Original Research Article

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Study on Effects of Metformin on Clinical and Endocrine Profile in Polycystic Ovarian Syndrome

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Abstract

Background: Polycystic ovary syndrome (PCOS) is thought to be one of the most common endocrinopathies in women. It is possible to hypothesize that metformin therapy would augment the induction of ovulation in CC – resistant women because of its favourable change in adrogens, gonadotrpins, and insulin through mechanisms distinct from those of CC. Hence, the present study was undertaken to study effects of Metformin on clinical and endocrine profile in PCOS patients. *Method:* A total of 35 patients coming to out patient department diagnosed as a case of PCOS on the basis of common complaint of irregular menstrual cycles in whom ultrasound finding of polycystic ovaries was confirmed. All patients will receive metromin per oral 1 gm per day after breakfast for 6 mths, baseline and at six month follow up clinical examinations and endocrine profile recorded and studied. *Result:* Hirsutism was a compliant only in the subjects of the study with 31.4% of subjects having demonstrable levels with varied gradation. The prevalence of acne in this subject group was 20.6%. There is significant improvement in menstrual cycles regularity, p =0.00016. There is no change in acne & hirsutism complaints. Metformin is not the drug of choice for hirsutism & acne treatment. *Conclusion:* Metformin was effective in restoring regular menses, metformin should be considered the first choice drug for treating oligomenorrhea in PCOS patients in whom OCs are contraindicated. LH levels improved after metformin treatment with beneficial effect on LH: FSH ratio and testosterone shows improved levels without change in DHEAS levels.

Keywords: Meformin; PCOS; Hirsutism; Menstrual Cycles.

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Introduction

Polycystic ovary syndrome (PCOS) is thought to be one of the most common endocrinopathies in women, affecting between 6.5 and 8 percent of women overall. The syndrome is characterized clinically by oligomenorrhea and hyperandrogenism, as well as the frequent presence of associated risk factors for cardiovascular disease, including obesity, glucose intolerance, and dyslipidemia [1,2].

However, serum LH concentrations are affected by body mass index and timing of the blood sample relative to the last menstrual period. Neither an elevated serum LH concentration nor a high LH: FSH ratio is part of the diagnostic criteria for PCOS. A clustering of risk factors for diabetics and cardiovascular disease, including obesity (and insulin resistance), glucose intolerance, and dyslipidemia Women with PCOS are at increased risk for type 2 diabetes, but an excess risk of cardiovascular disease has not yet been demonstrated definitively.

Metformin should be considered as initial intervention in (overweight or obese) PCOS patients in whom OCs are contraindicated or with an initial metabolic derangement. In fact, clinical evidence shows that this drug is an effective first treatment for restoring ovulatory menstrual cycles in oligomenorrheic PCOS patients. Improving insulin sensitivity and, unlike OCs

lipoprotein pattern [3]. Metformin could also be a valid option in those PCOS patients who absolutely wish to avoid multiple gestations and / or in patients who do not tolerate CC (i.e. secondary to mood changes, visual disturbances, etc.) [3]. On the other hand, PCOS patients who have failed to ovulate with CC (i.e. CC resistant) may benefit from the addition of metformin. It is possible to hypothesize that metformin therapy would augment the induction of ovulation in CC – resistant women because of its favourable change in adrogens, gonadotrpins, and insulin through mechanisms distinct from those of CC. The clinical effectiveness of metformin on hirsutism seems to be limited.

Metformin seems to be effective in amellorating several intermediate markers of CVD in PCOS women during its administration. In particular, benefits may be seen in atherogenic profiles, including markers of subclinical inflammation, dyslipidemia, and insulin resistance. Enhanced endothelial function, coronary microvascular function, and coronary flow rate may also be seen. Notwithstanding these improvements in secondary CVD markers under metformin therapy in PCOS women, conclusive and prospective long term studies have yet to be carries out [3].

Doubts existed until now regarding the use of metformin during pregnancy. Even if metformin is not a cosmetic or anti – obesity drug, further research should clarify whether it has a role in the management of PCOS – related hirsutism and obesity and, specifically, its potential usefulness for optimizing the first – line treatments (e.g. antiandrogens and lifestyle modifications, respectively).

