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and Great Ormond Street Hospital for Children NHS Trust

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The PONTI Study **Prevention Of Neural Tube Defects by Inositol, in conjunction with folic acid**

Participant Information Leaflet

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We are inviting women to take part in a research study on neural tube defects. If you have experienced a pregnancy involving a neural tube defect, and are now planning a further pregnancy, we are keen to hear from you. First, it is important for you to understand why the research is being carried out, and what it will involve. Please take time to read the following information carefully and to discuss it with others, if you wish. Feel free to ask us if there is anything that is not clear, and to take time to decide whether or not you wish to participate.

What is the purpose of the study?

One of the first parts of the body to develop, within the first 28 days of pregnancy, is the neural tube, from which the brain and spinal cord develop. Neural tube defects, such as spina bifida, occur when the neural tube fails to develop properly. Related defects are anencephaly (the absence of a brain) and encephalocele (a malformation of the brain and skull). We don't know why the neural tube develops incorrectly in some pregnancies, but it is thought to be a combination of genetic and environmental factors.

An important environmental factor for the developing fetus is folic acid, a B group vitamin. It has been shown conclusively in women who have had a pregnancy affected by a neural tube defect, that folic acid can reduce their risk of having a second affected pregnancy by 70%.

But what about the other 30%? This is where inositol comes in. Scientists now think that some types of neural tube defects are resistant to folic acid. Animal studies have suggested that another vitamin called inositol may help in these cases. In addition to this, there have been several case studies where women who have had two previous pregnancies affected by neural tube defects delivered a healthy unaffected baby when they took inositol in their third pregnancy.

We are conducting this study in order to test the idea that inositol, alongside folic acid, can further reduce the number of pregnancies affected with neural tube defects.

What will happen to me if I take part?

If you decide to take part in the study we will randomly allocate you to one of two groups. One group will receive the recommended dose of folic acid PLUS inositol. The other group will receive the recommended dose of folic acid PLUS a placebo. A placebo is a dummy treatment such as a pill which looks like the real thing but is not. It contains no active ingredient. The study will be conducted as a "double blind" clinical trial. This means that neither you, nor your doctor, nor the trial co-ordinator, will know which treatment group you are in (although if your doctor needs to find out he/she can do so). The information will be coded, and the code can be broken if necessary.

You will need to take three tablets (one folic acid + two inositol or placebo) each day, from the time you start planning for a pregnancy until the end of the 12th week of pregnancy. We will provide you with the tablets every three months at no cost. The trial co-ordinator will keep in regular contact with you by telephone to make sure there are no problems. You will be asked to provide your personal contact details and information about the upcoming pregnancy, once known.

As part of the study, you will also need to provide three urine samples: the first, before you start taking the tablets, the second when you have taken the tablets for 6 weeks, and the third when you become pregnant. We will send you a urine collection bottle and full details of how to collect your urine samples, in good time before a sample is needed. The urine samples will enable us to determine the level of inositol in your body at various times during the study.

When you know the final outcome of your pregnancy you will need to complete a "pregnancy outcome" questionnaire. This will involve answering questions about the pregnancy and whether it was affected by a neural tube defect or any other birth defect. We will also ask you for your baby's name, sex, date of birth and weight at birth. We may need to contact your GP or other health care professionals to gain further information.

Do you have to take part?

We are inviting all women to participate in the trial if they have experienced a pregnancy with an neural tube defect and are now are planning a further pregnancy. It is entirely up to you to decide whether or not you wish to take part. If you decide to participate, you need to contact us by telephone or e-mail (for details see bottom of page). Ideally we would like to hear from you as soon as you start planning your next pregnancy. You can also change your mind, after starting in the trial: you are free to withdraw at any time, without giving a reason. If you do not feel able to take part it will not in any way affect the medical or other care your family receives. Please note that you if decide to participate you will need to inform your GP. We will provide you with a letter and information sheet for you to give to your GP explaining all about the trial.

Am I suitable for this study?

When you first contact the trial co-ordinator, she will arrange for you to complete a telephone questionnaire to determine whether you are suitable for the study. This will involve asking you questions about the previous pregnancy, in which your baby had a neural tube defect, and other aspects of your health. We understand that talking about the previous affected pregnancy may cause some distress. We may need to contact your GP or other health care professionals to gain further information at this stage.

What are the benefits to me of taking part?

