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Long-Term Cardiovascular Risk in Women Prescribed Fertility Therapy

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Objectives The purpose of the study was to investigate whether fertility therapy might contribute to subsequent cardiovascular disease.

Background Fertility medications are used for 1% of births yet may also lead to endothelial injury with long-term adverse consequences for the mother.

Methods A population-based cohort analysis was performed of women who gave birth in Ontario, Canada, between July 1, 1993, and March 31, 2010, distinguishing those who did and did not receive fertility therapy in the 2 years before delivery. Cox proportional models were derived to estimate hazard ratios with and without adjustment for baseline characteristics. The primary outcome was a composite cardiovascular endpoint of death, nonfatal coronary ischemia, stroke, transient ischemic attack, thromboembolism, or heart failure.

Results Among 1,186,753 women who delivered during the study period, 6,979 gave birth after fertility therapy. After 9.7 years of median follow-up, women who delivered after fertility therapy had fewer cardiovascular events than controls (103 vs. 117 events per 100,000 person-years), equivalent to an unadjusted hazard ratio of 0.96 (95% confidence interval: 0.72 to 1.29, $p = 0.79$) and an adjusted hazard ratio of 0.55 (95% confidence interval: 0.41 to 0.74, $p < 0.0001$). An apparent relative lower risk was observed across all age and income groups. Women who received fertility therapy also had lower risk-adjusted all-cause mortality, thromboembolic events, subsequent depression, alcoholism, and self-harm ($p < 0.01$ for each).

Conclusions Successful fertility therapy was not associated with an increased risk of cardiovascular disease later in life. (J Am Coll Cardiol 2013;62:1704–12) © 2013 by the American College of Cardiology Foundation

Infertility affects approximately 1 in 8 reproductive-age couples globally (1,2) and can lead to enormous personal stress (3). General reproductive assistance improves the chance of pregnancy through medications that stimulate ovulation (4–6) and now represents approximately 1% of all infants born annually in North America (1,2,7). Many industrialized countries support fertility therapy under national health insurance programs (8). In addition, some American states and Canadian provinces guarantee access to affordable fertility care (1,9) whereas others offer no such programs (8,10).

Fertility therapy focuses attention toward achieving pregnancy rather than long-term health (4–7,11–13) Clinical decision making, to an extreme degree, prioritizes a successful pregnancy (14), yet unintended toxicity can occur. One concern is that fertility therapy might lead to downstream cardiovascular events due to increased risks of maternal metabolic syndromes (e.g., gestational diabetes mellitus and hypertension), direct endothelial dysfunction, and prothrombotic effects from ovarian hyperstimulation with hyperestrogenemia (9,15–27). Nevertheless, long-term data are lacking on the health effects associated with fertility therapy for women who have a successful pregnancy, in part because of a lack of uniform reporting of adverse outcomes after fertility therapy (28,29) and legislation sometimes prohibiting health data linkage (30).

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The potential association between fertility therapy and subsequent cardiovascular disease is increasingly relevant given societal trends for women to delay pregnancy until

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older age, and with a higher likelihood of baseline heart disease (31–33). We questioned whether fertility therapy might contribute to increased cardiovascular events after successful pregnancy. The goal of the GRAVID (General Reproductive Assistance and Vascular Illness Downstream) study was to assess the long-term risk of premature cardiovascular disease for women after successful fertility drug treatment.

Methods

Study design and participants. We conducted a population-based cohort analysis of all women age 15 to 55 years who gave birth in Ontario, Canada, between July 1, 1993, and March 31, 2010. During this time, patients were identified through the Ontario Health Insurance Plan, which covered prenatal care as well as hospital and postnatal care. We identified women through linked healthcare databases utilizing obstetrical delivery of a liveborn or stillborn infant after 20 weeks' gestation (hospital database main patient service code 51). For each woman, the first delivery during the study period was selected for inclusion so that patients counted only once in analyses to avoid statistical artifacts from clustered observations. Women with spontaneous miscarriages, therapeutic abortions, or home births were not included. We also excluded women who were not residents of Ontario and those who lacked a valid health-card identifier.

