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ORIGINAL INVESTIGATIONS

Cardiovascular Risk Following Fertility Therapy

Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND The longer term cardiovascular effects of fertility therapy are unknown.

OBJECTIVES The aim of this study was to summarize data linking fertility therapy with subsequent cardiovascular outcomes.

METHODS We systematically searched published reports for studies addressing the question "does fertility therapy increase the risk of longer term cardiovascular outcomes?" We included: 1) human studies; 2) case control, cohort, or randomized designs with 3) exposure to fertility therapy and 4) cardiovascular outcomes clearly reported; 5) presence of comparison group; 6) minimum 1-year follow-up; and 7) adjustment for age. Two independent reviewers screened abstracts, titles, and full texts, and assessed study quality. We used the DerSimonian and Laird random-effects models to pool hazard ratios (HRs) with 95% confidence intervals (CIs) of the following outcomes: acute cardiac event; stroke; venous thromboembolism; hypertension; and diabetes mellitus, comparing women who received fertility therapy with those who did not.

RESULTS Six observational studies met inclusion criteria including 41,910 women who received fertility therapy and 1,400,202 women who did not. There was no increased risk of a cardiac event (pooled HR: 0.91; 95% CI: 0.67 to 1.25; $I^2 = 36.6\%$), or diabetes mellitus (pooled HR: 0.93; 95% CI: 0.87 to 1.001; $I^2 = 0\%$). Results were not pooled for hypertension ($I^2 = 95.0\%$) and venous thromboembolism ($I^2 = 82.3\%$). There was a trend toward higher risk of stroke (pooled HR: 1.25; 95% CI: 0.96 to 1.63; $I^2 = 0\%$).

CONCLUSIONS The small number of studies and significant heterogeneity precludes definitive reassurance about the longer term cardiovascular safety of these treatments, particularly stroke. Future studies are needed to address ongoing knowledge gaps in this area. (J Am Coll Cardiol 2017;70:1203–13) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACROBAT-NRSI = A Cochrane Risk of Bias Tool: for Non-Randomized Studies of Interventions

CI = confidence interval

CV = cardiovascular

CVD = cardiovascular disease

DVT = deep vein thrombosis

HR = hazard ratio

IUI = intrauterine insemination

IVF = in vitro fertilization

PE = pulmonary embolism

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

VTE = venous thromboembolism

Cardiovascular disease (CVD) is a leading cause of death in the United States (1) and Canada (2), and women experience worse cardiovascular (CV) outcomes than similar-aged men (3,4). Sex-specific risk factors for CVD are increasingly recognized, which may explain the observed disparity in CVD outcomes and the rising incidence among young women (5). For example, ischemic placental syndromes that occur during pregnancy, such as pre-eclampsia (6,7), stillbirth (8), premature delivery (9), and fetal growth restriction (10), have each been associated with an increased risk of premature CVD 10 to 15 years following delivery. A proposed mechanism for disease may involve persistent endothelial dysfunction following the initial vascular injury in pregnancy (11), or may indicate that pregnancy complications are a marker for pre-existing CV risk (12).

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The use of fertility therapies to achieve pregnancy in infertile couples is rising in Western countries (13). Such therapy includes in vitro fertilization (IVF) and intrauterine insemination (IUI), often performed following high-dose hormonal stimulation protocols (14). IVF and IUI together account for 1% to 4% of pregnancies (15,16). Approximately 20% to 30% of all IVF cycles result in a live birth (17), indicating that many women are exposed, yet do not achieve viable pregnancy. Although fertility therapy represents a safe and feasible option for many couples with infertility, these treatments may confer unintended health risks to women. For example, recent observational data indicate double the risk of severe maternal morbidity (13,18,19) in fertility-treated pregnancy when compared with naturally conceived pregnancy. Adverse outcomes may be even more pronounced among women with a lower reserve, including those with pre-existing excess CV risk (20) or frank CVD (21). What happens years after pregnancy is less well studied.

Subfertility itself has been associated with metabolic syndrome and CVD in later life (22). We hypothesize that fertility therapy might further predispose women to downstream CVD outcomes, either as a marker or mediator of increased risk. Repeated cycles of ovarian hyperstimulation and associated hyperestrogenemia contribute to a prothrombotic state (23) and may also cause endothelial injury by affecting the renin-angiotensin system (24,25). Furthermore, the CV stress of pregnancy at advanced maternal age might itself contribute to CVD (26). However, despite the steady rise in its use over the past 3 decades, the long-term CV health effects to women exposed to fertility therapy have only recently been studied, and there is uncertainty about the nature of this relationship. A Swedish population-based study (27) revealed higher rates of hypertension and a trend toward more incident strokes in infertile women who received fertility therapy compared with women who did not. Conversely, our population-based cohort in Ontario, Canada, revealed no increased risk of CV outcomes resulting from fertility therapy (28).

Given the increased use of fertility therapy among women in the developed world and conflicting evidence regarding its impact on CVD, our aim was to systematically review and summarize existing data regarding an etiologic association between fertility therapy and relevant CV risk factors and outcomes, as well as to highlight ongoing knowledge gaps in this area.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (29) and Meta-Analysis of Observational Studies in Epidemiology (30) guidelines for reporting of systematic reviews and meta-analyses of observational studies. The study was conducted following an a priori protocol (Online Appendix 1).

