Use of metformin to treat pregnant women with polycystic ovary syndrome (PregMet2): a randomised, double-blind, placebo-controlled trial

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Summary

Background Women with polycystic ovary syndrome (PCOS) have an increased risk of pregnancy complications. Epi-analysis of two previous randomised controlled trials that compared metformin with placebo during pregnancy in women with PCOS showed a significant reduction in late miscarriages and preterm births in the metformin group. The aim of this third randomised trial (PregMet2) was to test the hypothesis that metformin prevents late miscarriage and preterm birth in women with PCOS.

Methods PregMet2 was a randomised, placebo-controlled, double-blind, multicentre trial done at 14 hospitals in Norway, Sweden, and Iceland. Singleton pregnant women with PCOS aged 18–45 years were eligible for inclusion. After receiving information about the study at their first antenatal visit or from the internet, women signed up individually to participate in the study. Participants were randomly assigned (1:1) to receive metformin or placebo by computer-generated random numbers. Randomisation was in blocks of ten for each country and centre; the first block had a random size between one and ten to assure masking. Participants were assigned to receive oral metformin 500 mg twice daily or placebo during the first week of treatment, which increased to 1000 mg twice daily or placebo from week 2 until delivery. Placebo tablets and metformin tablets were identical and participants and study personnel were masked to treatment allocation. The primary outcome was the composite incidence of late miscarriage (between week 13 and week 22 and 6 days) and preterm birth (between week 23 and week 36 and 6 days), analysed in the intention-to-treat population. Secondary endpoints included the incidence of gestational diabetes, preeclampsia, pregnancy-induced hypertension, and admission of the neonate to the neonatal intensive care unit. We also did a post-hoc individual participant data analysis of pregnancy outcomes, pooling data from the two previous trials with the present study. The study was registered with ClinicalTrials.gov, number NCT01587378, and EudraCT, number 2011-002203-15.

Findings The study took place between Oct 19, 2012, and Sept 1, 2017. We randomly assigned 487 women to metformin (n=244) or placebo (n=243). In the intention-to-treat analysis, our composite primary outcome of late miscarriage and preterm birth occurred in 12 (5%) of 238 women in the metformin group and 23 (10%) of 240 women in the placebo group (odds ratio [OR] 0·50, 95% CI 0·22–1·08; p=0·08). We found no significant differences for our secondary endpoints, including incidence of gestational diabetes (60 [25%] of 238 women in the metformin group *vs* 57 [24%] of 240 women in the placebo group; OR 1·09, 95% CI 0·69–1·66; p=0·75). We noted no substantial between-group differences in serious adverse events in either mothers or offspring, and no serious adverse events were considered drug-related by principal investigators. In the post-hoc pooled analysis of individual participant data from the present trial and two previous trials, 18 (5%) of 397 women had late miscarriage or preterm delivery in the metformin group compared with 40 (10%) of 399 women in the placebo group (OR 0·43, 95% CI 0·23–0·79; p=0·004).

Interpretation In pregnant women with PCOS, metformin treatment from the late first trimester until delivery might reduce the risk of late miscarriage and preterm birth, but does not prevent gestational diabetes.

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Introduction

Polycystic ovary syndrome (PCOS) is associated with increased prevalence of pregnancy complications, including pre-eclampsia, gestational diabetes, low birthweight, miscarriage, and preterm birth.[1,2] Preterm birth is a major contributor to neonatal morbidity and mortality. Despite attempts to prevent and treat imminent preterm birth, its incidence has remained unchanged or has slightly increased in most high-income countries.[3]

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Research in context

Evidence before this study

Metformin treatment in women with polycystic ovary syndrome (PCOS) has been suggested to prevent several pregnancy complications. However, data from randomised trials are lacking. We searched PubMed in January, 2012, and again in September, 2017, for English language publications, with the terms "metformin", "pregnancy", and "randomized trial", and then added the term "PCOS". We identified our two former studies as the only ones that assessed metformin treatment compared with placebo in women with PCOS throughout pregnancy. We identified two more studies in obese pregnant women and one in pregnant women with prediabetes. By adding "preterm birth" or "preterm delivery" to the search, we found only our own previous study, in which this was a secondary outcome. Preterm birth was reported as an adverse outcome in two of the studies in obese women treated with metformin in pregnancy. When we added "late miscarriage" to our search we found no results.

Added value of this study

Although our trial was underpowered, the results of a post-hoc pooled individual participant data analysis (including data from two previous trials) suggest that metformin treatment of pregnant women with PCOS might reduce late miscarriage and preterm delivery. Notably, we identified no effect on the incidence of gestational diabetes or need for additional insulin treatment.

Implications of all the available evidence

Metformin treatment might help to prevent late miscarriage and preterm birth among women with PCOS. However, metformin did not seem to prevent gestational diabetes. Further research is needed to identify the possible long-term effects of metformin in both mothers and offspring. Before the use of metformin in pregnancy is recommended, further follow-up studies of the offspring of treated mothers should be done.

Metformin is an insulin sensitiser and is predominantly used in the treatment of type 2 diabetes.[4,5] Data from recent studies suggest that metformin has anti-inflammatory effects independent of its glucose-lowering effect.[6–11] Use of metformin is considered safe in pregnancy and there are no reported teratogenic effects.[12,13] However, few randomised controlled trials have been done to assess the effect of metformin on pregnancy complications in any population.

We did the first two randomised trials[14,15] of metformin treatment in pregnant women with PCOS. Our pilot study[14] (n=40) showed promising results for overall pregnancy complications. The PregMet study[15] (n=273) was designed to explore the possible beneficial effects of metformin on pre-eclampsia, preterm delivery, and gestational diabetes. This study[15] was underpowered and showed no difference in pregnancy complications between the metformin and placebo groups. However, pooled data from these two studies,[14,15] which had essentially identical designs, showed a significant reduction in the combined endpoint of late miscarriage and preterm birth in favour of metformin.[16] Late miscarriage (between gestational week 13 and week 22 and 6 days) and preterm birth could be considered a pathophysiological continuum rather than separate conditions, since the clinical 22-week cutoff point between these two conditions is based on legal and pragmatic—rather than biological—considerations.

