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Is Metformin Indicated as Primary Ovulation Induction Agent in Women with PCOS? A Systematic Review and Meta-Analysis

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Key Words

Polycystic ovarian syndrome · Metformin · Clomiphene citrate · Ovulation induction · Randomized controlled trials

Abstract

Background: A recent meta-analysis has proven that metformin (M) is highly effective for ovulation induction in the clomiphene citrate (CC)-resistant patient. There is uncertainty whether M should be introduced as a primary ovulation induction agent in polycystic ovarian syndrome (PCOS). ***Methods:*** We conducted a systematic review and meta-analysis to establish if M is better when given alone or in combination with CC (CC+M) when compared with CC alone. This systematic review studied live birth delivery rate as the primary outcome. ***Results:*** We identified 14 prospective trials. Analysis of these results showed a reduction in the live birth rate in the group of patients treated only with M when compared with CC alone (OR = 0.48, 95% CI 0.31–0.73, p = 0.0006). An increase in ovulation (OR = 1.6, 95% CI 1.2–2.1, p = 0.0009) and pregnancy rate (OR = 1.3, 95% CI 1.0–1.6, p = 0.05) with CC+M when compared with CC alone was reported, but no difference was found when live birth rate was analyzed (OR = 1.1, 95% CI 0.8–1.5, p = 0.61). ***Conclusion:*** 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. Because of the side effects profile and contraindications of M, we believe M should not be indicated as a primary ovulation induction agent in women with PCOS.

Introduction

Polycystic ovarian syndrome (PCOS) is a very common endocrinopathy among infertile female individuals and affects approximately 6% of the general female population [1]. The most prominent presenting characteristics are anovulation and hyperandrogenism. The diagnosis of PCOS was recently debated and diagnostic criteria followed in the Rotterdam consensus statement [2]. This statement concluded that the diagnosis of PCOS could be made if two of the following are present: chronic anovulation, polycystic ovaries on ultrasound, and hyperandrogenism [2].

Insulin resistance and concomitant hyperinsulinemia are frequently found in obese women with PCOS (65%) [3, 4]. The incidence of insulin resistance among lean women with PCOS is nearly 20% [5]. This results in hyperinsulinemia and enhances the luteinizing hormone-driven production of androgens from ovarian theca cells [3]. Hyperinsulinemia, insulin resistance and an increase in androgen production are all linked in patients with PCOS [4, 5]. It is also known that patients with PCOS and insulin resistance are often resistant to ovulation induc-

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tion. Is the answer in the management of infertile women with PCOS the use of insulin sensitizers? Previous articles have been published where insulin sensitizers such as biguanides (metformin) [6, 7] and thiazolidinediones (troglitazone) have been used and proven to improve metabolic abnormalities in patients with PCOS [8].

Metformin, a biguanide, is normally used in non-insulin-dependent diabetes and the mechanisms of action include inhibition of gluconeogenesis in the liver and increasing the peripheral uptake of glucose. Metformin reduces levels of luteinizing hormone, hyperinsulinemia and also decreases ovarian production of androgens [9, 10]. Most frequent side effects of metformin include gastrointestinal symptoms such as diarrhea, nausea and vomiting. Due to the adverse effects of metformin, 30% of women under treatment may stop this medication. Lactic acidosis is a rare but a serious side effect with a case fatality rate as high as 50.3% [11].

Infertility secondary to chronic anovulation is one of the most common clinical presenting features [1]. Clomiphene citrate (CC) is the standard drug used for ovulation induction in women with PCOS [12–14]. Patients with PCOS are frequently resistant to CC and these results in numerous cycles where CC is unsuccessfully used. A recent meta-analysis has proven that metformin is highly effective for ovulation induction in the CC-resistant patient [15].

The question to be answered is whether metformin should be introduced as a primary ovulation induction agent in women with PCOS.

The aim of this literature search is to determine live birth rate with metformin (M) when given alone or in combination with CC (CC+M) when compared with CC alone in ovulation induction protocols for women with PCOS.

Methods

Identification of the Literature

The following electronic databases were searched: MEDLINE, Google Scholar, and *Cochrane Library:* CENTRAL Database for studies published from 1 January 2000 to 30 November 2010. A combination of Medical Subject Headings (MeSH) was used: metformin, side effects, CC ovulation induction, PCOS, randomized controlled trials. These subsets were combined with 'AND' to generate a subset of citations relevant to our research question. The reference lists of all known primary and review articles [16–18] were examined to identify cited articles not captured by electronic searches. Human reproduction and fertility and sterility journals were searched individually for additional articles. No language restrictions were placed in any of our searches. The searches were conducted independently by T.I.S. and M.I.V. No written protocol of this review has been made or published.

Study Selection

Clinical trials comparing two groups of patients were selected only if they met the inclusion criteria. The inclusion criteria were prospective randomized controlled trials where articles on metformin were randomized, and compared with CC+M, or with CC alone in ovulation induction protocols in women with PCOS. In all the studies mentioned, the recent Rotterdam statement [2] was used for the diagnosis. The dosage of metformin used in all articles was from 500 mg/day up to 2,000 mg/day maximum dose. The maximum dosage of CC was 200 mg/day. We reported live birth rate as a primary outcome and measures such as ovulation and clinical pregnancy as a secondary outcome.

