Review Article

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Insights in Reproductive Medicine

2017
Vol.1 No.1:3

Polycystic Ovary Syndrome and Metformin

Soyman Z[1], Demirel E[2] and Oliver Client[3]

[1]Department of Obstetrics and Gynecology, Ministry of Health, Istanbul Education and Research Hospital, Turkey

[2]Department of Obstetrics and Gynecology, Izmir Katip Celebi University School of Medicine, Turkey

[3]Department of Gynecology, Adamoas Health Institute, Costa Rica, USA

Corresponding author: Oliver C, Department of Gynaecology, Adamoas Health Institute, Costa Rica, Sur 605-1403, Col. Napoles, 03810 DF, USA, Tel: 14565985698; E-mail: oliverclient@gmail.com

Received date: January 03, 2017; **Accepted date:** March 16, 2017; **Published date:** March 22, 2017

Citation: Soyman Z, Demirel E, Client O. Polycystic Ovary Syndrome and Metformin. Insights Reprod Med. 2017, 1:1

Abstract

Polycystic Ovary Syndrome (PCOS) is the common endocrinological disorder of women in reproductive ages. It is generally accepted that insulin resistance plays a significant role in PCOS pathogenesis. Metformin is the most commonly studied insulin sensitizing drug in treatment of PCOS. The use of metformin may have a favorable effect in some subset of the population of women with PCOS. The aim of this review was to evaluate the uses of metformin in PCOS related infertility, pregnancy loss, hyperandrogenism, endometrial and cardiovascular abnormalities. Polycystic ovary syndrome (PCOS) is classically characterised by an accumulation of incompletely developed follicles in the ovaries due to anovulation. However, since the publication of the Rotterdam criteria, there is acceptance that menstrual cycle and endocrine dysfunction with hyperandrogenism is more important in reaching the diagnosis than ultrasound findings. It is diagnosed in up to 10% of women attending gynaecology clinics, but the prevalence in the population as a whole varies from 10% to 20%, depending on which diagnostic criteria are used. PCOS has been associated with hirsutism, infertility, acne, weight gain, type 2 diabetes, cardiovascular disease (CVD), and endometrial hyperplasia. We conducted a systematic review and aimed to answer the following clinical question: What are the effects of metformin on hirsutism and menstrual frequency in women with PCOS? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2014 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA).We found 14 studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. In this systematic review we present information relating to the effectiveness and safety of the following interventions: metformin compared with placebo/no treatment, metformin compared with weight loss intervention, or metformin compared with cyproterone acetate-ethinylestradiol.

Keywords:

Hyperandrogenism; Infertility; Insulin resistance; Metformin; Polycystic ovary syndrome

Abbreviations:

ART: Assisted Reproductive Technique; BMI: Body Mass Index; CVD: Cardiovascular Disease; CC: Clomiphene Citrate; CHD: Coronary Heart Disease; DM: Diabetes Mellitus; IR: Insulin Resistance; ICSI: Intra Cytoplasmic Sperm Injection; IVF: *In Vitro* Fertilization; MS: Metabolic Syndrome; OCP: Combined Oral Contraceptive Pill; OHSS: Ovarian Hyper-Stimulation Syndrome; PCO: Polycystic Ovary; PCOS: Polycystic Ovary Syndrome; RCT: Randomized Controlled Trial; rFSH: Recombinant Follicle Stimulating Hormone; SHBG: Sex Hormone Binding Globulin; WHR: Waist-to-Hip Ratio

Introduction

PCOS is a long-established endocrinopathy impacts approximately 5% to 10% of women of reproductive age [1]. In step with the Rotterdam criteria at least two of the followings are ample for the analysis of PCOS; oligo and/or anovulation, scientific and/or biochemical indicators of hyperandrogenism and polycystic ovaries at ultrasound with exclusion of alternative androgen excess or related problems [2]. Oligomenorrhea is outlined as less than eight intervals in one 12 months. Also amenorrhea is outlined as no period for more than three months. Polycystic Ovary (PCO) morphology has been outlined as the presence of 12 or extra follicles in each ovary measuring 2-9 mm in diameter, and/or accelerated ovarian volume (>10 ml). Medical manifestations for hyperandrogenism are hirsutism, zits and alopecia. Biochemical hyperandrogenism is evaluated by measuring serum androgen phases.

