OBSTETRICS

Risk of fetal or neonatal death or neonatal intensive care unit admission associated with gadolinium magnetic resonance imaging exposure during pregnancy

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BACKGROUND: Concerns have been raised about prenatal exposure to magnetic resonance imaging with gadolinium-based contrast agents because of nonclinical findings of gadolinium retention in fetal tissue and 1 population-based study reporting an association with adverse pregnancy outcomes.

OBJECTIVE: This study aimed to evaluate the association between prenatal magnetic resonance imaging exposure with and without gadolinium-based contrast agents and fetal and neonatal death and neonatal intensive care unit admission.

STUDY DESIGN: We constructed a retrospective cohort of >11 million Medicaid-covered pregnancies between 1999 and 2014 to evaluate the association between prenatal magnetic resonance imaging exposure with and without gadolinium-based contrast agents and fetal and neonatal death (primary endpoint) and neonatal intensive care unit admissions (secondary endpoint). Medicaid claims data were linked to medical records, Florida birth and fetal death records, and the National Death Index to validate the outcomes and gestational age estimates. Pregnancies with multiples, concurrent cancer, teratogenic drug exposure, magnetic resonance imaging focused on fetal or pelvic evaluation, undetermined gadolinium-based contrast agent use, or those preceded by or contemporaneous with congenital anomaly diagnoses were excluded. We adjusted for potential confounders with standardized mortality ratio weighting using propensity scores.

RESULTS: Among 5991 qualifying pregnancies, we found 11 fetal or neonatal deaths in the gadolinium-based contrast agent magnetic resonance imaging group (1.4%) and 73 in the non—gadolinium-based contrast agent magnetic resonance imaging group (1.4%) with an adjusted relative risk of 0.73 (95% confidence interval, 0.34—1.55); the neonatal intensive care unit admission adjusted relative risk was 1.03 (0.76—1.39). Sensitivity analyses investigating the timing of magnetic resonance imaging or repeat magnetic resonance imaging exposure during pregnancy and simulating the impact of exposure misclassification corroborated these results.

CONCLUSION: This study addressed the safety concerns related to prenatal exposure to gadolinium-based contrast agents used in magnetic resonance imaging and the risk thereof on fetal and neonatal death or the need for neonatal intensive care unit admission. Although the results on fatal or severe acute effects are reassuring, the impact on subacute outcomes was not evaluated.

Key words: drug safety, fetal death, gadolinium, magnetic resonance imaging, neonatal death, neonatal intensive care, teratogenicity

Introduction

Gadolinium-based contrast agents (GBCAs) are administered to enhance images for magnetic resonance imaging (MRI).[1] GBCAs carry a boxed warning about the risk for nephrogenic systemic fibrosis among patients with impaired renal function.[2] Concerns about adverse effects associated with gadolinium retention in the brain, skin, and organs, even among patients with normal renal function, have prompted cautionary statements by regulatory agencies and professional societies, although evidence that confirms and quantifies this risk is incomplete.[3–8]

Gadolinium can cross the placenta and accumulates in the fetal kidney and liver of primates, raising concerns about potential adverse effects of GBCAs on fetal development.[9,10] Accordingly, current guidelines discourage the use of GBCAs during pregnancy.[11–15] The first population-based study conducted by Ray and colleagues[16] to address this issue suggested that GBCA-enhanced MRI exposure during pregnancy was associated with an increased risk for fetal or neonatal death and broad rheumatological, inflammatory, or infiltrative skin conditions. However, as pointed out by the US Food and Drug Administration in its September 2017 Advisory Committee Meeting addressing GBCA safety, "while a well done study, it had a small number of outcomes, was not powered for a comparison of contrast MRI vs non-contrast MRI, and needs replication."[17] Importantly, given the chosen comparison between GBCA-enhanced MRI and no MRI, there is increased potential for confounding by indication.[18]

Based on a recent analysis in the Sentinel Distributed Database from 2006 to 2017, about 1 in 860 pregnancies ending in live deliveries were exposed to GBCA with most of the exposures being during the first trimester.[19] This study aimed to address the concerns regarding the safety of GBCA-enhanced MRIs during pregnancy and their effects on fetal or neonatal death and neonatal intensive care unit (NICU) admission.

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AJOG at a Glance

Why was this study conducted?

Nonclinical findings of gadolinium-based contrast agent (GBCA) retention in fetal tissue and 1 population-based study reporting an association with fetal or neonatal death when compared with pregnancies without magnetic resonance imaging (MRI) have raised concerns about the use of GBCA during pregnancy.

Key findings

After evaluating almost 6000 pregnancies exposed to MRIs with or without GBCA, we found no elevated risk for fetal or neonatal death (adjusted relative risk, 0.73; 95% confidence interval [CI], 0.34−1.55) or neonatal intensive care unit admission (adjusted relative risk, 1.03; 95% CI, 0.76−1.39).

What does this add to what is known?

This study does not corroborate the emerging safety concerns, suggesting that the results of previous findings could likely be attributed to confounding by indication. Although the results on fatal or severe acute effects are reassuring, the impact on subacute outcomes should be evaluated in future.

