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ASSISTED REPRODUCTION TECHNOLOGIES

Hospitalization before and after delivery in fertile, subfertile, and ART-treated women

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Abstract

Purpose Pre-pregnancy and post-delivery hospitalizations were compared as markers for health among women who conceived using assisted reproductive technology (ART), non-ART medically assisted reproduction (MAR), no treatment (unassisted subfertile), and who were fertile.

Methods We analyzed hospital discharge data linked to Massachusetts birth certificates from 2004 to 2013 within 5 years prior to pregnancy and 8–365 days post-delivery. ART deliveries were linked from a national ART database; MAR deliveries had fertility treatment but not ART; unassisted subfertile women had subfertility but no ART or MAR; and fertile women had none of these. Prevalence of diagnoses during hospitalization was quantified. Multivariable logistic regression models with fertile deliveries as reference were adjusted for maternal age, race, education, year, and plurality (post-delivery only) with results reported as adjusted odds ratios (AORs) and 95% confidence intervals (CI).

Results Of 170,605 privately insured, primiparous deliveries, 10,458 were ART, 3005 MAR, 1365 unassisted subfertile, and 155,777 fertile. Pre-pregnancy hospitalization occurred in 6.8% and post-delivery in 2.8% of fertile women. Subfertile groups had more pre-pregnancy hospitalizations (AOR, 95% CI: 1.84, 1.72–1.96 ART; 1.41, 1.24–1.60 MAR; 3.02, 2.62–3.47 unassisted subfertile) with endometriosis, reproductive organ disease, ectopic pregnancy/miscarriage, and disorders of menstruation, ovulation, and genital tract being common. Post-delivery hospitalizations were significantly more frequent in the ART (AOR 1.19, 95% CI 1.05–1.34) and unassisted subfertile (1.59, 1.23–2.07) groups with more digestive tract disorders, thyroid problems, and other grouped chronic disease conditions.

Conclusions Greater likelihood of hospitalization in the ART, MAR, and unassisted subfertile groups is largely explained by admissions for conditions associated with subfertility.

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Keywords Assisted reproductive technology · In vitro fertilization · Medically assisted reproduction · Hospitalization · Subfertility · Women's health

Introduction

The use of assisted reproductive technology (ART) has increased in the United States (U.S.) over the last 20 years [1, 2]. In Massachusetts, where an insurance mandate covering ART has been in place for many years, ART deliveries are 4.5% of those in the state [3]. Nevertheless, concerns about the health of women undergoing these procedures as well as that of the children born of them, have persisted.

Studies on hospitalization associated with ART have mostly focused on hospitalizations that occur during the ART cycle itself resulting from ovarian hyperstimulation syndrome (OHSS), or complications of retrieval [4, 5]. By contrast, hospitalizations that occur before treatment or following delivery

have been less well studied despite reports of increased pathology in these women during pregnancy and immediately following delivery [6–13]. It has long been suspected that health outcomes for women undergoing ART are compromised when compared with those for fertile women. Whether this is a function of the ART treatment itself or the underlying infertility is still in question [14]. Hospitalizations leading up to their cycles are one way to measure the health of these women. Hospitalizations following delivery are a way of measuring ongoing health complications.

We have previously studied hospitalizations among women who had ART cycles in which they either delivered a live birth, got pregnant and did not deliver a live birth, or did not get pregnant [15]. In the current study, we evaluated hospitalizations before pregnancy and after delivery in four groups of women, those who used ART treatment to conceive their pregnancy, those who used non-ART medically assisted reproduction (MAR), those who had an indication of subfertility but who did not have ART or MAR treatment, and fertile women. The goal was to compare these groups for frequency of hospitalization and indications for the hospital stay.

Methods

This retrospective cohort study used Massachusetts ART data linked to state vital records and hospital discharge records.

Data sources Data were obtained from (1) the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS), a national registry containing cycle-based ART data from the majority of U.S. ART clinics and (2) the Massachusetts-based Pregnancy to Early Life Longitudinal (PELL) data system, an ongoing population-based data system that compiles information from birth certificates, fetal death certificates and their corresponding hospital discharge records for mothers and infants, and non-birth-related hospital utilization over time. The study took place under a Memorandum of Understanding between SART, the Massachusetts Department of Public Health (MDPH), and the project principal investigators. Human subject approval was obtained from MDPH and the Committee for the Protection of Human Subjects at Dartmouth College.