PCOS sufferers have been suggested to have an extended chance of metabolic syndrome, sort 2 Diabetes Mellitus (DM), Coronary heart disease (CHD), infertility, hypertension, miscarriage, preeclampsia, gestational diabetes and endometrial melanoma [3]. Etiology of PCOS continues to be uncertain [4].

Insulin Resistance (IR) plays a massive function in the pathogenesis of PCOS. Compensatory hyperinsulinemia and IR are located in roughly 65-70% of ladies with PCOS [5]. IR is related to androgen extra and an ovulation. The better phases of insulin results elevated ovarian androgen secretion and diminished intercourse Hormone–Binding Globulin (SHBG) construction from the liver [6]. The expanded intra ovarian androgen prevents the progress of ovarian follicles by means of ovulation [7]. Hyperinsulinemia results in premature follicular atresia and an ovulation [8].

Weight discount and metformin are crucial components for development of insulin sensitivity in PCOS. Weight discount rates increase insulin sensitivity, toughen hyperandrogenism and repair ovulation in women with PCOS [9]. The extended insulin sensitivity with metformin therapy has additionally been demonstrated in non-diabetic women with PCOS [10]. Metformin is a biguanide currently used as an insulin sensitizing drug for the remedy of sort 2 DM. Metformin inhibits hepatic glucose production and enhances insulin sensitivity in peripheral tissues. Metformin reduces gluconeogenesis with the aid of lowering circulating free fatty acid concentrations. The use of metformin may just reinforce menstrual regularity, develop ovulation and reduce serum androgen levels [11].

Facet results of metformin are often gastrointestinal similar to diarrhea, nausea, vomiting, indigestion, constipation, disagreeable metal taste in mouth. To lower the incidence of gastrointestinal side results, it is recommended to provoke with low dose taken few minutes earlier than foods and expand the dose steadily. Also, sustained unlock components could have cut back expense of part results. Malabsorption of diet B12 and lactic acidosis are other facet results which have got to be kept in mind. The variable doses of metformin were utilized in clinical reports. Nonetheless, the therapeutic routine of metformin just isn't good standardized. On the whole dose of 850 mg twice a day for six months has been administrated in many reports with PCOS. This evaluates aims to evaluate the effectiveness of metformin in PCOS associated infertility, being pregnant loss, hyperandrogenism, endometrial and cardiovascular abnormalities.

Metformin and Sub-fertility

PCOS is the most common cause of chronic anovulation which leads to infertility. Metformin improves ovulation by reducing insulin levels and ovarian androgen production [12]. These beneficial effects on insulin and androgen levels justify the use of metformin in reproductive disturbances in PCOS.

Metformin Alone

Metformin has been proven to toughen ovulation rate when put next with placebo in women with PCOS [12]. A Cochrane overview of seven Randomized Controlled Trials (RCTs) demonstrated that scientific being pregnant expense used to be tremendously expanded in metformin crew when compared with the placebo group. However, same evaluation of three RCTs reported that the end result reside beginning was no longer modified with metformin treatment [13].

Metformin versus Clomiphene

Clomiphene Citrate (CC) is the most fashioned drug used for ovulation induction in women with PCOS. It has been identified that clomiphene is advanced to metformin as an ovulation induction agent [14]. A meta-analysis proven that clinical pregnancy and are living delivery cost weren't drastically different from metformin cure when put next with clomiphene cure in non-chubby females with anovulatory PCOS [15]. The pregnancy and are living beginning fee have been higher in clomiphene when put next with metformin in overweight females with anovulatory PCOS [13,16].

Metformin in Combination with CC

In a meta-analysis, metformin in combination with CC, as compared to metformin on my own, has been proven to increase the clinical being pregnant cost in women with PCOS [13]. Despite the fact that, it has been pronounced that the reside delivery fee was not drastically differ between companies [13]. It has been confirmed that mixed medication with metformin and CC increase live start price compared with CC on my own in CC-resistant women [12,17].

Metformin versus Aromatase Inhibitors

Despite, there are few RCT data comparing metformin with Aromatase inhibitors in the literature, letrozole may be superior to clomiphene in terms of live births [18].

Metformin in Assisted Reproductive Treatment

Yarali et al. found that pregnancy charges have been greater in the metformin+Recombinant Follicle Stimulating Hormone (rFSH) combination treatment in comparison with the placebo +rFSH cure. However, the change was no longer large [19]. There is no proof that metformin cure before or throughout Assisted Reproductive process (artwork) cycles could toughen are living beginning or clinical pregnancy price [20]. The risk of Ovarian Hyperstimulation Syndrome (OHSS) was once decreased with metformin In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) cycles [20]. Similarly, meta-analysis of randomized controlled trials tested that the important effect of metformin co-administration for the period of ovulation induction with gonadotropins and/or IVF cycles is unclear [21].