Materials and Methods

Data sources and pregnancy identification

We used Medicaid Analytic eXtract (MAX) data (data for 29 states for the period 1999−2010 and nationwide data for the period 2011−2014) to create a pregnancy cohort of live births and stillbirths. Medicaid is the largest insurance provider for pregnant women in the United States and covers more than 40% of pregnancies.[20] Because the Centers for Medicare and Medicaid Services were transitioning to a new information system, the most recent data available at conception of this study was for 2014. MAX files included information on diagnoses and procedures associated with inpatient and outpatient medical encounters, outpatient pharmacy records of dispensed prescriptions, and patient sociodemographic and enrollment information. We considered all beneficiaries enrolled in the fee-for-service plans and comprehensive managed care plans whose respective state's Medicaid files met the quality thresholds for comprehensive capture of all medical encounters.[21,22] Beneficiaries dually enrolled in Medicaid and Medicare or with partial managed care or other private insurance were excluded. To validate claims-based information, we linked the pregnancy cohorts' MAX records with a sample of electronic health records obtained nationwide, with Florida fetal death and birth certificates, and with the National Death Index (NDI) using social security numbers (SSNs) and date of birth.

Human and nonhuman experimentation

This study was approved by the institutional review and privacy boards of the University of Florida, the Florida Department of Health, and the Centers for Medicare and Medicaid Services.

Study design and participants

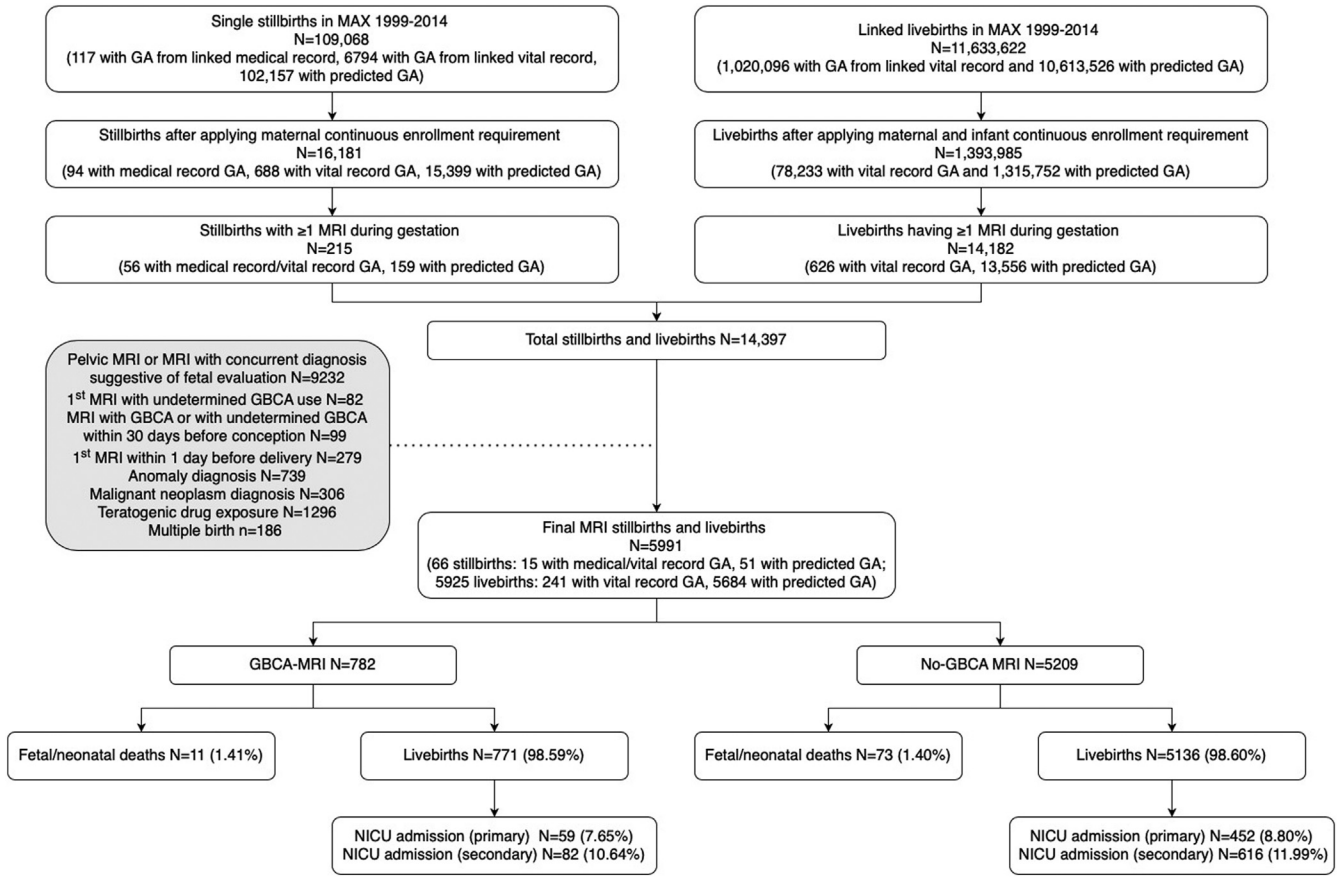
This was a retrospective cohort study including stillborn and live born deliveries. Deliveries were identified using a previously validated algorithm that captures pregnancy endpoints based on diagnoses and procedures during medical in- and outpatient encounters. For women with live deliveries, mothers and infants were linked within MAX using a previously validated algorithm (linkage yield of 77% of deliveries).[23] To be included, women with live births had to be enrolled in Medicaid from 90 days before conception until 30 days after delivery, whereas infants had to be enrolled for at least 30 days after birth unless death occurred before then. Women with stillbirths had to be enrolled from before 90 days before conception or 230 days (20 week's gestation plus 90 days look back) before delivery date until 30 days after delivery. We estimated the date of conception from the clinical estimate of gestational age (GA) recorded in medical records or in vital data or using validated claims-based algorithms that predicted GA at the time of stillbirth or live birth (Figure 1 and Figure A1).[24,25] In the linked Florida sample of MAX and vital records, which was used to validate the claims-based algorithms, we found that GA was accurately predicted to within a 2-week margin for 96% of live deliveries and 67% of stillbirths. In our final cohort, 23% of stillbirths had GA information obtained from medical or vital records, whereas 4% of live births had GA information obtained from vital statistics.

