Use of Clomiphene and Metformin in treatment of polycystic ovarian syndrome and its effects on fertility: Systematic Review

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Abstract

Introduction: Polycystic ovarian syndrome is the most common endocrinopathy among reproductive age women can cause long-term reproductive and metabolic consequences, including but not limited to infertility, heart disease, diabetes, and obesity. In almost all cases insulin resistance and hyperinsulinemia seem to have an important role in the etiology. The intention of this research was to review the role of Metformin in improving fertility outcomes as a stand-alone treatment or with the use of Clomiphene.

Methods: Databases were searched for articles that included more than 20 subjects, in english, published from 1980-present with selected keywords: polycystic ovarian syndrome or polycystic ovarian disease or polycystic ovary syndrome or PCOS or infertility AND Metformin AND Clomiphene. The selection process of the articles has been presented in PRISMA flow chart. A total, of 350 articles were found were found, 12 met criteria and were analyzed.

Results: Information from each article was summarized and presented in the form of a table. Relevant data taken from each article included: title, author(s), location, year, study design, sample size, diagnosis of polycystic ovarian syndrome criteria, intervention, ovulation measurement methods, pregnancy measurement and conclusion. Most studies support that Metformin and Clomiphene treatment increased ovulation statistically significant.

Conclusion: This systematic review has broadened the understanding of the use of Metformin in treating infertility in patients with PCOS alone and with the use of Clomiphene. The addition of Metformin to treatment protocols of PCOS was shown to have a statistically significant advantage on improving ovulation rate, which suggests the role of insulin resistance in PCOS etiology. More research and studies are needed to evaluate whether Metformin addition will provide a statistically significant benefit on live birth rates and pregnancy.

Keywords: polycystic ovarian syndrome or polycystic ovarian disease or polycystic ovary syndrome or PCOS or infertility AND Metformin AND Clomiphene

Introduction:

Polycystic ovarian syndrome (PCOS) is the most frequent endocrinopathy among women of reproductive age and leading cause of WHO Type 2 anovulatory infertility [1]. The syndrome, which is associated with absence of ovulation, high androgens levels or cysts on the ovaries, has long term reproductive and metabolic consequences.

The criteria to diagnose PCOS are varied and diverse due to the wide-ranging features of the syndrome and no accepted underlying etiologies [2]. At the US National Institutes of Health Conference in 1990, three key features were agreed upon; oligomenorrhoea, hyperandrogenism (clinical or biochemical) and absence of other endocrine disorders (congenital adrenal hyperplasia, thyroid dysfunction and androgen-secreting tumors[3]). The following diagnostic criteria's have been review by Nathan et al. (2014) and are summarized in Table 1.

Table 1: Diagnostic Criteria for PCOS

Name	**Rotterdam Criteria 2003[4]**	**NIH Criteria 1990**	**Androgen Excess and Polycystic Ovarian Syndrome Society guidelines (2009)**
Criteria	Requires 2/3 of: Hyperandrogenism * (clinical or biochemical) **AND/OR** Chronic Anovulation / Oligoovulation **AND/OR** PCO on ultrasound	Hyperandrogenism* (clinical or biochemical) **AND** Chronic Anovulation / Oligoovulation PCO not necessary for diagnosis	Diagnosis needs hyperandrogenism + one other feature: Hyperandrogenism *(clinical or biochemical) **PLUS** Chronic Anovulation / Oligoovulation **OR** PCO on ultrasound
	*Hyperandrogenism o Clinical (hirsutism or less commonly male pattern alopecia) or o Biochemical (Raised FAI or free testosterone) PCO = polycystic ovaries		

Clinical features can range from chronic anovulation, ovulatory infertility, heart disease, obesity and androgen-related symptoms. There are also long term sequelae of the disease. PCOS may also be associated with an increased risk of developing Type II

diabetes mellitus, the metabolic syndrome and endometrial cancer[5]. Endometrial cancer can be a result of endometrial hyperplasia that stems from chronic anovulation[6].

