News

Womb zoom: What advances in fetal and newborn imaging have revealed

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A keg-sized magnetic resonance imaging machine tucked into a corner of a neonatal-care unit in the maternity wing of the Royal Hallamshire Hospital in Sheffield, UK, is the smallest of its kind in the world. Since engineers put the final touches on this prototype more than a year ago, doctors have thus far used it to capture a snapshot of the postnatal brain in about 40 healthy newborns. With the consent of the babies' parents, clinicians prepare the infants for a single imaging session before they are sent home. Nurses first ensure that the babies are fed, and then swaddle them in blankets and muffle their ears with a pair of infant-sized headphones. After this, the researchers place the babies on trays just large enough for a newborn and slide them into the opening of the magnetic resonance imaging (MRI) scanner. “Usually, what we find is that the baby will go to sleep and stay very still for us to image,” says Martyn Paley, a bioengineer at the University of Sheffield who was involved in the conception of the new MRI technique.

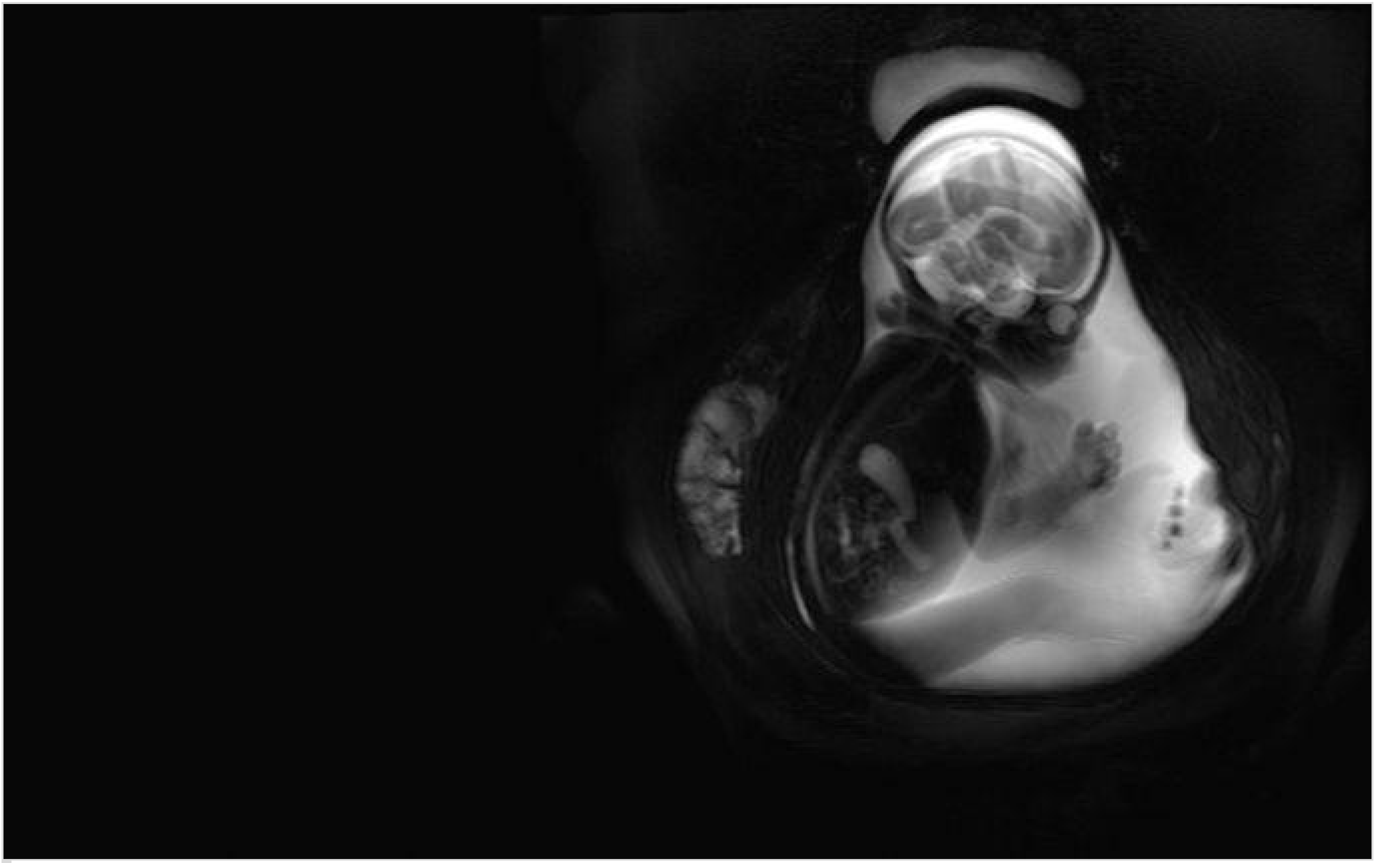

Image: Moriah Thomason

MRI scans capture detailed images of internal organs and structures by capitalizing on the natural proclivity of the electrons of the hydrogen atoms of water to rotate. As the hydrogen electrons rotate in response to the scanner's changing magnetic field, they emit energy that is then detected by receiver coils, which gives computers the information necessary to create a detailed anatomical image. Whereas conventional MRIs have an opening of approximately 70 centimeters to fit a human body, the diameter for this 'mini-MRI' is only half as wide—just larger than that of a basketball. Instead of transferring the baby between units, the smaller machine enables researchers to obtain clear images of the newborn directly in the neonatal wards. Within 20 minutes of placing the baby inside the machine, clinicians can capture a series of images that shows not only the structure but also various processes, such as blood flow and the movement of biochemicals, inside the neonatal brain—a feat that would have been impossible before the advent of this prototype.

Until approximately a decade ago, what researchers knew about the developing prenatal brain came primarily from analyzing the brains of aborted or miscarried fetuses. F studying postmortem brains can be confounding because scientists can't definitively pinpoint whether the injuries to the brain occurred before or during birth. Over the years, however, improvements to MRI—a combination of better magnets, receiving coils and algorithms that can account for motion in conventional machines and the miniature version—are finally enabling researchers to study the developing brain in real time.

