Could metformin be used as a treatment for preeclampsia: A pilot study

Hany Abdel-Aleem[a], Ayman H. Shamash[a], Hanan G. Abd El-Azeem[b], Alaa M. Makhlouf[a], Omar M. Shaaban[a]

Departments of [a]Obstetrics and Gynaecology, [b]Clinical Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Hany Abdel-Aleem, MD, Department of Obstetrics and Gynaecology, Faculty of Medicine, Women's Health Hospital, Assiut University, 71111 Assiut, Egypt
Tel: +20 100 203 3042; Fax: (+2088) 2333327; e-mail: hany.abdelaleem@yahoo.com

Received 21 August 2017
Accepted 10 October 2017

Journal of Current Medical Research and Practice
January-April 2018, 3:37–42

Objective
To test the effect of metformin on serum level of antiangiogenic factors, soluble endoglin (sEng) and soluble fms-like tyrosine kinase-1 (sFLT-1), in patients with preeclampsia (PE).

Patients and methods
A controlled before and after prospective study was conducted on 40 patients with nonsevere PE conducted in a tertiary hospital setting. At admission, clinical and laboratory investigations had been done. Metformin tablets (500 mg three times daily) with meals were given from the time of study admission till delivery or termination of pregnancy. Serum level of sEng and sFLT-1 were measured before and 1 week after metformin treatment. Outcome of delivery had been obtained.

Results
One week after metformin treatment, there was a statistically significant reduction in maternal sEng and sFLT-1, with a mean difference of –448.86 ± 238.48 and –397.72 ± 125.52 pg/ml, respectively. In addition, there were significant reductions in both systolic blood pressure from 147 ± 12.4 to 131 ± 10.6 mmHg and diastolic blood pressure from 92 ± 7 to 85 ± 8.2 mmHg 1 week after metformin use. Five (12.5%) cases progressed to severe PE.

Conclusion
Metformin use for 1 week reduces the antiangiogenic biomarkers sEng and sFLT-1, and it could have a role in the treatment of PE.

Keywords:
metformin, preeclampsia, serum endoglin, tyrosine kinase-1

J Curr Med Res Pract 3:37–42

2357-0121

Introduction

Preeclampsia (PE) is a pregnancy-related hypertensive disorder occurring usually after 20 weeks of gestation. Worldwide, the incidence of PE ranges between 2.0 and 10.0% of pregnancies. WHO estimates that the incidence of PE to be seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%) [1]. Moreover, if left untreated, it may progress to severe PE/eclampsia in ~20.0% of cases [2]. PE/eclampsia is responsible for 9.0% of maternal deaths in USA [3] and 15.0% in Egypt [4].

PE is associated with placental ischemia/hypoxia and secretion of soluble endoglin (sEng) and soluble fms-like tyrosine kinase-1 (sFLT-1) into the maternal circulation. This causes widespread endothelial dysfunction that manifests clinically as hypertension and multisystem organ injury. Several studies reported that inhibitors of hypoxia-inducible factor 1α could reduce sFLT-1 and sEng secretion [5–7]. Recently, Brownfoot *et al.* [8] confirmed that metformin reduced sFLT-1 and sEng secretion from primary human tissues, possibly by inhibiting the mitochondrial electron transport chain, reduced endothelial dysfunction, and induced angiogenesis. These effects if proved in a clinical study could pave the way for a possible therapeutic effect of metformin in PE [8].

Metformin is a medication that is safe during pregnancy (category-B in FDA classification of drugs used during pregnancy). It has been used during pregnancy in doses ranging from 500 to 2000 mg daily either accidentally during first trimester of pregnancy in polycystic ovarian syndrome and diabetic women or in the management of gestational diabetes or type II diabetes during pregnancy [9,10].

To the best of our knowledge, this is the first clinical study to test the hypothesis that metformin can reduce the serum level of sFLT-1 and sEng in patients with PE, which could be of benefit in the treatment of PE.

The current study aims to test the effect of metformin on serum level of antiangiogenic factors sEng and sFLT-1 in patients with PE.

Patients and methods

Study design

This was a controlled before and after prospective study conducted in the Department of Obstetrics and Gynaecology, Women's Health Hospital, Faculty of Medicine, Assiut University (Tertiary Hospital), during the period from April 2016 to April 2017.

