Metformin versus Clomiphene Citrate or a Combination of Both as First-Line Therapy in Aferile Anovulatory Women with PCOS

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Metformin versus Clomiphene Citrate or a Combination of Both as First-Line Therapy in Aferile Anovulatory Women with PCOS

Abstract
Background: Clomiphene citrate has been used as first-line therapy to enhance fertility in anovulatory aferile women with or without polycystic ovarian syndrome for forty years. Women with PCOS have a higher propensity to develop metabolic syndrome and infertility. Therefore, a secondary outcome in treating anovulatory aferile women with metformin, may be to delay the development of type 2 diabetes plus induce ovulation and achievement of pregnancy.

Methods: The focus of this study was to review the current literature on all studies pertaining to the first-line treatment of anovulatory aferile women with PCOS, by comparing the clomiphene citrate to metformin to induce ovulation and achieve pregnancy. The treatments reviewed included metformin, extended release metformin, clomiphene citrate or a combination of both metformin and clomiphene citrate.

Results: Of the 5 studies published, 2 studies still considered clomiphene citrate to be superior to metformin at inducing ovulation and achieving pregnancy at 6 months, two studies considered metformin superior to clomiphene citrate and one study considered both to be acceptable first-line treatment options.

Conclusion: Clomiphene citrate should still be considered first-line therapy for the treatment of inducing ovulation and achieving pregnancy in anovulatory aferile women with PCOS. However, further randomized, blinded studies are needed to better substantiate metformin’s long term (>6 months) use and secondary benefit of decreasing the likelihood of acquiring type 2 diabetes and other sequelae.

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Metformin versus Clomiphene Citrate or a Combination of Both as First-Line Therapy in A fertile Anovulatory Women with PCOS

Camille Kinzler

A Clinical Graduate Project Submitted to the Faculty of the
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Biography

Camille Kinzler is a native Austinite from Texas where she received her BA in Spanish and a minor in Geography at Texas State University. During the last 15 years, she has traveled throughout Latin American, Southeast Asian and Europe. She expanded her knowledge of the Spanish language and Latino culture when she lived in Bogota, Colombia and Valparaiso, Chile, as well as when she volunteered as an advocate for survivors of domestic violence in Portland, Oregon. After completion of her undergraduate degree, she moved to Portland, Oregon seven years ago. She worked for Planned Parenthood of the Columbia Willamette while attending Portland State University. At PSU, she completed post-baccalaureate science classes. She is now debating on starting her career as a Physician Assistant in beautiful Portland, Oregon or returning to Austin, Texas to be closer to her parents and in-laws.
Abstract

Background: Clomiphene citrate has been used as first-line therapy to enhance fertility in anovulatory afertile women with or without polycystic ovarian syndrome for forty years. Women with PCOS have a higher propensity to develop metabolic syndrome and infertility. Therefore, a secondary outcome in treating anovulatory afertile women with metformin, may be to delay the development of type 2 diabetes plus induce ovulation and achievement of pregnancy. METHODS: The focus of this study was to review the current literature on all studies pertaining to the first-line treatment of anovulatory afertile women with PCOS, by comparing the clomiphene citrate to metformin to induce ovulation and achieve pregnancy. The treatments reviewed included metformin, extended release metformin, clomiphene citrate or a combination of both metformin and clomiphene citrate. RESULTS: Of the 5 studies published, 2 studies still considered clomiphene citrate to be superior to metformin at inducing ovulation and achieving pregnancy at 6 months, two studies considered metformin superior to clomiphene citrate and one study considered both to be acceptable first-line treatment options. CONCLUSION: Clomiphene citrate should still be considered first-line therapy for the treatment of inducing ovulation and achieving pregnancy in anovulatory infertile women with PCOS. However, further randomized, blinded studies are needed to better substantiate metformin’s long term (>6 months) use and secondary benefit of decreasing the likelihood of acquiring type 2 diabetes and other sequelae. KEYWORDS: metformin, infertility, PCOS, pregnancy, clomiphene, ovulation
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To my friends: WOW! Seriously, um, couldn’t have made it without you supporting me with our once a week get togethers.

