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Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes

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IMPORTANCE Fetal safety of magnetic resonance imaging (MRI) during the first trimester of pregnancy or with gadolinium enhancement at any time of pregnancy is unknown.

OBJECTIVE To evaluate the long-term safety after exposure to MRI in the first trimester of pregnancy or to gadolinium at any time during pregnancy.

DESIGN, SETTING, AND PARTICIPANTS Universal health care databases in the province of Ontario, Canada, were used to identify all births of more than 20 weeks, from 2003-2015.

EXPOSURES Magnetic resonance imaging exposure in the first trimester of pregnancy, or gadolinium MRI exposure at any time in pregnancy.

MAIN OUTCOMES AND MEASURES For first-trimester MRI exposure, the risk of stillbirth or neonatal death within 28 days of birth and any congenital anomaly, neoplasm, and hearing or vision loss was evaluated from birth to age 4 years. For gadolinium-enhanced MRI in pregnancy, connective tissue or skin disease resembling nephrogenic systemic fibrosis (NSF-like) and a broader set of rheumatological, inflammatory, or infiltrative skin conditions from birth were identified.

RESULTS Of 1 424 105 deliveries (48% girls; mean gestational age, 39 weeks), the overall rate of MRI was 3.97 per 1000 pregnancies. Comparing first-trimester MRI (n = 1737) to no MRI (n = 1 418 451), there were 19 stillbirths or deaths vs 9844 in the unexposed cohort (adjusted relative risk [RR], 1.68; 95% CI, 0.97 to 2.90) for an adjusted risk difference of 4.7 per 1000 person-years (95% CI, −1.6 to 11.0). The risk was also not significantly higher for congenital anomalies, neoplasm, or vision or hearing loss. Comparing gadolinium MRI (n = 397) with no MRI (n = 1 418 451), the hazard ratio for NSF-like outcomes was not statistically significant. The broader outcome of any rheumatological, inflammatory, or infiltrative skin condition occurred in 123 vs 384 180 births (adjusted HR, 1.36; 95% CI, 1.09 to 1.69) for an adjusted risk difference of 45.3 per 1000 person-years (95% CI, 11.3 to 86.8). Stillbirths and neonatal deaths occurred among 7 MRI-exposed vs 9844 unexposed pregnancies (adjusted RR, 3.70; 95% CI, 1.55 to 8.85) for an adjusted risk difference of 47.5 per 1000 pregnancies (95% CI, 9.7 to 138.2).

CONCLUSIONS AND RELEVANCE Exposure to MRI during the first trimester of pregnancy compared with nonexposure was not associated with increased risk of harm to the fetus or in early childhood. Gadolinium MRI at any time during pregnancy was associated with an increased risk of a broad set of rheumatological, inflammatory, or infiltrative skin conditions and for stillbirth or neonatal death. The study may not have been able to detect rare adverse outcomes.

Author Video Interview and JAMA Report Video

Supplemental content

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With greater reliance on medical imaging by clinicians,[1] concern has been raised about the effects of ionizing radiation to a fetus during pregnancy.[2,3] There is general acceptance that whenever possible clinicians should choose an imaging modality during pregnancy that has little or no ionizing radiation, such as ultrasonography and magnetic resonance imaging (MRI).[4]

Magnetic resonance imaging during pregnancy is generally thought to be safe for the fetus, especially in the second or third trimester.[5,6] Concern has been expressed about the safety of MRI exposure in the first trimester, due to the heating of sensitive tissues by radiofrequency fields and exposure to the loud acoustic environment.[7-10] When indicated, MRI's diagnostic accuracy is improved with gadolinium, an intravenous contrast medium[11]; however, administration of gadolinium in pregnancy is discouraged because of possible teratogenicity in the first trimester during organogenesis. Additionally, gadolinium may cross the placenta in the second or third trimester,[12] where it may be excreted by the fetal kidneys into the amniotic fluid and then recirculated by the fetus. Theoretically, persistence of dissociated-free gadolinium could cause nephrogenic systemic fibrosis (NSF) in the child.[7,8,11] Although no cases of NSF have been reported, only one case series of gadolinium-enhanced MRI in pregnancy has been published.[13]

Current recommendations are to forgo use of gadolinium-enhanced MRI at any point during pregnancy, unless absolutely essential, and to carefully consider use of nonenhanced MRI in the first trimester.[3,5,7,8] Clinicians need more data about the long-term safety for the child exposed to MRI in the first trimester of pregnancy or to gadolinium at any time during pregnancy.

Key Points

Question What is the safety of magnetic resonance imaging (MRI) in the first trimester of pregnancy or that of gadolinium contrast any time during pregnancy?

Findings In a population-based cohort study involving more than 1.4 million pregnancies, first-trimester MRI was not significantly associated with stillbirth or neonatal death, congenital anomaly, neoplasm, or hearing loss. Gadolinium-enhanced MRI was associated with a higher risk of stillbirth or neonatal death and a broad set of rheumatological, inflammatory, or infiltrative skin conditions.

Meaning MRI use in the first trimester was not shown to be harmful to the fetus. Gadolinium-enhanced MRI at any time of pregnancy was associated with rare adverse outcomes in childhood.

Methods

Study Design

This retrospective cohort study used data sets of all Ontario births linked to their mothers, conducted at the Institute for Clinical Evaluative Sciences (ICES). Universal health care coverage is available to all Ontario residents through the Ontario Health Insurance Plan (OHIP). The Research Ethics Board of the Sunnybrook Health Sciences Centre granted ethics approval and waived informed consent.