Definition of fertility therapy. We used computerized search methods to screen for the use of fertility therapy during the 2 years (730 days) before the date of delivery for each woman (estimated gestational length of 270 days plus 460 days). We selected in advance a 2-year screening window to be inclusive for women who may have received several courses of fertility therapy before a successful pregnancy. Women were classified dichotomously as having received or not received fertility therapy according to whether they had a claim for reproductive treatment monitoring of iatrogenic ovulation (Ontario Health Insurance Plan code G334) according to the intention-to-treat approach. If >1 claim was present during the period, the date of the first claim was selected for primary analysis. Subsequently, patients who received fertility therapy were classified as having 1 or repeated claims for reproductive treatment monitoring to explore potential dose-response relationships.

We focused on ovulation monitoring because the standard of care generally involved adjuvant fertility therapy (4–7). Moreover, the Ontario Health Insurance Plan code was consistent during the entire accrual interval and identified women participating in intrauterine insemination, in vitro fertilization, and other forms of medically stimulated ovulation (12). The Ontario Drug Benefit Program database could not identify specific fertility medication because Ontario did not provide single-payer universal insurance coverage for fertility medications (10). Therefore, our study examined the physician's monitoring of fertility therapy but not the specific medications, doses, or strategies for the individual patient.

Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
ICD = International Classification of Diseases
OR = odds ratio

Patient characteristics. We collected baseline data on demographic and clinical factors from the Canadian Institute for Health Information hospital and outpatient databases during the 2 years before delivery. These databases, which also served as the source for identifying follow-up outcomes, admissions, and procedures, have high reported completeness (>99%) and diagnostic accuracy (>95%) in this setting (34,35). The hospital database contained the patient's age and sex, date of admission, and diagnoses coded using the International Classification of Diseases (ICD [as many as 16 diagnoses in ICD-9 and as many as 25 diagnoses in ICD-10]). Because some conditions were primarily diagnosed on an outpatient basis (e.g., hypertension), we also used the outpatient database to identify additional diagnoses for the 2 years before the index delivery. Demographic and health care utilization covariates were assessed during the half year before conception to identify additional determinants of health. Information about the patient's home location (urban versus rural) and estimated income category was defined using Canadian census data through home postal code information. Obstetrical characteristics and outcomes during the index delivery were also collected. Information about parity, neonatal outcomes, laboratory results, and prescription medications were not available.

Outcome definitions. We identified outcomes using the Canadian Institute for Health Information hospital database. Our primary outcome was the composite of death or hospitalization for a major adverse cardiovascular event; namely, nonfatal coronary ischemia, stroke, transient ischemic attack, thromboembolism, or heart failure. We used ICD-9 codes to identify study outcomes before March 31, 2002, and ICD-10 codes after April 1, 2002, to account for the changes in coding over time. Potential mediators of fertility treatment effects were explored along a plausible causal pathway. In particular, we considered differential effects in women with and without multiple gestations, ovarian hyperstimulation syndrome, and gestational metabolic disorders.

We conducted secondary analyses to examine additional events using inpatient and outpatient databases. These included individual components of the primary outcome as well as processes of care measures (e.g., coronary revascularization). We also analyzed for the emergence of 3 cardiovascular risk factors (hypertension, diabetes, and hyperlipidemia) as a supplement but not substitute for our primary outcome. For these secondary analyses we excluded patients with any history of prior cardiovascular disease, hypertension, diabetes (including gestational diabetes), and hyperlipidemia to provide a stringent assessment of the development of cardiovascular risk factors.

We further evaluated noncardiovascular outcomes potentially associated with fertility therapy including hormonally mediated cancers (e.g., breast cancer, ovarian cancer), depression, and self-harm. We also selected 5 common