DATA SOURCES AND SEARCH STRATEGY. T.L., health science librarian, conducted the search. The following databases were searched without language restriction for relevant studies: MEDLINE (via Ovid 1946 to April 5, 2016; via PubMed 1946 to April 5, 2016); Embase Classic + Embase (via OvidSP 1947 to April 5, 2016); BIOSIS Previews (via OvidSP 1969 to 2016, week 18); POPLINE; CINAHLPlus with Full Text (via EBSCO, 1937 to April 5, 2016); The Cochrane Central Register of Controlled Trials (via The Cochrane Library, to issue 3 of 12, March 2016); The Database of Abstracts of Reviews of Effects (via The Cochrane Library, to issue 2

College Hospital; Peter Munk Cardiac Centre, University Health Network; Department of Medicine and Heart and Stroke Richard Lewar Centre of Excellence in Cardiovascular Research, University of Toronto. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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of 4, April 2015); the Cochrane Database of Systematic Reviews (via The Cochrane Library, to issue 3 of 12, March 2016); and LILACS (via Bireme). The search strategy used text words and relevant indexing to query whether fertility therapy increases the risk of CVD. The full MEDLINE strategy (Online Appendix 2) was applied to all databases, with modifications to search terms as necessary.

Further studies were identified in Web of Science and Scopus (August 11, 2016) by carrying out citation searches for studies citing included papers as well as by examining their reference lists. Clinical Trials registries were searched to identify relevant research in progress. The MEDLINE strategy was rerun before submission (January 4, 2017), but no further eligible studies were identified.

STUDY SELECTION. Two independent reviewers (C.K., M.O.) screened titles and abstracts, and full-text papers for inclusion. Disagreements were resolved with discussion or involvement of a third party (N.D.). Pre-defined inclusion criteria were: 1) human study; 2) case-control study, cohort study, or randomized clinical trial; 3) exposure to fertility therapy clearly reported; 4) CV outcome reported (see definition provided later in this paper); 5) presence of a comparison group without fertility therapy; 6) follow-up of 1 year reported post-fertility therapy for outcome ascertainment; and 7) estimates adjusted at least for age.

STUDY QUALITY. Risk of bias was assessed using ACROBAT-NRSI (A Cochrane Risk of Bias Tool: for Non-Randomized Studies of Interventions) (31), which assesses the potential risk of bias in observational studies in 7 domains. Each domain and the overall risk of bias for each study were rated as low risk, moderate risk, serious risk, critical risk, or as having insufficient information. The scale was applied separately for cohort and case-control studies by 2 independent reviewers (C.K., N.D.). Studies that compared infertile women who received fertility therapy with other infertile women who did not receive fertility therapy were considered of the highest quality, as opposed to studies using pregnant women who conceived naturally as the reference group. No study was excluded on the basis of quality alone.

DEFINITION OF FERTILITY THERAPY. Our exposure of interest was treatment with a pharmacological fertility agent, such as a gonadotropin agonist or antagonist (ovarian stimulation drugs), clomiphene citrate, or letrozole (ovulation induction drugs). We included IVF-based as well as non-IVF-based approaches (e.g., IUI, isolated ovulation induction) to achieve pregnancy. Where possible, we planned to analyze studies assessing IVF specifically. We defined a comparison group as women (with or without baseline infertility) who did not receive fertility therapy, regardless of whether they ever became pregnant.

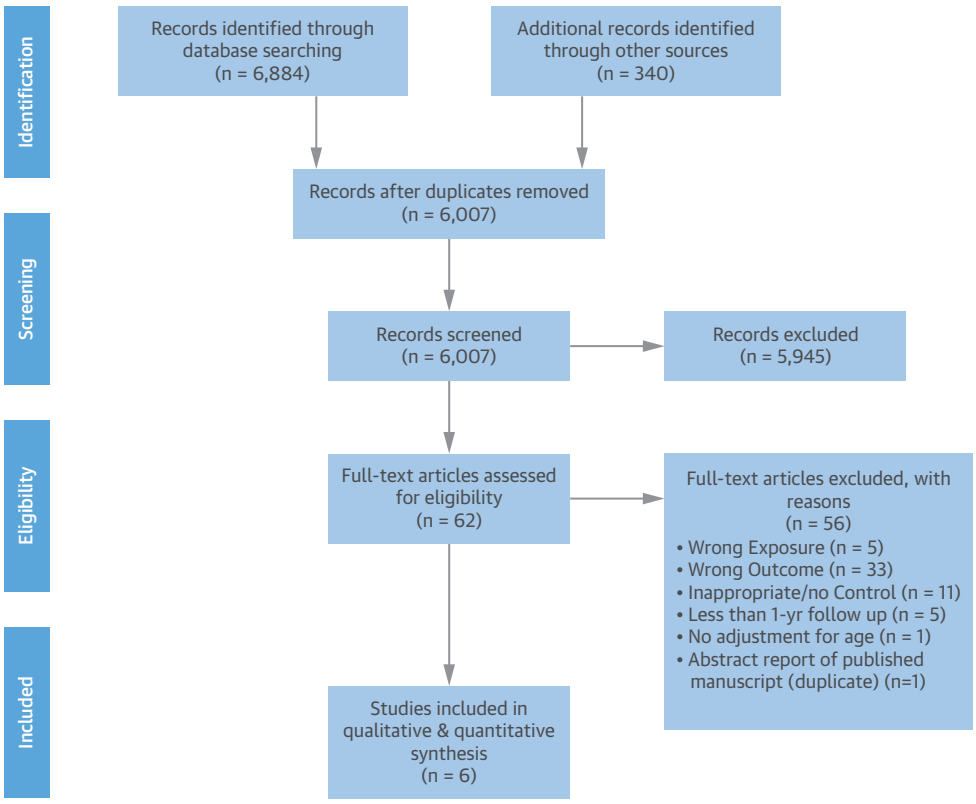
DESCRIPTION OF OUTCOMES. We considered incident CV risk factors (hypertension, diabetes mellitus) as well as overt CV diseases (including "acute cardiac events:" coronary ischemia, CV death, CV hospitalizations, heart failure, and myocardial infarction; and "other cardiovascular conditions:" cerebrovascular ischemia, stroke, or transient ischemic attack, and venous thromboembolism [VTE] including pulmonary embolism and deep vein thrombosis [DVT]). Given the heterogeneity of outcomes selected, they were reported and summarized separately.

