PATIENT INFORMATION SHEET – SEVERE DISEASE

RANDOMIZED TRIAL OF FETOSCOPIC ENDOLUMINAL TRACHEAL OCCLUSION (FETO) VERSUS EXPECTANT MANAGEMENT DURING PREGNANCY IN FETUSES WITH LEFT SIDED AND ISOLATED CONGENITAL DIAPHRAGMATIC HERNIA AND SEVERE PULMONARY HYPOPLASIA

You are being invited to participate in a research study. Before you decide whether or not to take part, it is important for you to understand why we are carrying out this research, and what it will involve. Your decision will not affect the standard of care that you receive in any way. If you do agree to take part, you remain free to withdraw your consent at any time. If you have any questions, please ask one of the doctors.

Thank you for reading this.

What is the purpose of the study?

Your fetus has diaphragmatic hernia and as far as we can tell there are no other obvious abnormalities.

In diaphragmatic hernia the content of the abdomen (belly) enter the chest and press on the lungs. This affects the normal development of the lungs. After birth these babies have breathing problems, which require immediate specialist medical attention. In the first instance this consists of appropriate ventilation. All surviving babies require at some stage an operation to close the defect in the diaphragm but this is usually carried out a few days after birth. The babies may also experience variable degrees of feeding problems and therefore may thrive less, need medication against reflux or in severe cases a special operation to prevent the reflux.

However, still around 70% of babies with CDH may die after birth, typically in the early days. This is because their lungs have been so much compressed that they were developed so poorly, that they either cannot maintain sufficient exchange of oxygen or cause so much hypertension, that eventually the baby does not make it.

The chances that the baby will die can now be predicted by appropriate assessment before birth. On the basis of this **prenatal assessment** the diaphragmatic hernia is classified as follows:

Mild: most of the babies survive, and the vast majority do not have any serious breathing problems.
Moderate: about 50% of the babies will unfortunately not survive mainly because of breathing problems and other complications after birth. In about 30% of the babies who survive there are breathing problems requiring oxygen therapy for at least one month after birth and in a few cases there are long term breathing.
Severe: most of the babies die soon after birth.

If one can make the lungs grow better before birth, a better outcome would be expected. There is some evidence that in babies with **severe** diaphragmatic hernia the outlook is improved by the placement of a balloon into their wind-pipe (trachea) at 26-28 weeks of pregnancy. The balloon is placed in the fetal trachea by introducing a thin endoscope through the abdomen and womb of the mother, into the amniotic cavity and through the fetal mouth into the trachea. This procedure is called **Fetoscopic Endoluminal Tracheal Occlusion** (FETO). Normally the fetal lungs produce fluid, which escapes through the trachea and mouth into the amniotic cavity. If there is a balloon in the trachea the fluid produced by the lungs remains within the lungs, which increases the pressure within the lungs and provokes their growth. In more than a two hundred of these babies, higher than expected survival rates have been observed. Also their need for prolonged oxygen administration was less.

There is a downside also to FETO. There is the need to make a small hole in the amniotic sac. This weakens the membranes and around 15% of the patients will rupture their membranes prior to term. This will increase the risk of infection and preterm delivery. Therefore we will perform FETO later in pregnancy (between 28 and 30 weeks) to minimize the risk of very early delivery (<28 weeks).

We are inviting you to take part in a **trial** to determine if FETO increases the survival chances. Furthermore we will determine if FETO will decrease the number of baby's that need long term oxygen therapy. Also we would like to follow the status of these children for several years after they are born.

We expect that FETO will provoke lung growth and as such improve their outcome. This is uncertain at this moment as FETO has till now only been offered to many babies with *severe* hypoplasia, without having good data on those patients who did not have this operation. They usually do not attend our center, were therefore not managed equally and therefore less is known about them. In other words the benefit of the intervention has not been truly proven. It is for instance possible that the babies who were born early due to rupture of the fetal membranes do less good, and this outweighs the benefit in the others. Also, it might that babies who are managed after birth do much better today than what is currently assumed.

When doubt is still present, doctors design a clinical trial. This trial will involve maximum 288 women and is estimated to take about four to five years to complete. We anticipate that FETO improves outcome of cases with severe diaphragmatic hernia.

