

# Past, Present and Future of Fetal Brain Assessment

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## ABSTRACT

The fetal brain as focus of scientific interest could not emerge before the 20th century. This was only possible after a long history of parallel advances in the fields of anatomy, physiology, pathology and imaging techniques. Some of these are presented in this article. We are providing (1) a historical overview about 'the brain in science' in general, (2) a historic overview about fetal brain assessment and (3) an overview of the present and reflections about the future of fetal brain assessment.

**Keywords:** Fetal brain, History of fetal brain in science, Fetal ultrasound, Fetal neurology, Fetal MRI, Fetal magneto-encephalography, Assessment of the fetus.

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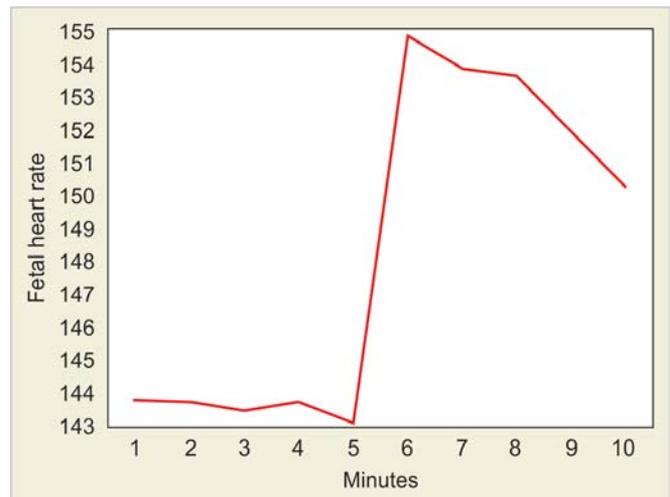
**Conflict of interest:** None declared

## INTRODUCTION

When prenatal medicine—this means the medicine which concerns mainly the infant within obstetrics—started in its broader applied form in the middle of the last century, there have been quite different aspects to make the fetus accessible for medicine, hardly to focus on a vision of fetal neurology. Such, a science was practically nonexistent because of the lack of intrauterine accesses and wrong assumptions such as, that the sensoric and neurological functions of the fetus are only present in first rudiments.



**Fig. 1:** Prof Erich Saling and PD Dr Ulrich Honemeyer in Dubrovnik 2012. © Honemeyer 2012 (private picture)



**Fig. 2:** Sontag 1936: Fetal heart rate after stimulation. After the stimulation, you see the increase of the fetal heart rate as a response of the fetus to vibratory stimulation (the heart rate was assessed by means of stop-watch and stethoscope). Figure newly drawn after the figure of Sontag 1936<sup>2</sup>, Figure 1, p. 586

These assumptions have been held despite the fact that already in the 1920s and 1930s first experiments on fetal reactions to sensory stimuli had been published: In 1924 Peiper<sup>1</sup> published about fetal movements after acoustic stimulation and in 1936 Sontag and Wallace<sup>2</sup> published about changes in the rate of the human fetal heart in response to vibratory stimuli (Fig. 2).

But it took quite a long time to change the old fashioned general opinion about the fetal brain function. For example, L Seitz wrote in the well accepted German textbook of obstetrics edited in 1951 by Walther Stöckel (translation by us): '...the cerebral functions of the fetus are only present in first rudiments. Undisturbed by sensory impressions and untouched by the outside world, the fetus is living in a sleep-like coma.' (Seitz 1951).<sup>3</sup>

Since then an explosive access to the human fetus has taken place. So in the more recent period, also the complicated neurological system could become investigated. In our overview, we will present:

- A historical overview about 'the brain in science' in general
- Then a historic overview about fetal brain assessment
- And finally present and future of fetal brain assessment.

*Note:* A substantial part of this article has been presented at the 3rd Symposium Fetal Neurology, Dubrovnik, 4 to 6 May 2012 by Erich Saling as 'Opening Lecture: Past, present and future of the fetal brain assessment'.

