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Review Article

The Effect of Ovarian Stimulation and Assisted Reproductive Technology (ART) on Cardio-Metabolic Risk: a Systematic Review and Meta-Analysis

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Abstract

Introduction: Concerns have been raised regarding potential long-term cardiovascular impacts of fertility treatment, but data available so far are inconsistent. This systematic review and meta-analysis aim to assess the association of fertility treatment with cardiovascular outcomes in women.

Methods: We performed a systematic search of PubMed, Scopus, Web of Science, and Google Scholar through February 2024, without language restrictions. We included observational studies and randomized controlled trials that assessed cardiovascular outcomes in women who received fertility treatment vs. women who did not receive fertility treatment. We used random-effects models to estimate pooled relative risks (RRs) and 95% confidence intervals (CIs). We assessed heterogeneity using the I^2 statistic. The risk of bias of studies was assessed using the Newcastle-Ottawa (NOS) scale.

Results: In total, the analysis included 13 studies with over 107 million women (1.2 million with fertility treatment) and a mean follow-up of 17.7 years. According to pooled estimates, there were no statistically significant associations found between fertility treatment and cardiac events (RR 0.90; 95% CI: 0.68-1.21), cardiovascular disease (RR 0.99; 95% CI: 0.66-1.20), venous thromboembolism (RR 1.10; 95% CI: 0.62-1.97), hypertension (RR 1.00; 95% CI: 0.80-1.25), or diabetes mellitus (RR 0.93; 95% CI: 0.87-1.00). However, we found a statistically significant 39% relative increase in the risk of stroke (RR 1.39; 95% CI: 1.14-1.68; $I^2=22.2\%$) with low heterogeneity. The higher rates of stroke persisted, especially in the peripartum period. Other outcomes are high heterogeneity (I^2 79.5-97.9%), indicating moderate to great variability in the studies.

Conclusion: Fertility treatment was associated with a higher relative risk of stroke, while no statistically significant associations were observed for other cardiovascular outcomes. It highlights the importance of assessing cardiovascular risk during fertility care, pregnancy, and postpartum. Personal risk and educational materials on cerebrovascular risk should be considered. Future research should focus on cardiovascular assessment, phenotyping, and understanding causal pathways to improve prevention strategies.

Introduction

Infertility affects nearly one in six people of reproductive age globally. It presents a major public health challenge.[1,2] These challenges have led to remarkable growth in the utilization of Assisted Reproductive Technology (ART) over the past 40 years. Since the first recorded birth from in vitro fertilization (IVF) in 1978, more than 13 million babies have been born globally through (ART), and in some developed nations the ART birth rate now exceeds 5%, indicating widespread utilization of ART.[3,4] This increase may reflect improvements in reproductive health but also changing lifestyles and delaying childbearing.

Although fertility therapy has revolutionized the prospects of women conceiving, questions have arisen about whether there are any long-term effects on cardiovascular health for women who undergo these treatments.[2,4] A variety of biological mechanisms could increase cardiovascular risk. Certainly, controlled ovarian stimulation results in supraphysiologic levels of estrogen —often 10 to 20 times baseline concentrations— as would

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Study Highlights

- Quantifying major cardiovascular events, such as myocardial infarction and stroke, in those undergoing fertility treatment compared to spontaneous conception;
- Assessing peripartum complications like hypertensive disorders and thrombotic events;
- Examining how risks vary by treatment type;
- Evaluating the role of pregnancy complications;
- Assessing evidence quality and study heterogeneity.

be expected to affect vascular function and endothelial integrity.[5] Ovarian hyperstimulation syndrome (OHSS), which affects 0.5-6% of stimulation cycles, leads to a pro-thrombotic environment due to hemoconcentration and increased levels of vasoactive mediators, with a thrombosis risk between 50-100-fold compared to spontaneous conception.[6,7] In addition, ART treatments may cause endothelial dysfunction and increase activity of the renin-angiotensin system, which could trigger vascular damage beyond the peripartum stage.[8]

Increasing pregnancy-related complications occurring in ART-conceived pregnancies add yet another layer of complexity to the cardiovascular issues that lie ahead.[4] Several studies have reported the increased risk of hypertensive disorders associated with ART, mainly gestational hypertension and preeclampsia, especially with programmed frozen transfer when there has been poor production related to the corpus luteum of vasoactive substances necessary for placenta anatomy and function.[9,10] These pregnancy complications are more than short-term or transient events during gestation; they are long-term risk factors for cardiovascular disease. Pregnancy has been considered a "natural test for stress" to reveal clinical cardiovascular disease vulnerability, as women with preeclampsia have 4-times the risk for heart failure, and a two-times increased risk for coronary heart disease and stroke.[11,12] Therefore, any increased risk of maternal outcomes associated with ART and their future consequences on cardiovascular health must be considered seriously.

Compounding this is the underlying reason for fertility treatment in some patients, which may also independently predispose to cardiovascular disease. Polycystic ovary syndrome (PCOS) occurs in 5-20% of reproductive-aged women with insulin resistance, hyperandrogenism, and dyslipidemia, and there is recent evidence that shows a 1.5- to 2-fold increased risk of acute myocardial infarction and stroke.[13,14] Similarly, endometriosis has emerged as a female-specific cardiovascular risk factor with a 20-35% higher risk of myocardial infarction and stroke in women with endometriosis, likely mediated by chronic systemic inflammation.[15] These are particularly illustrative of the confounding by indication challenge - disentangling the effects of treatment from the cardiovascular effects of the underlying cause of infertility, is methodologically difficult and often does not receive sufficient attention.[16]

Current studies on fertility treatment and long-term cardiovascular outcomes are mixed and suggest a lack of agreement in the findings. Some large cohort studies have found increased rates of hypertensive disorders and thromboembolic events in women who received fertility treatment, while others have found no elevation in cardiovascular disease or mortality after adjusting for possible confounding factors.[17,18] A systematic review published in 2017 posited potential elevation in cardiovascular risk after fertility treatment, but was limited by the number of studies, follow-up time, and inadequate adjustment for underlying infertility and cardiovascular risk factors.[8] Since that publication, a few large, long-term, well-designed cohort studies have expanded the literature but still introduce additional heterogeneity in definitions of exposure, outcome ascertainment, and analysis.[19]

The exponential rise in fertility treatment use highlights the need to assess the cardiovascular safety of these interventions. With millions of women undergoing fertility therapy, even slight increases in cardiovascular risk could significantly impact public health. Understanding the potential risks would inform pre-conception counseling and monitoring during and after pregnancy. This systematic review and meta-analysis aims to evaluate the link between fertility therapy and cardiovascular outcomes in women by: (1) quantifying major cardiovascular events, such as myocardial infarction and stroke, in those undergoing fertility treatment compared to spontaneous conception; (2) assessing peripartum complications like hypertensive disorders and thrombotic events; (3) examining how risks vary by treatment type; (4) evaluating the role of pregnancy complications; and (5) assessing evidence quality and study heterogeneity. The goal is to provide reliable information on the cardiovascular implications of fertility therapy to guide clinical practice and patient counseling.

