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Research Article

Metformin in Pregnant Polycystic Ovary Syndrome Women to Prevent Abortion and Preterm Labor: A Randomised Controlled Trial

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Abstract

Women with polycystic ovary syndrome have an increased risk of pregnancy complications. Previous randomised controlled trials of metformin during pregnancy in women with PCOS showed a significant reduction in miscarriages and preterm births.

The aim of this trial to test the hypothesis that metformin prevents miscarriage and preterm birth in women with PCOS.

This is a randomised placebo-controlled trial done at Prince Meshari Baljurashi hospital in Al-Baha area, KSA. The study took place between 1st December 2016, and 30th November 2018. Singleton 4 - 6 weeks pregnant women diagnosed with PCOS aged 18 - 45 years were eligible for inclusion. Participants were randomly assigned (1:1) to receive metformin or placebo by alternative randomisation. Participants were assigned to receive oral metformin

1000 mg twice daily or placebo during the trial until delivery. Placebo tablets and metformin tablets were identical. Participants and study personnel were masked to treatment allocation. The primary outcome was the incidence of early miscarriage (between week 4 and week 12 and 6 days), late miscarriage (between week 13 and week 23 and 6 days) and preterm birth (between week 24 and week 36 and 6 days). Secondary outcomes include gestational diabetes, preeclampsia, neonatal morbidity and admission of the neonate to the neonatal intensive care unit. Intention to treat analyses used.

1361 women randomly assigned to either metformin (n = 681) or placebo (n = 680). Early miscarriage occurred in 11 of 681 women in metformin group and 27 of 680 women in placebo group (odds ratio [OR] 0·27, 95% CI 0·9 - 0.001; p = 0·004). Late miscarriage occurred in three of 681 women in metformin group and 17 of 680 women in placebo group (OR 0·17, 95% CI 0·006 - 0.0001; p = 0·0008). Preterm birth occurred in 23 of 681 women in metformin group and 48 of 680 women in placebo group (OR 0·03, 95% CI 0·01 - 0.0002; p = 0·001).

Metformin had no effect on the development or severity of gestational diabetes. There is no evidence to recommend metformin as prevention or treatment for gestational diabetes in women with PCOS. However, metformin did reduce early miscarriage, late miscarriage and preterm birth. The results of this trial recommend the use of metformin for pregnant women with PCOS.

Keywords: *PCOS; Metformin; Double Blind Trial; GDM, Pre-eclampsia*

Introduction

Polycystic ovary syndrome [1] is a hormonal disorder common among women of reproductive age. Women with PCOS may have infrequent or prolonged menstrual periods or excess male hormone (androgen) levels. The ovaries may develop numerous small collections of fluid (follicles) and fail to release eggs [2-4]. There is also metabolic part of the PCOS. PCOS is one of the most common hormonal

endocrine disorders affecting 8-26.7% of childbearing age women, many of whom do not have a diagnosis [3,4]. PCOS is associated with the development of other medical conditions, such as insulin resistance, type 2 diabetes, high cholesterol, high blood pressure, and heart disease [2,4]. More than half of women with PCOS develop type 2 diabetes before the age of 40 years [2]. The exact cause of PCOS is unknown. PCOS is thought to have a genetic component. People who have a relative with PCOS are likely to develop PCOS. This family link is the main risk factor. On the other hand, excess insulin is thought to affect a woman's ability to ovulate because of its effect on androgen production, and this may represent another PCOS risk factor. On top, recent researches demonstrate that women with PCOS have low-grade inflammation that stimulates polycystic ovaries to produce androgens [1-4].

PCOS is a common and treatable cause of infertility. Around 70-80% of ovulatory fertility issues are related to PCOS. Accordingly, prevalence of infertility in women with PCOS varies between 70 and 80% [2,3]. Fertility rate with PCOS is thought to be around 20%, but still even after that, PCOS may impact pregnant mother and baby [2-5]. PCOS is associated with increased prevalence of pregnancy complications, including miscarriage, preterm birth, low birthweight, pre-eclampsia and gestational diabetes (GDM) [3,6-9]. Women with PCOS has three-fold increase in miscarriage risk in early pregnancy compared to women without PCOS [9]. Preterm birth as a major cause of neonatal morbidity and mortality has remained at the same incidence or even increased in developed countries [8]. GDM is treatable and, if controlled, does not cause significant problems for the mother or fetus [10]. Babies whose mothers have GDM can be macrosomic resulting in the need for cesarean delivery, have low blood sugar, and have trouble breathing [10,11]. Women with GDM, as well as their offspring, are at higher risk for type 2 diabetes later in life [10-12].