Material and Methods

The present study was conducted in department of OBGY during period of two years. A total of 35 patients coming to out-patient department diagnosed as a case of PCOS on the basis of common complaint of irregular menstrual cycles in which ultrasound finding of polycystic ovaries was confirmed.

Inclusion Criteria of Pcos

Oligoovulation or anovulation manifested by oligmenorrhea or amenorrhea, Hyperandrogenism (clinical evidence of androgen excess) – Acne, Hirsutism, Alopecia, Biochemical evidence of androgen excess – S. testosterone, LH, FSH, DHEAS, Prolactin, TSH, fasting insulin levels, Polycystic ovaries as defined as ultrasonography as 12 or more follicles in at least one ovary measuring 2-9 mm in diameter or a total ovarian volume of >10 cms, Other cutaneous changes like acanthosis nigricans, achrocordones, and hidradenitis suppurativa

Exclusion Criteria of PCOS

Exclusion of other disorder that can result in menstrual irregularity or hyperandrogenism like, Ovarian virllizing tumour or adrenal tumor, Late – onset congenital adrenal hyperplasia due to 21 – hydroxylase deficiency, Cushing's syndrome, Hyperprolactinoma, Irregular menses – hypothyroidism

All patients will receive metromin per oral 1 gm per day after breakfast for 6 months, baseline and at six month follow up clinical examinations and endocrine profile recorded and studied.

The diagnosis is made on the basis of clinical features, menustrual history, ultrasound findings.

Lab. Investigation include FSH, LH, TSH, fasting insulin, Prolactin, testosterone, DHEA – S, lipid profile, FBS, 17- alpha Hydroxyprogesterone, sr. creatinine, hsCRP. Were done for 35 clinically diagnosed patients of PCOS and 21 healthy volunteers who served as control.

After a written consent, detailed history was documented through a questionnaire. The emotional status of the subject was also marked on a scale of 1-10, 1 being always depressed and 10 being always cheerful. Dietary details taken into consideration Physical examination was performed by a trained nurse.

Body mass index (BMI) was calculated to evaluate obesity and overweight status in subjects.

Clinical signs included hirsutism (defined by Ferriman – Gallwey score) acne or alopecia. Biochemically, higher levels of androgens were confirmed with elevated levels of Total Testosterone or Dehydropiandrosterone sulphate (DHEAS).

No subject enrolled in this study had type II Diabetes Mellitus, renal dysfunction, liver dysfunction, or cardiovascular dysfunction.

Three subjects were found to have abnormal levels of prolactin. 21 healthy, age matched women (mean age 25.37±4.07 yr) volunteered to serve as the controls. They were used as a reference for hormonal and metabolic parameters. These healthy volunteers had a regular menstrual cycle, were ovulatory and had no hirsutism, acne or alopecia.

PCOS diagnosed women were given Metformin 1 gm after breakfast for 6 months. Follow up evaluation was done with detail history & biochemical tests

including total testosterone, dehydroepiandrosterone sulfate (DHEAS), and fasting insulin sr. FSH, LH & FBS.

Statistical Analysis

All continuous variables are reported as Mean± Standard deviation. Group comparisons of normally distributed variables were tested by t-test. The non parametric Mann – Whitney U test was used for comparisons of non – normally distributed variables. Chi – square test has been applied for comparisons of qualitative variables and categorical data. A P value 0.05 or less was considered to indicate a statistically significant difference.

Results

Clinical Characteristics and Anthropometry of Study Group

Both the subjects and the healthy controls were well matched in age (p = 0.457) (subjects = 24.38+ 5.41 yr, control = 25.37±4.07 yr). Measure of height and weight corresponded in both subjects and controls (height = 157.16±5.18 cms vs. 154.39 ±6.02 cms; weight = 62.4±12.6 kg vs., 57.07±9.99 kg; p = 0.145, 0.13 respectively).

The BMI was higher for the subjects (25.3±5.01 kg/m2) than the controls (23.99±4.25 kg/m2). No significant difference was found in the age at menarche between subjects (12.91±0.99 yr) and controls (13.07±1.14 yr).

Significantly increased values of systolic and diastolic blood pressure were seen in subjects than the controls; (systolic BP = 110±10.78 mm of Hg, diastolic BP = 80±6.91 mm of Hg in subjects, whereas systolic BP = 105±9.14 mm of Hg, diastolic BP – 70 ± 8.64 mm of Hg in controls; p = 0.0002 & 0.04 respectively).

