Utilization of IV iron among pregnant women with live births or stillbirths; A study in the Sentinel Distributed Database

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BACKGROUND

- Intravenous (IV) iron can aid in treatment of severe iron deficiency anemia after failure of oral iron in pregnant women.
- Reports of fetal adverse effects from maternal hypersensitivity reactions to IV iron have been received by FDA, including fetal bradycardia, and rarely, fetal demise (stillbirth).

STUDY OBJECTIVE

- Our study sought to evaluate the utilization of IV iron in pregnancy, compare IV iron utilization rates among stillbirths versus live-birth deliveries (LBD), and assess codes consistent with acute hypersensitivity reactions. Case reports of fetal demise in temporal association with IV iron administration are also described.

METHODS

- **Data Source:** The US Food and Drug Administration's Sentinel Distributed Database provides active surveillance using health-care data from multiple data partners to monitor the safety of regulated medical products. Data partners include public, private, and integrated delivery networks, but consist primarily of privately insured individuals. This study included pregnant women from 15 data partners between 2008 and 2019.
- We developed two cohorts, consisting of women aged 15 to 45 years having either an inpatient admission for a live birth delivery (cohort 1) or stillbirth (cohort 2). Women were required to have continuous enrollment in the 20 weeks prior to livebirth or stillbirth diagnosis and no evidence of dialysis during the same time period.
- Descriptive statistics were used to characterize exposure to IV iron during the 20 weeks prior to live birth delivery or stillbirth. The number of exposures was plotted by gestational week to assess trends in exposure. We additionally characterized the presence of coding for hypersensitivity reactions.
- All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina) with each data partner running a standardized distributed analytical program. This study was not under the purview of institutional review boards because the Sentinel Initiative is considered a public health surveillance activity.

RESULTS

Table 1. Population Characteristics for Live Births and Stillbirths

	Live-Births No.	Live-Births %	Stillbirths No.	Stillbirths %
	n = 4,355,252		*n = 68,469*	
Maternal Conditions During Pregnancy				
Pre-existing Hypertension/Pre-eclampsia	106,539	2.4	965	1.4
Markers for Anemic Conditions				
Anemia	393,206	9.0	4,934	7.2
Blood Transfusions	3,887	0.1	206	0.3
Oral Iron Dispensing	133,978	3.1	1,136	1.7
Hemolysis	66	0.0	4	0
Chronic kidney disease	60,848	1.4	875	1.3
Thalassemic disorders	8,696	0.2	163	0.2
General Comorbidity				
Underweight	1,352	0.0	32	0
Overweight	20,176	0.5	547	0.8
Obese	303,086	7.0	6,154	9
Diabetes	137,577	3.2	2,636	3.8
Autoimmune disease	20,842	0.5	642	0.9
Thyroid disorders	232,260	5.3	4,808	7
Liver disease	10,604	0.2	315	0.5
Cholestasis of pregnancy	5,164	0.1	35	0.1
Congenital abnormalities	92,920	2.1	3,193	4.7
Tobacco Use	127,853	2.9	2,969	4.3
Serious infections	142,515	3.3	2,669	3.9
Seizure disorder	18,701	0.4	376	0.5
Alcohol use	6,302	0.1	185	0.3
Substance use disorder	86,311	2.0	1,420	2.1
Prenatal vitamins	866,314	19.9	14,872	21.7

Table 2: Age and Calendar Year of Delivery

	Live-Births No.	Live-Births %	Stillbirths No.	Stillbirths %
	n = 4,355,252		*n = 68,469*	
Age				
Age: 15-20	245,413	5.6	4,001	5.8
Age: 21-25	688,811	15.8	9,422	13.8
Age: 26-30	318,610	30.3	17,633	25.8
Age: 31-35	388,504	31.9	20,846	30.4
Age: 36-40	606,919	13.9	13,033	19
Age: 41-45	106,995	2.5	3,534	5.2
Calendar Year				
2008	364,111	8.4	5,749	8.4
2009	422,599	9.7	6,665	9.7
2010	391,763	9	6,088	8.9
2011	379,572	8.7	5,989	8.7
2012	378,928	8.7	5,961	8.7
2013	392,782	9	5,977	8.7
2014	404,570	9.3	6,074	8.9
2015	411,540	9.4	6,609	9.7
2016	421,967	9.7	6,982	10.2
2017	409,676	9.4	6,545	9.6
2018	344,608	7.9	5,333	7.8
2019	33,136	0.8	497	0.7

Table 3: Parenteral Iron Exposures

	Exposed Pregnancies[a]	IV Iron Exposures[b]	Total Pregnancies
Live-Births	11,209 (0.26%)	31,467	4,355,252
Stillbirths	103 (0.15%)	261	68,469

[a] Represents the proportion of pregnancies exposed to one or more parenteral iron administrations in the 20 weeks prior to delivery.