The aim of this third randomised trial (PregMet2) was to test the hypothesis that metformin prevents late miscarriage and preterm birth in pregnant women with PCOS. Since all three of our studies had essentially identical designs, we also report findings from post-hoc pooled individual participant data analyses of these three studies.

Methods

Study design and participants

PregMet2 was a randomised, placebo-controlled, double-blind, multicentre trial, with participants recruited from 14 hospitals in Norway, Sweden, and Iceland. Patients were eligible for inclusion if they had an established diagnosis of PCOS according to the Rotterdam 2003 criteria,[17] were aged 18–45 years, were pregnant by any mode of conception with a singleton viable fetus (determined by ultrasound) between gestational week 6 and week 12 plus 6 days, had a minimum of 7 days washout of metformin (if used before inclusion), and were able to communicate in a Scandinavian language or English. If there was no certain PCOS diagnosis before inclusion, anamnestic data were gathered and medical files were checked to confirm the diagnosis. Patients were excluded if they had diabetes, known liver or kidney failure (alanine aminotransferase ≤100 IU/L and creatinine ≤110 µmol/L), conditions that could induce tissue hypoxia (ie, emphysema, severe asthma, or heart failure), known hypersensitivity to metformin, known alcohol or drug misuse, were using drugs known to interfere with metformin, were breastfeeding, or were unsuitable for participation for other reasons. After receiving information about the study at their first antenatal visit or from the internet, women signed up individually to participate in the study.

All participants provided written informed consent before inclusion in the study. Ethics approval was obtained from the Regional Committee for Health Research Ethics of Central Norway (number 2011/1434); the Regional Ethical Review Board in Stockholm, Sweden (number 2012/1200-31/2); and the National Bioethics Committee of Iceland (number VSNb2012100011/03.10). Clinical trial authorisation was obtained from the Norwegian Medicines Agency and the trial was also

approved in Sweden and Iceland. The study protocol, including the statistical analysis plan, is available in the appendix.

Randomisation and masking

We randomly assigned women (1:1) to receive metformin or placebo via computer-generated random numbers. Randomisation was in blocks of ten for each country and centre; the first block had a random size between one and ten to assure masking.

Randomisation of treatment packages was computer-generated and was done before inclusion. At inclusion, the local principal investigator logged on to a website and was given a randomisation number from one of the medication packages. Randomisation sequence was generated by personnel from the Unit of Applied Clinical Research, none of whom had any involvement in recriutment, assignment, or the rest of the trial.

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, a statistician masked to the treatment allocation did the statistical analyses, and the design of tables and figures were planned before the results were known.

Procedures

Participants were assigned to receive metformin (oral tablets; 500 mg twice daily) or matching placebo (both purchased from Weifa, Oslo, Norway, and later from Vistin Pharma, Oslo, Norway) during the first week of treatment, with the dose increased to 1000 mg twice daily (or matching placebo) from week 2 until delivery. Treatment was started in the first trimester as soon as possible, and at the latest 7 days after, the inclusion visit. Most participants started study medication the day after inclusion.

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 0·4 mg folic acid and one multivitamin tablet per day.

Structured questions at each study visit were used to assess adherence to and adverse effects of the study medication. If necessary because of side-effects, doses were adjusted to an acceptable level. We considered adherence good or excellent 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.

We recorded demographic information, maternal anthropometry, and previous and present obstetric and medical history at inclusion. Pregnancies were dated by transvaginal ultrasound according to local guidelines. We recorded PCOS phenotype information. If phenotype was not clearly stated at inclusion we gathered information 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 19 (±1 day), 28 (±1 day), 32 (±1 day), and 36 (±1 day). We obtained data from delivery and 8 weeks post partum for both the mother and the newborn from medical charts and telephone interviews. 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 gestational diabetes were referred for further assessment and treatment according to local guidelines, with no interference with the study medication. If errors occurred in OGTT analysis, or the woman was unable to do the procedure (ie, due to nausea, bariatric surgery, absolute reluctance towards the procedure, or other practical inconveniences), this did not lead to exclusion from the study. Fasting glucose was assessed throughout the study and medical files and antenatal care documentation were checked to support a possible diagnosis in all participants, both those with and without complete OGTT status. If a woman showed no signs of gestational diabetes, she was classified as not having the condition.

See Online for appendix

Transabdominal ultrasound scans were done at gestational weeks 19 (±1 day; routine in Nordic countries) and 32 (±1 day; for patient safety). Each study site used up-to-date ultrasound equipment and measurements were done according to local guidelines.

Clinical and anamnestic data were recorded in an internet-based case report form (WebCRF, version 2; Unit for Applied Clinical Research, Norwegian University of Science and Technology, Trondheim, Norway). Certified monitors monitored endpoints, case report forms, source data, and informed consent for quality control.

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 methods of our two previous studies have been reported elsewhere and had essentially identical designs to the present study.[14,15] The lower metformin dose (1700 mg daily) in the pilot study compared with the dose (2000 mg daily) in the PregMet and PregMet2 studies is the only notable difference between them.

Outcomes

The primary outcome of PregMet2 was the composite incidence of late miscarriage (between week 13 and week 22 and 6 days) and preterm birth (between week 23 and week 36 and 6 days), including spontaneous birth, induced vaginal deliveries, and operative deliveries for medical indications. All primary outcomes were reported to the study principal investigator (EV). All primary endpoints were centrally assessed by TSL and EV and an experienced obstetrician not involved in the study.