Metformin and Pregnancy Loss

A few numbers of reports have validated that metformin decreases the danger of pregnancy loss [22,23]. Identical spontaneous abortion premiums had been located between metformin, CC and metformin plus CC companies in a prospective randomized trial [14]. Moll et al. has mentioned no massive change in being pregnant loss expense among females handled with metformin plus CC compared with placebo plus CC [24]. In the end, invaluable influence of metformin on being

pregnant loss has now not been certainly demonstrated within the literature.

Metformin for Hyperandrogenic Symptoms in Women with PCOS

The favorable effect of metformin on the hyperandrogenism of patients with PCOS has been discovered in many reports [25-27]. It's possible that the reducing circulating insulin phases by healing of metformin may make stronger hyperandrogenemia; also hirsutism. A be taught evaluating metformin (2250 mg/day), rosiglitazone (four mg/ day) and the combo of each drugs with placebo in nonobese, non-IR females with PCOS; the mean serum-free testosterone levels in medication corporations have been drastically reduce than the phases in placebo workforce [28]. Ortega-Gonzalezetal have mentioned that free testosterone and androstenedione had been greatly diminished in metformin (2250 mg/day) and pioglitazone (30 mg/day) remedy agencies [29]. In distinction, metformin (1700 mg/day) compared with rosiglitazone (4 mg/ day) statistically significant cut down has been observed most effective within the rosiglitazone groups [30].

Additionally, an evaluation of metformin (2250 mg/day) with flutamide (250 mg/day) in nonobese younger females with PCOS demonstrated that the phases free testosterone decreased vastly in both cure organizations [31]. In a potential, randomized, placebocontrolled trial, placebo, metformin (1700 mg/day), flutamide (500 mg/day) or metformin plus flutamide administered for 6 months to sufferers with PCOS. This be taught has been published that Ferriman- Gallwey hirsutism rating was greatly reduced within the flutamide on my own arm than within the metformin alone arm; combo therapy with metformin didn't add any additional potential [32]. Antiandrogen healing is way strong than metformin alone for the therapy of hirsutism.

Two randomized trials have discovered higher lower within the hirsutism rating within the sufferers dealt with with the combined Oral Contraceptive tablet (OCP) compared with metformin [33,34]. Conversely, Harborne et al. said a greater slash within the hirsutism rating with metformin than the OCP treatment [35]. Constrained knowledge suggested that there's no evidence of difference in influence between metformin and the OCP on hirsutism and pimples [36]. OCP was once effective than metformin in reducing serum androgen levels [36].

Metformin, the Endometrium and Menstrual Regularity

Giudice et al. has located that hyperinsulinemia may just make a contribution to stimulation of endometrial proliferation [37]. Researchers have demonstrated that therapy with rosiglitazone or metformin could normalize endometrial histology [38]. Despite the fact that lack of definitive experiences, metformin administration may scale back the chance of unopposed endometrial proliferation and abnormal endometrial histology through making improvements to ovulatory operate and very likely reducing the stages of insulin.

It has been pronounced that metformin administration could beef up menstrual irregularity in patients with oligomenorrhea or amenorrhea [39-41]. Nonetheless, metformin was once less potent than OCP in making improvements to menstrual sample [36,42]. Periodicity of menstrual bleeding in sufferers receiving metformin should no longer be used to confirm ovulation [43].

Metformin and Weight Loss

Weight discount improves insulin resistance and compensatory hyperinsulinemia [44]. Tan et al. stated that metformin use was enormously related to diminished body weight and body Mass Index (BMI) in the chubby and overweight patients with PCOS [45]. An additional study discovered a massive reduction in waist circumference but no big difference in weight in obese females with PCOS dealt with metformin [46]. On the contrary, other studies have proven that metformin has no influence on BMI or waist circumference [47]. The diversities in weight reduction amongst the trials are probably triggered through utilization of variable doses. A potential cohort learns investigated the outcomes of two one-of-a-kind doses of metformin (1500 mg/day; 2550 mg/day) on weight and BMI [48]. Although, all organizations have huge rate reductions in weight and BMI, chubby ladies with PCOS proven higher weight reduction at the higher dose when compared with the low dose. An identical amount of weight reduction found at both doses of metformin in morbidly chubby women [48].