[b] Represents the total number of weeks with at least one parenteral iron exposure, assessed during the 20 weeks prior to delivery

Table 4: Parenteral iron administrations by product

	No. IV Iron Exposures Among Live-Births		No. IV Iron Exposures Among Stillbirths	
	n = 11,209		*n = 103*	
IV Iron Exposures by Product	No.	%	No.	%
Ferric carboxymaltose	496	4.4	10	9.7
Ferumoxytol	341	3.0	4	3.9
Iron dextran complex	1431	12.8	16	15.5
Iron sucrose complex	7307	65.2	59	57.3
Sodium ferric gluconate complex in sucrose	1521	13.6	17	16.5

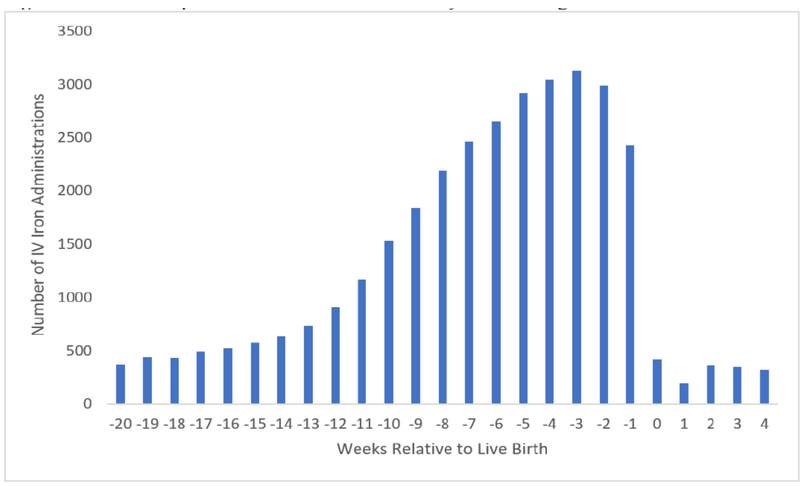
Percentages derived from overall parenteral iron administrations in 20 weeks prior to live-birth or stillbirth. The denominator for these percentages is the total number of pregnancies with parenteral iron administrations in the 20 weeks prior to delivery.

Table 5: Coding potentially related to hypersensitivity reactions with parenteral iron administration

	Hypersensitivity Codes with IV Iron Among Live Births		Hypersensitivyt Codes with IV Iron Among Stillbirths	
	n = 11,209		n = 103	
	No.	%	No.	%
IV iron + hypersensitivity (Any Component) same or following day	856	7.6	7	6.8
IV iron + hypersensitivity (Anaphylaxis - inpatient or emergency)	3	0.03	--	--
IV iron + hypersensitivity (Anaphylaxis - outpatient)	2	0.02	--	--
IV iron + hypersensitivity (Bronchospasm)	2	0.02	--	--
IV iron + hypersensitivity (Stridor)	1	0.01	--	--
IV iron + hypersensitivity (Hypotension)	19	0.2	--	--
IV iron + hypersensitivity (Epinephrine)	11	0.1	--	--
IV iron + hypersensitivity (Diphenhydramine)	827	7.4	7	6.8
IV iron + hypersensitivity (CPR)	0	--	--	--
IV iron + hypersensitivity (Allergy or adverse effects of drug)	8	0.1	--	--

Percentages derived from overall parenteral iron administrations in 20 weeks prior to live birth or stillbirth. The denominator for these percentages is the total number of pregnancies with hypersensitivity reactions during the day of or the day after receipt of parenteral iron during the 20 weeks prior to delivery.

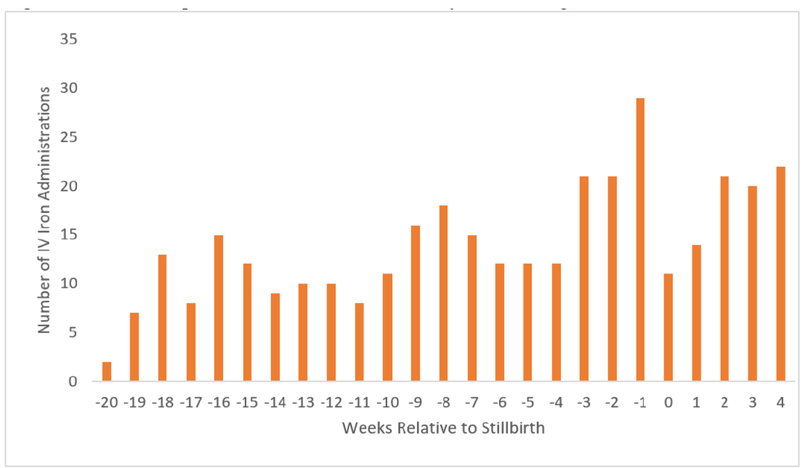
Figure 1. Number of parenteral iron administrations by week among live-births



Y-axis: Represents number of pregnancies with at least 1 parenteral iron exposure in each week.