Hirsutism was a compliant only in the subjects of the study with 31.4% of subjects having demonstrable levels with varied gradation.

The prevalence of acne in this subject group was 20.6% and Obesity affected 32% of individuals with 11 subjects having a BMI> 27 kg/m2; subjects found to be overweight (BMI of 23.1 – 27 kg/m2) were also 11 number, hence 32% of the group.

Emotional status was graded on a scale of 1-10 (1 being always depressed and 10 being always Cheerful). (Table 1).

Metabolic and Hormonal Characteristics

The two hormones which were primarily evaluated were total testosterone and DHEAS. The observed values of both these hormones were significantly elevated in the 27 patients than the controls (Testoerone value in patients = 1.05±0.81 ng/mL; controls = 0.35±0.14 ng/mL; p = 0.00001; DHEAS value in patients = 1.85±1.26 ng/mL; in controls = 0.85±0.24 pg/mL; p = 0.00004).

Insulin levels were highly elevated in patients on comparison with the controls (in patients = 14.44± 6.74 ulU/mL; in controls = 7±1.83 ulU/mL; p = 0.0001).

The levels of plasma glucose obtained in fasting state were also marginally higher than the plasma glucose values of the controls (90±8.41 mg/dL in patients, 88.7±3.25 mg/dL in controls; p = 0.43).

Leutinizing hormone (LH) was on the higher scale in the patients (8.81±6.40 mlU/mL) vs. controls (6.71 + 0.72 mlU/mL).

Table 1: Clinical profile of subjects and healthy controls

Parameters	Patients (N=35)	Controls (N = 21)	P - value
Age (yr)	24.38 ± 5.41	25.37 ± 4.07	0.457
Height (cms)	157.16 ± 5.18	154.39 ± 6.02	0.145
Weight (kg)	62.4 ± 12.6	57.07 ± 9.99	0.13
BMI (kg/m2)	25.3 ± 5.01	23.99 ± 4.25	0.39
Systolic BP (mm Hg)	110 ± 10.78	105 ± 9.14	0.0002
Diastolic BP (mm Hg)	80 ± 8.37	70 ± 8.64	0.04
Heart Rate	80 ± 6.91	77 ± 11.66	0.82
Age at menarche (yr)	13 ± 0.996	13 ± 1.14	0.653
Days of cycle	5 ± 2.22	5 ± 1.34	0.104
Irregularity of cycle	32 (91.4%)	0	<0.0001
Overweight	11 (32%)	5 (35.7%)	0.08
Obesity	11 (32%)	3 (21%)	0.15
Acne	7 (20.6%)	1 (7%)	0.12
Hirsutism	11 (31.43%)	0	**0.002**
Emotional status	7 ± 1.59	7.5 ± 1.82	0.75

Table 2: Hormonal profile of patients and controls

Parameters	Patients (N=35)	Controls	P - value
Fasting plasma Glucose (mg/dl)	90 ± 8.41	88.7 ± 3.25	0.43
FSH (mlU/mL)	9.56 ± 3.49	8.4 ± 0.98	0.072
LH (mlU/mL)	8.81 ± 6.40	6.71 ± 0.72	0.063
Insulin (mlU/mL)	14.44 ± 6.74	7 ± 1.83	0.0001
Testosterone (ng/mL)	1.05 ± 0.81	0.35 ± 0.14	0.00001
DHEAS (ug/mL)	1.85 ± 1.26	0.85 ± 0.24	0.00004
17 – Hydroxyprogesterone (ng/mL)	0.74 ± 0.54	0.6 ± 0.33	0.24
hsCRP (micg/mL)	7.44 ± 8.61	2.94 ± 1.19	0.004
TGL (mg/dL)	104.9 ± 63.41	78.33 ± 23.73	0.03
HDL (mg/dL)	40.82 ± 10.10	42.42 ± 7.37	0.49
LDL (mg/dL)	105.05 ± 43.26	89.71 ± 21.40	0.082
Cholesterol (mg/dL)	155.2 ± 36.6	146.38 ± 25.29	0.29
TSH (mi IU/mL)	2.46 ± 2.06	1.86 ± 0.70	0.12
Prolactin (ng/mL)	15.10 ± 8.77	12.19 ± 4.0	0.1
Creatinine (mg/dL)	0.80 ± 0.21	0.68 ± 0.19	0.033

