First Trimester Exposure to Gadolinium Contrast; A utilization study of 4.6 million live-birth pregnancies

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BACKGROUND

- Gadolinium is known to cross the placenta and enter fetal circulation.
- Eight publications reported a total of 101 exposures to gadolinium during pregnancy, nearly all of which resulted in term deliveries to healthy infants [*PMIDs: 17230297, 1566688, 9356634, 8228087, 10924595, 11672621, 15671363, 10873690*].
- A study of 1.4 million pregnancies in Ontario identified a 3.7-fold (95%CI: 1.55-8.85) increased risk for stillbirth and neonatal death with gadolinium exposure in utero. This study also identified a 1.36-fold (95%CI: 1.09-1.69) increased risk for rheumatological, inflammatory, or infiltrative skin conditions in the newborn after gadolinium exposure in utero. [*Ray JG et al, 2017, PMID: 27599330*]

METHODS

- **Data Source**: Pregnancies were identified from 16 data partners within the Sentinel Distributed Database.
- **Pregnancy Identification**: Live-birth pregnancies were identified using a validated algorithm based on International Classification of Diseases (ICD) codes. The start of pregnancy was indexed as the date of the Last Menstrual Period (LMP), estimated using codes for gestational age at delivery and codes for preterm and postterm delivery. A 273 day gestational length was assigned in absence of these codes.
- **Contrast and Non-Contrast MRI receipt**: We identified outpatient MRI with or without contrast from 2008 - 2017. Coding for MRI includes both the presence of gadolinium contrast and MRI anatomical location. MRI locations were: abdomen, breast, cardiac, chest, fetal, head, lower extremity, neck, pelvis, spinal canal, and upper extremity. MRIs performed during days 0-13 of pregnancy episode and date of delivery were not included in these analyses. Results were stratified by trimester: days 14 to 90 were defined as the first trimester; days 91–180 as the second trimester; and days 181 through the delivery admission date as the third trimester. Assessment of first trimester exposure started on day 14, which represents the timing of conception.
- **Matched Comparator Women**: Each pregnancy was matched 1:1, without replacement, by age, enrollment criteria and contributing data source, to a corresponding episode of equal length contributed by a randomly selected comparison woman who did not deliver a live-born infant during that period.
- **Statistical Analysis**: Descriptive statistics were used to characterize the prevalence of contrast and non-contrast MRI among pregnant and matched non-pregnant women. Rates of MRI receipt per 1,000 pregnancies and matched non-pregnant episodes were calculated by MRI location. A ratio of the rates of MRI utilization in non-pregnant women compared to pregnant women was calculated to assess differential prevalence rates. All analyses were performed using SAS version 9.4 (Cary, NC). This study was exempted from IRB Review.

RESULTS

Table 1. Prevalence of Contrast and Non-Contrast MRI Among Pregnant and Matched Comparator Women

	Pregnancies n = 4,692,744			Matched Comparator Women n = 4,692,744			Rate Ratio*
	No. MRI	No. Women	MRI / 1000 Pregnancies	No. MRI	No. Women	MRI / 1000 Controls	
Contrast MRI							
Total	6879	5457	1.2	93750	66605	14.2	12.2
Head	3499	3060	0.7	48180	39077	8.3	12.8
Pelvis	847	799	0.2	6676	5942	1.3	7.4
Abdomen	689	642	0.1	6238	5382	1.1	8.4
Spinal Canal	768	559	0.1	15921	10438	2.2	18.7
Breast	301	274	0.06	5691	5107	1.1	18.6
Lower Extremity	259	228	0.05	4429	3849	0.8	16.9
Upper Extremity	240	210	0.04	3718	3364	0.7	16.0
Neck	180	160	0.03	1864	1574	0.4	10.4
Cardiac	55	52	0.01	657	578	0.1	11.1
Chest	41	38	0.01	376	326	0.07	8.6
Non-Contrast MRI							
Total	72867	49044	10.5	163072	128276	27.3	2.6
Head	26698	16712	3.6	34517	28401	6.1	1.7
Pelvis	15266	13526	2.9	3104	2953	0.6	0.2
Abdomen	13248	11253	2.4	2429	2269	0.5	0.2
Spinal canal	8028	6296	1.3	62323	50998	10.9	8.1
Lower Extremity	4500	4150	0.9	46192	41741	8.9	10.1
Upper Extremity	1285	1176	0.3	12982	11952	2.6	10.2
Neck	1522	1292	0.3	1017	932	0.2	0.7
Fetal	1868	1549	0.3	--	--	--	--
Chest	280	237	0.05	264	256	0.05	1.1
Cardiac	172	156	0.03	226	208	0.04	1.3

* Rate Ratio calculated as exposure rate in matched comparator women versus exposure rate in pregnant women
MRI/1000 pregnancies = Number of pregnancies with MRI / 1000 pregnancies