With these advancements, researchers are just beginning to understand how normal brains develop, and how abnormalities can manifest over the course of development. In recent months, for example, MRI has helped to produce insights into the influence of Zika virus on connectivity in the fetal brain, as well as how congenital heart disease might affect cortical development. Just recently, on 15 February, researchers announced that an MRI study of 106 infants, some as young as six months, showed that more and deeper folds of the brain might be linked to an elevated risk of developing autism[1]. Meanwhile, scientists cataloging typical infant brain development with the mini-MRI hope to use it eventually to study the brains of premature babies, who have a high risk of brain damage. Ultimately, clinicians hope to intervene early with therapies, if available and approved, to prevent developmental disorders when there are signs of brain damage *in utero* or shortly after birth.

Advancements in MRI

Although MRIs have been used in hospitals since the 1980s, clinicians initially thought that these machines would not be safe for fetuses and newborns. Because MRI captures information by using radiation from heat-generating electromagnetic and radio fields, researchers worried that the fetus could overheat. Others were concerned that the machines were too noisy and could damage a neonate's hearing. However, in the late 1990s and early 2000s, research showed that fetuses scanned using MRI *in utero* did not experience long-term adverse effects, and so the doors for scanning fetuses during pregnancy began to open.

Over the course of gestation, the fetal brain evolves from a tube into a much more organized system. However, “fetal life before birth is still a widely unknown univer says Gregor Kasprian, a neuroradiologist at the Medical University of Vienna in Au .

"It needs to be further explored by noninvasive means, of which MRI currently is still the most promising one."

After researchers determined that it was safe to image fetuses, they had to confront another challenge: motion. "Some of the babies are doing somersaults when we capture their images on the MRIs," Paley says. MRI typically works best when the patient is still, but clinicians were initially hesitant to expose developing babies to sedatives either directly through the womb or through the mother's bloodstream.

Since 2005, engineers have worked around the issue of motion by increasing the number of receiver coils to improve the detail of images, and by taking images more frequently while the patient is in the MRI machine. Although scientists think that there's still room to improve motion-correction strategies for MRI, modifications over the past decade have enabled clinicians to perform MRI scans on pregnant mothers and to scan their babies' brains *in utero*.

From using MRI *in utero*, researchers have been able to better understand many of the normal developmental events that occur in the second half of pregnancy. Catherine Limperopoulos, a developmental neuroscientist at Children's National Health System in Washington, DC, and her colleagues followed the healthy pregnancies of 166 mothers—the largest published study cohort to date—and imaged their fetuses every week for 21 weeks[2]. The results from this study serve as a more accurate reference for what normal brain development looks like in the second half of pregnancy.