Participants

Included were all maternal-child pairs in the province of Ontario, with delivery of a liveborn or stillborn child occurring between April 27, 2003, and March 4, 2015. For multifetal pregnancies, the first-born child was selected. Excluded were non-Ontario residents, women younger than 16 years or older than 50 years, and women who delivered at 20 weeks' gestation or earlier (eTable 1 in the Supplement). More than 90% of births in Ontario have prenatal ultrasonography before 24 weeks' gestation,[14] enabling accurate dating of most pregnancies.[15] Gestational age at birth, in completed weeks, was provided within the newborn record.

Exposures and Outcomes

Two separate study exposures were evaluated, each assigned its own cohort. Cohort 1 comprised all women who had an MRI in the first trimester of pregnancy, between completed gestational weeks 2 to 14, for which gestational week 2 starts 14 days after the first day of the last menstrual period. Cohort 2 comprised all women who had a gadolinium-enhanced MRI between the second gestational week and up to 2 days before the index birth date, to ensure that the exposure occurred while the fetus was in utero. Magnetic resonance imaging, with or without gadolinium contrast, was identified using OHIP billing codes, which are assigned for every inpatient or outpatient MRI performed in the province (eTable 1 in the Supplement).

For first-trimester MRI (cohort 1), 5 study outcomes diagnosed before age 4 years were assessed: (1) stillbirth after 20 weeks' gestation or neonatal death before 28 days after birth (eTable 1 in the Supplement); (2) any congenital anomaly, excluding children with a concomitant chromosomal disorder; (3) neoplasm; (4) vision loss; and (5) hearing loss. The final date of follow-up was March 31, 2015. To ensure that the first-trimester MRI exposure preceded a recognized congenital anomaly, pregnancies in which there was a diagnosis of an anomaly plus a fee code for an ultrasound, amniocentesis, chorionic villous sampling, or genetics consultation preceding that MRI by at least 1 day were excluded (eTable 1 in the Supplement). The Ontario Infant Hearing Program provided universal newborn hearing screening during the period of study.[16]

For gadolinium-enhanced MRI during pregnancy (cohort 2), a specific NSF-like outcome of a connective tissue or skin disease was evaluated, diagnosed from birth to age 4 years (eTable 1 in the Supplement). Given that NSF is rare, largely found in adults with advanced kidney disease, and that it often necessitates invasive skin biopsy,[17] it could be misdiagnosed in a very young child. Accordingly, a broader outcome of any diagnosed rheumatological, inflammatory, or infiltrative skin condition was assessed. Examples include arthritis, vasculitis, bone disorder, dermatitis, or connective tissue calcification. Any congenital anomaly, as well as stillbirth or neonatal death, was also evaluated, as described above.

Database Sources

All data were linked using unique encoded identifiers and analyzed at ICES (see https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx). All maternal, fetal, and newborn infant hospitalizations and procedures were identified

using the Canadian Institute for Health Information Discharge Abstract Database, including up to 25 diagnoses according to the *International Classification of Diseases, 10th Revision, Canada* (*ICD-10-CA*), coding system. The MOMBABY Data set at ICES links the Discharge Abstract Database inpatient admission records of delivering mothers and their newborns from 2002 onward. Mothers and their newborns are deterministically linked using the maternal-newborn chart numbers recorded.

Because some conditions (eg, maternal prepregnancy hypertension and diabetes mellitus) may be diagnosed in outpatient settings, the OHIP Database was also used to identify diagnoses starting from 90 days before the estimated date of conception to the index birth date.[14] This database contains records of all physician billing information for outpatient and inpatient services, including the service date and a single diagnosis. The specialties of the physician requesting the MRI was obtained from the OHIP Database, as was the single diagnosis made on the date nearest the MRI, prioritized as the same day as the MRI, from 1 to 30 days after the MRI, and from 1 to 120 days before the MRI. Each diagnosis was broadly grouped according to the *ICD-9* coding system.

Child mortality was retrieved from the Registered Persons Database, which contains demographic information for all individuals eligible for OHIP.[14]

Statistical Analysis

Women who underwent an MRI during pregnancy were anticipated to systematically differ from those who did not, leading to potential confounding by indication and biased estimates. Therefore, separate propensity scores were derived for the probability of exposure to an MRI in the first trimester and a gadolinium-enhanced MRI at any time during pregnancy. Separate propensity scores were created in logistic regression models containing known maternal baseline characteristics, including maternal age (modeled continuously as a linear trend); parity; year of delivery; urban residence; neighborhood income quintile; conditions diagnosed within 90 days before the estimated conception date to the delivery date (chronic hypertension, diabetes mellitus, obesity, tobacco or substance abuse, cancer, kidney disease, stroke, systemic lupus erythematosus, rheumatoid arthritis, Crohn disease, ulcerative colitis, seizure disorder); undergoing prenatal ultrasonography before 24 weeks' gestation; and the number of prenatal visits, modeled as a continuous variable using a $\log_{10}$ transformation. Variables deemed prognostically important or likely confounders were selected a priori for the propensity score models (eTable 1 in the Supplement). Inverse probability weighting based on the propensity score was used to adjust for exposure group differences within regression models.[18] Standardized differences in the means and proportions of covariates between groups were separately calculated for the weighted and unweighted samples, with a standardized difference of less than 0.10 indicative of a balanced covariate.

For both cohorts, the relative risk (RR) of stillbirth or neonatal death before 28 days was estimated using modified Poisson regression with a robust error variance. Generalized estimating equations with an exchangeable correlation structure were used to account for the possibility of more than 1 delivery per woman. The adjusted risk difference between exposure groups per 1000 pregnancies was calculated directly within the model.

