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REVIEW

Does Metformin combined with Clomiphene Citrate improve fertility related outcomes in Clomiphene resistant women with PCOS: A systematic review



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KEYWORDS

Clomiphene Citrate resistance;
Metformin;
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Abstract *Background:* Polycystic Ovary Syndrome (PCOS) is clinically associated with infertility. Many women are resistant to Clomiphene Citrate and the addition of insulin sensitizers may help to overcome this challenge.

Objective: This review aims to assess if Metformin added to Clomiphene Citrate improves pregnancy outcomes in patients with PCOS and are resistant to Clomiphene Citrate.

Search strategy: A systematic search was conducted on four electronic databases published until May 2013.

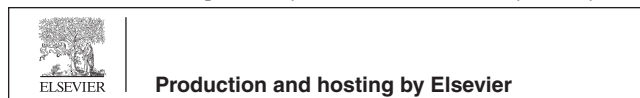
Selection criteria: Studies evaluating the use of Metformin in combination with Clomiphene Citrate resistant patients with PCOS compared to placebo. Outcomes assessed were ovulation rate, pregnancy by ultrasound, Sex Hormone Binding Globulin (SHBG), BMI, fasting insulin and testosterone levels.

Data collection and analysis: The reviewers carried out data extraction of specific outcomes and evaluated each study according to the sign guidelines.

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Main results: In total 40 citations were identified however only four were eligible for analysis. Two studies were found to have a statistically significant improvement in ovulation and pregnancy rates in the intervention group compared to the control group. These studies used the highest dose of Metformin and Clomiphene Citrate. In two studies we found statistically significant reductions in testosterone concentrations and BMI values.

Authors' conclusions: Metformin and Clomiphene Citrate have been shown to improve ovulation and pregnancy rates in the treatment of infertile patients with PCOS who are Clomiphene resistant. However, the optimal treatment regime remains ambiguous and needs further investigation with larger sample sizes of adequate power.

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1. Introduction

Infertility is a global problem affecting 48.5 million couples (1) and is defined as “a woman of reproductive age who has not conceived after 1 year of regular unprotected vaginal sexual intercourse” (2).

The main causes include ovulatory and uterine disorders, tubal damage and idiopathic (2). PCOS is an ovulatory disorder and is the most common cause of female infertility in UK affecting 5–10% of patients of reproductive age (3).

Three main patho-physiological features of PCOS are: polycystic ovaries, anovulation and hyperandrogenism (3). These lead to clinical features including amenorrhoea/oligomenorrhoea, hirsutism and acne (4). However, a third of patients are asymptomatic (5). Biochemical disturbances include:

hyperinsulinaemia, raised Luteinising Hormone (LH) and hyperandrogenism (6).

Hyperinsulinaemia, insulin resistance and increased androgen secretion may play a role in the pathogenesis of PCOS induced infertility (7). Insulin resistance indirectly causes anovulation through compensatory hyperinsulinaemia (8). Furthermore insulin directly effects ovarian androgen production. Therefore managing insulin resistance may be crucial to fertility treatment (4).

Negative feedback between Sex Hormone-Binding Globulin (SHBG) and fasting insulin suggest SHBG production is inhibited by insulin (8). Low SHBG concentrations lead to an increase in the bioactivity of testosterone resulting in hyperandrogenism. Thus, insulin resistance has a significant role in the pathogenesis and clinical manifestations of PCOS (8).

Disturbance of the hypothalamic–pituitary–ovarian axis is an external factor leading to ovarian dysfunction (9). This disturbance leads to increased Gonadotrophin Releasing Hormone (GnRH) resulting in hypersecretion of LH. This overexpression effects ovarian androgen production and oocyte development (9).

Other factors include lifestyle, nutrition and genetic abnormalities (9). Approximately half of patients with PCOS are overweight, and a third may develop type 2 diabetes (10).

The first line pharmacological treatment for infertility is Clomiphene Citrate which stimulates ovulation in 70–90% and pregnancy rates of 30–40% (11–13). However, evidence dictates 25% are unresponsive, described as Clomiphene Citrate resistance (14). It has recently become associated with insulin resistance.

In Clomiphene Citrate resistant woman, the standard treatment is gonadotrophins. However, these have increased risk of multiple pregnancies (14). Therefore, a safer treatment option is needed.