Table 3: Clinical profile of PCOS women pre & post metformin treatment

Parameters	PRE Metformin	POST Metformin	P - value
Weight (kg)	59.96 ± 16.73	62.52 ± 11.96	0.48
Systolic BP (mmhg)	117.33 ± 12.29	120 ± 13.13	0.49
Diastolic BP (mmhg)	77.33 ± 8.68	77.2 ± 8.67	0.935
Days of cycle	5.6 ± 2.36	5.46 ± 1.65	0.649
Irregularity of cycle	50.7 ± 11.89	43.4 ± 12.61	0.000167
Acne	7 (20.6%)	7 (20.6%)	-
Hirsutism	11 (31.43%)	11 (31.43%)	-

The levels of follicle stimulating hormone (FSH) were matched between the two (in patients = 9.56 ±3.49 mlU/mL and in controls – 8.4±0.98 mlU/mL).

As previously stated, two patients had elevated prolactin levels. The values of 17 alpha hydroxyprogesterone and TSH were matched in both patients and controls.

Significantly higher levels of Sr CRP were found in patient (7.44±8.61 ug/mL) than the controls (2.94 ±1.19 ug/mL), p = 0.004 (Table 2).

Evaluation of lipids; lipids Profile was studied in all the subjects and the controls. Levels of triglycerides were significantly elevated in the patients (104.9± 63.41 mg/dL) than the controls (78±23.73 mg/dL); p = 0.03. No significant variation was seen in the values of HDL – Cholesterol on comparing the two groups. The levels of both cholesterol and LDL – cholesterol did not differ significantly in patients than the controls, although higher levels of both were observed in patients than the controls (Cholesterol values in patients = 155 ±36.6 mg/dL as compared to controls = 146.38±25.29 mg/dL; values of LDL in patients = 105.05±43.26 mg/dL; in controls = 89.71±21.40 mg/dL) (Table 3).

There is significant improvement in Irregularity of cycle. Irregularity of cycle before treatment was 50.7± 11.89 when compare to post treatment it is 43.4+ 12.61. The p – value is significant (0.000167). Whereas other parameters such as weight (kg), SBP, DBP, Days of cycle, Acne, and Hirsutism were slightly improved but statistically significant was not found (p>0.05).

All the parameters were not repeated because of financial strains. There is significant improvement in insulin levels, LH and testosterone. FBS levels before treatment in 30 women is 90.2+8.96 when compare to post treatment it is 83.73+8.012. The p – value is significant (0.000732) FSH levels pretreatment = 9.17+ 2.84 Vs post treatment 8.286 + 3.88, p – value is 0.2369.

Luteinizing hormone post treatment shows marked decrease with p – value 0.0003. Testosterone value premetformin is 1.003+0.7595 Vs post metformin 0.7383+0.6236, with significant p – value 0.015. In DHEAS there is improvement in values but p – value is not significant (p = 0.2804) (Table 4).

Discussion

Effects of Metformin on Pregnancy

In the present study good number of patient conceived spontaneously, none of them were advised any contraceptive methods or ovulation induction

Table 4: Hormonal Profile Of Pecos Women Pre & Post Metformin Treatment

Parameters	Pre Metformin	Post Metformin	P - value
Fasting plasma Glucose (mg/dl)	90.2 + 8.96	83.73 + 8.012	0.0007
FSH (mlU/mL)	9.17 + 2.84	8.286 + 3.88	0.2369
LH (mlU/mL)	9.666 + 6.536	7.116 + 3.852	0.0336
Insulin (mlU/mL)	14.433 + 6.752	10.073 + 4.658	0.00037
Testosterone (ng/mL)	1.003 + 0.7595	0.7383 + 0.6236	0.0155
DHEAS (ug/mL)	1.906 + 1.283	1.554 + 0.9862	0.2804

medicines among 35 patients 5 became pregnant, there is successful pregnancy rate of 14.3%. This results are probably because decreased in anxiety levels after detail counselling with complete hormonal evaluation or & probable effects of metformin.