DATA EXTRACTION. Data extraction was performed for manuscripts meeting inclusion criteria by 2 independent authors (C.K. and N.D.) using clearly defined data extraction forms. Extracted data included study design and setting, population, number with fertility therapy, number of women without fertility therapy, type of fertility therapy or therapies evaluated, CV outcome(s) assessed, and effect measures used in analysis. We further extracted available data on participants from each study including age, parity, presence of chronic health conditions before pregnancy/fertility therapy, immediate complications resulting from fertility therapy (e.g., ovarian hyperstimulation syndrome), or any pregnancy complication (VTE, hypertensive disorder of pregnancy, gestational diabetes mellitus, mode of delivery, delivery complication). We contacted the investigators if there was uncertainty about data or missing data, and any discrepancies were accounted for in our final report.

DATA ANALYSIS. Data were pooled across studies using DerSimonian and Laird random-effects models with Mantel-Haenszel weighting for each CV outcome (cardiac event, stroke, VTE, hypertension, and diabetes mellitus) when outcomes were reported by at least 2 studies. Results of the meta-analyses are presented as pooled adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) comparing women who received fertility therapy with women who did not receive fertility therapy. We estimated the amount of between-study heterogeneity that was present using the I^2 statistic. Meta-analysis was not performed in the presence of substantial heterogeneity ($I^2 > 80\%$). In our primary analyses, all measures of relative effect were pooled; in sensitivity analyses, we restricted inclusion to studies that reported HRs.

Several subgroup analyses (by study design, study quality, number of treatments, duration since treatment, invasive treatment [IVF vs. non-IVF], or level of adjustment on pooled estimates) and sensitivity

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram



analyses (e.g., influence analyses, fill-and-trim method) were pre-specified. However, because of the limited number of studies included in our systematic review with heterogeneous outcomes, these analyses were not performed. Similarly, publication bias was not formally assessed by funnel plot and Egger's test for small study effects, as all analyses included fewer than 10 studies (32). All analyses were conducted using R, version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) (33).

RESULTS

SEARCH RESULTS AND CHARACTERISTICS OF INCLUDED STUDIES. Our initial search retrieved 6,007 titles and abstracts after duplicates were removed, of which 62 full-text articles were identified for detailed assessment (**Figure 1**); 6 studies were ultimately included in our systematic review and meta-analysis. Our data summary and synthesis included 1,441,392 women: 41,190 women who received fertility therapy and 1,400,202 who did not receive fertility therapy. The median duration of follow-up across included studies was 9.8 years (range 1 to >20 years).

Characteristics of the included studies are presented in **Table 1**. All studies were published between 2013 and 2016. Studies included were population-based retrospective cohort studies (n = 2) (28,34), secondary analysis of the longitudinal Nurses' Health Study II cohort (n = 1) (25), and a single nested case-cohort study that resulted in 2 publications (n = 2): 1 reporting on hypertension and CVD (27) and another reporting VTE incidence (23). One included study (35) was an observational analysis of CV events of a randomized trial evaluating electrocautery of ovaries versus gonadotropins in women with clomiphene-resistant polycystic ovarian syndrome (36).

The types of fertility therapy described varied in the studies and included IUI, IVF, ovulation induction, and controlled ovarian stimulation with gonadotropins. IVF was reported in 4 of the 6 included studies (23,25,27,34). Outcome comparison in most included studies was between women who achieved pregnancy using fertility therapy and women who achieved pregnancy without fertility therapy. The only exception was the cohort study by Farland et al. (25), in which outcomes were compared between infertile women who used fertility therapy and

