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ASSISTED REPRODUCTION TECHNOLOGIES

Inpatient hospitalizations in women with and without assisted reproductive technology live birth

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Abstract
Purpose The aim of this study is to evaluate frequency of hospitalization before, during, and after assisted reproductive technology (ART) treatment by cycle outcome.
Methods Six thousand and one hundred thirty women residing in Massachusetts undergoing 17,135 cycles of ART reported to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SARTCORS) from 2004 to 2011 were linked to hospital discharges and vital records. Women were grouped according to ART treatment cycle outcome as: no pregnancy (n = 1840), one or more pregnancies but no live birth (n = 968), or one or more singleton live births (n = 3322). Hospital delivery discharges during 1998–2011 were categorized as occurring before, during, or after the ART treatment. The most prevalent ICD-9 codes for non-delivery hospital discharges were compared. Groups were compared using chi square test using SAS 9.3 software.
Results The proportion of any hospitalization was 57.0, 58.3, and 91.3% for women with no pregnancy, no live birth, and ART singleton live birth, respectively; the proportion of non-delivery hospitalizations was 30.4, 31.0, and 28.3%, respectively. The non-ART delivery proportion after ART treatment did not differ by group (33.4, 36.2, and 36.9%, respectively, p = 0.17). Most frequent non-delivery diagnoses (including fibroids, obesity, ectopic pregnancy, depression, and endometriosis) also did not differ by group. A secondary analysis limited to only women with no delivery discharges before the first ART cycle showed similar results.
Conclusions All groups had live birth deliveries during the study period, suggesting an important contribution of non-ART treatment or treatment-independent conception to overall delivery and live births. Hospitalizations not associated with delivery suggested similarity in morbidity for all ART patients regardless of success with ART treatment.

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Introduction

Infertility affects an estimated 12% of women of reproductive age [1] and the use of fertility-enhancing therapies, in particular, assisted reproductive technologies (ART), has risen steadily in the USA over the past 20 years [2, 3]. ART is most often utilized by women who have not conceived by earlier stage therapy for infertility, which suggests that they may represent those with the most severe infertility. However, substantial evidence suggests that treatment-independent pregnancy

occurs concurrently with and subsequently to treatment, with incidence ranging from 5 to 24% [4–10].

It is well-established that ART pregnancies experience an excess of adverse health outcomes for both mothers and children, even in singleton deliveries [11–15]. These outcomes include higher risks for pregnancy hypertension, gestational diabetes, and cesarean delivery, as well as severe maternal morbidity [11, 16–21]. Few studies, though, have evaluated chronic health conditions in women who undergo ART, particularly those who fail to conceive or conceive but do not give birth. It has been suggested that women with primary infertility (those who have never been able to conceive) experience more underlying pathology and increased rates of health problems than those who ultimately have a successful pregnancy [22–24]. Thus, it would be expected that they might have more hospital admissions, which may be an indication of their overall health.

The purpose of this study was to compare frequency of delivery and non-delivery hospitalizations before, during, and after ART treatment in women who had no pregnancy, those who conceived but did not have a live birth, and those who had a live birth. We hypothesized that women who did not conceive with ART would have fewer non-ART deliveries after treatment, higher proportion of non-delivery hospitalizations, and differing etiologies for subsequent hospitalizations than the other two groups.

Materials and methods

Cycles of ART performed in Massachusetts and reported to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SARTCORS) from 2004 to 2011 were linked to inpatient hospital discharges during 1998–2011 using encrypted social security numbers. The research was performed under a memorandum of understanding between SART and all parties, and the study had IRB approvals from the Massachusetts Department of Public Health, Boston University, and the Dartmouth Committee for the Protection of Human Subjects.

Women were classified into three mutually exclusive groups according to cycle outcomes as having had no ART pregnancy in any cycle (no ART pregnancy), one or more ART pregnancies but no live birth in any cycle (no ART live birth), or one or more ART singleton live births (ART live birth). Women for whom there was no social security number recorded in SART CORS and those with one or more multiple pregnancy were excluded. Inpatient hospital discharges, categorized into delivery and non-delivery records, were further identified according to time period: whether they occurred before (prior to the start of the first ART cycle), during (between start of first and start of last ART cycles), or after (after the start of the last ART cycle) the ART treatment. Delivery hospitalizations and live births were identified through ICD-9 codes; non-delivery records were those without a delivery-related ICD-9 code. The most frequent ICD-9 codes for the non-delivery hospital discharges were compared for the three groups. To determine the most frequent, we computed the sum of all non-delivery ICD9 codes and grouped them by category. The groupings found most often included leiomyoma/fibroids (ICD-9 codes 2189, 2181, 2182,2180), morbid obesity (ICD-9 code 278), tubal ectopic pregnancy (ICD-9 codes 63310, 6331, 6338, 63320, 63380), asthma (ICD-9 codes 49392, 49390, 49302, 49322), specific malignancies (ICD-9 codes 193, 1820, 1419, 1541, 1748, 1830, 198.2), depression (ICD-9 codes 29620, 3004, 311), and endometriosis (ICD-9 codes 6171, 6170, 6179). We also assessed ovarian hyperstimulation syndrome (ICD 9 code 2561). A secondary analysis examined the discharge diagnoses in only those women without delivery discharges before the ART treatment and included only ART deliveries for those in the group with live births. Groups were compared using chi-square test and data were analyzed using SAS 9.3 software.

