Letters

RESEARCH LETTER

Safety of Assisted Reproductive Technology in the United States, 2000-2011

Use of assisted reproductive technology (ART) continues to increase in the United States and globally. In an effort to improve patient safety, stimulation protocols have become less aggressive, oocyte retrieval has transitioned from laparoscopic to transvaginal, and pregnancy rates have improved.[1] However, limited data exist regarding the incidence of maternal complications.[2] We explored incidence and trends in reported patient and donor complications in fresh ART cycles using the US Centers for Disease Control and Prevention National ART Surveillance System (NASS).

Methods | NASS is a federally mandated reporting system that collects cycle-level ART procedure information.[3] As of 2011, NASS included 97% of cycles and 94% of all US ART clinics.[4] Annually, 7% to 10% of reporting clinics undergo data validation (does not include complication variables).[4]

Table 1. Patient Complications in Fresh, Autologous ART Cycles as Reported to the US CDC National ART Surveillance System, 2000-2011

Year	Total No. of Cycles	No. of Complications (Rate/10 000 Cycle Starts) [95% CI][a]									
		Infections	Hemorrhages	OHSS	Severe OHSS	Medication Adverse Events	Anesthetic-Related Complication	Hospitalizations	Patient Death Within 12 wk of Stimulation Start	Maternal Death Prior to Infant Birth	Any Complications
2000	75 516	13 (1.7) [1.0-3.0]	16 (2.1) [1.3-3.5]	803 (106.3) [99.3-113.9]	151 (20.1) [17.2-23.6]	49 (6.5) [4.9-8.6]	NA[b]	263 (34.8) [30.9-39.3]	2 (0.3) [0.1-1.1]	4 (0.5) [0.2-1.4]	958 (126.9) [119.1-135.1]
2001	80 864	14 (1.7) [1.0-2.9]	20 (2.5) [1.6-3.8]	781 (96.6) [90.1-103.6]	190 (23.6) [20.4-27.1]	32 (4.0) [2.8-5.6]	NA[b]	269 (33.3) [29.5-37.5]	1 (0.1) [0-0.9]	2 (0.3) [0.1-1.0]	901 (111.4) [104.4-118.9]
2002	85 826	12 (1.4) [0.8-2.5]	17 (2.0) [1.2-3.2]	886 (103.2) [90.1-103.6]	219 (25.6) [22.4-29.1]	17 (2.0) [1.2-3.2]	6 (0.7) [0.3-1.6]	286 (33.3) [29.7-37.4]	1 (0.1) [0-0.8]	2 (0.2) [0.1-0.9]	971 (113.1) [106.3-120.4]
2003	91 032	23 (2.5) [1.7-3.8]	24 (2.6) [1.8-3.9]	1058 (116.2) [109.5-123.4]	288 (31.7) [28.4-35.7]	14 (1.5) [0.9-2.6]	NA[b]	313 (34.4) [30.8-38.4]	1 (0.1) [0-0.8]	4 (0.4) [0.2-1.2]	1158 (127.2) [120.1-134.7]
