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AHA SCIENTIFIC STATEMENT

Assessing and Addressing Cardiovascular and Obstetric Risks in Patients Undergoing Assisted Reproductive Technology: A Scientific Statement From the American Heart Association

Rina Mauricio, MD, Chair; Garima Sharma, MD, FAHA; Jennifer Lewey, MD, MPH; Rose Tompkins, MD; Torie Plowden, MD, MPH; Kathryn Rexrode, MD, MPH, FAHA; Mary Canobbio, MN, MPH; Jenna Skowronski, MD; Afshan Hameed, MD; Candice Silversides, MD; Harmony Reynolds, MD, FAHA; Arthur Vaught, MD, Vice Chair; on behalf of the American Heart Association Cardiovascular Disease and Stroke in Women and Underrepresented Populations Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and Council on Lifelong Congenital Heart Disease and Heart Health in the Young

ABSTRACT: The use of assisted reproductive technology (ART) is growing, both to assist individuals with infertility and for fertility preservation. Individuals with cardiovascular disease (CVD), or risk factors for CVD, are increasingly using ART. Thus, knowing how to care for patients undergoing ART is important for the cardiovascular clinician. In this scientific statement, we review the ART process and known short-term and long-term risks associated with ART that can adversely affect patients with CVD. We review current knowledge on risks from ART for specific cardiac conditions and provide a suggested approach to evaluating and counseling patients with CVD contemplating ART as well as suggested management before and during the ART process. Individuals with CVD are at increased risk for pregnancy complications, and management of this unique population has been discussed previously. The focus of this scientific statement is on ART. Therefore, discussions on risk assessment, counseling, and management of individuals with CVD during pregnancy are limited, and established guidelines are referenced.

Key Words: AHA Scientific Statements ■ assisted reproductive techniques ■ cardiology ■ obstetrics ■ pregnancy

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According to the World Health Organization, 1 in 6 adults worldwide experience infertility, and data indicate that 1 in 7 individuals in the United States experience subfertility (ie, have difficulty becoming pregnant or sustaining a pregnancy).[1,2] Assisted reproductive technology (ART) is increasingly used to help individuals achieve pregnancy or preserve fertility. In 2019, ≈2.1% of registered births in the United States were conceived using ART, and this number is expected to rise. Furthermore, the practice of egg and embryo freezing is becoming increasingly common for fertility preservation.

Knowing how to care for patients undergoing ART is becoming increasingly relevant for cardiovascular clinicians. A growing number of individuals are using ART because of advanced maternal age.[3] Individuals experiencing infertility have a higher burden of cardiovascular disease (CVD) risk factors.[3–6] In addition, patients with congenital heart disease are surviving longer into adulthood and may use ART, particularly those with congenital heart disease conditions that may affect fertility.[7] Although ART is well-tolerated in most patients, complications can occur and may be poorly tolerated in people with CVD. The literature on the risks of ART in patients with CVD is limited and guidance for the clinician is sparse.

This scientific statement provides guidance for cardiovascular clinicians caring for individuals contemplating ART and summarizes the available literature on risks of ART in individuals with CVD and possible adverse cardiovascular outcomes from ART. A suggested approach to

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the evaluation of patients with CVD seeking fertility treatment is proposed, as well as modifications to therapy that can be discussed in concert with a reproductive endocrinology and infertility (REI) specialist to minimize known risks. We identify knowledge gaps and future research directions. We use gender-neutral language and the term "individuals attempting pregnancy" when referring to data collected and reported in individuals identifying as women.

OVERVIEW OF ART

ART encompasses in vitro handling of oocytes, embryos, or both. In 2020, >326 000 ART cycles were performed at 449 clinics in the United States reporting data, which yielded 75 023 live births resulting in 79 942 live-born infants.[8]

Depending on the cause of infertility, various treatment options are available.[9] Options include ovulation induction or ovarian stimulation, which involve the use of pharmacologic treatments to induce ovulation in the former or induce multiple mature ovarian follicles in the latter.[9] This can then be followed by timed intercourse or intrauterine insemination to achieve fertilization. Various fertility treatment options exist and have been reviewed previously[9]; we focus on oocyte retrieval and embryo transfer, either to the patient or a gestational carrier, because these entail higher risk and cardiology clinicians are commonly asked to evaluate patients before these specific therapies.