Why have I been chosen?

This is just because your fetus has **severe** diaphragmatic hernia.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide not to take part in the study your standard of care or choices will not be affected.

What will happen to me if I take part?

You will be allocated to one or the other of two groups, either the expectant management group or the FETO group. A computer selects the group to which you are allocated and the chance of being allocated into each group is equal.

Randomisation

Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. People are put into groups and each group gets a different treatment. The results are compared to see if one is better than the other. To try to make sure the groups are the same to start with, each patient is put into a group *by chance* (which is also called "randomly"). This process is in our study done by a computer, so that nobody can influence this decision. The computer will assign you in one of the two treatments groups and the chance of being allocated into each group is equal.

FETO procedure

- If you are allocated into the FETO group the operation will be carried out at 28-30 weeks.
- The operation is performed under local anaesthesia.
- One hour before the operation you will be given painkillers either orally or through a drip, antibiotics to prevent infection, and medication to prevent contractions. We will also take a blood sample from you (20 mL of blood) as part of the routine for any operation.
- A thin needle is first passed through your abdomen to give an injection to the fetus for pain relief and also to stop any fetal movements. A thin cut is then made into your abdomen through which we introduce a thin endoscope into the uterus. The endoscope is passed through the mouth of the fetus into the trachea. The balloon is passed through the endoscope into the trachea and is left there.
- The operation takes on average 10-20 minutes to perform but at times depending on the position of the baby it may take longer.
- In about 3% of cases it may not be possible to place the balloon in the correct position or the balloon deflates and a second FETO may be offered after a few days. Also the balloon may deflate and might need to be replaced. All together around 5% of patients required a second intervention.
- The duration of your stay in the hospital after the FETO will vary from less than a day to a few days depending on your recovery as well as the anesthetic technique used, or the occurrence of unexpected events.
- The balloon must be removed ideally before birth, or if birth comes earlier, during labor or immediately after the baby is born otherwise the baby cannot breathe and dies. This means that between placement of the balloon and its removal, it is advisable that you stay close to the center where the balloon was placed because of the high experience for safe balloon removal. If not, you will need to be able to travel to the center where the FETO was done. Less ideally is delivery at another center, where they must be prepared to do so and be ready for it at all times. We also provide patients that undergo FETO with emergency instructions for balloon removal; however we do not recommend removal of the balloon at other centers than the ones doing the FETO procedure.
- We usually remove the balloon in the 35th week of pregnancy (this means 34 weeks till 34 weeks +6 days). This is done in essentially the same way as the placement of the balloon in the first place. If the fetal position is favorable it may be possible to puncture the balloon with a needle passed through your abdomen while watching by ultrasound.
- In case of premature birth, the balloon is removed as above or at the latest immediately after birth (again using either an endoscope or a needle).
- After the procedure, you will be given a bracelet, which will contain embossed information written on it. The will state that there is a balloon in the baby's windpipe which must be

immediately punctured at delivery of the baby. The back of the bracelet will have the contact number for University College London Hospital if anyone requires any further information.

- We would recommend that if the balloon is removed at 35 weeks, delivery in the local hospital with neonatal care facilities is appropriate. In case you go into spontaneous labor prior to the balloon being removed and you are not able to come to University College London Hospital, please report immediately to your local hospital as your consultant obstetrician has been trained to remove the balloon after delivery.

Expectant management

You will not undergo any operation during your pregnancy. For the remainder of pregnancy, the lung growth of your fetus will be monitored by means of ultrasound scan and/or magnetic resonance imaging. We will also monitor any signs of increased fluid around you baby that might need to be drained in order to avoid premature delivery.

Care after birth for both groups

The baby should be delivered in a hospital with facilities for intensive neonatal care and that has expertise in treating babies with diaphragmatic hernia. There is no need for the delivery to be by caesarean section unless there are other obstetric problems.

The main problem for the baby at birth is not the hole in the diaphragm, but the function of the lungs. Immediately after birth the baby will be placed on a ventilator to help with breathing. It will also have a small tube passed from the nose down to the stomach for feeding and to prevent the baby swallowing air, which could compress the lungs even more.

In the first few days after birth it usually becomes obvious whether the lungs have developed sufficiently for the baby to survive or not. Once the condition of the baby on the ventilator is stable an operation is carried out to close the hole in the diaphragm.

