Published in final edited form as:

Fertil Steril. 2022 March ; 117(3): 593–602. doi:10.1016/j.fertnstert.2021.11.012.

Hospitalizations up to 8 years following delivery in ART-treated and subfertile women

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Abstract

Objective: To investigate hospitalizations up to 8 years after livebirth among women who utilized ART or who were subfertile, compared to women who conceived naturally.

Design: Retrospective cohort

Setting: Massachusetts deliveries among privately insured women ≥18 years old between 2004–2017 from state vital records were linked to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS), and hospital observational/inpatient stays.

Patients: We compared patients with ART, medically assisted reproduction, and unassisted subfertile delivery to fertile delivery.

Intervention: NA

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Main Outcome Measured: Post-delivery hospitalization information was derived from ICD codes for discharges and were combined by type. The relative risks (RR) and 95% confidence intervals (CI) of hospitalization for up to the first 8 years post-delivery were modeled.

Results: Among 492,515 deliveries, 5.6% used ART, 1.6% used medically assisted reproduction, and 1.8% were unassisted subfertile. Compared to fertile deliveries, deliveries that utilized ART, medically assisted reproduction or were unassisted subfertile were more likely to have hospital utilization (inpatient or observational stay) for any reason for up to 8 years of follow-up (unassisted subfertile aRR:1.18 (1.12–1.25); medically assisted reproduction:1.20 (1.13–1.27); ART aRR:1.29 (1.25–1.34)). ART deliveries had an increased risk of hospitalization for conditions of the cardiovascular system(aRR: 1.31 (1.20–1.41)), overweight/obesity(aRR:1.30 (1.17–1.44)), diabetes(aRR:1.25 (1.05–1.49)), reproductive tract(aRR:1.62 (1.47–1.79)), digestive tract(aRR:1.39 (1.30–1.49), thyroid(aRR:2.02 (1.80–2.26)), respiratory system(aRR: 1.13 (1.03–1.24)), and cancer(aRR:1.40 (1.18–1.65)) up to 8 years after delivery. Deliveries with medically assisted reproduction and subfertility had similar patterns of hospitalization as ART deliveries.

Conclusion: Women who conceived through fertility treatment or who experienced subfertility were at an increased risk for subsequent hospitalization resulting from a variety of chronic and acute conditions.

Funding: NIH R01HD067270

Capsule:

Women who used fertility treatment or experienced subfertility were at increased risk for subsequent hospitalization up to 8 years after delivery resulting from a variety of chronic and acute conditions.

Keywords

ART; Infertility; Subfertility; cancer; cardiovascular disease; diabetes; chronic diseases

Introduction:

Infertility is estimated to affect over 1.5 million couples each year in the United States (1, 2) and utilization of fertility treatments including Assisted Reproductive Technology (ART) is common (3). Prior research has shown that deliveries to women who utilized fertility treatment and to women with underlying infertility are at greater risk of adverse pregnancy outcomes (4–6). There is increasing interest in understanding women's long-term health outcomes following ART delivery and infertility, given the exogenous hormonal exposures associated with fertility treatment and physiology associated with infertility itself (7).

It can be challenging to study the relationship between infertility, fertility treatment, and maternal health outcomes because of the need for detailed information on both the exposures: fertility treatment and infertility history, and the outcomes of interest: the incident diseases under study. Moreover, given the timescale of chronic disease development, a sufficient duration of follow-up is needed between fertility treatment utilization/subfertility and incident chronic disease diagnosis. Indeed, prior research from

our team found a similar level of non-delivery hospitalizations for women who did and did not utilize ART, however follow-up was limited to within one year after delivery (8). Prior research from other investigators has suggested that women with infertility and who utilized infertility treatment may have a greater risk of cardiovascular disease (9), type II diabetes (10), and breast cancer (11), however these findings have not been replicated across all studies (12). An additional complexity in this research area is that characteristics related to parity, which are inherently linked to infertility, are known to be associated with risk of certain chronic diseases (13). For example, later age at first birth and nulliparity are associated with greater risk of ovarian cancer and breast cancer (14, 15). Understanding the intersection between fertility treatment utilization as well as underlying infertility and risk of adverse health outcomes among the mothers may have important implications for patient counseling, as well as possibly disease screening recommendations. Therefore, the objective of this study was to investigate the risk of non-delivery hospitalizations during eight years of follow-up comparing ART-deliveries, deliveries conceived using non-ART medically assisted reproduction, and deliveries to women with indicators of subfertility but no assistance for conception compared to women with fertile deliveries. We hypothesized that parous women who utilized fertility treatment or who were subfertile would have greater risk of non-delivery hospitalization during follow-up for specific conditions compared to fertile women.