Two meta – analysis [4,5] demonstrated that metformin is an effective drug, when compared with placebo or no treatment in the restoration of normal menstrual cycles and in inducing ovulatory cycles in oligoamenorrheic PCOS patients.

In a Meta – analysis of 17 relevant placebo – controlled RCTs showed in overall benefit for PCOS patients receiving metformin over placebo. In the study by Palomba et al. [6] the cumulative ovulation rate was similar in women treated with CC or metformin, whereas the pregnancy rate was significantly higher in women treated with metformin compared with those treated with CC [3].

Some studies shows positive results of metformin when evaluating pregnancy rate while other were not shown good outcomes. Presently, only two RCTs [7,8] compared metformin plus CC with metformin alone. Both studies agreed in showing a clear advantage of combination therapy over metformin alone in terms of ovulation rate.

One small RCT [9] showed no beneficial effect on ovulation and pregnancy rates after 3 months of metformin pretreatment, despite the improvement of insulin resistance and hyperandrogenemia. On the contrary, other studies [4,10,11,12] demonstrated that metformin pretreatment, also when given in ultra short protocols [11,12], improved CC response in terms of ovulation and pregnancy in CC- resistant PCOS patients. The reason metformin was not effective in improving fertility could be related to the short – term follow – ups and/ or small population samples studied.

Effect of Metformin on Hypertension

In our study we could not find any significant effect of metformin on hypertension. Whereas some studies shown positive effect on hypertension.

A study RCT [13] showed metformin treatment decreased day time ambulatory blood pressure monitoring, whereas OCs exerted the opposite effect. In a while multicentertial [14], metformin reduced ambulatory blood pressure in patients with type 2 DM and the white coat hypertension in an unselected population of overweight and obese patients.

Lastly, other studies [15,16] suggested that the combination of thiazolinediones and metformin is associated with a slight but significant improvement in the long – term blood pressure control of patients with type 2 DM.

Effect of Metformin on Obesity

In our study there is positive correlation between obesity & PCOS patients. Data regarding the potential beneficial effects of metformin on obesity in PCOS patients are controversial.

Our study does not show statistical significant weight loss whereas other studies shown significant weight loss after metformin treatment

In our study lifestyle modification was not stressed as an effect of metformin was the main objective for study.

The link between obesity and insulin resistance is strong [17], and the data showing a significant improvement in insulin resistance seem to be a key factor in determining that metformin administration could be effective in reducing bodyweight in PCOS [18].

In a subsequent RCT [19] specifically designed to evaluate the effects of metformin therapy on body weight, BMI decreased significantly by approximately 4% in both obese and morbidly obese women with PCOS after metformin therapy (500 or 850 mg three times daily) without lifestyle intervention.

In the same study [19], obese PCOS patients benefited from greater weight loss at the highest does

(2550 vs. 1500 mg/d) of metformin, whereas a similar degree of weight loss at both doses of metformin was detected in morbidly obese PCOS subjects.

Lastly, as demonstrated in a recent 6- month clinical study [20] in a population of patients with excess weight that chose their own management, 2550 mg/d of metformin was significantly more effective than diet in reducing the incidence of overweight and obesity.

On the other hand, lifestyle modifications remain the comerstone for weight loss in obese PCOS patients, although metformin co treatment might improve the efficacy [3].

Effect of metformin on regularization of menses

In our studies we demonstrate beneficial effects of metformin on regularly of menstrual cycles. Al the patients were having irregular menstrual cycles, they were not advised any OCP or any treatment to regularize the menstrual cycles, after taking metformin for 6 months, there is significant improvement (p= 0.000167) in menstrual cycle regularity.

This study having similar outcomes of uncontrolled studies [21,22,23] demonstrated that metformin was effective in restoring regular menses in approximately 62% of PCOS women with oligomenorrhea. A significant improvemtn in the menses frequency under metformin was reported in two RCTs [24,25]. Metformin is an alternative therapy that will restore ovulatory menses in approximately 50 percent of women with PCOS [26]. These observations may indicate that the effectiveness of metformin on menstrual cyclicity is probably secondary not only to an indirect effect on the ovary but also to a direct effect on the endometrium. Some studies show OCP are better then metformin to regularize the cycle rhythm [27-28].

