2000 mg metformin pcos pregnancy

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"Metformin treatment should be carefully considered for women with PCOS undergoing in vitro fertilization."

Dan Zhang, MD, PhD

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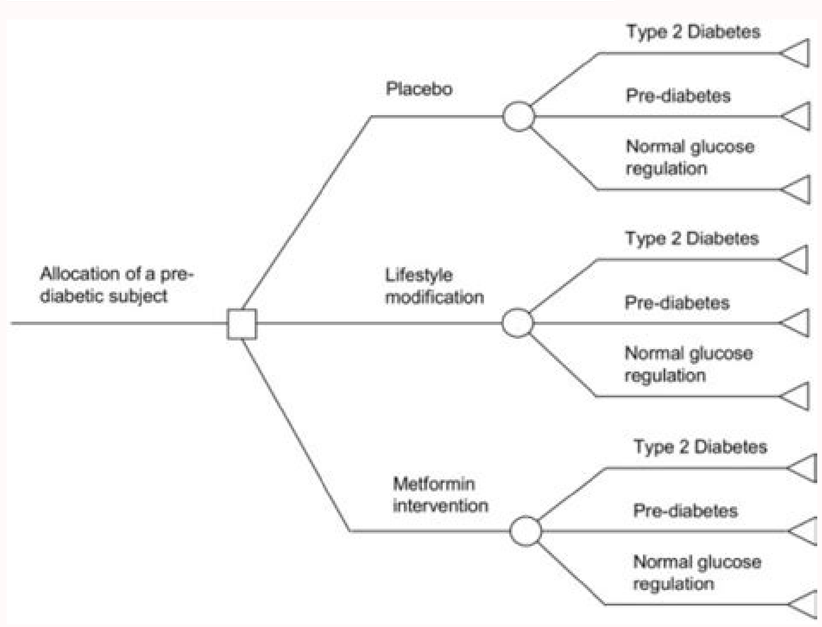

Drug	Dose	Adverse Events in Pregnancy	Comments
Methyldopa (PO)	500 mg to 3 g in two divided doses	Peripheral edema, anxiety, nightmares, drowsiness, dry mouth, hypotension, maternal hepatitis, no major fetal adverse events	Contraindicated in depression
Labetalol (PO)	100–1200 mg/d in two to three divided doses	Persistent fetal bradycardia, hypotension, neonatal hypoglycemia, asthma	Risk of bronchospasm, bradycardia
Labetolol (IV)	10–20 mg; repeat 20–80 mg iv every 30 min or 1–2 mg/min; maximum of 300 mg/d	Persistent fetal bradycardia, hypotension, neonatal hypoglycemia, asthma	Avoid in asthma or heart failure
Nifedipine (PO)	30–120 mg/d	Hypotension and inhibition of particularly if used in combination with magnesium sulfate	Contraindicated in aortic stenosis; Immediate release nifedipine not recommended
Hydralazine (PO)	50–300 mg/d in two to four divided doses	Hypotension, neonatal thrombocytopenia, lupus-like syndrome, tachycardia	Flushing, headache
Hydralazine	5–10 mg iv/im; may repeat every 20–30 min to a maximum of 20 mg	Tachycardia, hypotension, headache, fetal distress	Hypotension and inhibition of labor, especially when combined with magnesium sulfate
Nicardipine (IV)	Initial: 5 mg/h increased by 2.5 mg/h every 15 min to a maximum of 15 mg/h	Headache, edema, tachycardia	Increased risk of hypotension and inhibition of labor, especially when combined with magnesium sulfate
Nitroprusside (IV)	0.3–0.5 to 2 μg/kg per minute; maximum duration of 24–48 h	Risk for fetal cyanide toxicity	Use >4 h and dose >2 μg/kg per minute associated with increased risk of cyanide toxicity; use only as a last resort

PO, oral; IV, intravenous.

Does metformin for pcos work. Can i take metformin for pcos while pregnant.

