All images: Peter Soothill

A fetus in early gestation – the time of life in which the most rapid change occurs.

Research Before Birth

The Fetal Medicine Research Unit at Bristol University, located within an NHS hospital, is a complex collaboration between the University and the NHS, and a resource of international repute for the understanding and treatment of the diseases of the unborn. Professors ***Peter Soothill*** and ***Andrés López Bernal*** outline some of the research and advances that have recently been made there.

'Before birth' is the last period of human life to become available for study. The key to facilitating this access has been the successful development of ultrasound and genetic technologies. This ability to 'see' into the pregnant womb allows exciting research into the diagnosis and treatment of diseases in unborn babies. A further benefit is that such information can now be obtained non-invasively. A second 'insight' into the pregnant womb has progressed from our improved understanding of human reproductive biology. For example, comprehending the way that cells signal to each other is fundamental to answering questions about uterine muscle contraction which results in labour and birth. Thus the combination of a greater understanding of biological processes with new methods of access has allowed the principles of postnatal medicine to be applied to patients before birth. This has led to marked improvements in prognosis and many babies being alive today who might otherwise not have survived.

> Studying human diseases that are a challenge to current medical practice and knowledge requires a clinical setting of sufficient quality and standing for patients and doctors to respect and trust the statement 'we do not know'

A colour Doppler ultrasound image of the blood vessels supplying the brain of a fetus at about 20 weeks gestation.

Lethal anaemia

In the 1950s the response of a mother's immune system to her unborn baby's blood was one of the main causes of babies dying, but now this is rare. However, many women still have their pregnancies blighted by the concerns and interventions needed to allow the baby to survive. For example, in any pregnancy fetal blood can cross the placenta into the mother's blood which, if it is of a different blood group, the pregnant woman recognises as 'foreign'. If the fetal blood is antigen positive (an antigen is a substance capable of causing the production of antibodies), this triggers a reaction in the mother who will start making antibodies. These cross back through the placenta and destroy the baby's red blood cells, causing the baby to develop anaemia. Until recently, the developed in Bristol, have helped this problem considerably – the ability to detect, non-invasively, when a baby is becoming anaemic by measuring the speed of its blood using Doppler ultrasound and the ability to distinguish the baby's blood group from the mother's, also non-invasively.

If the blood of fetuses in subsequent pregnancies is antigen negative, the antibodies produced by the mother are of no concern. For many years researchers have tried to isolate fetal cells from the blood of pregnant women so that they can identify factors such as whether they are antigen negative or positive. While this can be done, the number of cells obtained is very few and, because it is such a difficult procedure, so far it is not practical. However, using a sensitive real-time Polymerase Chain Reaction test developed in Bristol (with a group including the Blood Transfusion Service and the University of the West of England), it is now possible to detect ➜

A picture through a fetoscope during an operation showing blood vessels on the surface of the placenta joining the circulation of identical twins about to be treated by laser.

➜ from DNA extracted from maternal blood whether positive antigens from the baby are present. This has proved to work extremely well and is now offered to suitable women throughout the country by the Blood Transfusion Service.

When the fetus is shown to be at risk of being affected by the maternal antibody, the next question is whether and when treatment may be required. In other words, is the baby already anaemic? Recent advances in ultrasound technology have made a significant difference to resolving this problem. When an adult is anaemic, the heart pumps harder to maintain oxygen delivery to the tissues. Anaemic blood is also less viscous and so for both these reasons it flows faster. The same is true in fetal life, so by using Doppler ultrasound it is possible to measure the speed of blood in the vessels in the head to indicate when treatment is required.

> Laser treatment can now be administered to outpatients under local anaesthetic, saving many babies who would otherwise be lost or very premature

Laser surgery

The first fetal condition to be treated by laser surgery was twin-to-twin transfusion syndrome, where the blood of identical twins sharing a placenta becomes trapped in one at the expense of the other. With this condition there is a very high chance of the pregnancy being lost, or of surviving babies being injured. By passing a fine telescope into the uterus, it is possible to see the joining vessels and then block them with laser treatment and so stop the flow of blood from one twin to the other. Recently we have also developed a way of using laser treatment under ultrasound guidance to stop the circulation of blood from a healthy baby into a twin with no heart beat. Without such treatment, which can now be administered to outpatients under local anaesthetic, most of these pregnancies would be lost or delivered very prematurely.

Preterm labour

Although fetal medicine is moving fast, some important areas are proving very difficult because of the complexity of the pathology involved. Birth before 37 weeks of pregnancy occurs in about five per cent of pregnancies, giving more than 40,000 preterm deliveries in the UK every year. It is a major cause of perinatal mortality, illness and handicap worldwide. The most common reason for this condition is that uterine contractions start prematurely, either because the normal mechanism of labour has been triggered too early, or because an abnormal mechanism has occurred instead. By studying biopsies of uterine muscle we are exploring how hormones and other physiological agents activate or inhibit contractions. Research in collaboration with the departments of Biochemistry and Pharmacology at Bristol University will increase our understanding of how hormones influence uterine activity through specific receptor molecules in the uterine muscle. Moreover, research in collaboration with the University of the West of England will look at better ways to diagnose and predict preterm labour, by looking for changes in uterine tissue and in the maternal and fetal circulations.

And in the future

This combination of skills and resources in both the NHS and University departments within Bristol is continuing to produce clinical innovations and scientific advances in the diseases of the unborn. In the next few years, we hope to work even more closely with other experts within the faculties of Medicine and Science to approach the questions that can now be addressed because of a combination of access and testable hypotheses. We also wish to extend research to events even earlier in pregnancy than is currently possible and so understand the activities relating to the formation of sperm and eggs, as well as those in embryology already under way in our Reproductive Medicine Unit. ■

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