We excluded pregnant women with malignant neoplasms (International Classification of Diseases, ninth Revision, Clinical Modification [ICD-9-CM] codes 140xx−2093xx), multiple gestation (ICD-9-CM codes V27.2-V27.7, V31-V39, 651, 651.0x-651.2x, 651.3x, 651.4x-651.9x, 652.6x, 660.5x, 662.3x, 761.5x), or prenatal exposure to a definite teratogenic medications (Table A1) to remove other causal etiologies of fetal death. Because misoprostol and methotrexate may be used to induce abortion or labor, we excluded pregnant women with misoprostol or methotrexate use only when the timing was between conception and the index MRI. Figure A2 depicts the study design.

Magnetic resonance imaging exposure

Women entered the cohort at the first qualifying MRI procedure any time after conception. Eligible pregnancies had exposure to MRI with or without GBCA, which were identified using relevant procedure codes recorded during in- or outpatient encounters that indicated both the procedure site and contrast agent used (Table A2). To reduce the risk for confounding by indication, we excluded pregnancies with the first MRI done during gestation with an indication for pelvic examination, because a previous study found that approximately one-third of those MRIs were likely to

FIGURE 1
Cohort assembly



GA, gestational age; *GBCA*, gadolinium-based contrast agent; *MAX*, Medicaid Analytic eXtract; *MRI*, magnetic resonance imaging; *NICU*, neonatal intensive care unit.

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evaluate the fetus.[19] In addition, pregnancies with a first MRI of any anatomic site that coincided with a diagnosis suggestive of fetal evaluation were also excluded (Table A3). MRI procedure codes do not specifically indicate fetal evaluations; thus, examination site and diagnoses codes were used instead. We also excluded pregnancies with congenital anomaly diagnoses between conception and up to 1 day after the first MRI procedure (Table A4) and those with first MRIs administered on the day of or day before delivery, which may have aimed to evaluate conditions associated with or precipitating the birth outcome, and those with MRIs that could have occurred postpartum. Pregnancies for which the use of GBCA was undetermined for the index MRI (Table A1) or for which conception was preceded by an MRI with known or undetermined use of GBCA within 30 days of conception were also excluded. If women had >1 MRI during the evaluation window, we used the first MRI to classify exposure status for the main analysis and addressed secondary MRI exposures in a sensitivity analysis.

Study endpoint

Our primary study endpoint was a composite of deliveries at or after 20 weeks' gestation ending in fetal or neonatal death. Fetal deaths were identified using a 2-step process. First, we used a broad set of diagnosis and procedure codes, considering both in- and outpatient encounters, to capture all potential fetal deaths with MRI exposure within 42 weeks before the delivery date. We retained fetal deaths that were validated using independent medical record review by 2 clinical reviewers and for which we could confirm MRI exposure during gestation based on the clinical estimate of gestation in the medical record (Figure 1). We then used the chart review results to refine the broad claims-based algorithm for identification of fetal deaths for which records could not be retrieved. This final algorithm used only inpatient encounters with ICD-9-CM diagnosis codes for single stillbirths (656.4, 656.40, 656.41, 656.43, V27.1) and yielded a positive predictive value (PPV) of 83% (manuscript is under review, data available on request).

Information on neonatal deaths was obtained from the linked NDI records.

Because some infants might have died before an SSN was issued, thus precluding linkage to the NDI, we also considered death information captured in MAX if these infants did not have a valid SSN that could be matched with a death certificate through the NDI. Because the pharmacologic pathways for gadolinium toxicity may vary, we included all deaths except those with chromosomal anomalies or injuries indicated in the NDI record or infant MAX claims.

The secondary endpoint was infant admission to a NICU within 7 days of birth based on the presence of a relevant Current Procedural Terminology (CPT) code (99295, 99296, 99299, 99468, 99469, 99479; PPV ranging from 93% to 97%)[26] in the infant or mother's claims records.

Covariates

Based on previous reported risk factors for fetal or neonatal death,[27–32] we considered the following covariates: maternal demographics, comorbidities ascertained within 3 months before conception to the end of the exposure evaluation window, first MRI characteristics (site, inflammatory or infection diagnosis accompanying the MRI claim), pregnancy characteristics (parity, time between conception and first pregnancy visit, prenatal ultrasound before 24 weeks' gestation, and use of prescribed multivitamins), use of potentially teratogenic drugs or opioids from conception to index date, and healthcare utilization frequency during the baseline period. Gestational hypertension, preeclampsia, and gestational diabetes diagnosed between conception and birth were considered in the main analysis but not in the sensitivity analyses in which MRI exposure during the first trimester or first 20 weeks of gestation was examined.