In meta-analyses of three trials [49-51] evaluating metformin with OCPs was once published no difference in BMI and Waist-To-Hip Ratio (WHR) [36]. A meta-evaluation of two reviews [52,53] did not detect a change in BMI between OCP on my own and OCP combined with metformin [36].

Subculture modifications and weight loss remains the cornerstone of potent development for obese or obese women with PCOS [54]. For that reason, metformin has minimal outcome on weight discount and should not be used purely hence.

Metformin and long run penalties of PCOS

PCOS has been said to have an elevated threat for Metabolic Syndrome (MS), dyslipidemia, hypertension, Cardiovascular disease (CVD) and diabetes [55,56]. There is a paucity of information on the efficacy of metformin for stopping the development of diabetes, CVD or endometrial melanoma [36]. Metformin may have a protecting outcome for the increased danger of endometrial cancer in ladies with PCOS by restoring menstrual cyclicity and ovulation.

Conclusion

In conclusion, polycystic ovary syndrome is the common endocrinological disorder of females in reproductive a while. It's by and large accepted that insulin resistance performs a significant function in PCOS pathogenesis. Using metformin will have a favourable result in some subset of the populace of women with PCOS. Good designed, blinded, placebo-controlled and properly powered RCTs must be performed to assess the

long-time period effects of metformin therapy on morbidity and mortality in women with PCOS. Although we found no significant benefit of the combination of metformin and clomiphene, as compared with clomiphene alone, the possibility of some benefit cannot be excluded. On the basis of the 95% CIs, plausible differences in the live-birth rate between groups range from a 12.6% absolute increase to a 4.2% absolute decrease in the combination-therapy group. Furthermore, when ovulation is used as the outcome, the combination of metformin and clomiphene was superior to either clomiphene alone or metformin alone. The pregnancy rates in our trial were lower than those reported by others, perhaps reflecting the inclusion of obese women and the fact that many of the subjects had a long-standing history of infertility. These factors may also have contributed to a high rate of pregnancy complications [6,7,30]. Our selection criteria were consistent with both National Institutes of Health criteria and the revised Rotterdam diagnostic criteria [8,9] for the polycystic ovary syndrome, and more than 90% of our subjects had polycystic ovaries on baseline ultrasonography. Our cohort was similar in age and BMI to the cohort in a large, multicenter trial that showed a benefit of the insulin sensitizer troglitazone on ovulatory frequency in the polycystic ovary syndrome. Our study demonstrates the limitations of relying on ovulation rates as a surrogate for live-birth rates. We found that pregnancy was approximately twice as likely when ovulation was induced by clomiphene as when it was induced by metformin. Our study did not address mechanisms for improved fecundity per ovulation with clomiphene, as compared with metformin.

