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Horizon Scanning Technology Horizon Scanning Report

MRI for the detection of foetal abnormalities

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Executive Summary

This report describes the use of MRI to detect foetal abnormalities or birth defects. Currently the Australian National Perinatal Statistics Unit defines a birth anomaly as "anatomical defects or chromosomal abnormalities that are present at birth". The use of MRI is *not* designed to replace ultrasound as the obstetric diagnostic tool of choice, but rather to act as an adjunct in cases where an ultrasound diagnosis is equivocal. Ultrasound remains the gold standard of foetal imaging.

MRI is considered a suitable foetal imaging technology as it is non-invasive, avoids the use of ionising radiation, and is not hampered by maternal obesity or foetal position. Although some safety concerns have been raised in the use of MRI for foetal imaging, surveys of children scanned with MRI *in utero* have found no adverse outcomes later in life from this exposure. MRI examinations are usually only conducted in the second trimester. Most MRI units used to conduct foetal MRI are 1.5 Tesla (T). Although MRI units of 2.5 and 3T have stronger gradients which allow acquisition of images with a higher signal-to-noise ratio and higher spatial resolution, they are not recommended for use in foetal imaging. With the advent of ultrafast MR sequences (sequence acquisition of 20 seconds), foetal motion is not usually an issue.

The majority of studies included for assessment in this report were diagnostic accuracy studies that compared a diagnosis with ultrasound (US) to a diagnosis with MRI. In most studies, these results were compared to the reference standard of either postnatal clinical follow-up or post-mortem confirmation of diagnosis.

Studies included in this report described a number of diverse outcomes including: the number of discordant diagnoses between ultrasound and MRI; the number of discordant diagnoses between MRI and postnatal clinical follow-up or post-mortem results; additional information gained from MRI which resulted in changes to counselling and clinical management of the pregnancy; and the sensitivity and specificity of MRI compared to ultrasound. The majority of studies reported on findings of only one type of foetal abnormality, whereas the studies which scanned foetuses for *all* abnormalities, MRI was incorrect in a high number of diagnoses (39%). The diverse nature of abnormalities was considered to be the main factor in misdiagnosis by MRI, however studies such as this are more likely to reflect the situation encountered in obstetric clinical practice. In addition, it was reported that the discordant rate between US and MRI was reported to be greatly reduced (6.2%) when women underwent a confirmatory US, prior to MRI and conducted by the same institution where the MRI was to be conducted. Generally studies with low numbers of enrolled women reported larger discrepancies between the diagnosis with US and MRI, which may be a reflection of the need for extensive clinical expertise being required for the diagnosis of foetal abnormalities.

No studies included in this report described any adverse events that occurred as a result of conducting an MRI examination on a foetus, either to the foetus

or the mother. Although no studies reported on the termination of pregnancies based on a false positive diagnosis obtained with MRI, a small number of studies reported on the misdiagnosis of foetal abnormalities by MRI. Of these, the largest number of misdiagnoses was described by Limperopoulos et al (2006). Of 19 foetuses diagnosed with vermian hypoplasia with prenatal MRI, six were confirmed as normal with postnatal MRI, a false positive rate of 32 per cent. None of these pregnancies were termination, however the over diagnosis of vermian hypoplasia may have led to the unnecessary terminations.

No cost-effectiveness data were available on the use of MRI as a complementary tool to ultrasound for the diagnosis of foetal abnormalities.

In conclusion, MRI appears to be a useful adjunctive tool, in combination with ultrasound, for the diagnosis of some foetal abnormalities. Ultrasound remains the gold standard in the screening of pregnant women. In cases of equivocal ultrasound diagnosis, MRI may provide additional information which may improve prenatal parental counselling, alter the clinical management of the pregnancy and improve postnatal therapeutic planning. A confirmatory ultrasound in addition to the referral ultrasound, conducted by the same institution where the MRI is to be conducted, may be beneficial. MRI scans for foetal abnormalities should only be conducted in tertiary centres where parents may access the appropriate level of counselling.

Foetal MRI promises to be a complementary tool in diagnosing a foetal abnormality or birth defect identified during routine second trimester US screening.

To date, published studies report inconsistencies concerning, *inter alia*, referral of patients, protocols and reporting requirements. In addition, the comparative diagnostic accuracy of foetal MRI and US, and its impact on patient management following MRI, as measured by postnatal follow up or *post mortem*, is not established. Further long-term data are needed to inform the usefulness and impact of foetal MRI on current screening and counselling paradigms.

Foetal MRI should only be carried out in tertiary referral medical centres in which the following have been considered and addressed established:

- counselling for patients is available;
- standardised and consistent referral and scanning protocols and reporting requirements are developed, implemented and evaluated on a regular basis;
- a confirmatory US prior to, and in the same institution providing, foetal MRI; and
- regular review and evaluation of outcomes.

Health Services will need to carefully address governance issues (credentialing, scope of practice and audit) if intending to provide foetal MRI following routine second trimester US screening.

In conclusion, MRI appears to be a useful adjunctive tool, in combination with US, for the diagnosis of some foetal abnormalities. US remains the gold standard in the screening of pregnant women. In cases of equivocal US diagnosis, MRI may provide additional information which may improve prenatal parental counselling, alter the clinical management of the pregnancy and improve postnatal therapeutic planning.

The National Horizon Scanning Unit, AHTA, Discipline of Public Health, University of Adelaide, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of magnetic resonance imaging (MRI) for the detection of foetal abnormalities.

MRI for the detection of foetal abnormalities should only be offered through specialist hospitals and is currently in limited use in Australia.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of MRI for the detection of foetal abnormalities, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with MRI for the detection of foetal abnormalities.

Background

Description of the technology

The procedure

A MRI scanner uses pulsed oscillating magnetic fields (radio-frequency energy) to organise the intrinsic magnetic behaviour of hydrogen nuclei in the body. This causes a change in the alignment of the nuclei so that they are oscillating perpendicular to the main field direction (excitation). Tuned receiver coils detect these magnetic field oscillations through electromagnetic induction (personal communication[1]). Once the pulse is removed, the nuclei realign or relax at different rates depending on the surrounding environment. The relaxation time is referred to as T1. In addition to relaxation time, MRI assesses the spin property of nuclei. When the radio-frequency pulse is applied, the nuclei align and the spins come into phase. When the pulse is removed, the spins of the nuclei "de-phase" and the signal decreases. When the spins are completely at random again the MR signal disappears. The time taken for the spins to de-phase is referred to as T2 (FASEB 2002).

Spatial localisation of the MR signal is achieved by the application of "gradient" magnetic fields at specific stages of the MR sequence, causing a predictable relationship between location and resonant frequency that can be

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[1]Senior Radiographer in MRI Research and Development Radiology in the Royal Adelaide Hospital

resolved. The excitation/ receive cycle is repeated with varying spatial encoding to deliver an array of coded signals that are reconstructed into a set of images with Fourier Transformation mathematics (personal communication).

Hydrogen nuclei in blood and cerebrospinal fluid have a long relaxation time, compared to nuclei in tissues, with hydrogen nuclei in fat cells having the shortest relaxation time of approximately 300 milliseconds. The differences in realignment and spin times appear as differences in brightness on the MR image. A series of consecutive two-dimensional images or slices are compiled and assembled by a computer program to produce a final three-dimensional image (FASEB 2002).

Foetal MRI has been performed since 1983 primarily to study the developing central nervous system (CNS) of the foetus. However, due to the length of time required for the attainment of meaningful images, these early studies required sedation of the pregnant woman and immobilisation of the foetus. With the advent of ultrafast MR sequences (sequence acquisition of 20 seconds), foetal motion is not an issue and MRI for foetal imaging has become an acceptable technique (Prayer et al 2004). Several artefacts may occur when conducting a foetal MRI scan. These include:

- motion artefacts from either the mother or foetus, resulting in a blurred image;

- fluid motion - which appear as signal voids within the image caused by amniotic fluid, cerebrospinal fluid or foetal urine, aliasing[2]. This occurs when objects outside the field of view wrap round and appear on the opposite side of the image (solution is to increase the field of vision); and

- partial volume artefacts when a thick slice is used and the same structure is found in two consecutive slices (solution is to use thinner slices and decrease the field of vision) (Roorda 2004).

Usually gadolinium is administered as a contrast agent during a MRI scan, but this is contraindicated in pregnant women. Gadolinium has been demonstrated to cross the placenta and appears rapidly in the foetal bladder. The contrast agent is then excreted into the amniotic fluid and swallowed by the foetus, having the potential to be reabsorbed into the gastrointestinal tract. The half-life of gadolinium in the foetal circulation is unknown, although studies in rats have indicated that developmental retardation occurs when high doses are administered *in utero*. Gadolinium is classified as a Category C drug which may only be administered to pregnant women if the potential benefit far outweighs the risk. Contrast agent is not required for pelvic and foetal imaging, but may be required for imaging maternal structures such as in cases of placenta accreta. This imaging procedure may be conducted shortly before delivery and therefore accumulation of gadolinium in the amniotic fluid is not an issue (Levine 2005; Levine 2006).

MRI examinations are usually only conducted in the second trimester. There is a theoretical risk to the developing foetus if MRI is conducted in the first

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[2] Aliasing refers to an effect that causes different continuous signals to become indistinguishable (or aliases of one another) when sampled.

trimester and prior to 13 weeks gestation the developing foetus is difficult to adequately visualise (Levine 2005; Roorda 2004). Most foetal MR images are conducted using a T2 single-shot fast spin echo (SSFSE) sequence which utilises only one radiofrequency pulse. Half-Fourier acquisition turbo spin-echo (HASTE) may also be used, which reduces image acquisition time (1 second), enabling multiple slice breath-holds, real time imaging and images free from foetal motion. Images are acquired in three planes (axial, coronal and sagittal to the head) orthogonal to the foetus. Patients are scanned in the supine or the left-lateral position to avoid aorta-caval compression. Those patients suffering from claustrophobia can enter the scanner feet first. To maximise image signal capture, a combination of coils may be placed over the pelvis or pregnant uterus and the lower spine. The average duration of a foetal MRI ranges between 10 to 35 minutes (Cannie et al 2006; Levine 2005; Prayer et al 2004; Roorda 2004; Sandrasegaran et al 2006). Most units used to conduct foetal MRI are 1.5 Tesla (T). Although MRI units of 2.5 and 3T have stronger gradients which allow acquisition of images with a higher signal-to-noise ratio and higher spatial resolution, they are not recommended for use in foetal imaging (Cannie et al 2006; Morris et al 2005).

Intended purpose

This report describes the use of MRI to detect foetal abnormalities or birth defects. Currently the Australian National Perinatal Statistics Unit defines birth anomalies as "anatomical defects or chromosomal abnormalities that are present at birth". The states and territories of Australia all use various combinations of birth anomalies in their definition including structural (eg spina bifida), anatomical, functional, chromosomal (eg Down's Syndrome), genetic and biochemical (eg phenylketonuria). No one state or territory uses all types of birth anomaly in their definition (Birch et al 2004). In the literature a birth anomaly is commonly referred to as a birth defect or a congenital anomaly. A list of birth defects as defined by the South Australian Birth Defects Register is listed in Appendix C.