TABLE 1 Characteristics of Studies Included in the Systematic Review

First Author, Year (Ref. #)	Study Design and Setting	Type of Fertility Therapy	Outcomes	Effect Measure	Adjustment Factors	Risk of Bias*
Udell, 2013 (28)	Retrospective population-based cohort of deliveries occurring from 1993 to 2011 in Ontario, Canada	Billing code for monitoring of OI, includes many forms of assisted reproduction	CV death, cardiac ischemia, stroke, TIA, heart failure, VTE, chronic hypertension, diabetes mellitus, others	HR	Age, calendar year, geographic residence, neighborhood income, prior physician visits, antenatal visits to an obstetrician, prior medical history, length of stay, and obstetrical complications for index delivery	Moderate
Henriksson, 2013 (23)	Case-cohort design of first births following IVF and matched unassisted births from 1990 until 2008 in Sweden	IVF, derived from national IVF register	VTE (DVT and PE) occurring during the antepartum, immediate postpartum and delayed postpartum periods (1 yr)	HR	Matched with non-IVF on age and calendar year of delivery. Adjusted further for parity, smoking, education, BMI, marital status, and country of birth.	Moderate
Westerlund, 2014 (27)	Case-cohort design of first births following IVF and matched unassisted births from 1990 until 2008 in Sweden	IVF, derived from national IVF register	Hypertension, diabetes mellitus, coronary heart disease, stroke	HR	Matched with non-IVF on age and calendar year of delivery. Adjusted further for parity, smoking, education, BMI, marital status, and country of birth.	Moderate
Farland, 2015 (25)	Prospective U.S. cohort study (Nurses' Health Study II) of fertile women, infertile women who used fertility therapy, and infertile women who did not use fertility therapy, who delivered between 1993 and 2009	Clomiphene citrate, gonadotropin, IUI, IVF	Hypertension (self-reported), validated with medical records and clinical measurement in subset	RR	Age, BMI, race, smoking, parity, diet, alcohol, physical activity, oral contraceptive use, breastfeeding, analgesic use.	Moderate
Ben-Yaakov, 2016 (34)	Retrospective population-based cohort of women who delivered between 1988 and 2012 in Soroka, Israel	IVF or OI, derived using physician billing claims in administrative health data	Composite CV hospitalizations for simple CV events, complex CV events, cardiac noninvasive diagnostic procedure	HR	Pre-eclampsia, diabetes mellitus, obesity, age, and parity	Moderate
Nahuis, 2016 (35)	Long-term observational follow-up of randomized trial of electrocautery vs. gonadotropins in women with anovulatory PCOS resistant to clomiphene citrate	Ovarian stimulation (gonadotropins) vs. electrocautery of ovaries in randomized trial	Diabetes mellitus type 2, hypertension, CVD (unspecified, composite of CVD, hypertension or diabetes)	OR	Age and BMI	Serious

*As assessed by the ABROBAT-NRSI (31).

BMI = body mass index (kg/m^2); CV = cardiovascular; CVD = cardiovascular disease; DVT = deep vein thrombosis; HR = hazards ratio; IUI = intrauterine insemination; IVF = in vitro fertilization; OI = ovulation induction; OR = odds ratio; PE = pulmonary embolism; PCOS = polycystic ovarian syndrome; RR = relative risk; TIA = transient ischemic attack; VTE = venous thromboembolism.

infertile women who did not use fertility therapy regardless of incident pregnancy. In this study, the investigators reported a separate comparison with never-infertile women; however, we preferentially reported the former comparison because this has the lowest potential for bias because of confounding by indication. The CV outcomes assessed in these studies included a diagnosis of hypertension, diabetes mellitus, stroke, CV death, CV ischemia, heart failure, CV intervention, hospitalization for a CV event, and VTE. Four of 6 studies reported HRs with associated 95% CIs (23,27,28,34), 1 reported risk ratios (25) and 1 reported odds ratios (35).

STUDY QUALITY. Five of the included studies were deemed to be at moderate risk of bias, as assessed by the ACROBAT-NRSI scale, mostly because of the potential for residual confounding in cohort and case-control designs evaluating treatment effects as well as variability in the ascertainment of exposure and outcome (Table 1). One included study was judged to have an overall serious risk of bias resulting from vague ascertainment and classification of CV outcomes (35).

PATIENT CHARACTERISTICS AND PREGNANCY COMPLICATIONS. Most of the studies included young women whose average age at delivery ranged from 28.5 years to 34 years (Table 2). A greater

TABLE 2 Patient Characteristics and Pregnancy Outcomes in Included Studies According to the Presence or Absence of Fertility Therapy

	Udell, 2013 (28)		Henriksson, 2013 (23)*		Westerlund, 2014 (27)*		Farland, 2015 (25)		Ben-Yaakov, 2016 (34)		Nahuis, 2016 (35)†	
	With Fertility Therapy	Without Fertility Therapy	With Fertility Therapy	Without Fertility Therapy	With Fertility Therapy	Without Fertility Therapy	With Fertility Therapy	Without Fertility Therapy	With Fertility Therapy	Without Fertility Therapy	With Fertility Therapy	Without Fertility Therapy
N	6,979	1,179,774	23,498	116,960	23,498	116,960	7,211	8,261	4,153	95,138	69	69
Time (yrs) since pregnancy (mean ± SD or median, IQR)	9.7 (4.6–14.0)	9.7 (4.6–14.0)	42–365 days postpartum	42–365 days postpartum	8.6 ± 4.6	8.6 ± 4.9	>20 yrs	>20 yrs	11.1 ± 7.0	11.2 ± 7.0	10 (9–12)	10 (9–12)
Age at delivery (mean ± SD or median, IQR)	34 (31–36)	29 (25–33)	33.3 ± 4.0	33.4 ± 3.9	33.3 ± 4.0	33.4 ± 3.9	43.8 ± 4.0	46.6 ± 4.5	30.9 ± 6.0	28.7 ± 6.0	28.7 (4.1)†	28.5 (3.7)†
Parity (% nulliparous or mean ± SD)	–	–	100	100	100	100	5.4	0.3	1.5 ± 1.0	2.8 ± 2.0	–	–
Polycystic ovary syndrome or ovulatory disorder, n (%)	–	–	788 (3.4)	563 (0.3)	788 (3.4)	563 (0.3)	11 (0.13)	34 (4.0)	–	–	69 (100.0)	69 (100.0)
Pre-eclampsia, n (%)	480 (7.0)	39,812 (3.0)	1,235 (5.3)	2,353 (2.0)	1,235 (5.3)	2,353 (2.0)	–	–	377 (9.1)	4,471 (4.7)	1 (1.0)	0 (0)
Gestational diabetes	536 (8.0)	34,176 (3.0)	–	–	–	–	–	–	–	–	4 (6.0)	3 (4.0)
Pregnancy-associated VTE	–	–	99 (0.42)	291 (0.25)			–	–	–	–	–	–
Prior cesarean delivery	2,853 (41.0)	314,960 (27.0)	–	–	–	–	–	–	–	–	–	–
Prior multiple gestation, n (%)	13 (0.2)	686 (0.1)	3,971 (16.9)	3,040 (2.6)	3,971 (16.9)	3,040 (2.6)	–	–	–	–	–	–