Maternal secondary outcomes were the prevalence of gestational diabetes (according to WHO 1999 criteria[18]), pre-eclampsia (all forms of pre-eclampsia, with and without pre-existing hypertension), and hypertension

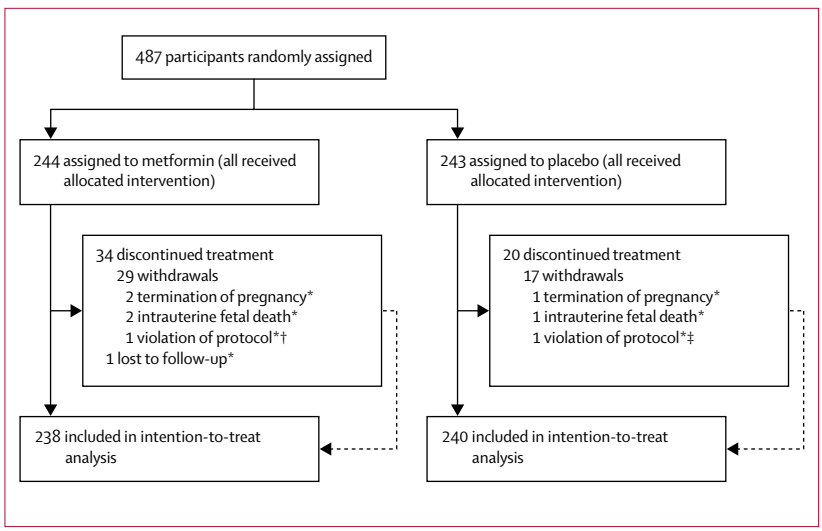

Figure: **Trial profile**
*These patients were removed as endpoints could not be evaluated, and because of missing data. †Patient incorrectly included with planned progesterone treatment, which was an exclusion criterion in Iceland. ‡Patient incorrectly included despite diagnosed anencephaly at inclusion. The patient did not start study medication.

(both pre-existing hypertension and hypertension that developed during pregnancy, not fulfilling criteria of pre-eclampsia) in pregnancy, treatment with vaginal progesterone to prevent imminent preterm delivery, vaginal bleeding during pregnancy, and admission to hospital of patients during pregnancy, except for delivery and post partum (the number of patients admitted to hospital and the total number of days in hospital per patient; because of errors in registrations we could not assess the total number of days in hospital per patient). Neonatal secondary outcomes were admission to neonatal intensive care unit (NICU) and the total number of days in NICU per baby. However, days in NICU were not assessed because registrations turned out to be a mixture of normal stays in the postnatal unit and actual admissions to the NICU. The maternal tertiary outcome was weight gain in pregnancy (weight gain from inclusion until week 36, excluding participants with delivery before week 36 or those without weight measurements in week 36). Neonatal tertiary outcomes were birthweight, birth length, head circumference, 5-minute Apgar score, and umbilical cord pH. Malformations, also a tertiary outcome, are listed separately as adverse events. We also report perinatal neonate death and intrauterine fetal death in those women included in the intention-to-treat analysis.

Because method of delivery is an important part of evaulating pregnancy outcomes, we assessed this as a post-hoc outcome. We also assessed incidence of post-partum haemorrhage, estimated bleeding, placental weight, offspring sex, and perinatal deaths as post-hoc outcomes. A final post-hoc outcome was insulin use due to gestational diabetes as a measure of severity of the condition.

Adverse events were recorded at each visit. Adverse events were any unfavourable 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. All serious adverse events were reported to the principal investigator (EV). We defined serious adverse events as any condition leading to hospital admission during pregnancy.

Statistical analysis

Our sample size estimation was based on the composite incidence of late miscarriage and preterm birth in the original pilot study and the first PregMet trial[14,15] (outcome events in about 10% of participants in the placebo group and 4% of participants in the metformin group). We aimed to show a 50% reduction in the combined incidence of late miscarriage and preterm birth with a power of 85% at $\alpha=0\cdot05$; therefore, we planned to include 1000 patients, with 500 in each treatment group. According to the inclusion rate of the previous studies, our estimated number of patients seemed achievable. The planned study period was 3 years, from 2012 to 2015. Because of slower enrolment than anticipated, we had to reduce the total number of patients to 500 so that it was possible to end the study within an extended period of close to 5 years. Power calculation of the post-hoc analysis was not done. No interim analyses were planned nor done.

We compared the groups with the independent *t* test or Mann-Whitney U test, as appropriate. We did univariate comparisons of dichotomous data, and compared participant baseline characteristics, with Fisher's exact test. Because gestational age has a major effect on offspring anthropometrics, we compared birthweight, birth length, and head circumference adjusted for mean gestational age at delivery, by logistic regression analysis.

We analysed all outcomes according to the intention-to-treat principle. According to our protocol, we planned to do per-protocol analyses, but the nature of these analyes was decided post-hoc. We did post-hoc sensitivity analyses to explore possible effects of missing data.

To increase the study power, we did a post-hoc analysis of individual participant data, merging data from our two previous randomised trials[14,15] and PregMet2 for all outcomes that could be retrieved from the three trials. This analysis was not planned a priori, because our original plan was to include a sufficient number of participants to reach adequate power in the PregMet2 study alone. With the data from these three studies, we also did several post-hoc subgroup analyses for the composite outcome of late miscarriage and preterm birth and gestational diabetes: BMI 30 kg/m² or greater versus less than 30 kg/m², hyperandrogenous versus normoandrogenous participants, use versus non-use of metformin at conception, and use versus non-use of artificial reproductive technology. We did an additional post-hoc logistic