Previous studies reveal that Metformin administration reduces ovarian production of androgens, leading to spontaneous or Clomiphene Citrate induced ovulation, independent of Body Mass Index (BMI) changes (4). Insulin sensitisers decrease gluconeogenesis and utilisation of glucose in the presence of insulin (15). Therefore, using an insulin sensitiser such as Metformin may improve metabolic abnormalities and ovulation (7,16–19).

The aim of this review is to assess if Metformin alters hormone levels, ovulation rates and pregnancy compared to placebo in Clomiphene Citrate resistant PCOS patients.

2. Methods

2.1. Literature search

Four electronic bibliographic databases were searched (Medline, Embase, AMED and Scopus) from 1946 (AMED 1985, Scopus 1960, 1947 Embase) until May 2013. The following terms were used as MeSH and mapping terms: Infertility, anovulation, randomised control trial, Polycystic Ovary Syndrome, PCOS, Metformin, Clomiphene resistance. These terms were all combined appropriately using the Boolean operators AND and OR. The search was limited to full text, English language and female humans (See Fig. 1).

2.2. Inclusion criteria

2.2.1. Type of studies and study population

All randomised controlled trials that involved patients of reproductive age ranging from 18 to 45 years of age who had been diagnosed with PCOS were included in the review. In addition, studies should include patients who had previous unsuccessful attempts with primary or secondary infertility treatment and also be Clomiphene resistant.

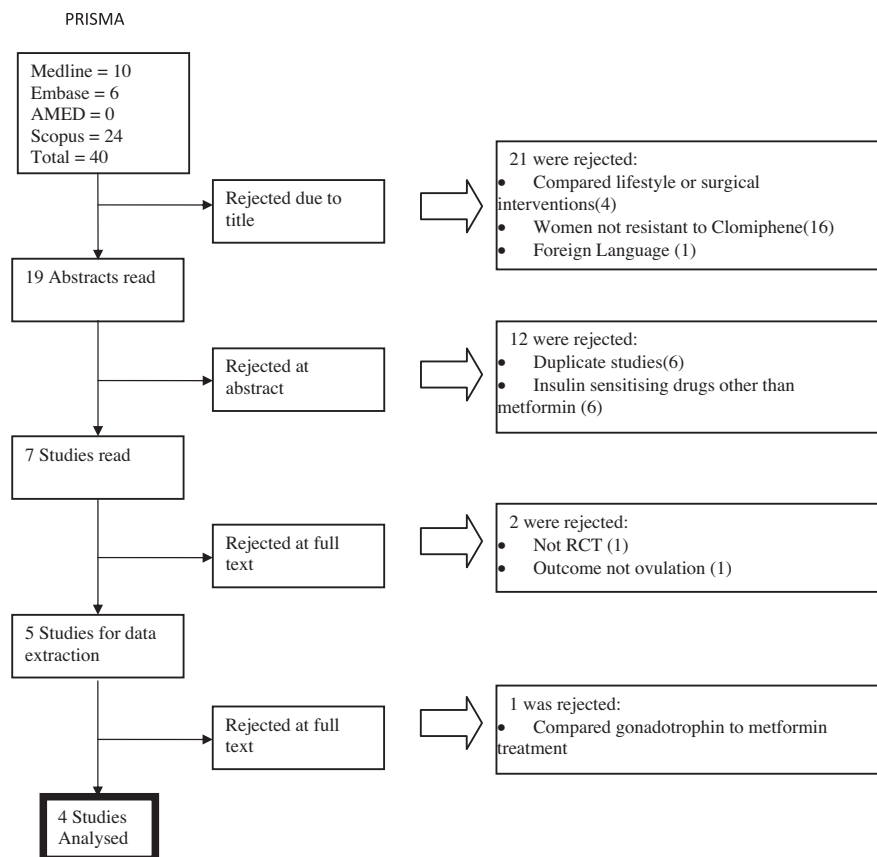


Figure 1 Flow diagram of literature search.

2.2.2. Intervention

All randomised controlled trials or clinical controlled trials that assessed Metformin against placebo and/or in combination with Clomiphene Citrate were included in the review.

2.2.3. Outcomes

Primary outcome measures assessed included ovulation rate and pregnancy by ultrasound. Secondary outcomes included SHBG, BMI, fasting insulin and testosterone.

2.3. Exclusion criteria

Firstly, studies involving surgical options with regard to treatment of infertility were excluded. Secondly, studies focusing on lifestyle interventions were excluded. Any studies that contained different combinations of insulin sensitising drugs used for treatment of infertility were excluded. Reviews and meta-analyses were excluded for analysis for this review.