To my in-laws: Thanks for your support! You are amazing friends! You’ve taken a lot of the pressure off of Mark and me throughout the last 27 months (and more). I am grateful!
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Table II: Comparison of First-Line Treatment of Metformin in Anovulatory Aferile Women with PCOS

List of Abbreviations

PCOS…………………………………………………………………….Polycystic Ovarian Syndrome

LH..........................................................................................Luteinizing Hormone

CC………………………………………………………………..Clomiphene Citrate

BMI………………………………………………………………Body Mass Index
Metformin versus Clomiphene Citrate or a Combination of Both as First-Line Therapy in A fertile Anovulatory Women with PCOS

Introduction

Polycystic ovarian syndrome (PCOS) affects 7%-8% of women in the general US population and is one of the most common causes of anovulatory infertility, at a rate of about 5%-10% of women of reproductive age. The Rotterdam diagnostic criteria of 2003 define PCOS as a syndrome consisting of two out of the three following disorders: chronic anovulation, clinical and/or biochemical evidence of hyperandrogenism and polycystic ovaries. Controversy exists surrounding both diagnosis and treatment of this disorder. It is unclear whether a woman with hyperandrogenism and polycystic ovaries who has a regular menstrual cycle should be included in the definition, or conversely, if an anovulatory women with polycystic ovaries without hyperandrogenism should be included. The purpose of this systematic review is to decide whether metformin should be used as a first-line treatment in the induction of ovulation and the achievement of pregnancy in anovulatory infertile women with PCOS.

In 19th century scientific publications, references were made to what we now understand as PCOS. However, the syndrome was not described until 1935, in a paper by Stein and Leventhal. The combination of anovulation and excess androgen were common findings in polycystic ovarian morphology and remained the mainstay for the next half century. The National Institute of Health met in 1990 to re-define PCOS as chronic anovulation associated with clinical and/or biochemical evidence of androgen excess in the absences of other pathologies. Hirsutism, acne, or male-pattern baldness clinically define hyperandrogenism and high serum levels of androgen define biochemical hyperandrogenemia. Anovulation can either manifest as infertility, oligomenorrhea, or amenorrhea. Abnormally regulating luteinizing hormone (LH) was thought to be the sole reason for these symptoms, but now studies indicate insulin resistance and hyperinsulinemia may play a role. More
recent studies have shown a connection between polycystic ovaries in women who have normal menses, but have biochemical features of PCOS. These women tend to have less insulin resistance and hyperinsulinemia than those with chronic anovulation.³

Obesity is associated with increased insulin resistance and therefore can cause chronic anovulation ⁴, which means obese women with PCOS are more likely to be anovulatory than lean, hyperandrogenemic women.³ Fifty percent of obese women who lose 5%-10% of their body weight over six months reestablish ovarian function. Recent evidence has shown that hyperinsulinemia and insulin resistance increase circulating ovarian androgen concentrations, thus impeding ovulation.⁴ Insulin-lowering and insulin-sensitizing medications have beneficial effects on ovulation and fertility in obese women with PCOS, as do diet and lifestyle modifications. This suggests a link between metabolic disturbances and ovulation.³ The exact mechanism of insulin resistance in PCOS remains unclear ⁴. The metabolic disturbances associated with PCOS³ are a potential health hazard with long-term sequelae including type 2 diabetes, cardiovascular disease and hyperlipidemia.⁵

PCOS has been associated with anovulation, obesity, hyperandrogenism, insulin resistance with compensatory hyperinsulinemia, ovarian morphologic changes, and hypergonadotropin secretion (particularly elevated LH), all of which can secondarily cause female infertility and pregnancy complications.¹ Infertility occurs in about 75% of women who have polycystic ovarian syndrome. Anovulation is the primary reason this occurs.⁴ Early pregnancy loss is about 10% to 15% in normal pregnancy and is higher in women with PCOS. Pregnancy loss in women with PCOS may be due to elevated plasma LH levels, hyperandrogenemia, and high plasminogen activator inhibitor, although the most compelling hypothesis is contributed to obesity. Insulin resistance increases in normal pregnancy, and therefore may “augment the preexisting insulin resistance and hyperinsulinemia” in women with PCOS resulting in spontaneous abortion.⁴

The lab used to test for serum androgen in women with moderate-severe hirsutism is total testosterone concentration, which is the most sensitive test to establish presence of
hyperandrogenemia. Elevated insulin levels and elevated androgen levels both inhibit hepatic production of sex hormone-binding globulin (SHBG), which is a glycoprotein that binds to testosterone and estrodiol. Serum dehydroepiandrosterone sulfate ester (DHEA-S) test is added when there is a concern regarding an androgen secreting tumor. Fifty to ninety percent of women with PCOS have an elevated androgen level that is either being secreted by the ovaries, adrenal cortex or both. Other causes of hirsutism are drugs, congenital adrenal hyperplasia (most often 21-hydroxylase deficiency), hyperthecosis, ovarian tumors, adrenal tumors, severe insulin resistance syndromes, hyperprolactinemia and Cushing's syndrome.