Studies were selected in a two-stage process. First, two reviewers (T.I.S. and M.I.V.) scrutinized the titles and abstracts from the electronic searches independently and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Secondly, final inclusion or exclusion decisions were made on examination of full manuscripts. In cases of duplication the most complete or the most recent publication was used. Any disagreements about inclusion criteria were resolved by consensus or arbitration by a third reviewer (T.F.K.).

Statistical Analysis

The data on the outcomes of each included trial were summarized in two-by-two tables. The Peto odds ratio (OR) with its 95% confidence interval (CI) was calculated for the use of metformin alone or in combination with CC (CC+M) when compared to CC alone in ovulation induction. Statistical significance was inferred when the OR did not include 1.

The weight of each study in each analysis was calculated as inversely proportional to the variance. The degree of heterogeneity of studies was calculated using the χ^2 test. Where the p value was <0.05, or where $I^2 > 50\%$ the OR and 95% CI are still reported, but the applicable studies were re-analyzed to find an explanation for any differences. We also applied a fixed effect and a random effect analysis to each dataset.

Results

The search strategy yielded 309 citations, all captured from electronic citations (fig. 1). Of these, 203 publications were excluded, as it was clear from the title that they did not fulfill the selection criteria. From the remaining 106 articles, 60 were excluded on the basis of the abstract. For the remaining 46, we obtained full manuscripts and following scrutiny of these, we identified 32 potentially relevant studies; 6 publications were duplicated [19–24]. From these 32, another 4 were excluded because they included women with PCOS who were CC resistant. The remaining 22 articles were excluded for not meeting the inclusion criteria by protocol. Therefore the total number of studies included in this review was 14 (fig. 1). All the

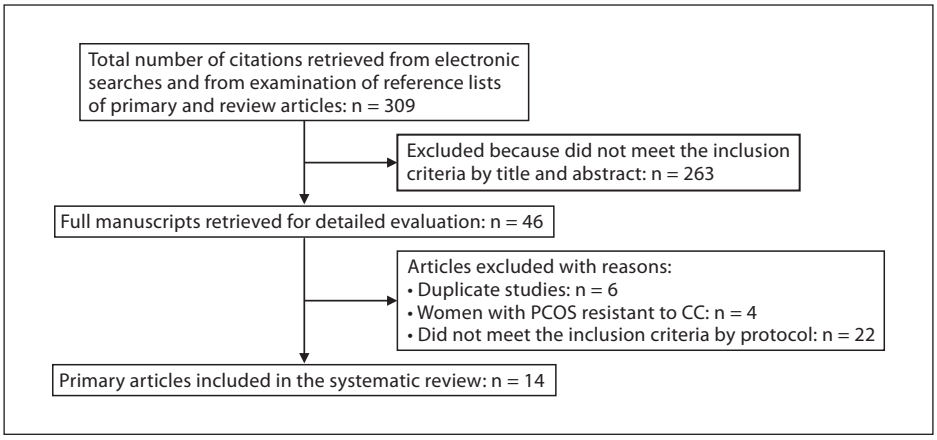

Fig. 1. Study selection process for systematic review.

studies were in English, 13 were full manuscripts and 1 was an abstract [25], only abstract is available.

All 14 included studies were prospective randomized controlled studies whereby the target population was women with PCOS and anovulation. In these studies, CC was compared with metformin alone or the combination of CC+M. The primary outcome was live birth rates and as a secondary outcome pregnancy and ovulation rates were reported. The main characteristics of the 14 studies included in the review are presented in table 1. Figures 2–9 show the results of comparisons assessing primary and secondary outcomes.

There were no differences between the OR for each outcome, irrespective of whether Peto fixed effect or random effects analyses were done.

Heterogeneity >50% can be mainly explained by the influence of specific clinical differences between studies. Different groups of PCOS patients between studies were noticed: overweight patients, non-obese patients, obese patients or a mixture of any of the above. Although doses for M and CC were comparable between studies, some of the publications expressed a doses range without specified number of patients treated with specific dose. Time of exposure was also different between some of the studies. Previous treatments received by different populations groups versus newly diagnosed patients not exposed to previous therapy or either diet should also be taken into consideration to explain heterogeneity.

Primary Outcome

Live Birth Rate

Pooling of results of the 4 prospective studies that compared CC alone with metformin alone showed a 53% reduction in the live birth rate in the group of patients treated only with metformin (OR = 0.48, 95% CI 0.31–0.73, p = 0.0006; fig. 2). Meta-analysis for the primary outcome of live birth rate showed a not statistically significant difference between the two groups when the combination (CC+M) was compared with CC alone (OR = 1.1, 95% CI 0.78–1.5, p = 0.61; fig. 3).

Secondary Outcomes

Ovulation

Pooling of results from 2 of the 14 studies that reported ovulation as an outcome showed a statistically significant 53% relative reduction in the occurrence of ovulation when metformin was used compared with CC alone (OR = 0.48, 95% CI 0.41–0.57, $p < 0.00001$; fig. 4) Women were randomized in studies comparing the use of CC alone with metformin.