Table 1 Baseline Characteristics

Characteristic		Fertility Therapy Absent (n = 1,179,774)	Fertility Therapy Present (n = 6,979)	p Value
Age, yrs		29 (25–33)	34 (31–36)	<0.001
Age <35 yrs		1,001,177 (85%)	4,064 (58%)	<0.001
Urban residence		1,037,554 (88%)	6,637 (95%)	<0.001
Income quintile	1	260,872 (22%)	766 (11%)	<0.001
	2	242,921 (21%)	1,144 (16%)	
	3	239,930 (20%)	1,465 (21%)	
	4	238,255 (20%)	1,799 (26%)	
	5	191,118 (16%)	1,799 (26%)	
	Unknown	6,678 (1%)	6 (<1%)	
Physician visits prior 6 months		12 (6–22)	49 (31–75)	<0.001
No. of antenatal visits		11 (9–13)	12 (10–13)	<0.001
No. obstetrician antenatal visits		8 (0–11)	11 (9–13)	<0.001
Weekday delivery		833,357 (71%)	4,911 (70%)	0.6
Charlson index	0	1,170,923 (99%)	6,936 (99%)	0.17
	≥1	8,851 (1%)	43 (1%)	
Prior operative vaginal delivery		50,843 (4%)	37 (0.5%)	<0.001
Prior Cesarean delivery		12,221 (1%)	10 (0.1%)	<0.001
Prior multiple gestation		686 (0.1%)	13 (0.2%)	<0.001
Prior abnormal pregnancy		85,476 (7%)	378 (5%)	<0.001
Endometriosis		2,403 (0.2%)	86 (1%)	<0.001
Prior ovarian hyperstimulation		243 (0.1%)	40 (4%)	<0.01
Sexually transmitted infection		25,827 (2.2%)	84 (1.2%)	<0.001
Pelvic inflammatory disease		4,565 (0.4%)	79 (1%)	<0.001
Cervix disorders*		236 (0%)	≤5 (0%)	0.6
Other genital tract disorders		5,300 (0.4%)	75 (1%)	<0.001
Renal disease		628 (0.1%)	≤5 (0%)	0.7
Liver disease		344 (0%)	0 (0%)	0.2
History of neoplasm		5,094 (0.4%)	71 (1.0%)	<0.001
History of major trauma		291 (0%)	≤5 (0%)	0.8
Alcoholism		6,184 (2.5%)	11 (0.2%)	<0.001
Depression		42,907 (3.6%)	234 (3.4%)	0.2
Self-harm		1,117 (0.1%)	≤5 (0%)	0.03
Ischemic heart disease		80 (<0.01%)	0 (0%)	0.5
Cardiomyopathy		51 (<0.01%)	0 (0%)	0.5
Cerebrovascular diseases		174 (<0.01%)	0 (0%)	0.3
Thromboembolic disease		89 (<0.01%)	0 (0%)	0.5
Pulmonary circulation disease		243 (<0.01%)	≤5 (0%)	0.7
Peripheral artery disease		138 (<0.01%)	≤5 (0%)	0.2
Cardiovascular risk factors				
Hypertension		29,083 (2.5%)	217 (3.1%)	<0.001
Hyperlipidemia		29,014 (2.5%)	263 (3.8%)	<0.001
Diabetes mellitus, including prior GDM		17,600 (1.5%)	153 (2.2%)	<0.001
Obstetrical characteristics				
Length of stay, days		2 (2–3)	3 (2–4)	<0.001
Multiple gestation, uncomplicated		9,701 (1%)	315 (4.5%)	<0.001
Multiple gestation, complicated		8,341 (1%)	315 (4.5%)	

Continued on the next page

illnesses to check for the lack of a difference where no difference would be expected (e.g., pneumonia, melanoma, lung cancer, nephrolithiasis, motor vehicle trauma). Finally, we explored the incidence of alcoholism and sexually transmitted infections to assess additional determinants of health.

Statistical analysis. Baseline demographic and clinical characteristics were compared between groups using the chi-square test for categorical variables and the *t* test or Kruskal-Wallis test for continuous variables. The association between fertility therapy and short-term pregnancy outcomes was assessed using the chi-square test and logistic regression. Probability curves and event rates for the primary and secondary outcomes followed the Kaplan-Meier approach. We followed up all patients until they had an outcome event or reached the end of follow-up (March 31, 2011), whichever came first. Survival time was estimated according to the date of

Table 1 Continued

Characteristic	Fertility Therapy Absent (n = 1,179,774)	Fertility Therapy Present (n = 6,979)	p Value
Obstetrical procedures			
Cesarean delivery	314,960 (27%)	2,853 (41%)	<0.001
Operative vaginal delivery	589,572 (50%)	2,527 (36%)	<0.001
Other procedures assisting labor	258,341 (22%)	1,424 (20%)	0.003
Malposition and malpresentation of fetus	66,128 (6%)	409 (6%)	0.355
Disproportion	37,988 (3.2%)	189 (2.7%)	0.02
Abnormality of pelvic organs	57,725 (5%)	197 (3%)	<0.001
Abnormality of the fetus	3,205 (0.3%)	26 (0.4%)	0.107
Suspected fetal problems†	142,263 (12%)	637 (9%)	<0.001
Misc. amniotic fluid and cavity abnormalities‡	83,899 (7%)	380 (5%)	<0.001
Serious obstetrical complications§	205,680 (17%)	702 (10%)	<0.001