The use of MRI as a non-invasive imaging technique to detect foetal abnormalities has increased in the last decade. Unlike ultrasound, MRI cannot be used to assess foetal motion which may be clinically important (Frates et al 2004). The use of MRI is *not* designed to replace ultrasound as the obstetric screening tool of choice, but rather to act as an adjunctive diagnostic tool in cases where an ultrasound is equivocal. Ultrasound remains the gold standard for foetal imaging. The additional information gained from performing MRI may change the initial ultrasound diagnosis, resulting in a changed approach to counselling or patient management. MRI is indicated for use during pregnancy for;

- Maternal health/abnormalities including conditions unique to pregnancy such as ectopic pregnancy, placenta accreta, placenta praevia, intrauterine bleeding, uterine dehiscence and rupture, as well as other medical conditions including haemorrhage, arteriovenous malformation, aneurysms, neoplasms and infarctions;
- Foetal pathologies including evaluation of the central nervous system, neck masses, thoracic viscera, abdominal-pelvic viscera and conjoined twins; or

- The need to perform foetal surgery for conditions including neural tube defects, congenital diaphragmatic hernia and airway obstructing masses (Levine 2006; Roorda 2004).

Foetal MRI has been demonstrated to be useful in the evaluation of the CNS, in particular for the diagnosis of ventriculomegaly, which may occur as a result of an abnormality in cerebrospinal fluid flow dynamics, abnormal cerebral development, or from an infection or infarction. MRI is not usually required for the diagnosis of neural tube defects but may be useful to detect other structural malformations of the CNS. MRI used to image the foetal lung can estimate lung volume, an important consideration for foetal survival if pulmonary hypoplasia is suspected. Other thoracic abnormalities successfully imaged by foetal MRI include congenital diaphragmatic hernia, cystic adenomatoid malformation and broncho-pulmonary sequestration. MRI is also particularly useful for imaging foetal abdominal abnormalities including defects in the genitourinary tract, the gastrointestinal tract and the abdominal wall (Laifer-Narin et al 2007; Sandrasegaran et al 2006).

Clinical need and burden of disease

The Australian Institute of Health and Welfare (AIHW) National Perinatal Statistics Unit (NPSU) was established in 1979 to provide information and statistics on reproductive and perinatal health. Data are provided to the NPSU by the states and territories and include information on diagnosis, method of prenatal diagnosis, sources of diagnosis, birth outcome, plurality and birth order, birth weight, and previous pregnancies and outcomes. The NPSU developed a classification of birth anomalies based on the Royal College of Paediatrics and Child Health's Classification of Disease (based on ICD-9-CM[3]). However, there is variation amongst the states and territories of Australia in the ICD classifications used to code birth anomalies, in addition to differences in methods of data collection, the sources of birth anomaly notifications and the scope of data collection. Currently the only states that are able to detect birth anomalies up to one year of age are New South Wales, Victoria, Western Australia and South Australia. A 2004 report recommended that a National Birth Anomalies Steering Committee be established, comprising state and territory members. This Committee is responsible for developing a nationally consistent definition of birth anomalies (Birch et al 2004).

The last full report produced by the NPSU contains data collected on birth anomalies during the period 1981-1997. In 1997, for the whole of Australia, there were 254,390 live births and 1,808 still births. During this same period there were a total of 4,489 congenital malformations (single and multiple), translating to a prevalence rate of 175 per 10,000 births[4]. Rates were much higher in both Victoria and the Australian Capital Territory (ACT) (229 and 222 per 10,000 respectively) which may reflect differences in classification or data collection between the states. Of these malformations, those that involved

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[3] ICD= International Statistical Classification of Diseases and Related Health Problems, currently in its 10th edition, ICD-10
[4] Data includes congenital malformations diagnosed in liveborn infants in the first 28 days, or in still births of at least 20 weeks gestation or 400 gram birth weight. Terminations of pregnancies at ≥ 20 weeks gestation are included.

the heart accounted for the highest rate at 35.5 per 10,000 births, followed by musculoskeletal (33.7) and malformations of the genital organs (24.2). The rate for chromosomal malformations alone was 22.5 per 10,000 births, with the majority of these being trisomy 21 or Down's Syndrome (13.0 per 10,000 births) (AIHW & UNSW 2001).

More recent data are available from birth defects registers from the individual states (Victoria, South Australia and Western Australia). The 2003 Annual Report of the South Australian Birth Defects Register indicates that in the year 2003 there were 798 birth defects representing 4.5 per cent of all births[5]. Birth defect rates increased in male children (4.7% versus 3.9% of females) and in multiple births (4.8% versus 4.5% of singleton births). In South Australia during the period from 1986-2003, there was a significant decrease in the prevalence of neural tube defects due to the introduction of the "folate before pregnancy" campaign. During the same time there was no change in the prevalence of cleft lip but there was a significant increase in the prevalence of Down's Syndrome, associated with increasing maternal age. In 2003 there were 171 deaths associated with birth defects in South Australia. Of these 119 (70%) were terminated pregnancies. A total of 81 pregnancies were terminated at less than 20 weeks, and of these 15 (8.8%) were diagnosed by chorionic villus sampling and/or ultrasound in the first trimester, and 66 (38.6%) were diagnosed by amniocentesis, cordocentesis and/or ultrasound after the first trimester. Thirty-eight pregnancies were terminated after 20 weeks gestation (Haan et al 2004).

Similarly the Western Australian Birth Defects Registry reported in 2003 that of 24,681 births there were 1,269 birth defects representing 5.1 per cent of all births[6]. This number has decreased in 2005 to 3.9 per cent of all births. Birth defects in Western Australia were also more common in male infants and multiple births. The reported lower prevalence of birth defects in Aboriginal children is thought to be due in part to an under-ascertainment of cases in this population. Similar trends as those observed in South Australia were reported in Western Australia for neural tube defects and Down's Syndrome. The total number of deaths associated with a birth defect was 217. Of these, 24 were spontaneous still births, 18 were neonatal deaths and six were post-neonatal deaths. The number of terminations following a prenatal diagnosis of a foetal abnormality was 169. Rates for termination of a pregnancy have increased in Western Australia from 1.2 per 1,000 births in 1980-1984 to 6.7 per 1,000 in 2005 (Bower et al 2006).

In Victoria during the period 2003-2004 the overall prevalence of birth defects was 435/10,000 or 4.4 per cent, representing approximately 2,700 babies. For 12 per cent of birth defects there was a termination of pregnancy before 20 weeks gestation. As in other states, males had higher rates of birth defects (4.7%) than females (3.7%) and approximately five per cent of multiple births

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[5] The SA Birth Defects Register defines a birth defect as a condition which originated before birth, but may be identified up to five years of age. SA data includes terminations of pregnancy at any gestation due to a diagnosis of a birth defect, stillbirths, newborn babies and children up to 5 years of age diagnosed with a birth defect.
[6] The WA Birth Defects Registry defines a birth defect as a condition which originated before birth, but may be identified up to six years of age. Terminations are not included in the data, only livebirths and stillbirths ≥ 20 weeks gestation are included.

had a birth defect. In Victoria during the period 2001-2004 obstructive defects of the renal pelvis had the highest recorded rate of 38 per 10,000 births, followed by hypospadias with a rate of 34.1, ventricle septal defects (33.7), congenital dislocation of the hip (28.5) and trisomy 21 (28.6). As in other states there was a significant decrease in the number of neural tube defects and spina bifida and significant increases in the rates of hydroplastic left heart syndrome, obstructive defects of renal pelvis, trisomy 21 and trisomy 18 over the period 1993-2004 (Riley & Halliday 2006).

In New Zealand during 2003, there were 56,134 registered live births (New Zealand Health Information Service 2007). New Zealand data indicates that there was a total of 4,657 malformations in 2003. Of these, 757 were congenital heart defects, 95 chromosomal anomalies, 55 were Down's Syndrome, 12 had neural tube defects and 100 had facial clefts (NZ Birth Defects Monitoring Programme, personal communication).

Stage of development

The state of Victoria is currently conducting an audit of all foetal MRIs for the detection of foetal abnormalities performed at three major centres. Three foetal medicine units within Melbourne are involved in referring patients to three different MRI units: The Mercy Hospital for Women refers patients to the Austin Repatriation Hospital, The Monash Medical Centre refers on to Southern Health, and The Royal Women's Hospital refers patients to the Royal Children's Hospital. Patients referred to any of these centres for a foetal MRI must undergo a repeat tertiary level ultrasound and have consulted a foetal medicine specialist. In addition, geneticists, counsellors and social workers may need to be consulted (personal communication, Southern Health).

It is likely that all states are conducting a limited number of foetal MRI scans, however it is strongly recommended that foetal MRIs should only be performed and interpreted in centres of excellence with appropriate experience and part of a multidisciplinary diagnostic team. Foetal MRI has been performed in France for over 15 years and is routinely performed in the United States (personal communication, Southern Health). The literature accessed at the time of preparing this report suggests that continued technical advances are likely to contribute to significant growth in the uptake of this technology in Australia and New Zealand (Glenn & Barkovich 2006).

Treatment Alternatives

Existing comparators

Two-dimensional ultrasonography is used as a routine screening tool for all pregnancies in Australia and New Zealand. Early pregnancy scanning allows determination of gestational age, appropriate management of non-progressing pregnancies, detection of multiple or ectopic pregnancies and assessment of pelvic masses. In addition, routine ultrasound is used for the diagnosis and

management of foetal abnormalities and may aid to reduce the number of perinatal deaths (RANZCR 1998a).

Ultrasound has proven to be a useful tool in the prevention, diagnosis and treatment of pregnancy complications including intrauterine foetal death and maternal death from placenta praevia. In addition, ultrasound delivers psychological benefits to mothers via the reduction of maternal anxiety relating to the health of the foetus and the progression of a normal pregnancy. A pre-12-week ultrasound is recommended to be performed in cases of recurrent (>2) abortion, maternal bleeding, suspicion of an ectopic pregnancy (based on clinical history), a very high risk pregnancy (severe rhesus disease, diabetes, previous intrauterine growth restriction (IUGR) or previous premature labour) or a previous foetal abnormality. Most scans are conducted at 18-20 weeks and at this time are capable of detecting foetal abnormalities, accurately assessing gestational age, detecting multiple gestations and of a low-lying placenta. Ultrasound scans are rarely indicated at 22-26 weeks gestation apart from foetal anomalies that have been previously diagnosed. Scans at greater than 26 weeks are indicated for suspected IUGR, previous still birth, moderate or severe maternal hypertension, pre-eclampsia or toxaemia, maternal type I diabetes, multiple pregnancy, clinical polyhydramnios, antepartum haemorrhage or suspected intrauterine foetal death (RANZCR 1998a).

In Australia, a number of Medicare Benefits Schedule (MBS) item numbers (26 in total) are used when pregnancy related ultrasounds are performed in private practice (statistics are not reported for procedures performed in public hospitals). A total of 1,450,174[7] pregnancy related ultrasounds were performed in Australia during the period July 2006 to June 2007. The vast majority of these ultrasounds (541,109) were conducted using the MBS item number 55731 (fee $98) for routine pregnancy screening at 18-20 weeks gestation. Several item numbers are used for ultrasounds associated with high risk pregnancies, including numerous maternal factors and a high risk of foetal abnormality (55700, 55703, 55704, 55705, 55706, 55707, 55708, 55709, 55712, 55715, 55718, 55721, 55723, 55725, 55759, 55762, 55766, 55768, 55770, 55772 and 55774). There were 802,476 ultrasounds performed using these item numbers during the same period of time (Australian Government 2007). In New Zealand during 2003, there were 56,134 registered live births. Although pregnant mothers had on average 2.1 ultrasound examinations, 14 per cent of mothers had none reported. A total of 46,110 ultrasounds were performed on pregnant women during the same period (New Zealand Health Information Service 2007).