The primary etiology of PCOS remains unclear. A defect in the ovarian cells is what most attribute to be the cause of the excess androgen synthesis and symptoms of the disease [7], but genetic and environmental factors both have implications in its development. Stein and Leventhal placed emphasis on an elevated ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH)[8]. Other underlying causes have been identified such as frequent pulses of gonadotropin-releasing hormone (GnRH) that stimulate theca cells to produce androgen, decreased levels of FSH, insulin resistance via a post-receptor defect in fat tissue and skeletal muscles, pancreatic beta-cell dysfunction and obesity[9].

Obesity contributes to the pathogenesis of PCOS through its contribution to insulin resistance. Obesity also increases menstrual disorders and hyperandrogenism, while weight loss helps alleviates symptoms. Weight gain in women with PCOS can exacerbate and worsen insulin resistance, leading to the development of metabolic syndrome, acanthosis nigricans and ultimately Type II diabetes.[10] Achard and Thiers first described a disorder of carbohydrate metabolism and hyperandrogenism in "diabéte des femmes à barbes", diabetes of bearded women in 1921[11]. Since the initial report by Burghen et al (5) in 1980 that PCOS is associated with hyperinsulinemia, it is clear that insulin has a major role on reproductive and metabolic morbidities. The relationship of insulin on gonadal function has been investigated extensively by Dunaif et al 1988[12], Barbieri et al 1983[13], Poretsky et al 1987[14] & 1991[15].

Insulin has varying effects on the gonadal and reproductive system that leads to dysfunction activity in the ovaries and menstruation. Hyperinsulinemia secondary to insulin resistance leads to an increased ovarian response to gonadotropins, which results in the overexpression of LH and IGF-1 receptors[16]. Insulin also exerts its effects by increasing the sensitivity of immature granulosa cells to LH, proliferation of thecal cells and up regulation of enzymes related to androgen synthesis[17]. Insulin also reduces the synthesis of sex hormone binding globulin (SHBG). Decreased levels of SHBG results increased bioavailability of testosterone to peripheral tissues[18]. Hyperinsulinemia also up regulates the activity of the hypothalamic-pituitary-adrenal axis, which results in excess androgen production from the adrenal glands[19]. The role of insulin resistance in PCOS is most promising considering the possibility therapeutic intervention with insulin sensitizing agents.

Lifestyle change is considered first-line treatment for infertility in women with PCOS. A loss of 5 to 10% in body weight regardless of BMI may be associated with improvement in central obesity, hyperandrogenism, and ovulation rate[20]. First line pharmacological treatment for improving fertility is Clomiphene citrate (CC), an estrogen receptor modulator. Advantages include low cost, oral administration and few side effects. One disadvantage is that approximately 15% of women with PCOS do not respond to the maximum dose of CC and are considered resistant to this medication[21]. Second-line pharmacological treatment of anovulation in women with PCOS includes the use of gonadotropins [recombinant follicle stimulating hormone or human menopausal gonadotropin] for timed intercourse of intrauterine insemination[20]. The cost associated with this treatment is higher compared to others and it is necessary to undergo tubal

patency testing prior to treatment. More invasive therapeutic modalities include laparoscopic ovarian drilling surgery, which has higher cost, requires general anesthesia and greater complications and in vitro fertilization[21].

While first line treatment should always be lifestyle changes, weight loss and decreasing circulating insulin levels has a promising effect on ovulation. Metformin is a widely prescribed oral agent approved for use in the treatment of Type II diabetes mellitus. A biguanide medication whose mechanism is to increase sensitivity to insulin, Metformin has been shown to improve hyperandrogenemia and hirsutism and reduce lipid levels in PCOS[22]. Some studies have shown that treatment with Metformin improved insulin resistance and increased the likelihood of ovulation and pregnancy, with and sometimes without Clomiphene[23]. The exact role of Metformin in the treatment of PCOS and its effects on fertility including ovulation and live birth rate is still unclear.