Risks of all other outcomes were evaluated from the live birth date to a maximum age of 4 years, using marginal Cox proportional hazard models, and were expressed as hazard ratios (HRs). Censoring occurred if the child died, had an outcome, or was alive and outcome-free at the end of 4 years. The rate of emigration out of Ontario is less than 1%[19]; these persons were classified as being event-free up to March 31, 2015. Risk estimates were adjusted using inverse probability weighting based on the propensity score, and gestational age at delivery was included as a covariate. Robust sandwich variance estimates were used to account for correlation among pregnancies within the same woman. Testing of the proportional hazards assumption was done by a Wald test for interaction between exposure status and a function of survival time. The adjusted risk difference between exposure groups per 1000 person-years of follow-up was calculated as the adjusted HR minus 1, multiplied by the crude incidence rate for pregnancies not exposed to MRI.

Two additional analyses were performed related to first-trimester MRI (cohort 1). The first was limited to MRI of the abdomen, pelvis, or spine, which are in closer proximity to the embryo. The second was restricted to exposure at gestational weeks 5 to 10, the main period of organogenesis. An additional analysis related to gadolinium-enhanced MRI (cohort 2) was performed, stratified by period of exposure: the first trimester (to consider the risk of congenital anomalies), and second and third trimester (to evaluate the risk of the NSF-like outcome, once amniotic fluid production occurs).

All *P* values were 2-sided, at a significance level of .05. All statistical analyses were performed using SAS version 9.4 for UNIX (SAS Institute Inc). No adjustment was made for multiple comparisons.

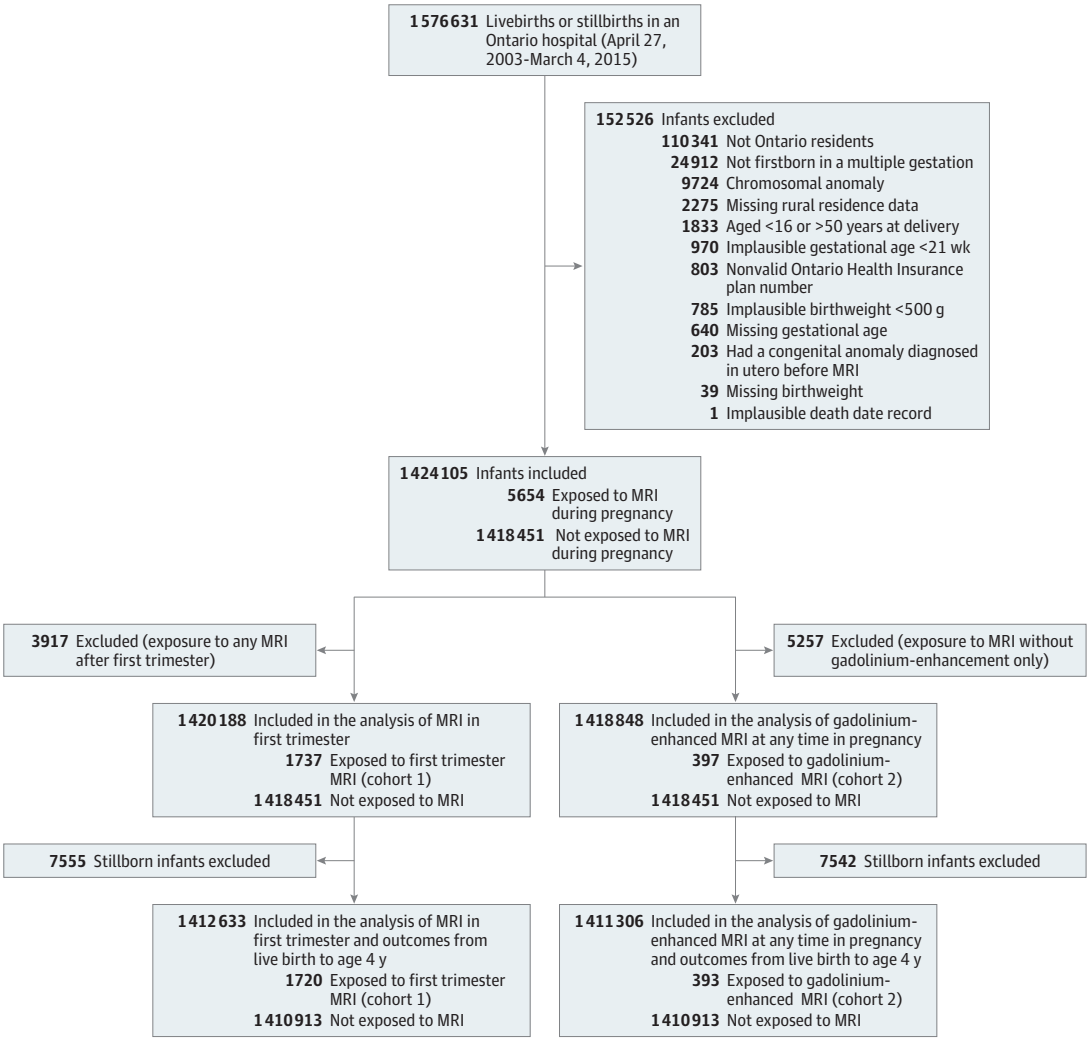
The minimum required sample size was 550 000 pregnancies, assuming a first-trimester MRI exposure rate of 1 in 1000 pregnancies, a 3% rate of congenital anomalies in the population, and an expected HR of 2.0 comparing MRI-exposed and MRI-unexposed pregnancies, at a statistical power of 80%.

Results

Of 1 576 631 maternal-child pairs that were initially eligible, 152 526 (9.7%) were excluded (**Figure 1**). Among those excluded, the rate of stillbirth was higher for mothers exposed to first-trimester MRI (2.8%) or gadolinium-enhanced MRI (1.7%) than those not exposed (1.1%).