The SART CORS contains demographic, ART diagnosis, ART cycle treatment, and pregnancy and delivery data from over 90% of U.S. ART clinics and all Massachusetts clinics. Data are entered by individual clinics throughout the country and reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102–493).

The PELL data system links over 98% of Massachusetts births and fetal deaths to corresponding hospital utilization data (hospital admissions, observational stays, and emergency room visits) for individual women and their children. The MDPH and the Massachusetts Center for Health Information and Analysis (CHIA) are the custodians of the PELL data. PELL is a relational data system composed of individual databases linked together by randomly generated unique IDs for mother and infant. The PELL data system is housed at MDPH.

Linkage of the SART CORS and PELL databases The Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) database was constructed by linking the SART CORS and PELL data systems for all Massachusetts resident women delivering in Massachusetts hospitals between July 1, 2004, and December 31, 2013. The starting date was chosen based on the availability of SART CORS data (January 1, 2004, cycle starts with first deliveries in July). A deterministic five-phase linkage algorithm methodology was used with matching based on mother's date of birth, her first name and last name, father/partner's last name, baby's date of birth, plurality, and infant gender [16]. Our linkage rate for 2004–2013 data was 90.2% overall and 94.5% for deliveries in which both mother's zip code and clinic were located in Massachusetts.

Patients The study sample included Massachusetts women ≥ 18 years of age with private health insurance and no prior deliveries (parity = 1) who had a live birth (> 20 weeks) in-state delivery occurring between July 1, 2004, and December 31, 2013. Only the first delivery to each woman following July 1, 2004, was included. We excluded multiparous women and those who had stillbirths. We also excluded deliveries with missing data upon which to calculate gestational age (Fig. 1).

Exposure groups Women were classified as ART-treated if the delivery was linked to an ART cycle in the SART CORS database. For this study, the subfertile group was subdivided and women were classified as MAR if the birth certificate for the delivery included a checked box that indicated that they had received fertility treatment but the delivery was not also linked to an ART cycle in SART CORS. They were classified as "unassisted subfertile" if they had a diagnosis of infertility (ICD9 628.9) in any hospital discharge, observational visit, or emergency room visit prior to the index delivery or if they had an unsuccessful ART cycle prior to the index delivery. Women were classified as fertile if they did not fall into the ART-treated, MAR, or unassisted subfertile groups. Definition of the MOSART subfertile group has been previously described [8]. There were no missing exposure (fertility status) data.

Outcome measures The primary outcomes were numbers of hospital stays (inpatient hospitalization and observational care visits, the latter of which serve as alternatives to admissions for observation, diagnosis, and treatment of less than 24 h) and