Results

The study population included 6130 women residing in Massachusetts who underwent 17,135 cycles of ART (Table 1), including women with no ART pregnancy (n = 1840), no ART live birth (n = 968), and ART live birth (n = 3322). Women with ART live births were more likely to be white and non-Hispanic and to have started treatment later in the study period, and were less likely to have the diagnoses of diminished ovarian reserve or tubal factor infertility (each p value comparing all three groups <0.001). Women in the no ART pregnancy group had a higher proportion of cancelled cycles and were more likely to have ART treatment prior to 2004 (both p values <0.0001).

The no ART live birth group had the most cycles per woman (3.6 versus 2.3 for the no ART pregnancy group and 2.9 for the ART live birth group, p value comparing all three groups $p < 0.0001$, Table 1).

The percentage of women with non-ART delivery hospitalizations did not differ significantly across groups (all non-ART hospitalizations: 39.1, 41.0, and 40.8% for the no ART pregnancy, no ART live birth, and ART live birth groups, respectively, Table 2). The percentage of non-ART deliveries that occurred after the last ART cycle also did not differ (14.7, 15.9, and 16.3%, respectively). A sensitivity analysis limited to women who had any non-ART delivery showed no differences in the percentages of non-delivery hospitalizations.

The most common diagnoses among all hospitalizations were uterine fibroids (7.4%), morbid obesity (2.7%), tubal or ectopic pregnancy (2.0%), specific malignancies (0.7%), depression (4.3), endometriosis (2.7%), and asthma (4.3%) (data

Table 1 Characteristics of women with and without ART pregnancy and live birth delivery

	No ART pregnancy	No ART live birth	ART live birth
Women *N*	1840	968	3322
Cycles *N*	4160	3435	9540
All ART pregnancies (% of cycles)	0	37.6	54.3
All ART deliveries (% of cycles)	0	0.2	41.4
Cycles per woman (mean ± SD)	2.3 ± 1.6	3.6 ± 2.1	2.9 ± 2.1
ART pregnancies per woman (mean ± SD)	0	1.33 ± 0.65	1.56 ± 0.86
ART deliveries per woman (mean ± SD)	0	0.01 ± 0.08	1.19 ± 0.45
Age at first cycle (mean ± SD)	37.9 ± 4.8	37.7 ± 4.6	35.3 ± 4.5
Race/ethnicity (% of women)			
Hispanic/Latino	2.8	1.8	1.8
White non-Hispanic	37.7	43.7	47.7
Black non-Hispanic	4.8	2.7	2.4
Asian/Pacific Islander non-Hispanic	5.9	5.3	5.7
American Indian/Alaskan/other	0.3	0.1	0.2
Unknown	48.5	46.5	42.2
Diagnosis/per woman at last cycle (% of women)			
Endometriosis	10.0	9.9	9.9
Ovulatory dysfunction	8.9	11.3	14.5
Diminished ovarian reserve	27.6	22.7	17.1
Uterine	5.9	5.7	4.2
Tubal	20.3	17.1	16.1
Other	15.9	17.5	14.3
Unexplained	14.2	15.3	16.3
Male factor	31.5	35.2	38.7
Year of cycle start (% of cycles)			
2004–2005	44.5	36.5	31.4
2006–2007	29.8	28.9	30.7
2008–2009	19.4	24.2	25.8
2010–2011	6.4	10.4	12.1
Fresh autologous cycles (% of cycles)	92.9	91.9	90.3
Canceled cycles (% of cycles)	15.4	7.1	6.0
Prior cycles reported to SART at first cycle (% of women)			
Prior fresh ART			
0	65.0	68.4	74.4
1	10.9	12.1	11.2
2+	24.1	19.5	14.4
Prior frozen ART			
0	93.5	94.0	94.9
1	4.8	3.9	3.7
2+	1.7	2.1	1.4
Prior gonadotropin			
0	63.3	58.8	63.5
1	4.7	7.9	5.7
2+	32.0	31.4	30.8

not shown in tables). The only difference between the three ART treatment outcome groups was for asthma, which was slightly more prevalent among women in the group with live birth (no ART pregnancy: 3.8%; no ART live birth 2.5%; ART live birth; 5.1%: p value comparing all three groups =0.0006). Less common was the diagnosis of ovarian hyperstimulation syndrome (0.6% across all groups) which did not differ among groups.