Study Design:

Cycles of ART reported in the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) that were performed in the state of Massachusetts to privately-insured women ≥ 18 years old between 2004 and 2017 were linked to delivery records (birth certificates and fetal death records) and delivery hospital discharge records linked in the Pregnancy to Early Life Longitudinal (PELL) data system to create the Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) database. A detailed description of the linkage methodology and development of MOSART has been described previously (16). Briefly, in-state resident deliveries between July 1, 2004, and December 31, 2017, were linked to SART CORS cycles using mother's first and last name, father's last name, mother's date of birth, and date of delivery. When in doubt, we further validated baby's sex, birthweight, and mother's zip code to adjudicate potential links. For 2004–2017, the linkage rates were 91.5% overall and 94.9% for deliveries in which both ART cycle patient zip code and treatment clinic were located in MA. Deliveries were excluded if they were to mothers <18 years of age (n=13,716), were paid by public insurance, self-pay, or uninsured (n=426,793), or were on or after July 1, 2017 (n=17,461) leaving 492,515 deliveries to women ≥18 years in Massachusetts between July 1, 2004 until June 30, 2017. A Memorandum of Understanding was executed among SART, the Principal Investigators on the grant that funds the research, and the entities that participate in the PELL project. The study had IRB approvals from the Massachusetts Department of Public Health, Boston University, and Dartmouth-Hitchcock Health.

SART CORS data are collected by SART to provide national-level data on ART under the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102–493) and to report these data to the Centers for Disease Control and Prevention (CDC). SART CORS

data are annually validated with some clinics having on-site visits for chart review based on an algorithm for clinic selection. During each visit, data reported by the clinic are compared with information recorded in patients' charts. In 2017, the 10 data fields selected for validation were found to have discrepancy rates of ≤5% (17).

Deliveries in our study were classified into four mutually exclusive groups based on fertility treatment history and utilization for the index delivery which have been described previously (18). Women could contribute multiple deliveries to the analysis and each delivery was classified individually. Deliveries were defined as having used ART, if the index delivery was linked with SART CORS. Deliveries were considered "non-ART medically assisted reproduction" (MAR) if the birth certificate for the index delivery indicated having used fertility treatment but the delivery was not linked to SART CORS. Deliveries were categorized as "unassisted subfertile" (USF) if the woman had a prior ICD code for infertility, prior ART, or prior other fertility treatment. Lastly, a delivery was classified as "fertile" if the woman did not fall into any of the above categories. Women could contribute person-time following each delivery until the minimum of the following events: follow-up ceased, eight years of follow-up, or a new delivery was reported.

Information on live birth was based on MA birth certificate data. Hospitalizations were identified via ICD-9 and ICD-10 codes, as has been done by our group previously (8). For up to eight years of follow-up, the non-delivery discharge codes that were most-frequently reported 6 months following index delivery in our data were categorized into groups based on organ system influenced (Supplemental Table 1). Categories for inpatient or observational hospitalizations included: Cardiovascular including hypertension, Infection, Overweight/Obesity, Anemia, Reproductive tract, Digestive tract, Thyroid, Respiratory including asthma, Breast (excluding breast cancer), Diabetes, Cancer, Psychiatric, Substance use disorder, and Other.

Analyses were conducted on the delivery-level, and a woman could contribute multiple deliveries to the analysis. Generalized estimating equations with a log link, Poisson distribution, and exchangeable correlation structure were used to take into account multiple deliveries per woman and estimate the relative risk of hospitalization overall and for specific conditions with the 95% confidence interval. To take into account varying lengths of follow-up, person-months of follow-up was used as the offset term in Poisson models. We modeled follow-up durations of 1 year, 3 years, 5 years, and 8 years. Not all participants were followed for 8 years, therefore, women contributed data to the follow-up duration which they fulfilled. Models were *a priori* adjusted for maternal age, parity, year of delivery, plurality, chronic hypertension prior to pregnancy, and chronic diabetes prior to pregnancy.

Results:

In total, there were 492,515 deliveries (506,346 infants) to privately-insured women between July 1, 2004 and December 31, 2017 in the state of Massachusetts; the majority of deliveries were to fertile women (91.0%) with 27,802 (5.6%) deliveries utilizing ART, 7,811 (1.6%) deliveries that utilized MAR, and 8,675 (1.8%) deliveries to unassisted subfertile women (Table 1). Women were followed for up to 8 years with a median follow-up time of 50

months. Compared to fertile deliveries, deliveries to women with subfertility or who utilized fertility treatment, the mothers were older and more likely to be non-Hispanic white, college graduates, married, and have preexisting hypertension and diabetes. Deliveries to women with subfertility or who utilized fertility treatment were also more likely to be twins or higher order multiples and to have lower birth weight compared to fertile deliveries.