Of 1 424 105 delivered pregnancies included, 48% of offspring were girls, with a mean gestation of 39 weeks. There were 5654 pregnancies with an MRI (3.97 per 1000 pregnancies)—1737 in the first trimester (cohort 1), 397 with a gadolinium-enhanced MRI in any trimester (cohort 2)—and 1 418 451 pregnancies without MRI exposure. Before applying

Figure 1. Flowchart of Formation of Cohorts Exposed to Magnetic Resonance Imaging Alone in the First Trimester, With Gadolinium Enhancement in Any Trimester, or Unexposed



inverse probability weighting, MRI-exposed women had more cancer, stroke, seizure disorder, prenatal visits, and deliveries after 2008 compared with those with no MRI exposure in pregnancy, with generally more pronounced differences for gadolinium-enhanced MRI exposure (eTable 2 in the Supplement). The *C* statistic for the propensity score model was 0.60 for cohort 1 and 0.59 for cohort 2. After inverse probability weighting, baseline covariates were well balanced with standardized differences of less than 10% (**Table 1**). The rate of preterm birth earlier than 37 weeks was 9% among women who had first-trimester MRI and 14% for those with a gadolinium MRI compared with 7% in the non-MRI cohort.

The specialties of the physician requesting a first-trimester MRI were family medicine (44%), brain sciences (14%), and other specialties (27%), including general surgery (5%), orthopedic surgery (6.5%), and internal medicine (5%) (Table 1). For gadolinium-enhanced MRI, the requesting specialties were mostly family medicine or other specialties.

MRI Exposure

The rate of exposure to first-trimester MRI was 1.2 per 1000 pregnancies, and 0.3 per 1000 for gadolinium-enhanced MRI, performed at a mean of 5.8 and 10.1 weeks, respectively. The largest proportion of first-trimester MRIs occurred at completed gestational weeks 2 to 5 (**Figure 2**). Of women who had a gadolinium MRI, 13% had at least one other nongadolinium MRI during pregnancy. A large percentage of all MRIs were of the head and spine (Table 1). The diagnostic categories nearest the time at which each first-trimester MRI was performed are shown in eTable 3 in the Supplement.

Outcomes: First-Trimester MRI

There were 19 stillbirths or neonatal deaths (10.9 per 1000) following first-trimester MRI (cohort 1), compared with 9844 events (6.9 per 1000) in the unexposed cohort, with a crude RR of 1.57 (95% CI, 1.00-2.47). After adjustment using inverse probability weighting, the adjusted RR was 1.68 (95% CI, 0.97

Table 1. Characteristics of Mothers and Offspring Exposed to Magnetic Resonance Imaging in the First Trimester, With Gadolinium in Any Trimester, or Not Exposed During Pregnancy[a]

Characteristic	MRI Exposure, No. (%)			MRI Exposure, No. (%)		
	Cohort 1: Any During the First Trimester (n = 1737)[b]	None During Pregnancy (n = 1 418 451)	Standardized Difference[c]	Cohort 2: Gadolinium-Enhanced Anytime During Pregnancy (n = 397)[b]	None During Pregnancy (n = 1 418 451)	Standardized Difference[d]
Pregnant women						
Age at delivery, mean (SD), y	30.4 (5.6)	30.1 (5.5)	0.05	30.6 (5.7)	30.1 (5.5)	0.09
Parity, median (IQR)	1 (0 to 1)	1 (0-1)	0.03	1 (0-1)	1 (0-1)	0.03
Income quintile						
Lowest	364 (21)	314 583 (22)	−0.04	87 (22)	314 579 (22)	0.00
Highest	305 (17)	232 086 (16)	0.03	73 (18)	232 091 (16)	0.06
Era of delivery, 2009-2014	904 (51)	717 774 (51)	0.02	218 (56)	717 545 (51)	0.10
Urban residence	1573 (89)	1 270 144 (90)	0.00	357 (91)	1 270 185 (90)	0.05
Conditions within 90 d before the conception date, up to the delivery date						
Chronic hypertension	55 (3)	47 034 (3)	−0.01	12 (3)	47 012 (3)	−0.01
Diabetes mellitus	119 (7)	100 181 (7)	−0.01	24 (6)	100 145 (7)	−0.04
Diagnosed obesity	34 (2)	26 363 (2)	0.00	10 (3)	26 335 (2)	0.05
Tobacco or substance use	72 (4)	61 593 (4)	−0.01	14 (3)	61 565 (4)	−0.04
Any cancer	13 (1)	9479 (1)	0.01	≤5 (<1)	9457 (<1)	0.01
Kidney disease	≤5 (<1)	2366 (<1)	−0.01	≤5 (<1)	2360 (<1)	−0.03
Stroke	≤5 (<1)	82 (<1)	0.00	≤5 (<1)	62 (<1)	0.00
Systemic lupus erythematosus	32 (2)	18 912 (1)	0.04	≤5 (<1)	18 881 (1)	−0.01
Rheumatoid arthritis	7 (<1)	3294 (<1)	0.01	≤5 (<1)	3283 (<1)	0.01
Crohn disease or ulcerative colitis	19 (1)	14 808 (1)	0.00	≤5 (<1)	14 788 (1)	0.01
Seizure disorder	8 (<1)	5266 (<1)	0.01	≤5 (<1)	5211 (<1)	0.01
Preeclampsia in current pregnancy	41 (2)	16 229 (1)	0.09	6 (2)	16 220 (1)	0.04
Ultrasound at <24 weeks' gestation	1617 (92)	1 299 075 (92)	0.01	363 (92)	1 299 042 (92)	0.03
No. of prenatal visits, mean (SD)	14.4 (7.2)	14.7 (6.0)	−0.03	14.7 (6.7)	14.6 (6.0)	0.00
Liveborn infants						
Female sex	817 (47)	687 866 (49)	−0.04	197 (51)	687 873 (49)	0.05
Gestational age at delivery, mean (SD), wk	38.7 (2.0)	38.9 (1.8)	−0.09	38.4 (2.2)	38.9 (1.8)	−0.22
Preterm birth <37 weeks' gestation	161 (9)	97 635 (7)	0.09	54 (14)	97 626 (7)	0.23
Birthweight, mean (SD), g	3349 (625)	3380 (562)	−0.05	3244 (627)	3380 (562)	−0.23
Follow-up, median (IQR), y	3.6 (1.5 to 4.0)	4.0 (2.5-4.0)		2.4 (0.9-4.0)	3.6 (1.4-4.0)	
Person-years included in the analysis	4815	4 480 330		901	3 812 128	
Stillborn infants						
Gestational age at delivery, mean (SD), wk	24.6 (4.8)	30.8 (6.8)	−1.07	23.1 (1.1)	30.8 (6.8)	−1.59
MRIs in the current pregnancy						
Specialty of physician requesting MRI						
Family medicine	768 (44)			131 (33)		
Neurology or neurosurgery	246 (14)			56 (4)		
Obstetrics and gynecology	105 (6)			62 (1)		
Emergency medicine	20 (1)			0 (0)		
Other specialty	468 (27)			130 (57)		
Unknown	130 (7)			18 (5)		
Estimated gestational age at first exposure, mean (SD), wk	5.8 (3.9)			10.1 (10.7)		
Estimated gestational age at first exposure, wk						
2 to 14	1737 (100)			293 (74)		
≥15	0 (0)			104 (26)		
No. of MRI tests, mean (SD)[e]	1.0 (0.2)			1.2 (0.5)		