Materials and Methods

Protocol and registration

This systematic review was performed by the meta-analysis of observational studies in epidemiology and the recommended reporting items for systematic reviews and meta-analyses.[20,21]

Information sources and search method

Studies have been identified by checking databases with no time restrictions until 10 February 2024. The databases were PubMed, Scopus, Web of Science, and Google Scholar Search Engine. This search was done without considering the language limits. Mesh keywords were utilized for this purpose. Appendix 1 provides an example of a combination search and mesh keywords.

Inclusion and exclusion criteria

Inclusion criteria included observational studies or randomized controlled trials, exposure to a clearly defined (fertility treatment), clearly defined cardiovascular disease (CVD) outcome (reported in primary or secondary

analyses), the presence of a control group that did not receive fertility treatment, a without illness control group, and at least one year of follow-up after the start of fertility treatment. Furthermore, animal studies, commentary, case reports, and case series were omitted. Also we rejected publications that did not provide enough epidemiological data to compute absolute or relative measures of impact. If several publications from the same data source were discovered, the most current one was chosen.

Selection study

Two reviewers (HGH, GE) independently selected studies based on the inclusion criteria. The initial display of the detected articles' titles and abstracts. All papers that one of the two reviewers recognized as probably relevant were retrieved for full-text analysis. The two authors reviewed the entire material, and any disagreements were settled by the third reviewer (SS).

Definition of exposure

Fertility treatment: exposure to a pharmacological fertility agent, such as a gonadotropin receptor or antagonist (ovarian stimulation medications), clomiphene citrate, or letrozole (ovulation stimulation drugs), was for both IVF (ART) and non-IVF techniques, such as intrauterine insemination (IUI).

Definition of outcomes

A composite of relevant cardiovascular outcomes, such as coronary ischemia, cardiovascular hospitalization, myocardial infarction, cerebrovascular ischemia, stroke, transient ischemic attack (TIA), heart failure, hypertension, diabetes mellitus, venous thromboembolism and cardiovascular death.

Data extraction

The data was extracted using data extraction forms by two authors. The extracted data consisted of the author's name, year of publication, Type of study, number of years of follow-up, population, number of women receiving fertility therapy, number of women not receiving fertility treatment, type of fertility treatment or treatments evaluated, and cardiovascular (CV) outcome(s) assessed. Investigators were contacted by phone or email if there was any ambiguity regarding data or missing data, as well as contradictions in our final report.

Study quality

Each included study will be assessed for validity by two independent reviewers (GE and HGH). The STROBE checklist was used to guide reporting quality, whereas the Newcastle–Ottawa Scale (NOS) was used for risk-of-bias assessment.[22] The authors utilized a baseline scoring technique. Each question was evaluated on a scale of 0 to 2. Studies with a Newcastle–Ottawa Scale score above the predefined threshold were considered high quality and included in the meta-analysis.

Statistical analysis

We utilized STATA version 16 software for statistical analysis and producing forest plots to represent the findings of individual experiments and pooled analysis using to the dbmetan command[23]. Data from many research were evaluated using random effects models. We were included when at least two researchers reported their results. Meta-analysis results are reported as relative risk with 95% confidence intervals (CIs), comparing women who had fertility therapy to women who did not get fertility treatment. The degree of heterogeneity between studies was evaluated using the I^2 statistic[24]. Sensitivity analysis was conducted to examine the impact of excluding each study on the final outcome. Visual assessment of the funnel plot asymmetry was used to determine publication bias. The p-value was regarded less than 0.05.

Results

Overview of Search

As previously stated, the search technique employed in this study consisted of four separate databases, yielding 7,496 articles, 1,307 of which were duplicate articles and were deleted using EndNote, as well as 5,994 irrelevant articles. No automation tools were used. A total of 195 records were screened for full text review, with 182 being removed due to relevance and inclusion/exclusion criteria. Thirteen papers were evaluated for quality and eligibility. After completing the evaluation, 13 studies were selected for analysis. Figure 1 displays the flow diagram of PRISMA and the search procedure was implemented in this investigation.

Risk of bias within the studies

Two independent researchers (GE and MH) performed the risk of bias assessment for each included study using the Newcastle–Ottawa Quality Assessment Scale (NOS), which was adapted explicitly for observational studies.[25] This tool evaluates the quality of each study across eight key domains, such as participant selection, comparability, and outcome measurement. Based on these factors, the highest possible score is 16. Studies with a score of 5 or less were considered to have a high risk of bias and were excluded from the analysis. Any disagreements in the risk of bias assessment were resolved through discussion and consensus between the two researchers (Table 1).

Identifying and Characterizing of Studies

Data summary and synthesis were included for 10,769,7045 women, with 1,244,803 receiving fertility therapy and 1,06452,242 not receiving it. The investigations were focused on a variety of reproductive therapies, including IUI, IVF, ovulation induction, and controlled ovarian stimulation with gonadotropins. The average period of follow-up in the studies was 17.7 years. Most studies compared the outcomes of women who became pregnant with and without fertility therapy. The lone exception was Farland et al.'s cohort research, which compared the results of infertile women who used fertility therapy