For the NICU admission endpoint, we added sexually transmitted infections and sex of the infant as covariates. Other risk factors for fetal and neonatal death such as low birthweight, GA, or uterine complications were not considered as covariates because of the unclear biologic pathways involved in the potential development of GBCA-associated adverse effects and we did not want to risk adjusting for direct effects of GBCA that might cause neonatal morbidity. For all covariate specifications refer to Tables A5 to A7.

Analysis

We used a logistic regression model to estimate the propensity score for first exposure to GBCA-enhanced or non-GBCA MRI based on all the previously referenced covariates.[33] Risk factor balance was assessed using standardized differences. After trimming for non-overlap in the propensity score between the GBCA- and non-GBCA MRI groups, pregnant women exposed to GBCA-enhanced MRI received a weight of 1, whereas women exposed to a non-GBCA MRI received a standardized mortality ratio (SMR) weight of the ratio of the estimated propensity score (1 minus the estimated propensity score). We then used the assigned weights and a generalized estimating equation model with a binominal distribution, log link function, and robust standard errors to estimate the adjusted risk ratios for the primary and secondary endpoints.

We conducted several sensitivity analyses. First, we restricted the analyses to scenarios in which the first MRI occurred before 20 weeks' gestation or in the first or the second trimester. Second, to account for multiple MRIs during pregnancy, we allowed pregnancies to switch exposure status if the second, but not the first MRI, was GBCA-enhanced (Figure A3). Third, to address imprecise estimates of GA for stillbirths, we added or subtracted 2, 4, and 8 weeks from the predicted GA, respectively. If this gave a stillbirth GA that was <20 weeks or >45 weeks, we used 20 weeks and 45 weeks as the assigned GA, respectively. Last, for the secondary outcome, we expanded the assessment time from 7 days in the main analysis to 30 days from birth and included a broader CPT code list to define NICU admission (Table A8).

Results

Final cohort

We identified 109,068 singleton stillbirths and more than 11 million singleton live deliveries for which mothers and infants could be linked. After imposing enrollment requirements and exclusion criteria, we identified a total of 782 pregnant women who were exposed to GBCA-enhanced MRIs and 5209 who were exposed to non-GBCA MRIs. The 3 most common reasons for exclusion were MRIs focus on pelvic examinations or with a diagnosis indicative of fetal evaluation, being exposed to a known teratogenic medication during gestation, and diagnoses of fetal anomalies (Figure 1). The first MRI typically occurred within the first 8 weeks of pregnancy (Figure A4). A total of 158 of 782 women (20.2%) in the GBCA-enhanced MRI group had their first prenatal visit before the MRI in contrast with 53.0% of women in the non-GBCA MRI group. Only 59 of 782 pregnancies in the GBCA MRI group had the first MRI during the third trimester, rendering assessments of outcomes associated with third trimester exposure statistically infeasible (Figure A5).

We identified 186 women with a second MRI before delivery with similar proportions among the 2 MRI groups (3.07% and 3.11% in the GBCA MRI and non-GBCA MRI group, respectively). All 24 women with a first GBCA MRI had the second MRI with a GBCA. Among 162 pregnant women with an initial non-GBCA MRI, 17 received a second MRI with a GBCA. There was no evidence of an emergent fetal risk that occurred between the first and second MRI for any of the pregnancies. Thus, these women's exposure status was updated to GBCA exposure in our sensitivity analysis.

Before SMR weighting, in both cohorts evaluating either fetal or neonatal death or NICU admission as the study endpoint, the GBCA-exposed MRI group had a larger proportion of teenagers, Black and Hispanic women, women living in rural areas, and women who qualified for Medicaid because of disability (Table 1 and Table A9). Women who received GBCA MRIs were less likely to have received prenatal care before 9 weeks' gestation, had slightly fewer recommended prenatal screening procedures, and were less likely to use

TABLE 1
Characteristics of pregnant women with GBCA MRI and non-GBCA MRI exposure for evaluation of fetal (stillbirth) or neonatal death