Compared to fertile women at up to 8 years post follow up, women whose delivery utilized ART (aRR:1.29, 95% CI: 1.25–1.34), or MAR (aRR: 1.20, (1.13–1.27), and who were subfertile (aRR: 1.18, 95% CI: 1.12–1.25) were at greater risk of hospitalization for any condition. However, when investigating hospitalization for specific conditions and time since delivery, some variability was observed. Compared to deliveries to fertile women, deliveries to women who used ART were more likely to have inpatient or observational hospitalizations for a variety of conditions at up to 8 years of follow-up including conditions of the cardiovascular system (aRR:1.31 95% CI: 1.20–1.41), infection (aRR: 1.36 95% CI: 1.18–1.56), overweight/obesity (aRR:1.30 95% CI: 1.17–1.44), anemia (RR:1.24 95% CI: 1.09–1.41), reproductive tract (aRR:1.62 95% CI: 1.47–1.79), digestive tract (aRR:1.39 95% CI:1.30–1.49), thyroid (aRR:2.02 95% CI:1.80–2.26), respiratory including asthma (aRR:1.13 95% CI:1.03–1.24), diseases of the breast (aRR:1.39 95% CI:1.14–1.69), diabetes (aRR:1.25 95% CI:1.05–1.49), and cancer (aRR: 1.40 95% CI: 1.18–1.65) (Table 2).

Compared to deliveries to fertile women, deliveries to women with a history of MAR and subfertility had similar patterns of hospitalization as ART deliveries and were found to be at an increased risk of infection, overweight/obesity, conditions of the reproductive tract, conditions of the digestive tract, conditions of the thyroid, and diabetes (Table 2). Across all time points, a greater risk of hospitalization for conditions of the cardiovascular system was consistently observed among ART and MAR-treated women. Whereas a greater risk of psychiatric conditions was only observed among ART and subfertile women. A greater risk of cancer and anemia across all time points was only observed among women who had utilized ART for an index pregnancy compared to fertile women. Risk of hospitalization was greatest including up to 8 years of follow-up for diabetes, respiratory conditions, and psychiatric conditions, but there was no statistically significant risk for these conditions after one year of follow-up.

Discussion:

Overall, deliveries to women who utilized fertility treatment to conceive or who had experienced subfertility prior to conception were at greater risk of inpatient and observational hospitalization for any reason after up to eight years of follow-up compared to those with fertile deliveries. Specifically, deliveries to women who utilized ART to conceive or who had experienced subfertility prior to conception were at risk for a greater number of inpatient or observational hospitalizations for cardiometabolic conditions (i.e., cardiovascular system, diabetes), cancer and non-malignant pre-cancerous conditions, conditions of the thyroid, digestive tract, respiratory tract, and reproductive tract, and psychiatric conditions. These observed associations may be due to causal as well as non-causal mechanisms. Heterogeneity was observed across fertility treatment utilization and time contributing to follow-up.

We observed that women who conceived via ART, other fertility treatment (MAR), or who were subfertile but did not receive fertility treatment to conceive, were at greater risk of inpatient or observational hospitalization for cardiometabolic conditions including, cardiovascular disease, hypertension, and diabetes, or overweight/obesity after 8 years. Among women who utilized ART, the risk of hospitalization for cardiovascular conditions, including hypertension, was modest or not statistically significant after one year of follow-up (RR:1.14) however the relative risk of hospitalization for cardiovascular conditions increased with increasing duration of follow-up compared to fertile women (RR 8 years: 1.31). These findings are supported by prior research on infertility and risk of cardiovascular conditions (9, 10, 19, 20). Within the Swedish Medical Birth Register, women with subfertility ≥5 years were found to have 20% greater risk of cardiovascular disease compared to women without a history of infertility (median follow-up=12 years) (9). However, these authors were unable to account for fertility treatment in their analysis. The Framingham Heart Study also supports this overall trend and reported that pre-menopausal women with a history of infertility (n=282) may have greater risk of type 2 diabetes (odds ratio:1.96 (95% CI:0.86–4.49)), but they had limited statistical power and therefore their findings were not statistically significant (10).

There are several potential mechanisms to support the observed associations of an increased risk of cardiometabolic diseases among women with infertility. Certain infertility diagnoses (i.e., polycystic ovary syndrome, endometriosis) and associated phenotypes, such as menstrual irregularity and excess adiposity, have been found to be associated with an adverse cardiometabolic profile (21–25). However, we were unable to separate those specific gynecologic conditions in this analysis. While information on body mass index (BMI) was not available for most years in our data sources, all analyses were adjusted for prevalent maternal hypertension and diabetes at delivery. Moreover, our research group and others have reported pregnancy-induced hypertension, preeclampsia, and gestational diabetes is more common in ART-treated deliveries (26). These conditions of pregnancy are known to increase risk of cardiovascular disease as well as diabetes later in life (27, 28), and therefore may mediate the association between fertility treatment and risk of adverse cardiometabolic health (29). However, we observed that risk of hospitalization for cardiometabolic conditions was greater among both deliveries to women who utilized fertility treatment and deliveries to women with subfertility.