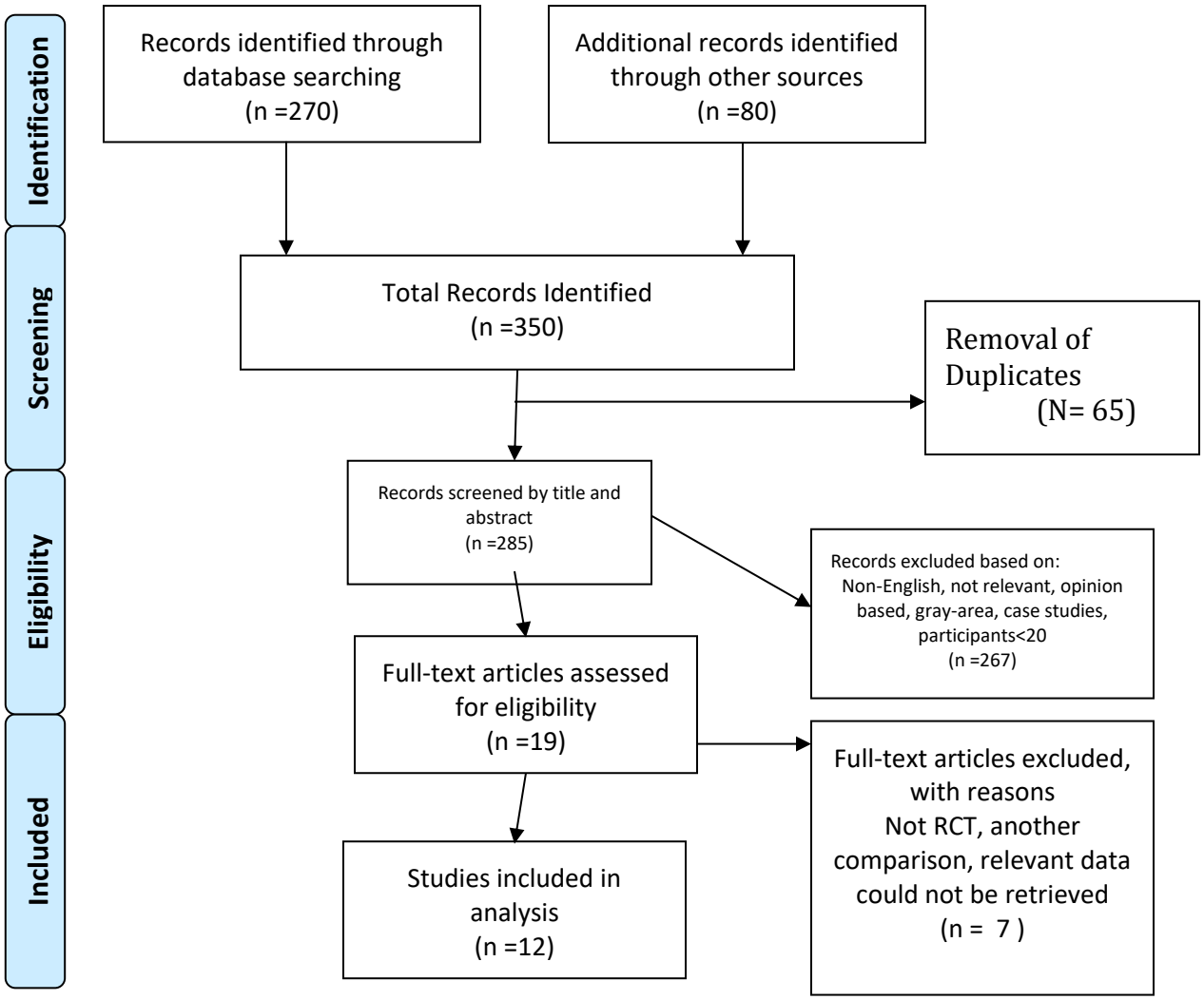
This paper's purpose is to review the role of Metformin in improving fertility outcomes as stand-alone treatment or with the use of Clomiphene.

Methods:

The Preferred Reporting Items for Systematic Review and Meta-Analysis, flow diagram was used to present the search strategy (Fig.1). PubMed was used to search for articles published from 1980 to the present day. The following keywords were searched; polycystic ovarian syndrome or polycystic ovarian disease or polycystic ovary syndrome or PCOS or infertility AND Metformin AND Clomiphene. A manual search was conducted from reference lists. Total articles found were 270 from database and 80 from manual search. After the removal of duplicate literature, 285 remained. Those abstracts were reviewed. Articles were then excluded due to non-relevance, non-English language,

opinion based, and case studies, gray-literature. The remaining 19 articles were reviewed in full.