Study population

The study included women diagnosed as having nonsevere PE, as defined by ACOG guidelines [11]. We have excluded patients with eclampsia or PE with severe features who are eligible for termination of pregnancy, diabetic patients receiving insulin therapy, those with chronic renal impairment, and those who refused to participate in the study. The institutional ethical review board approved the study protocol. All study participants signed a written consent after reading the patient information sheet that written in the local language or read to them if not able to do that themselves (be sure that they understood what is in the information sheet).

Study tools

Clinical assessment

Detailed history had been obtained from eligible participants including risk factors for PE and symptoms of severe PE. Full clinical examination had also been done, including vital signs, obstetric examination, and signs of severe PE (hyper-reflexia and abdominal right upper quadrant tenderness).

Investigations

The following investigations were done for each participant, including coagulation profile, liver functions, kidney functions, serum uric acid, urine analysis, random blood sugar, and 24-h urine protein. Additional, ultrasound examination was done to ensure foetal viability of the foetus, intrauterine growth restriction (IUGR), and amniotic fluid volume. Assessment of fetal well-being was done by nonstress test (NST), biophysical profile, and umbilical artery Doppler.

Biochemical markers

Assessment of sEng and sFLT-1 was done using human soluble endoglin/CD105 ELISA Kit (SinoGeneClon Biotech; http://www.sinogeneclon.com) and human soluble fms-like Tyrosine Kinase-1 ELISA Kit (SinoGeneClon Biotech, Hangzhou , China).

Intervention

Each eligible participant was given metformin tablets (Cidophage; CID) (500 mg three times daily) with meals till delivery or termination of pregnancy. Good counselling was done to ensure compliance from the patients.

Each participant received treatment as required according to hospital protocol, including additional medication like antihypertensive (α methyldopa), corticosteroids to enhance lung maturity, and magnesium sulfate if indicated in cases with severe PET.

Follow-up

The patients were followed up after 1 week of study admission. Women were asked about symptoms of PE, perception of fetal movement, compliance with metformin treatment, and adverse effects (recent development of nausea, vomiting, or diarrhea; manifestation of hypoglycemia; and manifestations of lactic acidosis). Each participant was asked to bring the box of metformin tablets to count the consumed tablets and ensure compliance. Any other medications that had been used at each flow-up period were also recorded.

The afore mentioned clinical assessment and investigations had been obtained after 1 week of metformin treatment. The second measurements of sEng and sFLT-1 were done 1 week after beginning of metformin treatment. Maternal and fetal data at delivery had been also reported.

Study outcomes

The primary outcome was the changes in the levels of sEng and sFLT-1 before and 1 week after metformin treatment. Secondary outcomes regarding maternal outcome included development of severe PE/eclampsia, placental abruption, disseminated intravascular coagulopathy (DIC) and HELLP syndrome, blood pressure and proteinuria at delivery or termination of pregnancy, mode of delivery, and admission to ICU and fetal outcomes included development of IUGR, intrauterine fetal death (IUFD), preterm/term live birth, birth weight, Apgar score at 5 min, and admission to neonatal ICU. Secondary outcomes also included compliance to treatment as defined by receiving all prescribed doses of metformin all through treatment duration and development of adverse effects.

Statistical analysis

Data were collected and entered into Microsoft Excel database and analyzed using the statistical package for the social sciences (version 21; SPSS Inc., Chicago, Illinois, USA). Comparisons between the results before and after metformin treatment were done using paired sample *t*-test to compare the mean difference values between groups in scale variables. Wilcoxon signed rank test was used in case the data of biomarkers were not normally distributed (skewed). χ^2-Test was used to compare the dichotomous and ordinal variables before and after treatment. For analysis, *P* value less than 0.05 was considered significant.

Results

The study included 40 patients with nonsevere PE. Table 1 shows the demographic and obstetric data of study participants. The mean age was 27.88 ± 5.9 years, and approximately one-quarter of them were primigravida. Only eight (20.0%) of 40 patients had a past history of PE.

The effect on sEng and sFLT-1 1 week after metformin treatment is demonstrated in Table 2. The mean sEng before metformin treatment was 2699.0 pg/ml, and it decreased 1 week after metformin treatment to 2210.13 pg/ml (mean difference −488.86 ± 238.48 and *P* = 0.047). The mean serum level of sFLT-1 before metformin treatment was 2336.82 pg/ml, and it decreased to 1939.10 pg/ml 1 week after metformin treatment (mean difference of −397.72 ± 125.52 and *P* = 0.003).