X-axis: Negative numbers represent exposures in each week prior to live birth, 0 represents exposures *only on the day* of live birth, and positive numbers represent exposures in each week after live birth.

Figure 2: Number of parenteral iron administrations by week among stillbirths



Y-axis: Represents number of pregnancies with at least 1 parenteral iron exposure in each week.

X-axis: Negative numbers represent exposures in each week prior to stillbirth, 0 represents exposures *only on the day* of stillbirth, and positive numbers represent exposures in each week after stillbirth.

DISCUSSION

MAIN FINDINGS

- Our study evaluated 4,355,252 live birth deliveries and 68,469 stillbirths. Population characteristics for LBD and stillbirths are shown in Table 1 and Table 2.
- As shown in Table 3, we identified 11,209 LBDs exposed to at least one parenteral iron administration, representing 0.26% of the total population of live-births. Among LBD exposed to IV iron during the 20 weeks prior to delivery, an average of 2.8 weeks with infusions per LBD were noted. We additionally identified 103 stillbirths exposed to at least one IV iron administration, representing 0.15% of the total population of stillbirths (Table 3). An average of 2.5 weeks with parenteral iron infusions per stillbirth were observed during the 20 weeks prior to delivery.
- A breakdown of parenteral iron administrations by product for LBDs and stillbirths is contained in Table 4. While use of all products was observed, parenteral iron sucrose comprised the majority of use in live births and stillbirths.
- Coding potentially related to hypersensitivity reactions, that was billed on the day or the day following parenteral iron administration is shown in Table 5. Of note, three women with a LBD had inpatient coding for anaphylaxis and 11 women with a LBD received epinephrine.
- Administration of parenteral diphenhydramine with IV iron was 2.4 times more likely to occur on the day of LBD (18.4% vs 7.6%) and was 4 times more likely on the day of stillbirth (27.3% vs. 6.8%), compared to the 20 weeks prior to delivery.

TRENDS BY GESTATIONAL AGE

- In live births, the IV iron exposures per week increased with proximity to delivery and peaked in the 3rd week prior to delivery (Figure 1). This frequency distribution of exposures could be expected as expansion of blood volume and growth of the fetus substantially increase the demand for iron in the second and third trimesters. Of total exposures during the 20 weeks prior to live birth, 80% of parenteral iron exposures were in the 10 weeks prior to delivery.
- Among stillbirths, administrations peaked on the week preceding and the day of delivery (Figure 2). Eleven parenteral iron administrations were observed on the day of stillbirth. Although this finding is consistent with same-day occurrence of parenteral iron administration and an adverse effect resulting in stillbirth, we could not differentiate whether these exposures occurred before or after the stillbirth delivery.

NEW CLASS LABELING REQUIRED FOR FETAL ADVERSE EFFECTS

- In June 2020, FDA required the addition of new safety information in the labeling for parenteral iron products class to include the following statement on the risk of fetal adverse reactions in pregnancy women: *"Severe adverse reactions including circulatory failure (severe hypotension, shock including in the context of anaphylactic reaction) may occur with [IV iron] which may have serious consequences for the fetus, such as fetal bradycardia, especially during the second and third trimester."*
- This regulatory action in the United States followed a July 2019 requirement in Europe, when the European Medicines Agency (EMA) advised all member states to revise labeling for IV iron products to add fetal bradycardia and a recommendation for fetal monitoring with IV iron administration.

CONCLUSIONS

- Although anemia is a frequent diagnosis among pregnant women, IV iron was administered uncommonly during the study period (2008-2019).
- This finding of infrequent use of IV iron is consistent with the American College of Obstetrics and Gynecologists guidelines which state that oral preparations are appropriate and sufficient in most clinical circumstances
- Given rare case reports of serious and fetal adverse effects in the fetus associated with IV iron administration during pregnancy, benefit-risk balance should be carefully considered and patients appropriately monitored, including fetal monitoring.

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