2.3.1. Quality assessment

Studies were initially appraised using the SIGN guidelines (Scottish Intercollegiate Guidelines Network, UK). Scores out of ten were allocated to each paper using the checklist of questions in the SIGN guidelines.

2.3.2. Management of the literature

All identified citations were scanned by titles and abstracts for relevant studies. Full texts of all potential eligible studies were obtained and critically appraised by two authors. Studies that complied with the *a priori* inclusion and exclusion criteria were included in the review. Any discrepancies were discussed and decisions were made about inclusion.

3. Results

Search of the four databases yielded 40 citations. Following the scanning of abstracts, full texts of ten potentially eligible studies

were obtained and critically appraised and finally four studies that fulfilled the criteria were included in this review. The basic study characteristics are presented in Table 1. All four studies were RCTs dating from 2001 to 2002 carried out worldwide. Sample sizes varied between studies with 56 participants being the largest cohort by Kocak et al. (20). Ng et al. recorded the lowest number of participants with 20 patients (21). After these inclusions there were 129 patients in this review between the 4 studies.

The inclusion criteria were similar between studies, with a diagnosis of PCOS, Clomiphene Citrate resistance and infertility being essential. In addition, several studies included further selection criteria. Vandermolen et al. included oligoovulation, hyperandrogenism and tubal patency in their inclusion criteria (22). Sturrock et al. and Ng et al. recruitment criteria sought patients less than 40 years of age, with PCOS, who were Clomiphene Citrate resistant and anovulatory (23,21).

The exclusion criteria varied between studies. In the study conducted by Vandermolen et al., patients younger than 18 years and those older than 35 years were excluded. Diabetes mellitus was another exclusion criteria (22). Kocak et al. also excluded patients with diabetes mellitus (20). Smokers, male infertility and those with renal impairment were excluded by Ng et al. (21). In the UK study by Sturrock et al. exclusion criteria were not identifiable from the published article (23).

The duration included time from enrolment into the study until completion of the intervention. The shortest duration was reported by Kocak et al. which lasted two months (20). Sturrock et al. had the longest study duration of 13 months (23).

The study design was standard among all trials. Two groups were assessed within each study. Groups consisted of a placebo plus Clomiphene Citrate arm versus a Metformin plus Clomiphene Citrate intervention arm.

3.1. Quality assessment

Vandermolen et al., Ng et al., and Kocak et al., are classified as high quality papers as they fulfilled the majority of the

Table 1 Study characteristics for 4 studies comparing placebo vs Metformin and Clomiphene Citrate.

Author	Sample size	Outcomes	
		Primary	Secondary
Vandermolen et al., (USA) (22)	27 (-2) ^a	Ovulation Pregnancy	<ul style="list-style-type: none"> • Hormone responses and biochemical milieu • BMI • Fasting insulin • SHBG
Ng et al., (China) (21)	20 (-2) ^a	Ovulation Pregnancy	<ul style="list-style-type: none"> • Hormone responses and biochemical milieu • BMI • Fasting insulin • Testosterone • SHBG
Kocak et al., (Turkey) (20)	56 (-1) ^a	Ovulation Pregnancy	<ul style="list-style-type: none"> • Hormone responses and biochemical milieu • BMI • Fasting insulin • Testosterone
Sturrock et al., (UK) (23)	26 (-) ^b	Ovulation Pregnancy	<ul style="list-style-type: none"> • Hormone responses and biochemical milieu • BMI • Fasting Insulin • Testosterone • SHBG

^a Attrition number.

^b Unable to determine.

assessment criteria scoring 8/8 (20–22). Whereas, Sturrock et al. was graded as a poor quality paper due to a lack of transparency with regard to the randomisation method, study design and statistical analysis used and scored 6/8 (23). The author of this paper was contacted for clarification on these issues, but was unable to elucidate these points.

3.2. Primary outcomes

3.2.1. Ovulation rates

All studies found an improvement in ovulatory rates as a primary outcome. (See Table 2) In the study by Vandermolen et al., baseline ovulatory rates for patients receiving placebo and Clomiphene Citrate were 27%. This increased to 75% in the intervention group who received Metformin in combination with Clomiphene Citrate (22). Similarly, Kocak et al. showed a fivefold increase in ovulatory rates between their control and intervention groups (20). These 2 studies showed statistically significant findings.

Further positive findings were described by Sturrock et al. where an improvement from 28.5% to 41.6% was observed between groups (23). However, these findings were not statistically significant.