	Before propensity score weighting					After propensity score weighting				
	GBCA MRI		No GBCA MRI		Absolute standardized difference	GBCA MRI		No GBCA MRI		Absolute standardized difference
Variable description	n	%	n	%		n	%	n	%	
Total	782		5209			774		751		
Maternal age at conception (y)										
<20	183	23.4	953	18.3	0.126	182	23.5	180	23.9	0.013
20–24	199	25.5	1625	31.2	0.128	198	25.6	195	26	0.011
25–29	229	29.3	1465	28.1	0.026	227	29.3	217	28.9	0.012
30–34	107	13.7	787	15.1	0.041	106	13.7	99	13.2	0.019
>34	64	8.2	379	7.3	0.034	61	7.9	60	8	0.006
Race										
Non-Hispanic White	486	62.2	3394	65.2	0.063	482	62.3	472	62.9	0.016
Non-Hispanic Black	203	26	1286	24.7	0.029	202	26.1	190	25.3	0.023
Hispanic	77	9.9	383	7.4	0.089	74	9.6	72	9.7	0.004
Other race or unknown race	16	2.1	146	2.8	0.049	16	2.1	16	2.2	0.01
Reason for Medicaid enrollment										
Poverty or cash subsidies	592	75.7	3966	76.1	0.01	588	76	579	77.1	0.036
Disability	76	9.7	296	5.7	0.152	71	9.2	68	9.1	0.004
Other reason	180	23	1209	23.2	0.005	178	23	168	22.3	0.021
Year at conception										
1999–2009	429	54.9	2440	46.8	0.161	422	54.5	417	55.5	0.026
2010–2014	353	45.1	2769	53.2	0.161	352	45.5	334	44.5	0.026
Urban residence at conception										
No	200	25.6	1102	21.2	0.105	196	25.3	185	24.7	0.02
Yes	494	63.2	3559	68.3	0.109	491	63.4	476	63.5	0.001
Missing	88	11.3	548	10.5	0.024	87	11.2	89	11.9	0.027
MRI site										
Head MRI	571	73	2195	42.1	0.658	563	72.7	538	71.7	0.03
Spinal MRI	128	16.4	1512	29	0.306	127	16.4	126	16.8	0.013
Abdominal MRI	50	6.4	480	9.2	0.105	50	6.5	49	6.6	0.006
Lower extremity MRI	36	4.6	845	16.2	0.387	36	4.7	37	4.9	0.015
Upper extremity MRI	24	3.1	260	5	0.098	24	3.1	25	3.3	0.014
Other MRI	32	4.1	83	1.6	0.151	31	4	35	4.7	0.047
Inflammatory diagnosis	76	9.7	459	8.8	0.031	70	9	71	9.5	0.021
Parity	470	60.1	3353	64.4	0.088	468	60.5	453	60.3	0.004
Time between conception and first pregnancy visit										
First visit before 9 wk	335	42.8	2515	48.3	0.109	331	42.8	327	43.6	0.022

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TABLE 1
Characteristics of pregnant women with GBCA MRI and non-GBCA MRI exposure for evaluation of fetal (stillbirth) or neonatal death *(continued)*

	Before propensity score weighting					After propensity score weighting				
	GBCA MRI		No GBCA MRI		Absolute standardized difference	GBCA MRI		No GBCA MRI		Absolute standardized difference
Variable description	n	%	n	%		n	%	n	%	
First visit between 9 wk and end of first trimester	220	28.1	1261	24.2	0.089	218	28.2	212	28.3	0.003
First visit during second trimester	159	20.3	1097	21.1	0.018	159	20.5	148	19.7	0.029
First visit during third trimester	55	7	259	5	0.087	53	6.9	51	6.8	0.004
No visit	13	1.7	77	1.5	0.015	13	1.7	13	1.7	0.003
First trimester ultrasound	273	34.9	2121	40.7	0.12	273	35.3	268	35.7	0.01
Integrated prenatal screening——first stage	57	7.3	440	8.5	0.043	57	7.4	54	7.2	0.01
Nuchal translucency measurement	77	9.9	701	13.5	0.113	77	10	74	9.8	0.007
Integrated prenatal screen——second stage	292	37.3	2132	40.9	0.074	291	37.6	274	36.4	0.031
Anatomic ultrasound	673	86.1	4660	89.5	0.104	667	86.2	648	86.3	0.003
Gestational age at time of first MRI (median, SD in wk)	4	10	13	12	0.657	4	10	5	4	0.044
Hospitalization during baseline	39	5	269	5.2	0.008	39	5	40	5.3	0.016
Number of outpatient visits during baseline										
First quartile (0—3 visits)	214	27.4	1462	28.1	0.016	210	27.1	198	26.3	0.024
Second quartile (4—5 visits)	179	22.9	1206	23.2	0.006	179	23.1	170	22.6	0.017
Third quartile (6—8 visits)	183	23.4	1237	23.8	0.008	182	23.5	185	24.6	0.034
Fourth quartile (>8 visits)	206	26.3	1304	25	0.03	203	26.2	199	26.5	0.007
Number of distinct prescription drugs during baseline										
First quartile (0 drug)	211	27	1438	27.6	0.014	206	26.6	195	26	0.018
Second quartile (1—2 drugs)	187	23.9	1197	23	0.022	187	24.2	183	24.4	0.006
Third quartile (3—5 drugs)	187	23.9	1430	27.5	0.081	187	24.2	184	24.5	0.009
Fourth quartile (>5 drugs)	197	25.2	1144	22	0.076	194	25.1	189	25.2	0.003
Prescribed prenatal multivitamins	150	19.2	1878	36.1	0.384	150	19.4	151	20.1	0.024
Potentially teratogenic medications	34	4.4	312	6	0.074	34	4.4	32	4.3	0.008
Opioid use	155	19.8	1820	34.9	0.344	155	20	159	21.2	0.038
Obesity or overweight	99	12.7	730	14	0.04	99	12.8	95	12.7	0.004
Preexisting hypertension	99	12.7	726	13.9	0.038	99	12.8	95	12.7	0.004
Preexisting diabetes mellitus	58	7.4	399	7.7	0.009	57	7.4	56	7.5	0.004
Multiple sclerosis	29	3.7	41	0.8	0.198	22	2.8	20	2.7	0.011

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TABLE 1
Characteristics of pregnant women with GBCA MRI and non-GBCA MRI exposure for evaluation of fetal (stillbirth) or neonatal death *(continued)*