2004[c]	94 242	33 (3.5) [2.5-4.9]	25 (2.7) [1.8-3.9]	1182 (125.4) [118.5-132.7]	331 (35.2) [31.6-39.2]	20 (2.1) [1.4-3.3]	5 (0.5) [0.2-1.3]	287 (30.5) [27.1-34.2]	2 (0.2) [0.1-0.8]	7 (0.8) [0.4-1.6]	1273 (135.1) [127.9-142.6]
2005[c]	97 442	20 (2.1) [1.3-3.2]	26 (2.7) [1.8-3.9]	1327 (136.2) [129.1-143.7]	341 (35.1) [31.6-39.0]	16 (1.6) [1.0-2.7]	5 (0.5) [0.2-1.2]	249 (25.6) [22.6-28.9]	3 (0.3) [0.1-1.0]	3 (0.3) [0.1-1.0]	1398 (143.5) [136.2-151.1]
2006[c]	99 199	21 (2.1) [1.4-3.2]	30 (3.0) [2.1-4.3]	1522 (153.5) [146.0-161.3]	411 (41.5) [37.6-45.6]	11 (1.1) [0.6-2.0]	NA[b]	312 (31.5) [28.2-35.1]	3 (0.3) [0.1-0.9]	3 (0.3) [0.1-0.9]	1620 (163.3) [155.6-171.4]
2007[c]	101 897	14 (1.4) [0.8-2.3]	20 (2.0) [1.3-3.0]	1449 (142.2) [135.1-149.7]	373 (36.7) [33.3-40.7]	12 (1.2) [0.7-2.1]	5 (0.5) [0.2-1.2]	270 (26.5) [23.5-29.8]	0	2 (0.2) [0-0.8]	1531 (150.3) [143.0-157.9]
2008[c]	104 673	7 (0.7) [0.3-1.4]	17 (1.6) [1.0-2.6]	1431 (136.7) [129.9-143.9]	448 (42.9) [39.1-47.0]	19 (1.8) [1.2-2.8]	6 (0.6) [0.3-1.3]	220 (21.0) [18.4-24.0]	2 (0.2) [0-0.8]	1 (0.1) [0-0.7]	1503 (143.6) [136.6-151.0]
2009[c]	102 478	13 (1.3) [0.7-2.2]	31 (3.0) [2.1-4.3]	1124 (109.7) [103.5-116.2]	312 (30.5) [27.3-34.1]	22 (2.2) [1.4-3.3]	NA[b]	260 (25.4) [22.5-28.6]	2 (0.2) [0-0.8]	7 (0.7) [0.3-1.4]	1241 (121.1) [114.6-128.0]
2010[c]	100 824	15 (1.5) [0.9-2.5]	25 (2.5) [1.7-3.7]	1068 (106.0) [99.8-112.4]	291 (28.9) [25.8-32.5]	13 (1.3) [0.7-2.2]	NA[b]	243 (24.1) [21.3-27.3]	0	2 (0.2) [0-0.8]	1172 (116.2) [109.8-123.0]
2011[c]	101 213	21 (2.1) [1.4-3.2]	30 (3.0) [2.1-4.2]	1124 (111.1) [104.8-117.7]	281 (27.8) [24.7-31.2]	15 (1.5) [0.9-2.5]	6 (0.6) [0.3-1.3]	232 (22.9) [20.2-26.1]	1 (0.1) [0-0.7]	3 (0.3) [0.1-0.9]	1234 (121.9) [115.3-128.9]
Total	1 135 206	206 (1.8) [1.6-2.1]	281 (2.5) [2.2-2.8]	13 755 (121.2) [119.2-123.2]	3646 (21.1) [31.1-33.2]	240 (2.1) [1.9-2.4]	53 (0.5) [0.4-0.6]	3204 (28.2) [27.3-29.2]	18 (0.2) [0.1-0.3]	40 (0.4) [0.3-0.5]	14 960 (131.8) [129.7-133.9]
Test for trend[d]											
P value		.40	.39	.44	.17	.02	.64	<.001	.31	.53	.64
R^2		0.07	0.07	0.06	0.10	0.43	0.02	0.78	0.10	0.04	0.02