Table 2. Timing of Contrast MRI by Trimester in Pregnant Women

	90 days Before	Any Time During Pregnancy	First Trimester	Second Trimester	Third Trimester
	n = 4,692,744	n = 4,692,744	n = 4,692,744	n = 4,692,744	n = 4,685,693
Contrast					
Total	21,863	5,457	3,907	883	753
Head	13,193	3,060	2,327	445	333
Pelvis	2,387	799	454	175	174
Abdomen	1,671	642	304	203	136
Spinal Canal	2,440	559	458	58	48
Breast	1,683	274	214	36	28
Lower Extremity	922	228	193	15	22
Upper Extremity	801	210	162	28	23
Neck	459	160	76	31	54
Cardiac	167	52	22	12	18
Chest	88	38	24	4	10
Non-Contrast					
Total	36,554	49,044	12,675	19,029	18,824
Head	8,651	16,712	3,586	6,421	7,103
Pelvis	1,281	13,526	1,382	5,930	6,565
Abdomen	874	11,253	2,144	5,500	3,818
Spinal Canal	13,706	6,296	3,352	1,650	1,368
Lower Extremity	10,834	4,150	2,556	948	687
Upper Extremity	2,987	1,176	739	286	161
Neck	264	1,292	235	438	630
Fetal	--	1,549	--	702	915
Cardiac	64	156	19	73	68
Chest	77	237	45	104	105

Imaging Locations (Table 1)

- A total of 6,879 gadolinium contrast MRIs were observed in 5,457 pregnancies, representing 1 contrast MRI in 860 pregnancies (0.12%).
- The most frequent location for contrast MRI among pregnant women was the head (0.7/1,000 pregnancies) and 2,874 of 3,499 contrast MRI of the head (82.1%) were for imaging of the brain (including brain stem).
- Abdominal and pelvic imaging locations represented 22.3% (1,536 of 6,879) of contrast and 39.1% (28,514 of 72867) of non-contrast MRI procedures during pregnancy.
- Spinal canal and contents (0.2/1,000 pregnancies) were the fourth most common imaging location in pregnancy, comprising 45.1% cervical, 32.6% lumbar, and 22.3% thoracic.

Non-Contrast MRI in Pregnancy (Table 1)

- Non-contrast MRI procedures (n=72,867) were 10.6-fold more prevalent during pregnancy than contrast MRI (n=6,879).
- The most common non-contrast MRI imaging locations were the head (3.6/1000 pregnancies), the pelvis (2.9/1000 pregnancies), and the abdomen (2.4/1000 pregnancies).
- Non-contrast fetal MRI codes were introduced in October 2015, and this type of MRI was ordered for 0.15% of pregnancies in 2015 and 0.23% of pregnancies in 2017.

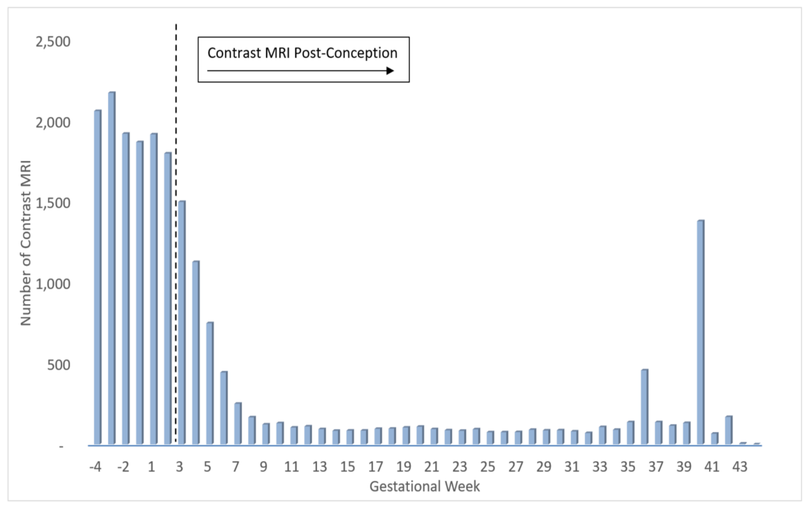
MRI Use In Matched Comparator Women (Table 1)

- Matched comparator women (14.2/1000 controls) were 12.2-fold more likely to receive a contrast MRI than pregnant women (1.2/1000 pregnancies).
- Non-contrast abdominal and pelvic MRI procedures were 4.7-fold more common among pregnant (5.3/1000 pregnancies) than non-pregnant women (1.1/1000 controls).

