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MRI safety considerations during pregnancy

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ABSTRACT

The use of magnetic resonance imaging (MRI) during pregnancy is on the rise due its ability to provide detailed cross-sectional anatomy without ionizing radiation. Despite the favorable radiation profile, theoretically concerns regarding the safety of MRI and gadolinium-based contrast agent (GBCA) administration have been raised. Currently there are no studies that have shown any attributable harms of MRI during any trimester of pregnancy although prospective and longitudinal studies are lacking. GBCA administration may be associated with a slightly higher rate of neonatal death, although this is based on a single, large cohort study. Understanding the available evidence regarding MRI safety during pregnancy in the context of current society guidelines will help the radiologist serve as a valuable resource to patients and referring providers.

1. Introduction

Ultrasound (US) and magnetic resonance imaging (MRI) are the favored modalities in the imaging of pregnant women because they lack ionizing radiation. MRI also has the advantage of providing non-operator-dependent, detailed cross-sectional anatomy. Overall, MRI use during pregnancy is increasing due to the lack of ionizing radiation, increasing availability, and advances in fetal MRI, which has steadily grown since its inception in the mid-1980s [1,2]. Despite the general acceptance of MRI as the safer alternative to radiography, computed tomography (CT), and nuclear scintigraphy, there have been concerns regarding theoretical teratogenicity of MRI. Additionally, the use of gadolinium-based contrast agents (GBCA) in pregnancy has generally been restricted due to the observation that it crosses the placenta. This is especially relevant in the context of the recently described gadolinium deposition phenomenon. Several theoretical risks to the fetus associated with MRI during pregnancy have been proposed including possible teratogenic effects of static magnetic fields, radiofrequency energy, and GBCAs. To date, none of these risks have been definitively shown to result in fetal harm, although prospective and longitudinal studies are lacking. The uncertainty regarding these risks is reflected in vaguely worded guidelines and variable practice patterns. For example, survey data have shown that 43–79% of academic hospitals have written policies about imaging in pregnancy including the use of informed consent for MRI [3–5].

Given these variable practice patterns, there is a need for radiologists to be familiar with available evidence regarding the safety of MRI in pregnancy. In this article, we review the literature pertaining to the safety of MRI and GBCAs in pregnancy as well as current society guidelines. Additionally, we briefly address the use of GBCAs in the breastfeeding patient. A summary of society guidelines (Table 1) and evidence tables for MRI safety and GBCA safety during pregnancy (Tables 2 and 3) can be found at the end at the end of the article.

2. MRI safety in pregnancy

2.1. Teratogenicity of MRI

Several mammal studies have suggested that MRI exposure during pregnancy was associated with abnormal eye development, decreased live birth rate, lower birth weight, and lower crown rump length [6–10]. The interaction of magnetic fields, both static and time-varying, on living organisms at the cellular level has been well-studied, particularly in the stem cell literature. Studies have shown magnetic fields can affect cell migration, differentiation, and proliferation *via* altered cell signaling [11,12], however this has been difficult to demonstrate *in vivo*. Tissue heating from radiofrequency pulses, as quantified by the specific absorption rate (SAR), is also important to consider given the well-documented link between maternal hyperthermia, whether from strenuous exercise, environmental exposure, or febrile illness, with congenital anomalies and fetal demise [13–16]. Although energy deposition and heating is greatest at the maternal surface, fetal SAR can range between 40 and 70% of the maternal SAR with a standard body coil [17].

Despite these concerns, no studies to date have demonstrated the teratogenic effects of MRI suggested by earlier animal models. Early

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Table 1
American College of Radiology (ACR) and American College of Obstetrics and Gynecology (ACOG) guidelines.

