Austin Journal of Reproductive Medicine & Infertility

Open Access

Austin Publishing Group

Review Article

Polycystic Ovary Syndrome and Metformin

Soyman Z[1], Demirel E[2] and Kelekci S[2]*

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

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

***Corresponding author:** Kelekci S, Department of Obstetrics & Gynecology, Izmir Katip Celebi University School of Medicine, Turkey

Received: July 27, 2015; **Accepted:** November 10, 2015; **Published:** November 15, 2015

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.

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 Hyperstimulation 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 common endocrinopathy affects approximately 5% to 10% of women of reproductive age [1]. According to the Rotterdam criteria at least two of the followings are sufficient for the diagnosis of PCOS; oligo and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries at ultrasound with exclusion of other androgen excess or related disorders [2].

Oligomenorrhea is defined as less than eight periods in one year. Also amenorrhea is defined as no period for more than three months. Polycystic Ovary (PCO) morphology has been defined as the presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter, and/or increased ovarian volume (>10ml). Clinical manifestations for hyperandrogenism are hirsutism, acne, and alopecia. Biochemical hyperandrogenism is evaluated by measuring serum androgen levels.

PCOS patients have been reported to have an increased risk of metabolic syndrome, Type 2 Diabetes Mellitus (DM), Coronary Heart Disease (CHD), infertility, hypertension, miscarriage, preeclampsia, gestational diabetes and endometrial cancer [3].

Etiology of PCOS is still unclear [4]. Insulin Resistance (IR) plays a significant role in the pathogenesis of PCOS. Compensatory hyperinsulinemia and IR are observed in approximately 65-70% of women with PCOS [5]. IR is associated with androgen excess and an ovulation. The higher levels of insulin results increased ovarian androgen secretion and decreased Sex Hormone–Binding Globulin (SHBG) production from the liver [6]. The increased intra ovarian androgen prevents the growth of ovarian follicles through to ovulation [7]. Hyperinsulinemia leads to premature follicular atresia and an ovulation [8].

Weight reduction and metformin are critical components for improvement of insulin sensitivity in PCOS. Weight reductions enhance insulin sensitivity, improve hyperandrogenism and restore ovulation in women with PCOS [9]. The increased insulin sensitivity with metformin therapy has also been demonstrated in non-diabetic women with PCOS [10].

Metformin is a biguanide currently used as an insulin sensitizing drug for the treatment of type 2 DM. Metformin inhibits hepatic glucose production and enhances insulin sensitivity in peripheral tissues. Metformin reduces gluconeogenesis by lowering circulating free fatty acid concentrations. The use of metformin may improve menstrual regularity, increase ovulation and decrease serum androgen levels [11].

Side effects of metformin are mainly gastrointestinal such as diarrhea, nausea, vomiting, indigestion, constipation, unpleasant metallic taste in mouth. To reduce the incidence of gastrointestinal side effects, it is recommended to initiate with low dose taken few minutes before meals and increase the dose gradually. Also, sustained release formulation may have lower rate of side effects. Malabsorption of vitamin B12 and lactic acidosis are other side effects which must be kept in mind. The variable doses of metformin were used in clinical studies. However, the therapeutic regimen of metformin is not well standardized. Usually dose of 850 mg twice a day for 6 months has been administrated in many studies with PCOS.

This review aims to evaluate the effectiveness of metformin in PCOS related infertility, pregnancy 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.

Citation: Soyman Z, Demirel E and Kelekci S. Polycystic Ovary Syndrome and Metformin. Austin J Reprod Med Infertil. 2015; 2(6): 1033.

Metformin alone

Metformin has been shown to improve ovulation rate compared with placebo in women with PCOS [12]. A Cochrane review of seven Randomized Controlled Trials (RCTs) demonstrated that clinical pregnancy rate was significantly increased in metformin group compared with the plasebo group. However, same review of three RCTs reported that the outcome live birth was not changed with metformin treatment [13].

Metformin versus clomiphene

Clomiphene Citrate (CC) is the most common drug used for ovulation induction in women with PCOS. It has been known that clomiphene is superior to metformin as an ovulation induction agent [14]. A meta-analysis demonstrated that clinical pregnancy and live birth rate were not significantly different from metformin therapy compared with clomiphene therapy in non-obese women with anovulatory PCOS [15]. The pregnancy and live birth rate were higher in clomiphene compared with metformin in obese women with anovulatory PCOS [13,16].