(continued)

Table 1. Characteristics of Mothers and Offspring Exposed to Magnetic Resonance Imaging in the First Trimester, With Gadolinium in Any Trimester, or Not Exposed During Pregnancy[a] (continued)

Characteristic	MRI Exposure, No. (%)			MRI Exposure, No. (%)		
	Cohort 1: Any During the First Trimester (n = 1737)[b]	None During Pregnancy (n = 1 418 451)	Standardized Difference[c]	Cohort 2: Gadolinium-Enhanced Anytime During Pregnancy (n = 397)[b]	None During Pregnancy (n = 1 418 451)	Standardized Difference[d]
No. of MRI tests[e]						
1	1673 (96)			346 (87)		
≥2	64 (4)			51 (13)		
MRI						
With gadolinium	287 (17)			397 (100)		
Without gadolinium	1450 (83)			52 (13)		
Anatomical location of the MRI[e]						
Head	726 (42)			199 (50)		
Neck	27 (2)			14 (4)		
Thorax or breast	51 (3)			41 (10)		
Abdomen	183 (11)			70 (18)		
Pelvis	187 (11)			74 (19)		
Extremities	331 (19)			29 (7)		
Spine	939 (54)			220 (55)		

Abbreviations: IQR, interquartile range; MRI, magnetic resonance imaging.

[a] Data are weighted using inverse probability weighting. eTable 2 shows the unweighted characteristics. Data are suppressed for counts of 5 or less.

[b] An additional 3520 pregnancies with an MRI in the second or third trimester are not in cohort 1 or cohort 2.

[c] Standardized differences comparing means and proportions of baseline characteristics between pregnancies in cohort 1 and those not exposed to MRI, after applying stabilized inverse probability weighting.

[d] Standardized differences comparing means and proportions of baseline characteristics between pregnancies in cohort 2 and those not exposed to MRI, after applying stabilized inverse probability weighting.

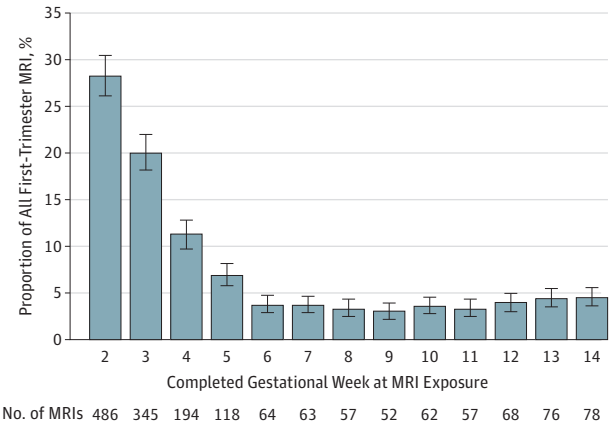
[e] A woman may have had an MRI at more than one anatomical location within the same pregnancy.

to 2.90) and the adjusted risk difference was 4.7 per 1000 person-years (95% CI, −1.6 to 11.0). Live-born children were followed up for a median of 3.6 years (interquartile range [IQR], 1.5-4.0 years) in the first-trimester MRI cohort (n = 1720 children) and 4.0 years (IQR, 2.5-4.0 years) in their unexposed counterparts (n = 1 410 913 children); 863 320 of 1 412 633 (61%) of all these children were followed up to age 4 years.

The incidence rate of a congenital anomaly was not significantly higher in the offspring of women with a first-trimester MRI (33.8 per 1000 person-years [165 events]) than among unexposed women (24.0 per 1000 person-years [109 053 events]), with an adjusted HR of 1.16 (95% CI, 0.96 to 1.40) and an adjusted risk difference of 3.8 per 1000 person-years (95% CI, −1.0 to 9.6) (**Table 2**). Among women who had a first-trimester MRI, the incidence rate of anomalies did not significantly differ by timing of MRI exposure (**Figure 3**). Anomalies of the circulatory, digestive, and musculoskeletal system were most common (eTable 4 in the Supplement). The risk of a neoplasm up to age 4 years did not significantly differ between groups nor did the risk of hearing or vision loss (Table 2). The proportional hazard assumption was not met for the analyses of vision loss or any neoplasm.