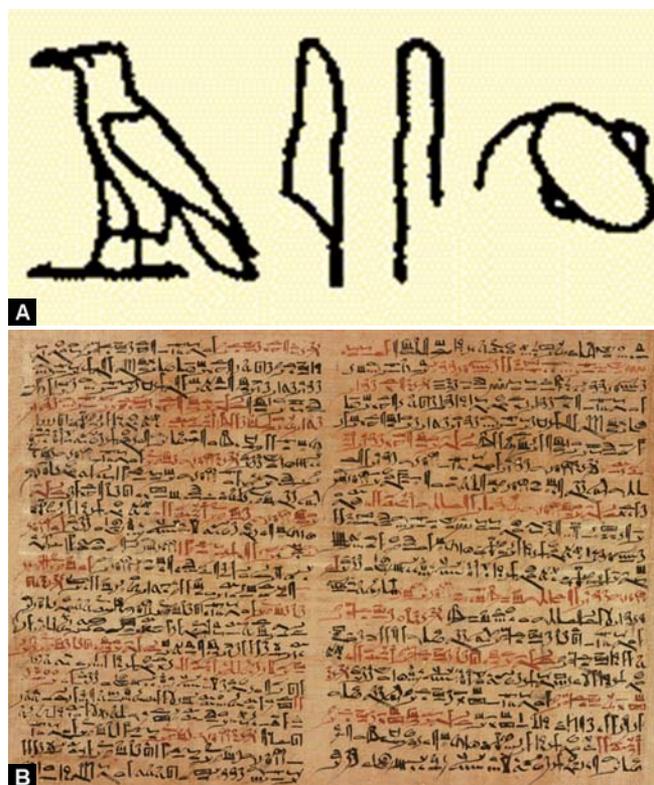
### Sensoric Stimulation of the Fetus for Assessment of its State

Before discussing some of the above mentioned new diagnostic tools in detail, let us mention a simple diagnostic measure in the field of neurologic and sensoric assessment of the fetus. It had its origin in the early historic stages of the activities in this field in the unit of Prof Saling in Berlin, and he has reported about the measure at the 6th Meeting of the International Academy of Perinatal Medicine in October 2010 in Osaka, namely the stimulation of the sensoric system of the fetus by the use of acoustic signals to assess its state. In a way, it was a further development and new application of the above discussed works of Peiper (1924) and Sontag and Wallace (1936). Saling developed a test using acoustic signals from a simple bicycle bell (published together with Arabin).<sup>4</sup> This was a practical attempt to use the reaction of the fetal heart rate for the assessment of the present state of the fetus, mainly in late pregnancy. As you see in Figure 3A to C, this vigorous fetus reacted with increases of its heart frequency depending on the intensity of stimulations.

### The Brain in Science—First Historic Stages

The fetal brain as focus of scientific interest could not emerge before the 20th century. This was only possible after a long history of parallel advances in the fields of anatomy, physiology, pathology and imaging techniques, which finally led the scientific community into the hitherto hidden mysteries of prenatal life.

Naturally, at first the brain of the adult was to become the object of research. The oldest written record using the word 'brain' appears on a papyrus called the Edwin Smith



**Figs 4A and B:** (A) Hieroglyphic for the word 'brain' (ca. 1700 BC). Source: Wikipedia<sup>68</sup>, (B) Edwin Smith Surgical Papyrus, ca. 1500 BC, written in hieratic, the Egyptian cursive form of hieroglyphs. Source: Wikipedia<sup>69</sup>

Surgical Papyrus (written around the year 1700 BC, see Fig. 4B, but it is based on texts that go back to about 3000 BC).<sup>5</sup> In Figure 4A, we present the hieroglyphic for the word "brain". The series of main scientific discoveries in human history includes the milestones listed in Table 1.

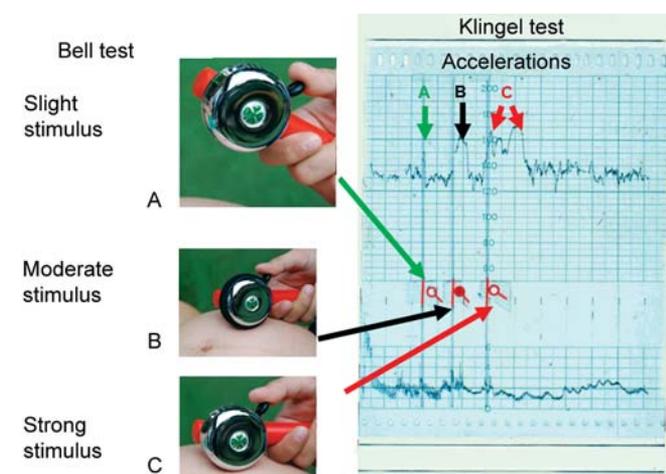
### Brain and Oxygen

These milestones in brain research are followed during the next century by a series of numerous anatomic and physiologic discoveries, descriptions of neurological and psychiatric disorders, and of pharmacological and surgical therapies. From the first description of obstructive sleep apnea 1836 by Charles Dickens (the novelist), until the comprehensive studies of oxygen blood saturation and cerebral perfusion of Kety and Schmidt, it took more than a hundred years to pass. Important discoveries regarding the connection between oxygen supplementation of the fetal brain and neurology are listed in Table 2.