Before polycystic ovarian syndrome is diagnosed other causes need to be eliminated. Other reasons for infertility also need to be assessed before starting a pregnancy enhancement treatment option. Some common causes of infertility (the most common to least) are ovulatory disorders, endometriosis, pelvic adhesions, tubal blockage, other tubal abnormalities, and hyperprolactinemia.

Clomiphene citrate (CC) has been used as first-line treatment for infertility in women with PCOS for 40 years. CC is uncomplicated to administer and manage and has been proven to be an effective low cost treatment with limited dose dependent side effects. It induces ovulation in oligomenorrheic women and has been used to treat anovulatory infertility. CC’s mechanism is to exert an antiestrogenic action on the hypothalamas thereby increasing the gonadotropin releasing hormone pulse frequency and the concentration of follicle stimulating hormone and luteinizing hormones which increase ovarian follicles until ovulation is reached. A common complication that has been proven in multiple studies has been the discrepancy between ovulation rates of 60%-85% and pregnancy rates of 30%-40%. The reason for this discrepancy is unknown. It could possibly be due to CC’s antiestrogenic effect on the cervix and endometrium which causes an increase in cervical mucus and risk of subclinical pregnancy, and a thinning of the endometrial layer. CC also has an influence
on uterine blood flow, tubal transport and oocyte quality and maturity. This combination leads to a hostile environment for sperm transport and implantation.

Metformin is a biguanide oral antihyperglycemic agent used to treat type 2 diabetes mellitus, and has recently been used as a second line treatment for CC resistant infertility in women with PCOS. Its mechanism of action is to lower blood glucose levels by inhibiting hepatic glucose production and by increasing peripheral glucose uptake, which can reduce peripheral insulin concentrations and improve glucose tolerance and metabolism. It is also a low cost treatment with limited side effects and simple administration and management. It too has been proven to improve ovulation rates, and chemical and biochemical features of PCOS. Hyperinsulinemia may contribute to hyperandrogenism and infertility; therefore, agents which increase insulin insensitivity and reduce insulin levels may be necessary.

Laparoscopic ovarian diathermy is a second line treatment for anovulation in the CC resistant population. Also gonadotropin treatment and in vitro fertilization (IVF) have been considered useful.

Although clomiphene citrate is used as first-line therapy for the induction of ovulation and the achievement of pregnancy in women who have polycystic ovarian syndrome, the use of metformin may be a more reasonable and responsible first-line option, as it addresses secondary effects of PCOS (i.e. hyperinsulinemia and insulin resistance).

**Methods**

An extensive literature search was performed using the following search engines: Medline (Ovid), PubMed, and CINAHL (EBSCO), and the following search terms: Metformin, infertility, PCOS, pregnancy, clomiphene, and ovulation. A total of thirteen articles were located under the above search terms and five of those published articles studied metformin versus clomiphene citrate (CC) as a first-line therapy for induction of ovulation and the achievement of pregnancy in anovulatory afertile women with PCOS. Inclusion criteria were adult women of all races and body mass index (BMI),
English only articles, metformin as first line treatment versus clomiphene citrate or both, afertile (primary or secondary) and anovulatory women with PCOS. Exclusion criteria were metformin compared to surgical intervention (laparoscopic ovarian diathermy), metformin compared to other medication treatment, metformin studied against placebo only, metformin alone studied as first line therapy, gonadotropin treatment and treatment with IVF, meta analysis and systematic reviews.

Results

After inclusion and exclusion criteria were applied five studies remained which met the necessary parameters. The five studies compared metformin or extended-release metformin, to clomiphene citrate or the combination metformin and clomiphene citrate as first-line therapy for the induction of ovulation and pregnancy in afertile anovulatory women with PCOS. The average sample size was 100 patients, with one outlier which included 628 patients. The largest study was also the only Prospective Parallel Randomized, Double-Blinded, Double-Dummy Controlled Clinical Trial. Two others were randomized, nonblinded, control studies. One was a multi-center, nonrandomized prospective control studies. And one was an observational comparative study.