Figure 1: PRISMA



Full Text articles were further evaluated and narrowed based on study type, number of subjects, relevance of research and type of outcome. Only primary research articles with greater than 20 subjects written in English in the last twenty years were chosen. 7 articles were excluded due to the reasons of having another comparison or relevant data could not be extracted. Considered studies evaluated the relationship of

Metformin and Clomiphene treatment on ovulation and pregnancy. Included studies described criteria for PCOS diagnosis. Valid exclusion of secondary causes like thyroid disorders, primary or secondary hyperprolactinemia, congenital adrenal hyperplasia and androgen-secreting tumors was expected. Exclusion of females with history of pelvic inflammatory disease or tubal disease and male factors (sperm quality / dysmotility) was expected. A diagnosis of PCOS must have been established using any of the following accepted methods: Rotterdam Criteria, ESHRE/ASRM Criteria or presence of irregular menstrual cycles, elevated plasma levels of testosterone, clinical symptoms of hyperandrogenism and presence of polycystic ovaries verified by transvaginal ultrasonography. No mandatory outcomes measures of pregnancy were required. The data was then extracted from remaining 12 articles into a table (Table 2). Information taken from each article included: Title, Author, Location, Year, Study Design, Sample size, Diagnosis of polycystic ovarian syndrome criteria, intervention, ovulation measurement methods, pregnancy measurement and conclusion

Study Population:

The population comprised of women of childbearing age with PCOS. In all of the studies, the number of participants and the criteria used to diagnose PCOS was recorded.

Outcome:

The effect of intervention on ovulation, and pregnancy was noted. The criteria for measuring ovulation and pregnancy were also recorded in the chart.

Results:

Table 2: Main Characteristics and Summary of Studies Included

Title	Author	Location	Year	Study Design	Sample size	Diagnosis Criteria	Intervention	Ovulation measurement	Pregnancy measurement	Conclusion
Efficacy of combined Metformin – Clomiphene citrate in comparison with Clomiphene citrate alone in infertile women with polycystic ovarian syndrome (PCOS)[24]	Ayaz et Al	Makkah, Saudi Arabia	2013	Randomized controlled trial	42	2 of the following: 1. Polycystic ovaries (either 12 or more peripheral follicles or increased ovarian volume (greater than 10 cm^3) 2. oligo- or anovulation (irregular cycles, amenorrhea) 3. clinical and/or biochemical signs of hyperandrogenism (Acne, hirsutism, voice changes, clitoromegaly)	Group A: Metformin + CC Group B: CC alone	follicle tracking (ovarian volume, size in mm and number of follicles) on ultrasonography	positive urine pregnancy test in those women who did not menstruate. Clinical pregnancy confirmed by gestational sac detection on ultrasonography.	A combination of Metformin and Clomiphene citrate significantly regulated the menstrual cycle and increased the ovulation and conception rates in study patients without complications
PCOSMIC: a multi-centre randomized trial in women with Polycystic Ovary Syndrome evaluating Metformin for Infertility with Clomiphene [25]	Johnson et al	Auckland, New Zealand	2009	double blind multi-centre randomized trial	171	Rotterdam consensus criteria	Women with high BMI>32kg/m2 received placebo or Metformin; women with bmi <or equal to 32kg/m2 received CC, Metformin or both	confirmed if pregnancy occurred or if serum progesterone level was > or equal to 25 nmol/l or suggested by serum progesterone 15-25 nmol/l	positive urine or serum pregnancy test plus intrauterine gestation sac on ultrasound scan or histological evidence of trophoblastic tissue with spontaneous abortion or ectopic pregnancy, live birth	There is no evidence that adding Metformin to 'standard care' is beneficial. Pregnancy and live birth rates are low in women with BMI>32 kg/m^2 whatever treatment is used, with no evidence of benefit of Metformin over placebo. For women with BMI ≤ 32 kg/m^2 there is no evidence of significant differences in outcomes whether treated with Metformin, CC or both.
Clomiphene citrate, Metformin or a combination of both as the first line ovulation induction drug for Asian Indian women with polycystic ovarian syndrome: A randomized controlled trial[26]	Kar et al	Bhubaneswar, Odisha, India	2015	randomized controlled trial	105	Rotterdam criteria: min 2 of the 3 criteria: (1) Chronic anovulation (2) clinical or biochemical hyperandrogenemia; (3)polycystic ovarian morphology	Group I : CC Group II Metformin Group III CC + Metformin	Transvaginal sonography	fetal cardiac activity documented at 6 weeks of pregnancy	Metformin was as good as CC in terms of "LBR" and the combination of CC and Metformin gave the highest ovulation and LBR.
Clomiphene, Metformin, or Both for	Legro et al	United States of America	2007	RCT	626	oligomenorrhea (with a hx of no more than 8 spontaneous menses/year)	Group 1: CC plus placebo Group 2: extended-	progesterone level above 5 ng per milliliter	urinary pregnancy test, ultrasonography for fetal viability	Clomiphene is superior to Metformin in achieving live birth in infertile women with the polycystic ovary

