

PATIENT INFORMATION LEAFLET: PI2 TRIAL

SUMMARY

Name of principal investigator: Dr Cathy Cluver

Name of research midwife:

Contact number:

What is pre-eclampsia?

Pre-eclampsia is a serious condition that is only found in pregnancy.

It is associated with high blood pressure and can affect different parts of your body like the kidneys.

At present there is no effective treatment for pre-eclampsia except for birth of your baby but premature birth may cause medical problems for the baby.

For this reason we will keep you in hospital to monitor your pregnancy and health so that we can try and safely prolong your pregnancy to prevent your baby from possibly suffering some of the complications of a premature birth. This is the normal care that all women with early pre-eclampsia receive.

The trial:

You are being invited to participate in a clinical trial that may help with finding a treatment for pre-eclampsia. This trial is to determine whether metformin (a medication that is commonly used for treating diabetes) can treat pre-eclampsia. This treatment may or may not improve your condition and may or may not delay the need for your baby to be born prematurely. This medication is safe in pregnancy and has been used by many pregnant patients.

If you decide to take part in the trial you may be given metformin tablets or you may be given a placebo (dummy) tablet. You, the doctors and the nurses will not know what treatment you are being given. There is a 1 in 2 chance that you will be given the placebo or the metformin tablet. Both tablets will look identical. Everyone in the study will receive exactly the same treatment as patients that are not in the study. If you are involved in the study you may have extra ultrasounds and we may need to collect extra blood from you while pregnant and at delivery a sample of blood from the cord and part of the placenta when you deliver.

If you would like to be involved in the clinical trial it will be important to start the medication as soon as possible. If you have any further questions about the study you can ask us questions at any time and we can be contacted on the telephone numbers given above.

BACKGROUND INFORMATION ON PRE-ECLAMPSIA

What is pre-eclampsia?

Pre-eclampsia is a serious medical condition that affects only pregnant women. It is caused by products released from the placenta that cause the mother to then suffer from high blood pressure. It commonly also affects the kidneys, and this is seen by measuring the amount of protein in the urine. Pre-eclampsia can affect other organs in the body and can cause liver problems, blood clotting problems, and in severe cases seizures and stroke.

How do we treat pre-eclampsia?

At present there is no known treatment for this condition apart from delivery of the baby and the placenta. Early delivery can be associated with medical problems for the baby. Babies that are born too early can suffer from breathing problems, problems with their intestines and can have bleeding in the brain. We know that every day in early pregnancy can make a difference to the babies' survival and for this reason we admit pregnant mothers with this condition early in pregnancy to the hospital. Many studies have shown that this is a safe form of management as long as mothers are monitored very closely in the hospital.

When will I have my baby?

When you reach 34 weeks we will consider delivering the baby as we know that most babies born at this age do well. If you develop any complications or if the baby is in distress we will deliver your baby before we reach 34 weeks.

What treatment will I receive?

During your stay in hospital we will be monitoring your blood pressure. We will be checking your urine everyday to see how much protein you are losing through the kidneys. Twice a week we will be doing blood tests to monitor for complications. A doctor will be seeing you every day to check you and your baby's health. Every week there will be a large number of doctors that come and do a ward round to make sure that you and your baby are well. Your baby will be monitored 4 times a day with a monitor on your tummy. Ultrasound examinations of your baby will be performed.

You will receive treatment to control your blood pressure if it is needed and we may prescribe some pregnancy vitamins and supplementations. If you lose a large amount of protein in your urine you may be started on a treatment to prevent blood clots.

INVITATION TO BE INVOLVED IN THE PI2 TRIAL

You are being invited to participate in a research project to find out whether a drug called metformin can be used to treat pre-eclampsia. The name of the study is the Pre-eclampsia Intervention 2 (PI2) Trial. It is important that you read all the information provided about the trial before you decide to take part and that you understand why we are doing the research and what you would need to do if you were involved in the study. If you have any questions about the trial you can ask your doctor, the midwives or any of the staff from the research project. You can talk to any of the other women who have decided to be involved or not involved in the study.

Why are we doing this study?

Pre-eclampsia is a dangerous condition in pregnancy. If we could find a treatment for pre-eclampsia we would possibly be able to save many pregnant mothers and babies. There is no known treatment for pre-eclampsia. Other researchers in England are doing studies with a drug called pravastatin but have not finished their study yet.

What is the purpose of this study?

Recent research has shown that there are substances produced by the placenta that can cause pre-eclampsia. Work done in a laboratory in Melbourne, Australia has shown that these substances may be reduced by metformin. The PI2 trial is the first trial in the world that will look to see if metformin can be used to treat pre-eclampsia.

Why have I been invited to be involved in this study?

You have been invited to be in this study as you have been diagnosed with pre-eclampsia. We would like to include 150 women with pre-eclampsia in this study.

Do I have to be in the study?

It is voluntary to be in the study and it is your choice to be involved or to not be involved. Your treatment will not be any different if you are not involved in the study. You can decide at any stage in the pregnancy to withdraw from the study and you will not have to give a reason for why you want to withdraw.

Will I need to do anything extra if I am in the study?

Once you have decided to be in the trial you will need to sign an informed consent document. This form will say that you want to be involved in the study and that you have read and understood the information we have given you about the trial.