Metformin is a medicine used in the treatment of type 2 diabetes mellitus (DM) and for PCOS, although it's not officially approved for PCOS [5,13]. Metformin improves insulin sensitivity, reduces hepatic gluconeogenesis, and increases peripheral glucose uptake [7,14]. It reduces fasting serum insulin by 40% and leads to a mean weight reduction of 5.8% [15]. The improvement in insulin sensitivity is mediated via several mechanisms including increased insulin receptor tyrosine kinase activity, enhanced glycogen synthesis, reduces the rate of glycogenolysis, decreased activity of hepatic glucose-6-phosphatase, and an increase in the recruitment and activity of GLUT4 glucose transporters [5,14,16]. Metformin also stimulates glucagon-like-peptide-1 (GLP-1) release thereby enhancing insulin secretion [7,17]. Metformin promotes the re-esterification of free fatty acids and inhibits lipolysis. This fatty acid oxidation suppression results in a reduction in hypertriglyceridemia, thus reducing the energy supply for gluconeogenesis. This is associated with decreased synthesis and increased clearance of Very Low Density Lipoprotein (VLDL). This may contribute to improved insulin sensitivity through reduced lipotoxicity [18].

Metformin use is safe in pregnancy with no reports of any teratogenic effects despite it crosses the placenta [19,20]. The National Institute for Health and Care Excellence recommends that women with GDM should be offered metformin if blood glucose targets are not met with diet and exercise within 1 - 2 weeks [5,21]. The Scottish Intercollegiate Guidelines Network (SIGN) recommend that metformin may be considered as initial pharmacological glucose lowering treatment in GDM [4,5]. Diabetes Canada states that metformin may be used as an alternative to insulin adding that women should be informed that metformin crosses the placenta [2,5].

Recent randomised controlled trials assessed the effect of metformin on pregnancy complications in any population. Most of these trials showed a significant reduction in late miscarriage and preterm birth with the use of metformin [4,7,15,16,18-20,22-25].

Aim of the Study

The aim of this clinical trial was to test the hypothesis that metformin prevents miscarriage and preterm birth in pregnant women with PCOS.

Methods

This is a randomised, placebo-controlled, double blind, clinical trial, with participants recruited from Prince Meshari Baljurashi hospital (PMH) in Al-Baha area, KSA. PMH is a secondary hospital where medical care is given free of charge under the umbrella of Saudi Ministry of Health (MOH). PMH has an average delivery rate of 6000 deliveries per annum, and caesarean section rate of 28.5%. This hospital serves Al-Baha area, which is located in the southwestern part of Saudi Arabia. It has an area of 9,921 km^2, with an elevation of 1,500 to 2,450m (4,920 to 8,040 ft.) above sea level. Al-Baha area has a total multi-ethnic population of 550,172.

Patients were eligible for inclusion if they had an established diagnosis of PCOS according to the Rotterdam 2003 criteria, were aged 18 - 45 years, were pregnant by any mode of conception with a singleton viable fetus (determined by ultrasound) between gestational week 4 and week 5 plus 6 days and planning to deliver in the hospital [1]. Patients were excluded if they had chronic diabetes, known liver or kidney failure, conditions that could induce tissue hypoxia (for example; emphysema, severe asthma, or heart failure), known hypersensitivity to metformin, were using drugs known to interfere with metformin, were breastfeeding, planning to deliver in any other hospital or were unsuitable for participation for other reasons. After receiving information about the study at their first antenatal visit, women signed up individually to participate in the study and provided written informed consent before inclusion in the study. Ethics approval obtained from Al-Baha University Medical College Ethical committee and Prince Meshari Hospital Ethical committee.

Women randomly assigned (1:1) to receive metformin or placebo using coin flip randomisation. Placebo tablets and metformin tablets were identical. In addition to masking of participants and study personnel, obstetricians not involved in the care or treatment of participants assessed the study outcomes, and the design of tables planned before the results were known.

Participants assigned to receive metformin (oral tablets; 1000 mg twice daily) or matching placebo until delivery. Treatment started in the first trimester as soon as possible. All women received diet and lifestyle advice according to national guidelines. No dietary supplements were recommended while the women participated in the study, with the exception of one multivitamin tablet per day containing recommended dose of Folic acid, ferrous sulphate, Calcium and Omega 3. Structured questions at each study visit were used to assess adherence to and adverse effects of the study medication. Excellent adherence is considered if the participant took more than 90% of the study medication, acceptable if 70 - 90% was taken, and poor if less than 70% was taken. At inclusion demographic information, maternal anthropometry, and previous and present obstetric and medical history were recorded. Pregnancies were dated by transvaginal ultrasound according to local guidelines. PCOS phenotype information were recorded. If phenotype was not clearly stated at inclusion information were gathered regarding menstrual cycles, clinical hyperandrogenism (hirsutism score and acne), and polycystic ovaries by vaginal ultrasound before pregnancy.

