Clinical trial results:
Metformin treatment of pregnant PCOS women and prevention of late miscarriages and preterm birth

The PregMet 2 Study

Summary

EudraCT number	2011-002203-15
Trial protocol	NO SE IS
Global end of trial date	31 October 2017
Results information	
Result version number	v1 (current)
This version publication date	20 August 2021
First version publication date	20 August 2021
Summary attachment (see zip file)	Use of metformin to treat pregnant women with polycystic ovary syndrome (PregMet2): a randomised, double-blind, placebo-controlled trial (18TLDE0705_Loevvik.pdf)

Trial information

Trial identification	
Sponsor protocol code	PregMet2
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01587378
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Norwegian University of Science and Technology
Sponsor organisation address	Erling Skjalgsons gate 1, Trondheim, Norway, 7491
Public contact	Maternity care, Outpatient Unit, Dept. of Obstetrics and Gynecology, St. Olavs Hospital, +47 72575715, Tone.Shetelig.lovvik@stolav.no
Scientific contact	Maternity care, Outpatient Unit, Dept. of Obstetrics and Gynecology, St. Olavs Hospital, +47 72575715, Tone.Shetelig.lovvik@stolav.no

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2017
Global end of trial reached?	Yes
Global end of trial date	31 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall aim and primary endpoint of the PregMet 2 Study is to investigate whether metformin prevents late miscarriages and preterm deliveries in PCOS women treated with metformin from first trimester of pregnancy to delivery in a large, randomized, controlled, multi-centre trial setting.

Protection of trial subjects:

Both mothers, fetuses and newborn were closely followed up through pregnancy and 8 weeks postpartum, by specialists in obstetrics, endocrinologists and midwifes. All AE were registered and evaluated continuously. In addition to standard antenatal care the participants had extra glucose controls, ultrasonography of the fetus and easy access to the responsible study investigators.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 390
Country: Number of subjects enrolled	Sweden: 46
Country: Number of subjects enrolled	Iceland: 51
Worldwide total number of subjects	487
EEA total number of subjects	487

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	487
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited in Norway (Trondheim, Bergen, Drammen, Tønsberg, Skien, Ålesund, Lillehammer, Bodø), Sweden (Stockholm, Uppsala, Örebro, Umeå) and Iceland (Reykjavik).
First participant included 2012-10-19, last 2016-12-28.

Pre-assignment

Screening details:

Inclusion criteria: diagnosis of PCOS according to the Rotterdam 2003 criteria, aged 18–45 years, pregnant by any mode of conception with a singleton viable fetus
between gestational week 6 and week 12 plus 6 days, had a minimum of 7 days washout of metformin
Exclusion criteria diabetes, known liver or kidney failure

Pre-assignment period milestones

Number of subjects started	505[1]
Number of subjects completed	487

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 5
Reason: Number of subjects	Protocol deviation: 13

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 18 potential participants were not suitable for inclusion after additional evaluation.

Period 1

Period 1 title	Inclusion period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

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. Randomisation of treatment packages was computer generated
and was done before inclusion. Randomisation sequence was
generated by personnel from the Unit of Applied Clinical
Research, none of whom had any involvement in
recruitment, assignment, or the rest of the trial.
Placebo tablets and metformin tablets were identical.

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin

Arm description:

Metformin 500mg tablets, 2 tablets in the morning and 2 tablets in the evening. Taken together with meal.

Arm type	Experimental

Investigational medicinal product name	metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:
500mg x 2 twice daily

Arm title	Placebo

Arm description:
Identical placebo tablets (to metformin)

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:
2 tablets twice daily

Number of subjects in period 1	Metformin	Placebo
Started	244	243
Completed	238	240
Not completed	6	3
Physician decision	2	1
Lost to follow-up	1	-
Protocol deviation	3	2

Period 2

Period 2 title	Intention to treat end points
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin

Arm description: -

Arm type	Experimental

Investigational medicinal product name	metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:
500 mg x2 - twice daily

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:
2 tablets twice daily

Number of subjects in period 2	Metformin	Placebo
Started	238	240
Completed	238	240

Baseline characteristics

Reporting groups	
Reporting group title	Metformin
Reporting group description:	
Metformin 500mg tablets, 2 tablets in the morning and 2 tablets in the evening. Taken together with meal.	
Reporting group title	Placebo
Reporting group description:	
Identical placebo tablets (to metformin)	

Reporting group values	Metformin	Placebo	Total
Number of subjects	244	243	487
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	29	29	
inter-quartile range (Q1-Q3)	24 to 34	24 to 36	-
Gender categorical			
Only women (pregnant)			
Units: Subjects			
Female	244	243	487
Male	0	0	0
Ethnicity			
Units: Subjects			
Caucasians	236	220	456
Non-Caucasians	8	23	31
Smoking			
Units: Subjects			
Smokers	8	13	21
Non-smokers	236	230	466
Mode of conceptio			
Units: Subjects			
spontaneous	111	97	208
Ovulation induction	49	64	113
IVF/ICSI	41	49	90
others	43	33	76
parity			