Abbreviations: ART, assisted reproductive technology; CDC, Centers for Disease Control and Prevention; NA, not applicable; OHSS, ovarian hyperstimulation syndrome.

[a] ProcCrosstab in SUDAAN was used to obtain 95% confidence intervals.

[b] Actual counts suppressed to protect patient confidentiality due to small cell sizes.

[c] Between 2004 and 2011, the numbers of repeat complications in the same individual at the same fertility center were 2 of 144 for infection; 2 of 204 for hemorrhage; 464 of 10 227 for OHSS; 96 of 2795 for severe OHSS; 24 of 2073 for hospitalization; and 481 of 10 491 for any complication.

[d] Bivariable linear regression (with complication rate as the outcome and calendar year as the explanatory variable) was used to assess increases or decreases over time. The 2-sided α level was .05.

Table 2. Oocyte Donor Complications in Fresh, Donor ART Cycles as Reported to the US CDC National ART Surveillance System, 2000-2011

Year	Total No. of Cycles	No. (Rate/10 000 Cycle Starts) [95% CI][a]			
		OHSS	Severe OHSS	Hospitalizations	Any Complications
2000	7919	18 (22.7) [14.3-36.0]	NA[b]	6 (7.6) [3.4-16.9]	28 (35.4) [24.4-51.2]
2001	8592	16 (18.6) [11.4-30.4]	NA[b]	9 (10.5) [5.5-20.1]	21 (24.4) [15.9-37.5]
2002	9261	19 (20.5) [13.1-32.1]	NA[b]	6 (6.5) [2.9-14.4]	22 (23.8) [15.6-36.1]
2003	9859	24 (24.3) [16.3-36.3]	8 (8.2) [4.1-16.2]	8 (8.1) [4.1-16.2]	32 (32.5) [23.0-45.9]
2004	10 256	26 (25.4) [17.3-37.2]	NA[b]	NA[b]	32 (31.2) [22.1-44.1]
2005	10 620	31 (29.2) [20.5-41.5]	6 (5.7) [2.5-12.6]	NA[b]	36 (33.9) [24.5-47.0]
2006	10 984	35 (31.0) [22.9-44.3]	11 (10.1) [5.5-18.1]	9 (8.2) [4.3-15.7]	41 (37.3) [27.5-50.7]
2007	11 275	35 (31.0) [22.3-43.2]	8 (7.1) [3.5-14.2]	8 (7.1) [3.5-14.2]	37 (32.8) [23.8-45.3]
2008	11 777	25 (21.2) [14.3-31.4]	8 (6.8) [3.4-13.6]	10 (8.5) [4.6-15.8]	29 (24.6) [17.1-35.4]
2009	11 038	8 (7.3) [3.6-14.5]	NA[b]	7 (6.3) [3.0-13.3]	13 (11.8) [6.8-20.3]
2010	10 849	26 (24.0) [16.3-35.2]	5 (4.6) [1.9-11.1]	5 (4.6) [1.9-11.1]	29 (26.7) [18.6-38.4]
2011	10 797	8 (7.4) [3.7-14.8]	NA[b]	7 (6.5) [3.1-13.6]	16 (14.8) [9.1-24.2]
Total	112 254	271 (22.0) [19.5-24.8]	60 (4.9) [3.8-6.3]	82 (6.7) [5.4-8.3]	336 (27.3) [24.5-30.3]
Test for trend[c]					
P value		.30	.93	.38	.09
R^2		0.11	0	0.08	0.25

Abbreviations: ART, assisted reproductive technology; CDC, Centers for Disease Control and Prevention; NA, not applicable; OHSS, ovarian hyperstimulation syndrome.

[a] ProcCrosstab in SUDAAN was used to obtain 95% confidence intervals. The total number of reported infections was 13 (1.1/10 000 cycle starts [95% CI, 0.6-1.8]); hemorrhage, 15 (1.2/10 000 cycle starts [95% CI, 0.7-2.0]); medication adverse event, 15 (1.2/10 000 cycle starts [95% CI, 0.7-2.0]); anesthetic complication, 2 (0.2/10 000 cycle starts [95% CI, 0-0.6]); and 0 deaths within 12 weeks of stimulation start.

[b] Actual counts suppressed to protect confidentiality due to small cell sizes.

[c] Univariate linear regression (with complication rate as the outcome and calendar year as the explanatory variable) was used to assess increases or decreases over time. The 2-sided α level was .05.

Reported complications (defined as having been directly related to ART and occurring within 12 weeks of cycle initiation) include infection, hemorrhage requiring transfusion, moderate or severe ovarian hyperstimulation syndrome (OHSS), medication adverse event, anesthetic complication, hospitalization, patient death within 12 weeks of stimulation, and other complications. We report severe OHSS and severe or moderate OHSS in a single category because the delineation between categories is subjective. We also report maternal death prior to infant birth.

Separate analyses using SAS version 9.3 (SAS Institute Inc) and SUDAAN version 11.0 (RTI International) were performed for autologous and donor cycles. We report complications (absolute numbers and rates/10 000 cycles annually) and maternal death prior to infant birth/100 000 ART-conceived live births from 2000-2011. The 2-sided α level was .05. Bivariable linear regression (complication rate as outcome, calendar year as explanatory variable) was used to assess trends over time.

