy rate for non-obese subjects receiving metformin alone vs metformin plus CC (28, 44). While a systematic review did find an increased pregnancy rate in non-obese patients on metformin vs CC alone, this increase did not correspond with an increased live-birth rate (28). Another systematic review found no difference in pregnancy or live-birth rate comparing metformin to CC in patients with BMI < 32 kg/m² (76) (Fig. 3).

Obese

Seven studies had subgroup analyses involving obese patients, defined typically as BMI ≥ 30 kg/m² (21, 23, 27, 38, 52, 56, 61). Again, there was significant variability in the comparison groups, and numbers are small in most studies with mixed results overall. With metformin alone vs placebo, one study showed no difference in pregnancy rate (21). Another study showed that only percentage weight loss was associated with menstrual frequency in a comparison of patients receiving metformin plus diet counseling vs diet counseling alone (27). One study of CC plus metformin vs CC alone showed increased ovulation rate and pregnancy rate with metformin (38). Another study of metformin plus additional non-ART treatments showed higher live-birth rate than placebo plus non-ART treatments with metformin (52). In CC-resistant patients, one study showed that LOD had a higher pregnancy rate than metformin (61), and another showed that CC plus metformin had a higher pregnancy rate than CC plus placebo in obese patients (56).

Accordingly, four systematic reviews that evaluated impact by BMI indicated significant heterogeneity among studies (28, 33, 44, 76). For non-obese patients, one review concluded that metformin alone had a higher pregnancy rate than CC, but results were not consistent for live-birth rate (28). The addition of metformin to CC did not result in an increased pregnancy rate vs CC alone in two reviews for non-obese patients (28, 44). An analysis of studies of patients with BMI < 32 kg/m² did not find a difference in ovulation, pregnancy, or live-birth rate between metformin vs CC (76). Three systematic reviews addressed obese patients. One showed improved pregnancy rates and live-birth rates with CC over metformin (28). Two studies showed CC plus metformin to have a higher pregnancy rate vs CC alone (28, 44), but a difference in live-birth rate in this setting was not demonstrated in the only analysis that reported on live-birth rate in this subgroup (28) (Fig. 1).

Although many of the studies of PCOS involved significant numbers of obese women, heterogeneity in patient populations and failure to carefully examine the impact of BMI limit the ability to make any definitive conclusions about the effects of metformin in obese compared with lean women. It should be kept in mind that for the management of obese patients adjunctive medical therapies are considered second line to lifestyle modification (80).

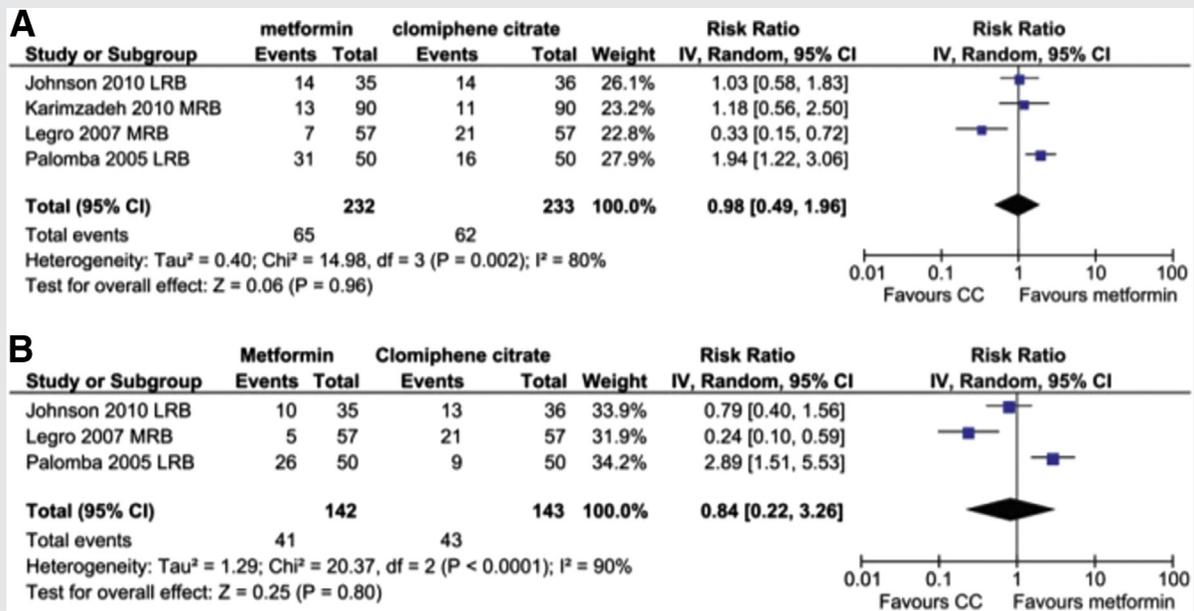
Summary statement.

- There is insufficient good-quality evidence to determine if metformin is more effective in non-obese or obese women with PCOS. (Grade C)

CONCLUSIONS

It is difficult to interpret studies in which metformin is used to induce ovulation in women with PCOS because of the heterogeneous nature of the populations treated. Metformin has been administered in several studies in which insulin resistance has not been documented and to both lean and obese women. The inclusion criteria for the various studies have

FIGURE 3



(A) Pregnancy and (B) live-birth rates in lean women with polycystic ovary syndrome treated with metformin vs clomiphene citrate (75). (Reprinted by permission of Oxford University Press. Misso 2012 Oxford University Press on behalf of the European Society of Human Reproduction and Embryology.)

