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Review Article

The Effect of Metformin on Reproduction–A Short Review

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Abstract

Reproductive health is an important domain of women's health care and broadly encompasses conditions which impact fertility, conception or birth of a healthy infant. Although numerous factors or conditions are associated with infertility, polycystic ovary disease is a well recognised cause. In this regard, metformin which belongs to the biguanide group of drugs and is commonly used as first line treatment in type 2 diabetes has also been commonly employed in the management of infertile women with PCOS with beneficial results. This review examines the evidence base of the utility of metformin in PCOS on ovulation and reproductive outcomes and discusses its role in different aspects of management and in future research.

Special Issue on
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INTRODUCTION

Reproductive health broadly relates to healthy functioning of male and female reproductive systems and the investigation and treatment of diseases or conditions which impact fertility, conception or a healthy live birth [1-3].

Infertility is defined as 'a disease of the reproductive system from failure to achieve a clinical pregnancy after 12 months or more of regular, unprotected sexual intercourse' [4]. Infertility can be unexplained though common causal factors include ovulatory dysfunction, tubular or uterine pathology, declining age and/or due to the "male" factor. For couples seeking conception, infertility can present with devastating consequences including depression, feelings of inadequacy and low self-esteem, breakdown of relationships and in certain cultures is associated with stigma and social ostracism [5].

The global prevalence of infertility observed over the last decade was estimated at approximately 9%, with nearly two third of couples seeking advice on conception [6]. Recent trends in infertility indicate that both levels of primary infertility (unable to have a single first live birth), and secondary infertility (with a previous live birth and unable to have an additional live birth) have hardly changed [7]. In recent years, reproductive health has increasingly been recognised as a priority of women's health care and adopted as one of the United Nations Millennium Development Goals to enable women to avail universal access to reproductive health by 2015[8].

In nearly a third of women attending infertility clinics, anovulatory infertility acounts for a majority of cases. Polycystic ovary syndrome (PCOS) is the underlying cause in nearly three quarter of women with anovulatory cycles [9]. It affects approximately 6-10% of women at their reproductive age and higher prevalence rates of up to 28% have been observed in overweight and obese women [10-13]. The beneficial effects of metformin, a commonly used anti-diabetic agent in women with PCOS was first proposed in 1994 [14]. Velazquez and colleagues showed that metformin can reverse metabolic abnormalities of hyperinsulinemia and gonadotrophin secretion and thereby regularise menstrual cycles, improve fertility and spontaneous pregnancy [14]. Since then numerous studies, both retrospective and randomised controlled trials exploring the role and efficacy of metformin in women with PCOS have been conducted.

The aim of this review is to look at the available evidence on the utility of metformin therapy on reproduction with a focus on its role in the management of women with PCOS.

PCOS

PCOS is a heterogenous disorder characterised by chronic anovulation or oligo-ovulation, irregular menstrual cycles, androgen excess manifest by hirsutism, acne, alopecia and polycystic ovaries detected on ultrasonography [15]. Biochemical features include raised concentrations of luteinising hormone (LH), low or normal concentrations of follicle stimulating hormone (FSH) and raised levels of testosterone and androstenedione [16]. Elevated LH concentrations of >10 IU/l are often associated with infertility and raised serum testosterone is often associated with an increased risk of hirsutism, infertility and menstrual cycle disturbance [16]. Obesity is a common association and may correlate with increased rates of infertility and menstrual cycle irregularities [16].

PCOS and insulin resistance

Insulin resistance is a common underlying pathophysiological abnormality in PCOS and predisposes individuals to an increased

risk of impaired glucose tolerance, type 2 diabetes mellitus and cardiovascular events [17-19]. Although insulin resistance is closely linked to obese or overweight patients with PCOS, it may be independent of obesity and changes in body composition [20-22].

The presence of insulin resistance with compensatory hyperinsulinemia plays an important role in androgen excess and anovulation [23,24]. Hyperinsulinemia has a dual fold effect on increasing free serum testosterone levels- firstly, insulin activates its homologous receptor and stimulates ovarian androgenesis and secondly, by reducing serum SHBG levels it increases tissue availability of circulating testosterone particularly affecting obese women with PCOS [25-28].

Multiple putative mechanisms of hyperinsulinemia responsible for anovulation in PCOS have been postulated. Insulin exerts a modulatory effect on the action of gonadotrophins on granulosa cells in the ovaries [29], enhances the effects of LH on theca interna cells of the ovary resulting in increased steroidogenesis [30] and increases ovarian cytochrome P450C17α thereby resulting in excessive ovarian androgen production [31]. Furthermore, in the presence of hyperandrogenism or altered gonadotrophic activity, follicular abnormalities and alterations in the normal intra-ovarian milieu result in anovulation [18,32]. Knowledge of these mechanisms are therefore important since therapies directed at lowering insulin resistance and hyperinsulinemia can reduce hyperandrogenism [31,33-35].