Meta-analysis of the 8 prospective studies that reported ovulation when CC+M was compared with CC alone showed a statistically significant difference between the two groups, in favor of the combination (CC+M) (OR = 1.6, 95% CI 1.2–2.1, p = 0.0009; fig. 5).

Pooled analysis of the 3 prospective studies that reported ovulation in the subgroup of obese patients (with body mass index, BMI >25) when CC+M was compared with CC alone, showed a statistically significant increase in ovulation in the patients treated with both drugs (CC+M). Ovulation was reported twice as often as compared with CC alone (OR = 2.2, 95% CI 1.2–4.0, p = 0.01; fig. 6).

Pregnancy Rate

Pooling of results from 6 of the 14 prospective studies that reported pregnancy as an outcome showed no statistically significant difference when CC alone was compared to metformin alone (OR = 0.78, 95% CI 0.59–1.0, p = 0.06; fig. 7).

Table 1. Main characteristics of the studies included

Trials (n)	Participants	Intervention	Comparison	Main outcomes	Quality features
Johnson et al. [26] 2010 (n = 171) 106 vs. 65	Anovulatory or oligo-ovulatory women with PCOS defined by the Rotterdam criteria	M 500 mg 3/day or CC 50–150 g/day or both or placebo	BMI ≤32 received CC or M or CC+M BMI >32 received placebo or M	Pregnancy and live birth	Randomized trial double-blind placebo and parallel
Karimzadeh et al. [27] 2010 (n = 343) 75 vs. 90 vs. 90 vs. 88	Overweight infertile women with PCOS diagnosed by Rotterdam criteria	CC 100 mg/day or M 500 mg 3/day or CC+M or lifestyle modification	Lifestyle modification and medical treatments: CC, M, and CC+M	Menstrual cycle, waist, endocrine and lipid profile Clinical pregnancy	Randomized trial double-blind Parallel
Khorram et al. [28] 2006 (n = 31) 16 vs. 15	Women with PCOS with BMI >29 and infertility (Rotterdam criteria)	M 500 mg 3/day from day 1 to 14 + CC 100 mg/day from day 5 to 9 Or CC alone 100 mg/day	CC+M vs. CC alone	Ovulation Serum insulin and total and free T	Randomized trial Not blinded Parallel
Sahin et al. [29] 2003 (n = 31) 11 vs. 10	Infertile women with PCOS (Rotterdam criteria)	M 1,700 mg/day for 3 months CC 100 mg/day for 5 days until pregnancy or 6 cycles were reached	CC+M vs. CC alone	Ovulation and pregnancy rates	Randomized trial Not clear if blinded Parallel
El-Biely et al. [30] 2001 (n = 90) 45 vs. 45	Infertile and obese patients with PCOS (Rotterdam criteria)	CC 50–100 mg/day for 5 days M 500 mg 3/day for 6 months	CC+M vs. CC alone	Ovarian response and pregnancy rate	Randomized trial Single-blinded Parallel
Ben Ayed et al. [31] 2009 (n = 32) 16 vs. 16	Women with PCOS diagnosed by Rotterdam criteria	CC 100 mg/day M 1,700 mg/day	CC+M or CC + placebo	Ovulation	Randomized trial Not blinded Parallel
Singh et al. [25] 2001 (n = 100) 53 vs. 47	Non-obese patients (BMI <25 with PCOS	CC 50 mg/day M 1,000 mg/day for at least 4 months	CC+M or CC alone	Pregnancy rate	Randomization not clear, presumed not blinded Only abstract available
Dasari et al. [32] 2009 (n = 40) 24 vs. 16	Infertile women with PCOS diagnosed by Rotterdam criteria	CC 50–150 mg/day M 1,500 mg/day	CC alone or CC+M	Ovulatory and pregnancy tests	Randomized trial Not-blinded Parallel
Palomba et al. [23] 2005 (n = 100) 45 vs. 47	Non-obese primary infertile anovulatory women with PCOS	M 850 mg twice/day CC 150 mg/day 6 months	M + placebo CC + placebo	Ovulation Pregnancy Abortion Live-birth rates	Randomized trial Double-blind Double-dummy Parallel
Zain et al. [24] 2009 (n = 115) 38 vs. 39 vs. 38	Newly diagnosed patients with PCOS based on ESHRE/ASRM criteria	M 1,500 mg/day CC 50–200 mg/day for 5 days during 6 months	M CC CC+M	Ovulation Pregnancy Live-birth rates	Randomized trial Not-blinded Parallel
Siebert et al. [22] 2009 (n = 107) 52 vs. 55	Patients with PCOS diagnosed by Rotterdam criteria Mean BMI >28	M 850 mg twice/day CC 50–150 mg/day for 5 days during 4 months	CC + pretreatment with M CC alone	Ovulation rate	Randomized trial Blinded Parallel
Legro et al. [20] 2007 (n = 626) 209 vs. 208 vs. 209	Infertile women with PCOS (Rotterdam criteria)	CC 50–150 mg/day M 500–2,000 mg/day during 30 weeks	CC M CC+M	Live birth and pregnancy rate	Randomized trial Blinded Parallel
Moll et al. [19] 2006 (n = 228) 111 vs. 114	Women with PCOS diagnosed by Rotterdam criteria	CC 50–150 mg/day M 500–2,000 mg/day during 6 months	CC+M CC + placebo	Ovulation Pregnancy Abortion Resistance to CC	Randomized trial Double-blind Placebo and parallel
Moll et al. [33] 2008 (n = 226) 111 vs. 114	Women with PCOS diagnosed by Rotterdam criteria	CC 50–150 mg/day for 5 days M 500–2,000 mg/day during 6 months	CC+M CC + placebo	Pregnancy rates	Randomized trial Double-blind Placebo and parallel

T = Testosterone; n = number of randomized patients.