The dash indicates not reported or not applicable. *Data from the same matched cohort study resulting in 2 separate publications reporting on distinct outcomes. †Derived from original randomized trial (36).
IQR = interquartile range; VTE = venous thromboembolism.

proportion of fertility-treated women were nulliparous. Furthermore, most studies that reported pregnancy complications noted increased complications in pregnancy among women exposed to fertility therapy compared with those who were not, including pre-eclampsia, gestational diabetes, cesarean delivery, and venous thromboembolism (Table 2).

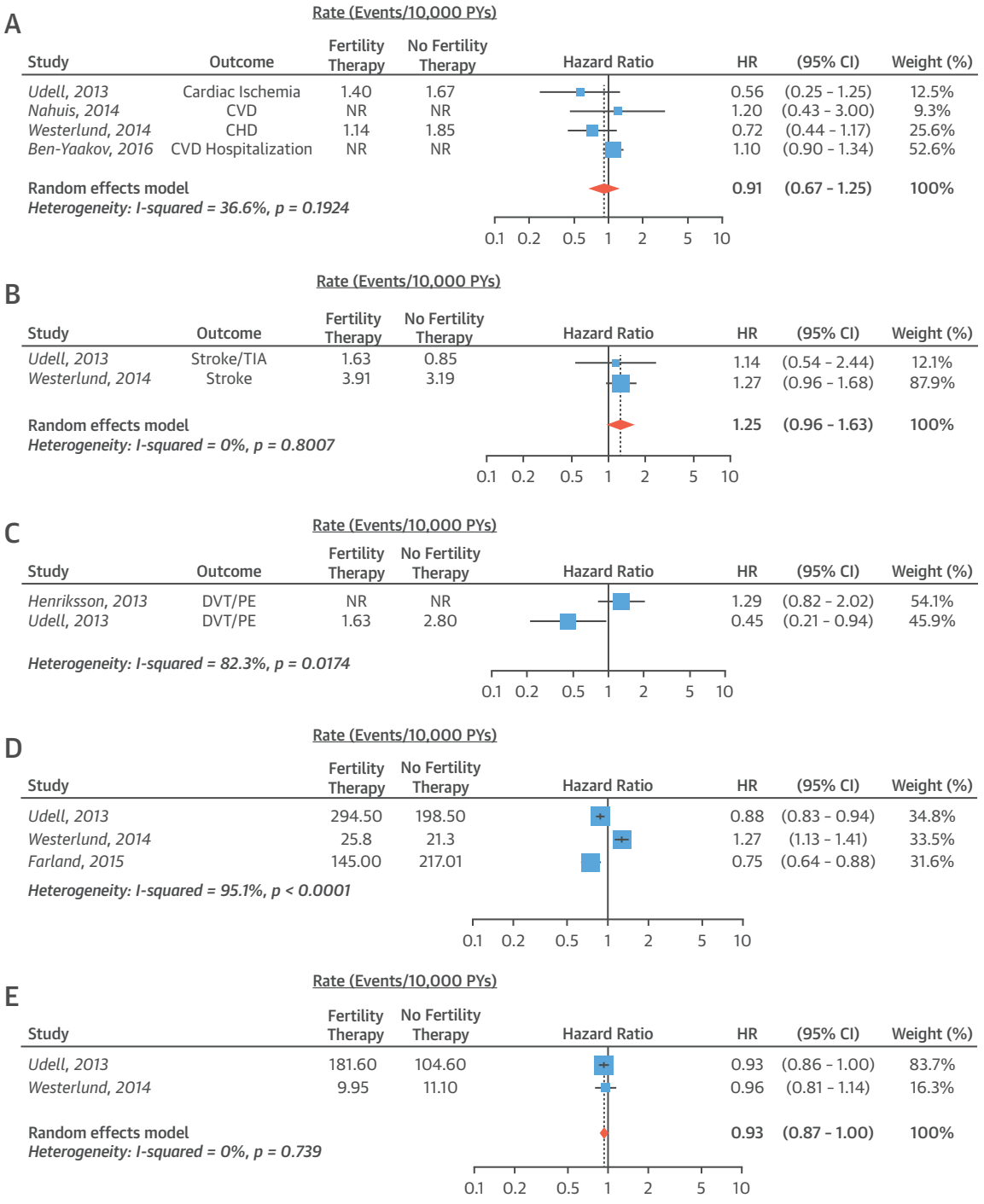
CARDIAC EVENTS. Four studies specifically reporting ischemic or other cardiac events (cardiac ischemia, coronary heart disease, CV hospitalization, and CVD not otherwise specified) among 34,699 women who received fertility therapy and 1,391,941 women who did not are summarized in Figure 2A. In the instances when they were reported, the absolute event rates were rare, at <2/10,000 person-years (27,28). Overall, the use of fertility therapy was not associated with the risk of a cardiac event (pooled HR: 0.91; 95% CI: 0.67 to 1.25; I^2 = 36.6%). We repeated the meta-analysis after removing results by Nahuis et al. (34), who reported an OR, as opposed to a HR, and the pooled estimate was similar (HR: 0.86; 95% CI: 0.58 to 1.28; I^2 = 56.6%).