PDF Split View Article contents Figures & tables Video Audio Supplementary Data The role of metformin in the treatment of infertility in women with polycystic ovary syndrome (PCOS) is still controversial.We investigated whether metformin decreases the early miscarriage rate and improves the pregnancy rates (PR) and live-birth rates (LBR) in PCOS.This was a multicenter, randomized (1:1), double-blind, placebo-controlled study. Three hundred twenty women with PCOS and anovulatory infertility were randomized to metformin (n = 160, Diformin; obese women, 1000 mg two times daily; nonobese subjects, 500 mg + 1000 mg daily) or identical doses of placebo (n = 160). After 3 months' treatment, another appropriate infertility treatment was combined if necessary. If pregnancy occurred, metformin/placebo was continued up to the 12th week.Miscarriage rates were low and similar in the two groups (metformin 15.2% vs. placebo 17.9%, P = 0.8). Intent-to-treat analysis showed that metformin significantly improved PR and LBR (vs. placebo) in the whole study population (PR: 53.6 vs. 40.4%, P = 0.006; LBR: 41.9 vs. 28.8%, P = 0.014) and PR in obese women (49.0 vs. 31.4%, P = 0.04), and there was a similar trend in nonobese (PR: 58.6 vs. 47.6%, P = 0.09; LBR: 46.7 vs. 34.5%, P = 0.09) and in obese women with regard to LBR (35.7 vs. 21.9%, P = 0.07). Cox regression analysis showed that metformin plus standard infertility treatment increased the chance of pregnancy 1.6 times (hazard rate 1.6, 95% confidence interval 1.13–2.27).Obese women especially seem to benefit from 3 months' pretreatment with metformin and its combination thereafter with routine ovulation induction in anovulatory infertility. Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 5–10% of women of reproductive age (1). Anovulation is the cause of infertility in about one third of couples seeking treatment, and PCOS accounts for 90% of these cases. Clinical manifestations of PCOS include irregular menses, hirsutism, and acne. In addition, insulin resistance and hyperinsulinemia play a central role in the pathophysiology of PCOS (1). Early pregnancy loss has also been reported to occur in 30–50% of women with PCOS (2, 3), which is 3-fold higher than in healthy women (4, 5).During the last decade, use of metformin has been under debate in the treatment of PCOS. Most earlier studies indicated that metformin improved hyperinsulinemia and hyperandrogenemia and restored ovulatory function and that its use, alone or combined with clomiphene citrate, could increase ovulation and pregnancy rates in women with PCOS (6–8). Moreover, nonrandomized prospective studies suggested that metformin may reduce first-trimester spontaneous abortions in women with PCOS (3, 9). Therefore, at the time of planning this study (January 2003), several factors supported the use of metformin in the treatment of PCOS with metabolic and hormonal disturbances and for the prevention of early miscarriages, but large randomized controlled trials (RCT) designed to evaluate the effectiveness of this clinical practice were lacking. However, more recent RCT have shown controversial results, with either a beneficial effect (10–13) or no effect of metformin on fertility in PCOS (14–17). In the present study, the aim was to explore the effectiveness of metformin in a study protocol reflecting routine clinical practice encountered when treating anovulatory infertility associated with PCOS. More importantly, we wanted to test the hypothesis that metformin needs time to exert its beneficial metabolic effects fully (18) by using it alone for at least 3 months before standard infertility treatment.The primary end point was to see whether metformin decreases early pregnancy loss, and the second one was to clarify whether it improves pregnancy rates (PR) and live-birth rates (LBR) in women with anovulatory infertility and PCOS. Materials and Methods Study design and randomization This was a multicenter randomized (1:1), double-blind, placebo-controlled, parallel-group study conducted in all university hospitals of Finland (five sites). During the study period (January 2003 to December 2009), the women with PCOS referred to the clinics because of anovulatory infertility were asked to participate in the study and assigned to intervention by the main investigators of the different University Hospitals (L.M.-P. in Oulu, L.U.