Follow-up visits were scheduled at gestational weeks 10 (± 1 day), 14 (± 1 day), 19 (± 1 day), 24 (± 1 day), 28 (± 1 day), 32 (± 1 day), and 36 (± 1 day). Data obtained from delivery and 6 weeks post-partum for both the mother and the newborn from medical charts and review visit. Women underwent a 75 g oral glucose tolerance test (OGTT) at inclusion. If negative, the OGTT was repeated at gestational week 28 (± 1 day). Women diagnosed with GDM were referred for further assessment and treatment according to local guidelines, with no interference with the study medication. Transabdominal ultrasound scans were done at gestational weeks 10 (± 1 day), 19 (± 1 day) and 32 (± 1 day). Up-to-date ultrasound equipment used. Participation in the study did not limit any examinations or treatments necessary or advisable during pregnancy. No participant was included in the study more than once or participated in any other trials.

The primary outcomes were the incidence of early miscarriage (between week 4 and week 12 and 6 days), late miscarriage (between week 13 and week 23 and 6 days) and preterm birth (between week 24 and week 36 and 6 days). Secondary outcomes were divided into maternal and neonatal. Maternal secondary outcomes were the prevalence of GDM, pre-eclampsia, hospital admission during pregnancy and method of delivery. Neonatal secondary outcomes were admission to neonatal intensive care unit (NICU), the total number of days in NICU per baby and 5-minute Apgar score ≤ 7.

Adverse events were recorded at each visit. These were any unfavorable and unintended sign (including an abnormal laboratory finding, symptom, or disease temporarily associated with the use of a medical product), whether or not related to the medical product.

Sample size estimation was based on that; outcome events is about 10% of participants in the placebo group and 4% of participants in the metformin group, to show a 50% reduction in the incidence of miscarriage and preterm birth with a power of 95% at α = 0·05. Therefore, 1000 patients were planned to be included, with 500 in each treatment group. The planned study period was 2 years, from 1st December 2016 until 30th November 2018.

Analyses was done using SPSS version 21 [26]. Categorical data was presented as frequencies and percentages and analysed using the Chi square test. Continuous variables were presented as means with standard deviation or medians with ranges and analysed using Student's t-test and Mann-Whitney U test as appropriate for normally distributed and skewed data respectively. All tests are two-tailed with statistical significance defined as a probability value of < 0.05.

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1361 women randomly assigned to either metformin (n = 681) or placebo (n = 680). Baseline characteristics were similar in the groups (Table 1).

Characteristics		Metformin group (N = 681)	Placebo group (N = 680)
Age (years)		29 (22 - 43)	28 (21 - 44)
Weight [12]		75 (48 - 109)	72 (47 - 112)
BMI (Kg/M^2)		27·5 (18·4 - 38)	27·7 (18 - 43)
Smoking		8 (1.2%)	7 (1%)
Saudi		676 (99.3%)	680 (100%)
Non - Saudi		5 (0.7%)	0
Education	High school	24 (3.5%)	18 (2.7%)
	University	639 (93.8%)	641(94.3%)
	Postgraduate	18 (2.6%)	21 (3%)
Mode of conception	Spontaneous	616 (90.5%)	604 (88.8%)
	Ovulation induction	54 (7.9%)	67 (9.9%)
	IVF	11 (1.6%)	9 (1.3%)
Parity		1 (1 - 5)	1 (1 - 4)
Previous Miscarriages		0.3 (0 - 2)	0.4 (0 - 4)

Table 1: *Baseline characteristics of participants.*

In the intention-to-treat analysis, early miscarriage, late miscarriage and preterm birth occurred in metformin group less than placebo group and that was statistically significant. Early miscarriage occurred in 11 of 681 women in metformin group and 27 of 680 women in placebo group (odds ratio [OR] 0·27, 95% CI 0·9 - 0.001; p = 0·004). Late miscarriage occurred in three of 681 women in metformin group and 17 of 680 women in placebo group (OR 0·17, 95% CI 0·006 - 0.0001; p = 0·0008). Preterm birth occurred in 23 of 681 women in metformin group and 48 of 680 women in placebo group (OR 0·03, 95% CI 0·01 - 0.0002; p = 0·001). Gestational diabetes was diagnosed in 57 of 681 women in metformin group and 56 of 680 women in placebo group (OR 1, 95% CI 0·9 - 0.4; p = 0·5). Pre-eclampsia was diagnosed in 35 of 681 women in the metformin group and 36 of 680 women in the placebo group (OR 1, 95% CI 0·02 - 0.5; p = 0·4) (Table 2).