Zain et al and Legro et al were two studies which were randomized. Both compared clomiphene citrate, metformin and a combination of metformin and clomiphene citrate. Zain et al randomly assigned 115 Asian female patients to one of the three groups. Legro’s et al study also randomly divided 626 subjects into three groups. Zain et al, however, used the extended release metformin to minimize the side effects of metformin.

The Zain et al study subjects were divided into three groups. Group 1 consisted of 38 patients who received 500 mg of metformin three times daily, group 2 consisted of 39 patients who received 50 mg of clomiphene citrate (CC) at an incremental dose (max dose 200 mg) and group 3 consisted of 38 patients who received both CC and metformin. The ovulation rate in Group 1, using metformin only, was 23.7%, in Group 2, using CC only, the rate was 59%, and in the combination group, Group 3, the ovulation rate was 68.4%. The pregnancy rates were translated similarly among the different groups;
7.9%, 15.4% and 21.1%, respectively. The live birth rate was the same in the metformin group and the CC group as the pregnancy rate percentage. In Group 3, the combination group, the live birth rate dropped to 18.4%, which was decreased to 21.1% pregnancy rate. There were no multiple pregnancies in any of the groups (see Table 1).

The Legro et al study also divided the subjects into three groups. Group 1 initially received 500 mg of extended release metformin, increasing the dose to a maximum of four 500 mg tablets (two tablets twice daily) for a total of 2000 mg. The second group received 50 mg of clomiphene citrate starting on day 3 and continuing treatment for five days. This dose was maintained if ovulation was documented. Otherwise, the dose was increased by one 50 mg tablet a day per treatment cycle (once a month) to reach a maximum of 150 mg. In the Legro study the percentage of live birth rates in Group 1 was 7.2%, Group 2 the rate was 22.5% and in Group 3 the rate is 26.8%. The P value in the combination group was P<0.001. The rate of multiple pregnancies was 6.0% in the clomiphene group, 0% in the metformin group and 3.1% in the combination group. The rate of spontaneous abortion in the first trimester did not differ significantly among the groups. Conception rate among participants who ovulated was significantly lower in the metformin group (21.7%) than either Group B or Group C (39.5%, P=0.002 and 46.0%, P<0.001, respectively). Adverse events rate were the same in all three groups. Although in the metformin group, GI symptoms were more frequent and vasomotor and ovulatory symptoms were less frequent than in the clomiphene group (see Table 1).

Another study comparing clomiphene citrate, metformin, or combination therapy as first-line treatment for ovulation induction and achievement of pregnancy was the Neveu et al study. This was an observational comparative trial that included 154 women with PCOS. The subjects were divided into three groups. Group 1, using CC only, consisted of 56 patients who received 50 mg of CC daily from days 5-9 of the cycle then titrated up by 50 mgs per cycle until they ovulated (maximum dose was not stated). Group 2 consisted of 57 patients who received 500 mg of metformin three times daily. Metformin was started at 250 mg three times daily for a week to reduce side effects then increased
progressively to 500 mg three times a day. The dose was increased to 1000 mg twice a day if ovulation had not occurred; otherwise the dose was 1500 mg. Patients who could not tolerate the side effects decreased their dose. The third group consisted of 41 patients who received both medications. In the third group, Clomiphene citrate was added after 2 or 3 months after the start of metformin use if ovulation had not occurred. Ovulation rate in the CC group was 50% compared to 75.4% in the metformin group and the combination group had an ovulation rate of 63.4%. Pregnancy rates in all three groups were (35.7%, 45.6%, and 31.7%, respectively). The spontaneous abortion rate for CC was 15%, metformin was 19.2%, and the combination therapy was 30.7%. A secondary analysis looked at metformin, CC, or combination therapy at 6-9 months, 9-12 months and 12 plus months.