More recently, a team of researchers from the Netherlands and the United Kingdom found that distinct patterns of brain development, such as the connectivity between the two hemispheres of the brain, can be noticeable as early as 24 gestational weeks[3]. They speculate that, with further validation, clinicians could perhaps one day look at the brain at this time point to assess whether there are deficits in neural wiring that can affect development. "Deviations from normal brain development can range from subtle to severe," Limperopoulos says. She adds that "we currently don't know the impact that changes in neural wiring at 24 weeks can have on later development." Because it's uncertain how these early variations in brain development can affect the child lon n, finding them could raise potential ethical concerns surrounding abortion. However, it is much too early to predict whether the new findings will be confirmed in further studies, or whether they will ultimately influence clinical practice.

Understanding disease

In addition to understanding normal brain development, researchers are also using MRI to investigate the neurological underpinnings of conditions such as prematurity, which affects 15 million babies a year worldwide. In January, researchers used MRI scans to show that babies born prematurely differ in the circuitry of their developing brains when compared to those delivered at term[4]. Although this study was small—it followed a total of only 32 women through the course of pregnancy—it was the first of its kind to show that preterm babies had weaker neural connectivity at 30 weeks in the left hemisphere of the brain in a region involved in language development. This observation suggested that the factors that influence preterm delivery also affect the central nervous system *in utero*.

MRI has also helped researchers to study cognitive disorders in babies born with congenital heart defects (CHD), the most common birth defect in the US. Although babies with CHD receive corrective heart surgery almost immediately after birth, many go on to develop learning, language, social or behavioral disorders. These observations led researchers to investigate whether or not children born with CHD were neurologically healthy before birth—and fetal MRI was the best technique to delve into these questions[5]. Scientists used MRI to scan fetuses diagnosed with CHD, and saw that these babies were developmentally delayed by up to three weeks when compared to healthy babies without CHD[6]. These differences can be detected as early as 25 weeks of gestation.

One of the newest and most urgent applications of advanced MRI technology is to understand how the Zika virus affects brain development. The virus is known to cause microencephaly, a condition in which babies are born with abnormally small heads brain damage. But scientists have yet to fully understand how Zika inflicts damage the fetus during pregnancy. Using MRI, researchers have, for the first time, documented the course of abnormal brain development in a fetus, after its mother has been infected with the Zika virus, in a non-human-primate model[7]. The virus attacks the fetal brain within ten days after infection, which is “bad news,” according to Kristina Adams Waldorf, first author on the study and an obstetrician–gynecologist at the University of Washington's School of Medicine who studies maternal and fetal infections. “By the time a mother realizes she develops symptoms, the fetal brain may already be damaged.”

Moreover, the Zika virus can cause a host of other symptoms in the fetal brain that are detectable only by MRI. These might include the enlargement of brain cavities that contain fluids, a smaller hindbrain (which typically controls movement and other functions), a loss of brain cells and brain cell connections and decreased connectivity between the two hemispheres of the brain. Collectively, these symptoms are part of the spectrum of congenital Zika virus syndrome. “If we don't assess brains with MRI, we will be limited in our assessment of Zika,” says Magdalena Sanz-Cortes, a maternal–fetal medicine specialist at Baylor College of Medicine in Houston.

Although the use of MRI *in utero* is gaining traction in the US and Europe, many developing countries that are susceptible to Zika outbreaks are unfamiliar with the practice. Therefore, for fetal MRIs to have any utility in Zika-prone countries, the field staff needs more specialized training and expertise in the administration and interpretation of fetal MRI.

Meanwhile, fetal and postnatal MRI advances are continuing to help scientists to investigate a range of questions. The mini-MRI will enable researchers to monitor how the brain continues to develop shortly after birth. And, whereas MRI has been used primarily to image babies *in utero* during the second half of pregnancy, some scientists are interested in answering basic questions relating to processes that occur during the first half of pregnancy. Fetal imaging during this earlier period is possible, but it can be more challenging because the brain is smaller and the baby moves faster.

Ultimately, the greatest utility of fetal MRI will be to investigate correlations between observations *in utero* and developmental outcomes. Moriah Thomason, a develop[illegible] l neuroscientist at Wayne University in Michigan, notes that there are challenges toward that goal. “We want to be able to have a crystal ball to diagnose and predict diseases *in utero*,” Thomason says. “But we still have a long way to go before we get there.”

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