Units: Subjects			
0-parous	143	132	275
multi-parous	101	111	212
Body mass index			
Units: kg/m2			
median	27.5	26.7	
inter-quartile range (Q1-Q3)	18.2 to 36.5	18.8 to 34.6	-
blood pressure systolic			
Units: mmHg			
median	114	112	
inter-quartile range (Q1-Q3)	101 to 127	98 to 127	-
blood pressure diastolic			
Units: mmHg			
median	73	71	
inter-quartile range (Q1-Q3)	60 to 86	58 to 84	-

End points

End points reporting groups

Reporting group title	Metformin
Reporting group description:	
Metformin 500mg tablets, 2 tablets in the morning and 2 tablets in the evening. Taken together with meal.	
Reporting group title	Placebo
Reporting group description:	
Identical placebo tablets (to metformin)	
Reporting group title	Metformin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Late miscarriage and preterm delivery

End point title	Late miscarriage and preterm delivery
End point description:	
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.	
End point type	Primary
End point timeframe:	
End of pregnancy	

End point values	Metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	240		
Units: subjects				
Late miscarriage	3	5		
Preterm delivery	9	18		
Composite	12	23		

Statistical analyses

Statistical analysis title	Composite endpoint
Comparison groups	Metformin v Placebo

Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.08
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.08

Statistical analysis title	late miscarriage
Comparison groups	Placebo v Metformin
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.72
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	3.13

Statistical analysis title	Preterm delivery
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.11
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	1.16

Secondary: Hypertension in pregnancy

End point title	Hypertension in pregnancy

End point description:

End point type	Secondary

End point timeframe:

During pregnancy

End point values	Metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	240		
Units: subjects				
Hypertension	16	13		
No hypertension	222	227		

Statistical analyses

Statistical analysis title	Hypertension in pregnancy
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.57
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	2.94

Secondary: preeclampsia

End point title	preeclampsia

End point description:

End point type	Secondary

End point timeframe:

After gestational week 20

End point values	Metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	240		
Units: subjects				
preeclampsia	8	17		
non-preeclampsia	230	223		

Attachments (see zip file)	Endpoint table/Endpoint table.pdf

Statistical analyses

Statistical analysis title	Preeclampsia
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	1.15

Secondary: gestational diabetes

End point title	gestational diabetes

End point description:

End point type	Secondary

End point timeframe:
during pregnancy

End point values	Metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	240		
Units: subjects				
gestational diabetes	60	57		
no gestational diabetes	178	183		

Statistical analyses

Statistical analysis title	gestational diabetes
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.75
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.66

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From inclusion to the study until 8 weeks post partum.	
Assessment type	Systematic

Dictionary used	
Dictionary name	ICD
Dictionary version	10

Reporting groups	
Reporting group title	Metformin
Reporting group description:	
Metformin 500mg tablets, 2 tablets in the morning and 2 tablets in the evening. Taken together with meal.	
Reporting group title	Placebo
Reporting group description:	
Identical placebo tablets (to metformin)	

Serious adverse events	Metformin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 244 (4.10%)	9 / 243 (3.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
uterus contractions			
subjects affected / exposed	0 / 244 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperemesis			
subjects affected / exposed	2 / 244 (0.82%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 244 (0.41%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	4 / 244 (1.64%)	4 / 243 (1.65%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
pneumonia			
subjects affected / exposed	1 / 244 (0.41%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Eating disorder symptom			
subjects affected / exposed	0 / 244 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Metformin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 244 (36.89%)	110 / 243 (45.27%)	
Cardiac disorders			
tachycardia			
subjects affected / exposed	4 / 244 (1.64%)	2 / 243 (0.82%)	
occurrences (all)	4	2	
Pregnancy, puerperium and perinatal conditions			
uterine trauma			
subjects affected / exposed	3 / 244 (1.23%)	3 / 243 (1.23%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
pain, reflux, rectal bleeding			
subjects affected / exposed	16 / 244 (6.56%)	24 / 243 (9.88%)	
occurrences (all)	16	24	
Respiratory, thoracic and mediastinal disorders			
Upper and lower respiratory infections			

subjects affected / exposed	57 / 244 (23.36%)	64 / 243 (26.34%)	
occurrences (all)	57	64	
Musculoskeletal and connective tissue disorders			
pain			
subjects affected / exposed	10 / 244 (4.10%)	16 / 243 (6.58%)	
occurrences (all)	10	16	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 244 (0.00%)	1 / 243 (0.41%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Slow inclusion resulting in a longer trial period.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30792154