In the additional analysis restricted to first-trimester MRI of the abdomen, pelvis, or spine, the main findings did not change (eTable 5 in the Supplement). Upon restricting to MRI exposure between 5 and 10 weeks' gestation, the risk of congenital anomalies and hearing loss was unchanged; however, the risk of vision loss was higher, with an adjusted HR of 2.28 (95% CI, 1.09-4.77) or adjusted risk difference of 2.7 per 1000 person-years (95% CI, 0.2-7.9) (eTable 6 in the Supplement).

Figure 2. Proportion of All First-Trimester Magnetic Resonance Imaging by Completed Gestational Week at Exposure



There were 1720 women who underwent magnetic resonance imaging during their first trimester of pregnancy. Error bars indicate 95% confidence intervals.

Outcomes: Gadolinium-Enhanced MRI

There were 7 stillbirths or neonatal deaths (17.6 per 1000) following gadolinium-enhanced MRI exposure (cohort 2) vs 9844 events (6.9 per 1000) in nonexposed women, an adjusted RR

Table 2. Risk of Adverse Outcomes at Birth and Up to a Maximum Age of 4 Years in the Offspring of Women Exposed to Magnetic Resonance Imaging in the First Trimester of Pregnancy vs Women Not Exposed

Outcome[a]	Magnetic Resonance Imaging Exposure				Hazard Ratio (95% CI)		Inverse Probability Weight-Adjusted Risk Difference (95% CI)[b]
	Cohort 1: Any During the First Trimester (n = 1737)		None During Pregnancy (n = 1 418 451)				
	No. (%)	Incidence (95% CI) per 1000 Person-Years	No. (%)	Incidence (95% CI) per 1000 Person-Years	Crude	Inverse Probability Weight-Adjusted[b]	
Stillbirth or neonatal death[c]	19 (1)	10.9 (6.6 to 17.0)	9844 (1)	6.9 (6.8 to 7.1)	1.57 (1.00 to 2.47)	1.68 (0.97 to 2.90)	4.7 (−1.6 to 11.0)
Congenital anomaly	165 (10)	33.8 (29.0 to 39.4)	109 053 (8)	24.0 (23.9 to 24.2)	1.29 (1.11 to 1.50)	1.16 (0.96 to 1.40)	3.8 (−1.0 to 9.6)
Vision loss[d]	21 (1)	4.0 (2.6 to 6.1)	10 124 (1)	2.1 (2.1 to 2.1)	1.98 (1.29 to 3.04)	1.50 (0.94 to 2.40)	1.1 (−0.1 to 2.9)
Hearing loss	50 (3)	9.6 (7.2 to 12.6)	38 978 (3)	8.1 (8.0 to 8.2)	1.24 (0.94 to 1.63)	1.04 (0.75 to 1.45)	0.3 (−0.5 to 3.7)
Any neoplasm[e]	≤5 (<1)	0.2 (0.0 to 1.3)	4831 (<1)	1.0 (1.0 to 1.0)	0.19 (0.03 to 1.31)	0.53 (0.08 to 3.67)	−0.5 (−1.0 to 0.3)

[a] For all outcomes, we excluded pregnancies exposed to MRI after 14 weeks' gestation, or pregnancies with first-trimester exposure to MRI, in which a congenital anomaly was diagnosed prior to the MRI. For the outcomes of congenital anomaly, vision loss, hearing loss, and any neoplasm, we further excluded 7555 pregnancies that resulted in a stillbirth.

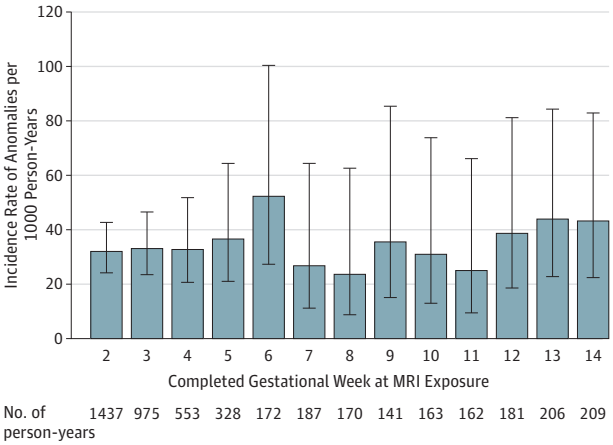
[b] Stabilized inverse probability weights were used to adjust for differences between exposure groups.

[c] For stillbirth or neonatal death the incidence rate is actually per 1000 pregnancies, the hazard ratio is a relative risk, and the adjusted risk difference is per 1000 pregnancies.

[d] Of all children with vision loss, 78.4% were diagnosed by an ophthalmologist.

[e] Data are suppressed for counts of 5 or less.

Figure 3. Incidence Rate of a Congenital Anomaly in Relation to Magnetic Resonance Imaging Exposure Within Each Completed Gestational Week



Data are presented for magnetic resonance imaging (MRI) completed within the first trimester of pregnancy. A total of 4884 completed person-years were included in this analysis. Error bars indicate 95% confidence intervals.

of 3.70 (95% CI, 1.55-8.85) and an adjusted risk difference of 47.5 per 1000 (95% CI, 9.7-138.2) (**Table 3**). Live-born children were followed up for a median of 2.4 years (IQR, 0.9-4.0 years) in the gadolinium-enhanced MRI cohort (n = 393 children) and 3.6 years (IQR, 1.4-4.0 years) in the unexposed cohort (n = 1 410 913 children); 643 128 of 1 411 306 (46%) of all these children were followed up to age 4 years.