Contrast MRI in Pregnancy (Table 2)

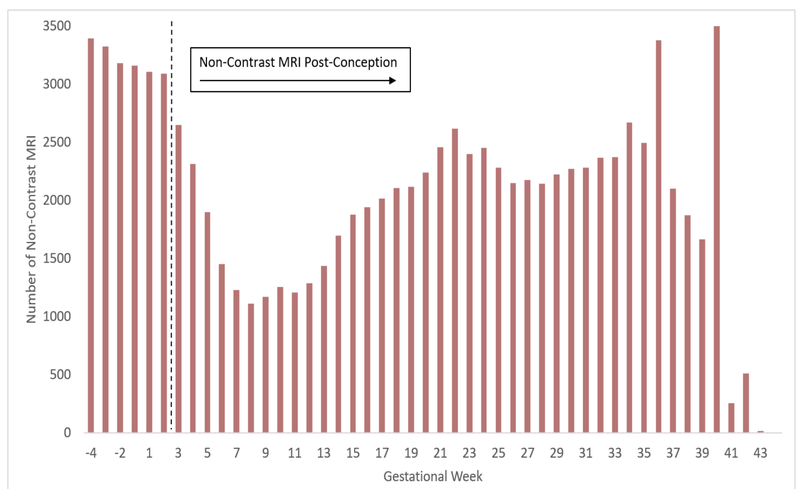
- Gadolinium exposure during the first trimester (n=3,907, 0.08%) was 4.4-fold greater than exposure in the second trimester (n=833, 0.02%) and 5.2-fold greater than third trimester exposure (n=753, 0.02%).
- First trimester gadolinium exposure was less frequent than during the 90 days prior to pregnancy (n=21,836, 0.46%).

Figure 1. Contrast MRI Exposure by Gestational Week



- Figure 1 depicts the utilization of contrast MRI by gestational week, starting -4 weeks prior to LMP.
- A trend can be seen towards decreasing use surrounding the start of pregnancy, with lower utilization levels in the second and third trimesters.
- A spike in contrast MRI was noted at hospital admission for delivery, particularly in week 40, the most commonly recorded gestational week at delivery.
- This figure incudes 2367 gadolinium exposures during the hospital admission for delivery not in our primary analysis.

Figure 2. Non-Contrast MRI by Gestational Week



- A similar depiction of non-contrast MRI by gestational week is provided in Figure 2.
- Decreased use of non-contrast MRI was observed after pregnancy start, which increased as pregnancy progressed.

Discussion

MAIN FINDINGS

- We identified 1.2 exposures to gadolinium per 1,000 live birth pregnancies, which correlates to one gadolinium exposure for every 860 pregnancies.
- This rate is approximately 4-fold larger compared to a recent study in Ontario which found 0.3 contrast MRI per 1,000 pregnancies [*Ray JG, 2016*].
- An additional 2,367 contrast MRI were administered during the hospital admission for delivery and not included in the primary analysis. We could not distinguish whether these MRI occurred prior to delivery to evaluate late-stage pregnancy complications or immediately after delivery to evaluate complications of childbirth.
- Gadolinium administrations in the first trimester represented 71.6% of all exposures in our study, a time where pregnancy may not have been recognized.
- The substantial decrease in gadolinium exposure with pregnancy progression likely represents changing use patterns with knowledge of a patient's pregnancy status. This is consistent with a survey of 20 academic centers reporting avoidance of gadolinium contrast in pregnancy due to potential risk to the fetus [*Sundgren PC, 2011; PMID 21928308*].

STRENGTHS AND LIMITATIONS

- Our study evaluated a large sample of U.S. pregnancies to allow robust inference into gadolinium exposure rates. Assessment of imaging location, trimester, and MRI exposure in a sample of matched comparators was conducted.
- We did not have access to information about the underlying diagnosis that prompted the imaging procedure.
- Additionally, we are currently unable to link to medical records to evaluate adverse effects in the liveborn infant.

FUTURE RESEARCH

- Registries and pharmacovigilance plans could identify pregnant women exposed to contrast and non-contrast MRIs and follow them through delivery, as well as postpartum, to assess adverse effects in exposed infants.
- Additional population based studies of pregnant women exposed to gadolinium and subsequent risk for stillbirth, neonatal death, and other adverse effects in the infant are needed.

CONCLUSIONS

Most U.S. radiology facilities have guidelines for use of gadolinium in pregnant women, including protocols to identify pregnant patients. Recommended approaches to avoid inadvertent administration of gadolinium to pregnant women include use of a safety screening form asking about potential for pregnancy, direct questioning of women regarding pregnancy, and prominently displayed signs asking women to notify radiology staff if they may be pregnant.

Use of gadolinium contrast in pregnant women is not recommended unless the benefit to the pregnant woman and fetus outweighs the potential risks. With the 45% prevalence of unintended pregnancies in the United States (PMID: 26962904), implementation of more rigorous safety screening practices (e.g. pregnancy screening and testing) may help reduce inadvertent exposures to gadolinium contrast during early pregnancy, particularly when pregnancy status may not be known.