We observed that deliveries to women who utilized ART and unassisted subfertile women were at greater risk of inpatient or observational hospitalization for cancer compared to fertile women. This risk was greatest after 1 year of follow-up (ART RR:1.66; Unassisted Subfertile RR:1.69) and attenuated over the remaining follow up periods (ART RR 8 years:1.40; Unassisted Subfertile RR 8 years:1.18). Research into the relationship between infertility, fertility treatment, and risk of cancer has been mixed (12, 15, 30–39). Research from Norway registry data observed a 30% higher risk of breast cancer among women treated with ART (11). However, a recent study of national data from the SART CORS found that after 4.9 years of follow-up, women who utilized IVF treatments had a lower risk of breast cancer (Standardized Incidence Rate:0.83 (95% CI:0.75–0.91))(12). A meta-analysis on ovarian cancer observed an elevated risk of ovarian cancer among women who underwent ART compared to the general population controls, but not when compared to

other infertile women, suggesting that both treatment and underlying fertility may influence risk (40). Moreover, later age at first pregnancy and number of pregnancies are known to be associated with some types of breast cancer (14, 41, 42) and ovarian cancer (15) and age at first pregnancy and number of pregnancies are associated with infertility and fertility treatment utilization. Additionally, pregnancy contributes to greater acute risk of breast cancer and this elevated risk of breast cancer following pregnancy has been suggested to peak approximately 5 years after delivery (43). Unfortunately, our analyses could not differentiate inpatient or observational hospitalization by cancer type. Women who experience subfertility or who utilize fertility treatment may also be better connected with the medical system compared to the fertile women and therefore may be more likely to be regularly screened and subsequently diagnosed with in-situ cancer. Indeed, we observed that women with subfertility or who utilized fertility treatment for delivery were at a greater risk of diseases of breast compared to fertile women. Diseases of the breast included infections as well as other benign disorders of the breast which may be more likely to be identified through regular screening and connection with the medical system.

Deliveries to women who utilized fertility treatment or with subfertility were more likely to have inpatient or observational hospitalization for conditions of the thyroid and reproductive tract. These conditions included hypothyroidism, thyroiditis, uterine leiomyoma, amenorrhea, and pain associated with the female reproductive tract. There has been limited prior research on these conditions as long-term health outcomes associated with infertility; these associations may be influenced by reverse causation given that the temporality of these conditions in relation to infertility/fertility treatment is not known due to the structure of the study. Therefore, it is possible that less severe phenotypes of these conditions were present prior to conception and led to women experiencing subfertility and/or utilizing fertility treatment. Indeed, women who utilized fertility treatment or who experienced subfertility were at a similar magnitude of risk for conditions of the thyroid and reproductive tract starting after 1 year of follow-up and continuing through 8 years of follow-up, suggesting that risk for these conditions does not increase with longer duration of follow-up. Additionally, diagnosis of these conditions may be influence by connection with medical system and education level which may be higher among women who accessed care and who received a diagnosis of infertility (44).

We observed that women with a history subfertility or who utilized fertility treatments were at a modest risk of inpatient or observational hospitalization for psychiatric conditions and conditions of the respiratory and digestive tracts. In our study, common psychiatric conditions included depressive disorders, anxiety disorders, and episodic mood disorders. Respiratory conditions included asthma, and digestive disorders included appendicitis, disease of the esophagus and gallbladder, diverticulitis, obstructions, and other non-specified digestive disorders. There has been limited prior research on these associations and they could be attributed to a variety of causal and non-causal mechanisms. Women who experience infertility may have other underlying risk-factors and/or health conditions that could influence both their fertility status and their risk of other chronic conditions later in life. All models were adjusted for prevalent maternal hypertension and diabetes, however there may be other unmeasured conditions which influence infertility and disease risk. Additionally, women who have access to fertility treatment or who receive a diagnosis of

infertility may have better access to the medical system (44) and therefore may be more likely to receive a diagnosis for other health conditions later in life; thus, these findings may be an artifact of detection bias. Indeed, there have been no clear data supporting strong mechanisms of association for these conditions, therefore future research should focus on these associations and on disentangling possible pathways of associations.