Infertility in the Polycystic Ovary Syndrome [27]						& hyperandrogenemia (with an elevated testosterone level documented within the previous year in an outpatient setting on the basis of local laboratory results, with a predetermined cutoff level set by principal investigator at each study site)	release Metformin plus placebo, Group 3: a combination of Metformin and Clomiphene for up to 6 months.	during a cycle		syndrome, although multiple births are a complication. The rate of ovulation was significantly higher in the combination group than in either of the single- agent groups
Effects of Metformin treatment on luteal phase progesterone concentration in polycystic ovary syndrome [28]	Meenakumari et al	Banaras, India	2003	Randomized controlled trial	24	criteria of the 1990 National Institutes of Health Conference includes : oligomenorrhea, hyperandrogenism, presence of 8 or more cystic follicles (about 10 mm in diameter) on ultrasound	i) natural cycle No treatment was given. ii) CC iii) Metformin plus CC	ovulation documented by ultrasound was later confirmed by serum progesterone levels	Pregnancy not measured but luteal phase progesterone was measured : Venous blood (~5 ml) was collected between 8:00 and 10:00 am after an overnight fast during the follicular and luteal phase of the cycle.	a significant enhancement in luteal progesterone concentration (16.97 ng/ml) in PCOS women treated with Metformin. deficiency of luteal phase progesterone synthesis and/or action is the leading cause of infertility or spontaneous abortion in cases of luteal phase defect
Effect of Clomiphene citrate plus Metformin and Clomiphene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomized double blind clinical trial [29]	Moll e al	Netherlands	2006	randomized double blind clinical trial	228	Rotterdam ESHRE/ASRM consensus	i) CC plus Metformin ii) CC plus placebo	biphasic basal temperature curve, a follicle with a diameter ≥ 16 mm on transvaginal ultrasonography, or progesterone ≥14 nmol/l in the second half of a menstrual cycle, or pregnancy	pregnancy test	Metformin may lead to an increase in the ovulation rate of up to 5%, though whether such a small difference is clinically relevant is doubtful. We conclude that Metformin should not be added to CC as primary method for induction of ovulation
Effects Of Metformin On Spontaneous And Clomiphen	Nestler et al	United States, Venezuela, and Italy.	1998	Randomized controlled trial	61	All had oligomenorrhea (fewer than six menstrual periods in	Group 1: Metformin Group 2: Placebo	serum progesterone, ovulation presumed if value	not measured	ovulatory response to Clomiphene can be increased in obese women with the PCOS by decreasing insulin secretion with Metformin