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varied widely, with different definitions for PCOS used in different studies. In those studies that have used metformin only in women with documented insulin resistance, the criteria and testing used to document insulin resistance have differed. It has been administered alone to induce ovulation as well as in combination with a number of other agents to induce ovulation in women with PCOS. At present, there is a lack of evidence that metformin increases the rate of live birth in women with PCOS, even if some studies show increased ovulation and pregnancy rates. In addition, there is no evidence that metformin decreases the rate of miscarriage in women with PCOS who conceive, one of the claims from early nonrandomized studies involving the use of metformin.

UNANSWERED QUESTIONS

This guideline failed to determine if long-term administration of metformin increases ovulation, pregnancy, and live-birth rates in women with PCOS, as all studies identified examined the short-term (i.e., typically less than 6 months) use of metformin. The existing literature does not make it possible to determine if metformin is more effective in certain women with specific PCOS phenotypes (i.e., obese, insulin resistant, various ethnic groups). There have been no head-to-head comparisons of metformin alone with aromatase inhibitors or robust studies of the addition of metformin to aromatase inhibitors. Large, adequately powered, randomized trials are needed in carefully defined populations of phenotype-specified women with PCOS to determine in whom the use of metformin may be of benefit.

SUMMARY

- There is good evidence that metformin alone vs placebo increases the ovulation rate in women with PCOS. (Grade A)
- There is insufficient evidence to suggest that metformin alone increases pregnancy rates or live-birth rates compared with placebo. (Grade C)
- There is fair evidence from one, large well-designed RCT that metformin alone is less effective than CC alone for the achievement of ovulation induction, clinical pregnancy, and live birth in women with PCOS. (Grade B)
- There is insufficient evidence to suggest that metformin alone increases pregnancy or live-birth rates compared with letrozole alone. (Grade C)
- There is fair evidence based on one well-designed trial in support of letrozole for ovulation induction. (Grade B). Therefore, letrozole is a reasonable first-line agent for ovulation induction in PCOS patients.
- There is good evidence that metformin in combination with CC improves ovulation and clinical pregnancy rates but does not improve live-birth rates compared with CC alone in women with PCOS. (Grade A)
- There is fair evidence from one RCT that pretreatment with metformin for at least 3 months followed by the addition of another ovulation-inducing drug increases live-birth rate. (Grade B)
- There is fair evidence that CC-metformin improves ovulation and pregnancy rates compared with CC alone in CC-resistant PCOS women. (Grade B). However, more studies are needed to determine whether there may be subgroups of women (e.g., specific BMI, ethnicity, absence of insulin

resistance, etc.) with PCOS and CC resistance for which CC-metformin provides the most benefit over CC alone.

- There is fair evidence that overall pregnancy rates are not different with CC-metformin, CC-LOD, or LOD alone in women with CC-resistant PCOS. (Grade B)
- There is insufficient evidence regarding pregnancy rate or live-birth rate with the use of metformin alone compared with LOD for ovulation induction in CC-resistant PCOS patients. (Grade C)
- There is insufficient evidence to compare metformin plus CC to aromatase inhibitors alone or metformin plus aromatase inhibitors for ovulation induction in CC-resistant women. (Grade C)
- There is insufficient or conflicting evidence regarding metformin use combined with CC compared with gonadotropins for ovulation induction in women with CC-resistant PCOS. (Grade C)
- There is fair evidence that metformin used while attempting pregnancy and stopped at the initiation of pregnancy does not affect the rate of miscarriage. (Grade B)
- There is insufficient evidence to recommend metformin during pregnancy to reduce the chance of miscarriage. (Grade C)
- There is good evidence that metformin alone does not increase the rate of multiple pregnancy. (Grade A)
- While there is no evidence of an effect (either increase or decrease) on multiple pregnancy rates in cycles using combination CC plus metformin vs CC alone, there remains insufficient data on this matter due to lack of adequate power to detect a difference. (Grade C)
- There is insufficient evidence of a reduced risk for multiple pregnancy with the addition of metformin to FSH compared with FSH alone. (Grade C)
- There is insufficient good-quality evidence to determine if metformin is more effective in non-obese or obese women with PCOS. (Grade C)

RECOMMENDATIONS

Metformin alone should not be used as first-line therapy for ovulation induction in women with PCOS, since ovulation induction agents such as CC or letrozole are more effective. CC alone or letrozole alone are reasonable first-line agents for ovulation in women with PCOS. Combination therapy with CC may be beneficial in women who are resistant to CC alone. While metformin alone is not likely to increase live-birth rate in women seeking pregnancy in the short term, utilizing metformin in individualized cases of PCOS with the goal of improving ovulation rates over the long term may be of benefit. In the context of increased ovulation rate and overall improved insulin resistance on metformin, the subsequent addition of other ovulation-inducing agents may be beneficial in increasing pregnancy rates, although there is insufficient evidence of an increase in live-birth rates. These data suggest that individualization of treatment may be warranted, particularly in younger women with PCOS. Additional large, adequately powered randomized trials are needed in carefully defined populations of women with

various forms of PCOS (i.e., phenotype specified) to determine in whom the use of metformin may be of benefit.

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