	ACR	ACOG
MRI in pregnancy	There is no known adverse effect of MRI on the fetus. The decision to scan during pregnancy should be made on an individual basis [43].	MRI is not associated with risk but should be used prudently and only when use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient [45].
GBCA in pregnancy	Because it is unclear how GBCAs will affect the fetus, these agents should be administered with caution to pregnant or potentially pregnant patients. GBCAs should only be used if their usage is considered critical and the potential benefits justify the potential unknown risk to the fetus [75].	The use of GBCAs with MRI should be limited; it may be used as a contrast agent in a pregnant woman only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome [45].
GBCA and breastfeeding	Cessation of breastfeeding after receiving GBCAs is not recommended although ultimately it is the mother's decision after an informed discussion is presented [75].	Breastfeeding should not be interrupted after gadolinium administration [45].

Table 2
Evidence table for MRI safety in pregnancy.

Study	Study design	CEBM level of evidence[a]	n exposed n control	Magnet strength	Trimester	Outcome/summary
Chartier et al. 2019 [22]	Retrospective cohort	2b	81 162	3 T	all	No difference in hearing impairment or birth weight
Strizek et al. [23]	Retrospective cohort	2b	751 10,042	1.5 T	2nd-3rd	No difference in hearing impairment or birth weight
Ray et al. 2016 [24]	Retrospective cohort with 4-year follow-up	2b	1737 1.4 M	Not recorded	1st	No difference between perinatal death rate, congenital anomalies, vision loss, hearing loss, or tumor
Bouyssi et al. 2015 [34]	Case series with 2-year follow-up	4	72 0	1.5 T	2nd-3rd	No hearing loss or functional impairment
Jaimes et al. 2019 [40]	Retrospective cohort (1.5 T v 3 T)	2b	62 62	1.5 T v 3 T	2nd-3rd	No difference in hearing between 1.5 T and 3 T
Reeves et al. 2010 [33]	Case series	4	103 0	1.5 T	2nd-3rd	No increased risk of hearing impairment
Kok et al. 2004 [18]	Case series	4	35	1.5 T	2nd-3rd	General review of health of 41 children (1–9 years old) found no negative effects attributable to MRI

[a] Level of evidence defined by the Oxford Centre for Evidence-Based Medicine [84].

small observational studies of children born to pregnant women exposed to MRI found no ill-effects attributable to MRI [18–21]. Few larger and more recent retrospective cohort studies have specifically found no differences in birth weight or perinatal death rate for fetuses exposed to MRI [22–24].

Two main limitations of the available human studies are the retrospective nature of these studies and lack of long-term data. The largest of these retrospective cohort studies utilized a large Canadian database and included up to four years of follow-up [24]. The group evaluated outcomes for two separate cohorts: fetuses exposed to MRI during the first trimester and fetuses exposed to GBCAs during any trimester, which is discussed below in the section addressing the safety of GBCAs during pregnancy. The first cohort included 1737 exposed neonates and 1.4 million unexposed controls. As the authors did not have data on MRI indications for the exposed group, they used propensity score weighting for important conditions such as diabetes, obesity, and substance use. The group found no differences in neonatal death rate, congenital anomalies, or cancer between the groups [24]. The greatest strength of the study was the large, population-based sample size; other studies have only included an exposed sample size on the order of tens to hundreds. A main limitation of the study was the exclusion of pregnancies ending prior to 21 weeks, which precludes the evaluation of spontaneous abortion risk.

2.2. Hearing damage

Fetal hearing damage has been proposed as a possible outcome of MRI during pregnancy. Acoustic noise generated by MRI typically ranges between 80 and 110 dB but can exceed that depending on the setup and sequence [25]. Although maternal tissue and amniotic fluid attenuate the sound intensity the fetus is exposed to, the degree of attenuation is uncertain. Additionally, there is greater attenuation of sound intensity for high frequency than low frequency noise with some studies even demonstrating that low frequency sound can be amplified by maternal tissue and amniotic fluid [26]. Thus, neonatal hearing loss, either mediated through hair cell damage or abnormal development of the hearing apparatus, is a theoretical risk.

Early animal models in sheep and guinea pigs have suggested this potential for hearing abnormalities due to acoustic noise exposure *in utero* [27–29]. Studies of occupational noise exposure during pregnancy and neonatal hearing loss have shown mixed results [26,30–32].