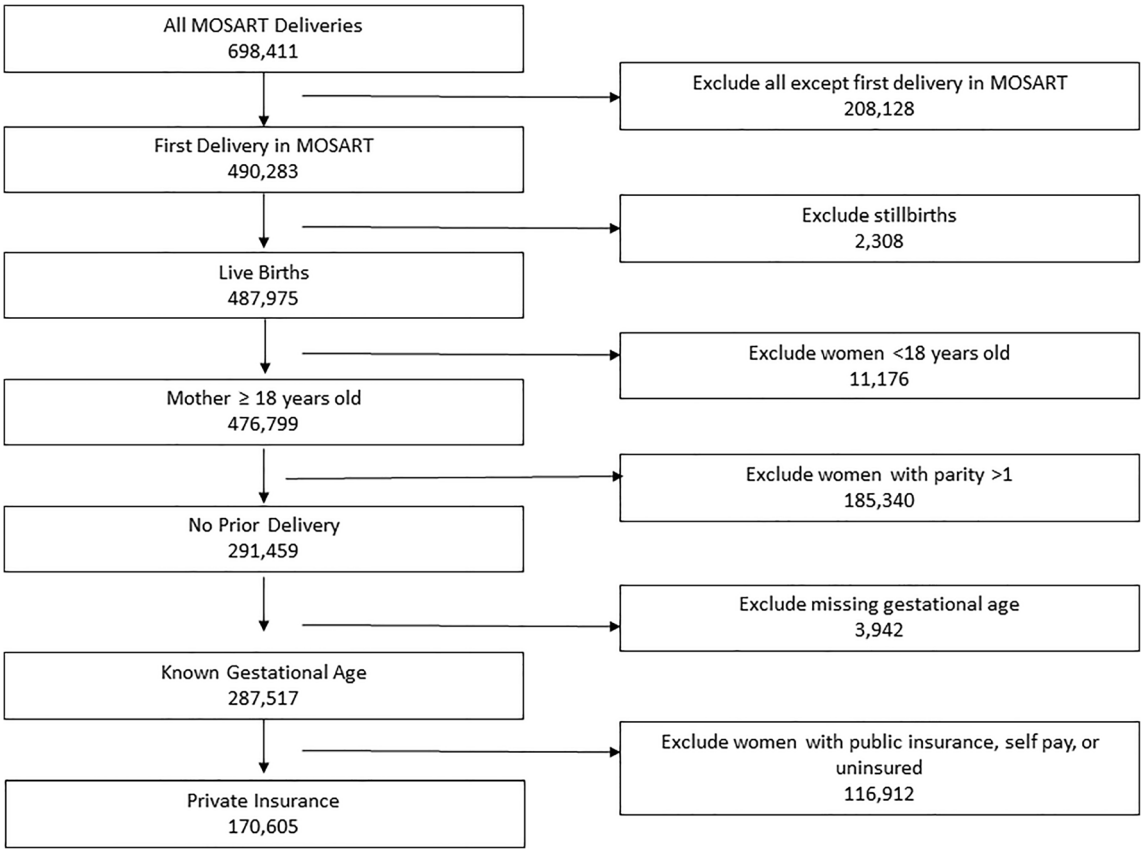

Fig. 1 Inclusion and exclusion criteria

diagnoses (measured by ICD9 codes for these visits). Hospital stays included those within 5 years prior to the pregnancy (pre-pregnancy hospitalizations) or in the time period between 8 and 365 days after the delivery (post-delivery hospitalizations). Each woman would have had one or more diagnoses for hospitalization listed as one of 15 ICD9 codes for hospital discharges and 6 codes for observational stays associated with that hospitalization. The top 30 most prevalent ICD9 codes were obtained from hospital stays in each fertility group. The one principle and up to 14 associated diagnoses were evaluated from the inpatient records, whereas the one principle and up to 5 associated diagnoses were evaluated from the observational stays. These ICD9 codes were then combined into the top 10 most prevalent types and compared across fertility groups. The unit of analysis was a unique woman. Women with the same diagnosis but multiple admissions were counted once during the study period. Pre-pregnancy hospitalization categories included uterine leiomyoma (ICD9 218); diseases of ovary, fallopian tube, pelvic cellular tissue, and peritoneum (614, 620); endometriosis (617); ectopic pregnancy and miscarriage (633, 634); asthma (493); other and unspecified anemias (285); other disorders of the peritoneum (568); diseases of the esophagus (530); overweight, obesity, and other hyperalimentation (278); disorders of fluid electrolyte and acid-base balance (276); general symptoms (780); disorders of menstruation, other abnormal bleeding from the female genital tract, and ovarian dysfunction (626, 256); drug misuse and addiction (292, 303, 304, 305); psychological disorders (296, E95, 301, V62, 300, 311, 309); diabetes and hypertension (250, 401); hypothyroidism (244); and other abdominal and pelvic abnormalities (789, 540, 560, 599).

Post-delivery categories included pregnancy- and delivery-related hospitalizations (648, 674, 646, 666, 669); hypertension (642, 401); non-reproductive tract infection (670, 615, 041, 647, 112, 079); obesity (278); anemia (280); diseases of the reproductive tract (625, 620, 615, 218), diseases of the digestive tract (530, 540, 562, 574, 575, 787, 560, 558), thyroid (244, 245), and breast (675, 611); diabetes (250); cancer (153, 196, V10, 193, 202); psychological (311, 300, 296, 309); drug misuse and addiction (305, 292, 303, 304); and other chronic disease (789, 780, 784, 786, 276, 682, 715, 427, 428, 346, 997).

Outcome measures of prematurity (< 37 weeks gestational age) and low birthweight (LBW, < 2500 g) were obtained from the birth certificates. Gestational age was calculated from clinical estimates modified by the estimated date of last menstrual period from the birth certificates where needed.

Potential confounding variables Demographic covariates (age, race/ethnicity, education, marital status) and birth

outcomes (gestational age, birthweight, plurality) were obtained from the birth certificates. Medical history and delivery characteristics were determined from a combination of birth certificates and hospital discharge data.