	Metformin (n=244)	Placebo (n=243)
Maternal age (years)	29 (24–34)	30 (24–36)
Maternal weight (kg)*	78 (54–102)	75 (53–97)
Maternal height (cm)	168 (160–176)	167 (159–175)
BMI (kg/m²)†	27·5 (18·2–36·5)	26·7 (18·8–34·6)
Systolic blood pressure (mm Hg)	114 (101–127)	112 (98–127)
Diastolic blood pressure (mm Hg)	73 (60–86)	71 (58–84)
Fasting blood glucose concentration (mmol/L)	4·8 (4·3–5·3)	4·7 (4·3–5·1)
2 h blood glucose concentration (mmol/L)	5·9 (4·1–7·7)	5·9 (4·1–7·7)
Smoker	8 (3%)	13 (5%)
Snus user	5 (2%)	3 (1%)
Ethnic origin		
White	236 (97%)	220 (91%)
Black	0	1 (<1%)
Middle Eastern	3 (1%)	4 (2%)
Hispanic	1 (<1%)	2 (1%)
Mediterranean	0	2 (1%)
South Asian	2 (1%)	8 (3%)
East Asian	1 (<1%)	5 (2%)
Other	1 (<1%)	1 (<1%)
Highest level of education		
Elementary school (9–10 years)	11 (5%)	10 (4%)
High school (2–3 years)	68 (28%)	57 (23%)
College (≤4 years)	95 (39%)	106 (44%)
University (>4 years)	70 (29%)	70 (29%)
Civil status		
Married	93 (38%)	95 (39%)
Cohabitant	147 (60%)	140 (58%)
Single	3 (1%)	4 (2%)
Other	1 (<1%)	4 (2%)
Working status‡		
Working	205 (84%)	199 (82%)
Student	28 (11%)	28 (12%)
Unemployed	9 (4%)	10 (4%)
Long-term sick leave	4 (2%)	5 (2%)
Rehabilitation	4 (2%)	2 (1%)
Disabled	2 (1%)	2 (1%)
Other	6 (2%)	7 (3%)
(Continued from previous column)		
Median gestational length of current pregnancy at randomisation (days)	74 (55–93)	75 (55–95)
Metformin use at conception of current pregnancy	64 (26%)	55 (23%)
Mode of conception‡		
Spontaneous	111 (45%)	97 (40%)
Ovulation induction	49 (20%)	64 (26%)
Gonadotrophin-releasing hormone analogue	6 (2%)	2 (1%)
In-vitro fertilisation or intracytoplasmic sperm injection	41 (17%)	49 (20%)
Metformin only	24 (10%)	28 (12%)
Other§	13 (5%)	12 (5%)
Parity		
0	143 (59%)	132 (54%)
1	74 (30%)	82 (34%)
≥2	27 (11%)	29 (12%)
Previous stillbirth	0	3 (1%)
Previous early miscarriage		
0	164 (67%)	161 (66%)
1	59 (24%)	47 (19%)
2	12 (5%)	20 (8%)
≥3	9 (4%)	15 (6%)
Previous late miscarriages (after week 12)	6 (2%)	5 (2%)
Medical history‡		
No former medical history	104 (43%)	116 (48%)
Chronic hypertension	10 (4%)	6 (2%)
Depression	60 (25%)	53 (22%)
Thyroid disorder	22 (9%)	19 (8%)
Bariatric surgery	15 (6%)	22 (9%)
Eating disorder	15 (6%)	15 (6%)
Asthma	21 (9%)	35 (14%)
Migraine	50 (20%)	52 (21%)
Other chronic condition	18 (7%)	23 (9%)
Polycystic ovary syndrome phenotype		
Hyperandrogenism, polycystic ovaries, and oligoamenorrhoea	152 (64%)	154 (64%)
Hyperandrogenism and oligoamenorrhoea	14 (6%)	9 (4%)
Hyperandrogenism and polycystic ovaries	17 (7%)	27 (11%)
Polycystic ovaries and oligoamenorrhoea	56 (23%)	49 (21%)
Missing	5 (2%)	4 (2%)

Data are median (IQR) or n (%). *Bodyweight at inclusion. †BMI was calculated at the inclusion visit. ‡Participants could be included in more than one category. §Other indicates acupuncture, herbal medicines, zone therapy, and other types of alternative medicine.

Table 1: **Maternal baseline characteristics and medical and obstetric history**

regression analysis to ensure balanced randomisation, and to assess possible differences between the groups.

The analyses were done using R version 2.13.1 and SPSS version 25.

The study was registered with ClinicalTrials.gov, number NCT01587378, and EudraCT, number 2011-002203-15.

Role of the funding source

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

	Metformin (n=238)*	Placebo (n=240)*	Odds ratio (95% CI) or mean difference (95% CI)†	p value
Primary outcomes				
Late miscarriage and preterm delivery	12 (5%)	23 (10%)	0·50 (0·22 to 1·08)	0·08
Late miscarriage	3 (1%)	5 (2%)	0·60 (0·09 to 3·13)	0·72
Preterm delivery	9 (4%)	18 (8%)	0·48 (0·19 to 1·16)	0·11
Gestational length at delivery (days)	280 (268–292)	282 (267–297)	..	0·36
Secondary outcomes				
Gestational diabetes	60 (25%)	57 (24%)	1·09 (0·69 to 1·66)	0·75
At inclusion‡	21 (9%)	22 (9%)	0·96 (0·49 to 1·89)	1·00
After inclusion§	39 (16%)	35 (15%)	1·15 (0·68 to 1·95)	0·61
Hypertension in pregnancy	16 (7%)	13 (5%)	1·25 (0·55 to 2·94)	0·57
Pre-existing hypertension	6 (3%)	3 (1%)	..	..
Pre-eclampsia	8 (3%)	17 (7%)	0·46 (0·17 to 1·15)	0·10
Vaginal progesterone treatment because of imminent labour	3 (1%)	3 (1%)	..	..
Admission to hospital during pregnancy	49 (21%)	55 (23%)	0·88 (0·55 to 1·37)	0·58
Transfer to neonatal intensive care unit	26 (11%)	24 (10%)	1·10 (0·59 to 2·08)	0·77
Neonate readmitted to hospital¶	14 (6%)	14 (6%)	1·05 (0·64 to 1·41)	0·85
Tertiary and post-hoc outcomes				
Weight gain until week 36 (kg)‖	9·1 (5·1)**	11·5 (4·9)††	−2·4 (−3·4 to −1·4)	<0·0001
Method of delivery‡‡				
Spontaneous vaginal§§	167 (70%)	169 (70%)	1·01 (0·67 to 1·51)	1·00
Instrumental vaginal	26 (11%)	26 (11%)	1·01 (0·54 to 1·88)	1·00
Caesarean section	45 (19%)	45 (19%)	0·98 (0·60 to 1·61)	1·00
Elective	15 (33%)	10 (22%)	1·42 (0·58 to 3·70)	0·41
Emergency¶¶	30 (67%)	35 (78%)	0·81 (0·46 to 1·43)	0·50
Estimated bleeding (mL)‡‡	300 (49–551)‖‖	350 (150–550)***	..	0·16
Post-partum haemorrhage (≥1000 mL)‡‡	10/233 (4%)	11/234 (5%)	0·91 (0·38 to 2·00)	0·83
Placental weight (g)‡‡	680 (241)†††	658 (143)‡‡‡	21·2 (−16·9 to 59·4)	0·28
Perinatal neonate death§§§	1/238 (<1%)	0	..	..
Intrauterine fetal death	0	1/240 (<1%)	..	..
Birthweight (g)	3488 (560)¶¶¶	3453 (633)¶¶¶	−35 (−108 to 38)	0·35
Birth length (cm)	50·1 (3·0)‖‖‖	49·8 (3·0)‖‖‖	−0·3 (−0·6 to 0·4)	0·09
Mean head circumference (cm)	35·2 (2·0)***	34·8 (2·0)****	−0·4 (−0·6 to −0·1)	0·006
5 min Apgar score <7	8/233 (3%)	7/232 (3%)	1·16 (0·41 to 3·23)	1·00
Umbilical cord pH	7·26 (0·10)††††	7·26 (0·10)‡‡‡‡	<0·00 (−0·02 to 0·02)**	0·95
Offspring sex‡‡				
Female	114/236 (48%)	112/237 (47%)	..	..
Male	122/236 (52%)	125/237 (53%)	..	..