References

1. Franks S (1995) Polycystic ovary syndrome. N Engl J Med 333: 853-861.
2. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 19: 41-47.
3. Genazzani AD, Ricchieri F, Lanzoni C (2010) Use of metformin in the treatment of polycystic ovary syndrome. Womens Health (Lond) 6: 577-593.
4. Dunaif A (1997) Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 18: 774-800.
5. DeUgarte CM, Bartolucci AA, Azziz R (2005) Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. Fertil Steril 83: 1454-1460.
6. Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, et al. (1991) A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab 72: 83-89.
7. Jonard S, Dewailly D (2004) The follicular excess in polycystic ovaries, due to intraovarian hyperandrogenism, may be the main culprit for the follicular arrest. Hum Reprod Update 10: 107-117.
8. Utiger RD (1996) Insulin and the polycystic ovary syndrome. N Engl J Med 335: 657-658.
9. Norman RJ, Davies MJ, Lord J, Moran LJ (2002) The role of lifestyle modification in polycystic ovary syndrome. Trends Endocrinol Metab 13: 251-257.
10. Diamanti-Kandarakis E, Kouli C, Tsianateli T, Bergiele A (1998) Therapeutic effects of metformin on insulin resistance and hyperandrogenism in polycystic ovary syndrome. Eur J Endocrinol 138: 269-274.
11. Nestler JE (2008) Metformin for the treatment of the polycystic ovary syndrome. N Engl J Med 358: 47-54.
12. Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Economou FN (2010) Metformin: An old medication of new fashion: Evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur J Endocrinol 162: 193-212.
13. Tang T, Lord JM, Norman RJ (2012) Insulin sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiroinositol) for women with polycystic ovary syndrome, oligoamenorrhoea and subfertility. Cochrane Database Syst Rev 5: CD003053
14. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. (2007) Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med 356: 551-566.
15. Johnson N (2011) Metformin is a reasonable first-line treatment option for non-obese women with infertility related to an ovulatory polycystic ovary syndrome--a meta-analysis of randomised trials. Aust N Z J Obstet Gynaecol 51: 125-129.
16. Zain MM, Jamaluddin R, Ibrahim A, Norman RJ (2009) 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 polycystic ovary syndrome: A randomized controlled trial. Fertil Steril 91: 514- 521.
17. Palomba S, Falbo A, Zullo F, Orio F Jr (2009) Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: A comprehensive review. Endocr Rev 30: 1-50.
18. Franik S, Kremer JA, Nelen WL, Farquhar C (2014) Aromatase inhibitors for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev CD010287.
19. Yarali H, Yildiz BO, Demirol A (2002) Co-administration of metformin during rFSH treatment in patients with clomiphene citrate-resistant polycystic ovarian syndrome: A prospective randomized trial. Hum Reprod 17: 289-294.
20. Tso LO, Costello MF, Albuquerque LE (2009) Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev CD006105.
21. Costello MF, Chapman M, Conway U (2006) A systematic review and meta-analysis of randomized controlled trials on metformin co-administration during gonadotrophin ovulation induction or IVF in women with polycystic ovary syndrome. Hum Reprod 21: 1387-1399.
22. Glueck CJ, Phillips H, Cameron D, Sieve Smith L, Wang P (2001) Continuing metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first trimester spontaneous abortion: A pilot study. Fertil Steril 75: 46-52.
23. Lord JM, Flight IH, Norman RJ (2003) Insulin sensitizing drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database Syst Rev CD003053.
24. Moll E, Bossuyt PMM, Korevaar JC, Lambalk CB, van der Veen F (2006) 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. BMJ 332: 1461-1462.
25. Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ (1994) Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 1994; 43: 647-654.
26. Nawrocka J, Starczewski A (2007) Effects of metformin treatment in women with polycystic ovary syndrome depends on insulin resistance. Gynecol Endocrinol 2007; 23: 231-237.
27. Marcondes JA, Yamashita SA, Maciel GA, Baracat EC, Halpern A (2007) Metformin in normal-weight hirsute women with polycystic ovary syndrome with normal insulin sensitivity. Gynecol Endocrinol 23: 273-278.
28. Baillargeon JP, Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Nestler JE (2004) Effects of metformin and rosiglitazone, alone and in combination, in non-obese women with polycystic ovary syndrome and normal indices of insulin sensitivity. Fertil Steril 82: 893-902.
29. Ortega-González C, Luna S, Hernández L, Crespo G, Aguayo P, Arteaga- Troncoso G, et al. (2005) Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome. J Clin Endocrinol Metab 90: 1360-1365.
30. Yilmaz M, Biri A, Karakoç A, Törüner F, Bingöl B, Cakir N (2005) The effects of rosiglitazone and metformin on insulin resistance and serum androgen levels in obese and lean patients with polycystic ovary syndrome. J Endocrinol Invest 28: 1003-1008.
31. Sahin I, Serter R, Karakurt F, Demirbas B, Culha C, Taskapan C, et al. (2004) Metformin versus flutamide in the treatment of metabolic consequences of non-obese young women with polycystic ovary syndrome: A randomized prospective study. Gynecol Endocrinol 19: 115-124.

32. Gambineri A, Patton L, Vaccina A, Cacciari M, Morselli-Labate AM, Cavazza C, et al. (2006) Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: A randomized, 12-month, placebo-controlled study. J Clin Endocrinol Metab 91: 3970-3980.

33. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, et al. (2000) Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: A randomized study. J Clin Endocrinol Metab 85: 3161- 3168.

34. Luque-Ramírez M, Alvarez-Blasco F, Botella-Carretero JI, Martínez-Bermejo E, Lasunción MA, et al. (2007) Comparison of ethinyl-estradiol plus cyproterone acetate versus metformin effects on classic metabolic cardiovascular risk factors in women with the polycystic ovary syndrome. J Clin Endocrinol Metab 92: 2453-2461.