Menstrual cycle irregularities in women with PCOS may be associated with insulin resistance and is a phenotypic marker of hyperandrogenism [36]. In a recent study, Panadis and colleagues showed that insulin resistance and hyperandrogenemia were more marked in ammenorrhoeic patients whereas markers of insulin resistance were less pronounced in those reporting oligomenorrhoea or regular menstrual cycles [37].

Few studies have examined the effects of insulin resistance on reproductive capacity in PCOS [19,38-40]. Insulin concentration in follicular fluid determined from oocytes at assisted reproduction from women with a negative pregnancy outcome have shown significantly high levels suggesting that underlying insulin resistance and hyperinsulinaemia affects the reproductive process [40]. Defects in local insulin signalling pathways can also affect endometrial function in hyperinsulinemic women with PCOS [39].

In summary, insulin resistance has a major influence on numerous factors which impact reproductive function. Interventions which lower circulating insulin levels or improve insulin sensitivity therefore have the potential to offer therapeutic success in women with PCOS seeking conception [28,41-43].

METFORMIN

Metformin is an oral antidiabetic drug commonly used in the treatment of individuals with type 2 diabetes. Its role in women with PCOS is primarily a function of reducing insulin resistance and has also been employed with other ovulation induction regimen.

Mechanism of action

Metformin (dimethylbiguanide) belongs to the biguanide group of drugs which was first discovered in 1957 [44]. Its mechanism of action includes reduced intestinal absorption of glucose, improved insulin sensitivity in the liver and muscle by inhibiting gluconeogenesis in the liver and increasing uptake and utilisation of glucose in muscle cells [45]. Metformin stimulates AMP-activated kinase (AMPK), a key enzyme of glucose and energy regulation. AMPK enhances cellular uptake of glucose, fatty acid oxidation and regulates glucose transporter 4 (GLUT4) which are important metabolic processes involved with energy uptake [46]. Stimulation of AMPK therefore ameliorates hyperinsulinaemia induced insulin resistance [47]. Ovulation induction with metformin may be due to a direct effect on ovarian tissue [48]. Studies have shown that metformin has an inhibitory effect on androgen production but results from studies have been conflicting [49-51].

Administration, dosing and side effects

Metformin is usually commenced at 500 mg a day at meal time to minimize gastrointestinal side effects. Depending on tolerability, the dose can be increased to 500 mg a day a week up to a maximum recommended dose of 1000 mg taken twice daily. Diet and regular exercise are generally advised. Common side effects with metformin include dyspepsia, abdominal cramps, diarrhoea or constipation. These effects are reversible with stopping therapy and are usually minimised by gradual titration of dosage and administration with or after a meal [45]. Metformin does not cause hypoglycaemia and lactic acidosis is rare [45]. It is contraindicated in renal impairment with an estimated GFR of less than 30 ml/min//1.73m^2, hepatic dysfunction and severe congestive heart failure. Metformin is safe for use in pregnancy [52].

Effects on weight

The effects of metformin on weight loss has been examined in a recent meta-analysis of studies comparing insulin sensitizing drugs to lifestyle or diet modification [53]. Treatment with metformin significantly reduced body mass index (BMI) and the effect was greater with maximal dose (>1500 mg/day) and longer duration of treatment (>8 weeks). Long term treatment has also shown sustained effects on weight loss [54].

Effects on Insulin Sensitivity

Early proof of concept experiments in PCOS women indicate that metformin improves insulin-stimulated glucose utilization resulting in improved insulin sensitivity [14,55]. Studies in morbidly obese, nondiabetic subjects with BMI > 30 have shown reductions in fasting insulin, weight and centripetal obesity [56]. Activation of AMPK and control of lipid metabolism have recently been postulated to also influence its insulin sensitising mechanism of action [57,58].

Effects on ovulation

Various treatment options such as weight loss, therapeutic agents such as clomiphene citrate (an ovulation inducing drug) and assisted reproductive techniques have been used to induce ovulation to improve fertility in women with PCOS. Recent practice based guidelines issued by the Endocrine Society and European Society of Endocrinology suggest that clomiphene is the preferred first line drug in the management of ovulation related infertility in women with PCOS [59].