STROKE. Two studies examined the risk of stroke following fertility therapy, involving 30,477 women who received fertility therapy and 1,296,734 women who did not receive fertility therapy followed for a median of 9.7 years (28) and 8.6 years (27), respectively. The absolute event rates were low in both cohorts. Pooled analysis suggested a possible increase in the risk of stroke (HR: 1.25; 95% CI: 0.96 to 1.63; I^2 = 0%) in women who received fertility therapy as compared with women who did not receive fertility therapy (Figure 2B).

VTE. Two studies evaluated the risk of incident VTE following fertility therapy involving 30,477 women who received fertility therapy and 1,296,734 women who did not receive fertility therapy. The individual estimates of effect were discordant, ranging from a possible protective effect (HR: 0.45; 95% CI: 0.21 to 0.94) in the study with a median of 9.7 years of follow-up to a possible harmful effect (HR: 1.29; 95% CI: 0.82 to 2.02) in the study with a 1-year follow-up. Owing to substantial heterogeneity (I^2 = 82.3%), these results were not pooled (Figure 2C).

CV RISK FACTORS: HYPERTENSION AND DIABETES MELLITUS. Three studies evaluated the incidence of diagnosed chronic hypertension involving 37,688 women who received fertility therapy and 1,304,995 women who did not. Two of the studies reported a protective effect of fertility therapy on the risk of hypertension (HR: 0.88; 95% CI: 0.83 to 0.94; HR: 0.75; 95% CI: 0.64 to 0.88), whereas 1 study (Westerlund et al. [27]) reported a potential harmful effect (HR: 1.27; 95% CI: 1.13

FIGURE 2 **Forest Plots Demonstrating Individual and Pooled Relative Risk(s) of Each CV Outcome in Women Who Have Received Fertility Therapy Compared With Women Who Have Not**



(A) Risk of a cardiac event in women previously exposed to fertility therapy compared with women who were not exposed. **(B)** Risk of stroke in women previously exposed to fertility therapy compared with women who were not exposed. **(C)** Risk of venous thromboembolism in women previously exposed to fertility therapy compared with women who were not exposed. **(D)** Risk of hypertension in women previously exposed to fertility therapy compared with women who were not exposed. **(E)** Risk of diabetes mellitus in women previously exposed to fertility therapy compared with women who were not exposed. CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; DVT = deep vein thrombosis, HR = hazard ratio; NR = not reported; PE = pulmonary embolism; PY = person-year; TIA = transient ischemic attack.

to 1.41). Removing the study of Westerlund et al. (27) resulted in slightly lower heterogeneity. The pooled result for Udell et al. (28) and Farland et al. (25) yielded an overall protective effect (HR: 0.83; 95% CI: 0.71 to 0.96; $I^2 = 70\%$) (**Figure 2D**).

Two studies reported on the development of diabetes mellitus including 30,477 women who received fertility therapy and 1,296,734 women who did not receive fertility therapy. The studies were concordant and the pooled result yielded a neutral effect, with a trend toward possible modest benefit on the development of diabetes mellitus (HR: 0.93; 95% CI: 0.87 to 1.001; $I^2 = 0$) (**Figure 2E**).

DISCUSSION

STUDY CONTEXT. This systematic review was designed to summarize the available evidence regarding whether the use of fertility therapy to achieve pregnancy is associated with increased longer term CV risk factors and CV outcomes, and to highlight knowledge gaps in this area. This question is increasingly relevant because fertility therapy is widely used to achieve pregnancy among older women, is associated with short-term maternal complications (13,18,19), and its long-term CV safety is unknown. In an era in which sex-based differences in CVD are increasingly recognized, reproductive factors, such as fertility therapy use, may be a sex-specific risk marker or mediator to appreciate when deciding on risk reduction strategies in women (5,37).

Both IVF and non-IVF approaches often involve repeated cycles of high-dose hormonal stimulation protocols, which lead to potential fluid shifts, endothelial dysfunction, and a prothrombotic state (23–25). Endogenous estrogens are thought to exert a protective effect on the vascular endothelium through complex mechanisms (38). However, the same is not necessarily true of exogenous or supraphysiological doses of estrogens, as demonstrated by conflicting reports about the effects of hormone replacement therapy on the risk of hypertension and incident CVD (39). Therefore, it is biologically plausible that enduring changes to the vasculature ensues following intense, repeated, high-dose exposure to reproductive hormones that occurs during fertility therapy. Furthermore, IVF may contribute to CVD risk through the development of hypertensive disorders of pregnancy such as pre-eclampsia, which is itself a potent sex-specific CVD risk factor (**Central Illustration**) (7).