The Palomba et al trial was a parallel randomized, double-blinded, double-dummy control clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in non-obese anovulatory women with polycystic ovary syndrome. One-hundred participants were divided into randomized groups. Group A was given 850 mg of metformin twice daily plus placebo and Group B was given 150 mg of CC plus placebo for 5 days starting at the third day of progesterone-induced withdrawal. The duration of the treatment was 6 months. Women who did not achieve ovulation in groups A and B at the six month mark were administered both metformin and CC, which ever one they were not on originally, at the same doses described above (cross-over). Women who did not achieve pregnancy as the outcome but who did ovulate were treated with three trials of controlled ovarian stimulation followed by intrauterine insemination before assisted reproductive techniques. The ovulation and pregnancy rates did not vary significantly in each group with 62% ovulating in the metformin group and 67% ovulating in the clomiphene group. Pregnancy per ovulatory cycle, however, was higher in the metformin group (15.1%) compared to the clomiphene group (7.2%) with a P=0.045. The spontaneous abortion rates comparatively were 9.7% in the metformin group and 37.5% in the clomiphene group with a P=0.045. The live birth rate was also higher in the metformin group at a rate of 83.9% versus 56.5% (P=0.07). None of the women had
multiple pregnancies in either group. After 6 months of treatment the cumulative pregnancy rate was 68.9% versus 24.0% (P<0.001) for metformin and clomiphene, respectively.

The Palomba2 et al multi-center nonrandomized, prospective, controlled study included 80 infertile anovulatory patients with PCOS. The study divided the women into two groups: an experimental group (metformin treatment) and the control group (clomiphene citrate). The experimental group (Group 1) was treated with 850 mg daily of metformin for the first week and then increased to one tablet twice daily. The control group (Group 2) received 50 mg clomiphene citrate starting on day 3 of progesterone induced withdrawal bleeding and it was continued for 5 days. The dose was either left at 50 mg or incrementally increased by 50 mg until ovulation was achieved or a maximum dose of 250 mg was reached. Patients who did not ovulate once the maximum dose was reached were considered CC-resistant. Otherwise, the patients continued with the treatment for six ovulatory cycles. There was no significant difference in ovulation between Group 1 or Group 2 (55.4% vs. 59.8%, respectively; P=0.396), pregnancy (10.8% vs. 11.2%, respectively; P=0.888) and spontaneous abortion (19.5 vs. 26.3%, respectively; P=0.530).

**Discussion**

The purpose of this review is to decide whether metformin should be used as a first-line treatment in the induction of ovulation and the achievement of pregnancy in anovulatory infertile women with PCOS through an extensive literature review. Since some trials were randomized, one non-randomized and another was observational non-randomized, it was difficult to compare trials head-to-head. Each article was reviewed and graded if possible, on the following criteria: the study design, (i.e. randomized, double-blinded, controlled, observational, and comparative), sample size, dosage, weight, other infertility factors, and age.

Each study had an adequate sample size of an average of 100 participants with one outlier of 626 participants. The Palomba et al study was the most well organized study in this review. The
method and randomization was described and it was a double-blinded trial. Participants lost to follow-up were adequately accounted for. The total JADAD score was four, losing one credit point for not describing the method for double-blinding the study. In the observational comparative by Neveu et al, the subjects were given the treatment option of metformin, clomiphene, or both. The patients had full disclosure as to the side effects and benefits of the drug options. Therefore, many overweight subjects chose metformin instead of clomiphene due to possible weight loss. This issue of allowing patients to choose their group may have led to an imbalance between the groups with most of the obese patients choosing to be in the same group causing a distortion in the results.

The study design in the observational comparative trial is relevant because the particular study design used by the investigators may have resulted in substandard results. For instance, in the combination therapy group (Group 3) the patients were started on metformin, and if ovulation did not occur within two to three months, they were started on clomiphene citrate. The patients stayed in Group 3 whether or not they had started taking clomiphene citrate in combination with metformin. This method creates the risk that the reader would draw an incorrect inference from the data because an unknown number of participants in Group 3 could have been treated with metformin only, making the results indistinguishable from the metformin only group.

The Zain et al and Legro et al trials did not blind investigators or patients, which subjected both parties to bias. Almost all participants in the Zain et al study were Asian Malay and less than 5% showed signs of clinical hirsutism, which is consistent with other studies examining PCOS in Asian women, but not representative of the general population of women with PCOS. A very selective population with unique qualities inherent to that particular population limits the study substantially. Metformin, with its antihyperandrogenemic qualities, could possibly not be as effective in Asian Malay women. Investigators were subjected to bias in the Palomba2 study as well. Variability also existed in the initiation and conclusion of medication because it was a clinic based trial and in multiple centers.
Anovulation and infertility are two complex hormonal and biological conditions that can affect women in their reproductive years. Some common causes of infertility (the most common to least) are ovulatory disorders, endometriosis, pelvic adhesions, tubal blockage, other tubal abnormalities, and hyperprolactinemia. In the Zain et al study, women were not evaluated for other clinical explanations of infertility like tubal patency and tubal disease, which account for 22% of women who are infertile. Therefore, the results could be distorted by including women who may have had a cause of infertility other than an ovulation disorder.