Metformin in combination with CC

In a meta-analysis, metformin in combination with CC, as compared to metformin alone, has been shown to increase the clinical pregnancy rate in women with PCOS [13]. Although, it has been reported that the live birth rate was not significantly differ between groups [13]. It has been demonstrated that combined treatment with metformin and CC enhance live birth rate compared with CC alone 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. observed that pregnancy rates were higher in the metformin + Recombinant Follicle Stimulating Hormone (rFSH) combination therapy in comparison with the placebo + rFSH therapy. However, the difference was not significant [19]. There is no evidence that metformin treatment before or during Assisted Reproductive Technique (ART) cycles could improve live birth or clinical pregnancy rate [20]. The risk of Ovarian Hyperstimulation Syndrome (OHSS) was decreased with metformin In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) cycles [20]. Similarly, meta-analysis of randomized controlled trials demonstrated that the beneficial effect of metformin co-administration during ovulation induction with gonadotropins and/or IVF cycles is unclear [21].

Metformin and pregnancy loss

A few numbers of studies have demonstrated that metformin decreases the risk of pregnancy loss [22,23]. Similar spontaneous abortion rates have been observed between metformin, CC and metformin plus CC groups in a prospective randomized trial [14]. Moll, et al. has reported no significant difference in pregnancy loss rate among women treated with metformin plus CC compared with placebo plus CC [24]. Finally, beneficial effect of metformin on pregnancy loss has not been clearly demonstrated in the literature.

Metformin for hyperandrogenic symptoms in women with PCOS

The favorable effect of metformin on the hyperandrogenism of patients with PCOS has been observed in many studies [25-27]. It is possible that the reducing circulating insulin levels by treatment of metformin may improve hyperandrogenemia; also hirsutism. A study comparing metformin (2250 mg/day), rosiglitazone (4 mg/day) and the combination of both drugs with placebo in nonobese, non-IR women with PCOS; the mean serum-free testosterone levels in treatment groups were significantly lower than the levels in placebo group [28]. Ortega-Gonzalezetal have reported that free testosterone and androstenedione were significantly decreased in metformin (2250 mg/day) and pioglitazone (30 mg/day) therapy groups [29]. In contrast, metformin (1700 mg/day) compared with rosiglitazone (4 mg/day) statistically significant decrease has been observed only in the rosiglitazone groups [30].

In addition, a comparison of metformin (2250 mg/day) with flutamide (250 mg/day) in nonobese young women with PCOS demonstrated that the levels free testosterone decreased significantly in both therapy groups [31]. In a prospective, randomized, placebo-controlled trial, placebo, metformin (1700 mg/day), flutamide (500 mg/day), or metformin plus flutamide administered for 6 months to patients with PCOS. This study has been revealed that Ferriman-Gallwey hirsutism score was significantly decreased in the flutamide alone arm than in the metformin alone arm; combination therapy with metformin did not add any further advantage [32]. Antiandrogen therapy is much effective than metformin alone for the treatment of hirsutism.

Two randomized trials have observed greater decrease in the hirsutism score in the patients treated with the combined Oral Contraceptive Pill (OCP) compared with metformin [33,34]. Conversely, Harborne, et al. reported a greater decrease in the hirsutism score with metformin than the OCP treatment [35]. Limited data reported that there is no evidence of difference in effect between metformin and the OCP on hirsutism and acne [36]. OCP was effective than metformin in reducing serum androgen levels [36].

Metformin, the endometrium and menstrual regularity

Giudice, et al. has found that hyperinsulinemia may contribute to stimulation of endometrial proliferation [37]. Researchers have demonstrated that treatment with rosiglitazone or metformin may normalize endometrial histology [38]. Although lack of definitive studies, metformin administration may reduce the risk of unopposed endometrial proliferation and abnormal endometrial histology through improving ovulatory function and possibly reducing the levels of insulin.

It has been reported that metformin administration may improve menstrual irregularity in patients with oligomenorrhea or amenorrhea [39-41]. However, metformin was less effective than OCP in improving menstrual pattern [36,42]. Periodicity of menstrual bleeding in patients receiving metformin should not be used to confirm ovulation [43].