Statistical analyses Binary outcomes among the four groups were analyzed using chi-square statistics; ANOVA was used to evaluate differences in continuous outcomes. Logistic regression analysis was applied to quantify crude and adjusted odds ratios (AORs) and 95% confidence intervals (95% CI) for each outcome comparing the ART-treated, MAR, or unassisted subfertile women to fertile women. Multivariable models for pre-pregnancy hospitalizations were adjusted for maternal age (≤ 30, 31–34, 35–37, 38–40, > 40), race (Hispanic, Non-Hispanic (NH)-White, NH-Black, NH-Asian, NH-Other), education (≤ High School, Some College, ≥ College, Unknown Education), and year of delivery (2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013), while post-delivery hospitalizations and birth outcomes were adjusted for these factors plus plurality (singleton, multiple). Rules about use of vital records data from the MDPH and CHIA require that all numbers below 11 in any publication be suppressed in ensure patient confidentiality: numbers lower than 11 are therefore shown in the tables as dashed lines.

Results

The study sample included 287,517 in-state resident deliveries in Massachusetts. Of these, 59.3% had private insurance resulting in a total of 170,605 women in the final study sample. Within this group, there were 10,458 ART-treated, 3005 MAR, 1365 unassisted subfertile, and 155,777 fertile women. Characteristics of the population are shown in Table 1. The ART, MAR, and unassisted subfertile groups were older, more often white and non-Hispanic, more often college educated and married. They also had more chronic hypertension and diabetes. There were a higher proportion of multiples in these groups.

Table 2 presents the AORs and 95% CIs for diagnoses in women with pre-pregnancy hospitalization in the ART, MAR, and unassisted subfertile groups compared with the fertile group. A total of 6.8% of fertile women had any hospitalization with adjusted odds of 1.84, 1.41, and 3.02 in the ART, MAR, and unassisted subfertile groups respectively, using fertile as referent. Women with deliveries conceived with ART had more pre-pregnancy hospitalizations than those conceived with MAR (AOR 1.30, 95% CI 1.13–1.50) (data not in table). The mean number of hospital stays per women ranged from 1.29 to 1.37 and did not differ among the groups (data not in table). The most common reasons for pre-pregnancy hospitalization in the ART, MAR, and unassisted subfertile groups included higher adjusted odds than fertile women of endometriosis (AOR, 95% CI: 10.85, 8.53–13.79 ART; 6.20, 3.99–9.64 MAR; 21.65, 15.03–31.18 unassisted subfertile); diseases of ovary, fallopian tube, pelvis, and peritoneum (AOR, 95% CI: 6.46, 5.51–7.59 ART; 2.05, 1.36–3.09 MAR; 8.03, 5.83–11.07 unassisted subfertile); ectopic pregnancy and miscarriage (AOR, 95% CI: 5.40, 4.47–6.53 ART; 2.51, 1.64–3.83 MAR, 5.03, 3.27–7.72 unassisted subfertile); and disorders of menstruation, ovulation, and ovarian dysfunction (AOR, 95% CI: 4.02, 3.15–5.14 ART, 4.32, 2.05–6.43 MAR, 7.51, 4.96–11.36 unassisted subfertile). Odds of overweight and obesity diagnosed during hospitalization did not differ significantly between the ART and fertile groups but were higher in the MAR group than the fertile group (AOR 2.05, 95% CI 1.41–2.97). There were insufficient numbers in the unassisted subfertile group to be reported.

The birth outcomes for the deliveries in these groups are presented in Table 3. AORs for preterm birth and low birthweight were higher in the three treated or subfertile groups compared with the fertile group.

Hospitalization 8–365 days post-delivery occurred in 2.8% of women in the population. Table 4 shows that the adjusted odds of any post-delivery hospitalization were higher for ART-treated (AOR 1.19, 95% CI 1.05–1.34) and unassisted subfertile (AOR 1.59, 95% CI 1.23–2.07) women and marginally though not significantly increased in MAR-treated (AOR 1.06, 95% CI 0.85–1.31) women. There was a higher rate of cesarean section in the ART (51.8%), MAR (42.6%), and unassisted subfertile (48.3%) women when compared with fertile women (33.4%). However, the increased risks of subsequent hospitalization for ART and untreated subfertile women were greater among those with vaginal delivery. ART-treated women had higher odds of hospitalization due to digestive tract disorders (AOR 1.42, 95% CI 1.15–1.75), thyroid problems (AOR 2.16, 95% CI 1.49–3.13), and other grouped chronic disease conditions (AOR 1.42, 95% CI 1.15–1.74) than fertile women. MAR-treated women also had higher odds than fertile women of thyroid disease (AOR 3.20, 95% CI 1.90–5.40), while unassisted subfertile women had higher odds than fertile of adverse conditions directly related to pregnancy and delivery (AOR 1.85, 95% CI 1.18–2.90). None of the subfertile groups had sufficient numbers of asthma cases or drug addiction for these to be reported. Over 60% of post-delivery hospitalizations for conditions related directly to pregnancy and delivery in all groups occurred within 30 days after delivery.