Despite this study's large sample size, longitudinal follow-up, and breadth of subfertility diagnoses and chronic conditions assessed, there are also important limitations that should be considered. In this analysis, we are not able to infer whether the observed associations were causal. The analysis was unable to determine whether the indication for inpatient or observational hospitalization was from a condition that developed prior to subfertility or following delivery. Therefore, there may be chronic conditions or conditions that are hard to diagnose that influenced fertility status that are prevalent after delivery and are captured in this study design. We lacked information on specific infertility diagnoses in the non-ART groups, such as endometriosis and polycystic ovary syndrome, which have been associated with long-term health outcomes in prior research (45–48), and may be contributing to observed associations. Our analysis focused on the most common conditions associated with inpatient or observational hospitalization and therefore, may not be representative of the entire spectrum of diseases, especially those conditions that do not require hospitalization. Additionally, while we were able to follow some participants for up to eight years (Median follow-up: 50 months), that duration of time may be an insufficient time window for development of some conditions, especially those that develop or that are more prevalent later in life such as cardiovascular disease. Our analyses were restricted to deliveries to women in Massachusetts with private insurance and therefore, we may have excluded women with the most severe infertility phenotypes who were unable to conceive or who lacked access to fertility care. This population does reduce confounding by parity as all women included in our analysis have experienced a delivery. Moreover, Massachusetts has state-mandated fertility treatment coverage by private insurance. Given that information on MAR was defined by birth certificate data, there may be misclassification of this information (49), however we would expect any misclassification of infertility history to be non-differential with respect to our outcomes of interest. Our analyses adjusted for maternal age, parity, year of delivery, plurality, chronic hypertension, and chronic diabetes. We were unable to adjust for BMI which may be a confounder of the association as it is positively associated with both infertility and hospitalization (50, 51). Given the directionality of the confounding, we would expect that residual confounding by BMI would overestimate the association between infertility and hospitalization, however we were able to adjust for cardiometabolic conditions associated with BMI that may also serve as potential confounders (hypertension and diabetes). While our analyses were restricted to women who utilized private insurance for the index delivery, we could not account for other socioeconomic factors which may act as confounders of our association. We would expect that uncontrolled confounding of socioeconomic factors may lead to an underestimate of associations. Women who give birth to twins and higher order multiples have been shown to be at increased risk of adverse pregnancy outcomes (52), possibly leading to an elevated risk of long-term health outcomes, including cardiovascular disease (53). While we adjusted for plurality in multivariable adjusted regression models, multiple births may also mediate (29)

or modify (51) the associations of interest. However, in sensitivity analyses we observed no statistically significant effect modification by plurality. Future research with larger samples of multiple gestations should try to disentangle these complex associations.

In summary, Massachusetts women who utilized fertility treatment, including ART, to conceive and women who delivered with a history of subfertility were observed to be at greater risk of any inpatient or observational hospitalization for up to eight years of follow-up compared to fertile women. Specifically, these women were more likely to have inpatient or observational hospitalizations for cardiometabolic conditions (i.e., cardiovascular system, diabetes), cancer and non-malignant conditions of the breast, conditions of the thyroid, digestive tract, respiratory tract, and reproductive tract, and psychiatric conditions. Future research should extend longitudinal follow-up and investigate incident disease diagnoses, possible pathways of association, and informative heterogeneity in chronic condition type and severity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

SART wishes to thank all of its members for providing clinical information to the SART CORS database for use by patients and researchers. Without the efforts of our members, this research would not have been possible. Funding was obtained from NIH: R01HD67270.

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Table 1.

Demographics for in-state live deliveries to Massachusetts women aged ≥ 18 years privately insured at delivery, 7/1/2004–6/30/2017

	ALL		Fertile		Unassisted Subfertile		Non-ART Medically Assisted Reproduction		ART	
	n	%	n	%	n	%	n	%	n	%
Total deliveries	492,515	100.0	448,227	91.01	8,675	1.8	7,811	1.6	27,802	5.6
Maternal age at delivery										
Mean (SD)	32.13 (4.72)		31.81 (4.62)		34.01 (4.38)		35.40 (3.87)		35.83 (4.50)	
Maternal race/ethnicity										
Hispanic	26,173	5.31	24,457	5.46	328	3.78	280	3.58	1,108	3.99
Non-Hispanic White	389,260	79.04	352,391	78.62	7,421	85.54	6,505	83.28	22,943	82.52
Non-Hispanic Black	21,461	4.36	20,221	4.51	232	2.67	178	2.28	830	2.99
Non-Hispanic Asian	48,638	9.88	44,770	9.99	575	6.63	764	9.78	2,529	9.10
Other	6,983	1.42	6,388	1.43	119	1.37	84	1.08	392	1.41
Maternal highest level of education										
< HS/HS graduate	84,592	17.18	80,453	17.95	948	10.93	641	8.21	2,550	9.17
Some college	67,269	13.66	62,269	13.89	1,050	12.10	886	11.34	3,064	11.02
College graduate	337,568	68.54	302,775	67.55	6,608	76.17	6,246	79.96	21,939	78.91
Missing	3,086	0.63	2,730	0.61	69	0.80	38	0.49	249	0.90
Marital Status										
Married	438,037	88.94	395,603	88.26	8,442	97.31	7,394	94.66	26,598	95.67
Parity										
1	234,090	47.53	212,060	47.31	1,280	14.76	4,794	61.37	15,956	57.39
2	179,074	36.36	163,064	36.38	4,524	52.15	2,290	29.32	9,196	33.08
3–16	77,664	15.77	71,576	15.97	2,819	32.50	708	9.06	2,561	9.21
Missing	1,687	0.34	1,527	0.34	52	0.60	19	0.24	89	0.32
Plurality										
Singleton	479,031	97.26	442,098	98.63	8,410	96.95	6,742	86.31	21,781	78.34
Twin or High Order Multiples	13,484	2.74	6,129	1.37	265	3.05	1,069	13.69	6,021	21.66
History of chronic conditions										
Hypertension	11,903	2.42	10,287	2.30	241	2.78	283	3.62	1,092	3.93