Table 2 Hospitalizations of women with and without ART pregnancy and live birth delivery

	No ART pregnancy	No ART live birth	ART live birth	*p* value*
Women *N*	1840	968	3322	
Women with any hospitalization[a] (%)	57.0	58.3	91.3	<0.0001
Women with delivery hospitalizations (%)				
All	39.2	41.7	90.3	<.0001
Before cycles	29.2	31.1	26.8	0.02
During cycles	0.6	2.1	29.8	<.0001
After cycles	14.8	16.1	74.7	<.0001
Women with non-ART delivery hospitalizations (%)				
All	39.1	41.0	40.8	0.45
Before cycles	29.2	31.1	26.8	0.02
During cycles	0.6	1.1	1.8	0.0009
After cycles	14.7	15.9	16.3	0.34
Women with non-delivery hospitalizations (%)				
All	30.4	31.0	28.3	0.12
Before cycles	19.2	18.8	14.4	<.0001
During cycles	2.2	5.8	5.2	<.0001
After cycles	14.1	13.0	13.2	0.61
All deliveries (live + stillbirths) (*N*)	983	575	4949	
Deliveries before ART (%)	65.4	62.6	20.0	<0.0001
Deliveries during ART (%)	1.1	3.7	21.4	<0.0001
Deliveries after ART (%)	33.4	35.8	46.5	<0.0001
Non-ART deliveries (live + stillbirths) (*N*)	983	563	1662	
Before ART (%)	65.5	61.8	59.3	0.0067
During ART (%)	1.1	2.0	3.7	<0.0001
After ART (%)	33.4	36.2	36.9	0.17

**p* value, test for heterogeneity, among the three ART treatment outcome groups calculated by the chi-square test

[a] Linkage to a hospital discharge

We also reviewed the hospitalization diagnoses restricting the population to women without deliveries (ART or non-ART) prior to ART treatment and including only deliveries resulting from ART in the ART live birth group (no ART pregnancy, $n = 1119$; no ART live birth, $n = 569$; ART live birth, $n = 2431$). Of this group, 29.3% of the no ART pregnancy group had non-delivery hospitalizations versus 28.3% of the no ART live birth group and 27.1% of with the ART live birth group (p value =0.38). Most frequent diagnoses for hospitalization did not differ statistically significantly among the groups, and included: uterine fibroids (8.0%), morbid obesity (2.7%), tubal or ectopic pregnancy (2.2%), specific malignancies (0.7%), depression (4.0%), endometriosis (3.0%), and asthma (3.6%). The only difference among groups was again in the proportion of asthma (no ART pregnancy, 2.5%; no ART live birth; 1.8%; ART live birth 4.6%: p value comparing all three groups =0.0004). In summary, there was little difference in hospitalization diagnoses among the three ART treatment outcome groups.

Discussion

This is the only study, to our knowledge, to analyze all hospital discharges among women who have received ART treatment over an extended period of time. We found that across this 13-year time period in Massachusetts, a substantial proportion of these women had both non-ART deliveries and hospitalization for reasons other than delivery. Contrary to our expectations, we found that all three groups had non-ART deliveries during the study period, a substantial proportion (over 33%) were after the ART treatment had ended. In addition, approximately 29% of women from all groups had non-delivery hospitalizations, most often for indications of fibroids, asthma, obesity, and depression.

This is the first linkage study in the USA to quantify the frequency of hospitalizations in an ART-treated cohort of women for all outcomes of treatment. Previous studies in the USA using SART data [17–19, 25] and from the CDC [21, 26–28] have evaluated deliveries and birth outcomes in ART patients who delivered a live or still birth. Because previous

linkage studies to vital records have used the birth certificate to link data, it was not possible to identify women who had ART but who did not have a birth using ART. Even if these women had a delivery prior to our review, there had been no way of identifying if they had ever been ART patients. Therefore, there has been very little information to date about the health issues for women who received ART treatment but did not deliver using ART. Our study provides reassuring data that hospitalizations for women without an ART delivery were neither significantly more frequent nor for different etiologies than those for women whose ART treatment had been successful. The study population was restricted to singleton live births, excluding twin pregnancies because they are well-known to increase maternal morbidity, and our study aim was specifically focused on comparing and contrasting those women who did not deliver a live birth.