Facilitated by the widespread availability of universal neonatal hearing screening data, several retrospective studies have found no differences in hearing abnormalities at birth between neonates exposed to MRI and nonexposed neonates including the large Canadian database study by Ray et al., which included up to 4 years of follow-up [23,24,33]. Similar to studies evaluating the possible teratogenicity of MRI, prospective data is lacking. The only available prospective study evaluating hearing abnormalities performed by Bouyssi et al. followed 72 children who were exposed to a standardized MRI exam during the second or third trimester up to preschool age (2 years mean follow-up). The group found normal hearing in all children although the study was mostly limited by its observational nature and lack of an unexposed control group [34].

2.3. Magnet strength

There is increasing use of higher field magnets, 3 T or greater, which offer increased signal to noise. Even fetal imaging, which is mostly performed at 1.5 T in current practice, is starting to gain acceptance at 3 T as we learn how to handle 3 T-specific artifacts [35,36]. Magnet strength is a key consideration in the context of the aforementioned safety concerns. For example, SAR is proportional to the square of the magnet strength (B_o), which in clinical practice translates to a fourfold

Table 3
Evidence table for gadolinium-based contrast agent (GBCA) safety in pregnancy.

	Study design	CEBM level of evidence[a]	n exposed n control	Outcome/summary
Ray et al. 2016 [24]	Retrospective cohort with 4- year follow-up	2b	397 1.4 M	Increased rate of neonatal death (HR 3.7) and rheumatological, inflammatory, infiltrative skin condition (HR 1.36); no difference in NSF-like disease or congenital anomaly
Shoenut et al. 1993 [59]	Case series	4	2	No adverse effects
De Santis et al. 2007 [57]	Case series	4	26	No adverse effects
Barkhof et al. 1992 [58]	Case series	4	1	No adverse effects
Marcos et al. 1997 [60]	Case series	4	11	Placental indication, no adverse effects (secondary outcome)
Millischer et al. 2017 [61]	Case series	4	21	Placental indication, no adverse effects (secondary outcome)
Spencer et al. 2000 [62]	Case series	4	8	MRU for maternal hydronephrosis, no adverse effects (secondary outcome)
Tanaka et al. 2001 [63]	Case series	4	6	Placental accreta, no adverse effect

[a] Level of evidence defined by the Oxford Centre for Evidence-Based Medicine [84].

difference in energy deposition between a 3 T exam and 1.5 T keeping all other factors constant. Extended imaging time on a 3 T magnet beyond 30 min can cause up to 2.5 °C increase in the gravid pig uterus, which is beyond the 1 °C limit of core temperature rise mandated by the Food and Drug Administration (FDA) [37]. Additionally, the acoustic noise generated during MRI increases with field strength although the relationship is not linear [38,39].

Most of the above-cited studies evaluated outcomes after exposure to a 1.5 T exam possibly due to availability or potential concerns regarding higher field strength. The large retrospective cohort study by Ray et al. did not track magnet strength although the authors comment that most exams were performed on a 1.5 T magnet given the availability during the study timeframe. As such, the group concluded that MRI is safe in the first trimester but magnet strengths > 1.5 T should be avoided.

Few studies have addressed the safety of 3 T in pregnancy. The retrospective cohort study by Chartier et al. included 81 neonates exposed to a 3 T exam and 162 unexposed neonates and found no differences in hearing impairment or birth weight [22]. A second retrospective cohort study by Jaimes et al. found no differences in hearing outcomes between 62 neonates exposed to 3 T exams and 62 neonates exposed to 1.5 T exams [40]. To our knowledge, no prospective or longer-term studies have evaluated potential harms of 3 T imaging during pregnancy.

2.4. Trimester considerations

A core principle in teratology is that earlier gestational insults have the higher potential for severe anomalies and fetal demise; as the major period of organogenesis, the first trimester of pregnancy is regarded as the most sensitive to insults. Thus, it is conceivable that first trimester exposure to MRI poses a higher risk for abnormal development than second or third trimester exposure. There is also a special theoretical consideration for hearing development, which develops throughout the second and third trimesters with some hearing apparatus structures such as the tympanic membrane continuing to develop to term [41].