	ALL		Fertile		Unassisted Subfertile		Non-ART Medically Assisted Reproduction		ART	
	n	%	n	%	n	%	n	%	n	%
Diabetes	30,825	6.26	26,876	6.00	678	7.82	761	9.74	2,510	9.03
Year of Delivery										
2004–2007	155,747	31.62	144,669	32.28	2,258	26.03	1,999	25.59	6,821	24.53
2008–2010	119,909	24.35	110,269	24.60	2,064	23.79	1,110	14.21	6,466	23.26
2011–2013	99,260	20.15	89,340	19.93	1,717	19.79	1,965	25.16	6,238	22.44
2014–2017	117,599	23.88	103,949	23.19	2,636	30.39	2,737	35.04	8,277	29.77
Number of deliveries per women analyzed										
Range	1–10		1–10		1–6		1–6		1–6	
Mean (SD)	1.80 (0.78)		1.81 (0.79)		2.08 (0.76)		1.62 (0.70)		1.60 (0.67)	
1	192,549	39.10	173,130	38.63	1,755	20.23	3,847	49.25	13,817	49.70
2	222,778	45.23	203,079	45.31	4,820	55.56	3,216	41.17	11,663	41.95
3–10	77,188	15.67	72,018	16.07	2,100	24.21	748	9.58	2,322	8.35
Birth weight[1]										
< 1500 gms	5,364	1.06	3,476	0.76	94	1.05	343	3.82	1,451	4.27
1500–2499 gms	29,344	5.80	20,895	4.60	514	5.75	1,322	14.74	6,613	19.45
>=2500 gms	470,155	92.85	428,751	94.35	8,288	92.66	7,278	81.14	25,838	75.98
Missing	1,483	0.29	1,301	0.29	49	0.55	27	0.30	106	0.31
Birth weight (singletons only)										
< 1500 gms	3,014	0.63	294	1.35	74	1.10	41	0.49	2,605	0.59
1500–2499 gms	17,674	3.69	1,351	6.20	344	5.10	283	3.37	15,696	3.55
>=2500 gms	456,956	95.39	20,075	92.17	6,299	93.43	8,041	95.61	422,541	95.58
Missing	1,387	0.29	61	0.28	25	0.37	45	0.54	1,256	0.28

[1]. Total number of infants= 506,346

Fertil Steril. Author manuscript; available in PMC 2023 March 01.

Table 2.

Risk of post-delivery hospital inpatient and observation stays, by fertility status for the 1st, 3rd, 5th, and 8th years post-delivery.