On the contrary, the antiangiogenic markers had been increased instead of decreasing in the five cases that had progressed to severe PET, with the mean difference in the sEng of + 27.80 ± 166.88 pg/ml, and in the sFLT-1 of +233.20 ± 431.34 pg/ml.

Table 3 demonstrated changes in the two readings of blood pressure (4 h apart) from before to 1 week after treatment. There was a significant decrease in both systolic and diastolic blood pressures before and 1 week after treatment. The mean differences of the two readings of the blood pressure before and 1 week after treatment were −15.25 ± 13.77 and −15.75 ± 14.65 mmHg, respectively, for systolic pressure and −7.25 ± 9.05 and −6.75 ± 10.95 mmHg, respectively, for diastolic blood pressure (*P* = 0.001). There were no significance changes in other maternal (liver functions, renal functions, complete blood count) or fetal outcomes including viability, rate of fetal growth, amniotic fluid index, daily foetal movement count, abnormal NST, and umbilical artery Doppler. In addition to metformin, all women had received antihypertensive medication, α methyldopa (250–750 mg three times daily until delivery).

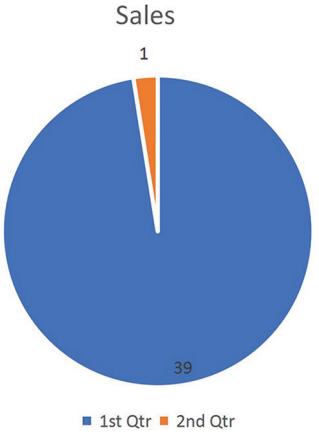
Fig. 1 summarizes the clinical follow-up of the recruited participants. Our patients had a good compliance to metformin until delivery (39 of 40 cases). Only one patient had stopped metformin treatment owing to severe nausea and vomiting not responding to antiemetics. Adverse effects encountered were mainly gastrointestinal in the form nausea with or without vomiting in eight (20.0%) participants and all of them improved overtime. No other adverse effects had been reported like hypoglycemia or symptoms of lactic acidosis.

Table 1 Demographic and obstetric data of the study population

Age (mean±SD) (years)	27.88±5.9
Number of previous deliveries [*n* (%)]	
Primigravida	10 (25)
Multipara (2, 3, 4)	25 (62.5)
Grand multipara (5 or more)	5 (12.5)
Previous CS [*n* (%)]	
No	24 (60)
One	5 (12.5)
>One	11 (27.5)
Previous abortions [*n* (%)]	5.0 (12.5)
Living children [median (range)]	2.0 (0-6.0)
Gestational age at recruitment (mean±SD) (weeks)	34.0±2.0
Systolic blood pressure at recruitment (first reading) (mean±SD)	147.0±12.44
Diastolic blood pressure at recruitment (first reading) (mean±SD)	92.50±7.76
Systolic blood pressure at recruitment (second reading) (mean±SD)	147.25±14.49
Diastolic blood pressure at recruitment (second reading) (mean±SD)	93.0±9.11
BMI (mean±SD)	23.90±2.71
Overweight BMI (25-30) [*n* (%)]	17.0 (42.5)
Risk factor for preeclampsia [*n* (%)]	
Past history of preeclampsia	8.0 (20)
Primigravida	10 (25)

Second reading was 6 h after first one.

Figure 1



Clinical follow-up of the study participants.

Table 2 Serum endoglin and soluble fms-like tyrosine kinase-1 before and 1 week after metformin treatment

Marker	Before metformin ttt (mean±SD)	One week after metformin ttt (mean±SD)	Mean difference±SD	*P*	*P* value 2
Serum endoglin (pg/ml)	2699.00±1789.05	2210.13±1152.40	−488.86±238.48	0.047	0.042
Serum tyrosine kinase-1 (pg/ml)	2336.82±1285.89	1939.10±1005.85	−397.72±125.52	0.003	0.001

P value estimated from paired *t*-test. *P* value 2 estimated from Wilcoxon signed rank test. ttt, treatment.