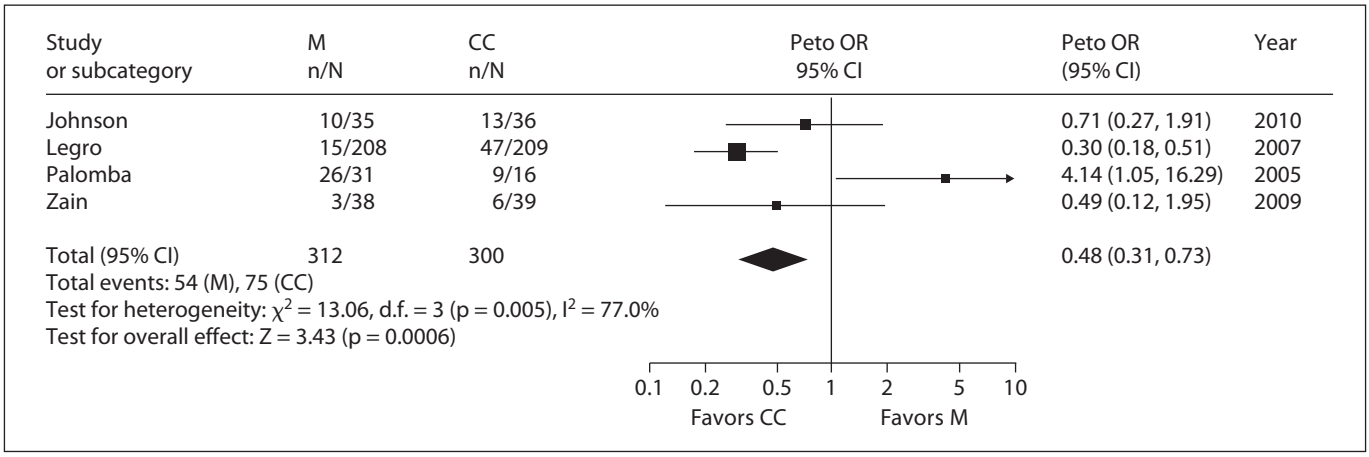

Fig. 2. CC vs. M: live birth. Better live birth rate with CC alone when compared with M alone. p = 0.0006.

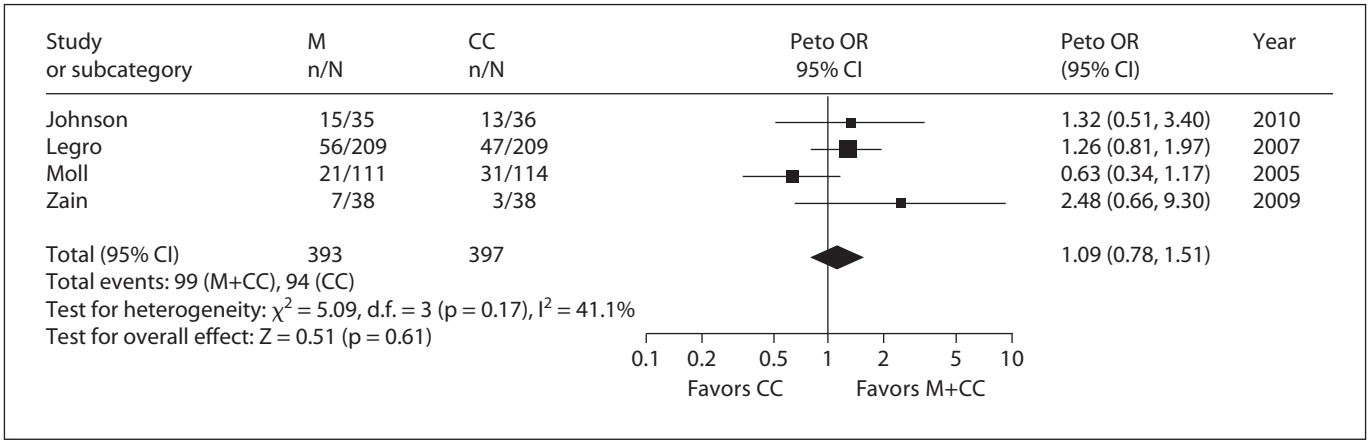

Fig. 3. M+CC vs. CC: live birth. No significant difference between the two groups. p = 0.61.