In conclusion, metformin should be considered the first choice drug for treating oligomenorrhea in PCOS patients in whom OCs are contraindicated.

Effect of Metformin on Hirsutism

In this study the prevalence of hirsutism is (31.43%). In PCOS group, the effect of metformin is not significant in our study group. They were not on other treatment for hirsutism. There is controversial results regarding effects of metformin on hirsutism, like A meta – analysis [24] of three RCTSs comparing the effects of metformin and OCs on hirsutism demonstrated no difference in efficacy between these two drugs.

Similarly, 3 months of metformin administration had poor effect on the acne score in young PCOS women [29].

Current guidelines derived from meta – analysis [30,31,32] of RCTs clearly stated that there is strong evidence that metformin is not a choice therapy for hirsutism and other strategies should be used [31].

The first line therapy for treatment of hirsutism caused by PCOS is an estrogenprogestin contraceptive, as recommended by the 2008 Endocrine Society Guidelines. An antiandrogen is then added after six months if the cosmetic response is suboptimal. Although metformin may reduce serum androgen concentrations, it has limited benefit for the treatment of hirsutism [32].

The best available evidence comes from a meta – analysis of nine placebo – controlled trials of insulin – lowering drugs [33].

When the metformin trials were analyzed separately, no significant benefit was seen. Based upon these findings, the Endocrine Society Clinical Practice Guidelines suggest against the routine use of metformin for the treatment of hirsutism [34].

Effect of Metformin on Androgen Levels

In our study significant positive effects of metformin on androgen levels seen.

An RCT found that metformin had similar androgen – lowering efficacy in both obese and morbidly obese women affected by PCO, whereas in another RCT nonobese women did not seem to benefit from metformin [35].

Hyperandrogenemia may be affected by metformin. Preliminary in vitro data [27] indicated that metformin may directly decrease ovarian androgen production, and excellent experimental data [28,35] demonstrated that metformin reduces the ovarian P450c17 alpha activity with a consequent decline in the serum free testrosterone concentration.

A study [36] on infertile PCOS patients undergoing in vitro fertilization (IVF) demonstrated that metformin pretreatment did not affect androgen levels. Furthermore, within 36 hours after metformin withdraw, an increase in androstenedione and free testosterone index was observed.

Effects of Metformin on Hyperinsulinemia

In our study there is significant decrease in insulin & fasting blood sugar levels.

These results indicate that improvement in insulin sensitivity, through either intensive lifestyle modification or metformin, reduces the risk of

developing DM in high – risk individuals [37]. Data obtained from the same population studied in the DPP demonstration that, after a short washout period, about 25% of the beneficial effect of metformin on type 2 DM prevention did not persist when treatment was withdrawn [38].

In another study [39] demonstrated that metformin monotherapy or metformin combined with sulfonylurea was associated with reduced all cause and CVD mortality.

One retrospective study of PCOS women treated with metformin for an average of 43 months found that metformin appeared to delay or prevent the development of IGT and type 2 DM [40].

Salpeter et al. [16] performed a meta – analysis shows Metformin treatment significantly reduced fasting glucose, fasting insulin and HOMA index compared with placebo or no treatment. No statistically significant differences were found between subgroups, i.e., PCOS vs. non – PCOS and obese vs. nonobese. Metformin decreased new – onset DM by 40% and reduced the absolute risk of DM by 6%, furthermore, no data on subgroups were provided.

Conclusion

Metformin is effective ovulation induction, but not the first choice in infertility management because of ovulation factor. It had a marginal effect on weight loss as monotherapy and does not show significant effect on hypertension. It does not decrease hirsutism & acne. But significantly decreases insulin & fasting blood sugar levels.

Metformin was effective in restoring regular menses, metformin should be considered the first choice drug for treating oligomenorrhea in PCOS patients in whom OCs are contraindicated

LH levels improved after metformin treatment with beneficial effect on LH: FSH ratio and testosterone shows improved levels without change in DHEAS levels.