Data are n (%), median (IQR), mean (SD), or n/N (%), unless otherwise specified. *Nine patients were excluded from the analysis. †Data are odds ratio (95% CI) for dichotomous variables or mean difference (95% CI) for continuous variables. ‡Five participants in the metformin group and one in the control group had missing data (included in the denominator for percentage calculation). §One participant in the placebo group had missing data (included in the denominator for percentage calculation). ¶Within 8 weeks after discharge from the delivery department. ‖85 women were missing data on weight gain: 31 delivered before week 36, 46 withdrew, and three had weight gain information missing on their case report form. **n=198. ††n=200. ‡‡Not predefined endpoints of the study. §§We included late miscarriages in vaginal deliveries (three patients in the metformin group and five in the placebo group). ¶¶Emergency included all non-planned caesareans. ‖‖‖n=233. ***n=234. †††n=213. ‡‡‡n=218. §§§Classified as death of the fetus or neonate at 22 + 6 weeks or later (or weight 500 g or greater) until 4 weeks after delivery. ¶¶¶n=235. ‖‖‖‖n=230. ****n=232. ††††n=151. ‡‡‡‡n=158.

***Table 2*: Pregnancy outcomes in the intention-to-treat population**

full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The study took place between Oct 19, 2012, and Sept 1, 2017. Few women attended an inclusion visit without an ultrasound having been done. As women signed up individually, they were not recruited from a given population. A small number of women were not enrolled in the study at the planned inclusion visit, but the exact number was not registererd. However, on the basis of numbers from the largest study centre, we impute around 10–20 women were excluded. We randomly

assigned 487 eligible women to either metformin (n=244) or placebo (n=243; figure). Randomisation resulted in balanced treatment allocation across centres (appendix). Perinatal deaths occurred in five pregnancies, two of which were diagnosed after the start of labour and were thus included in the intention-to-treat analyses. Study outcomes were not assessable in nine participants (three terminations of pregnancy because of severe malformations in the fetus not detected at inclusion, three intrauterine fetal deaths [onset of labour impossible to evaluate], two violations of protocol [one with planned progesterone treatment, part of Icelandic exclusion criteria, and one diagnosed with anencephaly at inclusion, wrongly included], and one lost to follow-up [not able to get in touch with the patient after inclusion]) and are thus reported as missing in the intention-to-treat analyses (figure).

Baseline characteristics were similar in the groups (table 1). Ethnicity was similar between the two groups. However, if we combined south Asian and east Asian women into a single category, there were more women of Asian origin in the placebo group compared with the metformin group (13 *vs* three; p=0·01). 267 (55%) of the participants suffered from one or more chronic conditions or had a history of bariatric surgery.

Adherence to study medication was good (>90%) in 144 (61%) of 238 women in the metformin group and 156 (65%) of 240 women in the placebo group (appendix). Mean adherence to study medication was 85% (SD 17). Information from tablet count and self-reported tablet intake were consistent.

In the intention-to-treat analysis, the composite primary outcome of late miscarriage and preterm birth occurred in 12 (5%) of 238 women in the metformin group and 23 (10%) of 240 women in the placebo group (odds ratio [OR] 0·50, 95% CI 0·22–1·08; p=0·08; table 2).

Gestational diabetes was diagnosed in 60 (25%) of 238 women in the metformin group and in 57 (24%) of 240 women in the placebo group (OR 1·06, 95% CI 0·68–1·64; p=0·83). Nine (4%) of 238 women in the metformin group and nine (4%) of 240 women in the placebo group needed additional insulin treatment (1·00, 0·35–2·93; p=1·00). 12 women did not undergo OGTT at inclusion or during pregnancy. These women had normal fasting blood glucose levels and showed no other signs of gestational diabetes throughout pregnancy (no glucosuria, fetal macrosomia, or polyhydramnios). No diagnosis of diabetes was given according to their health record card for pregnant women or in medical files; therefore we classified them as not having gestational diabetes. Pre-eclampsia was diagnosed in eight (3%) of 238 women in the metformin group and 17 (7%) of 240 women in the placebo group (OR 0·46, 95% CI 0·17–1·15; p=0·10; table 2). Vaginal bleeding througout pregnancy was found in 29 (13%) of 232 women in the metformin group (data missing for eight patients) and 41 (17%) of 236 in the placebo group (data missing for four patients; OR 1·47, 95% CI 0·9–2·5; p=0·16). Data for additional secondary outcomes are presented in table 2.