Outcome		Metformin group (N = 681)	Placebo group (N = 680)	P value
Early miscarriage		11 (1.6%)	27 (4%)	0.004
Late miscarriage		3 (0.4%)	17 (2.5%)	0.0008
Preterm delivery		23 (3.4%)	48 (7.1%)	0.001
GDM		57 (8.4%)	56 (8.2%)	0.5
Pre-eclampsia		35 (5.1%)	36 (5.3%)	0.4
Hospital admissions		134 (19.7%)	189 (27.8%)	0.0002
Mode of delivery	SVD	498 (73.1%)	501 (73.7%)	0.4
	Ventouse delivery	2 (0.3%)	1 (0.2%)	0.9
	LSCS	181 (26.6%)	178 (26.1%)	0.5
Admissions to NICU		32 (4.7%)	34 (5%)	0.4
Days in NICU		11 (5-19)	14 (7-21)	0.3
5min's APGAR score ≤ 7		3 (0.4%)	5 (0.7%)	0.2

Table 2: *Pregnancy outcomes of the trial.*

Adherence to study medication was good (> 90%) in 672 (98.7%) of 681 women in the metformin group and 665 (97.8%) of 680 women in the placebo group. Mean adherence to study medication was 97%. Information from tablet count and self-reported tablet intake were consistent.

Discussion

Polycystic ovary syndrome is the most common endocrine disorder in women of reproductive age [2]. PCOS produces symptoms in approximately 5 to 10% of reproductive age women. It is thought to be one of the leading causes of the female subfertility [17]. PCOS is a medical condition, in which there is an imbalance of the female sex hormones (elevated levels of testosterone, DHEA-S, androstenedione, prolactin, and LH along with a normal, high or low estrogen levels) [2, 17]. Hyperinsulinemia, insulin resistance and impaired glucose tolerance are very common in women with PCOS. Hyperinsulinemia has shown to increase androgen production by the ovaries and hence it may play a central role in the pathogenesis of PCOS [2,4,17]. Controversies in continuation of metformin therapy throughout pregnancy, also, continuation of metformin in women who have conceived after treatment of PCOS, has remained a controversial topic to date. This trial may give an insight into the problem.

The results of this clinical trial showed a significant reduction in the incidence of early, late miscarriage and preterm delivery. Notably, metformin had no effect on the incidence of gestational diabetes or the need for insulin treatment and on pre-eclampsia.

None of the previous studies found any effect of metformin on preterm delivery, miscarriage, GDM and pre-eclampsia [27-31]. In all these studies, duration of treatment was shorter, adherence poorer, and BMI substantially higher than in the present study, resulting in lower overall metformin exposure. Most of the participants in our trial had spontaneous onset of labour. A possible mechanism for metformin to reduce miscarriage and spontaneous onset of preterm birth could be the mammalian target of rapamycin complex 1 (mTORC1) pathway [32]. mTORC1 signaling has a key role in the timing of birth, as its activation induces preterm birth and its inhibition prevents or postpones the onset of labour [32,33]. Metformin inhibits mTORC1 by AMP activated protein kinase. In mice with premature decidual senescence, which triggers spontaneous onset of labour, metformin prevented preterm birth [8,32,33]. However, there are no such data from human pregnancies.

In this trial and all previous seven trials, metformin showed no effect on GDM [23,27-31,34]. Thus, in all eight trials discussed here, which included almost 3000 women at high risk for gestational diabetes, no effect of metformin on glucose homeostasis in pregnancy was identified. No obvious explanation can be proposed for the absence of effect of metformin on gestational diabetes. However, this trial findings support the notion that gestational diabetes might have a different cause to preexisting diabetes, and thus respond differently to treatment.

Strengths of this study include the randomised controlled design with strict adherence to good clinical practice, and close monitoring of clinical data. Further strengths include the well-documented and excellent adherence to treatment [27,29,30]. The main limitation of the study was that participants were of mainly Saudi women; therefore, our results might not be directly applicable to other nationalities. However, there is no evidence that ethnicity or nationality modulates the effect of metformin [17]. The study consisted of women with PCOS who were aware of their diagnosis. Previous studies have shown that most women with PCOS are unaware of their diagnosis [35].

Conclusion

Metformin is cheap, tolerable, and widely available. Metformin had no effect on the development or severity of gestational diabetes. There is no evidence to recommend metformin as prevention or treatment for gestational diabetes in women with PCOS. However, metformin did reduce early miscarriage, late miscarriage and preterm birth. The results of this trial recommend the use of metformin for pregnant women with PCOS.

Because of the increased risk of pregnancy complications and the high prevalence of comorbidities in pregnant women with PCOS, data suggests intensification and targeting of PCOS pregnancy surveillance as necessary. There is a need for more research regarding pregnant women with PCOS.

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