The majority of babies that survive will stay in hospital for at least 3-4 weeks but a few cases with severe breathing problems either due to the diaphragmatic hernia or premature delivery may have to stay in hospital for months.

Children with diaphragmatic hernia can have problems after discharge from the hospital as well. Therefore babies participating to this study will be invited to be followed up later on, so that their growth and development can be assessed as well. Actually this is recommended so that long term effects can be timely diagnosed and treated.

What are potential side effects of an expectant management during pregnancy?

The most common complications of CDH in pregnancy is the development of an excess of amniotic fluid. This might be related to the fact that CDH babies swallow less of that fluid. When the fluid is excessive it can lead to stretch of the uterus, with preterm labour and/or rupture of the membranes as a complication. Growth problems are uncommon and the spontaneous demise of the baby –usually for unknown reasons – is infrequent (1-2%). These are a few reasons why mothers carrying a baby with CDH are typically followed up more closely, including by ultrasound.

What are the side effects of FETO?

The centers participating in this study have extensive experience with keyhole surgery in pregnancy and over 200 FETO operations. Each of them has therefore performed several tens FETO procedures by now.

FETO is a minimally invasive operation (also known as keyhole surgery) and does not carry a risk of serious complications for the mother. Minor complications which may occur in more than 1% of cases include localized bleeding or wound infection at the entry site of the instruments.

The most common and important complication of FETO is **early rupture of the membranes with vaginal loss of amniotic fluid**. This problem occurs within three weeks from FETO in about 15% of cases. In some cases the leakage may stop and the pregnancy continues normally. The loss of amniotic fluid may also continue for several weeks until delivery.

In most of cases rupture of the membranes eventually leads to **premature delivery**. This is the reason why overall, FETO increases the risk for preterm delivery; in our hands the average gestation at delivery was 35 and a half weeks.

The FETO balloon will need to be removed at around 34 weeks. If you develop contractions and go into spontaneous labour prior to the balloon being removed, you should immediately present yourself to the delivery suite of the hospital as the balloon will need to be removed immediately after delivery. In the unfortunate event that the baby is delivered and the ballon is not removed in a timely fashion, there is a risk of serious complications to the baby due to lack of oxygen and in case of severe delays this may result in the baby's death.

The consequences of premature birth depend on the gestation at which this occurs. Normal babies born after 32 weeks usually survive without any long term problems but may require neonatal intensive care for a few days or even weeks. However, in babies with diaphragmatic hernia the added problem of prematurity may increase the risk of death or long term breathing and feeding problems. In that scenario, the survival chances depend on the gestation at delivery and the size of the lung prior to the FETO procedure.

Animal experiments have shown that the balloon does not cause any serious damage to the trachea. This has also been our experience with the majority of babies born after FETO. However, the balloon causes local widening of the trachea, which usually is without any consequences. In some it has led to a cough at deep breathing movements, but most of these were temporary.

What will happen if I don't want to carry on with the study?

If you desire not to participate in the randomized study or to withdraw, we will want to keep in contact with you to know your progress and the outcome. If you do not want us to contact you please let us know and we will respect your wish.

If you wish to withdraw from the study and the fetus has a balloon in the trachea it is important that this is removed by an expert.

What are the possible disadvantages or benefits of taking part?

We do not know at this stage of the trial whether in fetuses with severe diaphragmatic hernia FETO is beneficial or not. The results of this study will help us to manage severe diaphragmatic hernia better in the future. This might either be that the FETO procedure should be recommended or no longer offered, depending on the results of the study.

If during the course of the research new information becomes available about this treatment, we will discuss it with you. In the light of new information, you or your research doctors decide that you should withdraw from the trial this will be arranged.

What if there is a problem?

If you have a concern about any aspect of this study, please contact a member of the research team at the UCLH Fetal Medicine Unit at the contact number mentioned below, who will do their best to answer your questions. By agreeing to take part in the study you do not lose any legal rights. If you remain unhappy and wish to complain formally, you can contact the Patient Advice and Liaison Service (PALS) on Tel: 0203 447 3042, or Email: PALS@uclh.nhs.uk

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential and any information that leaves the hospital will have your name or address removed so that you cannot be recognized from it.