	Fertile			Unassisted Subfertile	Non-ART Medically Assisted Reproduction	ART
	n	%	Reference	aRR (95% CI)[1,2]	aRR (95% CI)[1,2]	aRR (95% CI)[1,2]
Hospitalization for any Condition						
1st year	16,613	3.71	1.00 (ref)	1.18 (1.07–1.31)	1.15 (1.03–1.28)	1.23 (1.15–1.30)
3rd year	37,814	8.44	1.00 (ref)	1.23 (1.15–1.32)	1.19 (1.11–1.28)	1.33 (1.28–1.39)
5th year	48,522	10.83	1.00 (ref)	1.19 (1.12–1.26)	1.19 (1.12–1.27)	1.31 (1.27–1.36)
8th year	56,277	12.56	1.00 (ref)	1.18 (1.12–1.25)	1.20 (1.13–1.27)	1.29 (1.25–1.34)
Cardiovascular disease including hypertension						
1st year	2,954	0.66	1.00 (ref)	1.11 (0.88–1.35)	1.29 (1.04–1.60)	1.14 (1.00–1.30)
3rd year	5,358	1.20	1.00 (ref)	1.15 (0.96–1.37)	1.31 (1.10–1.55)	1.32 (1.20–1.46)
5th year	7,091	1.58	1.00 (ref)	1.12 (0.96–1.31)	1.24 (1.07–1.45)	1.31 (1.20–1.43)
8th year	8,950	2.00	1.00 (ref)	1.15 (1.01–1.31)	1.23 (1.07–1.42)	1.31 (1.20–1.41)
Infection (not reproductive)						
1st year	1,801	0.40	1.00 (ref)	1.34 (0.98–1.82)	1.17 (0.85–1.62)	1.27 (1.06–1.53)
3rd year	2,707	0.60	1.00 (ref)	1.33 (1.03–1.73)	1.19 (0.90–1.57)	1.34 (1.15–1.58)
5th year	3,300	0.74	1.00 (ref)	1.21 (0.95–1.55)	1.21 (0.93–1.56)	1.41 (1.22–1.63)
8th year	3,870	0.86	1.00 (ref)	1.17 (0.93–1.47)	1.19 (0.93–1.52)	1.36 (1.18–1.56)
Overweight/Obesity						
1st year	991	0.22	1.00 (ref)	1.65 (1.18–2.32)	1.48 (1.00–2.19)	1.16 (0.90–1.50)
3rd year	3,075	0.69	1.00 (ref)	1.64 (1.36–1.98)	1.37 (1.08–1.74)	1.45 (1.26–1.67)
5th year	4,675	1.04	1.00 (ref)	1.50 (1.28–1.75)	1.37 (1.13–1.65)	1.32 (1.18–1.49)
8th year	6,436	1.44	1.00 (ref)	1.42 (1.23–1.63)	1.41 (1.19–1.66)	1.30 (1.17–1.44)
Anemia						
1st year	1,123	0.25	1.00 (ref)	1.25 (0.85–1.82)	1.12 (0.74–1.69)	1.48 (1.19–1.84)
3rd year	2,390	0.53	1.00 (ref)	1.18 (0.90–1.53)	0.97 (0.70–1.33)	1.44 (1.22–1.69)
5th year	3,388	0.76	1.00 (ref)	1.13 (0.91–1.41)	1.06 (0.81–1.38)	1.33 (1.16–1.54)
8th year	4,445	0.99	1.00 (ref)	1.03 (0.85–1.26)	0.93 (0.73–1.20)	1.24 (1.09–1.41)

	Fertile			Unassisted Subfertile	Non-ART Medically Assisted Reproduction	ART
	n	%	Reference	aRR (95% CI)[1,2]	aRR (95% CI)[1,2]	aRR (95% CI)[1,2]
Reproductive tract						
1st year	1,241	0.28	1.00 (ref)	1.34 (0.93–1.93)	1.54 (1.08–2.21)	1.50 (1.21–1.86)
3rd year	3,451	0.77	1.00 (ref)	1.32 (1.06–1.65)	1.64 (1.32–2.04)	1.79 (1.58–2.04)
5th year	4,932	1.10	1.00 (ref)	1.33 (1.10–1.60)	1.62 (1.35–1.96)	1.68 (1.50–1.87)
8th year	6,287	1.40	1.00 (ref)	1.24 (1.05–1.46)	1.52 (1.28–1.81)	1.62 (1.47–1.79)
Digestive tract						
1st year	3,860	0.86	1.00 (ref)	1.40 (1.14–1.72)	1.33 (1.07–1.66)	1.48 (1.31–1.68)
3rd year	8,633	1.93	1.00 (ref)	1.42 (1.24–1.62)	1.15 (0.98–1.35)	1.41 (1.29–1.54)
5th year	11,527	2.57	1.00 (ref)	1.34 (1.20–1.51)	1.20 (1.05–1.38)	1.39 (1.29–1.50)
8th year	14,457	3.23	1.00 (ref)	1.31 (1.18–1.45)	1.24 (1.10–1.40)	1.39 (1.30–1.49)
Thyroid						
1st year	756	0.17	1.00 (ref)	1.50 (1.01–2.22)	2.41 (1.73–3.34)	1.95 (1.57–2.42)
3rd year	1,791	0.40	1.00 (ref)	1.75 (1.36–2.24)	2.37 (1.89–2.97)	2.06 (1.77–2.39)
5th year	2,511	0.56	1.00 (ref)	1.62 (1.31–2.02)	2.18 (1.77–2.68)	2.09 (1.84–2.38)
8th year	3,202	0.71	1.00 (ref)	1.62 (1.34–1.96)	1.98 (1.63–2.41)	2.02 (1.80–2.26)
Respiratory including asthma						
1st year	1,560	0.35	1.00 (ref)	1.20 (0.87–1.66)	0.81 (0.53–1.24)	0.93 (0.74–1.16)
3rd year	4,080	0.91	1.00 (ref)	1.41 (1.17–1.69)	1.07 (0.84–1.36)	1.10 (0.96–1.27)
5th year	6,022	1.34	1.00 (ref)	1.27 (1.09–1.48)	1.21 (1.01–1.47)	1.18 (1.05–1.31)
8th year	8,027	1.79	1.00 (ref)	1.23 (1.08–1.41)	1.18 (1.00–1.40)	1.13 (1.03–1.24)
Breast						
1st year	772	0.17	1.00 (ref)	1.07 (0.65–1.75)[3]	1.05 (0.62–1.78)[3]	1.13 (0.85–1.50)[3]
3rd year	1,056	0.24	1.00 (ref)	1.78 (1.27–2.49)	1.06 (0.67–1.68)	1.43 (1.13–1.81)
5th year	1,306	0.29	1.00 (ref)	1.57 (1.15–2.15)	1.18 (0.79–1.75)	1.36 (1.10–1.68)
8th year	1,573	0.35	1.00 (ref)	1.41 (1.05–1.89)	1.41 (1.01–1.97)	1.39 (1.14–1.69)
Diabetes						
1st year	399	0.09	1.00 (ref)	1.36 (0.78–2.38)	1.32 (0.78–2.24)	0.90 (0.62–1.32)
3rd year	1,139	0.25	1.00 (ref)	1.55 (1.07–2.24)	1.70 (1.22–2.35)	1.27 (1.01–1.59)