In addition, some foetal anomalies may be detected through analytes in the maternal serum at approximately 15-20 weeks of gestation. For example, the South Australian Maternal Serum Antenatal Screening Programme measures four analytes in maternal serum (α-fetoprotein, free alpha subunit (α-hCG) and free beta subunit (β-hCG) of chorionic gonadotropin, and unconjugated oestriol), which are normally produced by, or in support of, a foetus and its placenta. These analytes have known values throughout each stage of

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[7] Statistics were not available for this same period of time on the number of births in Australia, however, during 2005 there were 259,800 registered births (Australian Bureau of Statistics).

pregnancy. A number of foetal abnormalities result in one or more of these analytes deviating (increasing or decreasing) from their normal range. Conditions that are routinely assessed in this program include: anencephaly (93% detected by screening), meningomyelocoele (92% detected by screening), encephalocoele (35% detected by screening), and trisomy 21 (74% detected by screening). Other conditions which may be detected but are screened for routinely are triploidy or 69XXX (78% detected by screening) and trisomy 18 (70% detected by screening). If these biochemical values fall outside of the normal range then the foetus is deemed to be at an *increased risk* of having an abnormality and mothers are offered counselling along with further information (SAMSAS 2005).

Pregnant women may be offered further invasive testing including amniocentesis and chorionic villus sampling (CVS), to confirm suspected foetal defects obtained either via an ultrasound scan or maternal biochemical testing. Some women may be offered these procedures based on maternal age alone. In South Australia maternal age was a factor in 57 and 63 per cent of all amniocenteses and CVSs, respectively, performed during 2003 (Haan et al 2004). Both of these techniques are deemed to be highly accurate but carry a small increased risk of miscarriage (0.5-2.6%). Amniocentesis can only be carried out at 15-17 weeks gestation, whereas CVS can be performed at 10-11 weeks. The time taken for cytogenic diagnosis can range from 1-3 weeks and this delay may have implications if the woman is considering termination. In addition, foetal blood sampling (cordocentesis or percutaneous umbilical blood sampling) may be performed from as early as 12 weeks, but usually after 16 weeks, gestation. Foetal blood sampling is indicated for karyotyping when a foetal defect is suspected after ultrasound, inborn errors of metabolism, platelet disorders and for rhesus isoimmunisation. The risk of miscarriage increases with this procedure to approximately 3.2 per cent. In addition, there is an increased risk (5-10%) that this procedure will induce foetal bradycardia, which may result in foetal morbidity and mortality (Chodirker et al 2001). In South Australia during 2003, a total of 17 foetal blood samplings were performed, which were all due to rhesus isoimmunisation (Haan et al 2004).

Safety

No studies included for assessment in this report described any adverse events that occurred as a result of conducting an MRI examination on a foetus, either to the foetus or the mother. In addition, no studies reported on the termination of pregnancies based on a false positive diagnosis obtained with MRI.

MRI is considered a suitable foetal imaging technology as it avoids the use of ionising radiation, and is not hampered by maternal obesity or foetal position (Laifer-Narin et al 2007). Safety concerns raised in the use of MRI for foetal imaging include the potential for the transfer of heat generated by the radiofrequency pulses, especially in fluids such as the eye, which are poor at dissipating heat. However studies have demonstrated that maternal temperature does not change during the course of an MRI and therefore it is unlikely for the foetus to suffer any deleterious over-heating effect. Excessive noise from the MRI apparatus has also been indicated as a potential hazard to the developing foetus. In addition, the foetal heart rate has been reported to increase during an MRI scan. However, surveys of children exposed to MRI *in utero* have found no adverse outcomes later in life from this exposure (Levine 2005; Sandrasegaran et al 2006).

Effectiveness

Central nervous system anomalies

Fifteen studies, where MRI was conducted for the confirmation of central nervous system (CNS) anomalies, were included for assessment in this report (Table 1). All of these studies, with the exception of the study by Limperopoulos et al (2006), were diagnostic accuracy studies that compared a diagnosis with ultrasound (US) to a diagnosis with MRI (level III-2 diagnostic evidence). Of these 15 studies, nine were conducted *prospectively* and were therefore considered better quality than the six retrospective studies.

Discordant diagnosis

The majority of studies reported the results of foetal MRI in terms of a discordant diagnosis with US. The number of discordant diagnoses reported was dependent on the type of CNS abnormality being screened for, with some abnormalities considered more difficult to diagnose accurately with US compared to MRI. Discordant diagnosis rates between US and MRI varied from a low of 20 per cent reported by Griffiths et al (2006) to 58 per cent reported by Whitby et al (2004b). Where a confirmatory US was conducted in addition to the referring US, the discordant rate between US and MRI was greatly reduced (6.2%) as reported by the large study (n=214) conducted by Levine et al (2003). In studies such as the ones conducted by Papadias et al (2007) and Tilea et al (2007), discordant diagnoses between US and MRI were 23 and 36 per cent, respectively. However, the diagnoses in these cases were misclassifications rather than a misdiagnosis, as all foetuses had a CNS defect,

with the correct diagnosis resulting in no change in clinical management or decision making. Several studies did, however, report on discordant diagnoses between US and MRI which changed the diagnosis from a suspected CNS abnormality to normal (Fjortoft et al 2007; Griffiths et al 2006; Salomon et al 2006). A small retrospective study of foetuses with suspected CNS abnormalities (n=7) found complete agreement between the diagnosis by US and MRI. The authors felt that offering MRI to parents who had already elected to terminate their pregnancy on the basis of an US diagnosis provided further evidence to support their decision to terminate and in so doing provided reassurance. In addition, MRI may elucidate further information which may assist parents in the management of subsequent pregnancies (Sharma et al 2003).

Misdiagnosis by MRI

Misdiagnosis by MRI was also reported by several studies, when compared to either postnatal clinical diagnosis or post-mortem findings (Fjortoft et al 2007; Ismail et al 2002; Limperopoulos et al 2006). Fjortoft et al (2007) reported 6/15 (40%) of foetuses were normal when scanned with MRI compared to when a suspected cranio-synostosis defect was diagnosed by US. Postnatal clinical follow-up indicated that the MRI diagnosis was incorrect for one case, where the foetus was not clinically normal and had a CNS defect as predicted by US. The converse was reported by Limperopoulos et al (2006) in their retrospective study where 19/19 (100%) of foetuses were reported to have vermian hypoplasia (a defect in the posterior cranial fossa). Postnatal MRI diagnosed that of these 19 foetuses, six were in fact normal (a false positive rate of 32% for prenatal MRI), leading the authors to conclude that vermian hypoplasia may be *over diagnosed* with prenatal MRI. This is of particular concern when past studies have reported termination of pregnancies based on a prenatal US diagnosis of inferior vermian hypoplasia with rates up to 80 per cent. The authors of this study postulate that the high false positive rate may be due to differences in foetal imaging technique and the accuracy of clinical interpretation, as this study was conducted over a five-year time frame, and that these factors may have improved with an increase in experience (Limperopoulos et al 2006).

Change in management

Only three studies reported their results in terms of a change in clinical management (Griffiths et al 2006; Levine et al 2003a; Whitby et al 2004a). Griffiths et al (2006) described the results of MRI scans of foetuses with suspected abnormalities of the spine or spinal cord. Change in clinical management was not originally considered an outcome in this study, as diagnosis with MRI was considered to be experimental. However after the first 20 cases it became apparent that the information gained from MRI would lead to changes in clinical management, and therefore a retrospective analysis of change in clinical management was conducted. There was a total of 10/50 (20%) discordant diagnoses between US and MRI. After US, all 10 foetuses were diagnosed as having a Category 3 abnormality, which would result in moderate to severe disability postnatally. Based on the US diagnosis it was recommended that all 10 pregnancies be terminated. The use of MRI changed the US diagnosis, and hence changed the clinical management of nine of the

ten discordant diagnoses. Eight foetuses were reclassified as Category 1 (normal) and one foetus was reclassified as Category 2 (minor disability). One foetus remained classified as Category 3 although the diagnosis with MRI differed to that reported with US, and the pregnancy was terminated. All MRI diagnoses were confirmed by postnatal clinical diagnosis. The authors went on to discuss the reasons why such a large number of US diagnoses would change, and impact on clinical management, when MRI was used adjunctively to diagnose suspected foetal abnormalities. The majority of discordant cases in this study were foetuses diagnosed by US with myelomeningoceles (MMC). It was postulated that this may be explained by *selection bias*, in that the referring clinicians only referred a high proportion of difficult and equivocal cases, which would be more likely to have a change of diagnosis with an MRI scan.

The large prospective study by Whitby et al (2004) reported that in 35/100 (35%) of cases, the additional information gained from an MRI scan changed the diagnosis and therefore clinical management. There were no cases reported in this study of a positive diagnosis on US that was not confirmed by MRI. Similarly there were no cases where MRI provided an incorrect diagnosis. However, there were 11 cases of suspected brain anomalies diagnosed with US, which were not confirmed by MRI or postnatal diagnosis. Of these 11 cases, two pregnancies were to be terminated on the basis of the US diagnosis, however the pregnancies were continued after an MRI was conducted. The authors of this study also discussed the issue of *selection bias*, where referred cases are only going to be those which present as problematic on US.

The study by Levine et al (2003) reported the results of foetal MRI, which was conducted after a confirmatory US, in terms of a change in diagnosis, counselling and clinical management. Although all women in this study were referred due to a suspect US, it was requested that a confirmatory US be performed two days prior to the MRI, so that both scans were carried out in the same institution. The confirmatory US in this study found that 69/214 (32%) of foetuses were normal. This finding was considered of great importance, as without a confirmatory US, there would be a perceived increase in the benefit of performing MRI. Of the remaining 145/214 (68%) foetuses, MRI changed the diagnosis in 46 (31.7%), changed maternal counselling in 73 (50.3%) and changed clinical management in 27 (18.6%). The mean gestational age of the foetuses where maternal counselling was changed (25.9 weeks $\pm$ 0.78) was significantly greater than for those foetuses without changes in maternal counselling (22.6 weeks $\pm$ 0.58, $p<0.01$). This was also true of the foetuses where a change in diagnosis post-MRI was reported, with the mean gestational age of those with a change in diagnosis (26.3 weeks $\pm$ 0.95) was significantly higher than those with no change in diagnosis (23.3 weeks $\pm$ 0.57, $p<0.01$). There was no significant difference in the gestational age of foetuses where a change in management occurred compared to those whose clinical management did not change. The authors also discussed the problems associated with an imperfect reference standard, where post-mortem confirmation of US or MRI findings could not be confirmed due to a lack of pathologic material after termination.

Additional information gained from MRI

Three studies reported the number of diagnoses where MRI provided additional information to the original ultrasound diagnosis (Garel et al 2004; Morris et al 2007; Salomon et al 2006). Salomon et al (2006) described the use of US and MRI to detect mild cases of ventriculomegaly, which are considered clinically difficult in terms of optimal management and counselling of patients. Ventriculomegaly is an excess of fluid in the lateral ventricles of the developing brain and is commonly diagnosed with ultrasound and may lead to the detection of other pathologies. Ventriculomegaly is considered to be severe when the ventricle size exceeds 15mm and mild ventriculomegaly refers to cases where the ventricle size is between 10-15mm. Foetuses with a ventricle size of 10-12mm will experience little morbidity. The prognosis and possible association of a chromosomal abnormality may be different for a ventriculomegaly of 10-12mm compared with that of 12-15mm. Therefore the authors suggest the use of MRI to confirm borderline ultrasound diagnoses of 10-12mm. When MRI was used to scan 185 foetuses with a suspected diagnosis of ventriculomegaly with a ventricle gap of 10-12mm, 43/185 (23.2%) had no abnormality and five (4.7%) had additional abnormalities. In addition, 36/185 (19.5%) had a ventricular gap >12mm, and of these MRI provided additional information in six foetuses indicating further abnormalities. Of the total 11 cases where additional information was gained by MRI, six underwent termination of pregnancy with the diagnosis confirmed at post-mortem. Although Morris et al (2007) and Garel et al (2004) reported additional findings with the use of MRI, they did not report the implications of their findings on the final diagnosis and outcome for the foetus and parent.