### New Diagnostic Tools for Brain Imaging

The development of new diagnostic tools made possible so far unbelievable progress in modern medicine and allowed not only brain imaging, but also insights into its function. The main new diagnostic tools have been:

- The use of ultrasound for medical diagnosis started in 1937 (see below).



**Figs 3A to C:** 'Bell test' developed by Saling.<sup>4</sup> (A) Small acceleration after a slight acoustic stimulus (uncovered bell in short distance of the abdomen), (B) moderate acceleration after a moderate stimulus (covered bell with direct contact to the abdomen) and (C) strong acceleration after a strong stimulation (uncovered bell with direct contact to the abdomen). © Erich Saling (private slide)

**Table 1:** Main scientific discoveries with regard to the brain (excerpt from the extensive list 'Milestones in Neuroscience Research' from Chudler<sup>6</sup>)

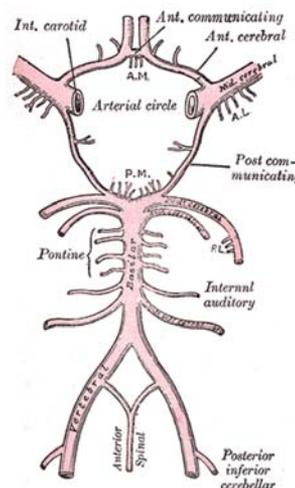
460-379 BC	Hippocrates explains epilepsy as a disturbance of the brain and confirms that the brain is involved with sensation and is the seat of intelligence
177	Galen lectures 'on the brain'
900	Rhazes in Baghdad describes seven cranial nerves and 31 spinal nerves in Kitab al-Hawi fi al-tibb (The comprehensive book on medicine), see Figure 5
1504	Leonardo da Vinci produces wax casts of human cerebral ventricles.
1573	Constanzo Varolio names the pons cerebri
1587	Guilio Cesare Aranzi describes ventricles and hippocampus. He also demonstrates that the retina has a reversed image.
1641	Francisco de la Boe Sylvius describes a fissure on the lateral surface of the brain (Sylvian fissure), and a narrow passage between the third and fourth brain ventricle (the aqueduct of Sylvius)
1664	Thomas Willis publishes Cerebri anatome in Latin and a few years later in English. In Figure 6, you see the Circulus (arteriosus) Willisii, named after him
1778	Samuel Thomas von Soemmerring presents the modern classification of the 12 cranial nerves

**Table 2:** Important anatomic and physiologic discoveries with regard to neurology and oxygen supplementation of the (fetal) brain

1667	Walter Needham postulates that the placenta acts in place of the lung (quoted in Kohlschütter 1849) <sup>7</sup>
1836	First description of obstructive sleep apnea by Charles Dickens <sup>8</sup>
1947	Kety and Schmidt's inert gas saturation method describes the effects of altered arterial tension of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption in normal young men, <sup>9</sup> see Figure 7
1954	Sir Joseph Barcroft coins the expression of 'Mount Everest <i>in utero</i> ' on the basis of oxygen content and saturation measurements in the cord blood. '... the lowest recorded levels of arterial oxygen in adult humans are similar to those of a fetus and were recorded just below the highest attainable elevation on the earth's surface: The summit of Mount Everest' (Martin et al 2010, p. 315) <sup>10,11</sup>
1957	Wilder Penfield in Canada develops maps of the sensory and motor cortices of the brain in the form of a cartoon. The sensory respectively motor homunculus (miniature human being) show how much brain area the individual parts of the human body cover. Therefore, lips and fingers (with a high number of nerve endings) are represented as larger than arms and legs <sup>12,13</sup>
1961	Breakthrough by Saling for direct intrapartum fetal access (see Fig. 8) in the form of various fetal blood examinations, preferably of blood gas content and acid base balance. This was an important step to prevent severe hypoxic damage, particularly in the brain <sup>14-16</sup>
1966	Development of Saling's concept of oxygen-conserving adaptation of the fetal circulation to hypoxemia, later by others erroneously called 'brain-sparing effect'. In fact, it is also a heart and adrenal sparing effect, <sup>17,18</sup> see Figures 9A and B
1975	Handford describes the link between pre-, peri-, and postnatal brain hypoxia, minimal brain dysfunction and schizophrenia <sup>19</sup>