Observational studies and randomised controlled trials

evaluating the benefits of metformin on ovulation have reported disparate results [60-62]. The first systematic review and meta-analysis of available evidence was published by Lord and colleagues in 2003 [63]. Metformin was effective in achieving ovulation in women with PCOS with an odds ratios of 3.88 (95% confidence interval (CI); 2.25 - 6.69) compared to placebo and combination of metformin and clomifene with an odds ratio of 4.41 (CI; 2.37 - 8.22) compared to clomifene therapy. Furthermore, metformin treatment induced ovulation in 46% women with PCOS versus 24% in the placebo arm. In combination therapy with metformin and clomifene, 76% women achieved ovulation compared to 42% those on clomifene alone [63].

Tang, reviewed the evidence from a meta-analysis of thirty one randomised controlled trials (n= 2537) women with PCOS. Metformin compared to placebo or compared to clomiphene, improved ovulation and clinical pregnancy with no effect on live births [64]. A subsequent review of the evidence which reviewed forty four studies (n= 3992), agreed with the results of the previous meta-analysis and suggest that metformin may have a limited role in improving reproductive outcomes in women with PCOS [65].

Emerging trial data indicate that metformin may be useful in certain subgroups of women with anovulatory infertility. In a meta-analysis of three randomised controlled trials [66-68] conducted among non obese women with PCOS and anovulatory infertility, both metformin and clomiphene were equi-efficacious and suitable as first line ovulation induction agents [69].

Enhancing endometrial implantation with metformin in PCOS

A healthy receptive endometrium is important for successful implantation of an oocyte. Impedance to blood flow in the uterine vasculature and endometrial thickness abnormalities can impede endometrial receptivity [70-72] and implicated in recurrent pregnancy loss [70]. Metformin improves uterine, sub-endometrial and endometrial blood flow although this may not directly translate to beneficial effects on reproductive outcomes [73].

Metformin and IVF

In vitro fertilisation (IVF) is an effective treatment option for women with PCOS who do not conceive with conventional treatment [74]. Broadly, IVF treatment encompasses hormonal stimulation of the ovaries by administration of recombinant FSH (r-hFSH), monitoring response to gonadotrophin stimulation, oocyte retrieval after HCG stimulation, in vitro fertilization or intracytoplasmic sperm injection (ICSI) and embryo transfer [75-77]. The earliest report on the role of metformin treatment in improving IVF outcomes in women with PCOS resistant to clomiphene was reported in a retrospective analysis of sixty patients treated in a private IVF unit [78]. Patients were administered 1000–1500 mg metformin a day prior to gonadotropin stimulation. Mean number of mature oocytes and embryos cleaved increased after metformin treatment and there were significant improvements in both fertilization and clinical pregnancy rates [78]. Metformin also reduces the risk of ovarian hyperstimulation which can occur as a complication of gonadotrophin administration [79]. In a randomised, double-blind placebo controlled study among women undergoing either IVF or ICSI, metformin treatment commenced three months before and continued during the duration of IVF showed significant improvements in pregnancy and live birth rates [80]. Improvements in the duration of r-hFSH stimulation, number of oocytes retrieved, fertilisation rates or embryo quality were not significantly affected. Small but significant reductions in weight as a result of metformin treatment may have influenced pregnancy outcomes in this study. However, a recent systematic review of the literature concluded that metformin administration in IVF/ICSI cycles had no effect on pregnancy or live birth rates [81]. Neither the dose of metformin, pretreatment duration or stopping time of metformin therapy had any effect on reproductive end points. Metformin reduced the risk of ovarian hyperstimulation syndrome and of miscarriage while improving the chances of implantation (OR 1.42, 95% CI 1.24-2.75) [81]. Further randomised trials are much needed to assess the reproductive effect of metformin in selected phenotypes of women with PCOS.

Effect of preconceptional metformin on abortion risk in PCOS

Individual studies indicate that metformin admistered before conception and continued during the entire pregnancy can reduce early pregnancy loss [82]. However, a systematic review and meta-analysis of randomised controlled trials reviewed up to June 2008, concluded that metformin administered prior to pregnancy had no effect on early pregnancy loss [83].

Metformin and pregnancy

Women with PCOS are more likely to suffer from early miscarriages, gestation diabetes and hypertensive states in pregnancy [84,85]. The most current updated review on the clinical benefits of metformin on pregnancy outcomes from a meta-analysis of data from thirty eight randomised controlled trials involving 3495 women where metformin was compared either with placebo or an ovulation inducing drug in women with PCOS, menstrual disturbance and subfertility [64]. Metformin improved clinical pregnancy rates but there was no significant improvements in live birth rates. However, in a sub group of trials conducted with metformin compared to clomiphene as monotherapy, there were significant improvements in both clinical pregnancy and live birth rates only in the group of obese women treated with clomiphene citrate [64].