Values are median (interquartile range) or n (%). Baseline characteristics were ascertained for 2 years before the date of index delivery. *Including incompetent cervix. †Including intrauterine growth restriction, intrauterine death, placental infarct. ‡Including polyhydramnios, oligohydramnios, premature rupture of membranes, infection of amniotic cavity. §Including obstructed labor, umbilical cord complications, major perineal trauma, postpartum hemorrhage, and obstetric shock.

GDM = gestational diabetes mellitus; Misc. = miscellaneous.

the outcome, with data censored at the time of the last available information for patients who had no event. We used proportional hazards models to estimate a hazard ratio (HR) and 95% confidence interval (CI) for the study outcomes comparing women with and without fertility therapy. The assumption of proportional hazards was confirmed by Schoenfeld's test.

Multivariable analyses were based on regression models that adjusted for maternal age, calendar year, multiple gestations, home location, neighborhood income, prior physician visits, antenatal visits to an obstetrician, history of cardiovascular risk factors, smoking, obesity, other baseline comorbidities, obstetrical characteristics, and length of stay. We constructed all multivariable models maintaining a ratio of 1:10 between outcomes and predictors. Given that past research has indicated an inverse association between income and fertility (36), we deliberately explored the consistency of findings across socioeconomic subgroups by examining interaction terms for fertility therapy with age or income. In addition, we explored whether a dose-response relationship was present by analyzing results according to whether patients received 1 or repeated fertility treatments. All p values were 2-sided and calculated with the Wald chi-square test with a threshold <0.05 considered significant using SAS for UNIX (version 8.02; SAS Institute, Cary, North Carolina).

Descriptive characteristics with cell sizes containing between 1 and 5 patients were censored according to local and provincial privacy reporting regulations. The ethics review board of Sunnybrook Health Sciences Centre approved the study. The funding agencies had no role in the design, analysis, interpretation of the data, nor in the preparation or decision to submit the manuscript for publication.

Results

Characteristics of patients. A total of 1,186,753 women had an obstetrical delivery during the study interval (Table 1). The mean age was 29 ± 5 years and 6,979 (0.6%) had received fertility therapy in the 2 years before delivery. Among women with an obstetrical delivery, the use of fertility therapy increased significantly over time from approximately 1 in 400 to approximately 1 in 80 during the 17-year study interval. Women with a delivery after fertility therapy were more likely to be older, living in the highest income quintile, and accumulated a greater number of pre-natal visits compared with women delivering without fertility therapy. At baseline, we observed a higher prevalence of 4 cardiovascular risk factors (older age, hypertension, hyperlipidemia, and diabetes) among women who used fertility therapy (Table 1). In contrast, we observed no significant differences in the rate of 6 indicators of established cardiovascular disease between the 2 groups. As expected, women who gave birth after fertility therapy more commonly had a history of pelvic inflammatory disease, endometriosis, and cancer. Women who gave birth after fertility therapy were also more likely to carry multiple gestations, deliver by Cesarean section, and have longer lengths of hospital stay.

Short-term outcomes. Women who gave birth after fertility therapy had an increased risk of having maternal metabolic syndromes (Table 2) including gestational diabetes (adjusted odds ratio [OR]: 1.29, 95% CI: 1.17 to 1.41, $p < 0.0001$), serious placental complications (adjusted OR: 1.16, 95% CI: 1.04 to 1.29, $p = 0.01$), and pre-eclampsia (adjusted OR: 1.10, 95% CI: 1.01 to 1.20, $p = 0.02$). Fertility therapy was also associated with developing pre-term threatened labor (adjusted OR: 1.41, 95% CI: 1.31 to 1.52, $p < 0.0001$), ovarian hyperstimulation syndrome (adjusted OR: 3.29, 95% CI: 2.37 to 4.57, $p < 0.0001$), and urinary tract infections (adjusted OR: 1.22, 95% CI: 1.08 to 1.40, $p = 0.006$). In contrast, the 2 groups had similar rates of gestational hypertension, hyperemesis gravidarum, renal complications, liver complications, and puerperium septicemia.

