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HYPATIA: A prospective randomised controlled trial of hydroxychloroquine to improve pregnancy outcome in women with antiphospholipid antibodies

Submission date
26/08/2020

Recruitment status
No longer recruiting

Registration date
27/08/2020

Overall study status
Ongoing

Last Edited
03/11/2023

Condition category
Pregnancy and Childbirth

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Antiphospholipid syndrome (APS) is the combination of persisting antiphospholipid antibodies (aPL) and a previous thrombosis (blood clot) and/or pregnancy problems. Antibodies are part of the immune system, and can sometimes be directed against part of our own cells, this is known as autoimmune disease, and APS is such a problem. aPL occur in about 1% of the population, so extrapolating this to a birth rate of 800,000/year in the UK, this means 8,000 women with aPL are giving birth every year.
Women with aPL (this term includes those with APS) are more likely to have pregnancy loss. During the first 12 weeks of pregnancy, aPL can inhibit the growth of the early fetal cells and later cause blood clots in the blood vessels of the placenta in the second and third trimester (14-36 weeks). This means that the placenta is unable to supply the fetus with enough nutrition, so the fetus may stop growing, grow slowly (intrauterine growth restriction) and in extreme cases may die. Some mothers in this situation also develop pre-eclampsia (high blood pressure during pregnancy and after labour).
Pregnant women with aPL are treated with aspirin, and sometimes heparin, depending on whether they had blood clots and/or obstetric problems before. This has improved the live birth rate to over 70%.
A study of women with aPL who were taking hydroxychloroquine (HCQ) during pregnancy to treat lupus found that women taking HCQ had a better pregnancy outcome compared to women who do not take it, with fewer miscarriages and preterm births and a higher live birth rate. HCQ is safe in pregnancy, well-tolerated, and costs only £0.10 per tablet in the UK.
To find out more about this, in this study women with aPL are treated either with HCQ or a placebo (dummy drug) throughout pregnancy in addition to their usual medications, and pregnancy outcomes are compared.

Who can participate?
Women aged 18 to 45 with persistent antiphospholipid antibodies who are planning a pregnancy

What does the study involve?
Participants are randomly allocated to take HCQ or a placebo (dummy drug) as one tablet each day until delivery. Pregnancy outcomes are assessed.

What are the possible benefits and risks of participating?
There are no immediate benefits, but participation will help to find out if hydroxychloroquine has positive effects on pregnancy outcomes. It might therefore be beneficial for the individual for their future pregnancy.

Where is the study run from?
St Thomas' Hospital (UK)

When is the study starting and how long is it expected to run for?
January 2016 to December 2025

Who is funding the study?
1. National Institute for Health Research (NIHR) Research for Patient Benefit Programme (UK)
2. Guy's and St Thomas' Charity (UK)

Who is the main contact?
Prof. Beverley Hunt
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2016-002256-25

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
8.1, CPMS 37234

Study information

Scientific Title
HYPATIA: A prospective randomised controlled trial of HYdroxychloroquine to improve Pregnancy outcome in women with AnTIphospholipid Antibodies

Acronym
HYPATIA

Study objectives
Hydroxychloroquine reduces antiphospholipid antibody-mediated pregnancy morbidity.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 09/03/2018, London Bridge Research Ethics Committee (London Bridge Ethics Committee, Skipton House, 80 London Road London SE1 6LH, UK; +44 (0)207 104 8019 or +44 (0) 207 104 8124; londonbridge.rec@hra.nhs.uk), REC ref: 170254

Study design
Multicentre interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)

Prevention

Participant information sheet
See additional file ISRCTN19920789_PIS_V3.0 (added 05/09/2020)

Health condition(s) or problem(s) studied
Women with persistent antiphospholipid antibodies who are planning pregnancy

Interventions
Method of randomisation is double-blind randomisation provided by the King's Clinical Trials Unit. Participants are randomized to take a hydroxychloroquine 200 mg tablet or a placebo once daily. The total duration of treatment is maximum 12 months before pregnancy and then the individual pregnancy length (max 9 months), maximum total of 21 months treatment.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Hydroxychloroquine

Primary outcome measure
A composite of three principal aPL-related adverse pregnancy outcomes: one or more pregnancy loss(es) (either < 10 weeks gestation or beyond 10 weeks of gestation of a morphologically normal fetus documented by ultrasound or by direct examination of the fetus), premature birth of a morphologically normal neonate before 34 weeks due to any of pre-eclampsia, eclampsia, recognized features of placental insufficiency. Premature birth for other reasons will not be included.