	Metformin (n=244)	Placebo (n=243)
Serious adverse events	10 (4%)	9 (4%)
Maternal adverse events		
Abdominal pain	4 (2%)	4 (2%)
Contractions	0	2 (1%)
Pneumonia	1 (<1%)	1 (<1%)
Migraine	1 (<1%)	0
Hyperemesis	2 (1%)	1 (<1%)
Eating disorder	0	1 (<1%)
Offspring adverse events		
Fetal malformations*	2 (1%)	0
Intrauterine fetal death†	2 (1%)	2 (1%)
Perinatal fetal death†	1 (<1%)	0
Other adverse events reported at study visits‡		
Upper respiratory tract infection	56 (23%)	61 (25%)
Lower respiratory tract infection	1 (<1%)	3 (1%)
Abdominal pain	12 (5%)	21 (9%)
Colitis rectal bleeding	1 (<1%)	0
Tachycardia	4 (2%)	2 (1%)
Musculoskeletal pain or arthralgia	10 (4%)	16 (7%)
Dental problems	1 (<1%)	0
Vitamin B_{12} deficiency§	3 (1%)	2 (1%)
Gastrointestinal reflux	3 (1%)	3 (1%)
Herpes zoster infections	0	1 (<1%)
Uterine trauma¶	3 (1%)	3 (1%)
Other	7 (3%)	3 (1%)
Neonatal conditions||		
Asphyxia	9/235 (4%)	10/237 (4%)
Infections	6/235 (3%)	9/237 (4%)
Icterus	9/235 (4%)	8/237 (3%)
Hypoglycaemia	4/235 (2%)	2/237 (1%)
Respiratory problems	5/235 (2%)	2/237 (1%)
Other	0	1/237 (<1%)
Neonatal anomalies		
Heart	3/235 (1%)	5/237 (2%)
Skeletal	5/235 (2%)	2/237 (1%)
Urinary	2/235 (1%)	2/237 (1%)
Gastrointestinal	2/235 (1%)	1/237 (<1%)
Genital	1/235 (<1%)	4/237 (2%)
Other	5/235 (2%)	1/237 (<1%)

Data are n (%) or n/N (%). *One giant omphalocele and one hypoplastic left ventricle—both were diagnosed during pregnancy. †These events are not included in the sum of serious adverse events. ‡More than one adverse event per participant might be reported. §No systematic screening done. ¶All trauma against the uterus—for example, falls or traffic accidents. ||Data are missing for six offspring: four late miscarriages, one preterm birth in which the fetus died before delivery, and one lost to follow-up.

Table 3: **Maternal and offspring adverse events**

	Metformin (n=391)	Placebo (n=399)	Odds ratio (95% CI) or mean difference (95% CI)*	p value
Primary outcomes				
Late miscarriage and preterm delivery	18 (5%)	40 (10%)	0·43 (0·23 to 0·79)	0·004
Late miscarriage	3 (1%)	8 (2%)	0·38 (0·06 to 1·59)	0·22
Preterm delivery	15 (4%)	32 (8%)	0·46 (0·23 to 0·89)	0·02
Gestational length (days)	280 (267–293)	280 (266–294)	..	0·77
Secondary outcomes				
Gestational diabetes	100 (26%)	104 (26%)†	0·97 (0·70 to 1·36)	0·94
At inclusion	35 (9%)	42 (11%)	0·84 (0·51 to 1·38)	0·47
After inclusion	65 (17%)	61 (15%)	1·10 (0·74 to 1·65)	0·63
Hypertension in pregnancy	28 (7%)	26 (7%)	1·11 (0·61 to 2·01)	0·78
Pre-existing hypertension	11 (3%)	7 (2%)	1·62 (0·57 to 4·98)	0·35
Pre-eclampsia	22 (6%)	22 (6%)	1·02 (0·53 to 1·97)	1·0
Tertiary outcomes				
Weight gain until week 36 (kg)‡	8·9 (5·8)§	11·5 (7·5)¶	–0·4 (–0·7 to 0·3)	<0·0001
Method of delivery				
Vaginal	274/389 (70%)	281/397 (71%)	..	0·82
Instrumental vaginal	38/389 (10%)	41/397 (10%)	..	..
Caesarean section	77/389 (20%)	75/397 (19%)	..	..
Elective	20/77 (26%)	16/75 (21%)	..	..
Emergency‖	54/77 (70%)	55/75 (73%)	..	..
Missing data	3/77 (4%)	4/75 (5%)	..	..
Estimated bleeding (ml)	300 (50–550)**	350 (150–550)††	..	0·27
Post-partum haemorrhage (≥1000 ml)	24/359 (7%)	21/361 (6%)	1·16 (0·63 to 2·12)	0·65
Placental weight (g)	673 (209)‡‡	652 (162)§§	21 (–7 to 49)	0·15
Perinatal neonate death¶¶	2/391 (1%)	1/399 (<1%)	..	..
Intrauterine fetal death	0	1/399 (<1%)	..	..
Birthweight (g)	3485 (560)‖‖	3483 (691)***	2 (–58 to 62)	0·94
Birth length (cm)	50·0 (3·5)†††	49·9 (3·8)‡‡‡	0·1 (–0·2 to 0·5)	0·53
Head circumference (cm)	35·6 (1·9)§§§	35·2 (2·3)¶¶¶	0·4 (0·2 to 0·6)	0·0004
5 min Apgar score <7	9/387 (2%)	9/388 (2%)	1·0 (0·3 to 2·9)	1·00
Umbilical cord pH	7·26 (0·10)‖‖‖	7·26 (0·10)****	–0·005 (–0·02 to 0·01)	0·62
Offspring sex				
Female	190/389 (49%)	196/396 (49%)	..	..
Male	199/389 (51%)	200/396 (51%)	..	..