e-Induced Ovulation In The Polycystic Ovary Syndrome [30]						the preceding year) and hyperandrogenemia (elevated serum free testosterone concentrations, determined at local clinics), All the women had findings on ultra-sonography of the ovaries consistent with the diagnosis of the polycystic ovary syndrome.		exceeded 8 ng per milliliter		
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 [31]	Neveu et al	Quebec, Canada	2006	observational comparative study	154	oligoanovulation (as defined by less than 9 menstrual periods per year) and either clinical or biochemical evidence of hyperandrogenism.	Group 1 : CC Group 2 : Metformin Group 3 : CC & Metformin	biphasic basal body temperature curve and/or a progesterone level in the luteal phase of at least 2.0 ng/mL (6.0 mmol/L) during their follow-up.	positive beta-hCG	Metformin is better for ovulation induction than CC alone and equivalent for pregnancy achievement. We suggest that Metformin can be used first for ovulation induction in patients with PCOS regardless of their weight and insulin levels because of its efficacy and known safety profile
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	Palomba et al	Catanzaro, Italy.	2005	Prospective Parallel Randomized, Double-Blind, Double-Dummy Controlled	100	National Institutes of Health criteria	Group A: Metformin + placebo Group B: placebo plus CC.	transvaginal sonography and ovulation was retrospectively defined with the observation of a decrease in follicular	rising beta-human chorionic gonadotropin and the sonographic evidence of intrauterine gestational sac	Six-month Metformin administration is significantly more effective than six-cycle CC treatment in improving fertility in anovulatory nonobese PCOS women

Polycystic Ovary Syndrome [32]				Clinical Trial				dimensions and liquid in the cul-de-sac and confirmed by plasma P assay greater than 10 ng/ml (SI 32 nmol/liter).		
Evaluating the equivalence of Clomiphene citrate with and without Metformin in ovulation induction in PCOS patients [33]	Siebert et al	Cape Town , South Africa	2009	Prospective randomized controlled study	107	Rotterdam consensus	Group A: pretreated with Metformin before Clomiphene Group B received Clomiphene without pre-treatment	n/a	n/a	Although identical ovulation rates were observed in both arms equivalence could not be concluded with respect to the specified criteria.
Clomiphene Citrate Versus Metformin as First-Line Approach for the Treatment of Anovulation in Infertile Patients with Polycystic Ovary Syndrome [34]	Palomba et al	Naples, Italy	2007	multicenter, nonrandomized, prospective, controlled study.	80	presence of clinical [Ferriman-Gallwey score 8] or biochemical hyperandrogenism [serum testosterone levels 2 sd above our reference mean values] and chronic anovulation [serum luteal progesterone (P) 2 ng/ml)].	Group 1: Metformin Group 2: CC	n/a	n/a	Metformin and CC administered in an escalation protocol are two effective first- line approaches for improving fertility in anovulatory PCOS women

An assessment of lifestyle modification versus medical treatment with Clomiphene citrate, Metformin, and Clomiphene citrate–Metformin in patients with polycystic ovary syndrome [35]	Mohammad Ali Karimzadeh and Mojgan Javedani	Yazd, Iran	2009	Prospective randomized double-blind study	343	European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine guidelines (Rotterdam criteria, 2003)	Group 1: CC Group 2: Metformin Group 3: Clomiphene + Metformin Group 4: Lifestyle modification	Transvaginal sonography and follicular tracking were done	beta-hcg, ultrasound detection of fetal heart	The clinical pregnancy rate was 12.2% in Clomiphene group, 14.4% in Metformin group, 14.8% in Clomiphene + Metformin group, and 20% in lifestyle modification group. Lifestyle modification group achieved a significant reduction in waist circumference, total androgen, and lipid profile. Lifestyle modification improves the lipid profile in PCOS patients. lifestyle modification may be used as the first line of ovulation induction in PCOS patients.

Discussion:

Although PCOS is the most frequent endocrine disorder among reproductive age women, the current treatment regimens and management depends on the symptoms. For women who want infertility treatment, Clomiphene citrate is still the first line treatment. Clomiphene citrate is an estrogen receptor modulator and its mechanism of action is directly on the hypothalamic-pituitary axis to help induce ovulation. Multiple pregnancy rates are under 10% and hyper stimulation syndrome is rare[36]. Some patients have reported CC resistance or failure.