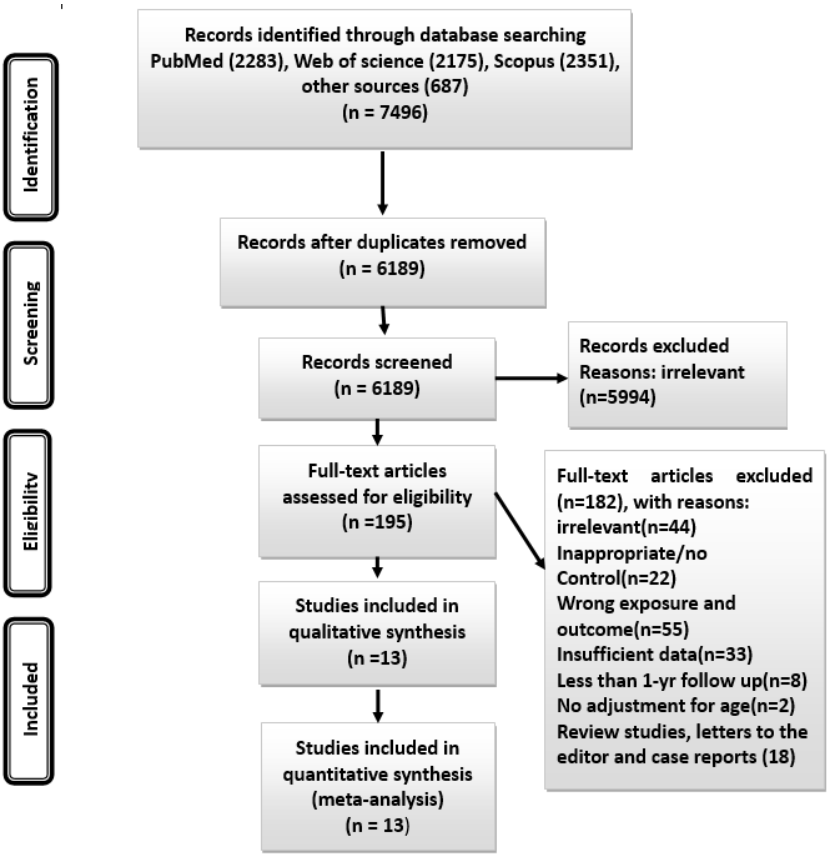


Figure 1. PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only

vs infertile women who did not use fertility treatment, regardless of an accidental pregnancy. In this study, the researchers made a separate comparison with infertile women. However, we presented the former comparison since it had the lowest potential for bias. All of the research was published between 2012 and 2024. The remaining features of the included studies are shown in Table 1.

Cardiac Event Risk Following Fertility Therapy

When 8 studies investigating the outcome of cardiac events were combined using the random effect model, the results showed that the risk of cardiac event in women who had previously been exposed to fertility treatment compared to women who had not been exposed was equal to 0.90 (95% CI: 0.68-1.21), which was not statistically significant. Furthermore, heterogeneity among studies was serious (I2 = 97.9%, $P = 0.0001$) (Figure 2).

CVD, Cardiac Ischemia and Congenital Heart Disease (CHD) Risk Following Fertility Therapy

After the five studies that assessed CVD outcomes were combined using a random effect model, the risk of CVD in women who previously had fertility therapy was 0.99 (95% CI: 0.66-1.20), which was not statistically significant. In addition, heterogeneity among studies was substantial (I2 = 97.2%, $P = 0.0001$) (Figure 2). Whenever two studies on the outcome of Cardiac Ischemia were pooled using a random effect model, the results showed that the risk of Cardiac Ischemia in women who had previously been exposed to fertility treatment compared to women who had not been exposed was 0.97 (95% CI: 0.40-2.31), which was not statistically significant. Additionally, heterogeneity among studies was substantial (I2 = 79.5%, $P = 0.027$) (Figure 2). Only one study investigated the outcome of CHD, and the estimated risk was 0.72 (95% CI: 0.44–1.17), which was not statistically significant.

Stroke Risk Following Fertility Therapy

A total of five studies on the outcome of stroke were pooled using a random effect model, the results showed that the risk of stroke in women who had previously been exposed to fertility treatment compared to women who had not been exposed was equal to 1.39 (95% CI: 1.14-1.68), which is statistically significant, suggesting that fertility treatment was associated with a higher relative risk of stroke. Furthermore, the heterogeneity between trials was minimal (I2 = 22.2%, $P = 0.273$) (Figure 3).

Venous thromboembolism Risk Following Fertility Therapy

When four studies investigating the outcome of venous thromboembolism were pooled using a random effect model, the results showed that the risk of venous thromboembolism in women who had previously been exposed to fertility treatment compared to women who had not been exposed was equal to 1.10 (95% CI: 0.62-1.97), which is not statistically significant. Also, heterogeneity among trials was substantial (I2 = 83%, $P = 0.001$) (Figure 4).

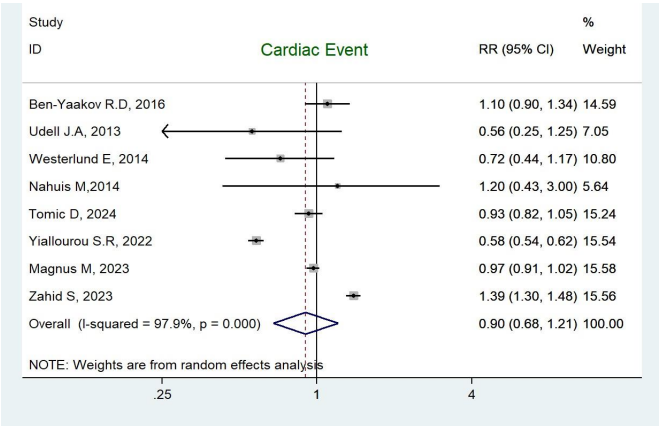
Table 1. Summary of included studies in a meta-analysis