Obesity is associated with increased insulin resistance, which causes chronic anovulation. Moreover, treating infertility with diet and lifestyle modifications would be extremely beneficial in obese women with PCOS. However, weight loss is a challenge for most women. Therefore, since insulin-lowering and insulin-sensitizing medications like metformin decrease insulin resistance, a beneficial effect on ovulation and fertility in obese women with PCOS can be achieved.

In the Legro et al study, the patients were morbidly obese with the highest BMI in the group who received CC only. There was a higher degree of pregnancy related adverse events in the CC only and combination therapy groups, which could be related to the higher BMI in these groups. In the Neveu et al study, the metformin group with a higher mean BMI also had a statistically significant increase in ovulation rate over the CC only group. The Neveu et al study observed that the ovulation rate was similar between the two groups when the BMI was <27 or >35, but with a BMI of between 27 and 35, the patients ovulated more on metformin. This could be due to increased difficulty to overcome insulin resistance with a higher BMI. In the Zain et al trial the women were morbidly obese with a mean BMI of all three groups of 33.3 and the end result, although statistically insignificant, showed a higher rate of live births on CC. The Palomba et al study excluded obese women. This could be due to the fact that in the general population non obese women have fewer propensities for infertility and
pregnancy complications than obese women and the investigators thought this would eliminate obesity related causes for infertility. Metformin was shown to be superior to CC in this study. As a side note, this was the only study that used ovarian stimulation followed by intrauterine insemination on women who did not achieve pregnancy. The study failed to disclose the number of patients who underwent this procedure or under which group they were allocated.

Clomiphene citrate is typically prescribed at a 50 mg daily dose for five days. It is increased in increments of 50 mg each month until ovulation occurs or a maximum dose of 150 mg has been reached. In the Palomba et al study, the investigators started the dose at 150 mg. CC affects the endometrium, cervical mucus and uterine blood flow, which can cause a hostile environment for implantation. The initial use of such a high dose could have had a deleterious effect. In fact, in the Palomba2 et al and Neveu et al study, there was no change in the efficacy of CC at 50 mg versus 200 mg. Also in the Palomba2 et al study, there was no effect on ovulation or pregnancy in a single case once 200 mg was reached. Immediate release metformin was used in all studies but the Legro et al study. Therefore, the extended release metformin could have less effect on women with PCOS to induce ovulation and pregnancy.

Other limitations that varied across all the studies were documentation relating to the frequency of sexual intercourse, monitoring of ovulation, number of months a female was anovulatory or number of days between menses (oligoamenorrhea), previous ovulation induction drug treatment, glucose intolerance, partners with sperm abnormalities and live birth. The Palomba et al, Palomba2 et al and the Legro et al studies required their participants to track the frequency of sexual intercourse. The other two studies did not, which obviously can affect the outcome of pregnancy. The definition of anovulation varied from absence of menses for greater than six months to greater than eight months and oligoamenorrhea ranged from menses occurring greater than every 35 days or less than nine months a year. Some of the patients in this study may have ovulated one month in the last year, and others may have ovulated ten times over the past year. Obviously, increased ovulation increases
pregnancy odds. In the Legro et al study, more than 50% of the participants had previously been on
ovulation induction treatment, which can potentially increase the odds of pregnancy. In the Neveu
study, the researchers did not exclude women who were glucose intolerant or whose partners had
sperm abnormalities. The degree of glucose intolerance may have had a greater effect on the efficacy
of metformin in treating anovulatory infertile women. The author of the study noted that lower fasting
blood sugars and lower systolic blood pressure is predictive of better ovulatory response on CC. The
metformin group, however, had lower testosterone and androstenedione.