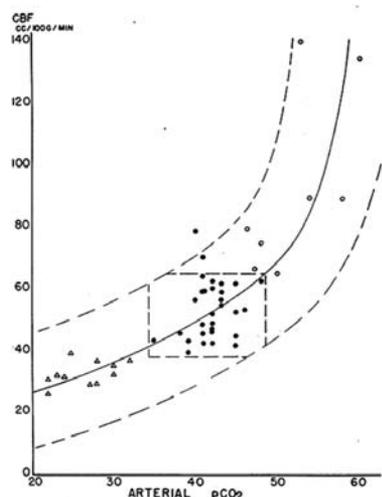
**Fig. 5:** Kitab al-Hawi fi al-tibb, which contains the first documented description of the seven cranial nerves and 31 spinal nerves by Rhazes in Baghdad. © The Bodleian Library, University of Oxford, MS Marsh 156, fol. 2v



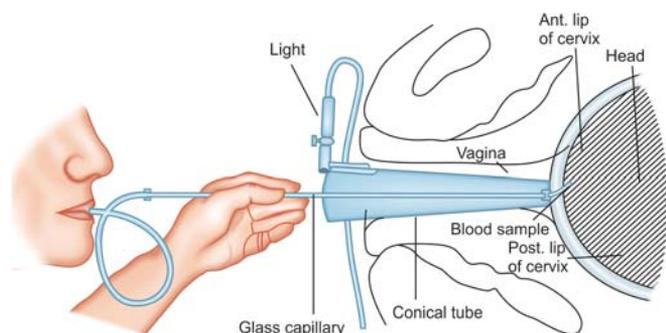
**Fig. 6:** Circulus (arteriosus) Willisii, named after the physician Thomas Willis (1621-1675). Source: Wikimedia<sup>70</sup>

- In 1971 Godfrey N Hounsfield developed X-ray computed tomography.<sup>20,21</sup>
- In 1974 E Phelps, J Hoffman and M Ter Pogossian developed the first positron emission tomography (PET)

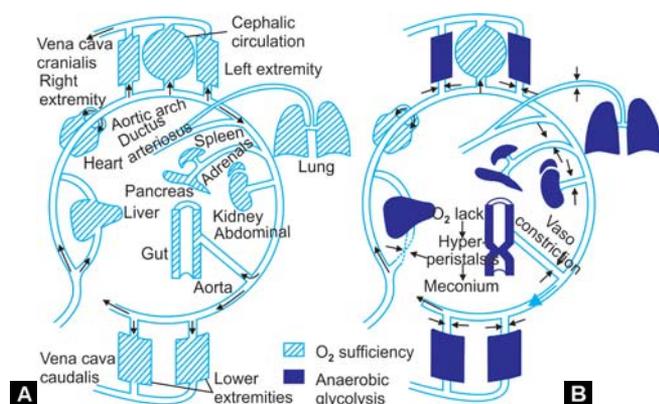
- scanner, and the first nuclear magnetic resonance image of a mouse was taken.<sup>22,23</sup>
- In 1983 FW Smith et al first described magnetic resonance imaging (MRI) of women during pregnancy in the Lancet.<sup>24</sup>



**Fig. 7:** Kety and Schmidt 1948: The relation between cerebral blood flow and arterial CO<sub>2</sub> tension. Republished with permission of American Society for clinical investigation from Kety and Schmidt 1948,<sup>9</sup> (Fig. 3); permission conveyed through Copyright Clearance Center, Inc



**Fig. 8:** Fetal blood examination. © Erich Saling (private figure)



**Figs 9A and B:** Saling's<sup>18</sup> concept of oxygen-conserving adaptation of the fetal circulation to hypoxemia (A) normal arterial supply, with full oxygenation, to heart, brain and all other parts. (B) Reduction of oxygen supply leading to vasoconstriction in extremities, abdominal viscera and lungs. Local hypoxemia leads to anaerobic glycolysis. © Erich Saling

**Fetal Brain Assessment in the Era of Ultrasound**

Karl Theo Dussik, a neurologist and psychiatrist at the University of Vienna, Austria, who started experiments in 1937, is considered to be the first physician to have used

ultrasound for medical diagnosis. By 1940 ultrasound was applied experimentally as a potential diagnostic instrument in medicine. In his 1941 publication 'Ueber die Moeglichkeit hochfrequente mechanische Schwingungen als diagnostisches Hilfsmittel zu verwenden' (Engl.: About the possibility of using high frequent mechanical oscillation as diagnostic tool) Dussik used ultrasound absorption translated into different shades of gray in the assessment of cerebral ventricles in formol preserved brain tissue.<sup>25</sup>

Gohr and Wedekind<sup>26</sup> in Germany, in 1940 released a publication 'Der Ultraschall in der Medizin' (Engl.: Ultrasound in medicine) describing the possibility of ultrasonic diagnosis by ultrasound based on echoreflexion similar to metal flaw detection. They assumed that the method could be used for detection of tumors, exudates and abscesses. Unfortunately they had no convincing results from their experiments. In 1950, Ballantine, Bolt, Hueter et al, USA, published data on ultrasonic detection of intracranial tumors.<sup>27</sup>

