

British Society for Paediatric Endocrinology and Diabetes.

Patient Information

Title: Pre-natal treatment of Congenital Adrenal Hyperplasia (CAH), due to 21-hydroxylase deficiency.

You are invited to take part in this study to assess the effects of antenatal treatment with dexamethasone, both on yourself and on your baby. The exact purpose and details of the study are explained below, and are meant to help you to decide whether you wish to have treatment during pregnancy in order to prevent a baby girl affected with CAH, from being born with ambiguous genitalia.

1. The aims of the study

The aims of this project are threefold.

First, to assess the effects in the mothers, of dexamethasone given during pregnancy, starting in the first trimester and continuing either for a few weeks or for the duration of the pregnancy

Second, to assess the effects of such dexamethasone treatment on the genital appearance at birth of the female babies who are affected with CAH.

Third, to monitor any long term effects in the offspring, of either short or long term dexamethasone treatment on parameters such as blood pressure and development.

2. Why is the study being done?

To answer this it is useful to provide a little background information. As you already have a child with CAH you will already have an understanding of the biochemical nature of the condition, and why your child is being treated with replacement steroids.

CAH is a genetic condition which usually has to be inherited from both parents in order to affect the offspring. If a mother has already had a child with CAH, then the chance that her next child (by the same partner) will also be affected is 1 in 4. There is a 1 in 2 chance that the child will be a girl, and so the risk that the same partners will have an affected girl is 1 in 8.

Antenatal treatment with dexamethasone is specifically given to prevent the development in the womb of ambiguous genitalia in an affected female. This abnormal genital appearance arises as a result of over production of male-like hormones from the adrenal gland. Dexamethasone (a related steroid to hydrocortisone) crosses the placenta and suppresses this overactivity of the adrenal gland while your baby is developing in the womb. This should mean that the baby girl's genitalia are normal at birth and that genital surgery will therefore not be necessary.

Several countries are routinely offering dexamethasone treatment to mothers during pregnancy, and results so far suggest that a near-normal genital appearance can be achieved in female babies affected with CAH. However there may be significant side effects in the mothers who have received this treatment and this needs to be studied further.

Also there is very little information as to whether there are any long term health risks to the children who have been treated. The reason that we are concerned about this question is because some studies in animals have suggested that dexamethasone can give rise to high blood pressure and to an increase in the risk of developing diabetes in adult life. We do not know whether this could happen in humans, but it is obviously important to follow any child who has been exposed to dexamethasone in the womb, so that we can answer the questions in the future, and be able to pick up any potential problems early on.

Because CAH is not a very common condition, we will be working very closely with colleagues in other European countries, so that we can be sure we have enough patients to give the answers needed.

3. How is the study to be done?

As the adrenal gland in the fetus starts working as early as 6 weeks of gestation, suppressive treatment with dexamethasone ideally has to be started at the same sort of time. This means that treatment needs to be started in every pregnancy before a genetic diagnosis of CAH is possible (11-12 weeks). At 11-12 weeks it is possible to tell whether the baby is a boy or girl, and whether they are affected with CAH, by means of a procedure called CVS, or Chorionic Villous Sampling. This is carried out by your Obstetrician either vaginally or through the abdominal wall (this depends upon the position of the placenta) and your Obstetrician will explain the details of the procedure fully to you.

Only in the case of your baby being an affected female will the dexamethasone be continued until the birth. Therefore in 7 out of 8 pregnancies, the dexamethasone treatment is stopped at around 3 months of pregnancy.

All pregnancies (whether the dexamethasone is stopped at 3 months or continued until term) will be monitored carefully and blood and urine samples will be collected from you at most antenatal visits. You will require more frequent antenatal visits than in previous pregnancies so that your Obstetrician can make sure that you are not developing worrying side effects. You will also have some extra ultrasound scans so that the growth of your baby can be followed carefully. These scans will occur at Booking, 11-12 weeks (at the time if the CVS), and then at 20, 28 & 34 weeks.

When your baby is born he or she will be examined very carefully. Blood tests will be carried out to check whether your baby is affected with CAH. This will be done even if the genetic results from the CVS showed that the baby was unaffected with CAH, just to be absolutely sure. If the tests confirm the presence of CAH, then your baby will be started on treatment with Hydrocortisone and fludrocortisone as in the case of your previous child.

Longer term monitoring, at about the age of 5 years, will be planned with you once the baby is born. We hope to be able to follow all children who have been treated antenatally, even if they were only treated for the first three months, and whether or not they are affected with CAH. This monitoring will be carefully explained to you closer to the time but will involve occasional blood tests, checks on blood pressure,

and developmental assessments. The initial 4 years will simply consist of routine measurements of height and weight.

4. What are the risks and discomfort?

1. There is a small risk of miscarriage after CVS, estimated at 1:100.
2. Dexamethasone may cause greater weight gain and more stretch marks than normal. It may also cause a rise in blood pressure and a mild form of diabetes. If these occur then treatment would be stopped.
3. There are no reports so far of any significant problems arising in the offspring of mothers treated antenatally with dexamethasone. The potential risks based on studies in animals have been outlined in section 2.

5. What are the potential benefits?

Any affected female baby will be born with normal genitalia and so will not require corrective surgery. Without such treatment girls born with genital ambiguity may require surgery early on to correct the external genitalia and to make them look like those of a normal baby girl. There may also be the need for further surgery as a teenager. Although the results of surgery are improving, they are not always perfect and some young women can have anxieties about the need for further surgery in adolescence. A few may have concerns about sexual relationships and potential fertility.

6. What other treatments are available?

Dexamethasone is the only treatment available for the treatment of babies in the womb.

Medical treatment of babies (both boys and girls) remains life long replacement with steroids (Hydrocortisone & Fludrocortisone). The treatment of your baby in the womb *does not cure the problem within the adrenal gland* itself and he or she will still need to take the replacement treatment regularly in order to remain healthy.

7. Who will have access to the case/project records?

All information collected on yourself and your baby (both before and after he/she is born) will be anonymous and no-one will have access to it other than the doctors co-ordinating the study and taking part in your care.

8. What are the arrangements for compensation?

This study has been approved by an independent Research Ethics Committee who believe that it is of minimal risk both to yourself and to your baby. However there may be 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 study.

No special arrangements have been made for this study but you 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.

9. Do I have to take part in this study?

Please do not feel concerned if you not wish to take part in this study. The above information is supplied in order to explain the full extent to which you would be involved should you wish to take part. **We should stress that you do not need to take part if you do not wish to, and that not taking part will not affect your care during pregnancy, nor the care of your baby after he/she is born.**

10. Who do I speak to if problems arise?

You should contact your Obstetrician straight away if you experience any problems during your pregnancy. If you have any concerns about your baby after he or she has been born, you should contact the Paediatric Endocrinologist who is looking after your family.

If you have any complaints about the way in which this study has been, or is being conducted, please in the first instance discuss them with your Paediatric Endocrinologist as it will be he or she who is co-ordinating your care. If the problems are not resolved, or you wish to comment in any way, please contact the Chairman of the Research Ethics Committee, by post (The Research and Development Office, Institute of Child Health, 30 Guildford Street, London WC1N 1EH), or if urgent, by telephone (0207 905 2620), and the committee administration will put you in contact with him.

11. Researcher who will have contact with the family

The name and contact details of the Co-ordinating Physician will be provided for each individual patient. That Physician (a Paediatric Endocrinologist) will have 24 hr access to the team co-ordinating the Study at the Middlesex Hospital.