Although metformin is safe [86], it not routinely indicated for use to prevent or reduce pregnancy complications in PCOS women who become pregnant. In a randomised control trial involving 257 women with PCOS, metformin compared to placebo administered from first trimester to delivery did not reduce a composite of preeclampsia, gestational diabetes mellitus or preterm delivery outcomes [87]. A meta-analysis of eight trials which included women with diabetes or PCOS exposed to metformin during the first trimester of pregnancy showed no increase in risk for major malformations and inferred that metformin offers a protective effect [52].

PREDICTORS OF METFORMIN TREATMENT – WHO BENEFITS?

Response to phenotype

The response to metformin may be dependent on BMI in infertile women with PCOS [88]. Although not a licensed indication, guidance from the National Institute of Clinical

Excellence (NICE) in the UK recommend that women with PCOS and anovulatory cycles who lack response to clomifene citrate and with a BMI of >25 kg/m^2 should be offered metformin combined with clomifene citrate to increase ovulation and pregnancy rates [89]. More recent studies suggest that metformin-responders are often those with lower BMI [88,90] though, overall trials in this regard have yielded conflicting results [66,67,88,91]. A systematic review conducted to clarify this clinically important question concluded there was insufficient evidence that either metformin or clomiphene citrate were more efficacious for ovulation, pregnancy, live birth, miscarriage and pregnancy outcomes in non obese women (BMI < 32 kg/m^2) with PCOS [90].

Response to genotype

Recent developments in pharmacogenomics may provide a better understanding of the relationship between response to drug therapy influenced by underlying individual genetic makeup. In a substudy among 312 women with PCOS randomised to either extended release metformin, clomiphene citrate or combination treatment to induce ovulation, individuals with polymorphism in the STK11 gene exhibited poor response to metformin therapy [92]. Furthermore, a study of C and G allele polymorphism of the STK11 gene showed that individuals who were GG homozygotes showed a more robust metabolic response to metformin therapy compared to GC heterozygotes with intermediate response and CC homozygotes who demonstrated no response at all [93]. Although the clinical impact of these findings needs to be tested in larger trials, they provide the impetus for further research in this area.

COMBINATION TREATMENT REGIMEN WITH METFORMIN

Long versus short course treatment with metformin and clomiphene citrate for ovulation induction in women with PCOS

Combination treatment with metformin and clomiphene has proven efficacy for ovulation induction in women with PCOS [63]. Few studies have suggested priming with metformin administration for approximately 7-8 weeks prior to clomiphene citrate therapy. However, a systematic review of the literature did not identify any trials which compared the efficacy of short course combination treatment (<4 weeks) to long course treatment (>4 weeks or more) on ovulation or pregnancy outcomes in women with PCOS [94].

Metformin co-administered with gonadotrophins

The clinical efficacy of treating women undergoing IVF was evaluated in a retrospective data analysis of women with PCOS, with a prior history of resistance to clomiphene citrate therapy and who received IVF in a private treatment facility [78]. Among forty six women with a total of sixty cycles of IVF embryo transfer with intracytoplasmic sperm injection, metformin was administered in approximately thirty IVF cycles. Treatment was initiated on the first day of the cycle prior to commencement of gonadotropins and continued to the day of the pregnancy test. Individuals were down-regulated with GnRH-agonist and then received recombinant FSH with doses adjusted depending on individual response. The results of this study showed that adding metformin to assisted reproductive procedures increased the mean number of mature oocytes and embryos cleaved. Importantly, fertilization and clinical pregnancy rates increased suggesting improved outcomes with such a combination regimen [78]. Modulation of insulin-like growth factors may be one mechanism by which metformin exerts a beneficial effect [78,95,96]. The combination of metformin with gonadotrophins used for ovulation induction was evaluated in a systematic review of available studies designed to estimate reproductive outcomes in women with PCOS [97]. The results of this meta-analysis concluded that metformin co-administered with gonadotrophins was beneficial and improved rates of live birth and pregnancy by two fold [97].

CONCLUSION

Metformin is a widely used oral agent for the treatment of individuals with type 2 diabetes. Its role in reproductive health particularly in women with PCOS is a function of ameliorating insulin resistance and has shown efficacy in combination with clomiphene citrate, a recommended first line ovulation inducing agent. By itself, metformin has a limited role in improving pregnancy outcomes. Administration alongside assisted reproductive procedures has shown conflicting results on pregnancy or live birth rates and as such no immediate recommendation can be made regarding its use in IVF/ICSI procedures. Although metformin is safe during pregnancy, it not indicated to prevent or reduce pregnancy complications in PCOS women who become pregnant. Finally, emerging data indicates the role of pharmacogenomics in guiding its use in infertile women with PCOS.