Your GP and your obstetrician will be informed of your participation in the trial unless you have a specific objection.

What will happen to the results of the research study?

Following the analysis of the information we get we will make conclusions and publish the results in scientific journals. Your name or personal details will not be identified on any of these. We will be happy to provide you with a copy of any published documents in relation to the study at your request.

Who has reviewed the study?

The study was reviewed by the London-Surrey Borders Research Ethics Committee.

Contact for further information

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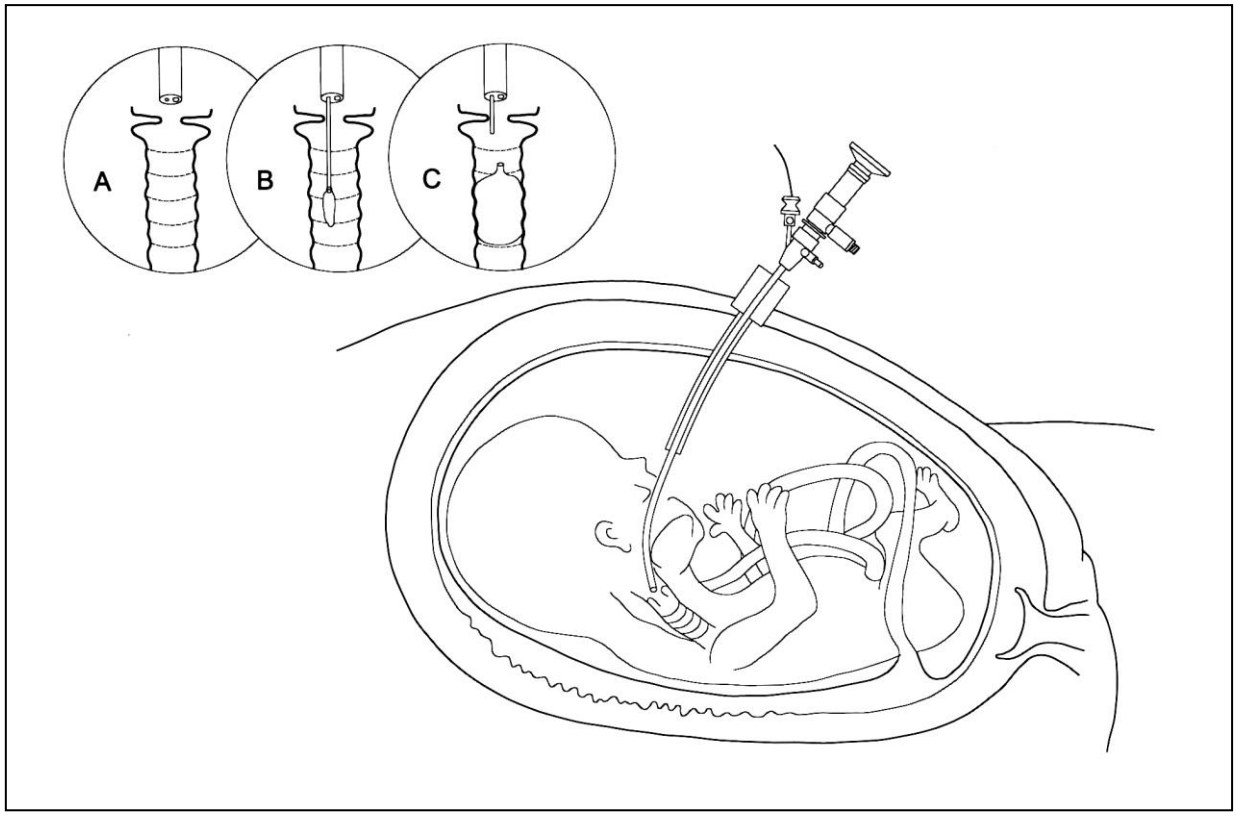
Figure:

Illustration of the FETO procedure: through a small cut in the mother's tummy, a miniature telescope is introduced into the mouth of the unborn baby and a balloon is delivered in the trachea. The diagram below shows the introduction of the balloon into the trachea.



Thank you for considering taking part in this research. You will be given a copy of this information leaflet and your consent form to keep.