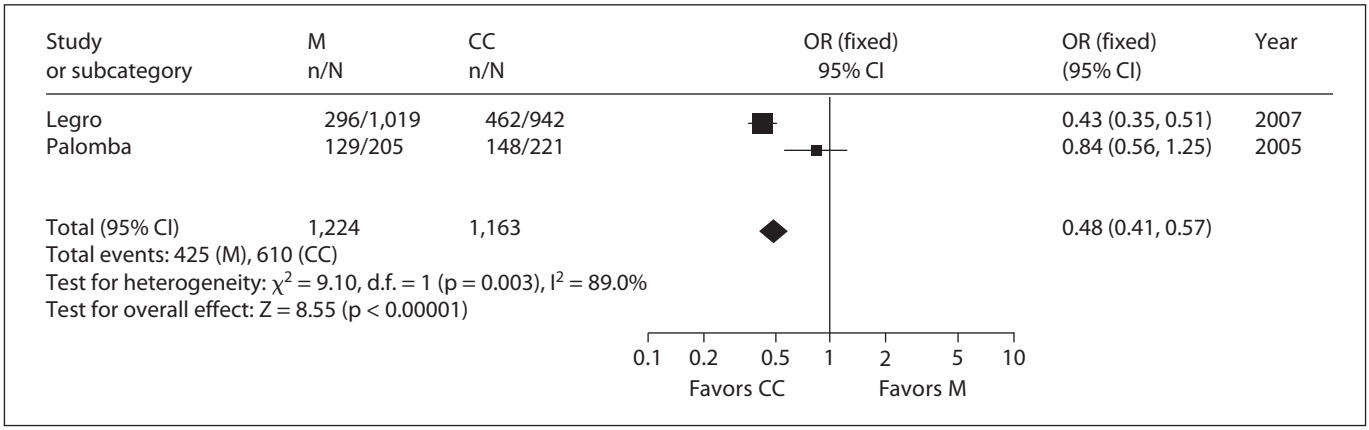

Fig. 4. CC vs. M: ovulation. When ovulation is the primary endpoint, CC alone performed significantly better than M alone. p < 0.00001.

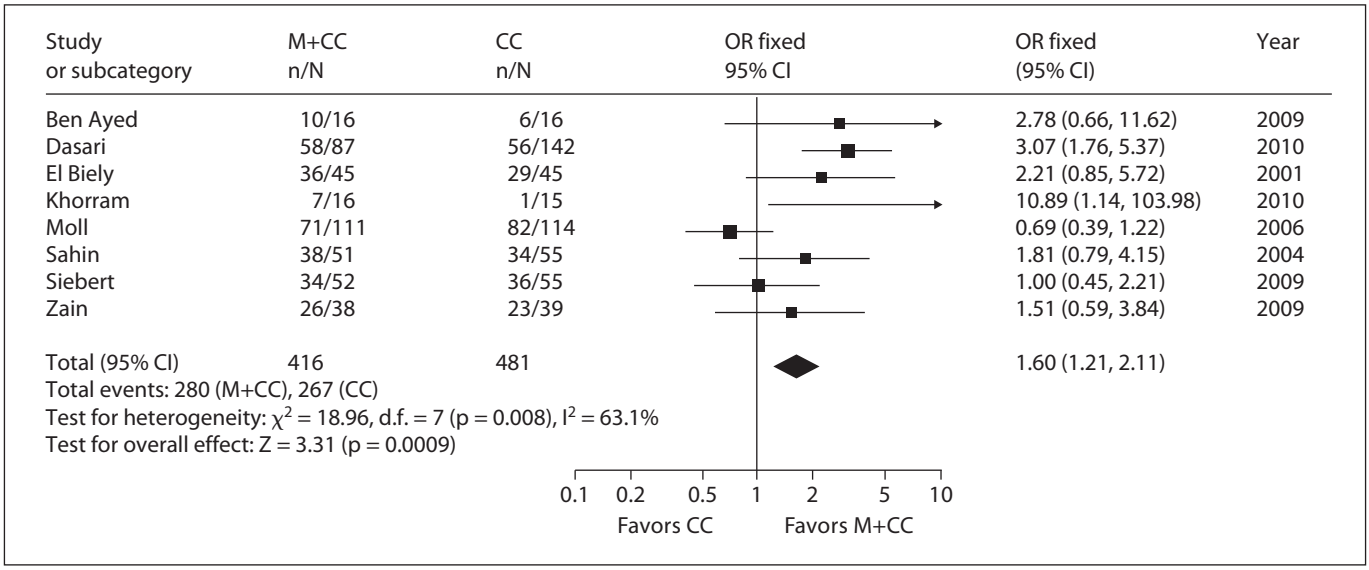

Fig. 5. M+CC vs. CC: ovulation. Ovulation was significantly better with the combination (CC+M) compared with CC alone. $p < 0.00001$.