Two studies reported the accuracy of diagnosing CNS abnormalities using MRI compared to US. One study reported that MRI had a higher sensitivity (85% vs 55%), specificity (80% vs 20%), positive predictive value (88% vs 55%) and negative predictive value (75% vs 20%) when compared to US, based on the reference standard of postnatal or post-mortem follow-up (Malinger et al 2004). The same foetuses also underwent a dedicated neurosonogram which was superior to MRI in terms of sensitivity, specificity, and positive and negative predictive values. The same study reported the kappa statistic for all modes of screening. Only neurosonography compared to postnatal diagnosis had a kappa value denoting almost perfect agreement (κ= 0.842), and MRI compared to postnatal diagnosis had a kappa indicating substantial agreement (κ= 0.642) (Chuang 2001). A small study of 12 pregnant women reported a chi-square value of 9.88 (*p*<0.01) indicating that the difference between ultrasound and MRI giving a correct diagnosis was statistically significant (Whitby et al 2004b).

Table 1   Central nervous system abnormalities detected by MRI

Study	Diagnostic level of evidence	Study design	Population	Outcomes
2007				
Papadias et al 2007	III-2	Prospective cross classification on US and MRI. Reference standard = postnatal clinical confirmation.	13 foetuses with suspected CNS defects diagnosed US, which could require immediate postnatal surgery. Postnatal MRI performed to confirm prenatal MRI findings.	13/13 (100%) foetuses had a CNS defect confirmed by MRI. 2/13 (15.4%) did not require postnatal surgery The actual diagnosis of a particular condition was incorrect (discordant) in some cases but all had a confirmed postnatal CNS defect. <u>Discordant diagnosis</u> Total 3/13 (23.1%) Myelomeningocele 1/7 (14.3%) Meningocele 1/1 (100%) Occipital meningocele 0/1 (0%) Diastematomyelia 1/1 (100%) Isolated hydrocephalus 0/3 (0%)
Tilea et al 2007	III-2	Prospective cross classification on US and MRI. Reference standard = post-mortem confirmation.	25 foetuses with suspected posterior fossa malformations diagnosed by US	25/25 (100%) foetuses had a malformation of the posterior fossa confirmed by MRI, resulting in the termination of the pregnancy at a mean gestational age of 33 weeks. The actual diagnosis of a particular condition was incorrect (discordant) in some cases but the decision to terminate was correct in each case. <u>Discordant diagnosis</u> Total 9/25 (36%) Vermian hypoplasia 4/25 (16%) Partial vermian agenesis 0/25 (0%) Cerebellar hemisphere hypoplasia 3/25 (12%) Brain stem hypoplasia 1/25 (4%) Destructive lesions 1/25 (4%)

Fjortoft et al 2007	III-2	Retrospective cross classification on US and MRI. Reference standard = postnatal clinical confirmation.	15 foetuses with suspected cranio-synostosis diagnosed by US.	Diagnosis MRI Ref standard Craniosynostosis 4/15 (26.7%) 4/4 (100%) Positional skull deformity 3/15 (20%) 1/3 (33.3%) Questionable skull deformity 2/15 (13.3%) 1/2 (50%) Normal 6/15 (40%) 5/6 (83.3%) Wrong diagnosis with MRI compared to postnatal clinical diagnosis 4/15 (26.7%). 1/15 (6.7%) lost to follow-up
Morris et al 2007	III-2	Retrospective cross classification on US and MRI. Reference standard = postnatal clinical confirmation.	30 foetuses with suspected isolated cerebral ventriculo-megaly diagnosed by US.	MRI confirmed US diagnosis in 30/30 (100%) cases 18/30 (60%) mild ventriculomegaly 12/30 (40%) severe ventriculomegaly Additional information gained from MRI in a total of 15/30 (50%) cases 8/18 (44%) of mild cases 7/12 (58%) of severe cases
2006				
Griffiths et al 2006	III-2	Prospective cross classification on US and MRI. Reference standard = postnatal clinical or post-mortem confirmation.	50 consecutive foetuses with suspected spine and spinal cord abnormalities diagnosed by US.	40/50 (80%) US and MRI agreed 10/50 (20%) discordant diagnosis between US and MRI. Of these: 8/10 (80%) MRI identified as normal 2/10 (20%) misclassified diagnosis by US, MRI diagnosis confirmed by final reference diagnosis Change in management Of the 10/50 (20%) discordant diagnoses, all were classified Category 3 (TOP) by US. Post-MRI 8/10 (80%) classified Category 1 (Normal) 1/10 (10%) classified Category 2 (minor disability) 1/10 (10%) remained Category 3 (TOP)

Salomon et al 2006	III-2	Prospective cross classification on US and MRI. Reference standard = postnatal clinical confirmation.	310 foetuses with suspected ventriculo-megaly diagnosed by US. Analysed only those foetuses with isolated ventriculo-megaly ≤ 12mm (n=185)	<u>US</u>
				185/310 (59.7%) considered to have suspected isolated ventriculomegaly with ventricle gap between 10-12mm
				114/185 (61.6%) suspected unilateral ventriculomegaly
				71/185 (38.4%) suspected bilateral ventriculomegaly
				
				<u>MRI</u>
				43/185 (23.2%) no abnormality
				106/185 (57.3%) isolated ventriculomegaly (10-12mm)
				    5/106 (4.7%) additional information provided by MRI indicated additional abnormalities
				
				36/185 (19.5%) MRI measured ventricles to be >12mm
				    6/36 (16.7%) additional information provided by MRI indicated additional abnormalities
				
				Of the 11 cases where additional information was gained:
				6/11 (54.5%) underwent TOP
				MRI abnormalities conformed by pathology
				5/11 (45.5%) postnatal imaging confirmed prenatal diagnosis

Limperopoulos et al 2006	IV	Retrospective study of diagnostic yield. Reference standard = postnatal MRI confirmation.	19 foetuses diagnosed prenatally with vermian hypoplasia by MRI	<u>Prenatal MRI</u> 19/19 (100%) vermian hypoplasia <u>Postnatal MRI</u> 6/19 (32%) normal 13/19 (68%) vermian hypoplasia Prenatal MRI false posisitves = 32%
2004				
Garel et al 2004	III-2	Prospective cross classification on US and MRI. Reference standard = postnatal clinical confirmation.	28 foetuses with suspected cerebral ischemic lesions diagnosed by US.	24/28 (85.7%) MRI added to US findings Of these: 16/24 (66.7%) were overlooked by US 8/24 (33.3%) MRI revealed more extensive abnormality

Malinger et al 2004	III-2	Prospective cross classification on US, MRI and neurosonography. Reference standard = postnatal clinical or post-mortem confirmation.	42 foetuses with suspected CNS abnormalities diagnosed by US.	

For Malinger et al 2004 results column:

	US	NS	MRI
Sensitivity (%)	55	96	85
Specificity (%)	20	87	80
PPV (%)	55	93	88
NPV (%)	20	93	75

Measure of agreement

	Kappa·	p
US/NS	-0.105	0.73
US/MRI	-0.175	0.33
US/postnatal	-0.244	0.18
NS/MRI	0.483	0.002
NS/postnatal	0.842	<0.0001
MRI/postnatal	0.642	<0.0001

Whitby et al 2004b	III-2	Prospective cross classification on US and MRI. Reference standard = postnatal clinical or post-mortem confirmation.	12 foetuses with suspected CNS abnormalities diagnosed by US.	5/12 (42%) concordant diagnosis between MRI and US 7/12 (58%) discordant diagnosis between US and MRI 12/12 (100%) correct diagnosis on MRI $\chi^2 = 9.88$ (1 df), $p < 0.01$
Whitby et al 2004a	III-2	Prospective cross classification on US and MRI. Reference standard = postnatal clinical or post-mortem confirmation.	100 foetuses with suspected CNS abnormalities diagnosed by US.	52/100 (52%) concordant diagnosis with MRI and US 51/52 (98.1%) both US and MRI diagnoses agreed with definitive clinical or post-mortem diagnosis 12/100 (12%) MRI provided extra information which didn't affect clinical management 35/100(35%) MRI diagnosis affected clinical management _Effect on clinical management_ 6/100 (6%) MRI gave additional information to have effect on clinical management confirmed by definitive clinical or post-mortem diagnosis 29/100 (29%) MRI changed diagnosis confirmed by definitive clinical or post-mortem diagnosis Of these 11/29 (37.9%) were diagnosed as normal. Median table occupancy for MRI 20 minutes (range 9-25 mins)
2003				
Levine et al 2003a	III-2	Prospective cross classification on US and MRI. Reference standard = postnatal clinical or post-mortem confirmation.	214 foetuses diagnosed with suspected CNS abnormalities by US.	Confirmatory US normal in 69/214 (32.2%) foetuses Of these: 13/69 (18.8%) change in counselling 3/69 (4.3%) change in diagnosis 2/69 (2.9%) change in management Of the remaining 145/214 (67.8%) foetuses: 9/145 (6.2%) discordant diagnosis with MRI and confirmatory US. 73/145 (50.3%) change in counselling

				46/145 (31.7%) change in diagnosis
				27/145 (18.6%) change in management
Sharma et al 2003	III-2	Retrospective cross classification on US and MRI. No reference standard.	7 foetuses with suspected CNS abnormalities diagnosed by US.	7/7 (100%) concordant diagnosis with MRI and US
2002				
Ismail et al 2002	III-2	Retrospective cross classification on US and MRI. Reference standard = postnatal clinical or post-mortem confirmation.	27 consecutive foetuses with suspected CNS abnormalities diagnosed by US.	26/27 (96.3%) follow-up 15/26 (57.7%) concordant diagnosis with MRI and US 7/26 (26.9%) MRI changed diagnosis correctly 4/26 (15.4%) MRI misdiagnosed

* Kappa is a level of agreement against that which might be expected by chance. A kappa of 1 indicates complete agreement; a kappa of 0 indicates no agreement, kappa = 0.01-0.2 slight agreement, kappa = 0.21-0.4 fair agreement, kappa = 0.41-0.6 moderate agreement, kappa = 0.61-0.8 substantial agreement, kappa= 0.81-1.0 almost perfect agreement (Chuang 2001)
MRI = magnetic resonance imaging, US = ultrasound, CNS = central nervous system, TOP = termination of pregnancy, df = degree of freedom, NS = neurosonography, PPV = positive predictive value (those with abnormality correctly identified), NPV = negative predictive value (those without the abnormality correctly identified)

> Although the outcomes reported by studies included in this section of the report varied, most authors concluded that MRI was a valuable adjunct in the screening of foetuses with a suspected CNS abnormality and should be used in conjunction with US. If possible a confirmatory US should be conducted within a short time frame of the MRI and within the same institution. The increase in information gained from MRI was viewed as a valuable tool in the counselling of expectant parents. Taken into account with factors including patient history, type of abnormality and patient's wishes, MRI as an adjunctive diagnostic tool may aid the clinical management of suspected CNS abnormalities.

Abdominal or urinary tract malformations

As with the studies of suspected CNS abnormalities, the three included studies that assessed the ability of MRI to detect abnormalities of the abdomen or urinary tract, reported on the rate of discordant diagnoses between US and MRI (Table 2). The small prospective study by Carcopino et al (2007) examined foetuses with suspected echogenic bowel. In the majority of cases echogenic bowel has no clinical significance, however one third of echogenic bowel cases are associated with poor perinatal outcome, disease such as cystic fibrosis and intrauterine foetal growth restriction. Suspected echogenic bowel should be confirmed with amniocentesis for the determination of karyotype, or prenatal diagnosis for cystic fibrosis, or screening of amniotic fluid for infectious agents. Despite the use of all these techniques, approximately two thirds of echogenic bowel cases remain undiagnosed. It is hoped that the use of MRI, in conjunction with US and amniocentesis, will give additional

information to aid in the detection of echogenic bowel. Of 17 foetuses suspected of having echogenic bowel, 11 (64.7%) were correctly determined by MRI to be normal. These foetuses had no associated pathology as determined by amniocentesis and had a good postnatal outcome. This study reported a false positive rate of 16.7 per cent for MRI determination of echogenic bowel, with one foetus being diagnosed with echogenic bowel but having no associated pathology.

