# HYPATIA: A prospective randomised controlled trial of HYdroxychoroquine to improve Pregnancy outcome in women with AnTIphospholipid Antibodies

## Introduction

This information sheet describes a research study that is taking place at several European University Hospitals. Guys' and St Thomas' Hospital in London is organising the trial. Your health care provider is recruiting participants for the study, and providing care. The study is called 'HYPATIA' and is assessing whether the tablet hydroxychloroquine in addition to standard treatment in mothers with antiphospholipid antibodies leads to more mothers having successful pregnancies.

## Invitation

You have antiphospholipid antibodies or antiphospholipid syndrome and you are currently planning for pregnancy, and so we would like to invite you to take part in the HYPATIA study.

Before you decide whether or not you are willing to participate, we would like to explain why the research is being done and what it will involve. Please take time to read the following information carefully and please feel free to discuss it with friends, relatives and your health care providers.

This information sheet explains the purpose of this study and what will happen to you if you decide to take part.

A member of the research team will go through this information leaflet with you. Please ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

Please be assured that taking part in this research is entirely voluntary. If you decide not to take part, your medical care will not be affected in any way.

## What is the purpose of the study?

Those with antiphospholipid antibodies may have an increased risk of having blood clots and pregnancy problems because blood becomes more 'sticky' than usual.
Antiphospholipid antibodies are present in about 1% of the population. Knowing that there are 800,000 births a year in the United Kingdom, this means 8,000 pregnancies are probably affected by antiphospholipid antibodies every year.

Women with antiphospholipid antibodies are more likely to have pregnancy loss and/or small babies and/or pre-eclampsia (high blood pressure and protein in the urine). During the first twelve weeks of pregnancy, antiphospholipid antibodies can limit the growth of the early cells and cause miscarriage. In the later weeks of pregnancy, it can cause blood clots to occur in the placenta. This means that the placenta is unable to supply the fetus with enough nutrition, so the fetus may grow slowly (intrauterine growth restriction) and in extreme cases may die. Some mothers in this situation also develop pre-eclampsia.

Current treatment for pregnant women with antiphospholipid antibodies is to give blood thinners (antithrombotic treatment) such as aspirin tablets, and sometimes heparin injections, depending on whether they had blood clots and/or pregnancy problems before. This has improved the live-birth rate to more than 70%. We have looked back at our women patients in St Thomas's with antiphospholipid antibodies who were given hydroxychloroquine during pregnancy to treat a related disease called lupus (or systemic lupus erythematosus). The study suggested, but did not prove, that taking hydroxychloroquine better pregnancy outcome compared to women who do not take it, with fewer miscarriages & preterm births and a higher live birth rate.

The purpose of the HYPATIA study is to answer the question as to whether hydroxychloroquine may help improve pregnancies in women with antiphospholipid antibodies. We are therefore proposing the first 'randomised controlled trial', treating consenting women with antiphospholipid antibodies either with hydroxychloroquine or a similar tablet without hydroxychloroquine (called a placebo) throughout pregnancy in addition to their usual medications, and comparing the pregnancy outcomes. 'Randomised controlled trial' means that women will be assigned to either hydroxychloroquine or placebo treatment by chance, which is the best way in clinical research to find out whether treatment works.

**Is hydroxychloroquine safe in pregnancy and for my child?**

Hydroxychloroquine is currently unlicensed in pregnancy, but it is known to be compatible with pregnancy and breastfeeding; indeed hydroxychloroquine is widely used in patients with conditions such as systemic lupus erythematosus in pregnancy. For more than a decade we have used hydroxychloroquine in pregnant women, which was based on research literature suggesting that several hundred women who were treated with hydroxychloroquine during pregnancy has normal healthy babies. More recently we reviewed the literature again and published our findings as the guideline for the British Society of Rheumatology (BSR). Since the first publication over a decade ago, over 800 more reports on women taking hydroxychloroquine during pregnancy did not reveal any birth defects in baby's born to mothers who took hydroxychloroquine before and during pregnancy. Therefore current national and international medical guidelines state that hydroxychloroquine is safe in pregnancy

**Why have I been invited?**

You have been invited to take part as you have antiphospholipid antibodies on more than one occasion in blood testing, and you are planning for pregnancy.