In the 1950s real ultrasound scanning began in the University Department of Midwifery in Glasgow, under Professor Ian Donald. At that time his experiments appeared as a quite outlandish venture. Prof Ian Donald's publication 'Investigation of abdominal masses by pulsed ultrasound' (see Fig. 10) was published in the Lancet in 1958.<sup>28</sup> It '...was considered as the most important paper on obstetrical and gynecological sonography that was ever written. The paper spanned 9 pages describing the group's experience in 100 patients. It contained 12 illustrations of B-mode sonograms of the gravid uterus, ovarian cysts, fibroids and ascites and various normal and pathological conditions. It also depicted the prototype B-mode scanner gantry and probe and the Mark 4 flaw detector with which images were made.'<sup>29</sup> Safety of diagnostic ultrasound was discussed in the same paper.

In 1969, the First World Congress on Ultrasonic Diagnostics in Medicine was held in Vienna. Ian Donald

ARTICLES THE LANCET

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**INVESTIGATION OF ABDOMINAL MASSES BY PULSED ULTRASOUND**

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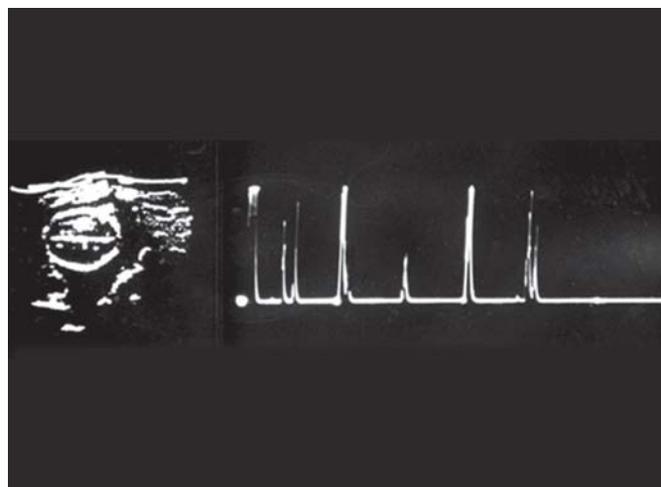
**Fig. 10:** Ian Donald's paper on ultrasound (1958)<sup>28</sup>

presented a hydrocephaly case in one of his early introductory papers on ultrasound, which described findings regarding ‘tissue interface within the body by ultrasonic echo sounding’.<sup>30</sup>

Already in 1968 Stuart Campbell’s landmark publication ‘An improved method of fetal cephalometry by ultrasound’ explained the application of both the A- and B-mode scan measuring the biparietal diameter of the fetus’s head, see Figure 11.<sup>31,32</sup> This easy and reproducible parameter soon became standard practice for fetal ultrasound examinations. Stuart Campbell documented the case of a 17 weeks anencephaly in 1972, using static B-mode equipment.<sup>33</sup> 1975 followed the ultrasonographic diagnosis of spina bifida.<sup>34</sup> Both reports were published in the *Lancet* as landmark papers. These were the first diagnosis and management cases of anencephaly and spina bifida with termination of pregnancy based on correct sonographic diagnosis.

In 1972 David Brock and R Sutcliffe measured alpha-fetoprotein (AFP) values in the amniotic fluid of six pregnancies with spina bifida and 31 pregnancies of anencephaly. They found significantly elevated AFP levels in all of the cases of anencephaly and most of the cases with spina bifida. This discovery was considered as a milestone in the history of prenatal diagnosis.<sup>35,36</sup>

Further progress in the diagnosis of spina bifida and myelomeningocele was made—again with the participation of Stuart Campbell—about 20 years after his first publications in this area. MC Van den Hof, K Nikolaides and S Campbell in 1990 coin the lemon and the banana sign, the cranial ‘botanical signs’ for spina bifida and myelomeningocele.<sup>37</sup> In 2009, R Chaoui describes the absent intracranial translucency as first trimester equivalent for the caudal-dislocation of the cerebellum in spina bifida.<sup>38</sup>



**Fig. 11:** Campbell’s combined A and B scan technique for accurate cephalometry.<sup>31,32</sup> Right picture: A-scan; left picture: B-scan. © Stuart Campbell (private slide) with kind permission

The advent of real-time sonography had raised hopes that observation of fetal behavior, physiological responses, and development of the fetal sensory system would soon be possible. However, these observational studies were time consuming, and the results were mostly questionable and useless for clinical tests. In 1978 Jason Birnholz at Harvard published several pioneering papers, characterizing intrauterine neurological developmental steps by using the evaluation of fetal movement patterns and movements of the fetal eye, to define states of fetal wakefulness and dreaming.<sup>39,40</sup>