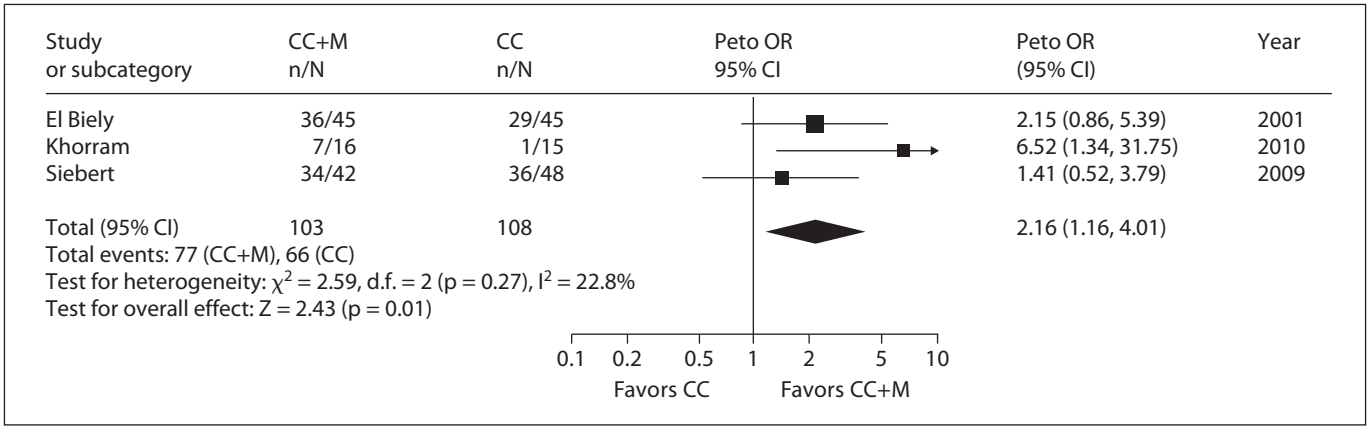

Fig. 6. CC+M vs. CC in obese women – BMI >25: ovulation. Ovulation was significantly better with CC+M when compared with CC alone in the obese patients. p = 0.01.

Meta-analysis of 10 studies that reported pregnancy as an outcome in which the combination (CC+M) was compared with CC alone showed a significant increase in pregnancy rate in the group of patients treated with the combination (CC+M) (OR = 1.3, 95% CI 1.0–1.6, p = 0.05; fig. 8).

Pooling of results of the 4 prospective studies that reported pregnancy in the subgroup of patients with BMI >25, showed a non-significant difference between outcomes in the two groups, when the patients received the combination (CC+M) or CC alone (OR = 1.2, 95% CI 0.82–1.8, p = 0.33; fig. 9).

Discussion

The aim of this review was to compare CC with metformin alone, or in combination when studied as a primary ovulation induction agent in women with PCOS. Live birth rate was our primary outcome and pregnancy rates and ovulation rates were also described as a secondary outcome. One of the first studies to address this topic was a multi-center study conducted by Nestler et al. [10]. They studied 61 obese women with PCOS and concluded that spontaneous ovulation induced by CC may be increased with the addition of metformin in obese women

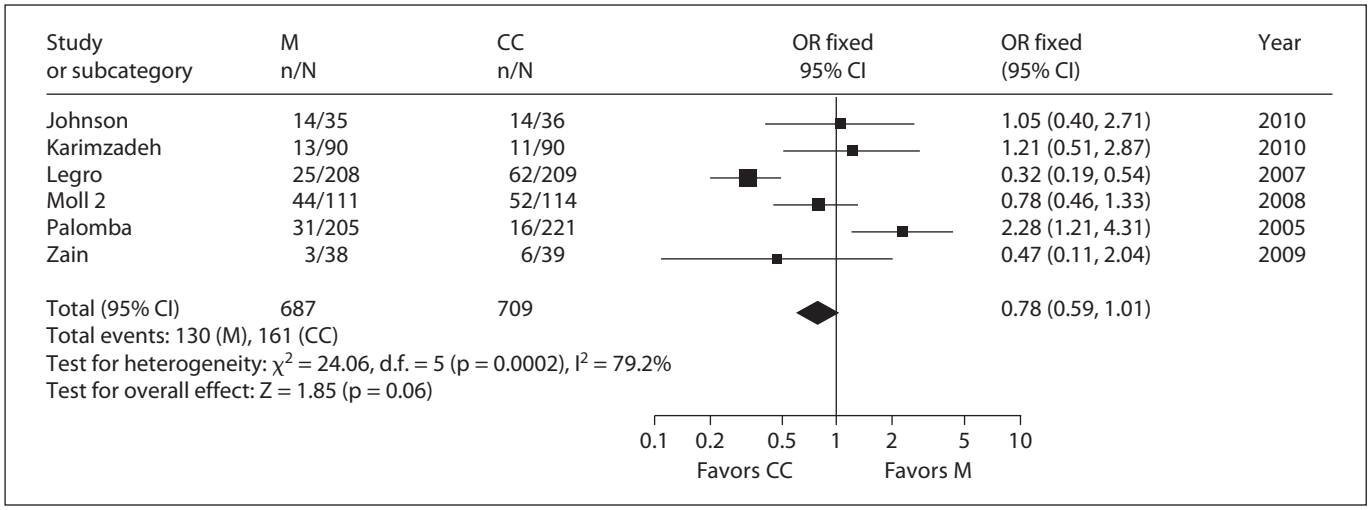

Fig. 7. CC vs. M: pregnancy. No significant difference between the two groups. p = 0.76.