**Do I have to take part?**

No. It is entirely up to you to decide whether or not to take part. If you do, you will be asked to sign a consent form. If you later change your mind about participating, you will be free to withdraw at any time and without giving a reason.

If you decide not to take part, or if after joining the study you decide to withdraw, the standard of care you receive will not be affected.

**Am I eligible?**

When you are seen in clinic, your doctor may find you are eligible for the HYPATIA study. This means that you in the past have been tested positive for antiphospholipid antibodies on two or more occasions more than twelve weeks apart and you are currently planning for pregnancy. If your bloods tests are not up to date, we might take new blood tests and review your medical history as we would do normally before a pregnancy. These results will be used for the HYPATIA study.

Finally, it is now recommended that all patients who are being treated with hydroxychloroquine have an eye check before they start taking hydroxychloroquine and afterwards on an annual basis if they keep taking it . This is to rule out any problems with the back of your eye (the retina), we will explain further down why this is important.

This information will be part of the eligibility check.

**What will happen to me if I take part?**

All who choose to take part in the HYPATIA study will be allocated treatment through randomisation using a computer and your health professional will not know whether you will be receiving hydroxychloroquine or placebo. You have an equal chance of receiving either treatment or placebo but you will not be able to choose.

You will be asked to start taking the trial medication (either hydroxychloroquine or placebo) once daily in addition to your usual medication after you have had your eyes checked and will be seen in our clinic as usual (but at least on a 3 monthly basis) during your pre-pregnancy period, during pregnancy and after you have given birth. You will also have a blood test every three months as we do normally during pregnancy.

You will be offered an eye check before starting the medication, (to check that you do not have any pre-existing problems with your eyes). After 12 months and after stopping the study medication, you will have a repeat eye check. **Imperial Hospital** participants will

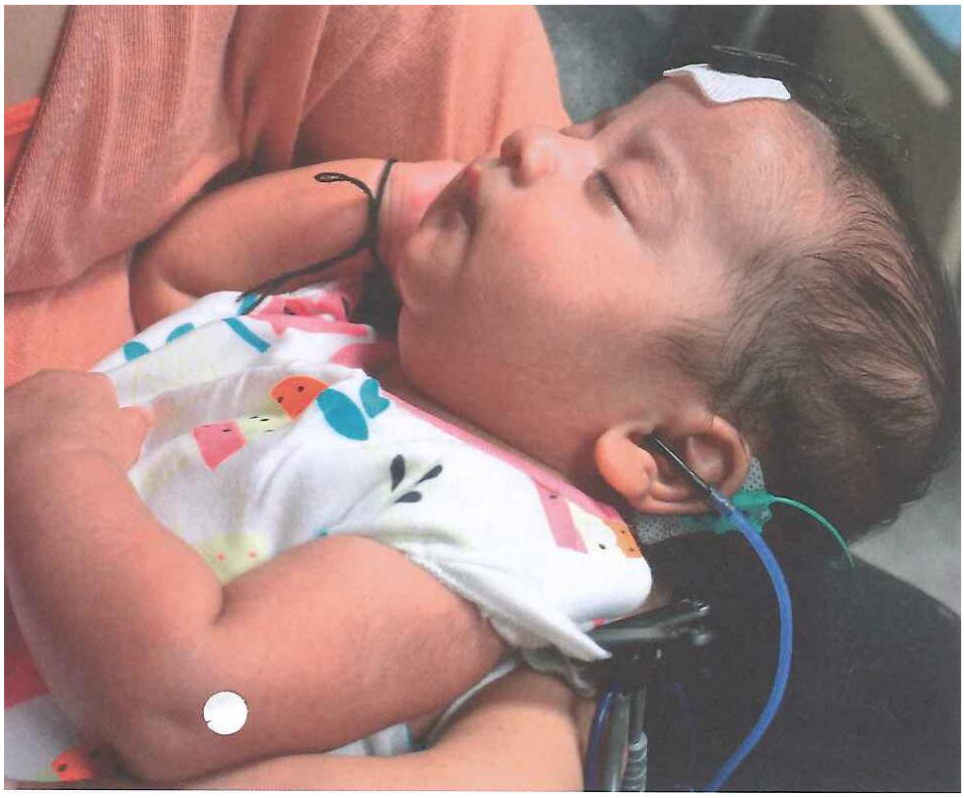
attend the ophthalmology department at Guy's & St Thomas' Hospitals 249 Westminster bridge Rd London SE1 7EH for their eye exams. You will have a physical exam at each visit as as you would normally (this includes that the doctor listens to your heart and lungs).
If you do not fall pregnant within a period of 12 months from randomisation, you will be asked to stop the medication. If you become pregnant you will be asked to stop the study medication once you have delivered your baby. There will be not particular long-term follow up as part of the HYPATIA study, however, most patients will remain under our care due to their antiphospholipid antibodies. This will be decided on an individual basis.