Before oocyte retrieval, patients undergo ovarian stimulation with injectable gonadotropins for ≈10 to 14 days (Figure 1). During this time, patients undergo frequent monitoring, including transvaginal ultrasound and serial blood tests to evaluate hormone levels. Once ovarian follicles reach at least 18 mm, an injection is administered to trigger the maturation process; ≈36 hours later, transvaginal oocyte retrieval (TVOR) is performed. TVOR is typically done under conscious sedation in an outpatient setting and lasts ≈20 minutes. Once the oocytes are retrieved, they are cryopreserved or fertilized, using conventional in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), to create embryos. Conventional fertilization in IVF is performed by placing both oocytes and sperm in a dish and allowing the sperm to fertilize the oocyte. During ICSI, 1 sperm is chosen and injected into the cytoplasm of the oocyte. The original indication for ICSI was to overcome male factor infertility and increase the fertilization rate. The resulting embryo can then be transferred into the uterus (of either the patient or a gestational carrier) if pregnancy is desired currently, in a process called fresh embryo transfer, or cryopreserved for future use. Cryopreserved embryos can be thawed and transferred into the uterus (of either the patient or a gestational carrier) in a process known as frozen embryo transfer.

Progesterone, with or without estrogen depending on the individual REI center's protocol, is given before fresh and frozen embryo transfer. In fresh embryo transfer, the presence of circulating estrogen after ovarian stimulation thickens the endometrial lining. Additional estrogen may or may not be given, depending on the center. The patient is then placed on progesterone for 5 days before transfer. For frozen embryo transfer, some centers may use natural cycle frozen embryo transfer, timing embryo transfer to the individual's own menstrual cycle without using exogenous estrogen. If natural cycle frozen embryo transfer is not used, the patient will typically be placed on estrogen for ≈14 days to stimulate the growth of the endometrial lining. After an acceptable endometrial thickness is reached, progesterone will be given before the embryo is thawed and transferred into the uterus. Estrogen can be given in transdermal, oral, or injectable formulations.

SHORT-TERM RISKS FROM ART THAT CAN ADVERSELY AFFECT PATIENTS WITH CVD

Ovarian stimulation and oocyte retrieval can affect cardiovascular hemodynamics and, in some cases, result in complications that are poorly tolerated in the CVD population. Under normal physiologic conditions, the hypothalamic-pituitary-ovarian feedback mechanism limits follicular recruitment to 1 dominant follicle per menstrual cycle. However, during ART, this protective mechanism is disrupted by use of exogenous gonadotropins that lead to recruitment of numerous follicles. This, along with an induced luteinizing hormone surge, supports continued follicular enlargement with subsequent massive luteinization of granulosa cells driven by human chorionic gonadotropin administration. The resultant corpus luteum produces supraphysiologic amounts of vascular endothelial growth factor, which can cause excessive perifollicular neovascularization and increased vascular permeability. This change in physiology results in leakage of large amounts of fluid from the perifollicular vessels and the surrounding peritoneal vasculature.[10]

Ovarian hyperstimulation syndrome (OHSS) is an exaggeration of this process and causes massive fluid shifts from the intravascular to the extravascular space. OHSS can be seen among 0.1% to 6% of ART cases, and severity varies from mild to critical.[11] The risk of OHSS increases with the number of oocytes retrieved,[11,12] but when using techniques recommended by established guidelines,[13] the incidence of OHSS is rare. The hallmark of OHSS is intravascular hypovolemia and third spacing with peripheral edema, ascites, hydrothorax, and multiorgan involvement including the heart. These massive fluid shifts may manifest as hypotension, arrhythmias, syncope, or all three. Intravascular volume depletion coupled with supraphysiologic estrogen levels leads to the other morbid sequalae of OHSS: an increased risk of both venous and arterial thromboembolism.