Our study suggests that a very small percentage of ART-treated women (<2%) had non-ART deliveries during ART treatment, and that between 13.0 and 14.1% had non-ART deliveries following treatment. Several previous studies have suggested that treatment-independent pregnancy is common among patients seeking infertility treatment. Olivius [4] found that of 167 ART patients who completed questionnaires in their study, 19% discontinued treatment due to treatment-independent pregnancy and Van Dongen [5], found that of 674 couples, approximately 5% on ART waiting lists achieved pregnancy independent of treatment while on the list. Schumizu [6] suggested the proportion of treatment-independent pregnancy after fertility treatment to be 18% and to depend on age, while Troude [8] put the percentage of treatment-independent pregnancies at between 17 and 24%.

Non-delivery hospitalization in women undergoing ART could be related to the ART cycle itself (for example hospitalization for uterine fibroids or endometriosis), or could be a result of dealing with infertility (for example hospitalization for depression). Prior estimates of hospitalization in ART patients have included only those hospitalizations during the ART cycle and reported to the national databases. The accuracy of this reporting has never been validated, but national ART data estimate approximately 20–30 hospital admissions per 10,000 ART cycles [29]. There is, however, the potential for hospitalization not directly attributable to the ART cycle treatment. Surgery in infertility patients, potentially resulting in hospital discharges, has been studied in relation to specific conditions such as myomectomy for treatment of fibroids [30, 31] or laparoscopy for treatment of endometriosis [32]. Polycystic ovarian syndrome has also been treated with surgery [33]. As expected, our study showed fibroids and endometriosis to be among the more common reasons for hospitalization in this group of patients. Depression was commonly included as a reason for hospitalization in our population. Hospitalization for psychiatric illness has previously been shown to be common in infertility patients [34, 35]. Morbid obesity was also a frequent diagnosis for hospitalization and could include hospitalization for bariatric surgery prior to ART treatment.

Our study allowed us access only to linked records for the ART population. However, the Massachusetts Center for Health Information and Analysis (CHIA) agreed to provide us with information on hospitalizations in a general population of 30–45-year-old women (personal communication). The numbers we obtained were calculated from the same ICD9 codes used for our population for years 1998 through 2007. They were specific to women who had been hospitalized in the inpatient hospitals for any reason and therefore not reflective of the general population as a whole. These numbers showed the following proportions among the women hospitalized for 2007: fibroids 5.1%, morbid obesity 0.3%, specific malignancies 0.9%, depression 10.7% endometriosis 2.1%, and asthma 8.9%. Roughly speaking, hospitalizations for fibroids, obesity, and endometriosis appear to be more common in the ART population while those for asthma and depression were less common for women receiving ART.

This study had several limitations. One issue was that ART treatment exposure could only be identified from 2004, since SARTCORS is left-censored at this year and therefore we were not able to identify whether deliveries before 2004 were ART or non-ART. In contrast to our prior studies linking SARTCORS to vital records in Massachusetts [36], hospital discharges for patients who did not deliver could not be linked to ART cycles by names, dates, or any identifiers other than social security numbers, as hospitalizations not linked to birth certificates can only be accessed by social security numbers. This resulted in limiting our linkage to the ART cycles for which social security numbers were recorded in SARTCORS (approximately 30% of all ART cycles in the study time period). An additional limitation was the potential of out-migration from Massachusetts during the study period, such that these women could have delivered or been hospitalized in another state. Nevertheless, there is no reason to believe that the percentage of these out of state treatments differed among our groups. Finally, it is not possible to differentiate whether the non-ART pregnancies were either treatment-independent or due to other non-ART fertility treatment. By contrast, the strengths of the study are in the large numbers of ART deliveries studied and the use of the hospital record system linkage available for individual women in Massachusetts which links all of her hospital discharges dating back to 1998.

This study showed that women treated with ART do have non-ART pregnancies either by other non-ART fertility treatments or independent of treatment, regardless of whether their ART treatment ended with a singleton live birth. Further, these analyses show that all women treated with ART were likely to have similar frequencies of non-delivery hospitalizations and to be hospitalized for similar reasons, regardless of the outcome of their ART treatment. In summary, for the groups as

defined, there was no difference in the overall non-ART delivery rates, number of non-delivery hospitalizations, or indications for hospital admissions.

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Compliance with ethical standards

Conflict of interest BL is a research consultant to the Society for Assisted Reproductive Technology (SART). JES, DG, SM, CCC have no conflicts to declare.

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