**What will happen to my baby if I take part?**

Hydroxychloroquine is widely used in pregnant women (outside of medical studies) and babies born to these mothers are usually not monitored. For it is recommended by the European League against Rheumatism (EULAR) and the British Society for Rheumatology (BSR) in pregnant women and breastfeeding women who require immunomodulation (which means a medication to 'calm down' the bodies defence mechanism).
A related drug to hydroxychloroquine, called chloroquine, has in the past been associated with ear and eye toxicity. For that reason, the safer form of the drug hydroxychloroquine is now widely used.

For babies born to mothers who take part in the HYPATIA study we will conduct an ear and an eye test within six weeks of delivery as part of the trial.
The eye test includes an exam of the back of the eye (the retina) by an Ophthalmologist (a doctor who specialises in care of the eye). For this exam the babies will receive one eye drop in each eye to dilate the pupil. It is a safe test to perform.
The ear test is a special hearing test called a diagnostic Auditory Brainstem Response (ABR) along with diagnostic transient-Evoked otoacoustic emissions (TEOAE). To do these test the audiologist will place a small soft tipped earpiece in the outer ear part of your baby's ear. The earpiece sends clicking sounds down the ear. The inner part of the ear, known as cochlea, usually produces a response when it receives sounds. The test equipment can pick up this response. For the ABR, small sensors are placed on your baby's head. Sounds of different frequencies are played into your baby's ears. A computer records the response so the audiologist can measure how well your baby's ears respond. Your audiologist will tell you what the results mean. These tests are more sensitive than the normal newborn hearing screen. **Imperial and UCLH hospital** participants will be asked to take babies born

during the trial to St Thomas' Hospital 249 Westminster Bridge Rd for the eye test and the hearing test appointment. (the picture below shows a baby having a TEOA and ABR and is taken from the official NHS webpage)



**Expenses and payments**

We are unable to pay you for taking part in the HYPATIA study. We will do our best to not cause any additional visits to the hospital. Most of your study visits will coincide with your regular clinic visit. However, in case any extra visits arise, we will reimburse your travel costs. The trial medication will be provided by us for free.

**What will I have to do?**

If you agree to take part in the HYPATIA study, you will be asked to attend your usual clinic appointments.

**What are the potential disadvantages and risks of taking part?**

**Side-effects of treatment**

Hydroxychloroquine is a well-tolerated medicine. Occasionally patients have a skin rash on starting due to an allergy to the packing in the tablet. Occasionally some patients experience gasto-intestinal disturbances (nausea) or headaches, but these side-effects usually disappear. Side-effects less frequently seen are ECG (electrocardiography) changes, convulsions, retinal changes, discolouration of the skin, nails and mucous membranes. Very rare side-effects include blood disorders, mood disturbances, muscle problems (myopathy), other skin conditions (such as acute generalised exanthematous pustolosis, exfoliative dermatitis, Stevens Johnsons syndrome, photosensitivity) and liver problems. On very rare occasions hydroxychloroquine accumulates on the back of the eye (the retina) and can cause visual problems. This is usually seen after years of use (10 years of use) of hydroxychloroquine or after very high doses (up to 1 gram per day). The British and American guidelines on how to monitor patients taking hydroxychloroquine have recently been updated, and they now recommend an eye check in the beginning of hydroxychloroquine treatment and follow up checks.

You will be asked to stop taking the medicine and you will be withdrawn from the study if you develop side effects or if you experience any unusual or concerning changes in your health. As mentioned above we will take a blood sample every three months to ensure that you tolerate hydroxychloroquine. You should inform your study team about any adverse events and medical concerns you may have.