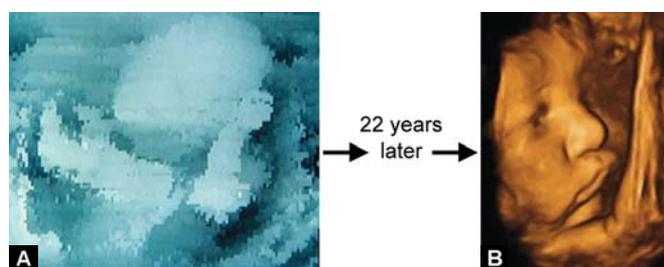
In 1981 Jury Wladimiroff et al were the first who described Doppler measurements of the middle cerebral arteries (MCA) for the assessment of fetal compromise. In 1986, Wladimiroff and his group confirmed the importance of the MCA spectral Doppler measurements in the evaluation of severity of compromise in growth restricted fetuses. The absence and reversal of end-diastolic flow (ARED) in the umbilical arteries of these fetuses were amazing demonstrations of fetal pathophysiology.<sup>41</sup> The observation of clear and unquestionable increase in diastolic flow in the MCA velocity waveforms in the presence of fetal hypoxia was completely in line with the results of Kety and Schmidt 40 years earlier.

Caused by the rapid development in this field, in 1984, ‘The Fetus as a Patient’ society was founded.

Publishing his results as early as 1989, Asim Kurjak, using the Aloka<sup>®</sup> machine, was the first to apply transvaginal color Doppler for studies of the pelvic circulation.<sup>42</sup> In the same year, Toshiyuki Hata and co-workers (Japan) did publish about “Transvaginal Doppler color flow Mapping”.<sup>43</sup> The Croatian group around Asim Kurjak has from 1989 until today continued to publish close to 80 trailblazing papers on the applications of transvaginal color Doppler in Obstetrics and Gynecology (PubMed research March 2012).

Many scientists dreamed of visualizing the fetus in 3D. 1984, in Japan Kazunori Baba<sup>44</sup> was the first to develop a 3D ultrasound system (Figs 12A and B) and to produce 3D fetal images by processing the raw 2D images on a mini-computer. In 1992, HC Kuo et al in Taiwan used a Combison 330 apparatus from Kretztechnik<sup>®</sup> and were able to visualize the fetal face, cerebellum, and cervical vertebrae in 3D.<sup>45</sup> In 1995, E Merz in Germany reported a large series of over 600 cases of fetal diagnosis using 3D ultrasound. They pioneered the use of 3D transvaginal ultrasound in early detection of fetal facial anomalies, often the most visible sign of abnormalities of the central nervous system (‘The face is the predictor of the brain’).<sup>46-48</sup>

The field of 3D ultrasonography grew to a high dimension, so that the time was ripe for the 1st World



**Figs 12A and B:** (A) First 3D ultrasound image of a fetus (19 gw) from Kazunori Baba,<sup>44</sup> © Kazunori Baba, republishing with kind permission, (B) 3D-ultrasound picture taken in 2010. © Honemeyer 2011, Welcare Hospital



**Fig. 13:** 4D or real-time 3D ultrasound. © Honemeyer 2012, Welcare Hospital

Congress organized by E Merz in September 1997 in Mainz, Germany.

F Chervenak in 1995 together with A Kurjak and C Camstock presented the book 'Ultrasound and the fetal brain'<sup>49</sup> with original new data along with authoritative analyses and syntheses of all available clinical and research findings on using ultrasound, including color Doppler and MRI. 'Fetal and Neonatal Neurology and Neurosurgery',<sup>50</sup> provided information on the developmental neurology and pathology of the developing central nervous system from conception through the first year of life.

### Present Status of Fetal Brain Assessment by Ultrasound

With the advent of 4D or real-time 3D ultrasound, straightforward visual transfer of fetal movements to the sonographer's eye had become possible (Fig. 13). The human eye can differentiate single images up to a frame rate of 12 Hz. Above this frame rate, serial images are perceived as continuous movement. At the moment, peak frame rates in high end equipment reach 20 Hz. This enables visualization of even small facial twitches of the unborn, and has opened the doors of perception to an abundant variety of fetal behavior.