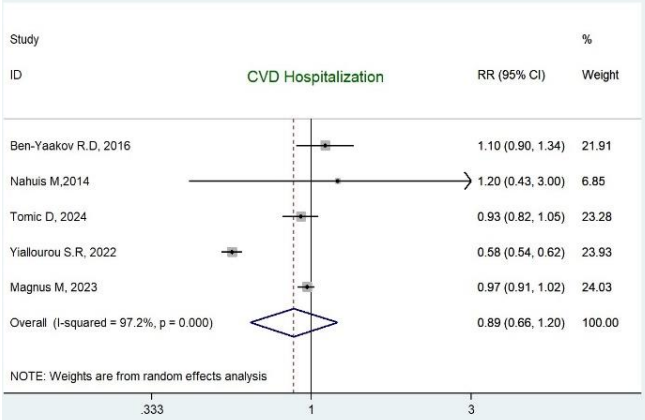
Author, Publication Year (Refernce)	Study Design	Continent	Type of Fertility Therapy	Inclusion period	N With Fertility Therapy	N Without Fertility Therapy	mean ± Age at delivery (With Fertility Therapy)	mean ± SD Age at delivery (Without Fertility Therapy)	Mean ± SD Time (yrs) since pregnancy (with fertility therapy)	Mean ± SD Time (yrs) since pregnancy (without fertility therapy)	Quality	Risk of bias
Ben-Yaakov R.D, 2016[26]	Retrospective Cohort	Asia	IVF or OI, derived using physician billing claims in administrative health data	1988 to 2012	4153	95138	30.9 ± 6	28.7 ± 6	11.1 ± 7	11.2 ± 7	High	15
Udell J.A, 2013[17]	Cohort	USA	Billing code for monitoring of OI, includes many forms of assisted reproduction	1993 to 2010	6979	1179774	34 ± 3.2	29 ± 4.1	9.7 ± 3.5	9.7 ± 3.9	High	16
Westerlund E, 2014[27]	Cohort	Europe	IVF, derived from national IVF register	1990 to 2008	23498	116960	33.3 ± 4	33.4 ± 3.9	8.6 ± 4.6	8.6 ± 4.9	High	16
Henriksson P, 2013[28]	Cross-Sectional	Europe	IVF, derived from national IVF register	1990 to 2008	23498	116960	33.3 ± 4	33.4 ± 3.9	8.6 ± 4.6	8.6 ± 4.9	Moderate	16
Nahuis M,2014[29]	Randomized Trial	Europe	Ovarian stimulation (gonadotropins) vs. electrocautery of ovaries in randomized trial		69	69	28.7 ± 4.1	28.5 ± 3.7	10 ± 3	10 ± 2.9	Moderate	13
Farland L.V,2014[30]	Prospective Cohort	USA	Clomiphene citrate, gonadotropin, IUI, IVF	1993 to2009	7211	8261	43.8 ± 4	46.6 ± 4.5			Moderate	13
Tomic D, 2024[31]	Retrospective Cohort	Australian	IVF clinical registry	1998 to 2014	24131	3131	35 ± 4	36 ± 5			High	16
Yiallourou S.R, 2022[18]	prospective cohort	Australian	IVF clinical registry	1975 to 2014	33520	10629	34 ± 3	33 ± 3			High	16
Monseur B.C, 2019[9]	Retrospective Cohort	USA	medication, intrauterine insemination, assisted reproductive technology, or other	2009 to 2015	2826	19058					Moderate	12
Sachdev D, 2023[32]	Retrospective Cohort	USA	intrauterine insemination and ART, including IVF or gamete intrafallopian transfer, fertility preservation procedures, or use of a gestational carrier	2010 TO 2016	287813	31052178					High	15
Magnus M, 2023[19]	prospective cohort	Europe	ART	1984 to 2015	691679	28047283	33.8 ± 4.7	29.1 ± 4.9			High	16
Zahid S, 2023[33]	retrospective Cohort	USA	ART	2008 to 2019	108542	45758544	35 ± 4	28 ± 3			High	13
Hansen H.A,2012[34]	prospective cohort	Europe	IVF or ICSI treatment	1994 to 2005	30884	44257					Moderate	16

Abbreviations: IVF (In vitro fertilization)/ OI (ovulation induction)/ IUI (Intrauterine insemination)/ ART (Assisted reproductive technology)/ ICSI (Intracytoplasmic sperm injection)

Hypertension Risk Following Fertility Therapy

When the four studies that evaluated the outcome of hypertension were pooled using a random effect model, the risk of hypertension in women who were previously exposed to reproductive therapy compared to women who had not was 1 (95% CI: 0.80-1.25) indicates that the link is not statistically significant. Moreover, heterogeneity among was substantial (I2 = 94.3%, $P = 0.0001$) (Figure 5).





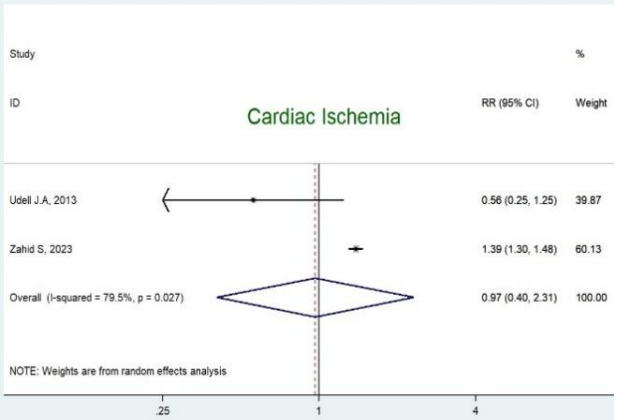


Figure 2. Forest plot for Cardiac event, CVD, Cardiac Ischemia and CHD Risk Following Fertility Therapy

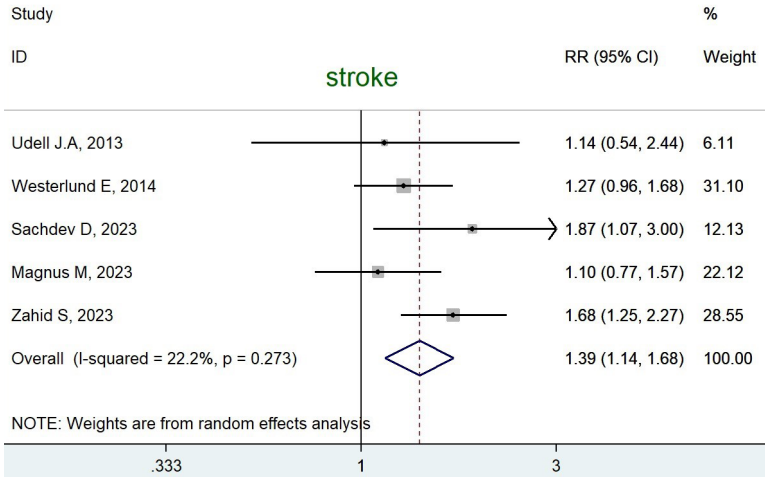


Figure 3. Forest plot for Stroke Risk Following Fertility Therapy

Diabetes mellitus Risk Following Fertility Therapy

When two studies on the outcome of diabetes mellitus were combined using a random effect model, the results showed that the risk of diabetes mellitus in women who had previously been exposed to fertility treatment compared to women who had not been exposed was 0.93 (95% CI: 1-0.87), which was not statistically significant (Figure 6).