Garel et al (2006) reported that although US wrongly diagnosed suspected gastrointestinal abnormalities in 8/24 (33.3%) of cases, MRI also wrongly diagnosed 3/24 (12.5%) cases. MRI was particularly good at detecting large bowel obstructions but overlooked two out of three rectourethral fistulas. Discordant rates between US and MRI when scanning for urinary tract abnormalities were reported by Cassart et al (2004) to be 31 per cent (n=16). Of the five discordant diagnoses, the MRI findings modified the initial US diagnosis and resulted in the correct decision to terminate (n=4) or to continue the pregnancy (n=1). The authors conclude that MRI is a complementary tool for the diagnosis of gastrointestinal malformations, but may not be as useful in the accurate diagnosis of multiple obstructions, the prediction of small bowel necrosis or anorectal malformations.

Table 2   Abdominal or urinary tract abnormalities detected by MRI

Study	Diagnostic level of evidence	Study design	Population	Outcomes
2007				

Carcopino et al 2007	III-2	Prospective cross classification on US and MRI. Reference standard = genetic (prenatal) and postnatal clinical confirmation.	17 foetuses with suspected echogenic bowel diagnosed by US.	Diagnosis
				11/17 (64.7%) US and MRI discordant diagnosis, normal
				6/17 (35.3%) US and MRI concordant diagnosis, abnormal
				
				        - pathology +pathology
				MRI Normal
				       11/11 (100%) 0 (0%)
				MRI Abnormal
				       1/17 (16.7%) 5/6 (83.3)
				
				MRI false positive = 1/17 (16.7%)

2006				
Garel et al 2006	III-2	Prospective cross classification on US and MRI. Reference standard = postnatal clinical or postmortem confirmation.	24 foetuses with suspected gastro-intestinal tract abnormalities diagnosed by US.	Total discordant diagnosis by US compared to postnatal diagnosis 8/24 (33.3%) Total discordant diagnosis by MRI compared to postnatal diagnosis 3/24 (12.5%) <u>Duodenojejunal obstruction</u> 6/7 (85.7%) correctly diagnosed on US 6/7 (85.7%) diagnosis confirmed by MRI and postnatal diagnosis 1/7 (14.3%) discordant MRI diagnosis <u>Small bowel obstruction</u> 9/11 (81.9%) correctly diagnosed on US 10/11 (90.9%) correctly identified by MRI, confirmed by postnatal diagnosis 1/11 (9.1%) discordant MRI diagnosis <u>Large bowel obstruction</u> 3/3 (100%) discordant diagnosis on US 3/3 (100%) correctly diagnosed by MRI <u>Anorectal malformations</u> 2/3 (66.7%) discordant diagnosis on US 2/3 (66.7%) correctly identified by MRI, confirmed by postnatal diagnosis 1/3 (33.3%) discordant diagnosis on MRI MRI also overlooked 2/3 (66.7%) of associated rectourethral fistulas
2004				
Cassart et al 2004	III-2	Prospective cross classification on US and MRI. Reference standard = postnatal clinical or postmortem confirmation.	16 foetuses with suspected urinary tract abnormalities diagnosed by US.	11/16 (68.8%) MRI and US concordant diagnosis 5/16 (31.2%) MRI modified the diagnosis 4/5 (80%) of these resulted in a correct decision to terminate (n=3) or correct decision to continue (n=1) the pregnancy.

MRI = magnetic resonance imaging, US = ultrasound

Multi-foetal gestations

Two studies reported on the detection of abnormalities in multi-foetal gestations, however neither of these studies reported whether MRI findings were confirmed by postnatal clinical diagnosis (Table 3). As such these studies add very little to the body of evidence presented in this report. In a study of 37 pregnancies where twin-twin transfusion syndrome was suspected, the use of MRI revealed additional pathology in both the donor and recipient foetuses, with some foetuses experiencing multiple pathologies (Kline-Fath et al 2007).

However, the effect of these findings on clinical management is unknown. The study by Hu et al (2006) reported rates of discordant diagnoses between US and MRI. In eight cases of suspected ventriculomegaly diagnosed by US, four were diagnosed as normal with MRI (50% discordant). Similarly, one of two US diagnosed cases of cerebral hypoplasia were diagnosed as normal with MRI. There was complete agreement between US and MRI for abnormalities associated with a shared placenta. These results were not compared to the reference standard of postnatal clinical diagnosis.

Table 3   Abnormalities detected by MRI in multi-foetal gestations

Study	Diagnostic level of evidence	Study design	Population	Outcomes
2007				
Kline-Fath et al 2007	III-2	Prospective cross classification on US and MRI. No reference standard.	37 multiple pregnancies (36 twin, 1 triplet) with suspected twin-twin transfusion syndrome diagnosed by US.	25/37 (67.6%) pregnancies confirmed by MRI to have TTTS 1/25 (4%) donors died 1/25 (4%) recipients died Of remaining foetuses all recipients had polyhydramnios and all donors had oligohydramnios Additional pathology revealed by MRI Recipients 24/24 (100%) bladder distension 15/24 (62.5%) asymmetric renal collecting system distension 1/24 (4.2%) lung lesions 15/24 (62.5%) cardiomegaly 3/24 (12.5%) nuchal oedema 2/24 (8.3%) hydrops 2/24 (8.3%) cerebral ischaemia 3/24 (12.5%) enlarged cerebral venous sinuses Donors 23/24 (95.8%) little or no visualisation of bladder 10/24 (41.7%) severe oligohydramnios 15/24 (62.5%) visibly smaller than co-twin 1/24 (4.2%) nuchal oedema 2/24 (8.3%) hydrops 12/24 (50%) enlarged cerebral venous sinuses 2/24 (8.3%) cerebral malformations

2006				
Hu et al 2006	III-2	Prospective cross classification on US and MRI. No reference standard.	32 multiple pregnancies (30 twin, 2 triplet) with suspected complications diagnosed by US.	15/32 (46.9%) complications not due or specific to monochorionic multi-foetal gestations. Of the remaining 17 cases: 1/17 (5.9%) weight discordance with no other foetal abnormality 8/17 (47.1%) suspected ventriculomegaly on US 4/8 (50%) confirmed by MRI 4/8 (50%) normal by MRI 2/17 (11.8%) suspected cerebral hypoplasia on US 1/2 (50%) confirmed by MRI 1/2 (50%) normal 6/17 (35.3%) abnormalities due to sharing placenta 6/6 (100%) MRI findings agreed with US diagnosis but provided more detail especially in 2 cases of co-joined twins

MRI = magnetic resonance imaging, US = ultrasound, TTTS = twin-twin transfusion syndrome

Foetal abnormalities (various)

Two studies where foetuses were scanned for a variety of suspected abnormalities (CNS, spine, genitourinary, thoracic, facial and abdominal) were included for assessment in this report (Table 4). These studies are likely to reflect the situation in the clinical obstetric setting, where all women are screened with US and any suspect scans would be referred on to a specialised MRI centre. It is expected that specialist radiologists examining the MR images would be required to have extensive experience interpreting diverse foetal MR images. The difficulties in scanning for all abnormalities may be reflected in the results reported by Frates et al (2004). Of 28 diagnoses, MRI was incorrect and US correct in four cases (14.3%), and both MRI and US was incorrect in seven cases (25%), two of whom were found to be normal at postnatal follow-up. The authors felt that the diverse nature of these abnormalities (CNS, thorax and genitourinary) was the main factor in the incorrect MRI diagnosis. In this study, MRI was accurate in 61 per cent of cases, and changed the US diagnosis in three cases (10.7%) from a suspected abnormality to normal.

The study by Breysom et al (2003) reported on the failure to complete an MRI foetal examination due to several reasons; maternal obesity, excessive foetal movement and maternal claustrophobia. This study reported a relatively low rate (7.5%) of discordant diagnosis of MRI or US prenatal diagnosis and postnatal confirmation. The authors reported that the additional information provided by MRI aided clinical decision making on whether to terminate the pregnancy or to proceed with surgery in five cases (12.5%). In addition, the authors felt that the information gained from scanning with MRI improved parental counselling and postnatal therapeutic planning and management in 15 pregnancies.

Table 4   Foetal abnormalities (various) detected by MRI

Study	Diagnostic level of evidence	Study design	Population	Outcomes
2004				
Frates et al 2004	III-2	Prospective cross classification on US and MRI. Reference standard = postnatal clinical confirmation.	27* foetuses with suspected abnormalities (CNS, genitourinary system, thorax and facial) diagnosed by US.	14/28 (50%) diagnoses by US and MRI correct when compared to post-natal diagnosis 7/28 (25%) MRI provided additional information to US 0/28 (0%) US provided additional information to MRI 3/28 (10.7%) MRI changed US diagnosis correctly 4/28 (14.3%) MRI diagnosis incorrect and US correct 7/28 (25%) both US and MRI incorrect diagnosis.
2003				
Breysem et al 2003	III-2	Retrospective cross classification on US and MRI. Reference standard = postnatal clinical or postmortem confirmation.	40 foetuses (1 set twins) with suspected abnormalities (head, neck, spine, thoracic, urogenital, abdominal) diagnosed by US.	36/39 (92.3%) MRI examinations successful. 30/40 (75%) with postnatal follow-up Effect on clinical management MRI provided additional information in 21/40 (52.5%) foetuses 5/40 (12.5%) MRI aided clinical decision for TOP (n=4) or surgery (n=1) 3/40 (7.5%) discordant MRI and US prenatal diagnosis and/or postnatal diagnosis

MRI = magnetic resonance imaging, US = ultrasound, TOP = termination of pregnancy
* One foetus had 2 diagnoses

Thoracic abnormalities

Only one included study reported on which foetuses that were scanned for thoracic abnormalities (Table 5). This study was retrospective and therefore not of high quality. Postnatal clinical or post-mortem confirmation was obtained in the majority of cases (85.1%), however in 11 cases either parental approval for a post-mortem was declined or there was a lack of foetal specimen available for an adequate diagnosis.

Confirmatory US changed or clarified the original US diagnosis in 19 (25.7%) cases or provided additional information in 28 (37.8%) of cases, however clinical care was only affected in 6/74 (8.1%) of cases. The authors concluded that although MRI provided additional information to that gained from US, this more often lead to changes in patient counselling but affected clinical management of cases to a lesser extent. The addition of a confirmatory US, by clinical staff at the same institution where the MRI was to be conducted, was reported to be a more obvious benefit to patients.

Table 5   Thoracic abnormalities detected by MRI

Study	Diagnostic level of evidence	Study design	Population	Outcomes
2003				
Levine et al 2003b	III-2	Retrospective cross classification on US and MRI	74 foetuses diagnosed with suspected thoracic abnormalities diagnosed by US.	11/74 (14.9%) had no postnatal follow-up due to lack of permission for autopsy or lack of foetal specimen for diagnosis 19/74 (25.7%) confirmatory US changed or clarified diagnosis 28/74 (37.8%) MRI provided additional information to US <u>Effect of MRI on clinical management</u> 6/74 (8.1%) affected care Of these: 19/28 (67.9%) diagnosis confirmed at postnatal follow-up. Follow-up not reported in 9/28 (32.1%).