Since 2001, a growing number of papers on 4D findings of fetal behavior have been published, reflecting the great interest of the medical research community in fetal neurology. A landmark in the study of fetal movements is certainly the creation of Kurjak Antenatal Neurodevelopmental Test (KANET).<sup>51</sup>

KANET evaluates eight fetal parameters and estimates variability, complexity, and fluency of isolated and general movements (for example isolated head anteflexion, hand to face movement, etc.) which hopefully will give insights into CNS maturation, as well as into functional and structural abnormalities.<sup>52,53</sup>

In 2009, R Pooh and A Kurjak published their book Fetal Neurology which contained a great amount of

contemporary knowledge about the fetal brain, with contributions from many leading scientists.<sup>54</sup>

### Magnetic Resonance Imaging

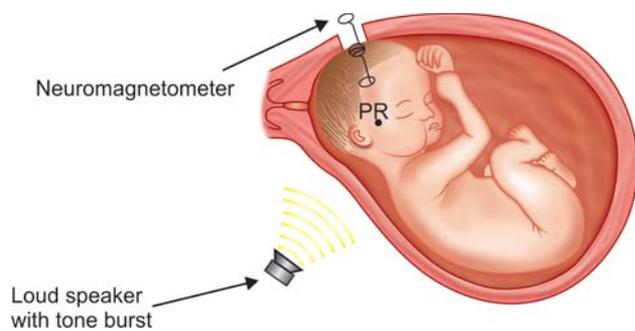
Although ultrasound provides adequate information in most cases and continues to be the initial prenatal examination of choice, there are instances in which the results of the ultrasound study may be equivocal. MRI may provide an extra dimension in diagnosis by showing clearer anatomic relationships in the pelvis. Smith et al in 1983, were the first to describe MRI of women during pregnancy.<sup>24</sup> The first obstetric applications were mainly related to maternal and placental abnormalities. Fetal applications were difficult because of the image degradation caused by fetal motion on standard sequences and thus largely confined to volumetric measurements.

### Very First Magnetoencephalography performed on a Human Fetus

The very first magnetoencephalographic recordings of the brain activity of a human fetus were performed in Berlin in 1984, in the unit of Prof Saling, together with the two physicists Thomas Blum and Rudolf Bauer.<sup>55,56</sup> During these first fetal magnetoencephalograms, auditory responses of the fetal brain were measured with a neuromagnetometer. The responses occurred when a loud sound stimulus—a tone burst—was transmitted through the mother's abdominal wall (Fig. 14). In Figure 15 you see the records. The magnetic response near the end of the pregnancy, referred to as 'the prenatal auditory evoked field', was similar to that observed afterwards in newborn infants. This was the very first fetal magnetoencephalogram at all.

### New Developments in Fetal MRI

During the early 1990s single-shot rapid acquisition sequence with refocused echoes was developed, which revolutionized fetal MRI.<sup>57</sup> In fetuses with sonographically



**Fig. 14:** Fetal magnetoencephalography (fMEG):<sup>55</sup> Localization of magnetometer and loud speaker. *Source:* Saling (private figure)

diagnosed central nervous system abnormalities, MRI shows additional central nervous system abnormalities in up to 50%.<sup>58</sup>

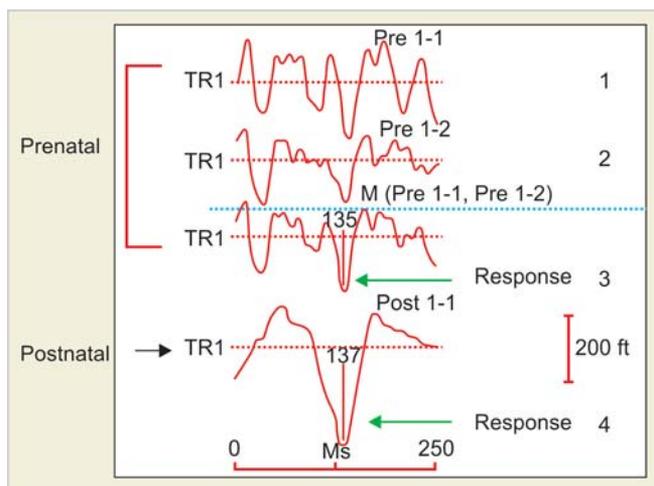
The advantages and disadvantages of both neurosonography (NS)—particularly transvaginal NS and MRI are best characterized by citing one of the latest publications in this field, by R Pooh and A Kurjak: ‘Transvaginal three-dimensional (3D) sonography ... (enables) multiplanar analysis of ... (intracranial) morphology, tomographic ultrasound imaging in any cutting section, 3D sonoangiography, and volume calculation of ventricles or intracranial lesions’ (Pooh, Kurjak).<sup>43</sup> ‘However, the transvaginal high-frequency approach has ... limitations due to lack of penetration and cranial bone ossification with advanced gestational age.’ (Pooh, Kurjak).<sup>43</sup>

Since, bony structures are no handicap for magnetic resonance, fetal MRI ‘of the intracranial cavity, brainstem and cortical gyral/sulcal ...’ structures provide excellent results (Pooh, Kurjak).<sup>43</sup> Depending on the case, MRI and 3D ultrasound imaging should be used complementary.