Nearly all of the above cited studies examined subjects exposed to MRI during second or third trimesters, perhaps due to safety concerns of first trimester MRI, institutional policies restricting first trimester MRI, or the limited role of MRI in first trimester fetal imaging. One of the first observational studies evaluated 15 neonates inadvertently exposed to MRI during their first trimester and found no attributable adverse outcomes [42]. The highest quality evidence for first trimester MRI safety comes from the large retrospective cohort study by Ray et al. who exclusively studied first trimester exposure [24]. There are currently no studies directly comparing outcomes by trimester exposure nor are there studies evaluating the interaction between magnet strength and trimester exposure.

2.5. Society guidelines

There are no current guidelines that have declared MRI in pregnancy absolutely risk-free. In their most recent practice parameter for performing and interpreting MRI from 2017, the American College of Radiology (ACR) states that although there is no known risk to the fetus, the decision to perform MRI during pregnancy should be made on an individual basis [43]. Nonetheless, ACR supports the use of non-contrast MRI during pregnancy for several indications in their Appropriateness Criteria including evaluation of acute abdominal pain and new headache [44]. For example, the Appropriateness Criteria narrative section for acute pancreatitis states that “MRI is particularly well suited for pregnant women…especially since studies have shown that patients who undergo early CT for acute pancreatitis are more likely to have repeat CT scans during the same admission.”

Similarly to the ACR, the American College of Obstetrics and Gynecology (ACOG) states that there are no risks associated with MRI

but it should be used prudently [45]. Notably, neither group addresses the issues of magnet strength, trimester consideration, or need for informed consent. In a briefer and somewhat more definitive position statement last updated in 2018, The Radiological Society of North America opines that MRI is regarded as safe to the fetus in normal clinical usage (*i.e.* ≤3 T) [46].

2.6. Summary

Theoretical concerns regarding the safety of MRI during pregnancy have not been definitively shown in human data although there is a paucity of prospective and longitudinal data. This is reflected in current society guidelines, which acknowledge that there are no demonstrable risks but do not support the liberal use of MRI during pregnancy.

3. Gadolinium-based contrast agents in pregnancy

3.1. Teratogenicity of GBCAs

Early animal models established the ability of GBCAs to cross the placenta [47–50]. More recent studies evaluating their transplacental pharmacokinetics in mice and nonhuman primates have shown that a small but measurable amount of gadolinium chelate can be detected in the amniotic fluid and fetal tissues at 24–48 h [51,52]. While it is established that maternal intravenous injection exposes the fetus to gadolinium chelate in animals, the teratogenic effects of GBCAs are unclear. Studies involving mice, rats, rabbits, and dogs have had mixed results with some studies showing higher spontaneous abortion rate, lower mean birth weight, and various congenital anomalies at supraclinical, daily doses while others show no harmful effects even at supratherapuetic doses [53–56]. Prior to the revamping of pregnancy category labeling in 2015, the FDA had rated GBCAs as Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Multiple case series of gadolinium administration during pregnancy, either inadvertent or for maternal indications, ranging from 1 to 26 subjects have not demonstrated any attributable harm at birth [57–63]. However, these studies are limited by sample size, observational nature, and lack of well-defined outcomes.

The only controlled study evaluating the safety of GBCAs with clearly defined outcomes was performed by Ray et al. In the second cohort of their large retrospective, longitudinal study, the group evaluated multiple outcomes for 397 children exposed to GBCAs during any trimester in pregnancy compared to 1.4 million controls who had no MRI exposure. The group found a higher rate of neonatal death (HR 3.70) in the exposed group compared to the unexposed group. Of note, this translated into a small absolute difference in incidence rate of 1%. There was no significant difference in rates of congenital anomaly. However, a main limitation of this study was the unavailability of MRI indications for the exposed cohort, which are potential confounders. Other limitations of the cohort analysis include no adjustment of significance cutoff for multiple comparisons, low follow-up rate (46%), blinding to specific GBCA, no trimester subset analysis, and a less than ideal control group. Arguably, a more appropriate control group would consist of patients exposed to non-contrast MRI exams rather than no MRI exposure at all. Nonetheless, the study represents the only cohort and longitudinal study available with a relatively large sample size.