-K., and A.T. in Helsinki, M.H. in Kuopio, A.P. in Turku, and H.T. in Tampere).Eligible participants were women aged 18–39 yr at entry, with a body mass index (BMI) greater than 19 kg/m2 and diagnosed with PCOS according to Rotterdam criteria (19). All the subjects had polycystic ovaries at ultrasound according the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine definition, and a large majority (n = 303, 94.7%) had oligoamenorrhea, 143 (44.7%) had hyperandrogenism [either serum T levels >48.7 ng/dl (2.3 nmol/liter) or hirsutism (Ferriman-Gallwey score >7), or both]. The characteristics of the women did not differ between the two randomization groups (Table 1). Table 1.Characteristics of the subjects of the study . Metformin (n = 160) . Placebo (n = 160) . All subjects (n = 320) . PCO + OA + HA 59 (36.9%) 69 (43.1%) 128 (40.0%) PCO + OA 90 (56.2%) 85 (53.1%) 175 (54.7%) PCO + HA 11 (6.9%) 6 (3.8%) 17 (5.3%) The women had suffered from anovulatory infertility for at least 6 months and a washout period of at least 3 months since the last infertility treatment was required. Exclusion criteria were type 2 diabetes mellitus, active liver disease (alanine aminotransferase >100 IU/liter), history of cardiac or renal failure, hormone medication, alcohol use, and regular smoking.The study population was divided into obese (BMI ≥27 kg/m2) and nonobese subjects, based on prior studies indicating increased insulin resistance at BMI of 27 kg/m2 in PCOS patients (20).Randomization (after simple randomization procedures) was performed by the hospital pharmacy with 1:1 allocation in random blocks of 10 using two computer-generated lists, one for the nonobese and one for the obese women. Metformin and placebo tablets were provided by Leiras (Turku, Finland) and prepacked in opaque identical containers of 100 tablets and consecutively numbered for each woman according to the randomization schedule. Each woman was assigned a number and received the tablets in the corresponding container. Randomization codes remained blinded until the database lock had taken place. The patients and all study site personnel were blinded to the study drug codes. Procedures Metformin (metformin hydrochloride depot tablets, Diformin 500 mg; Leiras) or placebo was initiated at a dose of one tablet once a day for the first week and increased thereafter by one tablet daily in weekly steps up to three tablets (one + two daily) in nonobese women and to four tablets (two + two daily) in obese women and was continued up to a maximum of 9 months. If pregnancy occurred, metformin/placebo was continued up to the 12th week. Previous studies of ours and others (21, 22) have shown that a dose of 1500 mg is efficient enough to restore ovulation in most of nonobese women with PCOS and to improve significantly hyperandrogenism and insulin sensitivity. The idea of using a smaller dose in nonobese patients was to minimize possible side effects and thereby dropouts. Partners' sperm was analyzed and tubal patency was tested at baseline.The women used metformin or placebo alone for at least 3 months. If pregnancy did not occur, ovulation induction was commenced: if the woman ovulated after clomiphene, she continued metformin/placebo with the same dose of clomiphene for four to six cycles or until the 12th week of pregnancy. After four to six unsuccessful cycles with metformin/placebo and clomiphene, either gonadotrophins or aromatase inhibitors were used. In cases of male subfertility, either insemination or in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) was performed, according to standard protocols.Pregnancy was defined as a positive pregnancy test result. First-trimester miscarriage was defined as lack of embryonic heart activity in ultrasonography before 12 completed weeks of gestation after a positive pregnancy test, i.e. preclinical spontaneous abortions were included. Birth was defined when the infant was born at a gestation of 22 weeks or longer or weighed 500 g or greater (23).Clinical, metabolic, and hormonal parameters were assessed 1–7 d after spontaneous menstruation (oligomenorrhoeic subjects) or at any other convenient time (amenorrhoeic subjects) at baseline and at 3 months of treatment with metformin/placebo. Urinary pregnancy tests were performed monthly. Study population The women were randomized to metformin (n = 160) or placebo (n = 160). Seventy women in the metformin group and 73 women