Long-term cardiovascular outcomes. During a median follow-up of 9.7 years (interquartile range: 4.6 to 14.0) a total

Table 2 Short-Term Pregnancy Outcomes

Peripartum Events	Fertility Therapy Absent (n = 1,179,774)	Fertility Therapy Present (n = 6,979)	p Value
Gestational hypertension*	46,919 (4%)	270 (4%)	0.6
Gestational diabetes	34,176 (3%)	536 (8%)	<0.001
Pre-eclampsia or eclampsia†	39,812 (3%)	480 (7%)	<0.001
Serious placental complications‡	37,314 (3%)	391 (6%)	<0.001
Abnormal pregnancy	1,089 (0.1%)	23 (0.3%)	<0.001
Excessive vomiting	10,416 (0.9%)	48 (0.7%)	0.08
Pre-term or threatened labor	98,019 (8%)	1,147 (16%)	<0.001
Late pregnancy	127,212 (11%)	576 (8%)	<0.001
Ovarian hyperstimulation syndrome	385 (0%)	51 (1%)	<0.001
Peripheral edema or excessive weight gain	1,998 (0.2%)	14 (0.2%)	0.5
Renal disorders in pregnancy	1,069 (0.1%)	≤5 (0%)	0.2
Liver disorders in pregnancy	448 (0%)	≤5 (0%)	0.3
Septicemia or genitourinary tract infections	25,341 (2%)	218 (3%)	<0.001
Other puerperium complications§	14,541 (1%)	136 (2%)	<0.001

Values are n (%). *Including benign essential hypertension complicating pregnancy, hypertension from renal disease complicating pregnancy, other pre-existing hypertension complicating pregnancy, transient hypertension in pregnancy, unspecified hypertension complicating pregnancy. †Including mild or unspecified pre-eclampsia (with either albuminuria or edema or both), severe pre-eclampsia, eclampsia, pre-eclampsia, or eclampsia superimposed on pre-existing hypertension. ‡Including antepartum hemorrhage, placenta previa, placental abruption. §Including puerperal infections.

of 12,774 primary outcome events were observed, of which 44 occurred among women after fertility therapy and 12,730 occurred among women who delivered without fertility therapy. Women who gave birth after fertility therapy had fewer primary outcome events than women who delivered without fertility therapy (103 vs. 117 events per 100,000 person-years; unadjusted HR: 0.96, 95% CI: 0.72 to 1.29, p = 0.79) (Fig. 1). The observed decreased risk associated with fertility therapy was further accentuated after adjustment for differences in age, year of delivery, demographic factors, baseline medical history, baseline obstetrical characteristics, and short-term complications of pregnancy (adjusted HR: 0.55, 95% CI: 0.41 to 0.74, p < 0.0001) (Table 3, Online Table 1). Subgroup analysis confined to women ≥30 years of age yielded similar results (unadjusted HR: 0.78, 95% CI: 0.56 to 1.08, p = 0.14; adjusted HR: 0.56, 95% CI: 0.40 to 0.78, p = 0.0007).

Individual components of the primary outcome occurred infrequently, yet fertility therapy was associated with lower rates of both mortality (adjusted HR: 0.50, 95% CI: 0.31 to 0.80, p = 0.004) and thromboembolic events (adjusted HR: 0.45, 95% CI: 0.21 to 0.94, p = 0.03). We observed an increase in crude rates of coronary ischemic events, heart failure, and cerebrovascular events among women who gave birth after fertility therapy, yet each association was not significant after multivariable adjustment (adjusted HR for coronary ischemic events: 0.56, 95% CI: 0.25 to 1.25, p = 0.15; adjusted HR for heart failure: 0.60, 95% CI: 0.30 to 1.22, p = 0.16; adjusted HR for cerebrovascular events: 1.14, 95% CI: 0.54 to 2.44, p = 0.73).