	Before propensity score weighting					After propensity score weighting				
	GBCA MRI		No GBCA MRI		Absolute standardized difference	GBCA MRI		No GBCA MRI		Absolute standardized difference
Variable description	n	%	n	%		n	%	n	%	
Other autoimmune disease	23	2.9	167	3.2	0.015	23	3	23	3	0.005
Adjustment disorder	30	3.8	244	4.7	0.042	30	3.9	30	3.9	0.004
Anxiety	136	17.4	816	15.7	0.046	135	17.4	134	17.9	0.015
Attention deficit disorder or conduct or disruptive behavior disorders	27	3.5	148	2.8	0.035	27	3.5	28	3.7	0.017
Depressive disorder	162	20.7	990	19	0.043	161	20.8	157	20.9	0.002
Bipolar disorder	61	7.8	366	7	0.03	60	7.8	61	8.2	0.019
Substance related disorders	88	11.3	648	12.4	0.037	88	11.4	88	11.7	0.013
Other psychiatric disorders	165	21.1	1125	21.6	0.012	164	21.2	161	21.4	0.007
Hypothyroidism	49	6.3	219	4.2	0.093	48	6.2	51	6.8	0.034
Asthma	119	15.2	820	15.7	0.014	118	15.3	116	15.4	0.006
Seizure or epilepsy	81	10.4	424	8.1	0.077	81	10.5	78	10.4	0.002
Thromboembolism	16	2.1	130	2.5	0.03	16	2.1	17	2.2	0.014
Tobacco use	157	20.1	1213	23.3	0.078	157	20.3	148	19.7	0.019

GBCA, gadolinium-based contrast agent; *MRI*, magnetic resonance imaging; *SD*, standard deviation.
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prenatal vitamins. Consistent with age distributions, they also had less healthcare encounters before conception and less opioid use during pregnancy, but they were more likely to have multiple sclerosis or epilepsy. As expected, MRI sites were disparate among exposure groups with most GBCA-exposed MRIs focused on the head, whereas non-GBCA–exposed MRIs were broadly distributed across the head, spine, and lower extremities. Presence of inflammatory diagnoses around the time of the first MRI were similar between the exposure groups. After SMR weighting, all covariates were balanced.

Fetal and neonatal death evaluation

There were 11 fetal or neonatal deaths in the GBCA-exposed MRI group (1.4%) and 73 fetal or neonatal deaths in the non-GBCA–exposed MRI group (1.4%) (Figure 2). The most common cause of death was extreme prematurity and no infant died because of an injury or a chromosomal abnormality. The GA at the time of stillbirth was similar between groups with a median of 32 weeks (interquartile range, 25–38) for the GBCA-exposed MRI cases and 30 weeks (26–33) for the non-GBCA–exposed MRI cases. In the primary analysis, the unadjusted relative risk (RR) for fetal or neonatal death when comparing GBCA MRI with non-GBCA MRI exposure was 1.00 (95% confidence interval [95% CI], 0.53–1.88). After applying SMR weighting, we did not observe a significantly increased risk for fetal death (adjusted RR [aRR], 0.73; 95% CI, 0.34–1.55) and recorded an adjusted absolute risk difference of negative 48 cases per 10,000 among GBCA MRI users (95% CI, −158 to 62). In the sensitivity analyses in which we shortened or lengthened the predicted GA at delivery for stillbirths, we observed similar adjusted risk ratios as was seen in our main analysis (Table 2).

Neonatal intensive care unit admission evaluation

Among live births, the percentage of infants with a NICU admission within 7 days of birth was 7.7% and 8.8% in the GBCA MRI and non-GBCA MRI groups, respectively. Consistent with our evaluation of fetal and neonatal deaths, there was no increased risk for NICU admission in our primary analysis (aRR, 1.03; 95% CI, 0.76–1.39) (Figure 3) and an adjusted absolute risk difference of 20 cases per 10,000 (95% CI, −213 to 252). We observed consistent findings across all sensitivity analyses.

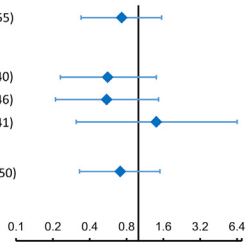
Comment

Principal findings

This study provided reassuring data on the risk for fetal and neonatal death and severe acute effects after prenatal exposure to GBCA MRI procedures when compared with non-GBCA MRI procedures.

FIGURE 2
Adjusted risk of fetal or neonatal death by GBCA-MRI exposed

Scenarios	GBCA-MRI*	No-GBCA MRI*	Adjusted risk ratio (95% CI)
1st MRI during any time of gestation (main analysis)	11/782 (1.4%)	73/5209 (1.4%)	0.73 (0.34, 1.55)
Varying gestational exposure window for first MRI			
1st MRI within first 20 weeks	<11/689 (<1.6%)	57/3535 (1.6%)	0.56 (0.23, 1.40)
1st MRI within 1st trimester	<11/614 (<1.8%)	47/2547 (1.9%)	0.55 (0.21, 1.46)
1st MRI within 2nd trimester	<11/104 (<10.6%)	21/1579 (1.3%)	1.40 (0.31, 6.41)
Updated exposure status based on 2nd MRI*			
1st and 2nd MRI any time of gestation	11/799 (1.4%)	73/5192 (1.4%)	0.71 (0.33, 1.50)



*Counts of deaths <11 are suppressed per CMS privacy rules.
* For pregnancies with first exposure to non-GBCA MRI, exposure status was updated if the second MRI used GBCA
**MRIs likely to focus on fetal evaluation were defined as MRIs indicating pelvic sites, or examination of any site with concurrent diagnosis that may warrant fetal evaluation.