Reference

1. Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome; towards a rational approach. In: Duniaf A, Gigens JR, Haseltine FP, Merriam GR, eds. Polycystic ovary syndrome. Bostone: Blackwell. 1992;337–384.
2. Sein, IF. Amenorrhea associated with bilateral polycystic ovaries Change RJ, Nakamura RM, Judd HL, Am J obstet Gynecol 1935;29:181.
3. Stefano Palomba, Angela Falbo, Fulvio Zullo, and Francesco Orio, Evidence – Based and Potential Benefits of Metformin in the Polycystic Ovary Syndrome: A Comprehensive Review Jr Endocrine Reviews, 2009;30(1):1–50.
4. Lord JM, Flight lH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and Meta – analysis. BMJ 2003;327:951–53.
5. Kashyap S, Wells GA, Rosenwaks Z. Insulin – sensitizing agents as primary therapy for patients with polycystic ovarian syndrome. Hum Reprod. 2004;19:2474–83.
6. Palomba S, Falbo A. Metformin in therapy naïve patients with polycystic ovary syndrome. Hum Reprod Update. 2008;14:193.
7. Tsilchorozidou T, Batterham RL, Conway GS. Metaformin increases fasting plasma PYY in women with PCOS. Clin Endo – crinol (Oxf). 2008;69:936-42
8. Romualdi D, De Marinis L, Campagna G, Proto C, Lanzone A. Alteration of gherlin – neuropeptide Y network in obese patients with polycystic ovary syndrome: role of hyperinsulinism. Clin Endocrinol (Oxf). 2008;69:562–67.
9. Strowitzki T, Halser B, Demant T. Body fat distribution, insulin sensitivity ovarian dysfunction and serum lipoproteins in patients with polycystic ovary syndrome. Gynecol Endocrinol. 2002;16:45–51.
10. Barbieri RL. Clomiphene versus metformin for ovulation induction in polycystic ovary syndrome: the winner is. J Clin Endocrinol Metab. 2007;92: 3399–3401.
11. Sohrabvand F, Ansari SH, Bagheri M. Efficacy of combined metformin letrozole in comparison with metformin – clomiphene ci-trate in clomiphene resistant infertile women with polycystic ovarian disease. Hum Reprod. 2006;21:1432–35.
12. Khorram O, Helliwell JP, Katz S, Bonpane CM, Jaramillo L. Two weeks of metformin improves clomiphene citrate – induced ovulation and metabolic profiles in women with polycystic ovary syndrome. Fertil Steril. 2006;85:1448–51.
13. Komajda M, Curtis P, Hanefeld M, Beck – Nielsen H, Pocock SJ, Zambanini Am Jones NP, Gomis R, Home PD; RECORD Study Group. Effect of the addition of rosiglitazone to metformin or sulfonyureas versus metformin / sulfonylurea combination ther – apy on ambulatory blood pressure in people with type 2 diabetes: 48 randomized controlled trial (the RECORD study). Cardiovasc Diabetol 2008;7:10.
14. Nestler JE. Metformin for the treatment of the polycystic ovary syndrome. N Engl J Med. 2008;358: 47–54.
15. Derosa G, Fogari E, Cicero AF, D'Angelo A, Ciccarelli L, Piccinni MN, Pricolo F, Salvadeo SA, Gravina A,

Ferrari I, Fogari R. Blood pressure control and inflammatory markers in type – 2 dia-betic patients treated with pioglitazone or rosiglitazone and met formin. Hypertens Res. 2007;30:387-394.