We observed no increased cardiovascular risk associated with fertility therapy in subgroups stratified by age (Online Fig. 1), presence of polycystic ovarian syndrome, method of assisted reproduction, number of cardiovascular risk factors, number of gestations, or development of ovarian hyperstimulation syndrome (p for interaction > 0.2 for all). As expected, the development of gestational diabetes was associated with an increased risk of long-term cardiovascular events (adjusted HR: 1.27, 95% CI: 1.16 to 1.38; p < 0.0001), as was the development of gestational hypertension, pre-eclampsia, or eclampsia (adjusted HR: 1.46, 95% CI: 1.38 to 1.55; p < 0.0001), independent of fertility therapy and other baseline characteristics. The lower risk of cardiovascular events associated with fertility therapy was consistent across all income groups (p for interaction = 0.7) (Online Fig. 2).

Emergence of cardiovascular risk factors. In an analysis restricted to patients without prevalent cardiovascular disease, hypertension, diabetes (including gestational diabetes), or hyperlipidemia at baseline, incidence rates of cardiovascular risk factor development occurred more frequently among women after fertility therapy than controls (5.91 vs. 3.83 events per 100 person-years; unadjusted HR: 1.53, 95% CI: 1.46 to 1.60, p < 0.0001) (Table 3). After multivariable adjustment, however, we observed less risk of emergent hypertension, diabetes, or hyperlipidemia after fertility therapy (adjusted HR: 0.86, 95% CI: 0.82 to 0.90, p < 0.0001; Online Table 1). In addition, we observed no significant difference in the risk of subsequent coronary revascularization with and without fertility therapy (adjusted HR: 1.18, 95% CI: 0.55 to 2.51, p = 0.67).

Other medical and mental health outcomes. After adjustment for age and other baseline characteristic differences between the 2 groups, we observed no significant increased risk associated with breast cancer development (adjusted HR: 0.74, 95% CI: 0.45 to 1.19; p = 0.2) or ovarian malignancies (adjusted HR: 1.12, 95% CI: 0.41 to 3.05; p = 0.8) among women who gave birth after fertility therapy. Fertility therapy was not associated with

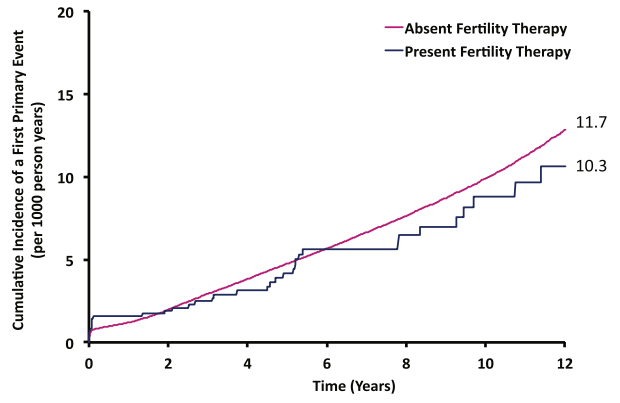

Figure 1 **Incidence of Primary Outcome With or Without Fertility Therapy**

Kaplan-Meier cumulative incidence curves for the primary outcome (composite cardiovascular endpoint of death, nonfatal coronary ischemia, stroke, transient ischemic attack, thromboembolism, and heart failure) among women giving birth according to fertility therapy status: absent **(red line)** or present **(blue line)**.

a significant increase or decrease in risk of pneumonia, melanoma, lung cancer, or nephrolithiasis (Table 4 , Online Table 2).

Women who gave birth after fertility therapy experienced fewer adverse mental health events compared to controls (Table 4). Specifically, the use of fertility therapy was associated with one-third of the rate of subsequent depression and one-seventh the rate of subsequent self-harm ($p < 0.001$ for both). In addition, fertility therapy was associated with a decrease in other potential adverse health behavior-related outcomes including about one-half the rate of incident alcoholism and two-thirds the rate of sexually transmitted infections among women with no prior history before delivery ($p < 0.0001$ for both). All observed associations persisted after adjustment for baseline characteristics, with or without further adjustment for obstetrical characteristics.

Discussion

Overall, we observed a 5-fold increase in the use of fertility therapy over the last 2 decades, particularly among older women. The use of fertility therapy was associated with an increase in several short-term pregnancy complications, yet women who delivered after fertility therapy had about half the risk of long-term death or major adverse cardiovascular events compared to controls. The decreased risk of long-term adverse events associated with fertility therapy was consistent across age and socioeconomic groups. Our analysis focused on women who achieved a pregnancy of at least 20 weeks' gestation, and we cannot comment on the cardiovascular risk among those women who did not achieve pregnancy or had a loss before delivery.