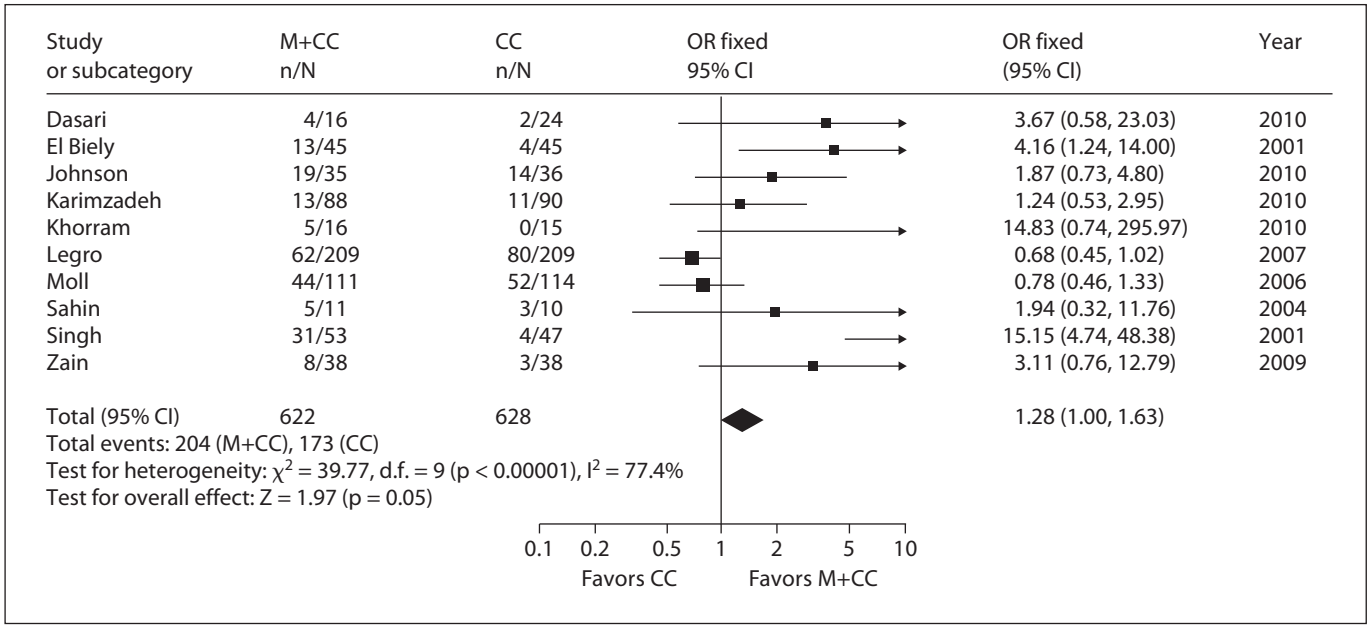

Fig. 8. M+CC vs. CC: pregnancy. Pregnancy rate was significantly better with the combination (CC+M) compared with CC alone. p = 0.05.

with PCOS by decreasing serum insulin concentrations. This was not a prospective randomized control trial and was also a very small study. Since 2000 many studies have been published questioning the role of metformin in ovulation induction protocols for women with PCOS.

Our review shows that CC alone is superior to metformin alone regarding ovulation rates and live birth rates. The question remains whether metformin in combination with CC is superior to CC alone when ovulation rates, pregnancy and live birth rates are assessed.

When evaluating the statistical results of this review, the combination (CC+M) was superior when compared with CC alone regarding ovulation (p = 0.0009) and pregnancy rate (p = 0.05). This may prompt us to use metformin in all ovulation protocols; however our primary endpoint should be live birth rates. When the live birth rate

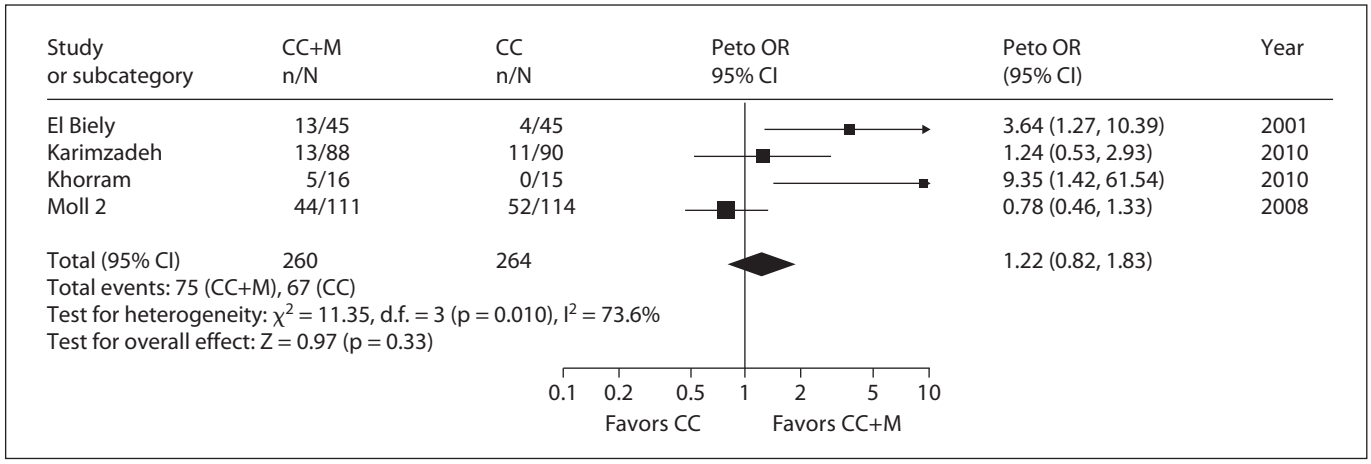

Fig. 9. CC+M vs. CC in obese women – BMI >25: pregnancy. No significant difference between the two groups. p = 0.33.

was evaluated, no evidence of an effect favoring CC+M versus CC alone could be reported. Only two studies addressed the issue of abortion rates [19, 23] but the numbers are very small and the results showed no difference when the groups were compared.