Secondary outcome measures
Measured using patient/child medical records:
1. Pregnancy loss < 10 weeks gestation
2. Pregnancy loss > 10th week of gestation of a morphologically normal fetus documented by ultrasound or by direct examination of the fetus
3. Premature birth of a morphologically normal neonate < 34 weeks due to any of pre-eclampsia, eclampsia, recognized features of placental insufficiency
4. Gestational age at delivery
5. Birth weight, measured at delivery
6. Delivery by Caesarean section, measured at delivery
7. Apgar score < 7 measured at 5 min from delivery
8. Neonatal morbidity (bleeding or thrombotic complications, infections, congenital abnormalities)
9. Days to hospital discharge following delivery (mother and child)
10. Thrombotic events in the mother during pregnancy and 6 weeks postpartum
11. Days of neonate in special care
12. Safety and tolerability of hydroxychloroquine in the mother and in the neonate measured until 6 weeks postpartum

Overall study start date

01/01/2016

Completion date
12/12/2025

Eligibility

Key inclusion criteria
1. Women with known aPL (i.e. isolated aPL or APS) who are planning pregnancy. aPL are defined by the presence of a positive test for anticardiolipin antibodies (IgG/IgM isotypes > 95th percentile) and/or lupus anticoagulant and/or anti- beta 2 glycoprotein-I (IgG/IgM isotypes > 95th percentile), on two or more consecutive occasions more than 12 weeks apart (a positive aPL test is defined under ‘glossary and definitions’). The last positive test must be within 12 months of study entry.
2. Written informed consent to participate

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
45 Years

Sex
Female

Target number of participants
400

Key exclusion criteria
1. Women who are already pregnant
2. Allergy or adverse event to hydroxychloroquine. Hypersensitivity to the active substance, 4-aminoquinoline or any of the compounds of the IMP or placebo
3. Current treatment with hydroxychloroquine
4. Age < 18 and > 45
5. Bodyweight < 45 kg
6. Psoriasis
7. Uncontrolled epilepsy
8. Anti-Ro antibodies
9. Renal replacement therapy
10. Other severe active co-morbidities (HIV, hepatitis B, severe gastrointestinal, neurological or blood disorders)
11. Porphyria
12. History of retinopathy or newly diagnosed retinopathy
13. History of galactose intolerance, lactase deficiency or glucose-galactose malabsorption

14. History of glucose-6-dehydrogenase deficiency
15. Participation in any other IMP trial at the time of consent
16. Previous pregnancy failure on hydroxychloroquine

Date of first enrolment
01/07/2017

Date of final enrolment
31/12/2024

Locations

Countries of recruitment
Denmark

England

Italy

Netherlands

United Kingdom

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
University College London Hostpitals
London
United Kingdom
NW1 2BU

Study participating centre
Imperial College London
London
United Kingdom
NW2 1NY

Study participating centre

University Hospitals Oxford
Oxford
United Kingdom
OX3 9DU

Study participating centre
Liverpool Women’s Hospital
Liverpool
United Kingdom
L8 7 SS

Study participating centre
Addenbrook's University Hospital Cambridge
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Rigshospitalet Copenhagen University Hospital
Copenhagen
Denmark
2600

Study participating centre
Odense University Hospital
Odense
Denmark
5000

Study participating centre
Academic Medical Centre
Amsterdam
Netherlands
1105

Study participating centre

Turin University Hospital
Turin
Italy
10124

Sponsor information

Organisation
Guy's and St Thomas' NHS Foundation Trust

Sponsor details
King’s Health Partners Clinical Trial Office
16th Floor
Tower Wing
Guy’s Hospital
Great Maze Pond
London
United Kingdom
SE1 7EH
+44 (0)20 71885732
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Sponsor type
Hospital/treatment centre

Website
http://www.guysandstthomas.nhs.uk/Home.aspx

ROR
https://ror.org/00j161312

Funder(s)

Funder type
Government

Funder Name
Research for Patient Benefit Programme

Alternative Name(s)
NIHR Research for Patient Benefit Programme, RfPB

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Guy's and St Thomas' Charity

Alternative Name(s)
Guy's and St Thomas' Charity, Guy's and St Thomas' Foundation, GSTTFoundation

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
On successful completion of the HYPATIA study, the results of the study will be disseminated to medical professionals and our patients. The final results will be submitted to major peer-review journals.
The researchers will present these findings at national and international conferences including obstetric, rheumatologic, haematological and vascular medicine conferences. They are well served by their PIs who come from disparate clinical areas and will therefore disseminate the results to a wide audience. As clinical guidelines are based upon evidence-based medicine, this multicentre trial is likely to reach clinical specialists all over the world.
Locally in the UK the researchers will update their teams about the outcome of the study and revise and update standard of care protocols. The treatment protocols are under continuous revision in order to improve the care of patients and the decisions of major changes comply with the principles of evidence-based medicine and, if not available, based on expert opinions.
The researchers will also present their findings at patients' days of Thrombosis UK & World Thrombosis Day.

Intention to publish date
01/07/2026

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	01/09/2017	27/08/2020	Yes	No
Participant information sheet	version V3.0		05/09/2020	No	Yes
Protocol file	version 10.0	12/12/2022	03/11/2023	No	No