Cost Analysis

There are currently no cost-effectiveness data available on the use of MRI as a complementary diagnostic tool to ultrasound for the screening of foetal abnormalities. No MBS item number exists that can be used for conducting a foetal examination utilising MRI. A standard MRI scan is covered under numerous item numbers on the MBS and fees range from $336 to $492.80. A , foetal MRI is likely to be less expensive as contrast agent is not required. There are currently in excess of 120 MRI scanners in Australia, situated in major private and public hospitals. Whether or not the use of these scanners to conduct foetal MRI examinations would impact greatly on the utilisation of these scanners and require the purchase of additional units remains to be seen. The cost of a new MRI scanner is estimated to be approximately $1.5-2.5 million depending on the options, specifications and building requirements. In addition to hardware considerations, the potential additional costs of parental counselling would need to be included in an economic analysis. A full economic analysis of foetal MRI would also need to consider the cost impact of any changes in the diagnosis (positive or negative) and subsequent management of a pregnancy.

Ethical and social issues

The ethical basis for foetal screening is twofold (Strong 2003). First, the provision of foetal screening expresses respect for the autonomy of the pregnant woman. One important component of autonomy is reproductive autonomy, which includes the freedom to continue or terminate a pregnancy. Traditionally, reproductive counselling places a very high value on reproductive autonomy (Bowles Biesecker & Marteau 1999). Women's reproductive autonomy is promoted when they receive accurate information about their pregnancy, including information about the health and wellbeing of their foetus, the presence or absence of abnormalities and the implications of any abnormalities for the future. Second, foetal screening can also promote wellbeing and minimise harms. Providing information about screening gives women the information they need to make decisions about what will be in the best interests of their family. This is as much the case for situations in which screening tests reveal anomalies as for those in which findings are normal.

MRI for the detection of foetal abnormalities has the potential to serve both ethical goals. First, it can enhance the quality of information women receive about results of screening tests for foetal abnormalities, since MRI appears to have higher sensitivity and specificity than US alone. More accurate information places women in a better position to make informed reproductive decisions. Second, MRI can provide benefits and minimise harms for women and their families, in that it may reduce anxiety and distress, particularly that caused by inconclusive test results, and it may also limit unnecessary terminations. The harms for both foetus and parents that attach to 'wrongful termination' is so substantial that it is difficult to imagine a situation in which these would be outweighed by other benefits that might be related to US screening alone.

The above comments paint a positive picture of the ethical acceptability of MRI for the detection of foetal abnormalities. However, the comparator, US, is ethically problematic itself. There is a large body of literature about the medicalisation of pregnancy and childbirth, in which routine ultrasound in pregnancy has played an important role (Oakley 1993).

More specifically the need for MRI to detect foetal abnormalities arises out of the problems with US screening. First, if US screening had higher sensitivity and specificity, the confirmation of findings by other means would not be necessary. Second, US screening allows us to detect a potentially large number of anomalies, some of which may not be clinically relevant. With these two limitations of US and the possibility of a 'back-up' MRI, we may set in motion an obstetric technology cascade.

Technology cascades such as this carry their own problems:

1. In the UK, "an estimated 2 per cent of pregnant women receive a risk label on the basis of soft markers detected by ultrasound (Baillie et al 2000, quoted in Getz and Kirkingen 2003)." If this rate is similar in Australia, there is potentially a large body of equivocal US findings to

be evaluated with the use of MRI. Once clinicians are aware that there is a 'backup' technology that can confirm or rule out suspicious findings, there may be *much* wider use of the technology.

2. If the adjunct role of MRI is limited to specific disorders (for example CNS conditions) this may create other ethical problems for health professionals. For example, they will need to make decisions about whether to inform women of findings that may not be of major clinical significance but which could be assessed more precisely with foetal MRI screening. This may lead to the provision of private MRI screening services available to those who can afford to pay for it in the private sector, raising questions of equity of access.

3. In addition, does MRI screening have its own accuracy problems in identifying anomalies that may not be of clinical significance?
Getz and Kirkengen (2003) note that the history of the detection of soft markers in obstetric ultrasound can not be explained in terms of increasing accuracy leading to decreasing uncertainty about risk. Rather, each soft marker seems to have its 'rise and fall' as uncertainty about the role of one marker is replaced over time with uncertainty about the role of another marker (Getz & Kirkengen 2003). This may well be the case with MRI.

4. There are a number of additional issues that are raised by this technology including:
    - Risk management issues associated with potential differential access to MRI scanning for confirmation of foetal anomalies;

    - Need for standard policies and practices to manage a wide range of potential anomalies identified by its use; and

    - Variations in policies and practices around 2nd trimester terminations of pregnancy.

Access Issues

This technology is currently available in a select number of large public hospitals in Australia. Due to the need for clinical expertise in a number of areas of foetal medicine, in addition to the potential need for extensive parental counselling, MRI for the detection of foetal abnormalities is only likely to be offered in large tertiary centres. In addition, due to the expense of acquisition of MRI scanners, it is likely that they will only be purchased by these large tertiary hospitals and would not be made available in rural areas of Australia.

Women diagnosed as carrying a foetus with a suspected abnormality who live in rural areas have already encountered access problems, as they must travel to tertiary centres for further prenatal and counselling services. These women would also need to travel to large regional centres to be screened, away from the support of family and friends, representing a further emotional and financial burden for rural women.

Training

The Royal Australian and New Zealand College of Radiologists (RANZCR) conducts a training course for radiologists intending to use MRI. For admission into the RANZCR training program, candidates must be a graduate of a recognised medical school, be fully registered as a medical practitioner and have completed two full years in an approved hospital as an intern or resident. In order to be recognised as a Specialist in Radiodiagnosis and Fellow of the College (FRANZCR), the trainee must complete Parts I and II of the FRANZCR examinations in radiodiagnosis and complete a minimum of five years in practical training positions accredited by the RANZCR. The training program aims to provide experience and training in general radiology, computed tomography (CT), nuclear medicine, ultrasound, MRI, angiography and basic interventional techniques. A minimum of three months full-time MRI training, including image interpretation and appropriate protocol selection and modification is required, although registrars should receive ongoing training in this modality throughout their five year practicum (RANZCR 2007).

Clinical Guidelines

There are currently no clinical guidelines for the use of MRI in the detection of foetal abnormalities. The RANZCR guidelines for the use of MRI on pregnant patients (for conditions other than screening for foetal abnormalities) state that the MRI scan must be needed before the end of pregnancy to guide management and provide information not available by any other means of non-ionising diagnostic method. MRI should be avoided in the first trimester and the use of gadolinium-based intravenous MRI contrast agents should be avoided. It is also considered prudent to minimise the exposure of the foetus to excessive noise (RANZCR 2004).

The clinical guidelines for the use of ultrasound during pregnancy may be applicable to the similar use of MRI. The Royal Australian and New Zealand College of Radiologists (RANZCR) have produced a consensus statement on the best use of diagnostic ultrasound in obstetric practice. As previously stated in the comparator section, ultrasounds at 12-weeks should only be performed in cases of recurrent (>2) abortion, maternal bleeding, suspicion of an ectopic pregnancy (based on clinical history), a very high risk pregnancy (severe rhesus disease, diabetes, previous intrauterine growth restriction (IUGR) or previous premature labour) or a previous foetal abnormality. Most scans are conducted at 18-20 weeks and at this time are capable of detecting foetal abnormalities, predicting gestational age, detection of multiple gestations and of low-lying placenta. Ultrasound scans are rarely indicated at 22-26 weeks gestation apart from previously diagnosed foetal anomalies. Scans at greater than 26 weeks are indicated for suspected IUGR, previous still birth, moderate or severe maternal hypertension, pre-eclampsia or toxaemia, maternal type I diabetes, multiple pregnancy, clinical polyhydramnios, antepartum haemorrhage or suspected intrauterine foetal death (RANZCR 1998a). The

RANZCR's policy on the conduct of ultrasounds states that whereas the "sonographers scan the patient, the responsibility for the conduct of the study lies with the radiologist. Communication between the sonographer and radiologist should be maximised to obtain the most accurate diagnostic study possible. The radiologist's report should draw upon all the available information, which may include communication with the sonographer, reviewing the sonographer's images, attending the patient to talk to, examine or scan the patient and/or observing the sonographer in real time." (RANZCR 2003). The RANZCR have also produced guidelines for medical practitioners performing and interpreting diagnostic ultrasound and for diagnostic ultrasound services (RANZCR 1998c; RANZCR 1998b).

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of MRI for the detection of foetal abnormalities, its present and potential use in the Australian public health system, and future implications for the use of this technology.

Search Strategy used for the Report

The medical literature (Table 6) was searched utilising the search terms outlined in Table 7 to identify relevant studies and reviews, until August 2007. In addition, major international health assessment databases were searched.

Table 6   Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University library
Australian Medical Index	University library
Australian Public Affairs Information Service (APAIS) - Health	University library
Cinahl	University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University library
Current Contents	University library
Embase	Personal subscription
Pre-Medline and Medline	University library
ProceedingsFirst	University library
PsycInfo	University library
Web of Science – Science Citation Index Expanded	University library
Internet	
Australian Clinical Trials Registry	http://www.actr.org.au/default.aspx
Current Controlled Trials metaRegister	http://controlled-trials.com/
Health Technology Assessment international	http://www.htai.org
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
Medicines and Healthcare products Regulatory Agency (UK).	http://www.medical-devices.gov.uk/
National Library of Medicine Health Services/Technology Assessment Text	http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/grey.shtml
Trip database	http://www.tripdatabase.com
U.K. National Research Register	http://www.update-software.com/National/
US Food and Drug Administration, Center for Devices and Radiological Health.	http://www.fda.gov/cdrh/databases.html

Table 7   Search terms utilised

Search terms
MeSH
Fetal Diseases/diagnosis, Fetus/abnormalities, Magnetic Resonance Imaging, Prenatal Diagnosis/methods
Text words
fetal AND disease, fetal AND abnormalities, foetal AND disease, foetal AND abnormalities, MRI
Limits
English, Human

Availability and Level of Evidence

The current literature abounds with case reports and small case series reporting on the use of MRI to detect foetal abnormalities. Many of the abnormalities are rare, hence the use of case reports. In this Horizon Scanning report, case reports and case series with less than three foetuses were not considered for assessment but are listed in Appendix E. Large, prospective studies were

lacking. A total of 58 papers were retrieved as potential inclusions, however due to time the constraints involved in writing this Horizon Scanning report only 22 have been included. A full HTA would be required to canvass this material appropriately.

In previous reports case series would be ranked according to the number of patients enrolled in the study. However, in the case of the detection of foetal abnormalities this may bias the report away from the diagnosis of rare foetal defects. Therefore a mix of study sizes, starting with the most recent (2007), were presented. Twenty-two of the included studies were level III-2 diagnostic evidence, and of these 14 were prospective cross-classification studies and seven were poorer quality retrospective cross-classification studies. One study reported diagnostic yield (level IV diagnostic evidence). In addition, it is hoped that preliminary unpublished data from the Victorian Foetal MRI Program will be included (level III-2 diagnostic evidence).

Sources of Further Information

The state of Victoria is currently conducting an audit of all MRIs conducted for the detection of foetal abnormalities in three major Victorian centres. The audit is being coordinated by Associate Professor Stacy Goergen and includes data from Monash Medical Centre, the Royal Children's Hospital and the Austin Hospital.

This report describes the use of MRI to detect foetal abnormalities or birth defects. Currently the Australian National Perinatal Statistics Unit defines a birth anomaly as "anatomical defects or chromosomal abnormalities that are present at birth". The use of MRI is *not* designed to replace ultrasound as the obstetric diagnostic tool of choice, but rather to act as an adjunct in cases where an ultrasound diagnosis is equivocal. Ultrasound remains the gold standard of foetal imaging.

