

Early identification of women at high risk for pregnancy complications

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One in 200 babies dies before birth in the UK. A study aimed at determining how to reduce the risk of a pregnancy coming to a devastating end is now producing its first results.

"I've spoken to many bereaved parents and the loss of a baby has a profound and life-long impact," said Gordon Smith, Professor of Obstetrics and Gynaecology. "There's a whole life to be gained if you identify a baby who will die in the womb at 40 weeks of pregnancy, and this huge gain can be achieved relatively easily by early delivery of the baby at 38 or 39 weeks."

Smith leads the Pregnancy Outcome Prediction (POP) study, which aims to determine both the risk women face of losing their baby during their first pregnancy and how this can be reduced.

Although some women are identified as [high risk](#) for pregnancy complications from their family or medical history – and might be offered ultrasound, biochemical screening and genetic analysis, as well as an early delivery if their baby should show signs of difficulty – most stillbirths occur in women with no known risk factors.

For these low-risk women, the current provision of antenatal care – established in 1929 – still relies on the use of a tape measure.

"We estimate that over half of the 4,000 stillbirths a year in the UK are the result of placental dysfunction, which is frequently associated with impaired growth of the fetus. Apart from urine and blood pressure monitoring for pre-eclampsia – one of the conditions that can cause stillbirth – the standard means of identifying a baby that's small for gestational age in low-risk women is measuring the mother's 'bump' with a tape measure," Smith explained.

Globally, every year 2.6 million babies are stillborn and 3.2 million live-born children die in the first month of life. "Growth-restricted and premature children can also suffer difficulties at delivery, childhood diseases, and educational, social and health problems in later life. The emotional cost to families, coupled with the associated healthcare and social costs, means that research into the prevention of these conditions is more crucial than ever."

Smith's approach in the Department of Obstetrics and Gynaecology, funded by the National Institute for Health Research (NIHR), was to monitor more than 4,500 women during their first pregnancy at several stages until the end of pregnancy. As well as regular ultrasound scans and

blood sampling, maternal and paternal DNA samples were taken and, at the time of delivery, samples of placenta, fetal membranes and umbilical cord were collected, together with details of the delivery and baby.

Completed a few months ago, the study has been a massive undertaking, but one that Smith says has laid the basis for years of in-depth analysis: "With this core resource of data and biological samples we can now ask whether there are novel biomarkers to identify women at high risk of developing pre-eclampsia – something that would be especially useful in low – and middle-income countries where scanning may not be available. We can also ask questions such as is inflammation of the placenta more common in complicated pregnancies and can this be detected by measuring circulating markers?"

One of the first questions the team asked was how effective routine ultrasound scans are as a screening test for babies who are small for [gestational age](#); such babies are thought to account for about 30–40% of stillbirths.

"Although previously published research had shown no beneficial effect of routine screening for identifying small babies in the third trimester of pregnancy," said Smith, "it was unclear whether this was because ultrasound performed poorly as a screening test, or whether the associated interventions were ineffective." Smith and colleagues have now clearly shown that routinely scanning women during pregnancy increases the detection of the smallest babies from 32% to 77%.

"The problem with previous studies is that they were designed without any information on how well scanning performed as a screening test. We now know that ultrasound actually performs very well compared with [screening tests](#) used in other areas of medicine. We are now focusing on how to differentiate between healthy small babies and those who are small due to a pathological process. When we can achieve this, we will

be able to identify the babies most likely to benefit from intervention."

"Practice only changes when guidelines change, and guidelines only change when the evidence to support change is strong," said Smith.

"When we have refined our screening test, a next step may be large-scale trials of screening. The interventions will include more-intensive monitoring and earlier delivery."

The situation with stillbirth has parallels with sudden infant death syndrome (Sids), explained Smith: "In the 1980s, 1 in 500 [babies](#) died of Sids. But when research showed that sleeping on the front was a risk factor for the baby, this was followed by a public health campaign that reduced Sids by 80–90%. Although the strategy to reduce stillbirth is unlikely to be as simple, one area that we can look at is whether we can generate biomarkers for the antecedents of stillbirth, and use these for population-based screening."

Smith believes that placental dysfunction might result in 'a signature' of biomarkers that can be used to identify a problem with the placenta even in a mother showing no symptoms, and he and others have identified several potential candidates.

Many of these studies address identifying a failing placenta. However, what remains uncertain is why the placenta is dysfunctional in the first place. "One possible initiating factor is infection. Consistent with this, some studies have reported high rates of placental inflammation in pregnancies with adverse outcomes, but the evidence so far is poor."

The search for an infectious agent, possibly even a currently unrecognised bacterium or virus, has now begun, thanks to a new four-year £1.6 million project funded by the Medical Research Council using the data and biological samples gathered by the POP study. Smith and colleagues will be working with Professor Sharon Peacock from the

Department of Medicine and Dr Julian Parkhill and Professor Paul Kellam from the Wellcome Trust Sanger Institute, as well as industrial partners.

It's an intriguing possibility that some hitherto unrecognised infectious agent might lead to a significant proportion of pregnancy complications. If so, there would be the possibility of treatment or vaccination to prevent complications, in the same way that women are now vaccinated against human papilloma virus to prevent cervical cancer.

"That said, the idea that we could come up with one magic solution for pre-eclampsia or stillbirth is beyond everyone's expectations at the moment. More realistically, it would seem plausible that diverse infectious agents could impair the function of the placenta, perhaps by activating some common pathway," he explained.

The overarching goal of the Department's research is to apply state-of-the-art approaches in clinical study design, biostatistics, molecular biology and sequencing to develop novel tools that will help differentiate between a healthy and an unhealthy pregnancy. "Our primary aim is to generate clinically useful screening tests that allow us to focus medical care on women who are truly high risk for complications, and to avoid 'medicalising' the experience of pregnancy and birth for the women who are at low risk."

Provided by University of Cambridge

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