16. Salpeter SR, Buckley NS, Kahn JA, Salpeter EE. Meta-anal- ysis: metformin treatment in persons at risk for diabetes mellitus. Am J Med. 2008;121:149–157e2.
17. Despre's JP, Couillard C, Gagnon J, J, Leon AS, Rao DC, Skinner JS, Wilmore JH, Bouchard C. Race, visceral adipose tissue, plasma lipids, and lipoprotein lipase activity in men and women: the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) family study. Arterioscler Thromb Vasc Biol. 2000;20:1932–38.
18. Hermansen K, Mortensen LS. Body weight changes associated with antihyperglycaemic agents in type 2 diabetes mellitus. Drug Saf. 2007;30:1127–42.
19. Harbone LR, Sattar N, Norman JE, Fleming R. Metformin and weight loss in obese women with polycystic ovary syndrome: comparision of doses. J Clin Endocrinol Metab. 2005;90:4593–98.
20. Helvaci MR, Kaya H, Borazan A, Ozer C, Seyhanli M, Yalcin A. Metformin nd parameters of physical helath. Intern Med.2008;47:697–703.
21. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med. 2005 Mar 24;352(12):1223-36.
22. Unluhizarci K, Kelestimur F, Bayram F, Sahin Y, Tutus A. The effects of metformin on insulin resistance and ovarian steroidogenesis in women with polycystic ovary syndrome. Clin Endocri. 1999;51:231–36.
23. Lbanex L, Valls C, Ferrer A, Macros MV, Rodriguez – Hierro F, de Zegher F. Sensitization to insulin induces ovulation in non – obese adolescents with anovulatory hyperandrogenism. J Clin En docrinol Metab .2001;86: 3595–98.
24. Crave JC, Fimbel S, LejeuneH, CugnardeyN, DechaudH, Pugeat M. Effects of diet and metformin administration on sex hormone –binding globulin, androgens, and insulin in hirsute and obese women. J Clin endocrinol Metab. 1995;80:2057–62.
25. Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, ColittaD, Florini S, CognigniGE, FillcoriM, Morselli – Labate AM. Effect of long- term treatment with metformin added to hypocaloric diet on body composition, fat distribution and androgen and insulin levels I abdominally obese women with and without the polycystic ovary syndrome. *J* Clin Endocrinol Metab. 2000;85:2767–74.
26. Pastor CL; Griffin – Korf ML; Aloi JA; Evans WS; Marshall JC Polycystic ovary syndrome: evidence for reduced sensitivity of the gonadotropin – releasing hormone pulse generator to inhibition by estradiol and progesterone. – J Clin Endocrinol Metab 1998;83(2):582–90.
27. Korytkowski MT, Mokan M, Horwitz MJ, Berga SL. Metabolic effects of oral contraceptives in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 1995;80:3327–34.
28. Costello M, Shrestha B, Eden J, Sjoblom P, Johnson N. Insulin – sensitizing 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 Jan 24;(1):CD005552.
29. Kelly CJ, Gordon D. The effect of metformin on hirsutism in polycystic ovary syndrome. Eur J Endocrinol. 2002;147:217–21.
30. Koulouri O, Conway GS. A systematic review of commonly used medical treatments for hirsutism women. Clin Endocrinol (Oxf). 2008;68:800–05.
31. Cosma M, Swiglo BA, Flynn DN, Kurtz DM, Labella ML, Mullan RJ, Elamin MB, Frwin PJ, Montori VM. Clinical review: insulin sensitizers for the treatment of hirsutism: a systematic re-view and Meta analyses ofrandomized controlled trials. J Clin Endocrinol Metab. 2008;93:1135–1142.
32. Cosma M, Swiglo BA, Flynn DN, Kurtz DM, Labella ML, Mullan RJ, Elamin MB, Erwin PJ, Montori VM.Clinical review: Insulin sensitizers for the treatment of hirsutism: a systematic review and metanalyses of randomized controlled trails. J Clin Endocrinol Metab. 2008;93(4):1135–42.
33. Martin KA, Chang RJ, Ehrmann DA, Ibanez L, Lobo RA, Rosenfield RL, Shapiro J, Montori VM, Swiglo BA. Evaluation and treatment of hirsutism in premenopausal women: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008 Apr;93(4): 1105–20. Epub 2008 Feb 5.
34. Legro RS, Gnatuk CL, Kunselman AR, Dunaif A. Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study J Clin Endocrinol MEtab 2005;90:3236-42.
35. 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;22:2967–73.
36. Heijnen EM, EijemansMJ, Hughes eG, Laven JS, MAcklon NS, Fauser BC. A meta – analysis of outcomes of conventional IVF in women with polycystic ovary syndrome. Hum Reprod Update. 2006;12:13-21.
37. Diabetes Prevention Program Research Group. Effects of withdrawal from metformin on the development of diabetes in the diabetes prevention program. Diabetes Care 2003;26:977–80.
38. Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. Diabetes Care. 2002;25:224–48.
39. Sharma ST, Wickham EP, Nestler JE. Changes in glucose tolerance with metformin treatment in polycystic ovary syndrome: a retrospective analysis. Endocr Pract. 2007;13:373–79.

40. UK Prospective Diabetes Study (UKPDS) group. Effect of intensive blood – glucose control with metformin on complications in overweight patients with type 2 diabets (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:854–65.