If you have psoriasis you cannot participate in the HYPATIA study as your condition may worsen. If your bodyweight is below 45 kg you will also not eligible for the HYPATIA study. Lastly, if you have problems with the back of your eye, you will not be eligible to be part of the study.

**What are the possible benefits of taking part?**

If the results of the HYPATIA study shows that hydroxychloroquine in addition to standard treatment is beneficial to pregnant women with antiphospholipid antibodies, this may affect your treatment in possible future pregnancies and treatment of women with antiphospholipid antibodies around the world

**What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [insert Principal Investigator name, telephone number and e-mail address]**.**

**If you remain unhappy and wish to complain formally, you can do this through the** [insert local PALS, telephone number and e-mail address & location].

**The PALS team are based** [insert local PALS, telephone number and e-mail address & location]**.**

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for legal action for compensation **against Guy's and St Thomas' NHS Foundation Trust** but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

**What happens if I don't want to carry on with the study?**

If you withdraw or are unable to continue the study for any reason, we will only use the information that you have already given us to that point; unless you ask us to remove all your information

**What happens if new information about hydroxychloroquine becomes available?**

In case new information becomes available whilst taking part in the HYPATIA study you will be informed and asked if you would like to continue in the study. You would then have to sign a new consent form.

**Will my taking part in this study be kept confidential?**

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

**Contacts for further information**

Your local contact for the study is:
[INSERT NAME]
[INSERT CONTACT DETAILS]
Local Researcher: [Insert name and contact details of local investigator]

**This completes Part 1 of the Information Leaflet. If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making your decision**.

# Patient Information Leaflet: Part 2
# The HYPATIA study

## A prospective randomised controlled trial of HYdroxychloroquine versus placebo during Pregnancy in women with AnTIphospholipid Antibodies

**Will information about me be kept confidential?**

Yes; we follow professional, ethical and legal practice and so all information, which is collected about you during the course of the research will be kept strictly confidential and you will be allocated a study number. Allocating a study number means, that your personal data will not be used and the study number will be used instead, therefore your information will be pseudonymised . Your initials and date of birth will be sent to the King's College London Clinical Trials Unit at the time of trial entry. Any information about you which leaves the hospital will have your name and address removed.

Data collected for the study will be coded and the Chief Investigator will act as custodian of the data and regulate access. Authorised persons (e.g. representatives from the Sponsor (Guy's and St Thomas' NHS Foundation Trust), regulatory authorities and Research & Development departments) may need to look at information collected about you, including your medical notes. Confidentiality will be maintained at all times.

With your permission, your GP will be notified that you are taking part in this study. He/she will be provided with a copy of this Patient Information Leaflet.
In order to collect all relevant data on your pregnancy (for example how you delivered your child etc) and child (for example your child's gender, how much they weigh etc), we will ask for your permission to access your medical records and your child's medical records. Medical records for trial patients are kept for 25 years. Trial related documents will be kept for 25 years in accordance with the UK regulations.

**What will happen to any samples I give?**

The routine blood sample we take to ensure that you tolerate hydroxychloroquine will be taken on the day of your routine appointment as this is standard of care.

**What will happen to the results of the research study?**
The results of the research will be published in scientific journals over the next few years. You will not be identified in person in any report or publication arising out of this study. If you wish, you can request a summary of the main results of the study when available.

**Who is organising and funding the research?**
The HYPATIA study is being co-ordinated by the King's College Clinical Trials Unit based in London.

Guy's and St Thomas' NHS Foundation Trust is the Sponsor for this study.

The study is funded by the National Institute for Health Research – Research for Patient Benefit (NIHR RfPB). The study is part of Dr Schreiber's PhD thesis.

**Who has reviewed the study?**
The study has been reviewed and given a favourable opinion by the London Bridge Ethics Committee and the Medicines and Healthcare Products Regulatory Agency (MHRA) [*please amend for relevant competent authorities for EU sites*]. We have also worked with patient representatives who have regularly reviewed the study protocol and will continue to work with us throughout the study.

**What to do if you wish to take part in the study?**
If you wish to participate in this study you will be asked to sign a consent form after discussion with the researcher. You will also be given a copy of this information leaflet and a signed copy of the consent form to keep.

If you decide that you do not want to take part, it will have no effect on any treatment or care that you will receive.

Thank you for taking time to read this information leaflet and for considering the study.