You will then need to take extra tablets each day until the baby is delivered. One of the research team will visit you every day to see how you are feeling and to collect information about your pregnancy. When your routine blood tests are done we will take an extra sample of blood for the study. On the first day that you take the medication we will need to take an extra sample of blood. We may need to do extra ultrasound examinations of your baby. Once your baby is born and the cord has been cut we will take a small amount of blood from the placenta. We will take a small sample from the placenta which will be sent for testing.

We will follow you up after the delivery of the baby. The samples taken may be sent overseas for further testing to try to find a treatment for pre-eclampsia. Only tests related to finding a cure for pre-eclampsia will be performed on the samples taken.

Is metformin treatment safe in pregnancy?

Metformin is used in pregnancy to treat diabetes. There have been no reports of fetal problems in humans or complications in human pregnancies caused by this medication or other medications in the same class of drug.

Are there any side effects of metformin?

All drugs may have side effects. Side effects that have been associated with the use of metformin include headache, diarrhea, nausea, flatulence, abdominal pain, constipation and a dry mouth. There are certain drugs that cannot be used with metformin. If you are taking one of these drugs you will not be asked to participate in the trial. A very rare complication that occurs in 3 per 100 000 women taking metformin is lactic acidosis. This can present with malaise, muscle pains, breathing difficulty and abdominal pain. We will monitor you for any signs of this very rare complication. We will provide you with a copy of the product information leaflet if you would like more information.

Will I receive the placebo treatment or the metformin treatment?

We will not know until the study is completed whether you were taking the dummy/placebo tablet or the metformin tablet. The tablets will look identical and the midwives, nurses and doctors will not know which tablet you are taking. The tablet packages will be the same and only the pharmacy organizing the tablets will know what is in each packet. Once the study is completed we will then find out what tablets you were taking.

What will happen to the blood samples and the samples taken from the placenta?

These samples will be stored and may be sent to a laboratory at Melbourne University, Australia. The laboratory staff may do tests to see if metformin can be used to treat pre-eclampsia. Only tests related to pre-eclampsia will be done on the samples. Your samples will not be used for genetic testing.

Will my information be kept confidential?

All information collected in the study will be kept strictly confidential. Information collected will only be available to people directly involved in the study. Your information will be given a study number and your name will not be used for identifying any of your samples. The data collected will be locked in a secure location and only people involved in the study will have access to this information. Study monitors will have access to the information on a confidential basis. Your name will not appear on any presentations or publications relating to this study. Only your study number will be on the samples taken and none of the laboratory staff will have access to your name or contact details.

Are there any benefits of me for being involved with this study?

Only half of the women in this trial will be given metformin. If you do receive this treatment you may or may not benefit from the effects of this drug and you may or may not have improvement in your pre-eclampsia. There are no other direct benefits for you being

involved in this study. By being involved you may help us find a treatment for pre-eclampsia which could help many pregnant mothers in your situation in the future.

What are the disadvantages of being in the study?

You will need to take extra tablets and we may need to take a few extra samples of your blood for testing.

What will happen if there is any new information while I am involved in the study?

There will be an independent committee that will be reviewing the results of the trial on an ongoing basis. If there is any new information you will be informed about it and will then be able to decide if you would like to continue with the trial

What will happen with the results of this research project?

The results of this study will be published in medical journals and will be presented at medical conferences. Your private details will not be included in the articles or presentations

Who has developed this study and who has reviewed the study?

This study has been developed by a team of researchers from Melbourne University in Australia and Stellenbosch University, South Africa. We have had experts in the field of pre-eclampsia involved with the study. This study has been approved by the Research Ethics Committee at the University of Stellenbosch and by the South African Medical Research Council.

Who has paid for this study?

This study has been funded by grants from the University of Melbourne. Dr Cluver's salary has been paid for by grants from the Discovery Foundation and the South African Medical Association.

Who do I contact if I have a problem?

If you have any concerns or problems, you will be able to speak to the researchers involved in the study at anytime. If you have a more serious concern there is a safety and adverse event committee that you will be able to contact.

This study has been approved by the **Health Research Ethics Committee (HREC) at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

You can contact Dr Cathy Cluver at telephone number 082 321 0298 if you have any further queries or encounter any problems.

You can contact the **Health Research Ethics Committee** at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

If you have questions about this trial, you should first discuss them with your doctor or the ethics committee (contact details as provided above). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar of Medicines
Medicines Control Council
Department of Health
Private Bag X828
PRETORIA
0001

Fax: (012) 395 9201
e-mail: mogobm@health.gov.za

What do I do if I do not want to continue with the study?

If you decide to not continue with the trial at any stage, you may withdraw and it will not affect the care that you are receiving in any way. You will not be asked to give us a reason for why you want to withdraw from the study. We will ask you if it will be possible to collect information about your pregnancy and delivery and we will ask you if it is possible for us to use the samples that we have already collected.

Who do I speak to if I have questions about the study?

If you have any questions you can discuss these with the research team, your doctor, the midwives involved in your care or with any of the other participants in the trial.

Thank you for taking the time to read this information leaflet about the PI2 trial.

We hope that you will consider being involved in our study.

Please keep this copy of the information leaflet. If you do decide to be involved in the study you will be given a copy of the consent form