Discussion

In this study, we found elevated odds of hospitalization both before pregnancy and within 1 year after delivery in women who were subfertile and conceived with or without treatment

Table 1 Characteristics of ART, MAR, unassisted subfertile, and fertile populations

	ALL	Fertile	Unassisted subfertile	MAR	ART
All deliveries (women)	170,605	155,777	1365	3005	10,458
Maternal age (years)					
Mean (SD)	30.60 (4.84)	30.19 (4.67)	35.32 (4.54)	33.53(4.44)	35.26 (4.65)
≤ 30 (%)	49.8	52.9	15.3	26.4	15.5
31–34	30.3	30.2	28.1	34.5	30.7
35–37	11.9	10.9	24.4	19.4	22.5
38–40	5.6	4.5	17.7	13.5	17.3
> 40	2.4	1.5	14.6	6.3	14.0
Race/ethnicity (%)					
Hispanic	4.8	4.9	4.2	3.9	3.8
NH-White	79.3	78.9	79.7	84.6	82.9
NH-Black	4.1	4.2	4.0	2.2	2.9
NH-Asian	10.6	10.7	10.9	8.5	9.4
NH-Other	1.3	1.3	1.2	0.9	1.1
Education (%)					
≤ High School	19.3	20.1	13.8	10.7	11.2
Some College	11.5	11.6	11.4	9.8	10.2
College	69.0	68.1	74.8	79.4	78.4
Unknown	0.2	0.2	–	–	0.2
Marital status (%)					
Married	85.0	84.0	95.9	93.7	95.4
Chronic disease[1] (%)					
Diabetes	1.1	1.0	1.9	1.2	1.9
Hypertension	1.9	1.8	2.9	2.5	3.3
Gestational age (weeks) (%)					
17–27	0.4	0.3	1.1	1.3	1.3
28–33	1.6	1.3	3.0	3.7	4.7
34–36	5.5	5.0	7.9	8.2	12.2
≥ 37	92.5	93.4	88.0	86.8	81.8
Birthweight (grams) (%)					
< 1500	1.0	0.8	2.3	2.7	3.0
1500–2499	5.5	4.9	8.1	9.3	12.8
≥ 2500	93.5	94.3	89.7	88.0	84.2
Plurality (%)					
Singleton	98.2	99.2	96.6	91.2	84.4
Multiple	1.8	0.8	3.4	8.8	15.6
Delivery year (%)					
2004	6.3	6.5	6.0	9.0	3.4
2005	11.7	11.8	11.2	11.5	10.3
2006	11.5	11.6	12.5	10.3	10.4
2007	11.4	11.4	13.2	8.4	10.8
2008	11.4	11.6	11.2	6.9	10.3
2009	10.8	10.9	9.4	7.8	10.9
2010	10.3	10.3	11.3	6.8	12.2
2011	8.5	8.5	7.1	10.5	8.6
2012	9.2	8.9	9.5	14.6	11.3
2013	8.9	8.6	8.6	14.3	11.9

[1] Composite variables based on birth certificate and hospital discharge data

for this subfertility, including both ART and non-ART treatments. All three subfertile groups had a greater prevalence of hospitalizations. Women with deliveries conceived with ART also had more pre-pregnancy hospitalizations than those conceived with MAR. ART is the most advanced treatment for infertility suggesting that ART patients are those with more

Table 2 Reasons for pre-pregnancy hospitalization[1] in ART, MAR, unassisted subfertile, and fertile women[2]