35. Harborne L, Fleming R, Lyall H, Sattar N, Norman J (2003) Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. J Clin Endocrinol Metab 88: 4116-4123.

36. Costello M, Shrestha B, Eden J, Sjoblom P, Johnson N (2007) Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease and endometrial cancer in polycystic ovary syndrome. Cochrane Database Syst Rev CD005552.

37. Giudice LC (2006) Endometrium in PCOS: Implantation and predisposition to endocrine CA. Best Pract Res Clin Endocrinol Metab 20: 235-244.

38. Legro RS, Zaino RJ, Demers LM, Kunselman AR, Gnatuk CL, et al. (2007) The effects of metformin and rosiglitazone, alone and in combination, on the ovary and endometrium in polycystic ovary syndrome. Am J Obstet Gynecol 196: 402.

39. Glueck CJ, Wang P, Fontaine R, Tracy T, Sieve-Smith L (2001) Metformin to restore normal menses in oligo-amenorrheic teenage girls with polycystic ovary syndrome (PCOS). J Adolesc Health 29: 160-169.

40. Ibáñez L, Valls C, Ferrer A, Marcos MV, Rodriguez-Hierro F, et al. (2001) Sensitization to insulin induces ovulation in non-obese adolescents with anovulatory hyperandrogenism. J Clin Endocrinol Metab 86: 3595- 3598.

41. Patel K, Coffler MS, Dahan MH, Yoo RY, Lawson MA, et al. (2003) Increased luteinizing hormone secretion in women with polycystic ovary syndrome is unaltered by prolonged insulin infusion. J Clin Endocrinol Metab 88: 5456-5461.

42. Morin-Papunen L, Vauhkonen I, Koivunen R, Ruokonen A, Martikainen H, et al. (2003) Metformin versus ethinyl estradiol-cyproterone acetate in the treatment of non-obese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab 88: 148-156.

43. Moghetti P, Castello R, Negri C, Tosi F, Perrone F, et al. (2000) Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo controlled 6-month trial, followed by open, long-term clinical evaluation. J Clin Endocrinol Metab 85: 139-146.

44. Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, et al. (2000) Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. J Clin Endocrinol Metab 85: 2767-2774.

45. Tan S, Hahn S, Benson S, Dietz T, Lahner H, et al. (2007) Metformin improves polycystic ovary syndrome symptoms irrespective of pre-treatment insulin resistance. Eur J Endocrinol 157: 669-676.

46. Tang T, Glanville J, Hayden CJ, White D, Barth JH, et al. (2006) Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome: A randomized, placebo controlled, double-blind multicenter study. Hum Reprod 21: 80-89.

47. Lord JM, Flight IH, Norman RJ (2003) Insulin sensitizing drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database Syst Rev 3: CD003053.

48. Harborne LR, Sattar N, Norman JE, Fleming R (2005) Metformin and weight loss in obese women with polycystic ovary syndrome: comparison of doses. J Clin Endocrinol Metab 90: 4593-4598.

49. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, et al. (2000) Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab 85: 3161-3168.

50. Harborne L, Fleming R, Lyall H, Sattar N, Norman J (2003) Metformin or anti-androgen in the treatment of hirsutism in polycystic ovary syndrome. J Clin Endocrinol Metab 88: 4116-4123.

51. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, et al. (2003) Metformin versus ethinyl-estradiol-cyproterone acetate in the treatment of non-obese women with polycystic ovary syndrome: A randomized trial. J Clin Endocrinol Metab 88: 148-156.

52. Cibula D, Fanta M, Vrbikova J, Stanicka S, Dvorakova K, et al. (2005) The effect of combination therapy with metformin and combined oral contraceptives (COC) versus COC alone on insulin sensitivity, hyperandrogenaemia, SHBG and lipids in PCOS patients. Hum Reprod 20: 180-184.

53. Elter K, Imir G, Durmusoglu F (2002) Clinical, endocrine and metabolic effects of metformin added to ethinyl-estradiol-cyproterone acetate in non-obese women with polycystic ovarian syndrome: a randomized controlled study. Hum Reprod 17: 1729-1737.

54. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, et al. (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346: 393-403.

55. Wild S, Pierpoint T, McKeigue P, Jacobs H (2000) Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. Clin Endocrinol (Oxf) 52: 595-600.

56. Legro RS (2003) Polycystic ovary syndrome and cardiovascular disease: A premature association? Endocr Rev 24: 302-312.