Subgroup analysis

To understand the cause of heterogeneity, subgroup analysis by region was done. However, several subgroup strata were informed by only one or two studies; therefore, these findings should be interpreted as exploratory rather than conclusive. Formal tests for subgroup differences were not consistently statistically significant. The findings indicated that difference in hypertension risk might be explained by regional variety reported independently (Table 2).

Publication bias

The funnel plot revealed no publication bias in cardiovascular outcomes (cardiac event: *P*-value = 0.432, stroke: *P*-value = 0.521, venous thromboembolism: *P*-value = 0.121, and hypertension: *P*-value = 0.543) (Figure 7).

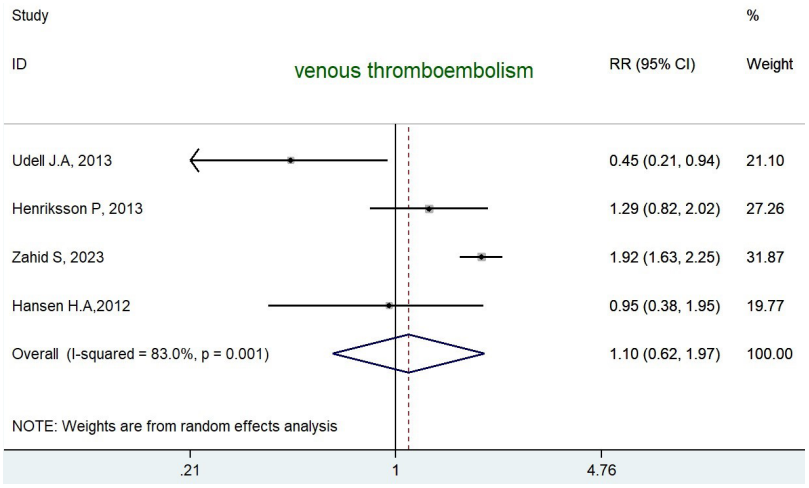


Figure 4. Forest plot for venous thromboembolism Risk Following Fertility Therapy

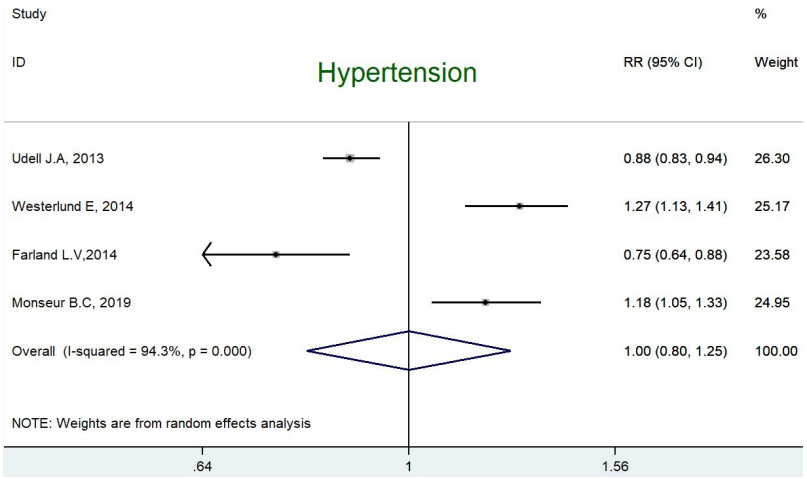


Figure 5. Forest plot for Hypertension Risk Following Fertility Therapy

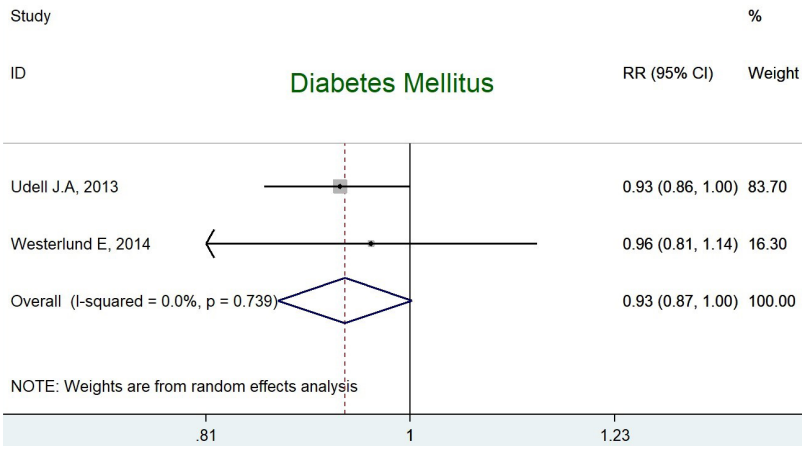


Figure 6. Forest plot for diabetes mellitus Risk Following Fertility Therapy

Sensitivity analysis

Removing a single investigation from the sensitivity analysis had no significant influence on the results in terms of CV Outcome in Women Who Have Received Fertility Therapy Vs Women Who Have Not (Figure 8).

Discussion

This systematic review and meta-analysis, which includes 13 studies comprising over 107 million women, (including 1.2 million women who underwent fertility treatment), represents the most thorough synthesis of the association between fertility treatment and long-term cardiovascular outcomes. Overall, our findings suggest a unique cardiovascular risk profile. While the pooled analyses showed statistically insignificant associations between fertility treatment and cardiac events (RR 0.90;

Table 2. Subgroup analysis impact of Fertility Therapy on Cardiovascular Risk based on effect size relative risk

	Asia			Europe			America			Australia		
	OR (CI)	I^2 (%)	*P*-value[3]	OR (CI)	I^2 (%)	*P*-value*	OR (CI)	I^2 (%)	*P*-value	OR(CI)	I^2 (%)	*P*-value*
Cardiac event	1.10(0.90-1.34)	.	.	0.97(0.91-1.02)	0	0.452	0.97(0.40-2.31)	79.5	0.027	0.73(0.46-1.16)	97.7	0.0000
Stroke				1.20(0.96-1.50)	0.0	0.534	1.65(1.29-2.11)	0.0	0.559			
venous thromboembolism				1.20(0.81-1.78)	0	0.521	0.98(0.24-4.03)	92.7	0.0001			
Hypertension				1.27(1.14-1.42)	.	.	0.92(0.74-1.16)	92.1	0.0001			
Diabetesmellitus				0.96(0.81-1.14)	.	.	0.93(0.86-1)	.	.			