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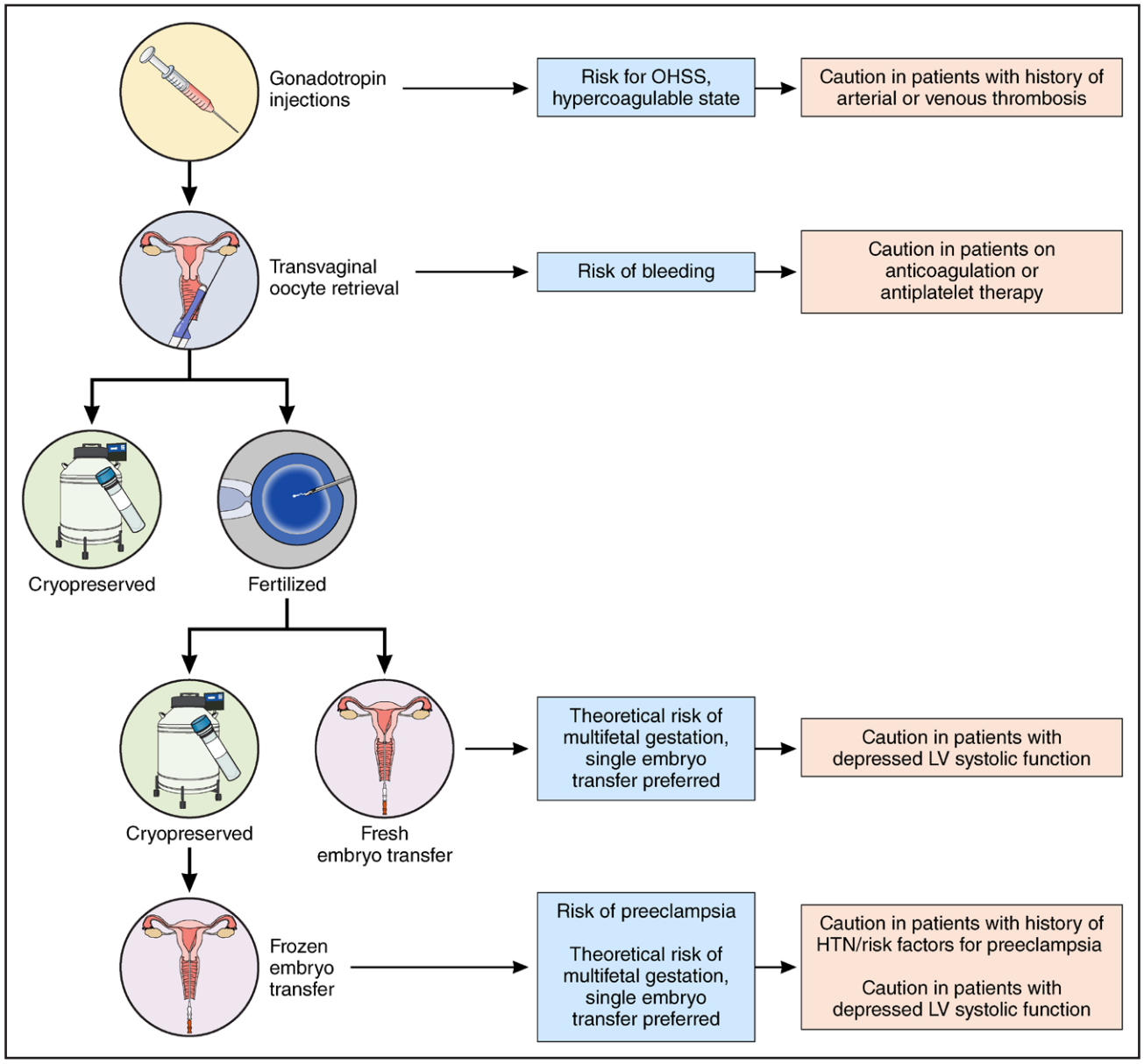

Figure 1. Overview of assisted reproductive technology.
The process begins with ovarian stimulation with injectable gonadotropins and frequent monitoring for follicular development. Once deemed appropriate, the patient receives a "trigger" injection, usually with human chorionic gonadotropin. Approximately 36 hours later, the patient undergoes transvaginal oocyte retrieval, which is typically done under conscious sedation and lasts ≈20 minutes. Retrieved oocytes are either cryopreserved or fertilized to create embryos. A resulting embryo can then be transferred into the patient's uterus if pregnancy is desired immediately or can be cryopreserved for future use. Before frozen embryo transfer, the patient will typically be placed on oral or injectable estrogen medication for 14 days, then subsequent progesterone injections for several days before the embryo is thawed and transferred into the uterus. HTN indicates hypertension; LV, left ventricular; and OHSS, ovarian hyperstimulation syndrome.