This study may or may not help your unborn baby directly. This will depend on which treatment group you are allocated to and whether it is true that inositol can prevent neural tube defects. Overall, we hope that the information from this study will help doctors to prevent future pregnancies from being affected by a neural tube defect. However the results of this study will take some time to be completed, and will not be available during the course of your pregnancy.

What are the risks and discomfort?

We do not anticipate any risk or discomfort to be caused by participating in this study. Inositol occurs in human cells and is present in many foods. On average each day we consume about 1 g of inositol. Previous clinical trials of inositol in adults with other disorders have shown that taking less than 6 g a day produces no side effects. The tablets you may be allocated to take each day will contain 1 g of inositol. If you do not conceive after taking the tablets for twelve months we will stop treatment to prevent any unknown effects that might result from long-term treatment.

If you do experience any side effects during the study, then you need to contact the trial co-ordinator immediately (for details see top of information sheet).

What else should I know?

Whilst participating in the study, certain medications will not be permitted before and up to the twelfth week of pregnancy. These include anti-epileptics such as valproate, additional inositol supplements, additional folic acid supplements and multi-vitamin preparations (including vitamin preparations for pregnant women) that contain folic acid or inositol. Vitamin preparations that do not contain folic acid or inositol are acceptable.

All the women who participate in this study will receive folic acid at the dose typically used in pregnancies at risk of a neural tube defect. This means you do not need to take any more folic acid before and up to the twelfth week of pregnancy.

This study is being funded by the Medical Research Council. This funding will cover all necessary expenses including the manufacture of the tablets.

This is a short-term study which will run for two years. We will no longer be recruiting any new patients after the 30/9/2012. We will also stop providing treatments for participants after 30/9/2012 unless you are pregnant. A larger-scale trial is planned for the future - please contact us for further details.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the trial co-ordinator will tell you about it and discuss with you whether you want to continue in the study. It is then up to you to decide whether you wish to continue to participate. If, on reviewing the information, the researchers consider it to be in your best interests to withdraw from the study, they will contact you to explain the reasons.

Who will have access to the samples and case/research records?

Any information you give us, and the results of the urine tests, will be kept completely confidential. Only the researchers listed above will have access to the data collected in the course of this study. For the purpose of dispensing and sending the medication to you, your contact details will be made available to the relevant pharmacy staff of Great Ormond Street Hospital for Children NHS Trust. Representatives of the Research Ethics Committee and the MHRA (Medicines

and Health Care Products Regulatory Authority) may require access to data for monitoring and auditing purposes. The use of some types of personal information is safeguarded by the Data Protection Act 1998 (DPA). The DPA places an obligation on those who record or use personal information, but also gives rights to people about whom information is held. If you have any questions about data protection, please contact the Data Protection officer via the switchboard on 020 7405 9200 extension 5217. The results from our project will be published as papers in medical journals. No data will be published that allows participating individuals to be identified in any way.

What about the results of the tests?

The results of the tests we perform on your urine samples will not be sent to you or discussed with you or your doctors. If you wish to discuss these further then please contact the trial co-ordinator.

What are the arrangements for compensation?

This research project has been approved by the University College London Hospital's Committees on the Ethics of Human Research, an independent Research Ethics Committee which believes that there is no risk to your unborn child. However, research can carry unforeseen risks and we want you to be informed of your rights in the unlikely event that any harm should occur as a result of taking part in this project. This research is covered by a no-fault compensation scheme which may apply in the event of any significant harm resulting to you or your unborn child. Under this scheme it would not be necessary for you to prove fault. You also have the right to claim damages in a court of law. This will require you to prove a fault on the part of the hospital/institute and/or any manufacturer involved.

Who do I speak to if I would like an independent opinion?

If you require an independent opinion about the study may we suggest you talk with your GP or any other health professional involved in the care of your pregnancy. You may also wish to contact one of the two patient support groups:

- Antenatal Choices and Results (ARC; <http://www.arc-uk.org/>)
- Association for Spina Bifida and Hydrocephalus (ASBAH; <http://www.asbah.org/default.html>).

Who do I speak to if I have further questions or worries?

Please contact the PONTI team to discuss any questions or worries about the study. Contact details are given at the top of this information sheet. If required, a time can be arranged for one of the medically-qualified senior researchers to contact you.

If you have any complaints about the way in which the project is being or has been conducted, in the first instance please discuss them with the PONTI team. If the problems are not resolved, or you wish to comment in any other way please contact the Chairman of the Research Ethics Committee, by post via The Research and Development Office, 1st floor, Maple House, 1st Floor, Maple House, 149 Tottenham Court Road, London, W1P 9LL.

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