3.2. Gadolinium deposition

Apart from the potential teratogenicity of GBCAs, another theoretical concern is gadolinium deposition, a phenomenon that has received great attention in the past five years after T1 signal changes were reported in the dentate nucleus and globus pallidus associated with multiple administrations [64]. Gadolinium is biologically inert in its complexed, chelated form but toxic in its free ionic form (Gd^{3+}). The implication of long-term gadolinium deposition is the potential for dechelation leading to harmful effects. Numerous additional studies have confirmed GBCA-related signal changes in the brain since 2014 associated with multiple lifetime exposures to linear and, to a lesser extent, macrocyclic GBCAs in a dose-dependent fashion even in patients with normal renal function. Biopsy and autopsy studies have also shown gadolinium deposits in multiple tissues but largely brain, skin, bone, and liver associated with both macrocyclic and linear agents [65]. Despite these reports, other than nephrogenic systemic fibrosis, no disease or symptoms have been definitively attributed to GBCAs [66,67]. As such, the clinical significance of gadolinium deposition remains uncertain.

Gadolinium deposition in the pediatric patient, and perhaps by extension the fetal patient, is of special concern given the ongoing rapid development of brain and bone as well as longer lifetime potential for repeat GBCA exposure [68,69]. Postnatal animal studies have found detectable gadolinium concentration in mouse brain tissue at 28 days of life after daily exposure *in utero* [70] and barely detectable levels in the femur and liver tissues of rhesus macaques at 7 months of life after single exposure [71]. Currently there are no human studies that have examined the degree, if any, of gadolinium deposition associated with *in utero* exposure.

3.3. Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis (NSF) was first recognized in 2000 [72] and represents a rare disease characterized by fibrosing skin lesions. NSF has been raised as a possible risk of *in utero* exposure of GBCAs. Although the link between GBCA and NSF is widely accepted, the mechanism and pathogenesis of GBCA-associated NSF is unknown. It is theorized be related to poor clearance of the agent based on the observation that nearly all reported cases have occurred in patients with end-stage renal disease. As discussed above, animal models have shown detectable amounts of gadolinium in the amniotic fluid after maternal intravenous injection. Given the unknown duration of exposure of the fetus to GBCA after administration, neonatal NSF has been proposed as possible risk of GBCA use during pregnancy.

In their large cohort study, Ray et al. also examined rates of skin or connective-tissue disease resembling NSF between children who were exposed to GBCA during pregnancy and the unexposed group. Because NSF is rare, largely described in adults with end-stage renal disease, and requires invasive biopsy, the authors postulated that neonatal or pediatric NSF could be misdiagnosed; as such, they included a separate broad outcome of any diagnosed rheumatologic, inflammatory, or infiltrative skin condition. The group found no differences in rates of NSF-like conditions between the exposed and unexposed groups with the incidence rates for both groups under 0.5%. A slightly higher rate of rheumatologic, inflammatory, or infiltrative skin condition (HR 1.36) in the exposed group with an absolute difference in incidence rate of 4% (31% *vs* 27%) was also reported. The significance of this finding is difficult to interpret as it relates to NSF given the ambiguity of the category and small absolute difference. And as noted earlier, the lack of MRI indication data raises the question about potential confounding maternal factors. Of note, there has been no report of biopsy-confirmed NSF in a child under 6 years of age worldwide [73]. Further diminishing the concern for neonatal or pediatric NSF from GBCA use during pregnancy is the overall rapid decline in NSF reports after 2008, which is likely due to a combination of routine screening for renal impairment prior to administration and the decline in use of GBCAs with the highest NSF association, which the ACR has labeled “group I” [74,75].