For the rare NSF-like outcome, the incidence rate was higher in the gadolinium MRI group (3.3 per 1000 person-years [≤5 events]) than in the non-MRI group (1.8 per 1000 person-years [8705 events]), but the CIs for the adjusted HR (1.00, 95% CI, 0.33 to 3.02) and the adjusted risk difference (0.0, 95% CI, −2.2 to 6.7) were wide (Table 3). The broad outcome of any rheumatological, inflammatory, or infiltrative skin condition was higher following gadolinium MRI (125.8 per 1000 person-years [123 events]) than no MRI (93.7 per 1000 person-years [384 180 events]), with an adjusted HR of 1.36 (95% CI, 1.09 to 1.69) and an adjusted risk difference of 45.3 (95% CI, 11.3 to 86.8). The risk of a congenital anomaly following gadolinium-enhanced MRI did not significantly differ from unexposed women (Table 3).

In the additional analyses of gadolinium MRI, only first-trimester exposure was associated with a higher risk of any rheumatological, inflammatory, or infiltrative skin condition (adjusted HR, 1.41; 95% CI, 1.11-1.79) (eTable 7 in the Supplement).

Discussion

Within a large population of pregnant women who received universal health care and whose pregnancies lasted a minimum of 21 gestational weeks, 1 in 250 had an MRI in pregnancy, including 1 in 1200 in the first trimester and 1 in 3000 with gadolinium contrast. Maternal MRI in the first trimester was not associated with a higher risk of stillbirth or neonatal

death, congenital anomalies, neoplasm, or hearing loss. The risk of vision loss was only seen in a subgroup analysis of MRI exposure at 5 to 10 weeks' gestation. Exposure to gadolinium-enhanced MRI at any gestation was not associated with a greater risk of congenital anomalies. Although the NSF-like outcome was extremely rare, gadolinium-enhanced MRI was associated with an adjusted HR of 1.36 for any rheumatological, inflammatory or infiltrative skin condition up to age 4 years, and an adjusted RR of 3.70 for stillbirth or neonatal death, albeit with just 7 events in the gadolinium MRI group.

Study Strengths and Limitations

The strengths of the study include the large size and population-based sample. The method for ascertaining MRI exposure and timing in pregnancy was robust. All MRI testing in Ontario is billed under a universal system. Among women with a first-trimester MRI, the rate of prenatal sonography was 95%, enabling accurate pregnancy dating in most cases. The additional analysis restricted to exposure between 5 and 10 weeks' gestation increased the likelihood that a woman was pregnant at the time of the MRI and within the period of embryonic organogenesis.

The study also has limitations. Among those exposed to first-trimester MRI, analyses were underpowered to assess uncommon outcomes. Combining congenital anomalies as a single outcome has limitations, in that malformations are highly heterogeneous with diverse causes. Although birth defects were grouped largely by anatomical region, specific anomalies might not be detected. The proportional hazard assumption was not met for the outcomes of vision loss or any neoplasm; however, the small number of outcome events among exposed women precluded stratification of the analyses for these 2 outcomes. Among the fetuses exposed to gadolinium at any time in pregnancy, the detection of NSF was challenging because of its rarity and the possibility that it could be missed in a very young child. For the broader outcome of any rheumatological, inflammatory, or infiltrative skin condition, power was about 93% to detect an RR of 1.5 or higher following gadolinium exposure. Several models with different outcomes were created, heightening the probability of a type 1 statistical error due to multiple comparisons. Because the latter was not accounted for and some analyses were underpowered, the current findings should be considered exploratory.

Information was not available about whether a woman's pregnancy was known at the time of MRI exposure. Because all pregnancies ending before 21 weeks' gestation were excluded, the risk of MRI and spontaneous or induced abortion prior to 21 weeks is unknown. Accordingly, the risk posed by the first-trimester MRI may have been underestimated. Although an MRI to assess fetal anomalies is unlikely to be completed in the first trimester of pregnancy,[20] those cases for which an anomaly was diagnosed before the index MRI were excluded. Data were not available on the indications for MRI. Women who underwent MRI differed in some ways from those who did not. To minimize bias due to confounding by indication, a propensity score for having an MRI was generated and improved the balance of important conditions, such as maternal diabetes,[21] obesity,[22] and tobacco or substance use.[23]

Table 3. Risk of Adverse Outcomes From Birth to a Maximum Age of 4 Years in the Offspring of Women Exposed to Gadolinium-Enhanced Magnetic Resonance Imaging During Pregnancy vs Women Not Exposed to Any Magnetic Resonance Imaging During Pregnancy[a]

Outcome	Magnetic Resonance Imaging Exposure				Hazard Ratio (95% CI)		Inverse Probability Weight-Adjusted Risk Difference (95% CI)[c]
	Cohort 2: Gadolinium-Enhanced at Any Time During Pregnancy (n = 397)		None During Pregnancy (n = 1 418 451)				
	No. (%)	Incidence per 1000 Person-Years (95% CI)	No. (%)	Incidence per 1000 Person-Years (95% CI)	Crude	Inverse Probability Weight-Adjusted[c]	
Stillbirth or neonatal death[b]	7 (2)	17.6 (7.1 to 36.0)	9844 (1)	6.9 (6.8 to 7.1)	2.60 (1.26 to 5.37)	3.70 (1.55 to 8.85)	47.5 (9.7 to 138.2)
Connective tissue or skin disease resembling nephrogenic systemic fibrosis	≤5 (<1)[d]	3.3 (1.3 to 8.9)	8705 (1)	1.8 (1.8 to 1.8)	1.76 (0.66 to 4.68)	1.00 (0.33 to 3.02)	0.0 (−2.2 to 6.7)
Broad rheumatological or inflammatory or infiltrative skin condition	123 (31)	125.8 (105.3 to 149.9)	384 180 (27)	93.7 (93.4 to 94.0)	1.33 (1.11 to 1.58)	1.36 (1.09 to 1.69)	45.3 (11.3 to 86.8)
Congenital anomaly	39 (10)	34.8 (25.4 to 47.6)	109 053 (8)	24.0 (23.9 to 24.2)	1.33 (0.98 to 1.82)	1.25 (0.84 to 1.86)	8.7 (−5.6 to 29.9)

Abbreviation: MRI, magnetic resonance imaging.