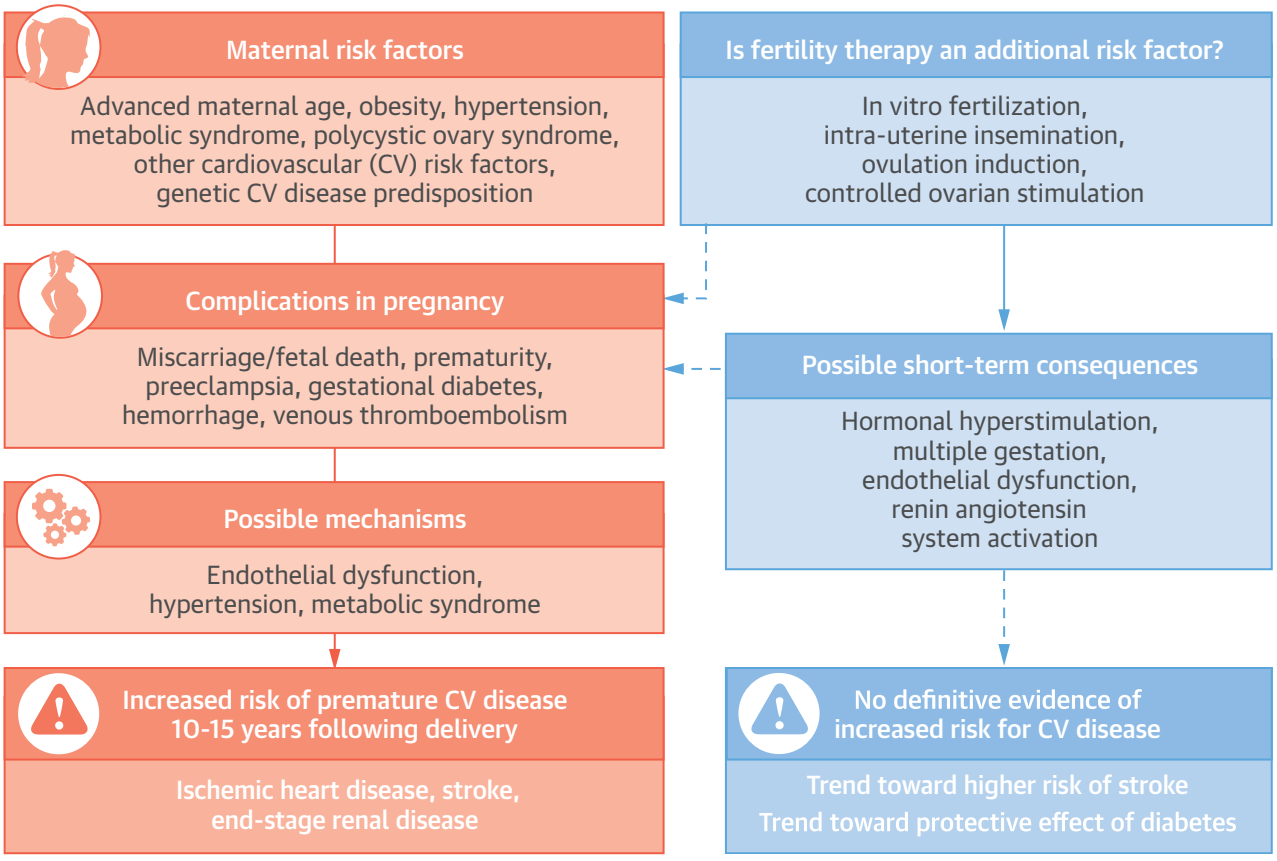
SUMMARY AND DISCUSSION OF FINDINGS. Overall, our findings derived from 6 cohorts reporting on CV risk factors and a variety of heterogeneous CVD outcomes indicate no increased risk in the development of an acute cardiac event following exposure to fertility therapy. There was a trend toward a possible modest benefit on risk of diabetes mellitus. Because there is an inevitable selection bias for undergoing fertility therapy, this apparent benefit on diabetes may simply reflect a healthy user effect rather than an established biological effect.

We detected a potential increased risk for stroke among fertility-treated women, although the CIs were wide and crossed the null, given the limited data on this outcome. The limited number of studies in this area precludes further assessment of potential risk according to stroke subtype, or of possible etiologies. Interestingly, recent data from the Women's Health Initiative suggested that, compared with younger women, women who had a pregnancy at advanced maternal age (defined as older than 40 years), experienced a 50% higher risk of both ischemic and hemorrhagic stroke 12 years following delivery (26); thus, the metabolic demands of pregnancy in older women may contribute to a downstream increased risk for cerebrovascular disease. Whether the rising use of fertility therapy among women may explain the rise in hospitalizations seen for ischemic stroke among middle-age women independent of traditional risk factors (40) is unknown; thus, the potential increased risk of stroke associated with fertility therapy should be investigated further and confirmed or refuted.

Substantial heterogeneity in the studies reporting on VTE and chronic hypertension precluded our ability to provide summary estimates for these conditions. The variation in risk estimates across studies of VTE may be at least partly explained by differences in duration of follow-up (i.e., higher risk of VTE at 1 year postpartum, but not at a median 9.7 years postpartum), suggesting that the heightened risk for VTE dissipates with time. However, the longer term risk of VTE requires further study.