Table 3 Changes in clinical parameters before and 1 week after metformin treatment

	Before metformin	One week after metformin	Mean difference±SD	*P*
Blood pressure (mmHg)				
Systolic first reading (mean±SD)	147.00±12.44	131.75±10.59	−15.25±13.77	<0.00*
Diastolic first reading (mean±SD)	92.50±7.76	85.25±8.16	−7.25±9.05	<0.00*
Systolic second reading (mean±SD)	147.25±14.49	131.50±9.75	−15.75±14.65	<0.00*
Diastolic second reading (mean±SD)	93.0±9.11	86.25±8.67	−6.75±10.95	<0.00*
Proteinuria [*n* (%)]				
Urine dipstick +	39 (97.5)	40.0 (100)		1**
Urine dipstick ++	1.0 (2.5)	0 (0)		
Symptoms [*n* (%)]				
Headache	1 (2.5)	1 (2.5)		1**
Epigastric pain	0 (0)	0 (0)		1**
Blurring of vision	0 (0)	0 (0)		1**
Fetal parameters				
Gestational age (mean±SD) (weeks)	33.57±2.27	34.47±2.23	0.90±0.44	<0.001*
Range	29-36	33-40		
Decreased daily fetal movement count [*n* (%)]	0 (0)	0 (0)		1**
Decreased AF [*n* (%)]	3.0 (7.5)	3.0 (7.5)		1**
Nonreactive NST [*n* (%)]	0 (0)	1.0 (2.5)		1**
Umbilical Doppler [*n* (%)]				
Normal indices	35.0 (27.5)	35.0 (27.5)		
Raised indices	5.0 (12.5)	5.0 (12.5)		1**
Reversed indices	0 (0)	0 (0)		

Decreased AF: AF I<5 cm. NST, nonstress test. **P* value was estimated from paired t-test. **Categorical variables are calculated using χ^2-test, if necessary fissure ranked test.

Five of our participants progressed to severe PE (two of them after 1 week, one after 2 weeks, one after 3 weeks, and one after 4 weeks of recruitment). Three patients had pregnancy terminated prematurely (two at 33 weeks and one by 35 weeks). However, the remaining two cases of severe PET terminated at the 37th week of pregnancy. All the five cases had pregnancy terminated by Cesarean Section (CS) owing to different indications (repeat CS, multiple pregnancy, and nonreassuring fetal heart rate monitoring).

The remaining 35 cases were managed conservatively and delivered at term (29 patients) and preterm in six patients (they developed either IUGR, foetal distress, or passed into definite uterine contractions).

Three newborns had been admitted to neonatal ICU owing to prematurity, and all discharged alive. No other maternal complications had been reported, for example, eclampsia, DIC, placental abruption, or HELLP syndrome.

Discussion

This clinical study tested the possible effect of treating nonsevere PET with metformin. Metformin treatment was associated with statistically significant reduction in the serum antiangiogenic factors, sEng and sFLT-1, after 1 week of treatment. These biomarkers are increased during pregnancy with advanced gestational age and increased more in cases of PE [12]. So, the reduction noticed in the current study is most probably owing to the effect of metformin.

The effect of metformin on sEng and sFLT-1 was proved in in-vitro and ex-vivo studies. Brownfoot *et al.* [8] examined the special effects of metformin on sEng and sFLT-1 secretion from placenta, endothelial cells, and placental villous explants through functional in-vitro and ex-vivo experiments. They concluded that metformin reduced sEng and sFLT-1 through inhibiting the mitochondrial electron transport chain. Metformin reduced endothelial dysfunction and enhanced vasodilatation in omental arteries and induced angiogenesis [8].

Metformin was reported to have vasoprotective properties; it reduces cardiovascular morbidity in patients with polycystic ovarian syndrome and diabetes

mellitus. This has been attributed to its ability to reduce vascular cell adhesion molecule 1, which is a molecule that is expressed on the luminal surface of blood vessels in the presence of inflammation and is increased in PE. Metformin has also been reported to induce vasodilation of diabetic rat vessels [13].

To our knowledge, this is the first clinical study that confirmed the findings of in-vitro and ex-vivo studies. We chose the assessment of the biomarkers after 1 week, because if metformin is to be used for treatment of PE, its effect should be rather rapidly assessed. Moreover, the before and after controlled design of the study aimed to assess the effect of metformin on individual patients by comparing the mean change in level of the biomarkers.

Regarding the clinical outcomes of this study, the use of metformin in our patients with PET was associated with significant reduction in blood pressure. Systolic pressure decreased from 147.0 ± 12.4 to 131.0 ± 10.6 mmHg and diastolic blood pressure decreased from 92.0 ± 7.0 and 85.0 ± 8.2 mmHg 1 week after metformin use. However, all patients received in addition to metformin, α methyldopa, following the management plan in our setting. Metformin, through its vasodilatory effect [13] could add to the effect of antihypertensive treatment. However, this needs to be confirmed in a randomized placebo-controlled study.