Contrasting these positive findings, Ng et al. reported higher ovulation rates within their control cohort who received placebo and Clomiphene Citrate (70%) as opposed to those receiving Metformin and Clomiphene Citrate (40%). However, this conclusion cannot be verified as the statistical significance has not been reported (21).

3.2.2. Pregnancy rates

Pregnancy rates improved between the control and intervention groups in the same two studies that also reported statistically significant improvements in ovulation rates. Vandermolen et al. showed an improvement from 7% to 55% following treatment with Metformin and Clomiphene Citrate (22). Four patients conceived while receiving Metformin and Clomiphene Citrate within the study conducted by Kocak et al. (20). This contrasted with the control group, where no patients became pregnant while receiving the placebo

and Clomiphene Citrate. Sturrock et al. reported an increase in pregnancy rates of 14.2% in the control group compared to 25% within the intervention group. However, these results were not statistically significant (23) (see Table 2).

Ng et al. contradicts the other studies stating an increase in pregnancy rates following the use of Metformin and Clomiphene Citrate in the control group. Two patients became pregnant within the control group compared with one pregnancy within the intervention group (21).

3.3. Secondary outcomes

3.3.1. Hormonal concentrations

While many different hormonal parameters were evaluated in these studies, four main variables were selected, due to consistency between studies, for analysis: testosterone, fasting insulin, BMI and SHBG (See Table 3). Three studies recorded changes in testosterone concentrations following treatment (21–23), of which two were statistically significant (20,23). Two studies noted a reduction in fasting insulin levels in patients receiving Metformin and Clomiphene Citrate. However, these reductions were not of statistical significance (20,21). SHBG concentrations were recorded in three trials. Of these, two reported a reduction in SHBG levels within both the control and intervention arms post treatment (21,22). However, these findings were not statistically significant. Sturrock et al. was the only study that found increased concentrations of this hormone following treatment with Metformin and Clomiphene Citrate (23).

3.4.1. Anthropometric measures

Each study found a reduction in BMI measurements following treatment with Metformin and Clomiphene Citrate, however, two studies reported a statistically significant reduction in BMI in the intervention group compared to the control group (20,21). Ng et al. recorded a baseline BMI value of 24.1, which dropped to 23.0 after treatment ($P < 0.01$) (21). Similar results are seen in the study by Kocak et al. where BMI fell from 31.91 ± 5.38 to 30.47 ± 5.25 ($P = 0.01$) (20) (see Table 3).

Table 2 Primary outcomes.

Author	Ovulation		Pregnancy	
	Control	Intervention	Control	Intervention
Vandermolen et al., (USA) (22)	$N = 4/15$ (27%) ^a	$N = 9/12$ (75%) ^a $P = 0.02$	$N = 1/14$ (7%) ^a	$N = 6/11$ (55%) ^a $P = 0.02$
Ng et al., (China) (21)	$N = 7/10$ (70%)	$N = 4/10$ (40%) $P = \text{NR}$	$N = 2/9$ (22%)	$N = 1/9$ (11%) $P = \text{NR}$
Kocak et al., (Turkey) (20)	$N = 4/28$ (14.2%) ^a	$N = 21/27$ (77.7%) ^a $P = 0.001$	$N = 0$ (0%) ^a	$N = 4$ (11%) ^a $P = 0.04$
Sturrock et al., (UK) (23)	$N = 4/14$ (28%)	$N = 5/12$ (42%) $P = 0.63$	$N = 2/14$ (14.2%)	$N = 3/12$ (25%) $P = 0.59$

NR = Not reported.

^a Statistically significant.

Table 3 Secondary outcomes.