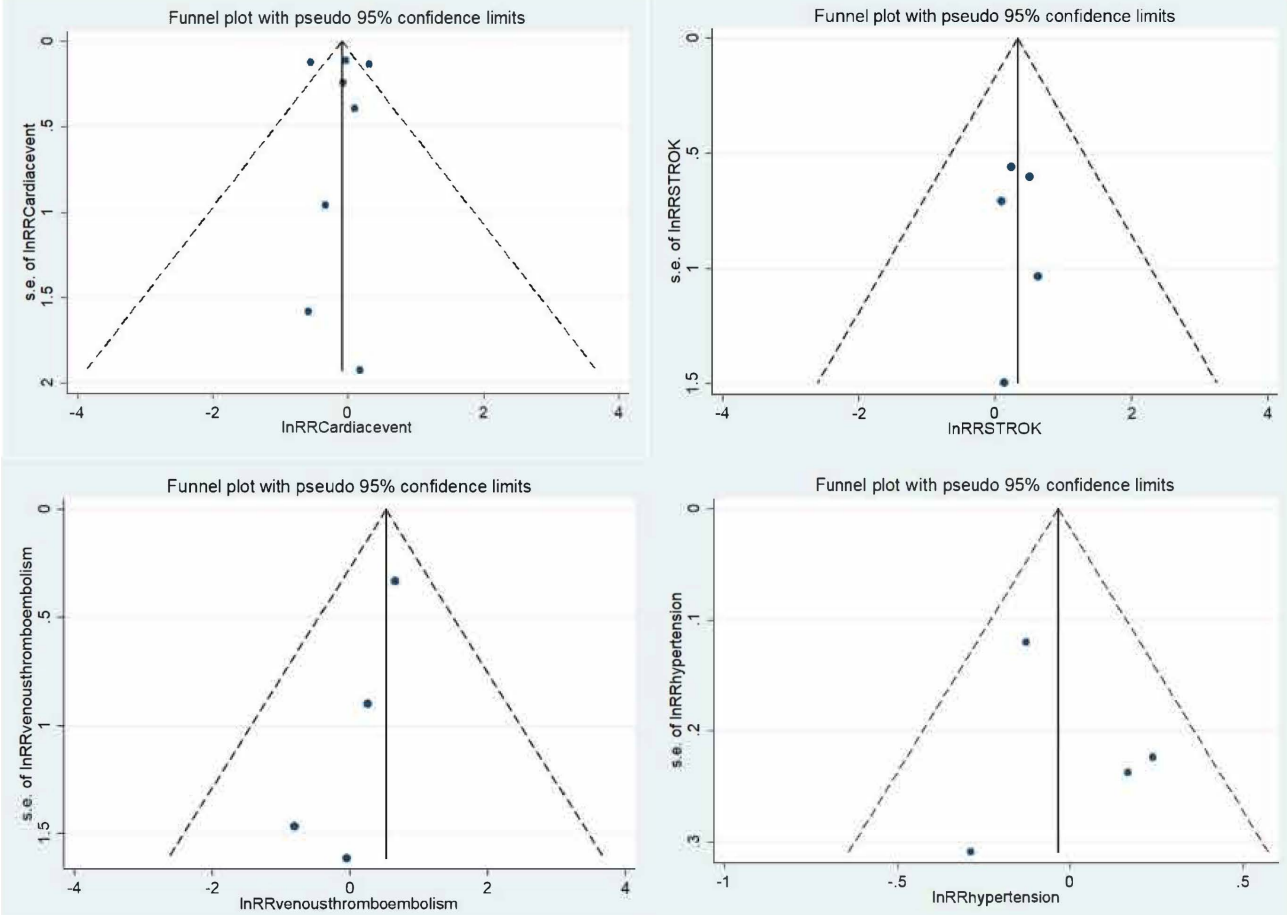


Figure 7. publication bias impact of Fertility Therapy on Cardiovascular Risk to Separately(A: Cardiac Event, B: Stroke Risk, C: Venous Thromboembolism, D: Hypertention)

95% CI: 0.68-1.21), cardiovascular disease (RR 0.99; 95% CI: 0.66-1.20), venous thromboembolism (RR 1.10; 95% CI: 0.62-1.97), hypertension (RR 1.00; 95% CI: 0.80-1.25), or diabetes mellitus (RR 0.93; 95% CI: 0.87-1.00), we observed a 39% relative increase in the risk of stroke (RR 1.39; 95% CI: 1.14-1.68, $I^2 = 22.2\%$).[31] However, substantial heterogeneity was observed across several other outcomes, which should be considered when interpreting the pooled estimates. This study's average follow-up of 17.7 years provides ample support to address long-term cardiovascular safety. The strikingly classic finding of elevated risk of stroke, yet no association with other cardiovascular outcomes, would suggest that fertility treatment either has a specific cerebrovascular effect or the underlying biology of infertility predisposes to particular vascular phenotypes. There was a consistent finding for stroke with low heterogeneity ($I^2 = 22.2$), providing greater confidence in our association, compared with Previous Literature.[27,34]

Our research builds on the 2017 meta-analysis by Dayan et al., which consists of six studies of 41,910 women undergoing fertility treatment reporting a non-significant trend toward stroke (pooled HR: 1.25; 95% CI: 0.96-1.63, $I^2 = 0\%$).[8] We now analyzed 13 studies with considerably larger sample sizes and 7 years of additional follow-up, strengthening and confirming this association to statistical significance. This evolution is a result of increasing evidence and maturation of the cohort, which leads to a larger number of stroke events.[8,35]

Even so, our results do not agree with those of several recent studies that reported reassuring findings regarding cardiovascular disease in these populations. The Nordic