CI, confidence interval; *GBCA*, gadolinium-based contrast agent; *MRI*, magnetic resonance imaging.

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Results in the context of what is known

This study presents an effort to address concerns arising from known sequelae secondary to gadolinium retention,[2] pharmacologic findings documenting the accumulation of gadolinium in fetal tissue,[10,11] and the Ray et al[16] study that suggested an increased risk for fetal or neonatal death when comparing pregnancies exposed to GBCA MRIs with pregnancies with no MRI exposure. Our analyses comparing pregnancies exposed to GBCA MRIs with pregnancies exposed to non-GBCA MRIs found no association with death or neonatal morbidity requiring NICU admission. Although we developed our cohort from more than 11 million pregnancies, study power was constrained by the limited sample size of only 782 pregnancies with GBCA MRI exposure that met all the criteria for inclusion, yielding an upper confidence limit of 1.55 in our main analysis and highlighting the challenge of studying rare outcomes. However, the consistency of our results across all sensitivity analyses and examination of the NICU admission risk, which had slightly more power, corroborates our findings.

Clinical implications

This study provides reassurance about the use of gadolinium during pregnancy when indicated, although our analyses were focused only on evaluating acute severe effects. Thus, the use of gadolinium during pregnancy should be limited and in accordance with professional society guidelines.

Research implications

Considering gadolinium retention in various tissues, the impact of exposure on subacute and chronic adverse outcomes in infants needs further evaluation.

Strengths and limitations

Our study population was composed of pregnancies covered by Medicaid, thus representing a more vulnerable population with a higher disease burden and common constraints in accessing medical care. We found that pregnancies among Black and Hispanic persons and among persons who qualified for Medicaid because of disability were slightly overrepresented among the GBCA MRI group when compared with the population mix among the no-GBCA MRI group. Although our study was underpowered to support subgroup analyses, our null finding is encouraging in this regard because adverse effects might most likely manifest among high-risk pregnancies.

Our study aimed to overcome methodological concerns related to confounding by indication, which was an important limitation of the previous population-based study.[16] In an attempt to reduce confounding, the Ray et al[16] study excluded MRIs that were preceded by a prenatal diagnosis of congenital anomaly within up to 1 day before the MRI procedure, although fetal or pelvic examinations were generally included and no attempt was made to capture a broader range of prenatal concerns that may have triggered the MRI procedure. This study identified 393 live births or stillbirths exposed to GBCA MRIs at any time during pregnancy and 7 fetal or neonatal deaths, giving an adjusted hazard ratio of 3.70 (95% CI, 1.55−8.85).

We used an active comparator design of women who received non-GBCA MRIs during pregnancy, eliminating confounding that may have been introduced by the general need for an MRI procedure. However, considering the observed differences between MRI anatomic sites, indications for MRIs were likely different between those with and those without GBCAs. We excluded pregnancies with congenital anomalies not only preceding MRI exposure but also considering diagnoses up to 1 day after the MRI procedure. We further addressed confounding by indication by excluding pelvic MRIs or any MRI with an accompanying diagnosis indicative of a pregnancy concern. Removal of these pregnancies also reduced alternative causal pathways for fetal and neonatal death, which could have obscured the GBCA effect. We balanced comparison groups for a host of comorbidities and other risk factors for the study outcomes and specifically adjusted for diagnoses suggestive of infections or inflammation that accompanied the index MRI, which might increase the probability of GBCA use and pose independent risks for fetal death or other pregnancy complications.[33] Adjustment for risk factor imbalances via SMR weighting showed limited effect and thus suggests limited presence of appreciable (measured) confounders. The limited impact of confounding on the study findings is further supported by the study period (ending 2014), which precedes the period of emerging concerns about fetal and neonatal death.

TABLE 2
Unadjusted and adjusted risk for fetal or neonatal death among GBCA MRI and non-GBCA MRI groups at any time during gestation after shortening or lengthening the predicted fetal death gestational age

Sensitivity analysis scenarios: changes to predicted fetal death GA	Fetal or neonatal death							
	Before propensity score weighting				After propensity score weighting			
	GBCA MRI	No-GBCA MRI	Excess fetal or neonatal deaths per 10,000 among GBCA MRI users	RR (95% CI)	GBCA MRI	No-GBCA MRI	Excess fetal or neonatal deaths per 10,000 among GBCA MRI users	RR (95% CI)
Shortened by 2 wk	12/783 (1.5%)	69/5205 (1.3%)	21 (−71 to 112)	1.16 (0.63–2.12)	11/775 (1.4%)	10/754 (1.4%)	3 (−94 to 101)	1.02 (0.51–2.04)
Shortened by 4 wk	12/783 (1.5%)	62/5198 (1.2%)	34 (−57 to 125)	1.28 (0.70–2.37)	11/774 (1.4%)	11/750 (1.5%)	−11 (−117 to 96)	0.93 (0.45–1.93)
Shortened by 8 wk	<11/781 (<1.41%)	51/5187 (1.0%)	30 (−54 to 113)	1.30 (0.66–2.55)	<11/772 (<1.4%)	9/749 (1.1%)	3 (−89 to 95)	1.02 (0.46–2.27)
Lengthened by 2 wk	17/788 (2.2%)	78/5214 (1.5%)	66 (−41 to 173)	1.44 (0.86–2.42)	16/782 (2.1%)	14/761 (1.9%)	17 (−110 to 144)	1.09 (0.57–2.08)
Lengthened by 4 wk	17/788 (2.2%)	84/5220 (1.6%)	55 (−52 to 162)	1.34 (0.80–2.25)	16/781 (2.1%)	15/761 (2.0%)	2 (−123 to 127)	1.01 (0.55–1.86)
Lengthened by 8 wk	21/792 (2.7%)	92/5228 (1.8%)	89 (−28 to 207)	1.51 (0.94–2.41)	20/786 (2.5%)	14/764 (1.8%)	74 (−53 to 202)	1.41 (0.81–2.47)