Pregnancy increases the risk of venous thromboembolism (VTE), with the highest risk in the first 6 weeks postpartum. The strongest risk factor for VTE during pregnancy is previous VTE, which increases the risk by ≈25-fold.[14] In addition, there is a 2.5- to 3-fold increased risk of VTE in pregnancies conceived through ART, above the baseline risk of pregnancy, and particularly during the first trimester.[15–18] This increased risk may be secondary to, or independent of, OHSS. IVF with fresh, but not frozen, embryo transfer was identified as a risk factor for VTE, which may be attributable to the differences in resulting estrogen levels between them.[18] In a recent systematic review, factor V Leiden, G20210A prothrombin gene variant, protein C and S deficiency, and antiphospholipid antibodies were not associated with a higher risk of VTE during ART[18]; however, data are scant. The increased risk of thromboembolism may have important implications in patients with CVD who are at high risk for thromboembolic complications, including those with atrial fibrillation, previous stroke, or both, Fontan circulation, or mechanical heart valves.

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Bleeding is another short-term risk of ART, particularly during TVOR, but the overall rate is low (<1%).[19]

Proper pain control during ART procedures is also integral. Procedures to work-up or treat infertility (ie, hysteroscopy or laparoscopy) and TVOR require sedation and regional or general anesthesia for adequate pain control. Embryo transfer is less invasive, requiring cervical visualization and subsequent insertion of a small catheter, so may only occasionally require sedation or anesthesia.[20] Clinicians should be aware of a possible vagal response during TVOR or during cervical manipulation at embryo transfer.[20] Many anesthetics and analgesics can have hemodynamic effects based on the dose administered and may affect patients differently depending on their underlying CVD process.

RISK FOR ADVERSE PREGNANCY OUTCOMES AND FUTURE CVD AFTER ART

Individuals using ART tend to have a higher burden of CVD risk factors, and therefore may be a high-risk subgroup that would benefit from additional counseling on possible cardiovascular risk after ART.[3–5]

Risk of Adverse Pregnancy Outcomes After ART

ART has been associated with an increased risk of adverse pregnancy outcomes and perinatal outcomes. In ART, the oocytes and embryos are exposed to high levels of estradiol, fluctuations in levels of vascular endothelial growth factor, and altered hormonal environments during oocyte retrieval, which have been proposed as possible mechanisms for adverse perinatal outcomes.[21] In addition, vascular endothelial growth factor has been implicated not only in preeclampsia but also in CVD of nonpregnancy origin.[22,23]

It is unclear whether the increased risk of adverse pregnancy outcomes after ART is secondary to intrinsic risk of the infertile person versus exogenous administration of hormones during ART. The increased risk is likely multifactorial and inclusive of both. The cardiovascular clinician needs to be aware of known adverse pregnancy outcomes associated with ART. Known associations between ART and adverse pregnancy outcomes are outlined in Table 1.

Hypertensive Disorders of Pregnancy

IVF or ICSI singleton pregnancies have an elevated risk for hypertensive disorders of pregnancy versus unassisted conception, even after controlling for confounders such as age and the presence of traditional cardiovascular risk factors.[24–26] A few studies have explored the association between unassisted pregnancies and fresh or frozen embryo transfer and found that frozen embryo transfer is associated with higher odds of hypertensive disorders of pregnancy (versus unassisted pregnancy: frozen embryo transfer odds ratio [OR], 1.74 [95% CI, 1.58–1.92]; fresh embryo transfer, OR 1.43 [95% CI, 1.33–1.53]).[25,31,32] This was confirmed in a population-based study of nearly 2.4 million individuals, comparing patients who had IVF versus naturally conceived pregnancy, and found that pregnancies resulting from frozen embryo transfer had a significantly higher risk of hypertensive disorders of pregnancy when compared with naturally conceived pregnancies at the population level (7.4% versus 4.3%; OR, 1.74 [95% CI, 1.61–1.89]).[33] The reason for this is not fully understood. It may be due to epigenetic changes driven by the freezing and thawing of the embryo, increased vascular endothelial growth factor levels associated with frozen cycles, or improper trophoblastic invasion, as seen in preeclampsia.[33] There are ongoing clinical trials examining the outcome of preeclampsia in fresh versus frozen protocols (NatPro [Natural Versus Programmed Frozen Embryo Transfer]; https://www.clinicaltrials.gov; unique identifier: NCT04551807).