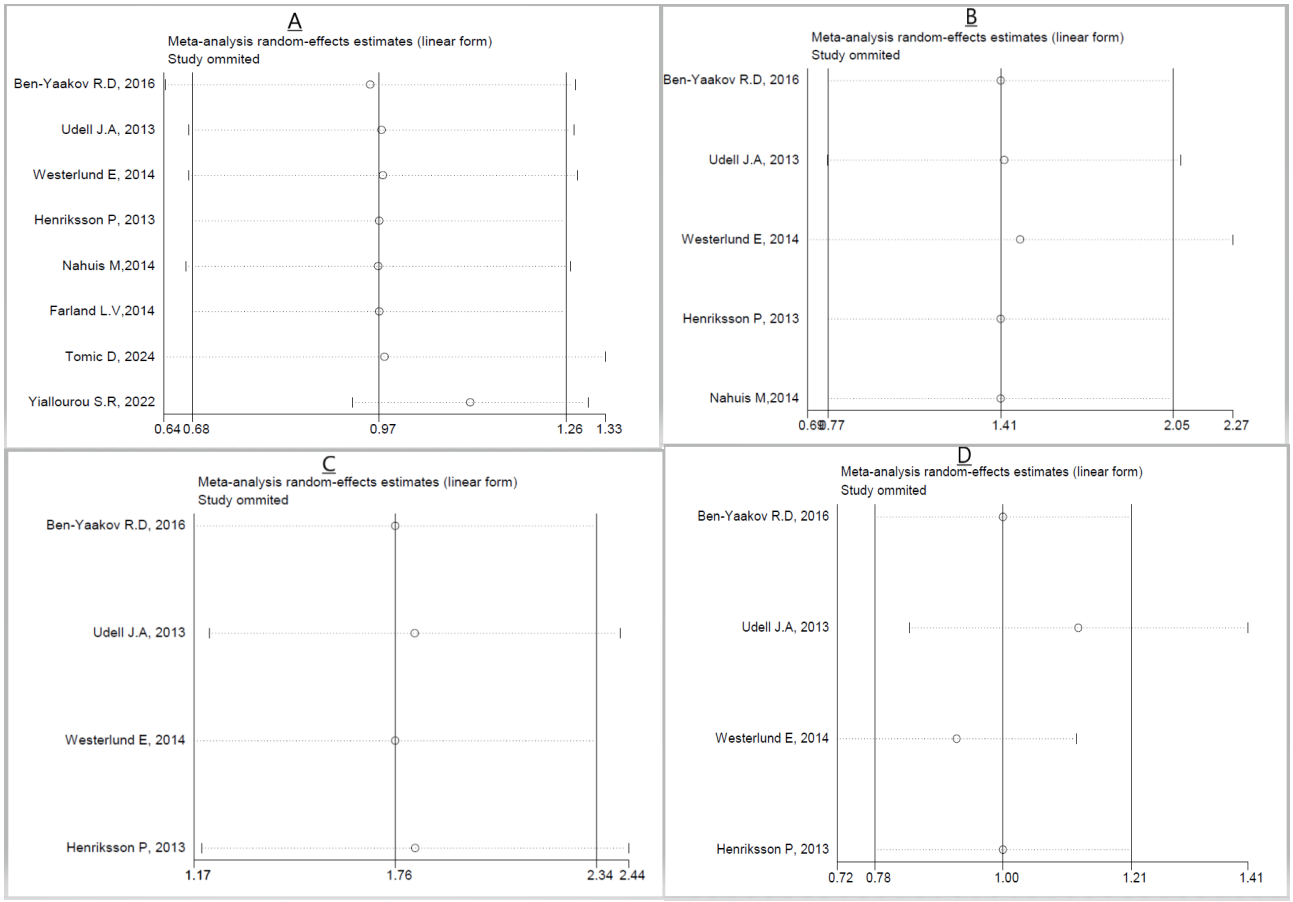


Figure 8. sensitivity analysis impact of Fertility Therapy on Cardiovascular Risk to Separately(A: Cardiac Event, B: Stroke Risk, C: Venous Thromboembolism, D: Hypertention)

cohort study by Magnus et al. [19] included data on 2.5 million women, including 97,474 women who underwent ART for median of 11 years, and reported no association between ART and risk of CVD (HR 0.97; 95% CI: 0.89-1.06), or CVD stroke (HR 0.93; 95% CI: 0.78-1.11).[19] Similarly, the Australian cohort study by Yiallourou et al. [18] reported women treated for fertility had significantly lower cardiovascular mortality than those who were untreated (SMR 0.29; 95% CI: 0.19-0.43).[18] In the recent meta-analysis published in the European Heart Journal by Pivato et al,[36] which included 10 studies with over 500,000 women, there was no association between ART and risk of stroke (ES 1.21; 95% CI: 0.92-1.59).[36]

These variations are likely attributed to considerations related to the method. Nordic and Australian cohorts may have healthier study populations, reflecting both healthcare accessibility and socioeconomic factors. The study conducted by Magnus indicated that women who accessed ART typically had a good baseline health profile and lower cardiovascular risk factors.[19,37] Differences in how confounders are adjusted for across studies can also affect outcomes. While some cohorts made adjustments for multiple confounders, including pregnancy complications, infertility diagnoses, and metabolic factors, there may have been some studies without data on confounding variables, which would lead to residual confounding.[16] The finding in our meta-analysis regarding stroke may be due to the inclusion of several recent studies, including the analysis by Sachdev et al. [32], using over 62 million deliveries in the US, showing increased risk of hemorrhagic (adjusted HR 2.02; 95% CI: 1.13-3.61) and ischemic stroke (adjusted HR 1.55; 95% CI: 1.01-2.39) in the first year postpartum after a treatment cycle for infertility.[32,38]

Several interconnected processes may account for the association with stroke. Controlled ovarian stimulation causes supraphysiologic estrogen levels, often 10-20×baseline, which creates a procoagulant state, and increased levels of coagulation factors (VII, VIII, X, fibrinogen), decreased levels of natural anticoagulants (protein S, antithrombin), and activation of the fibrinolytic state.[5,39] This prothrombotic state is maintained following the first trimester and likely contributes to thrombotic episodes. In patients with ovarian hyperstimulation syndrome (0.5-6% of ovulatory stimulation cycles), these factors are compounded by hemoconcentration, increased vascular permeability, and elevation of vascular endothelial growth factor (VEGF).[6] This prothrombotic state may increase stroke risk between 25-100-fold.[7]

In addition to hormonal effects, supraphysiologic estrogen can paradoxically reduce endothelial function by causing oxidative stress, altering the bioavailability of nitric oxide, and activating inflammatory pathways.[40] Renin-angiotensin systems activated during the stimulation may cause vascular dysfunction, which extends beyond when treatment stops.[41] Abnormal placentation, particularly

in programmed frozen embryo transfer when vasoactive factors from the corpus luteum are absent, can increase the incidence of hypertensive disorders, which are themselves established stroke risk factors.[10,42]

Confounding by indication poses a serious methodological concern. Women who need fertility treatment often have conditions that increase cardiovascular risk in isolation. For example, PCOS affects 5-20% of reproductive-aged women and is associated with insulin resistance, hyperandrogenism, dyslipidemia, and chronic systemic inflammation; recent studies suggest women with PCOS have a 1.5-2-fold higher risk for myocardial infarction and stroke.[13,43] Endometriosis has a 20-35% higher risk of developing myocardial infarction and stroke as well, and is mediated in part through mechanisms associated with chronic systemic inflammation and endothelial dysfunction.[15,44] Thus, associations with stroke may be reflecting cardiovascular consequences of the underlying infertility rather than effects associated with the fertility treatment itself.