MRI is considered a suitable foetal imaging technology as it is non-invasive, avoids the use of ionising radiation, and is not hampered by maternal obesity or foetal position. Although some safety concerns have been raised in the use of MRI for foetal imaging, surveys of children scanned with MRI *in utero* have found no adverse outcomes later in life from this exposure. MRI examinations are usually only conducted in the second trimester. Most MRI units used to conduct foetal MRI are 1.5 Tesla (T). Although MRI units of 2.5 and 3T have stronger gradients which allow acquisition of images with a higher signal-to-noise ratio and higher spatial resolution, they are not recommended for use in foetal imaging. With the advent of ultrafast MR sequences (sequence acquisition of 20 seconds), foetal motion is not usually an issue.

There is great variation amongst the states and territories of Australia in the ICD classifications used to code birth anomalies, in addition to differences in methods of data collection, the sources of birth anomalies notifications and the scope of data collection. The last full report produced by the Australian National Perinatal Statistics Unit contains data collected on birth anomalies during the period 1981-1997. In 1997, for the whole of Australia, there were 254,390 live births and 1,808 still births. During this same period there were a total of 4,489 congenital malformations (single and multiple), translating to a prevalence rate of 175 per 10,000 births.

No studies included in this report described any adverse events that occurred as a result of conducting an MRI examination on a foetus, either to the foetus or the mother. In addition, no studies reported on the termination of pregnancies based on a false positive diagnosis obtained with MRI.

The majority of studies included for assessment in this report were diagnostic accuracy studies that compared a diagnosis with ultrasound (US) to a diagnosis with MRI. In most studies, these results were compared to the reference standard of either postnatal clinical follow-up or post-mortem confirmation of diagnosis. Fourteen studies were included which assessed the ability of both modalities to detect abnormalities of the central nervous system (CNS). Three studies described the detection of abdominal or urinary tract abnormalities, two reported on scanning multi-foetal gestation and one study reported on the detection of thoracic abnormalities. In addition, two studies were assessed, which scanned foetuses for a variety of suspected abnormalities (CNS, spine, genitourinary, thoracic, facial and abdominal), more accurately reflecting the situation in the clinical obstetric setting.

The number of discordant diagnoses appeared to be dependent on the type of abnormality being screened for, with some abnormalities, such as echogenic bowel, considered more difficult to diagnose accurately with US compared to MRI. Discordant diagnosis rates between US and MRI for the diagnosis of central nervous system abnormalities varied from a low of 20 per cent reported by Griffiths et al (2006) to 58 per cent reported by Whitby et al (2004b). Interestingly, when women underwent a confirmatory US, prior to MRI and conducted by the same institution where the MRI was to be conducted, the discordant rate between US and MRI was reported to be greatly reduced (6.2% Levine et al, 2003). For all the included studies, the highest rate of discordant diagnoses (64.7%) between US and MRI was reported by Carcopino et al (2007) for the diagnosis of echogenic bowel. Generally studies with low numbers of enrolled women reported larger discrepancies between the diagnosis with US and MRI, which may be a reflection of the need for extensive clinical expertise being required for the diagnosis of foetal abnormalities.

A small number of studies reported on the misdiagnosis of foetal abnormalities by MRI. Of these, the largest number of misdiagnoses was described by Limperopoulos et al (2006). Of 19 foetuses diagnosed with vermian hypoplasia with prenatal MRI, six were confirmed as normal with postnatal MRI, a false positive rate of 32 per cent. The authors concluded that the over diagnosis of vermian hypoplasia may have led to the unnecessary termination of pregnancies.

Three studies reported on a change of clinical management when MRI was utilised in addition to US as a means of diagnosing foetal abnormalities. The additional information gained from an MRI scan changed the diagnosis and therefore clinical management and parental counselling in a number of cases. Ten discordant cases between US and MRI were reported by Griffiths et al (2006). All of these women were advised to terminate their pregnancy on the evidence of the US scan, however the MRI scan altered the diagnosis correctly in nine of the ten cases and in only one pregnancy were the parents correctly advised to terminate based on the combined results of the US and MRI scans.

Two studies were included which scanned foetuses for *all* abnormalities, not just one specific type, reflecting the situation likely to be encountered in obstetric clinical practice. In the study by Frates et al (2004) diagnosis by MRI was incorrect in 39 per cent of diagnoses. The authors concluded that the diverse nature of abnormalities was the main factor in misdiagnosis by MRI.

Only the study by Malinger et al (2004) reported on the sensitivity and specificity of US and MRI for the diagnosis of CNS abnormalities. MRI was more sensitive (85% vs 55%) and more specific (80% vs 20%) than US.

No cost-effectiveness data were available on the use of MRI as a complementary tool to ultrasound for the diagnosis of foetal abnormalities.

In conclusion, MRI appears to be a useful adjunctive tool, in combination with ultrasound, for the diagnosis of some foetal abnormalities. Ultrasound remains the gold standard in the screening of pregnant women. In cases of equivocal ultrasound diagnosis, MRI may provide additional information which may alter the clinical management of the pregnancy. A confirmatory ultrasound in

addition to the referral ultrasound, conducted by the same institution where the MRI is to be conducted, may be beneficial. MRI scans for foetal abnormalities should only be conducted in tertiary centres where parents may access the appropriate level of counselling.

Appendix A: Levels of Evidence

Designation of levels of evidence according to type of research question

Level	Intervention §	Diagnosis **	Prognosis	Aetiology †††	Screening
I *	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§ among consecutive patients with a defined clinical presentation ††	A prospective cohort study ***	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§ among non-consecutive patients with a defined clinical presentation††	All or none §§§	All or none §§§	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial † Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study ‡ Interrupted time series without a parallel control group	Diagnostic case-control study ††	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ‡‡	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Tablenotes

[*] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

[§] Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

[†] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C).

[‡] Comparing single arm studies ie. case series from two studies.

[**] The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: www.msac.gov.au .

[§§] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 2003, 3: 25.

[††] Well-designed population based case-control studies (eg population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

[‡‡] Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

[***] At study inception the cohort is either non-diseased or all at the same stage of the disease.

[§§§] All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

[†††] If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: (Bandolier editorial 1999; Phillips et al 2001; NHMRC 1999; Lijmer et al 1999)

Prenatal	Occurring before birth.
Neonatal	Before 28 days of age.
Post neonatal	Between 28 days of age and one year.
Birth defect	any abnormality of prenatal origin, either present at conception or occurring before the end of pregnancy, including structural, functional, genetic, chromosomal and biochemical abnormalities.
MRI	Magnetic resonance imaging.
Ventriculomegaly	Occurs when the lateral ventricles of the brain become dilated (10-15 mm mild to moderate ventriculomegaly, >15mm severe ventriculomegaly). Enlargement of the ventricles may occur due to loss of brain volume (perhaps due to infection or infarction), or due to impaired outflow or absorption of cerebrospinal fluid from the ventricles.
Malformations of the posterior fossa	Congenital malformations of the structures of the posterior fossa, namely the midbrain, cerebellum, pons, and medulla.
Trisomy 21	Down's syndrome, a congenital disorder in which a person is born with three copies of chromosome 21.
Anencephalus	Without a brain.
Spina bifida	A congenital defect in the spinal column, characterised by the absence of the vertebral arches through which the spinal membranes and spinal cord may protrude.
Hydrocephalus	A condition marked by dilatation of the cerebral ventricles accompanied by an accumulation of cerebrospinal fluid within the skull. May be congenital or acquired.
Microcephalus	Having a small head; having a small cranial cavity.
Chorionic villus sampling	A form of prenatal diagnosis to determine genetic abnormalities in the foetus. It involves sampling the chorionic villus and is generally carried out only on pregnant women over the age of 35 and those whose offspring have a higher risk of chromosomal malformations. The advantage of CVS is that it can be carried out 10-12 weeks after the last period, earlier than amniocentesis.
Amniocentesis	A needle is inserted through the uterine wall and a small amount of amniotic fluid is extracted from the amnion around a developing foetus. It is usually offered when there may be an increased risk for genetic defects in the pregnancy. Standard amniocentesis is usually performed between 15-20 weeks gestation. Results take about two weeks.

Hypospadias	A congenital defect in which the urethra opens on the ventral surface of the penis rather than on the glans.
Polyhydramnios	Too much amniotic fluid in the amniotic sac.
Oligohydramnios	Too little amniotic fluid in the amniotic sac.
Meningomyelocoele	A congenital defect that is characterised by the protrusion of the membranes and cord through a defect in the vertebral column.
Encephalocoele	Hernia of the brain.
Triploidy	The presence of three haploid sets of chromosomes, instead of two, in all cells, resulting in foetal or neonatal death.
Rhabdomyoma	A rare benign tumour derived from striated muscle. May occur in the tongue, neck muscles, larynx, uvula, nasal cavity, axilla, vulva, and heart. Treated by simple excision.

Appendix C: Birth defects inclusions

Inclusions (not a complete listing) (Haan et al 2004)

Nervous System
Anencephaly
Spina bifida
Encephalocoele
Congenital hydrocephalus
Microcephaly
Dandy Walker syndrome
Craniosynostosis
Cerebral palsy

Gastro-Intestinal System
Cleft lip, palate
Tracheo-oesophageal fistula
Pyloric stenosis
Intestinal atresia
Hirschsprung disease
Ectopic anus
Imperforate anus
Exomphalos

Genital System
Undescended testis
(requiring treatment)
Hypospadias
Indeterminate sex

Musculo-Skeletal System
Developmental dysplasia of hip
Congenital talipes equinovarus
Polydactyly
Syndactyly
Absence (complete or partial)
of limbs
Osteogenesis imperfecta
Congenital spinal anomalies
Congenital torticollis
Congenital scoliosis
Bone dysplasias
Muscular dystrophy

Cardiovascular System
Congenital heart defects
Coarctation of the aorta
Patent ductus arteriosus
Dextrocardia

Eye
Microphthalmia/Anophthalmia
Congenital glaucoma
Congenital cataract
Coloboma

Urinary System
Cystic kidney
Absent kidney
Ectopic kidney
Double ureter
Ectopic ureter + ureterocoele
Vesico-ureteric reflux

Chromosomal Anomalies
Down Syndrome
Trisomy 13
Trisomy 18
Trisomy 21
Turner syndrome
Cri-du-chat syndrome
Fragile X

Skin
Cystic hygroma
Birthmarks ⎤ if > 4cm^2
Haemangiomas ⎬ multiple or
Naevi ⎦ requiring
surgery
Ichthyosis congenita
Epidermolysis bullosa

Respiratory System
Pulmonary hypoplasia
Diaphragmatic hernia
Choanal atresia
Congenital lung cyst

Blood
Thalassaemia major
Sickle cell anaemia
Haemophilia
G6PD deficiency

Metabolic Disorders - Inborn
Errors of Metabolism
Phenylketonuria
Cystic fibrosis
Congenital hypothyroidism
Adreno-genital syndrome
Glycogen storage disorders
Lipid storage disorders
Mucopolysaccharidoses
Albinism

Teratogens
Fetal alcohol syndrome
Fetal hydantoin syndrome

Congenital Infection
Toxoplasmosis
Rubella
Cytomegalovirus
Herpes simplex
Syphilis