Gestational Diabetes

Meta-analyses have shown a higher risk for gestational diabetes in pregnancies conceived by ART compared with spontaneous conception (Table 1).[24,27] However, these studies have several potential confounders, such as polycystic ovary syndrome, maternal age ≥40 years, and history of diabetes in a first-degree relative in those undergoing ART, all of which increase the odds of gestational diabetes.[34,35]

Preterm Birth

There may be an increased risk of preterm birth after IVF (Table 1).[24] One study of statewide perinatal linkage data showed that, compared with unassisted pregnancy, IVF pregnancies with fresh and frozen embryo transfer and ICSI pregnancies with fresh embryo transfer had higher odds of preterm birth (OR, 2.20 [95% CI, 1.79–2.70] for IVF with fresh embryo transfer; OR, 1.63 [95% CI, 1.24–2.15] for ICSI with fresh embryo transfer; OR, 2.02 [95% CI, 1.49–2.75] for IVF pregnancies with frozen embryo transfer).[36] However, in a study using data from sibling pairs, the absolute difference in risk of preterm birth was low (absolute risk 9.7% with IVF or ICSI versus 7.9% with spontaneous conception; absolute difference 1.8%).[37] Higher risks of preterm births with IVF are superimposed on the already increased risk of preterm births seen in the cardiac population overall.[38]

Risk of CVD After ART

Studies have analyzed the association between ART and future risk for CVD. Conclusions on the association between ART and future CVD are likely confounded by causes of infertility known to increase risk of CVD,

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Table 1. Risk for Adverse Pregnancy Outcomes and Future Cardiovascular Disease After Assisted Reproductive Technology

Adverse pregnancy outcome or future cardiovascular disease	Study type or population	Adjusted RR, OR, or HR (95% CI)*	Event rate (ART vs No ART)
Adverse pregnancy outcome			
Hypertensive disorder of pregnancy			
Pandey et al[24]	Meta-analysis	RR, 1.49 (1.39–1.59)	Not reported
Chih et al[25]	Meta-analysis	OR, 1.70 (1.60–1.80)	Not reported
Zahid et al[26]	Population-based cohort study/NIS	OR, 1.48 (1.45–1.51)	10 574 vs 4895†
Gestational diabetes			
Pandey et al[24]	Meta-analysis	RR, 1.48 (1.33–1.66)	Not reported
Bosdou et al[27]	Meta-analysis	RR, 1.53 (1.39–1.69)	Not reported
Preterm birth			
Pandey et al[24]	Meta-analysis	RR, 1.54 (1.47–1.62)	Not reported
Future cardiovascular disease			
Ischemic heart disease			
Udell et al[28]	Population-based cohort study/Ontario, Canada	HR, 0.56 (0.25–1.25)	14.0 vs 16.7‡
Dayan et al[29]	Meta-analysis	HR, 0.91 (0.67–1.25)	Not reported
Magnus et al[30]	Registry-based cohort study/Nordic ART registry	HR, 0.90 (0.81–1.01)	370/695 886 vs 10 019/28 230 865§
Stroke			
Udell et al[28]	Population-based cohort study/Ontario, Canada	HR, 1.14 (0.54–2.44)	16.3 vs 8.5‡
Dayan et al[29]	Meta-analysis	HR, 1.25 (0.96–1.63)	Not reported
Magnus et al[30]	Registry-based cohort study/Nordic ART registry	HR, 0.97 (0.86–1.09)	298/696 191 vs 9892/28 225 884§
Heart failure			
Udell et al[28]	Population-based cohort study/Ontario, Canada	HR, 0.60 (0.30–1.22)	18.6 vs 14.6‡
Magnus et al[30]	Registry-based cohort study/Nordic ART registry	HR, 0.76 (0.59–0.97)	65/697 408 vs 2559/28 267 472§

ART indicates assisted reproductive technology; HR, hazard ratio; NIS, National Inpatient Sample; OR, odds ratio; and RR, relative risk.
*Referent group for all studies is spontaneous conception.
†Per 100 000 delivery hospitalizations.
‡Per 100 000 person-years.
§Events/person-years.