Pregnancy complications are another important mediating pathway. Several studies have documented higher rates of hypertensive disorders in ART-conceived pregnancies.[9,33] These complications are well-established risk factors for future cardiovascular disease, with preeclampsia reducing the risk of heart failure four-fold and increasing the risk of stroke two-fold in the ensuing decades.[11,45] Recent data suggest that adverse pregnancy outcomes may account for significant proportions of (possibly over 50% of) the associations between assisted reproductive technologies and long-term cardiovascular disease.[46,47]

Our results have meaningful clinical implications. First, preconception cardiovascular risk assessment may be considered for women seeking fertility treatment, especially for women who meet criteria for PCOS, endometriosis, obesity, and/or systemic hypertension, or have a family history of cardiovascular disease. The American Heart Association Scientific Statement in 2025 recommended comprehensive cardiovascular screening before ART in women over 35 or with multiple risk factors.[48] Second, increased surveillance during pregnancy and peripartum could be beneficial given the observed association, especially in the first month after childbirth which is the highest incidence of peripartum stroke.[32,49] This surveillance may particularly focus on blood pressure monitoring, with a low threshold for evaluating headache, visual changes, or neurologic symptoms. Third, providers may provide ongoing cardiovascular follow-up for women beyond the peripartum period in future reproductive healthcare. As part of future post-reproductive care, primary care providers should ask about reproductive history, as fertility treatment and pregnancy complications should be included in a future consideration of female-specific cardiovascular risk factors not included in traditional algorithms.[12] Finally, counseling the patient about the cardiovascular risk factors regarding fertility treatment in the informed consent process should be part of future care to ensure comprehensive care. Although the absolute stroke rate remains low (approximately 37 strokes per 100,000 person-years), the 39% relative increase in stroke risk factors is meaningful information to convey (will need to strike a balance when relaying this).[32,33]

Strengths and Limitations

This review has important strengths. The sample size was substantial —more than 107 million women —which provided considerable statistical power. The robust search strategy across multiple databases, without language restrictions, minimized the potential for selection bias. The extended average follow-up time of 17.7 years provided for the evaluation of outcomes that may emerge years after treatment. The review also included more recent high-quality studies conducted from 2012 to 2024 to support the contemporary relevance of the findings.

Nevertheless, there were limitations that needed to be acknowledged. First, the observational design precludes us from making definitive causal inferences due to residual confounding. While many studies adjusted for age, parity, and some metabolic factors, adjusting for PCOS, endometriosis, Body mass index (BMI), smoking, and socioeconomic status was inconsistently reported.[50,51] Second, there was substantial heterogeneity across most outcomes (I^2 79.5%–97.9%), indicating considerable variability in study populations, exposure definitions, outcome ascertainment, and adjustment strategies. This degree of heterogeneity substantially limits the interpretability and certainty of pooled estimates, particularly for non-stroke outcomes. Third, since exposure ranged from ovulation induction to complex IVF/ICSI, it makes it difficult to conclude a specific treatment. Fourth, there was limited information on specific protocols, and therefore, subgroup analyses could not be performed. Fifth, the majority of studies were limited to women with successful pregnancies and may therefore reflect selection bias. Sixth another limitation is that the included studies reported different effect measures, including RR, HR, OR, and SMR. Although these measures may be broadly comparable when outcomes are rare, such differences could have introduced some imprecision into the pooled estimates. Finally, we cannot rule out potential publication bias in favor of positive findings, though numerous large neutral cohorts somewhat mitigate it.

Future Research Directions

Significant knowledge gaps need examination, including prospective cohort studies with thorough baseline assessments, standardized treatment recording, and long-term follow-up; mechanistic studies on stroke risks involving coagulation, endothelial function, inflammation, and cerebrovascular imaging; comparative risk assessments of treatments like ovulation induction, IUI, and embryo transfer; IPD meta-analyses for subgroup and risk estimation; studies on preventive interventions

such as aspirin and blood pressure control; and cost-effectiveness analyses of screening and prevention strategies for future guidelines.

Conclusion

This thorough systematic review and meta-analysis indicate that fertility treatment is linked to a 39% higher risk of stroke. At the same time, all other major cardiovascular outcomes, including heart events, cardiovascular disease, venous thromboembolism, hypertension, or diabetes mellitus, were not significantly correlated. These results build on the previous meta-analyses with substantially larger sample sizes and follow-up times, adding more substantial support to specific cerebrovascular risk. There is a large degree of heterogeneity in most of the results, along with probable confounding by underlying infertility and pregnancy complications in this patient group, so the results should be interpreted with caution. Despite an association between fertility treatment and a 39% relative increase in stroke risk, this should be balanced with reassuring findings for other cardiovascular outcomes and a low absolute risk of stroke.

These warrants provide support for the inclusion of cardiovascular risk assessments in fertility treatment protocols, enhanced monitoring during pregnancy and peripartum for women conceiving via fertility therapy, and long-term cardiovascular follow-up well after reproductive years. Specifically noting stroke risk should guide patient communication and patient-centered decision-making, while acknowledging that most women have a low absolute cardiovascular risk. Future studies using prospective designs with a variety of cardiovascular phenotyping, detailed characterizations for fertility treatment, and systematic assessments for mediators and confounders will be necessary to determine causality, understand mechanisms, and develop prevention based on evidence. Until robust evidence is available, a cautious interpretation that emphasizes clinical assessment of individual risk, informed patient conversations, and appropriate clinical monitoring is anticipated to provide the best cardiovascular health for women receiving fertility support.

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Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

This study was approved by the Ethics Committee of Urmia University of Medical Sciences, Urmia, Iran, under the ethics approval code IR.UMSU.REC.1403.018.

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