3.4. Risk-benefit considerations

Thus far the possible risks associated with GBCA administration

during pregnancy have been discussed; however, the potential benefits of GBCA administration should also be considered in the context of risk-benefit discussion. The value of contrast in fetal imaging has not been established but GBCAs may play a role for certain maternal or obstetric indications. For example, there is a growing body of evidence that dynamic contrast-enhanced MRI improves the diagnostic accuracy of placenta accreta [61,63,76,77]. Accurate diagnosis of placenta accreta spectrum disorders has implications for maternal and fetal health as well as surgical management. The value of contrast-enhanced cardiac MRI during pregnancy has been explored for ischemic and non-ischemic disease. A retrospective study of 83 pregnant women undergoing cardiac MRI found that 16 patients were determined to benefit from contrast and that in 50% of those cases, the contrast-enhanced images altered management [78]. The authors raise the point that because hemodynamic compromise carries immediate high risk for the fetus, accurate diagnosis of certain cardiac conditions with a GBCA is warranted. More broadly this highlights the link between maternal health and fetal health when considering the potential benefits of GBCA use.

3.5. Society guidelines

In contrast to their stance on non-contrast MRI during pregnancy, the ACR takes a more measured approach in addressing the use of GBCA during pregnancy. In their most recent Contrast Manual last updated in 2018, the ACR states that because it is unclear how GBCAs will affect the fetus, they should be administered with caution in pregnant or potentially pregnant patients and only if the potential benefits justify the potential unknown risk to the fetus [75]. They also recommend the use of informed consent and documentation of discussion with the ordering provider confirming that the information cannot be obtained with a non-contrast MRI or other imaging modality, that the diagnostic information will affect the care of the patient and/or fetus, and that it would not be prudent to delay the study until after pregnancy. Similar to the ACR, the ACOG states that the use of GCBA with MRI should be limited and only used if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome [45]. Of note, in their respective narrative discussions, both the ACR and ACOG cite the large Canadian cohort study by Ray et al. as rationale for the judicious use of GBCAs during pregnancy. Other non-American societies have similarly-worded guidelines including the Royal College of Radiology and European Society of Urogenital Radiology [79,80].

3.6. Summary

GBCA use during pregnancy may be associated with a slightly higher rate of neonatal death although this risk is based only on a single large cohort study [24], which had significant limitations and demonstrated only a small absolute difference. As such, additional studies are needed to confirm these results. The degree and significance of gadolinium deposition from *in utero* exposure remains uncertain. The risk of NSF is felt to be exceedingly low given the lack of confirmed cases in children under 6 years of age and overall rapid decline of NSF in the past decade. In addition to the potential benefits of GBCA administration during pregnancy for maternal or fetal care, the alternatives and the timeliness of the exam should also be considered with the ordering provider as supported by current guidelines.

4. Gadolinium-based contrast agents in breastfeeding

Intravenously administered GBCAs are excreted into breast milk in very small quantities due to its poor binding to milk proteins. It is estimated that < 0.04% of the injected dose is excreted into the breastmilk, of which < 1% is absorbed by the neonatal gastrointestinal tract [81,82]. Together, this translates to the widely cited figure of < 0.0004% neonatal absorption, which is well below the weight-based recommended doses for pediatric MRI [83]. Prior to the establishment of these figures, a 24-h precautionary suspension of breastfeeding after GBCA administration was widely practiced, although this has fallen out of favor. To date, no studies have demonstrated any adverse effects of continued breastfeeding after GBCA injection. In fact, temporary cessation of breastfeeding has the potential harm of early weaning. As such, the ACR and the ACOG recommend continued breastfeeding, although the former acknowledges the decision is ultimately the mother's and offers a 12–24 h “pump and dump” period as an alternative [45,75].

5. Conclusion

MRI has been a favored imaging modality during pregnancy due to the lack of ionizing radiation, however there are unique safety considerations that the radiologist should be familiar with in the context of the available evidence and current society guidelines. Non-contrast MRI appears safe during all trimester although there is a lack of prospective and longitudinal data. Additionally, there may be a slightly increased risk of neonatal death associated with GBCA use during pregnancy based on a single large cohort study. As such, its use during pregnancy should be limited to only when it is expected to alter maternal or fetal management during the course of pregnancy. Understanding these risks and uncertainties will help the radiologist serve as a valuable resource to patients and referring providers.

Declaration of competing interest

None.

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