Our findings contrast with other epidemiologic and clinical research that suggested cardiometabolic monitoring after fertility therapy to detect cardiothoracic disease (24,25,27,29,37–40). A recent study from the Netherlands reported an in vitro fertilization–associated maternal mortality rate of 42.5 per 100,000 live births, which is 4 times higher than the baseline. In the United Kingdom, 25% of maternal deaths associated with fertility therapy were considered directly related to development of ovarian hyperstimulation syndrome (38). Other studies, however,

Table 3 **Long-Term Cardiovascular Outcomes**

Outcome	Event Rate by Fertility Therapy (per 100,000 Person-Years)		Hazard Ratio (95% CI)	
	Absent	Present	Unadjusted	Adjusted*
Major cardiovascular events	(n = 1,179,774)	(n = 6,979)		
Death or cardiovascular event	117.0	102.6	0.96 (0.72–1.29)	0.55 (0.41–0.74)
Death	53.8	41.9	0.94 (0.59–1.50)	0.50 (0.31–0.80)
Cardiac ischemia	16.7	14.0	1.23 (0.55–2.74)	0.56 (0.25–1.25)
Heart failure	14.6	18.6	1.13 (0.56–2.26)	0.60 (0.30–1.22)
Venothromboembolic events	28.0	16.3	0.54 (0.26–1.13)	0.45 (0.21–0.94)
Cerebrovascular events	8.5	16.3	2.14 (1.02–4.50)	1.14 (0.54–2.44)
Emergent cardiovascular risk factors†	(n = 1,108,322)	(n = 6,394)		‡
Any hypertension, diabetes, or hyperlipidemia	3,831	5,907	1.53 (1.46–1.60)	0.86 (0.82–0.90)
Hypertension	1,985	2,945	1.52 (1.43–1.61)	0.88 (0.83–0.94)
Diabetes mellitus	1,046	1,816	1.68 (1.56–1.81)	0.93 (0.86–1.00)
Hyperlipidemia	1,393	2,094	1.63 (1.52–1.75)	0.85 (0.79–0.91)

Hazard ratios represent the risk among women with fertility compared with women without fertility therapy (reference). *Risk adjusted for age, calendar year, geographic residence, neighborhood income, prior physician visits, antenatal visits to an obstetrician, prior medical history (including hypertension, hyperlipidemia, diabetes mellitus [including gestational diabetes], neoplasm, alcoholism, female infertility, endometriosis, polycystic ovarian syndrome, sexually transmitted infections, pelvic inflammatory disease, other genital tract disorders, prior ovarian hyperstimulation syndrome, prior vaginal delivery, prior Cesarean delivery, prior multiple gestation, and prior abnormal pregnancy), length of stay and obstetrical characteristics for the index delivery (including number of gestations, number of complicated gestations, Cesarean delivery, operative delivery, assisted labor procedures, disproportion, abnormality of pelvic organs, suspected fetal problems, amniotic fluid and uterine cavity abnormalities, and other serious obstetrical complications). †Analyses restricted to patients without history of prior cardiovascular disease, hypertension, diabetes (including gestational diabetes), or hyperlipidemia at baseline. ‡Risk adjusted for all variables listed above except hypertension, diabetes (including gestational diabetes), and hyperlipidemia.

CI = confidence interval.

Table 4 Long-Term Risk of Other Serious Events

Outcome	Events Rate by Fertility Therapy (per 100,000 Person-Years)		Hazard Ratio (95% CI)	
	Absent (n = 1,179,774)	Present (n = 6,979)	Unadjusted	Adjusted*
Malignancies				
Breast	33.1	39.6	1.42 (0.88–2.28)	0.74 (0.45–1.19)
Ovarian	5.6	9.3	2.04 (0.76–5.46)	1.12 (0.41–3.05)
Melanoma	0.9	2.3	2.85 (0.40–20.5)	1.80 (0.24–13.7)
Pneumonia	49.5	49.0	1.00 (0.65–1.54)	0.73 (0.47–1.13)
Nephrolithiasis	40.7	32.6	0.75 (0.45–1.27)	0.71 (0.42–1.21)
Alcoholism	164.7	84.2	0.53 (0.38–0.73)	0.48 (0.35–0.67)
Sexually transmitted infections	538.2	351.0	0.63 (0.54–0.74)	0.64 (0.55–0.76)
Motor vehicle collisions	37.1	16.3	0.44 (0.21–0.92)	0.51 (0.24–1.07)
Depression	76.0	26.0	0.32 (0.18–0.58)	0.33 (0.18–0.59)
Self-harm	48.1	4.7	0.09 (0.02–0.35)	0.15 (0.04–0.62)