[a] For all outcomes, we excluded pregnancies with first-trimester exposure to MRI, in which a congenital anomaly was diagnosed prior to the MRI. For the outcomes of connective tissue or skin disease resembling nephrogenic systemic fibrosis, broad rheumatological or inflammatory or infiltrative skin condition, and congenital anomaly, we further excluded 7542 pregnancies resulting in a stillbirth.

[b] For stillbirth or neonatal death the incidence rate is per 1000 pregnancies, the hazard ratio is a relative risk, and the adjusted risk difference is per 1000 pregnancies.

[c] Stabilized inverse probability weights were used to adjust for differences between exposure groups.

[d] Data are suppressed for counts of 5 or less.

Although the current study lacked data on exposure to specific teratogens in pregnancy, such as prescription medications or alcohol, the propensity score–weighted models included maternal conditions for which potentially teratogenic medications are commonly indicated, such as rheumatoid arthritis or a seizure disorder.

Follow-up to age 4 years was 61% in cohort 1 and 46% in cohort 2. A large proportion of children not followed up to age 4 years reached a study outcome, rather than being lost to follow-up or the study period ending before reaching age 4 years. A longer duration of follow-up may have revealed a different pattern of outcome events. Information was not available on the type of gadolinium agent that was administered or the mother's estimated creatinine clearance, both of which can influence the risk of NSF in adults.[24]

Other Studies

To the best of our knowledge, there are no prior controlled studies of first-trimester MRI in human pregnancy. One retrospective study compared 751 neonates exposed to MRI in utero (35% for a fetal indication) with 10 042 unexposed newborns.[25] Following universal newborn hearing screening, the respective rates of hearing impairment or deafness at birth were 0% and 0.34%; other outcomes were not assessed. The median gestational age at MRI was 37 weeks, with the earliest at 16 weeks.[25] An uncontrolled case series described 15 pregnancies exposed to 1.5-T (Tesla) MRI in the first trimester, at a mean gestational age of 3.8 weeks.[26] Of the 15 live born infants, there were 2 congenital malformations (13%), probable unilateral renal agenesis and an overlapping toe. One single-center study reported on 24 Italian women who received intravenous gadopentetate dimeglumine in the first trimester of pregnancy, with one congenital anomaly.[13] Animal studies have shown that gadolinium crosses the placenta.[12,27]

Mechanisms

Concerns about potential fetal effects after MRI stem from heating of the tissues by radiofrequency fields. Elevation of temperature in embryonic or fetal tissues can occur under conventional MRI following continuous exposures over 7.5 minutes' duration.[28] The current study could not determine the magnetic field or radiofrequency field of the MRI scanner. In the era in which it was done, however, almost all sites used a 1.5-T scanner,[29] which tends to have decreased whole-body specific absorption rates compared with 3.0-T scanners. More than half of the MRIs in the study were of the abdomen, pelvis, or spine, which would introduce more radiofrequency energy to the fetus than MRIs of other regions. In anatomically simulated dosimetry studies of MRI, whole-body specific absorption rates in the fetus exceed limits by 7.5 times.[30] However, most dosimetry models assume fetal and placenta size and amniotic fluid volume equivalent to a 26 to 32 weeks' gestation pregnancy, rather than a first-trimester embryo. Yet, there is little evidence from animal models that MRI is teratogenic, and any possible deleterious effect seen with eye development in the mouse[31] have yet to be demonstrated in other animals.

Clinical Implications

The current findings inform published recommendations about the safety of MRI in the first trimester of pregnancy.[4,5,8,9] Pregnancy is not a contraindication to MRI, which provides highly detailed images without the use of ionizing radiation.[32] We did not evaluate the safety of MRI after the first trimester, as some nongadolinium MRIs are performed in the second or third trimester for a fetal indication, such as a fetal anomaly[33] or tumor,[34] heightening the chances of confounding by indication. Others suggest that MRI exposure in the second and third trimester appears to be safe in terms of normal vision and hearing in childhood.[25,35] Following inadvertent or prior to intentional MRI exposure in the first trimester, a discussion about a potentially slightly higher risk of vision loss in the child should be balanced by an acknowledgment that it is not known to be associated with a higher risk of other adverse outcomes. Since tissue energy deposition generally increases with field strength and, for most indications, standard 1.5-T MRI scanners generates quality diagnostic images,[31] it seems prudent to avoid more than 1.5-T MRI for pregnant women. Until further studies are done, these findings suggest that gadolinium contrast should be avoided during pregnancy.

Conclusions

Exposure to MRI during the first trimester of pregnancy, compared with nonexposure, was not associated with increased risk of harm to the fetus or in early childhood. Gadolinium MRI at any time during pregnancy was associated with an increased risk of a broad set of rheumatological, inflammatory, or infiltrative skin conditions and risk of stillbirth or neonatal death. The study may not have been able to detect rare adverse outcomes.

ARTICLE INFORMATION

Author Contributions: Ms Park had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study Concept and design: Ray, Vermeulen, Park.
Acquisition, analysis, or interpretation of data: All Authors.
Drafting of the manuscript: Ray, Park.
Critical revision of the manuscript for important intellectual content: All Authors.
Statistical analysis: Ray, Park.
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Study supervision: Ray.

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