Clinical trial results:
Efficacy of Metformin in Pregnant Obese Women, a Randomised Controlled Trial.

Summary

EudraCT number	2009-017134-47
Trial protocol	GB
Global end of trial date	30 April 2015

Results information

Result version number	v1 (current)
This version publication date	04 July 2020
First version publication date	04 July 2020
Summary attachment (see zip file)	SAP (EMPOWaR signed SAP_Nov 2014.pdf) PUBLICATION (EMPOWAR Publication LANCET 2015.pdf)

Trial information

Trial identification

Sponsor protocol code	EMPOWaR

Additional study identifiers

ISRCTN number	ISRCTN51279843
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	CTA Number: 01384/0217/001-0001, UKCRN Ref: 8851, NIHR FUNDER REF: 8/246/09, Scotland A Research Ethics Committee: 10/MRE00/12

Notes:

Sponsors

Sponsor organisation name	University of Edinburgh
Sponsor organisation address	47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Marise Bucukoglu, University of Edinburgh, marise.bucukoglu@ed.ac.uk
Scientific contact	Marise Bucukoglu, University of Edinburgh, marise.bucukoglu@ed.ac.uk
Sponsor organisation name	NHS Lothian
Sponsor organisation address	47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Dougla Young, NHS Lothian, douglas.young@luht.scot.nhs.uk
Scientific contact	Dougla Young, NHS Lothian, douglas.young@luht.scot.nhs.uk

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	30 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2015
Global end of trial reached?	Yes
Global end of trial date	30 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to determine if metformin, administered to obese women during pregnancy, reduces the future life risk of obesity and metabolic syndrome in their babies.

Protection of trial subjects:

Participants who fulfilled all the potential eligibility criteria and who express an interest in the study had a blood test for renal and liver function and a formal glucose tolerance tests. These tests were performed after consent for the study is signed but before randomisation and women excluded where appropriate.

Background therapy:

None

Evidence for comparator:

An intervention with the drug metformin (an insulin sensitizing agent) using a comparator placebo to measure the outcome birthweight centile, a surrogate marker of future life risk of obesity and metabolic syndrome.

Obesity causes adverse pregnancy outcomes, with a particular focus on insulin resistance (IR). Metformin reduces insulin resistance and is widely used to treat type II diabetes. Metformin has been shown to be safe during pregnancy and the National Institute for Health and Clinical Excellence (NICE) in the UK now recommends metformin as an alternative to insulin in women with established diabetes in pregnancy.

Birthweight centile is an appropriate surrogate marker for the lifetime risk of obesity and metabolic syndrome. Increasing evidence suggests that adult obesity has its origins at or prior to birth, and that intrauterine events leading to high birthweight cause later life obesity.

Actual start date of recruitment	01 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 449
Worldwide total number of subjects	449
EEA total number of subjects	449

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)	449
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

449 obese pregnant women in the UK were recruited between 01st Feb 2011 and 16th Jan 2014

Pre-assignment

Screening details:

Participants who fulfilled the intial eligibility criteria were sent an invitation letter and if women agreed they were consented to have a blood test. The results of which confirmed eligibiltiy prior to randomisation. Women were excluded, if they were identified with Gestational Diabetes, liver or Kidney disease.

Period 1

Period 1 title	Overall Trial (overall 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:

Blinding was conducted externally by Merck Sante who supplied both the treatments. Unblinding envelopes (emergency or otherwise) were supplied to the local pharmacist. The pharmasist collected the name of the clinician requesting the unblinding, the reasons for it and sent notification of any unblinding to the sponsors.

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin

Arm description:

Metformin (Glucophage) 500mg film-coated tablet (500- 2500mg) maximum tolerated dose.

Arm type	Active comparator
Investigational medicinal product name	Metformin
Investigational medicinal product code	PL 03759/0012-0013
Other name	Glucophage
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Women prescribed metformin tablets up to 2500mg from 12-16 weeks gestation and will stop once they have delivered their baby.

Women will be asked to start with 500mg metformin (1 tablet, Once Daily) taken with food, increasing in week 2 by an increment of 500mg per day (in other words to 1 tablet, twice daily). Week 3: a further increment of 500mg per day (in other words to 1 tablet, three times daily). In the fourth week the women will increase the evening dose of metformin by a further 500mg and in the fifth week the morning dose will also be increased by a further 500mg.

Arm title	Placebo

Arm description:

Matching Placebo

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

Dosage and administration details:
500mg up to 2500mg

Number of subjects in period 1	Metformin	Placebo
Started	226	223
Completed	214	220
Not completed	12	3
Consent withdrawn by subject	4	1
Stillbirth	2	-
miscarriage	4	-
Lost to follow-up	1	-
Termination of pregnancy	1	2

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	449	449	
Age categorical			
Pregnant women			
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			
arithmetic mean	28.7		
standard deviation	± 5.8	-	
Gender categorical			
Pregnant women			
Units: Subjects			
Female	449	449	
Male	0	0	

End points

End points reporting groups

Reporting group title	Metformin
Reporting group description: Metformin (Glucophage) 500mg film-coated tablet (500- 2500mg) maximum tolerated dose.	
Reporting group title	Placebo
Reporting group description: Matching Placebo	

Primary: Z score of birthweight percentile

End point title	Z score of birthweight percentile
End point description:	
End point type	Primary
End point timeframe: Birth	

End point values	Metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214	220		
Units: g				
arithmetic mean (standard deviation)	0.2664 (± 1.0179)	0.2680 (± 1.0055)		

Statistical analyses

Statistical analysis title	BirthWeight Centile
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	434
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05
Method	t-test, 2-sided

Notes:
[1] - Intention to Treat

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All AEs and SAEs were recorded from the time a participant was randomised until after the last baby is born and discharged from hospital or the end of the postnatal period (28 days after the birth), which ever is sooner.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	0

Frequency threshold for reporting non-serious adverse events: 5 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Not collected. AEs recorded in participant notes only.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2010	Additional information provided to the MHRA who considered this an amended request for CTA.
20 September 2010	Protocol modified Version 2 Expanded details about the substudies PIL and consent forms amended
13 April 2011	Table of study assessments - errors corrected 1 hour GTT blood sample removed from visits Para 6.1 additional text added
30 September 2011	Change to reference range for entry liver function test clarification re exclusion criteria for GDM - in future relate just to WHO and not SIGN guidelines
01 September 2012	Revision to the protocol for clarifications and addition of new sub study.
30 September 2013	Para 6.4 amendment and additional documents created for Qualitative interviews
10 March 2014	Para 6.4 and 9.11 updated to include payment for participants and inclusion of women as controls for a vascular function, sub study.
24 September 2014	Updated protocol for clarification of outcomes to harmonise with statistical analysis plan Removal of sub-studies to which subjects were not recruited

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26165398

http://www.ncbi.nlm.nih.gov/pubmed/27606384

http://www.ncbi.nlm.nih.gov/pubmed/25588785