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such as endometriosis and polycystic ovary syndrome.[4,5] Future studies are warranted but to date have not demonstrated a statistically significant elevated risk for CVD among patients undergoing ART (Table 1).[28–30] However, patients who have failure of fertility therapy are at higher risk of long-term CVD events.[39]

Stroke

A meta-analysis of 6 studies, which included 41 910 parous individuals who had used ART and 1.4 million who had not, with a median follow-up of 9.8 years, concluded that there was weak statistical evidence for a higher risk of stroke among individuals who had used ART (Table 1).[29] Additional data from a population-based cohort study distinguishing those who did and did not receive fertility therapy in the 2 years before delivery, with a median 9.7 years of follow-up, did not find a statistically significant elevated risk for cerebrovascular events (Table 1).[28] Most recently, a large Nordic registry linkage study (n=2 496 441, with 97 474 having used ART) with a median follow-up of 11 years found no elevated risk for cerebrovascular disease or stroke (Table 1).[30]

Ischemic Heart Disease

In both a meta-analysis and a population-based cohort study, there was no evidence of increased risk of ischemic heart disease after ART.[28,29] This finding was replicated in a recent large Nordic registry study (Table 1).[30]

Heart Failure

Few studies have evaluated the risk of heart failure after ART. No evidence of increased risk for heart failure after ART has been found (Table 1).[28,30]

EVALUATION AND MANAGEMENT BEFORE UNDERGOING ART

Evaluation and management before undergoing ART are detailed in Figure 2. Most preconception counseling for individuals with CVD is focused on pregnancy and may neglect the possible use of ART. Changes in hemodynamics and coagulation associated with ART, or multiple gestation and OHSS resulting from ART, may be less well tolerated among those with congenital or acquired

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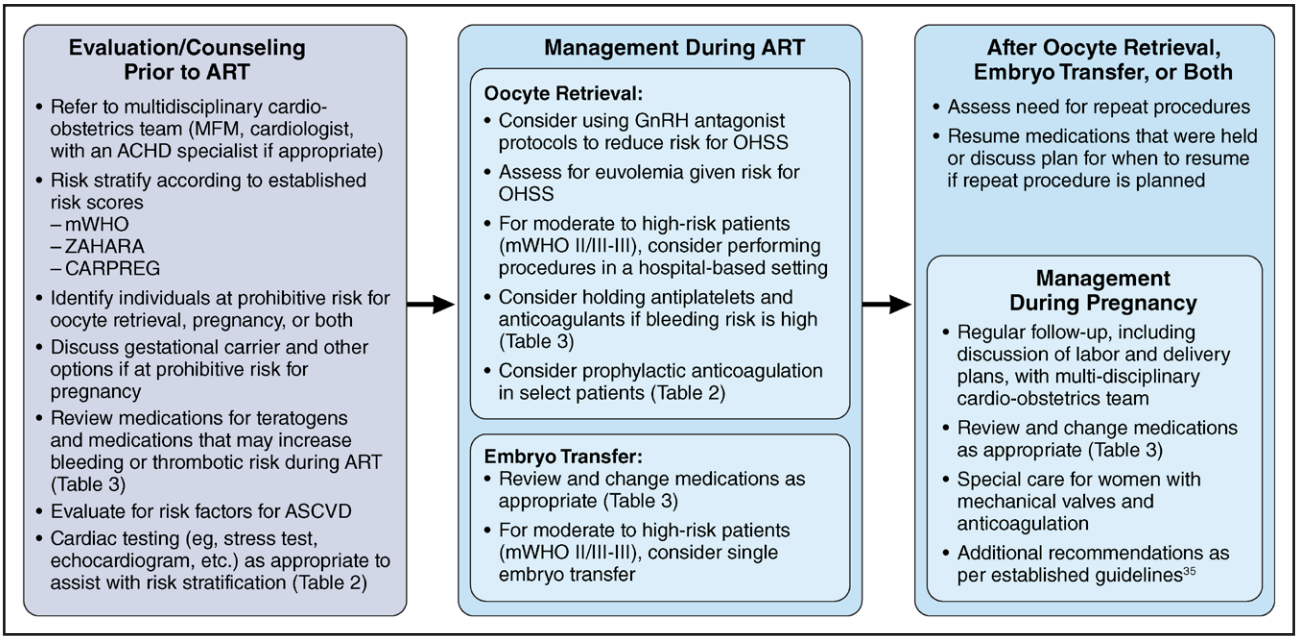