Author	Testosterone		Fasting insulin	
	Control	Intervention	Control	Intervention
Vandermolen et al., (USA) (22)	No data	No data	12.5 ± 1.9 (pre) 14.4 ± 4.2 (post)	8.9 ± 1.8 (pre) 10.4 ± 2.1 (post) <i>P</i> = 0.524
Ng et al., (China) (21)	1.3 (pre) ^a 1.5 (post) ^a	1.8 (pre) ^a 1.2 (post) ^a <i>P</i> = 0.05	12.1 (pre) 7.3 (post)	10.8 (pre) 8.2 (post) <i>P</i> = NR
Kocak et al., (Turkey) (20)	1.3 ± 0.6 (pre) ^a 1.31 ± 0.4 (post) ^a	1.47 ± 0.84 (pre) ^a 1.04 ± 0.34 (post) ^a <i>P</i> = 0.001	21.3 ± 27.1 (pre) 22.3 ± 29.1 (post)	28.11 ± 36.1 (pre) 21.3 ± 29.7 (post) <i>P</i> = NR
Sturrock et al., (UK) (23)	−0.15 ^b	+0.4 ^b <i>P</i> = 0.17	−2.1 ^b	+1.5 ^b <i>P</i> = 0.83
Author	BMI		SHBG	
	Control	Intervention	Control	Intervention
Vandermolen et al., (USA) (22)	38.4 ± 2.2 (pre) 38.4 ± 2.0 (post)	37.6 ± 4.3 (pre) 35.4 ± 3.1 (post) <i>P</i> = 0.146	74 ± 8.3 (pre) 71 ± 9.8 (post)	74 ± 8.3 (pre) 71 ± 9.8 (post) <i>P</i> = 0.893
Ng et al., (China) (21)	20.7 (pre) ^a 23.1 (post) ^a	24.1 (pre) ^a 23.0 (post) ^a <i>P</i> = 0.01	36.6 (pre) 32.9 (post)	28.7 (pre) 26.6 (post) <i>P</i> = NR
Kocak et al., (Turkey) (20)	30.8 ± 4.4 (pre) ^a 31.1 ± 3.5 (post) ^a	31.91 ± 5.38 (pre) ^a 30.47 ± 5.25 (post) ^a <i>P</i> = 0.01	No data	No data
Sturrock et al., (UK) (23)	+0.1 ^b	−1.1 ^b <i>P</i> = 0.41	+3 ^b	+4.5 ^b <i>P</i> = 0.29

NR = Not reported.

^a Statistically significant.^b Not Significant unreported by author due to unclear method of statistical analysis.

4. Discussion

4.1. Main findings

Our systematic review was to assess whether Metformin combined with Clomiphene Citrate improves pregnancy and ovulation rates in PCOS patients who were resistant to Clomiphene Citrate.

The data suggest the combination of Metformin and Clomiphene Citrate may succeed in inducing a higher rate of ovulation (20,22,23). However, this increase does not correlate to a direct increase in pregnancy rates. A number of mechanisms can be proposed as having pivotal roles, particularly in reference to the prolonged exposure of Clomiphene Citrate. Previous studies have concluded that the repetitive exposure of Clomiphene Citrate has a deleterious consequence on the endometrial receptivity to the ovulated follicle, and oocyte quality (24). These effects may offset the beneficial effects offered by Metformin therapy.

In addition, the variations observed in pregnancy rates may be attributed to the study designs. The dose regime and treatment duration of Metformin and Clomiphene Citrate may account for the variabilities observed. Interestingly, the study design with the smallest number of participants recorded no increase in either ovulation or pregnancy rates under the treatment arms (21). These results suggest that studies using the higher concentrations of Metformin and Clomiphene Citrate over an extended period may yield the most positive effects.

As impaired ovulation is thought to be linked to insulin resistance, the potential benefits of Metformin could be attributed to an increase in insulin sensitivity, therefore improving ovulation rates (25). Research has shown that use of insulin-sensitising agents within a non-diabetic cohort reduces insulin levels, while blood glucose levels remain unaffected (26). Studies within the confines of this review attested that Metformin targets hyperinsulinaemia associated with PCOS. Therefore, it can be postulated that this mechanism is the basis on which positive results were observed in these studies.

In order to achieve a valid comparison, all of the patients who were included in these studies had previously failed to achieve pregnancy using Clomiphene Citrate only. Clomiphene Citrate resistance was defined in all studies as a failure to ovulate to a dose schedule of 150 mg/day for 5 days during three consecutive menstrual cycles (27). The Clomiphene Citrate cut-off dose was 50–200 mg/day in all studies. Consequently, this target population was standardised across all studies – adding validity to the comparisons concluded.

Testosterone levels were the only statistically significant reduction reported in the hormonal parameters (20,21). However, the clinical significance of a reduction in any of the hormonal parameters under evaluation remains debatable (28). As increased testosterone levels are thought to impair folliculogenesis (25), a reduction in this parameter may improve ovulation and pregnancy rates.

Insulin stimulates the synthesis of androgens within the ovary (25). Metformin acts as an insulin sensitiser thereby reducing testosterone concentrations. Kocak et al., reported

an almost 30% reduction in testosterone levels in patients receiving Metformin and Clomiphene Citrate (20). As the pre-treatment group showed no changes in testosterone levels, this reduction could be solely attributed to Metformin. Ng et al. also reported a statistically significant reduction in testosterone levels in their intervention arm (21). These studies reinforce the potential benefit of Metformin in reducing this parameter.