Values are %. Hazard ratios represent the risk among women with fertility compared with women without fertility therapy (reference). *Risk adjusted for age, calendar year, geographic residence, neighborhood income, prior physician visits, antenatal visits to an obstetrician, prior medical history (including hypertension, hyperlipidemia, diabetes mellitus [including gestational diabetes], neoplasm, alcoholism, female infertility, endometriosis, polycystic ovarian syndrome, sexually transmitted infections, pelvic inflammatory disease, other genital tract disorders, prior ovarian hyperstimulation syndrome, prior vaginal delivery, prior Cesarean delivery, prior multiple gestation, and prior abnormal pregnancy), length of stay and obstetrical characteristics for the index delivery (including number of gestations, number of complicated gestations, Cesarean delivery, operative delivery, assisted labor procedures, disproportion, abnormality of pelvic organs, suspected fetal problems, amniotic fluid and uterine cavity abnormalities, and other serious obstetrical complications).

CI = confidence interval.

report no increased short-term cardiovascular risk with fertility therapy. The present study's substantially longer duration of follow-up may partly explain the difference in observed risk associated with fertility therapy in contrast to prior reports (17,24,27,37–39,41). Most prior studies report no large association between fertility therapy and increased long-term risk of estrogen-related malignancies, consistent with our observations (42–44).

One interpretation of our findings is a widespread selection bias associated with fertility therapy that might offset a potential detrimental biologic consequence. That is, perhaps women who have fertility challenges and seek fertility therapy are prone toward healthier behavior after successful obstetrical delivery (45,46), a pattern that extends across diverse age and income groups. An alternative hypothesis is that fertility therapy offers an unknown pleiotropic biologic protective mechanism (47,48). A third possibility is that women with distinctly adverse lifestyles do not generally seek fertility treatment (49). The full explanation is unclear and requires more research on these determinants of health.

Study limitations. Our findings should be interpreted with caution. Population-based cohort studies have limitations due to potentially missing clinical data yet remain powerful designs to examine adverse outcomes otherwise missed in randomized trials. We focused on women who achieved a first pregnancy of at least 20 weeks' gestation, and that may have overlooked adverse effects among women who did not achieve pregnancy, had a gestation shorter than 20 weeks, or experienced adverse subsequent deliveries. The utilization of ovulation monitoring to estimate fertility therapy was an efficient method to test the core hypothesis although we could not directly ascertain specific medication or dose. As a result, our approach provided a sensitive but not specific method of determining the safety of fertility therapy. Potential unmeasured confounders such as education, functional status, body mass index, smoking history, glycemic control, and parity were not fully accounted. The effects of psychological stress, marital status, sexual orientation, or cultural motivators were also not available.

Further re-evaluation of patients for emergence of cardiovascular events at a later age will be important given the relative young age and brief duration of follow-up in this report. The major difference between unadjusted and adjusted relative risk estimates for the primary results was mostly explained by the higher age, income status, number of prenatal visits, and cardiovascular risk factor profile among women who received fertility therapy. The contrasting unadjusted and adjusted results regarding the risk of emergent cardiovascular risk factors among the subset of women at baseline without prevalent cardiovascular disease, hypertension, diabetes, or hyperlipidemia was primarily explained by adjustment for imbalances between groups in age and year of entry into the study.

Conclusions

This is the first large population-based study to assess the long-term risk of cardiovascular disease after fertility therapy. Fertility treatment has become popular over the past 3 decades, leading to a growing need to ascertain its long-term safety (29,37,38). A better understanding of the long-term risks associated with fertility therapy might help inform decision-making around reproductive technology and motivate cardiovascular risk reduction. The current findings provide some reassurance that fertility therapy does not appear to increase long-term risk of cardiovascular events after successful pregnancy.

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Key Words: cardiovascular disease ■ fertility therapy ■ medical outcomes ■ risk factors ■ women's health.

APPENDIX

For supplementary figures and tables, please see the online version of this article.