CI, confidence interval; *GBCA-MRI*, gadolinium-based contrast agent magnetic resonance imaging; *RR*, relative risk.
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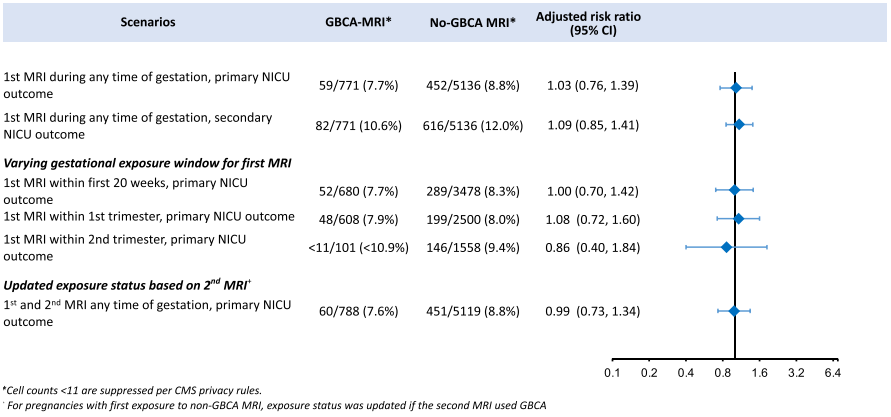
Our restrictive inclusion criteria, which aided in establishing balanced comparison groups, produced a population with a small number of fetal or neonatal deaths, similar in magnitude as the Ray et al[16] study, but the results did not corroborate previous concerns. Exclusion of pregnancies with MRIs linked to emerging pregnancy concerns reduced the study population appreciably and likely removed some pregnancies at higher risk for fetal or neonatal death. Considering that the administration of gadolinium is uniform in route and dose regardless of anatomic site, thus leading to similar fetal exposure, we expect that study findings translate to this higher-risk population, but caution should be warranted in absence of specific evidence.

Besides confounding, outcome and exposure misclassification could also introduce bias. Taking advantage of the ability to link Medicaid data, we addressed such bias via an optimized combination of claims and supplemental data from vital and medical records and validated algorithms to identify pregnancy outcomes and to determine pregnancy onset. We used an elaborate approach to ensure accurate timing of pregnancy to reduce exposure misclassification, especially caused by overestimates of GA, which would lead to erroneous assignment of MRI exposure during pregnancy when the exposure actually occurred before conception. We further addressed this in our sensitivity analysis in which the predicted GA was varied, which corroborated the findings and did not suggest measurement bias as a primary mechanism for our null finding. We have not assessed the accuracy of CPT codes indicating use of GBCA but have identified no reason to assume appreciable coding errors.

We selected NICU admission as a proxy for severe acute neonatal effects of GBCA retention. NICU admission could have been for other neonatal conditions unrelated to the adverse effect of GBCA MRI, which could obscure our ability to identify an

FIGURE 3
Adjusted risk for NICU admission by GBCA MRI exposur



*Cell counts <11 are suppressed per CMS privacy rules.
' For pregnancies with first exposure to non-GBCA MRI, exposure status was updated if the second MRI used GBCA

CI, confidence interval; *GBCA*, gadolinium-based contrast agent; *MRI*, magnetic resonance imaging; *NICU*, neonatal intensive care unit.

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elevated risk, although the consistency and precision of risk ratios close to 1 is noteworthy. Finally, retention of gadolinium varies across GBCA types[17] but claims data do not provide this level of detail. During the study period, the vast majority of GBCAs sales included linear products,[34] which have a higher propensity for gadolinium retention when compared with macrocyclic agents, a finding that has led to suspension of the marketing application in Europe.[3] Thus, our findings, representing the effect of predominantly linear products evaluated among a population of publicly insured women who are at higher risk for pregnancy complications, are reassuring in terms of potential severe acute fetal effects following gadolinium exposure.[35]

Conclusions

In summary, we are unable to confirm the safety concerns previously raised regarding prenatal exposure to GBCA MRI procedures and the risk for fetal and neonatal death or NICU admission. Our study, which excluded MRIs indicated for potential pregnancy complications and adjusted for a broad range of other potential confounders and carefully addressed measurement biases, revealed no association between GBCA use and the examined adverse outcomes. The impact of gadolinium on other subacute outcomes identified in the literature was not evaluated. Although this study provides some reassurance, the use of gadolinium during pregnancy should be limited and in accordance with professional society guidelines. ■

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