Both Farland et al. (25) and Udell et al. (28) reported a reduced risk of incident hypertension in fertility-treated women compared with women without such treatment, whereas Westerlund et al. (27) found a significant 27% increase in this risk. The reason for this heterogeneity is likely multifactorial. Both the Westerlund et al. (27) and Udell et al. (28) cohorts were constructed from physician insurance claims in administrative health data, which increases the probability of misclassification, in particular when evaluating CV risk factors that may be prevalent long before being coded by a physician in a clinical encounter. However, the Udell et al. findings (28) are comparable to those reported in the Nurses' Health Study (Farland et al. [25]), in which hypertension was ascertained prospectively via self-report, validated

CENTRAL ILLUSTRATION **Relationship Among Infertility, Fertility Therapy, and Cardiovascular Disease**



Dayan, N. et al. J Am Coll Cardiol. 2017;70(10):1203–13.

Conceptual diagram depicting possible link between fertility therapy and cardiovascular disease, accounting for infertility and pregnancy events.

against medical records, and confirmed in a subset with clinical blood pressure measurement. In analyses estimating the rate and risk of hypertension, Westerlund et al. (27) excluded cases with pre-existing hypertension and hypertensive disorders of pregnancy, which may explain the low absolute risk of chronic hypertension (25.8 per 10,000 in women who received IVF and 21.3 per 10,000 in women not treated with IVF). Ethnic differences in Sweden versus North America, as well as differences in access to fertility therapy under government health insurance, might further contribute to the observed heterogeneity; therefore, we are unable to conclusively summarize the direction of the effect of fertility therapy on the future risk of hypertension.

STRENGTHS OF STUDY DESIGN. Our study has several strengths. We searched published and unpublished data without language restriction, and closely followed PRISMA guidelines in our approach. Studies were summarized using a random-effects model, which considers within- and between-study variance, and therefore provides a conservative estimate of the pooled effect size (41). Although the small number of studies precluded adequate assessment of publication bias, most studies were large and reported a null effect. Although only 6 studies were eligible for our analysis, all had been published since 2013, possibly reflecting the growing interest in the assessment of long-term CV health following fertility therapy. Despite the limited number of included studies, our review summarized data in more than 1.4 million women (41,190 women who received fertility therapy and 1,400,202 women who did not receive fertility therapy).

STUDY LIMITATIONS AND KEY KNOWLEDGE GAPS. Our systematic review highlights the inherent difficulty in studying long-term health effects of fertility therapy and underlines several limitations to the present study. First, any treatment effect reported in

observational studies may be due to confounding by indication; that is, the infertility itself may confer an increased risk for CV outcomes. For example, polycystic ovarian syndrome leads to infertility by anovulatory dysfunction and is also associated with metabolic syndrome and an accelerated atherosclerotic risk profile (42). A recent population-based cohort study conducted in Ontario, Canada, by our group (43) demonstrated that failed fertility therapy may increase the risk of heart failure and stroke when compared with successful therapy, which indicates that severe infertility may unmask a woman's predisposition toward vascular events. This paper was not included in our systematic review because of the absence of an untreated control group; however, it underscores the importance of an adequate comparison group when evaluating effect of fertility therapy, such as infertile women who were not exposed to fertility therapy. Only 1 of our included studies, a large longitudinal cohort of women, had sufficient data to report such comparisons (25).

Second, classification of exposure varied among studies and often relied on operational coding without sufficient detail on the type or dose of fertility therapy used. As a result, there may be potential for misclassification bias, resulting in an underestimate of harm from fertility therapy. This classification also does not allow the evaluation of a dose-response effect because studies did not report how many times repeated cycles were prescribed. Furthermore, some studies were limited to ascertainment of exposure using public health insurance records and potentially missing private treatments (28,34). These studies however did report methods to either approximate public and private treatment using publically covered monitoring provider codes or validated self-reported treatment with medical record review. In all cases, classification of exposure was unrelated to the outcome, rendering systematic recall bias unlikely. Finally, the follow-up for most of the studies may have been too short to find a meaningful difference in CVD outcomes among young women; as an example, prior studies reporting an increased risk of ischemic heart disease, stroke, and hypertension following preeclamptic pregnancy had between a 10- to 15-year follow-up period for most outcomes (6).

CONCLUSIONS

This is the first systematic review of the longer term CV safety associated with fertility therapy across a spectrum of women. Given the small number of studies to date and significant between-study heterogeneity, our findings indicate the presence of ongoing knowledge gaps to inform the longer term CV risk or safety of fertility therapy. Multicenter prospective studies of fertility-treated women and unexposed control subjects, or large nested case-control studies of young women with stroke and heart disease will hopefully provide further data to inform decision-making regarding fertility therapy.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Premenopausal women often lack traditional atherosclerotic risk factors, so reproductive risk factors should be carefully sought. Fertility therapy is often used to achieve pregnancy and involves repeated cycles of hormonal stimulation. In a systematic review of observational studies of fertility therapy, there was no increased risk of developing a cardiac event, but there was a trend toward an increased risk of stroke, and data were inconclusive regarding risks of hypertension and VTE.

TRANSLATIONAL OUTLOOK: Large-scale, prospective studies are needed to clarify the safety of fertility therapy and the impact of reproductive factors on CV risk.

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KEY WORDS cardiovascular disease, female infertility, ovulation induction, risk factors, stroke, women's health

APPENDIX For supplemental material, including the full Medline strategy and the predefined protocol, please see the online version of this article.