in the placebo group were obese, and 90 and 87 nonobese, respectively (Fig. 1). Open in new tabDownload slideFlow diagram of the study.The study was approved by the Ethics Committee of Northern Ostrobothnia Hospital District and the Finnish National Agency of Medicines. Written informed consent was obtained from all participants. Clinical parameters and assays Weight and waist and hip circumferences (measured to the nearest centimetre with a soft tape at the narrowest part of the torso and at the widest part of the gluteal region) were assessed at each visit, and the waist to hip ratio (WHR) was calculated. Oral glucose tolerance tests (OGTT) After an overnight fast of 10–12 h, all subjects underwent an OGTT (a load of 75 g glucose in 300 ml of water). Venous blood samples for blood glucose and serum insulin assays were drawn at 0, 30, 60, and 120 min. Glucose tolerance was defined according to World Health Organization criteria: impaired fasting glucose level (IFG) was diagnosed when in OGTT the fasting glucose concentrations were 110–125 mg/dl (6.1–6.9 mmol/liter), impaired glucose tolerance (IGT) when glucose levels at 2 h were 140–200 mg/dl (7.8–11.0 mmol/liter) and diabetes when fasting glucose concentrations were greater than 125 mg/dl (6.9 mmol/liter) and/or 2-h concentrations greater than 200 mg/dl (11.0 mmol/liter) (24).Incremental insulin area under the curve (AUCins) and glucose area under the curve (AUCgluc) were calculated by the trapezoidal method. To quantify the degree of insulin resistance, the whole-body insulin sensitivity index, i.e. the Matsuda index, was calculated (25).Plasma glucose and alanine aminotransferase were determined by chemical analyzer (Advia 1800; Siemens Healthcare Diagnostics, Tarrytown, NY), serum insulin, SHBG by chemiluminescent enzyme immunoassays (Immulite 2000; Siemens Healthcare, Llanberis, UK), androstenedione by RIA (Siemens Healthcare Diagnostics, Los Angeles, CA), and high-sensitivity C-reactive protein (hs-CRP) (BN ProSpec; Siemens Healthcare Diagnostics, Marburg, Germany) by immunonephelometry. Testosterone (T) was analyzed using Agilent triple-quadrupole 6410 liquid chromatography/mass spectrometry equipment with an electrospray ionization source operating in positive-ion mode (Agilent Technologies, Wilmington, DE). Multiple reaction monitoring was used to quantify T by trideuterated testosterone with the following transitions: m/z 289.2 to 97 and 289.2 to 109 for T and 292.2 to 97, and 292.2 to 109 for d3-T. Intraassay coefficients of vartiation of the method were 5.3, 1.6, and 1.2% for T at 0.6, 6.6, and 27.7 nmol/liter, respectively. Interassay coefficients of variation were 5.3, 4.2, and 1.0% for the respective concentrations. The free androgen index (FAI) was calculated according to the following equation: (T × 100)/SHBG. Sample size and statistical methods Power analysis indicated that a total number of 120 pregnant women would be needed to reveal a possible decrease in risk of miscarriage from 45 to the 15% observed in the general population (4, 5) (α = 0.05 and power [1-β] = 0.9). At the time of onset of the study, most investigators had shown significantly elevated risks of miscarriage (30–50%) in women with PCOS. The rate of 45% was chosen because it was the mean value calculated from the studies published at that time (2, 3). Additionally, it was estimated that at least 120 patients would be needed in each group to demonstrate an increase of 15% (from 35 to 50%) in clinical pregnancy rate in the metformin group (α = 0.05 and power [1-β] = 0.8), which can be considered as a clinically meaningful difference. To allow for dropouts, the planned sample size was at least 150 in each group.For normally distributed variables, independent-sample t tests were used for comparisons between PCOS women and controls, and paired t tests were applied to evaluate changes between measurements at baseline and after 3 months of treatment. Logarithmic conversions were performed to approximate normal distribution when data were not normally distributed. Mann-Whitney and Wilcoxon tests were performed for variables with persisting skewed distribution after logarithmic transformation.Pregnancy rates were assessed using intent-to-treat analysis (including all women randomized to treatment) with Kaplan-Meier estimation, using as a variable the time to get pregnant, which was calculated as the number of