The Centers for Disease Control and Prevention institutional review board approved this study; a waiver of informed consent was obtained.

Results | Among 1 135 206 autologous cycles, the most commonly reported patient complications were OHSS (peak of 153.5/10 000 autologous cycles; 95% CI, 146.0-161.3) and hospitalizations (peak of 34.8/10 000 autologous cycles; 95% CI, 30.9-39.3); rates of other complications remained below 10/10 000 cycles (**Table 1**). Rates declined from 2000-2011 for reported medication adverse events ($P = .02$) and hospitalizations ($P < .001$); no other significant trends were detected among reported infections, hemorrhages, OHSS, severe OHSS, anesthetic-related complications, and deaths within 12 weeks of stimulation start or during pregnancy ($P > .10$ for trend for all tests).

Fifty-eight total deaths were reported (18 stimulation-related and 40 maternal deaths prior to infant birth). No temporal patterns were noted. Of the 40 maternal deaths, 16 women carried a singleton, 16 carried twins, 2 carried triplets or higher-order multiples, and 6 did not report plurality. The maternal death rate ranged from 1.6 per 100 000 ART-conceived live births in 2008 to 14.2 in 2004.

Reported complications following donor ART cycles (n = 112 254) were less frequent; none showed a significant trend ($P > .05$ for trend for all tests; **Table 2**). The most common donor complications were OHSS (peak of 31.0/10 000 cycles; 95% CI, 22.9-44.3) and hospitalizations (peak of 10.5/10 000 cycles; 95% CI, 5.5-20.1). Rates of other complications remained below 5/10 000 cycles. No donor deaths were reported; 13 maternal deaths prior to infant birth were reported among oocyte donor recipients.

Discussion | In the United States from 2000-2011, autologous and donor ART procedures were associated with low reported stimulation and surgical complication risks; no concerning trends or patterns were identified. The most frequently reported complication among autologous and donor cycles was OHSS, though less frequent in donor cycles. Obstetric mortality was rare.

The lack of significant change in most adverse events may reflect the low baseline rate of such occurrences, making it harder to detect temporal change.

This study is the first, to our knowledge, to quantify US ART-associated patient risks. A 1984-2008 report from the Netherlands found a higher ART-related maternal death rate (42.5/100 000 pregnancies) compared with our study (peak of 14.2/100 000 pregnancies).[5] Underreporting of complications remains an inherent limitation of surveillance systems[6] and must be considered when interpreting our findings. Additionally, our outcomes are cycle-based rather than patient-based, validation does not include complication variables, and available data do not explain the noted trends.

Increased awareness of the most common complication, OHSS, may prompt additional study to characterize predictors of this and other adverse events to inform the development of effective approaches necessary to decrease complication occurrence.

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COMMENT & RESPONSE

Management of Patients With Sickle Cell Disease

To the Editor The Special Communication reporting a summary of the National Heart, Lung, and Blood Institute expert panel report on the management of patients with sickle cell disease (SCD)[1] distilled best practice recommendations from the extensive sickle cell anemia literature. However, the recommendation that chelation therapy should be standard for patients with SCD and iron overload failed to consider an important aspect of the problem.

The value of iron unloading with chelating agents in children with thalassemia is unquestioned. The expert panel suggested that this should be extrapolated to the management of patients with SCD and iron overload. But in thalassemia, unlike SCD, hepcidin production ranges from undetectable to diminished.[2] Recent animal experiments have demonstrated that in the absence of hepcidin, (1) iron entering the liver is incorporated into lysosomes, (2) the lysosomes are damaged and release proteases, and (3) nonferritin-bound iron in the lysosomes supports the production of free radicals.[3]

The pathophysiology of liver disease in human patients with thalassemia may be similar; however, it may not be for patients with SCD. Considering these differences, and without evidence that treating iron overload improves morbidity or mortality in patients with SCD, chelation treatment with deferasirox (outside of a controlled study) seems questionable. Deferasirox can be hepatotoxic, nephrotoxic, and sometimes lethal.[4] The cost of the intervention also must be considered; chelation can cost up to $40 000 per year.

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1. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA*. 2014;312(10):1033-1048.