REFERENCES

1. National Institute of Environmental Health Sciences.
2. Gurunath S, Pandian Z, Anderson RA, Bhattacharya S. Defining infertility--a systematic review of prevalence studies. Hum Reprod Update. 2011; 17: 575-588.
3. Chachamovich JR, Chachamovich E, Ezer H, Fleck MP, Knauth D, Passos EP. Investigating quality of life and health-related quality of life in infertility: a systematic review. J Psychosom Obstet Gynaecol. 2010; 31: 101-110.
4. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009?êù. Fertility and sterility. 2009; 92: 1520-1524.
5. Cui W. Mother or nothing: the agony of infertility. Bull World Health Organ. 2010; 88: 881-882.
6. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod. 2007; 22: 1506-1512.
7. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med. 2012; 9: e1001356.
8. We can end poverty. Millennium development goals and beyond 2015.
9. Balen A, Michelmore K. What is polycystic ovary syndrome? Are national views important? Hum Reprod. 2002; 17: 2219-2227.
10. Tsilchorozidou T, Overton C, Conway GS. The pathophysiology of polycystic ovary syndrome. Clin Endocrinol (Oxf). 2004; 60: 1-17.

11. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab. 2004; 89: 2745-2749.

12. Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab. 2000; 85: 2434-2438.

13. Alvarez-Blasco F, Botella-Carretero JI, San Millán JL, Escobar-Morreale HF. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. Arch Intern Med. 2006; 166: 2081-2086.

14. 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.

15. The 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). Human Reproduction. 2004; 19: 41-47.

16. Balen AH, Conway GS, Kaltsas G, Techatrasak K, Manning PJ, West C, et al. Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. Hum Reprod. 1995; 10: 2107-2111.

17. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004; 81: 19-25.

18. Dunaif A, Hoffman AR, Scully RE, Flier JS, Longcope C, Levy LJ, et al. Clinical, biochemical, and ovarian morphologic features in women with acanthosis nigricans and masculinization. Obstet Gynecol. 1985; 66: 545-552.

19. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. 1997; 18: 774-800.

20. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes. 1989; 38: 1165-1174.

21. Dunaif A. Insulin action in the polycystic ovary syndrome. Endocrinol Metab Clin North Am. 1999; 28: 341-359.

22. Stepto NK, Cassar S, Joham AE, Hutchison SK, Harrison CL, Goldstein RF, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulaemic clamp. Hum Reprod. 2013; 28: 777-784.

23. Burghen GA, Givens JR, Kitabchi AE. Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. J Clin Endocrinol Metab. 1980; 50: 113-116.

24. Robinson S, Kiddy D, Gelding SV, Willis D, Niththyananthan R, Bush A, Johnston DG. The relationship of insulin insensitivity to menstrual pattern in women with hyperandrogenism and polycystic ovaries. Clin Endocrinol (Oxf). 1993; 39: 351-355.

25. Nestler JE, Jakubowicz DJ, Falcon de Vargas A, Brik C, Quintero N, Medina F. Insulin Stimulates Testosterone Biosynthesis by Human Thecal Cells from Women with Polycystic Ovary Syndrome by Activating Its Own Receptor and Using Inositolglycan Mediators as the Signal Transduction System. The Journal of Clinical Endocrinology & Metabolism. 1998; 83: 2001-2005.

26. 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. The Journal of Clinical Endocrinology & Metabolism. 1991; 72: 83-89.

27. Micic D, Popovic V, Nesovic M, Sumarac M, Dragasevic M, Kendereski A, et al. Androgen levels during sequential insulin euglycemic clamp studies in patients with polycystic ovary disease. J Steroid Biochem. 1988; 31: 995-999.

28. Nestler JE, Barlascini CO, Matt DW, Steingold KA, Plymate SR, Clore JN, et al. Suppression of Serum Insulin by Diazoxide Reduces Serum Testosterone Levels in Obese Women with Polycystic Ovary Syndrome. The Journal of Clinical Endocrinology & Metabolism. 1989; 68: 1027-1032.

29. Willis D, Mason H, Gilling-Smith C, Franks S. Modulation by insulin of follicle-stimulating hormone and luteinizing hormone actions in human granulosa cells of normal and polycystic ovaries. The Journal of Clinical Endocrinology & Metabolism. 1996; 81: 302-309.

30. 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.

31. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. N Engl J Med. 1996; 335: 617-623.

32. 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.

33. Attia GR, Rainey WE, Carr BR. Metformin directly inhibits androgen production in human thecal cells. Fertil Steril. 2001; 76: 517-524.

34. Dunaif A, Scott D, Finegood D, Quintana B, Whitcomb R. The insulin-sensitizing agent troglitazone improves metabolic and reproductive abnormalities in the polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. 1996; 81: 3299-3306.