## THE FUTURE

**Fetal 3D MRI:** Multiplanar, anatomical projections are essential for assessment of the fetal supratentorium, posterior fossa, brain stem and spinal cord and canal. The 3D MRI is valuable in swiftly depicting gross anatomy and pathology, as well as quantifying fetal biometry.<sup>59</sup>

**Functional MRI (fMRI)** serves to highlight areas of the brain using oxygen. These areas are presumably engaged in neuronal activity, such as thinking. With the help of echo planar imaging (EPI), fMRI allows to distinguish oxygenated blood flowing into more active areas of the brain, from less active areas with deoxygenated blood. fMRI machines function similarly to standard MRI in creating magnetic fields that differ slightly throughout the brain. Thus, a different magnetic environment for hydrogen atoms in different areas is provided. fMRI has the ability to scan the brain in under 400 milliseconds and allows capturing of



**Fig. 15:** Auditory-evoked neuromagnetic fields (1) and (2) are prenatal recordings and (3) is the mean value of both observations (see upper green arrow); (4) is recorded postnatally (see lower green arrow), you see the concerned pattern in the same individual as newborn. Modified after Blum, Saling, Bauer 1985,<sup>56</sup> p. 1226. *Source:* Saling (private figure)

very rapid sequences of events in the brain. This fact moves fMRI closer to electroencephalography (EEG).<sup>60</sup>

Brain regions simultaneously activated during any cognitive process are functionally connected, forming large-scale networks. These functional networks can be examined during active conditions and also in passive states.<sup>61</sup>

**Structural and functional brain studies—MRI:** Several neurologic and psychiatric disorders (for example autism and schizophrenia) are suspected to be brain connectivity disorders. fMRI might give evidence of what normal and abnormal structural and functional connectivity look like.<sup>62,63</sup>

**Computing power:** A large amount of computing power is required to support all the processing needs in B-mode imaging, color-flow imaging, and image processing/display. Incorporating new features, such as advanced image-processing applications, panoramic imaging, 3D- and 4D imaging with higher frame rates and better resolution, will require even more computing power in future machines. The recent development of computer technique and forward-looking statements promise a continuous improvement of the central processing unit (CPU) – the computer ‘brain’, of the hard drives, monitors, and random access memory (RAM) which is crucial in allowing the computer to interface almost all of the hardware peripherals and relay them back and forth with software functions.

**Matrix array probes:** For discussing the current advantages and disadvantages of matrix array probes, let us cite from an article of Gonçalves et al (2006): ‘Although today’s mechanical 3D volume acquisition transducers have

provided an interim approach for ‘real-time’ imaging, they are currently unable to achieve acquisition speeds that are potentially achievable using 2D matrix array transducers.’ (Gonçalves et al)<sup>64</sup> ‘The strength of the 2D matrix array approach for examination of fetal structures lies in the possibility of directly acquiring a pyramidal volume of ultrasonographic data, currently at rates of 24 volumes per second. When compared to reconstructive 3D/4D ultrasonography, this technique minimizes artifacts related to maternal and fetal motion ...’ (Gonçalves et al).<sup>64</sup>

## CONCLUSION

The ‘wire-frame’ images which Ian Donald produced with his apparatus more than half a century ago, have now transformed into ‘fetoscopy-realistic’ computer generated 3D real-time images. Sonography has become the primary technique for fetal imaging due to its proven utility, widespread availability and relatively low cost in comparison to MRI.

If testing/screening for fetal behavioral abnormalities, as early sign of neurodevelopmental abnormality, was to be introduced into clinical practice then this is conceivable only by means of 4D sonography.

KANET scoring system appears to have the potential to detect and discriminate normal from borderline and abnormal fetal behavior in normal and in high-risk pregnancies, and has already been applied in multicentric studies.<sup>51,65-67</sup> The results are promising.

## FINAL GENERAL COMMENT

The history of research about the brain and nervous system goes back for at least 5000 years. However, history of fetal brain assessment is very ‘young’. It is an important component of the so rapidly growing prenatal medicine.

We, the living generation, are witnesses of bringing forward human medicine now for the very first time also into the uterus and more than this to experience how explosive this new development is. In view of the prime importance of the neurologic system we can also hope for convincing practical progress in prevention of neurologic impairments in the near future.

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