Given the strong data that support the pathogenesis that hyperinsulinemia plays in PCOS, it is reasonable to opt for insulin lowering medications as treatment. Metformin is a biguanide, which is approved for the treatment of Type 2 diabetes. Its main mechanism of action is to inhibit the production of hepatic glucose, although it also decreases intestinal glucose absorption and promotes insulin sensitivity in peripheral tissues[37]. The metabolic benefits have been show to decrease weight loss and improve insulin

resistance, which helps alleviate symptoms of PCOS. Metformin has shown in PCOS to improve menstrual regularity, ovulation and reducing androgenemia[38]. Side effects that are the most commonly experience include diarrhea and nausea. In patients with kidney disease, congestive heart failure and sepsis, lactic acidosis is a concern. Although there was concern of teratogenicity if used during pregnancy, recent data supports that Metformin does not cause major birth defects and has no effect on motor and social development[39].

The purpose of this review was to compare Metformin in improving fertility outcomes as stand-alone treatment or with the use of Clomiphene. Outcomes measured include ovulation, pregnancy rate and live birth rate.

Nestler et al[18] was one of the first studies to evaluate the use of Metformin and Clomiphene on ovulation. Nineteen of the 21 women who received combined Metformin and Clomiphene ovulated; while only 2 of the 25 women in the group given placebo and Clomiphene ovulated ($P<0.001$). They concluded that the ovulatory response to Clomiphene can be increased in obese women with PCOS by decreasing insulin levels with Metformin vs. placebo. This fact suggests that hyperinsulinemia impedes ovulation in obese women with PCOS.

Ayaz et al[24] found that the rate of ovulation was higher in Group A (Metformin & Clomiphene group) vs. Group B (group with Clomiphene and placebo). Group A similarly had an increased rate of conception by confirmation of urine pregnancy test (66.6% vs. 28.6%, $P=0.01$) and presence of gestational sac on ultrasound (61.9% vs. 28.6%, $P=0.03$). They concluded that both Metformin and Clomiphene significantly

increased ovulation and conception rate without complication and would be preferred as the first line therapy.

Kar et al[26] found that Metformin is as efficient as Clomiphene on live birth rates. Combined therapy off Clomiphene and Metformin had statistically significantly higher effect on ovulation rate as compared to CC alone P=0.03; odds ratio: 95% confidence interval: 3.888 [1.08–13.997]). No difference in ovulation was found between Metformin only group and Clomiphene only group (P=0.11).

Karimzadeh et al[35] found that clinical pregnancy rates between Metformin alone, Clomiphene alone, Metformin-Clomiphene, lifestyle change showed no significant difference from another (P =.56) and reported that all 3 groups had an increase in live birth rates.

Neveu et al[31] found that Metformin is better for ovulation induction than CC alone 75.4% vs. 50%; P=.005). Weight loss was comparable between the three groups, therefore efficacy of Metformin is not just due to weight loss alone.

Legro et al[27] found that the rate of live birth was lower in Metformin group in comparison to the Clomiphene group, and the combination-therapy group (P <0.001). The rate of ovulation was higher in the combination of Metformin-Clomiphene group than any other group. However, the increased difference of ovulation did not translate into an increase for a live-birth rate. They did find that the Metformin group had a significant decrease in other parameters such as BMI and total testosterone. Also a significant increase in sex hormone-binding globulin levels was observed. Similarly, the Clomiphene and Metformin group showed similar changes. This study in comparison to others measured live birth rate for primary outcomes. Although they were unable to find

a statistically significant benefit of the Metformin-Clomiphene combination, the possibility of some benefit cannot be excluded. When ovulation was measured as the primary outcome, the combination of Metformin-Clomiphene was superior to either Clomiphene alone or Metformin alone. Also, some of their subjects had a long-standing history of infertility, which may have had a confounding effect.

Palomba et al[34] compared Metformin vs. Clomiphene, in terms of efficacy as the first line treatment for treating anovulation in PCOS patients. They found that both CC and Metformin are two effective-first line options with different efficacy depending on time. Metformin was higher in efficacy after 6 months of treatment. No significant differences between the experimental and control groups were observed in ovulation (55.4 vs. 59.8%, respectively; P =0.396), pregnancy (10.8 vs. 11.2%, respectively; P=0.888), and abortion (19.5 vs. 26.3%, respectively; P = 0.530) rates. This conclusion differed from their earlier study that showed that Metformin was more effective in comparison with CC in pregnancy (Palomba et al, 2005[32]). They found that in the earlier study, the study population consisted of only nonobese patients and that the subjects were prescreened for diabetes and/or glucose intolerance. This segregation was not representative of PCOS populations.