Appendix D: Profiles of studies

Study	Location	Study design	Study population	Study details	Outcomes assessed
Breyson, L. Bosmans, H. Dymarkowski, S. van Schoubroeck, D. Witters, I. Deprest, J. Demaerel, P. Vanbeckevoort, D. Vanhole, C. Casaer, P. Smet, M. (2003)	Leuven, Brussels	Diagnostic evidence level III-2	40 foetuses (1 set twins) with suspected abnormalities (head, neck, spine, thoracic, urogenital, abdominal) diagnosed by US.	All foetuses underwent MRI at a mean gestational age of 28.3 weeks (range 19-39 weeks)	Postnatal clinical or post-mortem confirmation of abnormality.
Carcopino, X. Chaumoitre, K. Shojai, R. Akkawi, R. Panuel, M. Boubli, L. D'ercole, C. (2007)	Marseille, France	Diagnostic evidence level III-2	17 foetuses with suspected echogenic bowel diagnosed by US.	All foetuses underwent MRI after US at a mean gestational age of 24 weeks (range 21-32 weeks)	Genetic (prenatal) and postnatal clinical confirmation of cranio-synostosis.
Cassart, M. Massez, A. Metens, T. Rypens, F. Lambot, M.A. Hall, M. Avni, F.E. (2004)	Brussels, Belgium	Diagnostic evidence level III-2	16 foetuses with suspected urinary tract abnormalities diagnosed by US.	All foetuses underwent MRI after US at a mean gestational age of 31 weeks (range 27-37 weeks)	Postnatal clinical (n=12) or post-mortem (n=4) confirmation of abnormality.
Fjørtoft, M.I. Sevely, A. Boetto, S. Kessler, S. Sarramon, M.F. Rolland, M. (2007)	Toulouse, France	Diagnostic evidence level III-2	15 foetuses with suspected cranio-synostosis diagnosed by US.	All foetuses underwent MRI after US at a gestational age of 26-37 weeks.	Postnatal clinical confirmation of cranio-synostosis.
Frates, M.C. Kumar, A.J. Benson, C.B. Ward, V.L. Tempany, C.M. (2004)	Boston, US	Diagnostic evidence level III-2	27 foetuses with suspected abnormalities (CNS, genitourinary system, thorax and facial) diagnosed by US.	All foetuses underwent MRI after US at a gestational age of 18-37 weeks.	Postnatal clinical confirmation of diagnosis.
Garel, C. Dreux, S. Philippe-Chomette, P. Vuillard, E. Oury, J-F. Muller, F. (2006)	Paris, France	Diagnostic evidence level III-2	24 foetuses with suspected gastro-intestinal tract abnormalities diagnosed by US.	All foetuses underwent MRI after US at a median of 33 weeks gestation (range 30-39 weeks).	Postnatal clinical or postmortem confirmation of abnormality.

Garel, C. Delezoide, A-L. Elmaleh-Berges, M. Menez, F. Fallet-Bianco, C. Vuillard, E. Luton, D. Oury, J-F. Sebag, G. (2004)	Paris, France	Diagnostic evidence level III-2	28 foetuses with suspected cerebral ischaemic lesions diagnosed by US.	All foetuses underwent MRI after US at a median of 31.8 ± 3.3 weeks gestation (range 23-39 weeks).	Postnatal neurofeto-pathologic confirmation of abnormality.
Griffiths, P.D. Widjaja, E. Paley, M.N.J. Whitby, E.H. (2006)	Sheffield, United Kingdom	Diagnostic evidence level III-2	50 consecutive foetuses with suspected spine and spinal cord abnormalities diagnosed by US.	All foetuses underwent MRI after US at a median 26.5 weeks gestation (range 18-37 weeks).	Postnatal clinical or post-mortem confirmation of abnormality.
Hu, L.S. Caire, J. Twickler, D.M. (2006)	Texas, USA	Diagnostic evidence level III-2	32 multiple pregnancies (30 twin, 2 triplet) with suspected complications diagnosed by US.	All foetuses underwent MRI after US at 18-34 weeks gestation.	Postnatal confirmation of findings were not reported. Only results of MRI.
Ismail, K.M.K. Ashworth, J.R. Martin, W.L. Chapman, S. McHugo, J. Whittle, M.J. Kilby, M.D. (2002)	Stoke-on-Trent, United Kingdom	Diagnostic evidence level III-2	27 consecutive foetuses with suspected CNS abnormalities diagnosed by US.	All foetuses underwent MRI at a median gestational age of 27 weeks.	Postnatal clinical or post-mortem confirmation of abnormality.
Kline-Fath, B.M. Calvo-Garcia, M.A. O'Hara, S.M. Crombleholme, T.M. Racadio, J.M. (2007)	Cincinnati, USA	Diagnostic evidence level III-2	37 multiple pregnancies (36 twin, 1 triplet) with suspected twin-twin transfusion syndrome diagnosed by US.	All foetuses underwent MRI after US at a mean gestational age of 20 weeks (range 18-23 weeks).	Postnatal confirmation of findings were not reported. Only results of MRI.
Levine, D. Barnewolt, C.E. Mehta, T.S. Trop, I. Estroff, J. Wong, G. (2003)	Boston, USA	Diagnostic evidence level III-2	74 foetuses diagnosed with suspected thoracic abnormalities diagnosed by US.	74 foetuses underwent 83 MRI examinations at a mean gestational age of 25.2 ± 6.3 weeks (range 16-38 weeks).	Postnatal clinical or post-mortem confirmation of abnormality.
Levine, D. Barnes, P.D. Robertson, R.R. Wong, G. Mehta, T.S. (2003)	Boston, USA	Diagnostic evidence level III-2	214 foetuses diagnosed with suspected CNS abnormalities by US.	214 foetuses (20 sets of twins) underwent confirmatory US followed by 242 MRI examinations at a mean gestational age of 24.7 ± 6.1 weeks (range 14-40 weeks).	Postnatal clinical or post-mortem confirmation of abnormality.

Limperopoulos, C. Robertson, R.L. Estroff, J.A. Barnewolt, C. Levine, D. Bassan, H. du Plessis, A.J. (2006)	Boston, USA	Diagnostic evidence level IV	19 foetuses diagnosed prenatally with vermian hypoplasia by MRI	All foetuses underwent prenatal MRI with postnatal follow-up by MRI.	Postnatal MRI confirmation of vermian hypoplasia.
Malinger, G. Ben-Sira, L. Lev, D. Ben-Aroya, Z. Kidron, D. Lerman-Sagie, T. (2004)	Tel Aviv, Israel	Diagnostic evidence level III-2	42 foetuses with suspected CNS abnormalities diagnosed by US.	All foetuses underwent neuro-sonography and MRI at a mean gestational age of 30.2 weeks (range 23-37 weeks)	Postnatal clinical or post-mortem confirmation of abnormality.
Morris, J.E. Rickard, S. Paley, M.N.J. Griffiths, P.D. Rigby, A. Whitby, E.H. (2007)	Sheffield, United Kingdom	Diagnostic evidence level III-2	30 foetuses with suspected isolated cerebral ventriculo-megaly diagnosed by US.	All foetuses underwent MRI after US at a mean gestational age of 22.8 weeks (median 22 weeks)	Postnatal clinical confirmation of isolated cerebral ventriculo-megaly. Final diagnosis confirmed at discharge for live births or from post-mortem imaging.
Papadias, A. Miller, C. Martin, W.L. Kilby, M.D. Sgouros, S. (2007)	Birmingham, United Kingdom	Diagnostic evidence level III-2	13 foetuses with suspected CNS defects diagnosed by US, which may require immediate postnatal surgery. Postnatal MRI performed to confirm prenatal MRI findings.	All foetuses underwent MRI after US.	Postnatal clinical confirmation of CNS defects.
Salomon, L.J. Ouahba, J. Vuillard, E. Oury, J-F. Sebag, G. Garel, C. (2006)	Paris, France	Diagnostic evidence level III-2	310 foetuses with suspected ventriculo-megaly diagnosed by US. Analysed only those foetuses with isolated ventriculo-megaly ≤ 12mm (n=185)	All foetuses underwent MRI post US at a mean gestational age of 33.2 weeks (± 2.03, range 30-38 weeks). Postnatal imaging (MRI) conducted at 2 and 24 months and clinical follow-up at 2,6,9,12,18 and 24 months	Postnatal clinical confirmation of ventriculo-megaly.

Sharma, G. Heier, L. Kalish, R.B. Troiano, R. Chasen, S.T. (2003)	New York, USA	Diagnostic evidence level III-2	7 foetuses with suspected CNS abnormalities diagnosed by US.	All foetuses underwent MRI after US..	Improvements in parental counselling. Postnatal confirmation of findings were not reported. Only results of MRI.
Tilea, B. Delezoide, A.L. Khung-Savatovski, S. Guimiot, F. Vuillard, E. Oury, J.F. Garel, C. (2007)	Paris, France	Diagnostic evidence level III-2	25 foetuses with suspected posterior fossa malformations diagnosed by US	All foetuses underwent MRI after US at a mean gestational age of 31 weeks.	Post-mortem confirmation of posterior fossa malformation at a mean gestational age of 33 weeks.
Whitby, E.H. Variend, S. Rutter, S. Paley, M.N.J. Wilkinson, I.D. Davies, N.P. Sparey, C. Griffiths, P.D. (2004)	Sheffield, United Kingdom	Diagnostic evidence level III-2	12 foetuses with suspected CNS abnormalities diagnosed by US.	All foetuses underwent MRI after US.	Post-mortem or postnatal MRI confirmation of diagnosis.
Whitby, E.H. Paley, M.N.J. Sprigg, A. Rutter, S. Davies, N.P. Wilkinson, I.D. Griffiths, P.D. (2004)	Sheffield, United Kingdom	Diagnostic evidence level III-2	100 foetuses with suspected CNS abnormalities diagnosed by US.	All foetuses underwent MRI after US.	Post-mortem, postnatal MRI or postnatal clinical confirmation of diagnosis. Time of procedure.

MRI = magnetic resonance imaging, US = ultrasound, CNS = central nervous system

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  http://www.med.monash.edu.au/healthservices/cce/evidence/

- Health Economics Unit, Monash University
  http://chpe.buseco.monash.edu.au

AUSTRIA

- Institute of Technology Assessment / HTA unit
  http://www.oeaw.ac.at/ita/welcome.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/site/index.php?accueil

- Alberta Heritage Foundation for Medical Research (AHFMR)
  http://www.ahfmr.ab.ca/publications.html

- Canadian Coordinating Office for Health Technology Assessment (CCHOTA) http://www.cadth.ca/index.php/en/

- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca

- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca

- Health Utilities Index (HUI)
  http://www.fhs.mcmaster.ca/hug/index.htm

- Institute for Clinical and Evaluative Studies (ICES)
  http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA)
  http://www.dihta.dk/publikationer/index_uk.asp

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FINLAND

- FINOHTA http://www.stakes.fi/finohta/e/

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)
  http://www.anaes.fr/

GERMANY

- German Institute for Medical Documentation and Information (DIMDI)
  / HTA http://www.dimdi.de/dynamic/en/

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad
  http://www.gr.nl/adviezen.php

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA)
  http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM)
  http://www.kunnskapssenteret.no/

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud
  "Carlos III"I/Health Technology Assessment Agency (AETS)
  http://www.juntadeandalucia.es/salud/orgdep/aetsa/default.asp

- Catalan Agency for Health Technology Assessment (CAHTA)
  http://www.aatrm.net/html/en/dir394/index.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU)
  http://www.sbu.se/www/index.asp

- Center for Medical Health Technology Assessment
  http://www.cmt.liu.se/

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA)
  http://www.snhta.ch/

UNITED KINGDOM

- NHS Quality Improvement Scotland
  http://www.nhshealthquality.org/nhsqis/qis_display_home.jsp?pContentID=43&p_applic=CCC&pElementID=140&pMenuID=140&p_service=Content.show&

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- University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/

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UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ)
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