days from the baseline (when the medication was started) until the day of the positive pregnancy test. Miscarriage rates and LBR were analyzed by percentage calculations and $\chi 2$ tests. Statistical analyses were performed using SPSS for Windows (version 16.0; Chicago, IL). For all analyses, $P < 0.05$ was considered statistically significant. Data are reported as mean ± sd. Results Clinical, hormonal, and metabolic parameters Baseline characteristics of the women did not differ between the metformin and placebo groups (Tables 2 and 3). As expected, obese women were more hirsute, more hyperandrogenic, insulin resistant, and hyperinsulinemic and had a more unfavorable metabolic profile than nonobese women at baseline (Table 4). All women had patent tubes in sonosalpingography. There was slightly more primary infertility in the metformin group ($P = 0.047$; Table 5). There were no significant differences between the two groups in duration or etiology of infertility, frequency of abnormal sperm (Table 5), or distribution of infertility treatments after the 3-month period with metformin/placebo only (Table 6). At baseline, 13 women (4%) had impaired glucose tolerance and eight women (2.5%) had impaired fasting glucose level. None of the women had diabetes. Table 2.Clinical parameters at baseline and at 3 months of treatment with metformin/placebo only in the whole study population . Metformin baseline (n = 142–160)a . Metformin 3 months (n = 106–128)a . Placebo baseline (n = 145–160)a . Placebo 3 months (n = 111–125)a . Age (yr) 28.4 ± 3.9 27.9 ± 4.1 Weight (kg) 74.8 ± 18.7 73.5 ± 18.0b 75.1 ± 18.1 76.0 ± 18.0 BMI (kg/m2) 27.1 ± 6.3 26.9 ± 6.2b 27.4 ± 6.2 27.7 ± 6.2 Waist (cm) 84.2 ± 14.5 84.3 ± 15.0 85.8 ± 15.4 86.1 ± 15.2 WHR 0.80 ± 0.1 0.80 ± 0.1 0.81 ± 0.1 0.81 ± 0.1 Hirsutism score 5.4 ± 4.5 5.3 ± 4.9 5.4 ± 4.5 5.2 ± 4.6 Ov vol dx (cm3) 8.7 ± 4.2 8.8 ± 4.5 10.2 ± 7.5 10.1 ± 10.7 Ov vol sin (cm3) 9.1 ± 9.1 9.1 ± 6.2 10.1 ± 13.3 8.6 ± 4.9 Table 3.Metabolic and hormonal parameters at baseline in the whole study population . Normal range . Metformin (n = 140–160)a . Placebo (n = 136–159)a . Fasting glucose (mg/dl) 70–110 91.9 ± 7.2 91.9 ± 9.0 Fasting insulin (μIU/ml) 0–29 11.0 ± 11.2 11.4 ± 11.8 AUCgluc 13720.7 ± 3158.6 13964.0 ± 2877.5 AUCins 8085.5 ± 6819.4 8730.2 ± 7036.2 Matsuda index ≤4.5 6.7 ± 4.6 6.3 ± 4.2 A (ng/dl) 49–370 510.0 ± 217.8 527.2 ± 196.3 T (ng/dl) 12–66 43.2 ± 17.3 45.8 ± 20.2 SHBG (μg/dl) 0.5–3.5 1.25 ± 0.66 1.29 ± 0.73 FAI 3.8 ± 2.4 3.9 ± 2.6 DHEAS (μg/dl) 29–403 152.7 ± 69.2 155.6 ± 74.9 hs-CRP (mg/liter) 0.2–3 2.9 ± 4.1 2.5 ± 3.6 Table 4.Clinical and metabolic parameters of the obese and nonobese subjects at baseline . Obese 0 months (n = 131–143)a . Nonobese 0 months (n = 156–177)a . P value . Age (yr) 28.2 ± 4.4 28.1 ± 3.7 0.75 Weight (kg) 91.0 ± 13.8 61.8 ± 7.7

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