A reduction in BMI was of statistical significance in the same two studies that also found a reduction in testosterone levels (20,21). While Ng et al. recorded a statistically significant reduction in BMI values in the intervention arm, their baseline values for BMI were the lowest of all the studies (21). Additionally, in spite of this reduction, this study did not show an improvement in ovulation and pregnancy rates following interventional treatment.

The benefits of Metformin observed in this study are regarded as a consequence of increased insulin sensitivity. Studies have provided supporting evidence to this theory, by assessing the endocrine profiles of non-diabetic patients with PCOS treated with Metformin (18,24). Confirmation of this fact could be explored further by the direct assessment of insulin sensitivity.

4.2. Strengths and limitations

There were many strengths of this review beginning with the thorough and concise search method utilised in the preparation. This ensured that the RCTs selected for review clearly addressed the aims and objectives within our research question. Of the four trials selected, three were assessed as being of high quality (20,21). One study was assessed as being of poor quality, but was included in this review to ensure completeness of the current literature in this field (23).

Despite a robust search in four databases there are numerous limitations in this review. It is worth highlighting the lack of published RCTs in this research field and could be strengthened with the support of further trials. Larger sample sizes are also needed to add power to the results obtained and to provide a more representative overview of this intervention. The most recent trial conducted in 2002 highlighted the need for more research in this area.

The doses of Metformin and Clomiphene Citrate varied between studies, as did their duration, thus being ineligible for a meta-analysis. Discrepancies reported within the primary and secondary outcomes may be due to such disparities. Therefore, further RCTs using similar doses and durations of treatment are essential to conclude if the benefits can be attributed to a specific treatment regime.

A distinct lack of follow-up and monitoring was observed throughout all trials. This review would benefit from a follow-up period with details of monitoring protocols. This is important when assessing changes within hormonal concentrations and anthropometric measures, as these may not be fully evident within the current study durations.

Only papers written in the English language were selected, omitting potentially eligible articles. Important issues including the frequency of coital practices were also not included.

4.3. Interpretation

It is important to consider that while assessing the outcomes of this review, a lack of statistical significance does not correlate with a lack of clinical significance. The intervention arm in Vandermolen et al. demonstrated a reduced BMI value following treatment, but it was not of statistical significance (22). However, a reduced BMI could play an important role in fertility treatment. This is also true of the hormonal parameters that were assessed such as fasting insulin concentrations (29).

While the benefits of Metformin and Clomiphene Citrate treatment in improving ovulation and pregnancy rates have been highlighted, it is important to consider the practicalities of this intervention. In relation to Metformin, side effects were observed throughout the trials including nausea and vomiting (21). Another practical issue is the time consuming nature of this intervention, particularly when a more rapid fertility treatment option may be necessary in elderly patients (25).

The standard second line treatment option for Clomiphene Citrate resistant patients is gonadotrophin therapy. By utilising Metformin and Clomiphene Citrate, this could provide an alternative treatment option prior to progressing to gonadotrophin therapy. This could be beneficial to patients due to the substantial costs of this therapy and undesirable administration via injection (25).

5. Conclusion

These results suggest that the dose combination and duration of exposure to Metformin and Clomiphene Citrate may play a pivotal role in determining the effectiveness of this intervention. While this systematic review is limited by the number of RCTs available, overall it presents a positive portrayal for the use of Metformin as an adjunct to Clomiphene Citrate for Clomiphene Citrate resistant patients. Further research using a larger sample size is required to identify the optimal dosage and duration of this intervention. More recent trials would be desirable to further consolidate these scientific results.

Contribution to authorship

Students were assigned a topic and tutor for 4 weeks. The specific question was chosen by all authors after deliberation of research of databases. All authors carried data analysis of equal papers. SG was responsible for methodology, creation of the figures, and the final production of the manuscript for publishing. AG was responsible for the introduction and background reading. NW produced the quality assessment for the studies. RC and HO contributed to the results and discussion. All authors gave final approval of the version to be published. AP provided guidance, expert knowledge, finalisation and support throughout the production of this manuscript.

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Details of ethics approval

This study was exempt from review by the institutional review board.

Conflict of interest

The authors confirm that this article content has no conflicts of interest. This project was unfunded and therefore no organisation had an influence into the submission of this article. All studies were chosen independently removing any bias that could be involved.

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