Data are n (%), median (IQR), or n/N (%), unless otherwise specified. *Data are odds ratio (95% CI) for dichotomous variables or mean difference (95% CI) for continuous variables. †One patient was diagnosed according to local criteria rather than the criteria given in the study protocol. ‡Weight gain from inclusion until week 36, not including those with delivery before week 36 or those without weight measurements in week 36. §n=324. ¶n=315. ‖Emergency included all non-planned caesareans. **n=359. ††n=361. ‡‡n=343. §§n=344. ¶¶Classified as death of the fetus or neonate at 22 + 6 weeks or later (or weight 500 g or greater) until 4 weeks after delivery. ‖‖‖n=389. ***n=395. †††n=383. ‡‡‡n=388. §§§n=386. ¶¶¶n=390. ‖‖‖‖n=226. ****n=243.

Table 4: **Individual participant data analysis of pregnancy outcomes in the intention-to-treat population (three trials)**

Women in the metformin group gained less weight from inclusion to gestational week 36 compared with those in the placebo group (mean 9·1 kg *vs* 11·5 kg; mean difference –2·3, 95% CI –3·4 to –1·4; p<0·0001; table 2). We found no significant difference in method of delivery between the groups. Birthweight and birth length did not differ significantly between the groups, whereas head circumference was significantly larger in the metformin group than in the placebo group (mean difference –0·4, –0·6 to –0·1; table 2). We identified no difference between the two groups in Apgar score or umbilical cord pH (table 2). Data for additional tertiary outcomes are presented in table 2.

We noted no substantial between-group differences in serious adverse events in either mothers or offspring, and no serious adverse events were deemed to be drug-related by the principal investigator (table 3). Women in the metformin group had more diarrhoea than women in the placebo group at weeks 19 and 28, but later in pregnancy there was no difference between the groups (appendix).

We did sensitivity analyses to explore potential missingness (counting all missing data from intention-to-treat analysis as primary endpoints, and also counting all these data as non-endpoints [worst case *vs* best case

scenario]) and found the study outcomes did not change substantially (data not shown). We also did per-protocol analyses excluding withdrawals and according to adherence to study medication (appendix). Regression analysis adjusting for possible differences in baseline data in the post-hoc pooled analysis showed a correlation between randomisation and the primary outcome (appendix).

In the post-hoc pooled individual participant data analysis of the three studies (the present study and our two previous studies[14,15]), 800 women were randomly assigned to either metformin or placebo (40 women from the pilot study, 273 from PregMet, and 487 from PregMet2; 397 to metformin and 403 to placebo). We found no between-group differences at baseline (appendix). As in the primary analysis, if we combined south Asian and east Asian ethnic groups, there were more Asian women in the placebo group than in the metformin group (13 *vs* four). 18 (5%) of 391 women had late miscarriage or preterm delivery in the metformin group compared with 40 (10%) of 399 women in the placebo group (OR 0·43, 95% CI 0·23–0·79; p=0·004; table 4). 44 (76%) of 58 women with late miscarriages or preterm delivery had spontaneous onset (data not shown).

Primary endpoint subgroup post-hoc analyses according to androgenicity, BMI, and need of assisted reproductive technology to concieve showed a more profound effect in the metformin group compared with placebo in women with hyperandrogenism (OR 0·43, 95% CI 0·19–0·89; p=0·01), BMI greater than 30 kg/m² (0·34, 0·11–0·91; p= 0·02), and with need of assisted reproductive technology (0·22, 0·04–0·84; p=0·02; appendix). In the overall pooled individual participant data analysis population, the number needed to treat to avoid one late miscarriage or preterm birth was 18·4. We identified no differences in the incidence of gestational diabetes, pregnancy-induced hypertension, or pre-eclampsia between the treatment groups (table 4). Re-analysis of gestational diabetes diagnoses according to WHO 2013 criteria[19] also showed no difference between the groups (appendix).

Discussion

The results of PregMet2 showed a non-significant reduction in the incidence of late miscarriage or preterm delivery—however, this difference was significant in a post-hoc pooled analysis of individual participant data including our two previous trials. Notably, metformin had no effect on the incidence of gestational diabetes or the need for insulin treatment.

Strengths of our study include the randomised controlled design in a multicentre setting (done across three Nordic countries), strict adherence to good clinical practice, and close monitoring of clinical data. Further strengths include the well documented and excellent adherence to treatment, which was better than in other comparable studies;[20,21] the broad spectrum of PCOS in the participants, according to phenotype, severity, mode of conception, BMI, and metformin use at conception; and the extensive masking approach used. Although post hoc, our use of pooled data from all three studies[14,15] strengthened the results.

The main limitation of the study was the reduction from the anticipated sample size, meaning the study was underpowered compared with our original plan. The individual participant data analysis done by pooling data from our three trials increased the sample size and power, although this analysis was post hoc. Another possible limitation is that participants were of mainly Nordic white ethnicity, therefore our results might not be directly applicable to other ethnic groups. However, there is no evidence that ethnicity modulates the effect of metformin.[22] Combining south Asian and east Asian women resulted in more women of Asian origin in the placebo group than in the metformin group. However, the total number of Asian women was small and the difference between the groups might have been due to a small sample size; thus we believe this difference is unlikely to have had any effect on our results.

The heterogeneity of the study population might also be considered a limitation of our study. 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.[23] Women who are aware of their PCOS might have a more severe phenotype than those who are undiagnosed, and this could be a limitation of our study. Inclusion of only women with a known PCOS diagnosis was a decision made for practical reasons, since we relied on women volunteering to participate in the study. Our study population also consisted of 15–20% of women in need of assisted reproductive technology. These women might also have a more severe form of PCOS; however, they were equally distributed between the treatment groups. Inclusion of women in need of assisted reproductive technology was essential for us to recruit an adequate number of women in our study, since we depended on women being aware of their diagnosis before pregnancy. In our post-hoc subgroup analysis of pooled data from the three trials according to the need for assisted reproductive technology, we identified a more profound effect of metformin on the primary outcome, although the subgroups were too small to reach a definitive conclusion. The risk of gestational diabetes was equal in the subgroup analyses. The risk of various pregnancy complications might differ between different phenotypes of PCOS. In all our studies,[14,15] the different phenotypes of PCOS were equally distributed between the metformin group and the placebo group. Analysis of our data according to each phenotype would make the groups too small to conclude possible different levels of risk. Notably, in the subgroup analyses of hyperandrogenous and normoandrogenous women in our pooled individual

participant data analysis, both groups showed the same tendency as our main results (although the effect of metformin was non-significant in the smaller normoandrogenous subgroup).