Diagnoses	Fertile			Unassisted subfertile			MAR			ART		
	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI
Any hospital stay	6.81	1.00	Referent	18.61	3.02	2.62–3.47	9.15	1.41	1.24–1.60	12.01	1.84	1.72–1.96
Any hospital stays excluding fertility or pregnancy related[3]	3.21	1.00	Referent	7.18	2.26	1.83–2.79	4.66	1.52	1.28–1.81	5.01	1.56	1.41–1.72
Uterine leiomyoma	0.25	1.00	Referent	4.98	9.09	6.89–12.01	1.06	2.67	1.85–3.87	2.17	4.09	3.42–4.90
Diseases of ovary, fallopian tube, pelvis, peritoneum	0.46	1.00	Referent	3.15	8.03	5.83–11.07	0.80	2.05	1.36–3.09	2.41	6.46	5.51–7.59
Endometriosis	0.12	1.00	Referent	2.86	21.65	15.03–31.18	0.77	6.20	3.99–9.64	1.40	10.85	8.53–13.79
Ectopic pregnancy/miscarriage	0.31	1.00	Referent	1.68	5.03	3.27–7.72	0.77	2.51	1.64–3.83	1.68	5.40	4.47–6.53
Asthma	0.69	1.00	Referent	1.25	1.86	1.14–3.03	1.00	1.57	1.09–2.28	1.00	1.52	1.23–1.88
Other and unspecified anemias	0.30	1.00	Referent	0.95	2.72	1.55–4.78	0.50	1.56	0.93–2.62	0.85	2.49	1.94–3.18
Other disorders of peritoneum	0.11	1.00	Referent	0.88	7.53	4.13–13.71	–	–	–	0.81	7.07	5.32–9.39
Diseases of esophagus	0.44	1.00	Referent	1.10	2.15	1.27–3.62	1.06	2.25	1.57–3.23	0.89	1.72	1.36–2.17
Overweight, obesity, other hyperalimentation	0.46	1.00	Referent	–	–	–	1.00	2.05	1.41–2.97	0.58	1.02	0.78–1.35
Disorders of fluid electrolyte and acid-base balance	0.64	1.00	Referent	0.88	1.65	0.92–2.93	0.67	1.16	0.74–1.82	0.74	1.36	1.07–1.74
General symptoms	0.48	1.00	Referent	1.10	2.25	1.34–3.79	0.67	1.43	0.91–2.24	0.82	1.69	1.34–2.14
Disorders of menstruation/abnormal bleeding and ovarian dysfunction	0.19	1.00	Referent	1.98	7.51	4.96–11.36	0.93	4.32	2.05–6.43	1.03	4.02	3.15–5.14
Drugs abuse/addiction	0.69	1.00	Referent	1.25	2.13	1.30–3.49	0.63	1.14	0.72–1.80	0.56	0.98	0.74–1.28
Psychological	1.10	1.00	Referent	1.68	1.63	1.07–2.49	1.26	1.25	0.90–1.73	1.28	1.24	1.03–1.49
Diabetes or hypertension	0.30	1.00	Referent	0.95	2.23	1.27–3.92	0.63	1.81	1.13–2.88	0.70	1.70	1.31–2.21
Hypothyroidism	0.16	1.00	Referent	1.03	4.07	2.34–7.08	0.63	2.89	1.80–4.65	0.58	2.30	1.70–3.11
Other abdomen/pelvis	1.31	1.00	Referent	2.93	2.68	1.94–3.70	1.33	1.14	0.83–1.57	1.86	1.66	1.42–1.94

[1] Hospitalizations within 5 years prior to pregnancy

[2] Adjusted for maternal age, race, education, and delivery year

[3] Includes asthma, other unspecified anemias, diseases of the esophagus, overweight, obesity, and hyperalimentation, disorders of fluid electrolyte and acid-base imbalance, general symptoms, drugs, psychological, diabetes or hyper tension, hypothyroidism

underlying pathology compared with MAR patients which is consistent with the higher odds of hospitalization. The magnitude of the increased hospitalization in the unassisted subfertile group was approximately 3 times the likelihood in the fertile group and approximately 1.5 times that in the MAR and ART groups. While the unassisted subfertile group had no assistance with conception, the group is partly defined as having a prior hospitalization with an infertility ICD9 code and is thus likely to have more pathology than a random sample of subfertile women. Post-delivery hospitalizations were also somewhat more frequent (AORs 1.06–1.59) in all subfertility groups than those in the fertile group. We found that the ART, MAR, and unassisted subfertile population had a 40–50% increase in premature delivery over that in the fertile group.

The study used a cohort with private insurance since privately insured patients make up the vast majority of the ART and subfertile groups. Inclusion of privately insured patients avoided confusion by any hospitalizations that occur as a result of patients using hospitals rather than a primary care physician, for routine care. This, however, is also likely a group with more access to medical care than their uninsured counterparts or those on public medical assistance.