The data presented regarding the role of metformin in obese women with PCOS are similar to the data for nonobese women. When metformin is added for ovulation induction, there is a significant benefit (p = 0.01). When pregnancy rate is the outcome, the benefit is not statistically significant (p = 0.33). Given the strong evidence that hyperinsulinemia plays a pivotal role in the pathogenesis of PCOS, it is reasonable to believe that intervention aimed at reducing circulating insulin levels might also help to restore normal reproductive endocrine function [5, 8]. After 10% weight loss, ovulatory function may return in many obese women with PCOS. Compared with no intervention or treatment with metformin, intensive lifestyle modifications have also been observed to significantly reduce the risk for progression from impaired glucose tolerance to diabetes mellitus among patients who have an average BMI of 30 [34, 35]. In small studies of obese women with PCOS and in adolescents, metformin was observed to improve impaired glucose tolerance [36, 37]. Metformin has also been shown to improve lipid profiles [38]. Nevertheless, in the absence of any long-term studies, metformin cannot be considered as first-line treatment for PCOS when the only goal is the prevention of long-term complications. Lifestyle intervention should always be regarded as the best initial treatment [11, 39, 40].

We have to bear in mind that metformin is associated with side effects reported by a recent Cochrane systematic review and meta-analysis by Tso et al. [41]. This study described significantly higher side effects in the metformin group when compared to placebo (p = 0.049) in a group of PCOS patients undergoing ART treatment [41]. The 3 studies used for the meta-analysis were prospective randomized, placebo-control, double-blind, but only reported side effects with metformin as a secondary outcome. The only adverse event acknowledges was gastrointestinal symptoms [42–44]. Lactic acidosis is a rare but a serious side effect with a case fatality rate as high as 50.3% [45]. Therefore, metformin should not be prescribed to patients with renal, hepatic or major cardiovascular disease because such patients are predisposed to elevated lactate levels [11]. There are currently no adequate data to support the use of metformin in early pregnancy [11].

This review included only prospective randomized control trials. We have to emphasize that there is a substantial difference in the number of patients included in the study groups when comparing ovulation, pregnancy and live birth rates. In the ovulation group, there were 416 and 481 patients, respectively, in the pregnancy group 622 and 628, respectively. As mentioned, in both these groups there was a significant benefit when metformin was used in combination with CC. When assessing live birth rates, we assessed only 393 and 397 patients, respectively. Only this group did not show a significant benefit when metformin was added to CC, but did show a definitive trend in favor of the combination. It is evident that only recently have live birth rates been included in studies as the pri-

mary outcome, hence the smaller numbers. Will this positive trend become significant if we have greater numbers? It is therefore of utmost importance that this important question is visited on a regular basis as more data becomes available.

In a recent Cochrane review [46] the authors also concluded that the addition of metformin does not improve live birth rates. The main difference between our review and the Cochrane review is that we specifically focused on the use of metformin in different ovulation protocols for patients with PCOS. We only included prospective randomized control trials and excluded trials in CC-resistant patients. Regarding ovulation rates when CC and metformin was compared with CC alone, our review had 416 and 481 patients in the respective arms compared with 365 and 397 in the Cochrane review. Regarding pregnancy rates, we have 622 and 628 in the respective arms versus 486 and 490 in the Cochrane review. The main question to answer is whether the addition of metformin to CC improves live birth rates? In our review we had 393 and 397, respectively, versus 373 and 379 of the Cochrane review addressing the issue of live birth rates. Unfortunately, the latest article of Moll et al. [33] in 2008 only had ongoing pregnancy to 12 weeks' gestation as final primary outcome. These numbers highlights the fact that we need more data on live birth rates.

Strength of our review lies in the extensive search strategy, the valid data synthesis methods and the prospective randomized studies included. The weaknesses are mainly related to the clinical heterogeneity among studies. There is also the potential danger of publication bias due to the lack of submission or acceptance of negative outcome trials.

Based on the results of the trials discussed in our study we conclude that: (1) metformin alone is less effective than CC alone when addressing live birth rate in PCOS patients undergoing ovulation induction, and (2) metformin should not be added to CC as a primary method for ovulation induction in women with PCOS due to no evidence of an effect favoring the combination regarding live birth rates and the side effect profile as discussed.

However, it is important to emphasize that these findings may change as more data on live birth rates becomes available and highlights the importance that the question of live birth rates should continuously be revisited. We therefore encourage future prospective randomized control trials addressing the issue of live birth rates when metformin is added to CC in ovulation induction protocols. In the treatment of obese women with PCOS, they should first lose weight and then follow similar guidelines as for non-obese women. The addition of metformin is advised in CC-resistant women with PCOS. However, it is of utmost importance that all obese women with PCOS should first be placed on an active and sustainable exercise and weight loss program before any treatment is offered.

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