35. Kiddy DS, Hamilton-Fairley D, Bush A, Short F, Anyaoku V, Reed MJ, et al. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. Clin Endocrinol (Oxf). 1992; 36: 105-111.

36. Strowitzki T, Capp E, Eye Corleta H. The degree of cycle irregularity correlates with the grade of endocrine and metabolic disorders in PCOS patients. European journal of obstetrics, gynecology, and reproductive biology. 2010; 149: 178-181.

37. Panidis D, Tziomalos K, Chatzis P, Papadakis E, Delkos D, Tsourdi EA, et al. Association between menstrual cycle irregularities and endocrine and metabolic characteristics of the polycystic ovary syndrome. Eur J Endocrinol. 2013; 168: 145-152.

38. Detti L, Uhlmann RA, Fletcher NM, Diamond MP, Saed GM. Endometrial signaling pathways during ovarian stimulation for assisted reproduction technology. Fertil Steril. 2013; 100: 889-894.

39. Fornes R, Ormazabal P, Rosas C, Gabler F, Vantman D, Romero C, et al. Changes in the expression of insulin signaling pathway molecules in endometria from polycystic ovary syndrome women with or without hyperinsulinemia. Mol Med. 2010; 16: 129-136.

40. Takikawa S, Iwase A, Goto M, Harata T, Umezu T, Nakahara T, et al. Assessment of the predictive value of follicular fluid insulin, leptin and adiponectin in assisted reproductive cycles. Gynecol Endocrinol. 2010; 26: 494-499.

41. Ciotta L, De Leo V, Galvani F, La Marca A, Cianci A. Endocrine and metabolic effects of octreotide, a somatostatin analogue, in lean PCOS patients with either hyperinsulinaemia or lean normoinsulinaemia. Hum Reprod. 1999; 14: 2951-2958.

42. 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.

43. Penna IA, Canella PR, Reis RM, Silva de Sá MF, Ferriani RA. Acarbose in obese patients with polycystic ovarian syndrome: a double-blind, randomized, placebo-controlled study. Hum Reprod. 2005; 20: 2396-2401.

44. Stern J. Pharmacology and mode of action of the hypoglycemic guanidine derivatives. Campbell GD, editors. In: Oral Hypoglycemic Agents Pharmacology and Therapeutics. Academic Press, New York. 1969; 193-245.

45. Dunn CJ, Peters DH. Metformin. A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. Drugs. 1995; 49: 721-749.

46. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest. 2001; 108: 1167-1174.

47. Habegger KM, Hoffman NJ, Ridenour CM, Brozinick JT, Elmendorf JS. AMPK enhances insulin-stimulated GLUT4 regulation via lowering membrane cholesterol. Endocrinology. 2012; 153: 2130-2141.

48. Palomba S, Falbo A, Russo T, Orio F, Tolino A, Zullo F. Systemic and local effects of metformin administration in patients with polycystic ovary syndrome (PCOS): relationship to the ovulatory response. Hum Reprod. 2010; 25: 1005-1013.

49. Mansfield R, Galea R, Brincat M, Hole D, Mason H. Metformin has direct effects on human ovarian steroidogenesis. Fertil Steril. 2003; 79: 956-962.

50. Duleba AJ, Pawelczyk LA, Yuen BH, Moon YS. Insulin actions on ovarian steroidogenesis are not modulated by metformin. Hum Reprod. 1993; 8: 1194-1198.

51. De Conciliis B, Passannanti G, Romano L, Santarpia R. [Effects of metformin on insulin resistance and on ovarian steroidogenesis in women with polycystic ovary syndrome]. Minerva Ginecol. 2001; 53: 239-250.

52. Gilbert C, Valois M, Koren G. Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. Fertil Steril. 2006; 86: 658-663.

53. Nieuwenhuis-Ruifrok AE, Kuchenbecker WK, Hoek A, Middleton P, Norman RJ. Insulin sensitizing drugs for weight loss in women of reproductive age who are overweight or obese: systematic review and meta-analysis. Hum Reprod Update. 2009; 15: 57-68.

54. Glueck CJ, Aregawi D, Agloria M, Winiarska M, Sieve L, Wang P. Sustainability of 8% weight loss, reduction of insulin resistance, and amelioration of atherogenic-metabolic risk factors over 4 years by metformin-diet in women with polycystic ovary syndrome. Metabolism. 2006; 55: 1582-1589.

55. 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.

56. Glueck CJ, Goldenberg N, Wang P, Loftspring M, Sherman A. Metformin during pregnancy reduces insulin, insulin resistance, insulin secretion, weight, testosterone and development of gestational diabetes: prospective longitudinal assessment of women with polycystic ovary syndrome from preconception throughout pregnancy. Human Reproduction. 2004; 19: 510-521.