We have previously reported on hospitalizations in women undergoing ART and compared women with ART deliveries to those whose ART cycle did not result in pregnancy or whose ART pregnancy did not result in delivery [15]. The study found no differences within the ART population as a function of cycle outcome. Prior to that study, estimates of hospitalization in U.S. ART patients came primarily from the national ART database maintained by the Center for Disease Control and Prevention and these studies addressed only those hospitalizations that occurred during the ART cycle itself [17]. The estimate of hospital admissions was approximately 20–30 hospital admissions per 10,000 ART cycles; however, the accuracy of reported hospitalization among the national ART data has never been validated.

The current study evaluated hospitalization before pregnancy, not directly attributable to the ART cycle treatment. We found a higher odds of hospitalization in women with ART, MAR, and unassisted subfertility compared with the

Table 3 Birth outcomes[1]

	Fertile			Unassisted subfertile			MAR			ART		
	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI
Preterm (< 37 weeks)	6.64	1.00	Referent	12.01	1.58	1.33–1.88	13.18	1.40	1.24–1.58	18.16	1.56	1.46–1.68
LBW (< 2500 g)	5.69	1.00	Referent	10.33	1.49	1.23–1.79	12.02	1.42	1.25–1.61	15.80	1.37	1.27–1.48

[1] Adjusted for maternal age, race, education, plurality, and delivery year

fertile group. Observation of the common reasons for this hospitalization suggests that issues related to the underlying subfertility account for much of this increase since it includes such conditions as fibroids, endometriosis, diseases of ovary, fallopian tube, uterus and peritoneum, and ectopic pregnancy. Surgery prior to fertility treatment is not uncommon for treatment of fibroids [18, 19], endometriosis [20], or polycystic ovarian syndrome [21]. Conditions of psychological abnormalities and drug abuse were less often found in the subfertile groups although hospitalization for psychiatric illness has been reported to be common in infertility patients [22, 23]. Hypothyroidism also contributed to elevated hospitalizations in all subfertile groups. Nevertheless, the rate of hospitalization was greater in the ART and subfertile groups even when fertility and pregnancy-associated conditions were removed from consideration (Table 2).

Hospitalizations within 1 year after delivery were also more common in the subfertile groups although the magnitude of this difference in the adjusted model was small and the difference was not statistically significant in the MAR group. A major factor accounting for this hospitalization among the MAR and ART groups was thyroid conditions. Also contributing to hospitalizations were diabetes, hypertension, and other chronic conditions, further suggesting that underlying medical conditions are elevated in these groups and that these contribute to ongoing morbidity after delivery in these women. We have previously reported on the higher rate of cesarean delivery in the ART treated and subfertile compared with the fertile group [24]. The current study also demonstrated more hospitalizations in the ART and subfertile groups following vaginal but not cesarean delivery. Exploration of the reasons for this difference requires further study.

The unassisted subfertile and MAR groups differed in whether or not they had treatment for infertility for the index delivery. They also differed in that the unassisted subfertile group was defined in by having had a prior hospital (including emergency room) diagnosis of infertility or a prior ART cycle that did not result in delivery, suggesting that these women

Table 4 Reasons for post-delivery hospitalizations[1] in ART, MAR, unassisted subfertile, and fertile women[2]

	Fertile			Unassisted subfertile			MAR			ART		
Diagnoses	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI
Any hospital stay	2.8	1.0	Referent	4.5	1.59	1.23–2.07	3.0	1.06	0.85–1.31	3.5	1.19	1.05–1.34
Cesarean section	3.5	1.0	Referent	4.9	1.38	0.96–1.98	4.4	1.27	0.96–1.67	3.8	1.04	0.88–1.23
Vaginal delivery	2.4	1.0	Referent	4.1	1.78	1.22–2.60	1.9	0.80	0.56–1.13	3.2	1.33	1.12–2.60
Pregnancy/delivery	0.7	1.0	Referent	1.5	1.85	1.18–2.90	1.1	1.30	0.91–1.86	1.0	1.07	0.85–1.34
Hypertension	0.2	1.0	Referent	–	–	–	0.4	1.20	0.65–2.20	0.5	1.22	0.87–1.70
Infection (not reproductive)	0.4	1.0	Referent	–	–	–	0.4	1.00	0.56–1.78	0.5	1.18	0.86–1.62
Obesity	0.1	1.0	Referent	–	–	–	–	–	–	0.2	1.10	0.63–1.91
Anemia	0.0	1.0	Referent	–	–	–	–	–	–	0.1	1.90	0.91–4.00
Reproductive tract	0.2	1.0	Referent	–	–	–	0.4	1.70	0.97–3.00	0.4	1.42	0.99–2.03
Digestive tract	0.8	1.0	Referent	1.2	1.52	0.92–2.51	0.9	1.16	0.79–1.70	1.1	1.42	1.15–1.75
Thyroid	0.1	1.0	Referent	–	–	–	0.5	3.20	1.90–5.40	0.4	2.16	1.49–3.13
Breast	0.2	1.0	Referent	–	–	–	–	–	–	0.2	0.71	0.42–1.19
Diabetes	0.0	1.0	Referent	–	–	–	–	–	–	0.1	1.38	0.61–3.09
Cancer	0.1	1.0	Referent	–	–	–	–	–	–	0.2	1.77	0.99–3.17
Psychological	0.3	1.0	Referent	–	–	–	0.5	1.53	0.90–2.57	0.3	0.88	0.60–1.30
Other chronic disease	0.8	1.0	Referent	1.0	1.26	0.74–2.16	1.1	1.41	0.99–2.01	1.2	1.42	1.15–1.74

