Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 18, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.05.085

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

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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).

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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Manuscript received February 23, 2013; revised manuscript received May 9, 2013, accepted May 21, 2013.

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