Metformin and weight loss

Weight reduction improves insulin resistance and compensatory hyperinsulinemia [44]. Tan, et al. reported that metformin use was

significantly associated with decreased body weight and Body Mass Index (BMI) in the overweight and obese patients with PCOS [45]. Another study found a significant reduction in waist circumference but no significant difference in weight in obese women with PCOS treated with metformin [46]. On the contrary, other studies have demonstrated that metformin has no effect on BMI or waist circumference [47]. The differences in weight loss amongst the trials are possibly caused by usage of variable doses. A prospective cohort study investigated the effect of two different doses of metformin (1500 mg/day; 2550 mg/day) on weight and BMI [48]. Although, all groups have significant reductions in weight and BMI, obese women with PCOS demonstrated greater weight loss at the higher dose compared with the low dose. Similar amount of weight loss observed at both doses of metformin in morbidly obese women [48].

In meta-analyses of three trials [49-51] comparing metformin with OCPs was revealed no difference in BMI and Waist-To-Hip Ratio (WHR) [36]. A meta-analysis of two studies [52,53] did not observe a difference in BMI between OCP alone and OCP combined with metformin [36].

Lifestyle modifications and weight loss remains the cornerstone of effective improvement for overweight or obese women with PCOS [54]. Consequently, metformin has minimal effect on weight reduction and should not be used purely for this reason.

Metformin and long term consequences of PCOS

PCOS has been reported to have an increased risk for Metabolic Syndrome (MS), dyslipidemia, hypertension, Cardiovascular Disease (CVD) and diabetes [55,56]. There is a paucity of data on the efficacy of metformin for preventing the development of diabetes, CVD or endometrial cancer [36]. Metformin may have a protective effect for the increased risk of endometrial cancer in women with PCOS by restoring menstrual cyclicity and ovulation.

Conclusion

In conclusion, polycystic ovary syndrome is the common endocrinological disorder of women in reproductive ages. It is generally accepted that insulin resistance plays a significant role in PCOS pathogenesis. The use of metformin may have a favorable effect in some subset of the population of women with PCOS. A well designed, blinded, placebo-controlled, and adequately powered RCTs should be performed to evaluate the long-term effects of metformin treatment on morbidity and mortality in women with PCOS.

References

1. Franks S. Polycystic ovary syndrome. N Engl J Med. 1995; 333: 853-861.
2. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004; 19: 41-47.
3. Genazzani AD, Ricchieri F, Lanzoni C. Use of metformin in the treatment of polycystic ovary syndrome. Womens Health (Lond Engl). 2010; 6: 577-593.
4. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. 1997; 18: 774-800.
5. DeUgarte CM, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. Fertil Steril. 2005; 83: 1454-1460.
6. Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, et al. A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab. 1991; 72: 83-89.
7. Jonard S, Dewailly D. The follicular excess in polycystic ovaries, due to intra-ovarian hyperandrogenism, may be the main culprit for the follicular arrest. Hum Reprod Update. 2004; 10: 107-117.
8. Utiger RD. Insulin and the polycystic ovary syndrome. N Engl J Med. 1996; 335: 657-658.
9. Norman RJ, Davies MJ, Lord J, Moran LJ. The role of lifestyle modification in polycystic ovary syndrome. Trends Endocrinol Metab. 2002; 13: 251-257.
10. Diamanti-Kandarakis E, Kouli C, Tsianateli T, Bergiele A. Therapeutic effects of metformin on insulin resistance and hyperandrogenism in polycystic ovary syndrome. Eur J Endocrinol. 1998; 138: 269-274.
11. Nestler JE. Metformin for the treatment of the polycystic ovary syndrome. N Engl J Med. 2008; 358: 47-54.
12. Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Economou FN. Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur J Endocrinol. 2010; 162: 193-212.
13. Tang T, Lord JM, Norman RJ. Insulin sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiroinositol) for women with polycystic ovary syndrome, oligoamenorrhoea and subfertility. Cochrane Database Syst Rev. 2012; 5: CD003053.
14. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med. 2007; 356: 551-566.
15. Johnson N. Metformin is a reasonable first-line treatment option for non-obese women with infertility related to anovulatory polycystic ovary syndrome--a meta-analysis of randomised trials. Aust N Z J Obstet Gynaecol. 2011; 51: 125-129.
16. Zain MM, Jamaluddin R, Ibrahim A, Norman RJ. 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. 2009; 91: 514-521.
17. Palomba S, Falbo A, Zullo F, Orio F Jr. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. Endocr Rev. 2009; 30: 1-50.
18. Franik S, Kremer JA, Nelen WL, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2014; 2: CD010287.
19. Yarali H, Yildiz BO, Demirol A. Co-administration of metformin during rFSH treatment in patients with clomiphene citrate-resistant polycystic ovarian syndrome: a prospective randomized trial. Hum Reprod. 2002; 17: 289-294.
20. Tso LO, Costello MF, Albuquerque LE. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2009: CD006105.
21. Costello MF, Chapman M, Conway U. 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. 2006; 21: 1387-1399.
22. Glueck CJ, Phillips H, Cameron D, Sieve Smith L, Wang P. Continuing metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first trimester spontaneous abortion: a pilot study. FertilSteril. 2001; 75: 46-52.
23. Lord JM, Flight IH, Norman RJ. Insulin sensitizing drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database Syst Rev. 2003: CD003053.
24. Moll E, Bossuyt PMM, Korevaar JC, Lambalk CB, van der Veen F. 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. 2006; 332: 1461-1462.

25. Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ. 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. 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. Metformin in normal-weight hirsute women with polycystic ovary syndrome with normal insulin sensitivity. Gynecol Endocrinol. 2007; 23: 273-278.

28. Baillargeon JP, Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Nestler JE. Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. Fertil Steril. 2004; 82: 893-902.

29. Ortega-González C, Luna S, Hernández L, Crespo G, Aguayo P, Arteaga-Troncoso G, et al. Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005; 90: 1360-1365.

30. Yilmaz M, Biri A, Karakoç A, Törüner F, Bingöl B, Cakir N. 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. 2005; 28: 1003-1008.

31. Sahin I, Serter R, Karakurt F, Demirbas B, Culha C, Taskapan C, et al. Metformin versus flutamide in the treatment of metabolic consequences of non-obese young women with polycystic ovary syndrome: a randomized prospective study. Gynecol Endocrinol. 2004; 19: 115-124.

32. Gambineri A, Patton L, Vaccina A, Cacciari M, Morselli-Labate AM, Cavazza C, et al. 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. 2006; 91: 3970-3980.

33. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, Tapanainen JS. 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. 2000; 85: 3161-3168.

34. Luque-Ramírez M, Alvarez-Blasco F, Botella-Carretero JI, Martínez-Bermejo E, Lasunción MA, Escobar-Morreale HF. 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. 2007; 92: 2453-2461.

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

36. Costello M, Shrestha B, Eden J. 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. 2007: CD005552.

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

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

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

40. Ibáñez L, Valls C, Ferrer A, Marcos MV, Rodriguez-Hierro F, de Zegher F. Sensitization to insulin induces ovulation in nonobese adolescents with anovulatory hyperandrogenism. J Clin Endocrinol Metab. 2001; 86: 3595-3598.

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

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

43. Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, et al. 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. 2000; 85: 139-146.

44. Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, et al. 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. 2000; 85: 2767-2774.

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

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

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

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

49. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, Tapanainen JS. 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. 2000; 85: 3161-3168.

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

51. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, Tapanainen JS. Metformin versus ethinyl-estradiol-cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized trial. J Clin Endocrinol Metab. 2003; 88: 148-156.

52. Cibula D, Fanta M, Vrbikova J, Stanicka S, Dvorakova K, Hill M, et al. 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. 2005; 20: 180-184.

53. Elter K, Imir G, Durmusoglu F. 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. 2002; 17: 1729-1737.

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

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

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

Austin J Reprod Med Infertil - Volume 2 Issue 6 - 2015
ISSN : 2471-0393 | www.austinpublishinggroup.com

Citation: Soyman Z, Demirel E and Kelekci S. Polycystic Ovary Syndrome and Metformin. Austin J Reprod Med Infertil. 2015; 2(6): 1033.