	Fertile			Unassisted Subfertile	Non-ART Medically Assisted Reproduction	ART
	n	%	Reference	aRR (95% CI)[1,2]	aRR (95% CI)[1,2]	aRR (95% CI)[1,2]
5th year	1,603	0.36	1.00 (ref)	1.54 (1.12–2.11)	1.60 (1.20–2.14)	1.25 (1.03–1.52)
8th year	2,024	0.45	1.00 (ref)	1.35 (1.00–1.82)	1.70 (1.32–2.19)	1.25 (1.05–1.49)
Cancer[4]						
1st year	350	0.08	1.00 (ref)	1.69 (1.30–2.19)[3]	1.30 (0.96–1.77)[3]	1.66 (1.42–1.93)[3]
3rd year	865	0.19	1.00 (ref)	1.20 (0.82–1.76)	1.17 (0.73–1.87)	1.54 (1.22–1.94)
5th year	1,321	0.29	1.00 (ref)	1.12 (0.82–1.54)	1.39 (0.97–1.98)	1.42 (1.17–1.72)
8th year	1,810	0.40	1.00 (ref)	1.18 (0.90–1.53)	1.38 (1.01–1.89)	1.40 (1.18–1.65)
Psychiatric conditions						
1st year	1,834	0.41	1.00 (ref)	0.95 (0.68–1.32)	1.08 (0.77–1.51)	1.11 (0.91–1.35)
3rd year	4,776	1.07	1.00 (ref)	1.23 (1.03–1.48)	1.18 (0.96–1.46)	1.19 (1.05–1.35)
5th year	7,170	1.60	1.00 (ref)	1.29 (1.11–1.49)	1.19 (0.99–1.41)	1.24 (1.12–1.37)
8th year	9,622	2.15	1.00 (ref)	1.28 (1.13–1.45)	1.16 (0.99–1.36)	1.26 (1.15–1.37)
Substance use disorder						
1st year	672	0.15	1.00 (ref)	0.62 (0.28–1.38)	0.40 (0.13–1.24)	0.64 (0.37–1.10)
3rd year	2,085	0.47	1.00 (ref)	0.88 (0.61–1.28)	0.69 (0.43–1.12)	0.78 (0.59–1.03)
5th year	3,233	0.72	1.00 (ref)	1.11 (0.85–1.44)	0.72 (0.49–1.06)	0.92 (0.75–1.14)
8th year	4,479	1.00	1.00 (ref)	1.05 (0.84–1.32)	0.70 (0.50–0.98)	1.01 (0.86–1.20)
Other (Chronic Disease)						
1st year	5,114	1.14	1.00 (ref)	1.19 (0.99–1.43)	1.21 (0.99–1.47)	1.34 (1.20–1.50)
3rd year	12,687	2.83	1.00 (ref)	1.29 (1.15–1.45)	1.21 (1.06–1.38)	1.40 (1.30–1.51)
5th year	17,409	3.88	1.00 (ref)	1.26 (1.14–1.39)	1.26 (1.12–1.41)	1.36 (1.28–1.45)
8th year	21,704	4.84	1.00 (ref)	1.22 (1.12–1.33)	1.24 (1.12–1.37)	1.36 (1.28–1.43)

1. GEE with Poisson distribution, exchangeable correlation structure, logarithm person-month as offset term

2. Adjusted for maternal age (continuous 18–57), parity (1,2,3–16,missing), year of delivery (4–7, 8–10, 11–13, 14–17), plurality (Singleton,multiples), chronic hypertension (yes/no), chronic diabetes (yes/no). aRR=adjusted relative risk, CI=confidence interval

3. Multivariable models did not converge, crude estimates presented

[4]Determined from inpatient ICD codes and not from the Massachusetts cancer registry