Besides pregnancy and ovulation rates, the Legro et al and Zain et al studies measured
metabolic and hormonal effects associated with the three groups (CC, metformin or both therapies)
initially and at six months. The Legro et al study measured other outcomes like testosterone (as
metformin also has an antiandrogenemic effect), BMI and sex hormone-binding globulin. Although the
conception rate among the women who ovulated in the metformin group was lower than the other
groups, the baseline metabolic and hormonal laboratory results were significant when compared to the
results at the end of the study. When each particular group is compared to the remaining groups, a
decrease in BMI and total testosterone was observed. Also, a significant increase in sex hormone-
binding globulin levels, with a corresponding decrease in free androgen index was found when each of
these groups was compared. In the clomiphene group, there was an increase in BMI, insulin levels, and
insulin resistance, although all of these were insignificant. However, there was a significant increase in
sex hormone-binding globulin and a decrease in free androgen. The combination group had similar
results to the metformin group which were significant for all comparisons. The Zain et al study did not
see a notable difference in body weight or waist-to-hip measurement at three or six months of
treatment with metformin, although there was a significant increase in menstrual cycle regularity from
three months to six months. In this study, even though there was a decrease in BMI in the metformin
only group, this did not change the outcome of pregnancy. In the combination group, the live birth rate
was high, although statistically insignificant, with the additional positive secondary outcomes of lower
BMI and insulin sensitivity. Although this was not the purpose of these studies or this review, examining the effects metformin has on metabolic and hormonal levels can be the basis for a defense of the decision to use metformin to treat infertility in women with PCOS.

Examining the live birth rate is an important consideration when comparing the efficacy of metformin to CC, as this is the goal of women who seek pregnancy enhancement treatment. However, only three studies reviewed had live births as the outcome: Legro et al, Zain et al and Palomba et al. The other two trials only used ovulation and conception as their outcome.

The studies mentioned in this review were limited by the study design and method. In order to avoid these limitations, more blinded, randomized trials need to be implemented. These improvements on the study design will lead to more conclusive results. The patient population should be more heterogeneous and representative of women with PCOS. These studies should compare the efficacy of metformin, CC, and combination therapy on live birth rates in obese and non obese women. Additional studies need to be performed to analyze the long term effects of metformin to achieve pregnancy. As for more studies surrounding the effects of clomiphene citrate, examining the long term effects of CC on pregnancy (i.e. gestational diabetes) and health of mothers (i.e. type 2 diabetes) would be beneficial.

**Conclusion**

Although clomiphene citrate is the medication currently used as first-line therapy for fertility treatment in women with PCOS, the scope of its effects are limited only to ovulatory issues. The results of the studies in this review indicated that metformin may increase ovulation, pregnancy and live birth outcomes in certain circumstances. In addition to these outcomes, the results showed that metformin also addresses other contributing factors of PCOS, such as hyperinsulinemia. However, the studies in this review did not render conclusive results regarding these particular issues. If these results could be confirmed by further studies, metformin may be a more reasonable and responsible option in certain scenarios where the secondary effects of the drug would be beneficial to the patient.
References


2. Neveu N, Granger L, St-Michel P, Lavoie HB. Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction and achievement of pregnancy in 154 women with polycystic ovary syndrome. *Fertil Steril.* 2007;87:113-120.