57. Fullerton MD, Galic S, Marcinko K, Sikkema S, Pulinilkunnil T, Chen ZP, et al. Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. Nat Med. 2013; 19: 1649-1654.

58. Shaw RJ. Metformin trims fats to restore insulin sensitivity. Nat Med. 2013; 19: 1570-1572.

59. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Endocrine Society. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013; 98: 4565-4592.

60. Trolle B, Flyvbjerg A, Kesmodel U, Lauszus FF. Efficacy of metformin in obese and non-obese women with polycystic ovary syndrome: a randomized, double-blinded, placebo-controlled cross-over trial. Hum Reprod. 2007; 22: 2967-2973.

61. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. N Engl J Med. 1998; 338: 1876-1880.

62. Heard MJ, Pierce A, Carson SA, Buster JE. Pregnancies following use of metformin for ovulation induction in patients with polycystic ovary syndrome. Fertil Steril. 2002; 77: 669-673.

63. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ. 2003; 327: 951-953.

64. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2010; 1: CD003053.

65. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2012; 5: CD003053.

66. Johnson NP, Stewart AW, Falkiner J, Farquhar CM, Milsom S, Singh VP, et al. PCOSMIC: a multi-centre randomized trial in women with PolyCystic Ovary Syndrome evaluating Metformin for Infertility with Clomiphene. Hum Reprod. 2010; 25: 1675-1683.

67. Palomba S, Orio F, Falbo A, Manguso F, Russo T, Cascella T, 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. The Journal of Clinical Endocrinology & Metabolism. 2005; 90: 4068-4074.

68. 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.

69. Johnson N. Metformin is a reasonable first-line treatment option for non-obese women with infertility related to anovulatory polycystic ovary syndrome? Çô A meta-analysis of randomised trials. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2011; 51: 125-129.

70. Habara T, Nakatsuka M, Konishi H, Asagiri K, Noguchi S, Kudo T. Elevated blood flow resistance in uterine arteries of women with unexplained recurrent pregnancy loss. Hum Reprod. 2002; 17: 190-194.

71. Dickey RP, Olar TT, Taylor SN, Curole DN, Matulich EM. Relationship of endometrial thickness and pattern to fecundity in ovulation induction cycles: effect of clomiphene citrate alone and with human menopausal gonadotropin. Fertility and sterility. 1993; 59: 756-760.

72. Nakatsuka M, Habara T, Noguchi S, Konishi H, Kudo T. Impaired uterine arterial blood flow in pregnant women with recurrent pregnancy loss. J Ultrasound Med. 2003; 22: 27-31.

73. Palomba S, Russo T, Orio F Jr, Falbo A, Manguso F, Cascella T, et al. Uterine effects of metformin administration in anovulatory women with polycystic ovary syndrome. Hum Reprod. 2006; 21: 457-465.

74. Homburg R, Berkowitz D, Levy T, Feldberg D, Ashkenazi J, Ben-Rafael Z. In vitro fertilization and embryo transfer for the treatment of infertility associated with polycystic ovary syndrome. Fertil Steril. 1993; 60: 858-863.

75. Dor J, Ben-Shlomo I, Lipitz S, Levran D, Etchin A, Rudak E, et al. Ovarian stimulation with gonadotropin-releasing hormone (GnRH) analogue improves the in vitro fertilization (IVF) pregnancy rate with both transvaginal and laparoscopic oocyte recovery. J In Vitro Fert Embryo Transf. 1990; 7: 351-354.

76. Ludwig M, Finas DF, al-Hasani S, Diedrich K, Ortmann O. Oocyte quality and treatment outcome in intracytoplasmic sperm injection cycles of polycystic ovarian syndrome patients. Hum Reprod. 1999; 14: 354-358.

77. Swanton A, Lighten A, Granne I, McVeigh E, Lavery S, Trew G, et al. Do women with ovaries of polycystic morphology without any other features of PCOS benefit from short-term metformin co-treatment during IVF? A double-blind, placebo-controlled, randomized trial. Human Reproduction. 2011; 26: 2178-2184.

78. Stadtmauer LA, Toma SK, Riehl RM, Talbert LM. Metformin treatment of patients with polycystic ovary syndrome undergoing in vitro fertilization improves outcomes and is associated with modulation of the insulin-like growth factors. Fertil Steril. 2001; 75: 505-509.

79. Aboulghar MA, Mansour RT. Ovarian hyperstimulation syndrome: classifications and critical analysis of preventive measures. Hum Reprod Update. 2003; 9: 275-289.