[1] Hospitalizations within 8–365 days post-delivery

[2] Adjusted for maternal age, race, education, plurality, and delivery year

may have had more severe disease than those in the MAR group. Both groups had a greater number of pre-pregnancy hospitalizations than the fertile group, and the unassisted subfertile group had an increased risk for post-delivery hospitalization. While we recognize that the unassisted subfertile group is not the perfect infertile comparison group, the data strongly suggest that infertility itself is related to morbidity even in the absence of fertility treatment. Given the increase in hospitalizations in both groups, it would be advisable for providers to be aware that these women may deserve special attention during pregnancy and the post-delivery period. This is particularly true of women who did not use fertility treatment to conceive and who may not be immediately recognized as being at greater risk than the general population.

Thyroid conditions were common diagnoses in both pre-pregnancy and post-delivery hospitalizations. Thyroid disease has been known to influence both fertility and pregnancy [25, 26]. The Endocrine Society, the American Thyroid Association, and the American Society for Reproductive Medicine all recommend that thyroid hormone be evaluated in the pre-pregnancy state as well as in infertility patients [27, 28]. Uncontrolled thyroid abnormalities have been linked to early pregnancy loss [25], and thyroid dysfunction can lead to postpartum depression and mental health disorders [26, 27]. Thus, it should not come as a surprise that thyroid abnormalities were a common etiology for hospitalization in our patient cohort.

This study has both strengths and limitations. The strengths lie in the fact that we have been able to evaluate hospital stays linked to birth certificates in a large number of deliveries due to the availability of both the SART CORS and PELL databases. The MOSART database was the first U.S. dataset to provide this information. Limitations include that treatment exposure could only be identified from 2004 due to unavailability of the SART CORS prior to this date. Further, the fertile group could contain some subfertile women not identified by our methods. Nevertheless, the direction of bias is such that the larger numbers in the fertile group would lessen the magnitude of the effect of this inclusion. Further, the unassisted subfertile group could have contained treated individuals whose infertility treatment was not indicated on the checkbox of the birth certificate. We unfortunately do not have a way to assess the magnitude of this problem. Proportions of MAR patients may also have shifted following a change to the birth certificate checkbox questions in 2011 also accompanied by a plateau in ART cycles after this time, making it appear that numbers of MAR deliveries increased in these years. An additional limitation was the possible immigration or out-migration of patients to or from Massachusetts during the study period. This could result in hospitalizations having taken place in another state and thus not being observed in our records. Nevertheless, we have no reason to believe that the percentage of these out-of-state hospitalizations would have differed among our groups. Further, we did not evaluate the time from pre-pregnancy diagnoses to first pregnancy and diagnoses out of hospital could not be ascertained. It is also possible that ART and MAR women have greater access to care and thus greater likelihood of hospitalization compared with untreated subfertile or fertile women. Finally, the population in this study is from a single U.S. state and the data may not be generalizable to other states or countries.

In summary, we found elevated odds of pre-pregnancy and post-delivery hospitalization in both treated and untreated subfertility groups. The indications for many of these hospitalizations included diagnoses related to infertility as well as other medical conditions that can affect fertility such as thyroid disease. The data suggest that underlying disease, separated from infertility treatment, is a major contributor to increased morbidity in subfertile populations.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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