Meenakumari et al[28] found that women treated with Metformin demonstrated a significant enhancement in luteal progesterone concentrations compared to women on a natural cycle and women treated with only Clomiphene citrate. The deficiency of luteal phase progesterone synthesis and/or action is the leading cause of infertility or spontaneous abortion in cases of luteal phase defect, resulting in pregnancy loss. This study measured luteal progesterone as a final outcome but it is unsure if this related to

successful pregnancy.

Whereas, Johnson et al[25] found no evidence that adding Metformin to standard care is beneficial on improving pregnancy and live birth rates in women with PCOS. The main limitation of this study was that the trial was insufficiently powered. In order to detect an increase in a live birth rate, 590 participants would have been required (as opposed to 136).

Moll et al[29] similarly also found that Metformin is not an added benefit to Clomiphene citrate at inducing ovulation when compared to Clomiphene-placebo group. The ovulation rate in the Metformin group was 64% compared with 72% in the placebo group, a non-significant difference (risk difference − 8%, 95% confidence interval − 20% to 4%). They found an increase in ovulation with Clomiphene and Metformin of 5% but whether difference that small has clinically relevant is doubtful. Their study examined patients for a total of 6 ovulations or until Clomiphene resistance developed, the downside being the unexpectedly high rate of dropouts, which was not accounted for in power calculations.

Siebert et al[33] found that although identical ovulation rates were observed between patients treated with pretreatment with Metformin and Clomiphene and Clomiphene citrate only, equivalence could not be concluded. The limitations and weakness of their study included not using a placebo for the pretreatment in the Clomiphene citrate group only, and their sample size.

Many variables exist within the study that explains the conflicting findings of the efficacy of Metformin. While the review has shown that most of the studies agree that Metformin and Clomiphene are superior in respect to ovulation rates. Whether

Metformin and Clomiphene are superior to Clomiphene treatment alone on pregnancy and live birth rates remains to be unclear. Most studies seem to support the use of Metformin for anovulatory PCOS patients, to help with ovulation. When the primary outcome measurement was ovulation, adding Metformin showed a significant benefit. When the primary outcome measurement was pregnancy or live birth rate, the benefit was not statistically significant. In the most recent studies did they start to measure outcomes such as pregnancy, live birth and pregnancy complications.

The roles of Metformin in obese and nonobese women with PCOS were similar in data. In some studies, weight loss achieved by lifestyle changes, also provided a statistically significant effect on ovulatory rates. Ultimately there is a correlation between improving insulin resistance and androgens levels, and ovulation rates.

Most studies reported that subjects experienced side effects limited to gastrointestinal symptoms. While Metformin is known to cause lactic acidosis in patients with renal/hepatic impairment and cardiac disease, none of the studies reported any incidence of lactic acidosis.

Another area was the power of the study, and the sample size that varied from study to study. Most studies that followed the patients for a longer period of time experienced patient dropout rates. One study supported that the benefit of Metformin and Clomiphene was time dependent, at least 6 months to show a statistically significant difference.

Our review is strengthened by the detailed search strategy, and the types of randomized studies included. Our review is limited by the heterogeneity among the study in the clinical intervention, and outcomes.

Conclusion:

This systematic review provides a broader understanding of the use of Metformin and Clomiphene in the treatment of PCOS with its effects on fertility. While Metformin and Clomiphene have been shown to have a significant effect on ovulation rates vs. Clomiphene or Metformin alone, it remains unclear if Metformin alone or the addition of Metformin improves live birth rates and pregnancy.

However, as more studies are done and live birth rates are more commonly employed as the main outcome measure, this is an area that needs to be explored. With this systematic review, it shows a statistically significant benefit of adding Metformin to PCOS treatment regimens to help with ovulation and insulin resistance. Before commencing Clomiphene Citrate, patients with PCOS obese and nonobese can benefit from the use of to improve ovulation rates. Metformin also seems to improve the metabolic profile of PCOS patients, thus decreasing the associated risks of having PCOS such as heart disease and diabetes mellitus.

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