80. Kjotrod SB, Carlsen SM, Rasmussen PE, Holst-Larsen T, Mellembakken J, Thurin-Kjellberg A, et al. Use of metformin before and during assisted reproductive technology in non-obese young infertile women with polycystic ovary syndrome: a prospective, randomized, double-blind, multi-centre study. Human Reproduction. 2011; 26: 2045-2053.

81. Palomba S, Falbo A, La Sala GB. Effects of metformin in women with polycystic ovary syndrome treated with gonadotrophins for in vitro fertilisation and intracytoplasmic sperm injection cycles: a systematic review and meta-analysis of randomised controlled trials. BJOG. 2013; 120: 267-276.

82. Khattab S, Mohsen IA, Foutouh IA, Ramadan A, Moaz M, Al-Inany H. Metformin reduces abortion in pregnant women with polycystic ovary syndrome. Gynecol Endocrinol. 2006; 22: 680-684.

83. Palomba S, Falbo A, Orio F Jr, Zullo F. Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2009; 92: 1646-1658.

84. Zolghadri J, Tavana Z, Kazerooni T, Soveid M, Taghieh M. Relationship between abnormal glucose tolerance test and history of previous recurrent miscarriages, and beneficial effect of metformin in these patients: a prospective clinical study. Fertility and sterility. 2008; 90: 727-730.

85. Okon MA, Laird SM, Tuckerman EM, Li TC. Serum Androgen Levels in Women who Have Recurrent Miscarriages and their Correlation with Markers of Endometrial Function 11 Supported by a research grant from the Special Trustees of the former United Sheffield Hospitals, Royal Hallamshire Hospital, Sheffield, Yorkshire, United Kingdom. Fertility and sterility. 1998; 69: 682-690.

86. Bolton S, Cleary B, Walsh J, Dempsey E, Turner MJ. Continuation of metformin in the first trimester of women with polycystic ovarian syndrome is not associated with increased perinatal morbidity. Eur J Pediatr. 2009; 168: 203-206.

87. Vanky E, Stridsklev S, Heimstad R, Romundstad P, Skogoy K, Kleggetveit O, et al. Metformin Versus Placebo from First Trimester to Delivery in Polycystic Ovary Syndrome: A Randomized, Controlled Multicenter Study. The Journal of Clinical Endocrinology & Metabolism. 2010; 95: E448-E455.

88. Johnson NP, Bontekoe S, Stewart A. Analysis of factors predicting success of metformin and clomiphene treatment for women with infertility owing to PCOS-related ovulation dysfunction in a randomised controlled trial. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2011; 51: 252-256.

89. National Institute for Clinical Excellence (NICE) guideline 11. Fertility: Assessment and treatment for people with fertility problems, Clinical Guideline. RCOG press, London. 2004.

90. Romualdi D, Giuliani M, Cristello F, Fulghesu AM, Selvaggi L, Lanzone A, et al. Metformin effects on ovarian ultrasound appearance and steroidogenic function in normal-weight normoinsulinemic women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. Fertility and sterility. 2010; 93: 2303-2310.

91. Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippelñinen M, Perheentupa A, et al. Metformin Improves Pregnancy and Live-Birth Rates in Women with Polycystic Ovary Syndrome (PCOS): A Multicenter, Double-Blind, Placebo-Controlled Randomized Trial. The Journal of Clinical Endocrinology & Metabolism. 2012; 97: 1492-1500.

92. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Ovulatory response to treatment of polycystic ovary syndrome is associated with a polymorphism in the STK11 gene. J Clin Endocrinol Metab. 2008; 93: 792-800.

93. López-Bermejo A, Díaz M, Morán E, de Zegher F, Ibáñez L. A Single Nucleotide Polymorphism in STK11 Influences Insulin Sensitivity and Metformin Efficacy in Hyperinsulinemic Girls with Androgen Excess. 7. Diabetes Care. 2010; 33: 1544-1548.

94. Sinawat S, Buppasiri P, Lumbiganon P, Pattanittum P. Long versus short course treatment with metformin and clomiphene citrate for ovulation induction in women with PCOS. Cochrane Database of Systematic Reviews. 2012; CD006226.

95. Palomba S, Falbo A, La Sala GB. Effects of metformin in women with polycystic ovary syndrome treated with gonadotropins for in vitro fertilization and intracytoplasmatic sperm injection cycles: a systematic review and meta-analysis of randomized controlled trials. BJOG. 2013; 120: 267-276.

96. De Leo V, La Marca A, Ditto A, Morgante G, Cianci A. Effects of metformin on gonadotropin-induced ovulation in women with polycystic ovary syndrome. Fertil Steril. 1999; 72: 282-285.

97. Palomba S, Falbo A, La Sala GB. Metformin and gonadotropins for ovulation induction in patients with polycystic ovary syndrome: a systematic review with meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2014; 12: 3.

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