Of 40 cases of nonsevere PE, five (12.5%) had developed severe PE. This is a much smaller number than that reported by Barton *et al.* [2], where 72 (20.1%) of 343 women with PE progressed from mild to severe PET during pregnancy.

Interestingly, in the five cases that developed severe PE, sEng and sFLT-1 were increased rather than reduced in the course of treatment. The mean difference of serum sEng was +27.80 ± 166.88 pg/ml and of sFLT-1: 233.20 ± 431.3 pg/ml.

Moreover, there were no other maternal complications in terms of eclampsia, HELLP syndrome, disseminated DIC, placental abruption, or ICU admission.

For the fetal outcomes, only one case had nonreactive NST 1 week after metformin treatment. There was no statistically significant difference in the number of patients who had abnormal umbilical cord (raised indices) from the time of study admission to after metformin treatment.

The neonatal outcome in the studied cases was fairly good, with no event of stillbirth, no neonatal death, or newborn with Apgar score less than 7 at 5 min. Previous study by Aabidha *et al.* [14] demonstrated that ~10% of neonates delivered from patients with PE had lower Apgar score at 5 min after delivery.

The results of our study may support a hypothesis that metformin can be a possible drug for treatment of PE and has the potential to reduce its complications. A randomized clinical trial is promptly needed to test the therapeutic effect of metformin in PE.

Limitations of the current study were the absence of a control group and having the soluble markers measured only 1 week after treatment. Repeated measurements may show whether the effect of metformin is temporary or sustained.

Conclusion

Metformin use for 1 week reduces the antiangiogenic biomarkers sEng and sFLT-1 and could have a role in the treatment of PE.

Acknowledgements

The researchers acknowledge a research grant (#2016/06/29-005) from Assiut Faculty of Medicine Grant's Office.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 WHO. *Make every mother and child count, in the world health report*. Geneva, Switzerland: World Health Organization; 2015.

2 Barton JR, O'Brien JM, Bergauer NK, Jacques DL, Sibai BM. Mild gestational hypertension remote from term: progression and outcome. Am J Obstet Gynecol 2001;184:979–983.

3 Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science 2005;308:1592–1594.

4 IGCME RefNA, WHO 2014. *Report onregionalestimates for Northern Africa 2013*. London, UK: WHO; 2014.

5 Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, *et al*. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003;111:649–658.

6 Nagamatsu T, Fujii T, Kusumi M, Zou L, Yamashita T, Osuga Y, *et al*. Cytotrophoblasts up-regulate soluble fms-like tyrosine kinase-1 expression under reduced oxygen: an implication for the placental vascular development and the pathophysiology of preeclampsia. Endocrinology 2004;145:4838–4845.

7 Venkatesha S, Toporsian M, Lam C, Hanai J, Mammoto T, Kim YM, *et al*. Soluble endoglin contributes to the pathogenesis of preeclampsia. Nat Med2006;12:642–649.

8 Brownfoot FC, Hastie R, Hannan NJ, Cannon P, Tuohey L, Parry LJ, *et al*. Metformin as a prevention and treatment for preeclampsia: effects on soluble fms-like tyrosine kinase 1 and soluble endoglin secretion and endothelial dysfunction. Am J Obstet Gynecol 2016;214:356.e1–56.e15.

9 Lautatzis ME, Goulis DG, Vrontakis M. Efficacy and safety of metformin during pregnancy in women with gestational diabetes mellitus or polycystic ovary syndrome: a systematic review. Metabolism 2013; 62:1522–1534.

10 Rowan JA, Hague WM, Gao W, Battin MR, Moore MP; MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med 2008;358:2003–2015.

11 American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists'Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–1131.

12 Taylor RN, Grimwood J, Taylor RS, McMaster MT, Fisher SJ, North RA. Longitudinal serum concentrations of placental growth factor: evidence for abnormal placental angiogenesis in pathologic pregnancies. Am J Obstet Gynecol 2003;188:177–182.

13 Sena CM, Matafome P, Louro T, Nunes E, Fernandes R, Seica RM. Metformin restores endothelial function in aorta of diabetic rats. Br J Pharmacol 2011;163:424–437.

14 Aabidha PM, Cherian AG, Paul E, Helan J. Maternal and fetal outcome in pre-eclampsia in a secondary care hospital in South India. J Family Med Prim Care 2015;4:257–260.