<table>
<thead>
<tr>
<th></th>
<th>Legro</th>
<th>Zain</th>
<th>Neveu</th>
<th>Palomba</th>
<th>Palomba2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live Birth Rate: clomiphene</strong></td>
<td>22.5%</td>
<td>15.4%</td>
<td>na</td>
<td>68.9%</td>
<td>na</td>
</tr>
<tr>
<td><strong>Live Birth Rate: metformin</strong></td>
<td>7.2%</td>
<td>7.9%</td>
<td>na</td>
<td>34.0%</td>
<td>na</td>
</tr>
<tr>
<td><strong>Live Birth Rate: clomiphene and metformin</strong></td>
<td>26.8%</td>
<td>18.4%</td>
<td>na</td>
<td>na</td>
<td>na</td>
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<tr>
<td><strong>Rate of multiple pregnancies: clomiphene</strong></td>
<td>6.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>&lt;1</td>
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<tr>
<td><strong>Rate of multiple pregnancies: metformin</strong></td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
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<tr>
<td><strong>Rate of multiple pregnancies: combination</strong></td>
<td>3.1%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
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<tr>
<td><strong>First-trimester spontaneous abortions clomiphene</strong></td>
<td>22.6%</td>
<td>0.0%</td>
<td>15.0%</td>
<td>9.7%</td>
<td>48.6%</td>
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<tr>
<td><strong>First-trimester spontaneous abortions: metformin</strong></td>
<td>40.0%</td>
<td>0.0%</td>
<td>19.2%</td>
<td>37.5%</td>
<td>67.9%</td>
</tr>
<tr>
<td><strong>First-trimester spontaneous abortions: both</strong></td>
<td>30.0%</td>
<td>na</td>
<td>30.7%</td>
<td>Na</td>
<td>na</td>
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<tr>
<td><strong>Conception rate among women who ovulated: clomiphene</strong></td>
<td>39.5%</td>
<td>15.4%</td>
<td>45.6%</td>
<td>Na</td>
<td>11.2%</td>
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<tr>
<td><strong>Conception rate among women who ovulated metformin</strong></td>
<td>21.7%</td>
<td>7.9%</td>
<td>35.7%</td>
<td>Na</td>
<td>10.8%</td>
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<tr>
<td><strong>Conception rate among women who ovulated: both</strong></td>
<td>46.0%</td>
<td>21.1%</td>
<td>37.0%</td>
<td>na</td>
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<td><strong>Ovulation rate: clomiphene</strong></td>
<td>na</td>
<td>59.0%</td>
<td>50.0%</td>
<td>62.9%</td>
<td>59.8%</td>
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<td><strong>Ovulation rate: metformin</strong></td>
<td>na</td>
<td>24.0%</td>
<td>75.4%</td>
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<td>55.4%</td>
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<td><strong>Ovulation rate: clomiphene and metformin</strong></td>
<td>na</td>
<td>66.6%</td>
<td>63.4%</td>
<td>na</td>
<td>na</td>
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</table>

Table I: Comparing Metformin to Clomiphene Citrate, or combination therapy in each of the five studies
<table>
<thead>
<tr>
<th>Author/ Title/ Journal</th>
<th>Yr. published</th>
<th>Patients/ Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Study type</th>
<th>Validity (Jadad score)</th>
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<tbody>
<tr>
<td>Stefano Palomba et al/ Prospective Parallel Randomized, Double-Blind, Double-Dummy Controlled Clinical Trial Comparing Clomiphene Citrate and Metformin as the First-Line Treatment for Ovulation Induction in Nonobese Anovulatory Women with Polycystic Ovary Syndrome/Journal of Clinical Endocrinology and Metabolism</td>
<td>July 2005</td>
<td>100 Non obese Anovulatory Women with PCOC</td>
<td>Metformin as first line therapy</td>
<td>Clomiphene Citrate PLUS placebo and Metformin PLUS placebo</td>
<td>Ovulation, pregnancy, spontaneous abortion, live birth rates</td>
<td>Prospective Parallel Randomized, Double-Blind, Double-Dummy Controlled Clinical Trial</td>
<td>4</td>
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<tr>
<td>Neveu et al/ Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction and achievement of pregnancy in 154 women with polycystic ovary syndrome/American Society for Reproductive Medicine</td>
<td>January 2007</td>
<td>154 Infertile women with PCOS</td>
<td>Metformin</td>
<td>CC, Metformin or both</td>
<td>Ovulation and pregnancy</td>
<td>Observational comparative study</td>
<td></td>
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<tr>
<td>Legro et al/ Clomiphene, Metformin or Both for Infertility in the Polycystic Ovarian Syndrome/The New England Journal of Medicine</td>
<td>Feb 8, 2007: 626 people</td>
<td>626 anovulatory women with PCOS</td>
<td>Metformin Extended release Met plus placebo, CC plus placebo, and metformin and CC</td>
<td>Primary outcome live birth rate and the secondary outcome ovulation</td>
<td>Randomized control study</td>
<td></td>
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<td>Zain et al/ Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction, achievement of pregnancy and live birth in Asian women with PCOS/ American Society of Reproductive Medicine</td>
<td>Feb 2009</td>
<td>115 anovulatory afertile Asian women with PCOS</td>
<td>Metformin Comparing CC, Metformin or both therapies</td>
<td>Ovulation, pregnancy and live birth</td>
<td>Randomized controlled study</td>
<td></td>
<td></td>
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</table>
Table II: Comparison of Literature on the First-Line Treatment of Metformin in Anovulatory Infertile Women with PCOS