Three previous randomised trials (MOP,[20] EMPOWaR,[21] and GRoW[24]) investigated whether metformin reduced neonatal birthweight compared with placebo in obese pregnant women. A fourth trial[25] compared metformin with placebo for prevention of gestational diabetes in a population of women with prediabetes. None of these studies found any effect of metformin on their primary endpoints. The results of the MOP study[20] showed a non-significant effect of metformin on preterm delivery and late miscarriage. EMPOWaR[21] did not show any such trend in the combined outcome of late miscarriage, pregnancy termination, and stillbirth. The GRoW study[24] did not show any difference in birthweight or incidence of preterm birth, gestational diabetes, or pre-eclampsia between the placebo and metformin group. The fourth trial[25] did not show any significant difference in preterm birth between the metformin and placebo groups. In all these studies,[20,21,24,25] 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 late miscarriage and spontaneous onset of preterm birth could be the mammalian target of rapamycin complex 1 (mTORC1) pathway. mTORC1 signalling 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.[26] Metformin inhibits mTORC1 by AMP activated protein kinase. In mice with premature decidual senescence, which triggers spontaneous onset of labour, metformin prevented preterm birth.[27] However, to our knowledge there are no such data from human pregnancies.

We identified no difference between the metformin and placebo groups in PregMet2 in the prevalence of gestational diabetes at inclusion or later in pregnancy. Moreover, in our analysis of individual participant data from all three trials there was no difference in incidence of gestational diabetes between the metformin group and the placebo group, despite less weight gain in pregnancy in the metformin group. It is surprising that metformin—a well known antidiabetes drug that is routinely used to treat gestational diabetes worldwide[28,29]—had no effect on the development or severity (whether or not insulin treatment was needed) of the disease in this high-risk population. When we used the WHO 2013 criteria[19] to classify gestational diabetes, the prevalence of the disease increased further, but we still found no difference between the treatment groups. To our knowledge, our three trials[14,15] are the only such studies in women with PCOS. However, our finding of no effect on gestational diabetes[30] is supported by the results of three trials[20,21,24] in obese women and one trial[25] in women who were insulin resistant before pregnancy. Thus, in all seven trials discussed here, which included almost 1800 women at high risk for gestational diabetes, no effect of metformin on glucose homeostasis in pregnancy was identified. We can propose no obvious explanation for the absence of effect of metformin on gestational diabetes. However, our findings support the notion that gestational diabetes might have a different cause to pre-existing diabetes, and thus respond differently to treatment.

Five (1%) perinatal deaths occurred in the PregMet2 study. Perinatal deaths occurred in both study groups—three in the metformin group and two in the placebo group—suggesting no association with metformin treatment. Three perinatal deaths (all intrauterine fetal deaths) were excluded from the intention-to-treat analysis, and therefore we could not assess study outcomes for these patients. The high amount of perinatal mortality was unexpected considering the high socioeconomic equality and free health-care services in the Nordic countries, and the fairly high educational level of the participants. However, increased perinatal mortality has been reported in pregnancies in women with PCOS compared with women without PCOS.[31,32]

All three of our trials[14,15]—separately and in the pooled analysis—showed a larger head circumference in the metformin group compared with the placebo group. A substudy of the PregMet trial[33] showed larger head circumference in metformin-exposed children compared with placebo-exposed ones, but this effect was modified by maternal pre-pregnancy BMI. We cannot offer an obvious explanation for this, but we consider this finding to have little clinical significance. The head circumferences were all within the normal range and did not increase the number of operative deliveries. In conclusion, our findings suggest that metformin might reduce late miscarriage and preterm birth in pregnant women with PCOS. Metformin is cheap, tolerable, and widely available. However, the possible benefit of metformin on pregnancy outcomes should be balanced by recent findings of overweight among in-utero metformin-exposed offspring at age 4 years.[34] Metformin had no effect on the development or severity of gestational diabetes, although it led to reduced weight gain compared with placebo. There is therefore no evidence to recommend metformin as prevention or treatment for gestational diabetes in women with PCOS. However, metformin did reduce late miscarriage and preterm birth. Because of the increased risk of pregnancy complications and the high prevalence of comorbidities in pregnant women with PCOS, our data suggest intensification and targeting of PCOS pregnancy surveillance are necessary.

Contributors

TSL and EV wrote the first draft of the report. EV was the principal investigator of the PregMet2 study; TSL was the national coordinating principal investigator in Norway and corresponded with the study centres. EV wrote the study protocol with SMC and TSL. SMC was responsible for randomisation and monitoring. MB was the principal

investigator in Sweden and BS was the principal investigator in Iceland. MB and BS translated and sent applications for ethics committee approvals in their respective countries. ØS was the study statistician and did the first (masked) data analysis together with TSL and EV. MU is an obstetrician and was not involved in the study directly, but controlled the study material and data gathered in Trondheim with patient files, before masking was broken. ML was the study midwife at the second-largest study centre. TSL, BS, MB, FG-R, KVH, RZ, ALH, AT, ST, SH, AHB, FA, ISP, and JM were principal investigators at the 14 study centres. All authors participated in the writing process by making comments and suggestions and by approving the report.

Declaration of interests

ISP reports personal fees for teaching and for being part of a review board panel from Gedeon Richter and Bayer, outside the current study. All other authors declare no competing interests.

Data sharing

Individual participant data from this study (after de-identification) will be available from the publication date of this manuscript for the following 24 months, on a collaborative basis for individual participant data meta-analyses. Proposals should be directed to Eszter Vanky (eszter.vanky@ntnu.no).

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