Figure 2. Suggested care pathway for individuals with cardiovascular disease undergoing assisted reproductive technology.
ACHD indicates adult congenital heart disease; ART, assisted reproductive technology; ASCVD, atherosclerotic cardiovascular disease; GnRH, gonadotropin hormone-releasing hormone; MFM, maternal–fetal medicine; mWHO, modified Word Health Organization; and OHSS, ovarian hyperstimulation syndrome.

CVD. There is also variable time to conception with ART. Often the first attempt at any treatment is unsuccessful, with the live birth rate per intended egg retrieval ranging from 50.8% to 3.9% depending on the individual's age.[40] Thus, some individuals may use ART and exogenous hormones for several years before conceiving.

Individuals with CVD interested in ART should be evaluated by a multidisciplinary team, including their cardiologist, obstetrician, and fertility specialist, before initiating therapy. When assessing individuals with CVD before ART, the following should be considered: (1) the risk of pregnancy and whether pregnancy is contraindicated, (2) candidacy for gamete retrieval, (3) the safety of medications used during the ART process in context of the individual's CVD, (4) the risk of ART procedures, including those performed to work-up infertility, egg retrieval, and possible embryo transfer, (5) potential ART complications (eg, OHSS, bleeding), and (6) the long-term effect of ART on future CVD risk.

Candidacy for gamete retrieval should be made separately from that for pregnancy. Individuals with CVD are at increased risk for pregnancy complications based on the type and severity of their disease; therefore, risk for pregnancy should be assessed using established risk scores.[38,41–43] Modified Word Health Organization class IV CVDs, defined previously,[38] are contraindications to pregnancy. However, contraindication to oocyte retrieval remains unclear. For those with modified Word Health Organization IV CVD, carrying a fetus to delivery is contraindicated, but they may be candidates for gamete retrieval. Patients with these severe CVDs may want to pursue oocyte retrieval before needed surgery or medical treatment, or for a gestational carrier. Undergoing ART with their own oocytes and subsequently using a gestational carrier may be a safe option for conceiving a genetically related child. Clinicians must be aware that there are a wide range of family-building options (including use of donor gametes, use of a gestational carrier, traditional adoption, and embryo donation) that may be explored by their patients. Patients may wish to pursue pregnancy despite risk counseling, but a multidisciplinary team should discuss risks and benefits of all family-building options with the patient and discuss the use of gestational carriers when gamete retrieval is feasible, but pregnancy is contraindicated.

When assessing risk for fertility therapy, a multidisciplinary team should determine the individual's risk for undergoing procedures included in the fertility assessment (ie, hysteroscopy, laparoscopy, or both) and oocyte retrieval (ie, TVOR and embryo transfer). Discussions should include modifications to the ART protocol, such as single embryo transfer, antagonist protocols to reduce the likelihood of OHSS, and using low doses of gonadotropins, to limit the individual's risk of complications. Patients should be counseled on specific risks associated with their type of CVD and if those risks can be modified (Table 2). Review of the patient's current medication list and deciding when to hold and subsequently resume specific medications should be made by the cardiologist in concert with the REI specialist on the basis of where the patient is in the ART process (Table 3).[44] Given the importance of adequate pain control, anesthesia should

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Table 2. Recommended Management Before and During Assisted Reproductive Technology For Specific Cardiovascular Diseases or Cardiovascular Disease Risk Factors

Cardiovascular disease	Pre-ART considerations	Monitoring during ART	Consultants
VTE	If previous VTE after hormonal exposure or unprovoked VTE, initiate thromboprophylaxis at the start of ovarian gonadotropin stimulation Use ART protocol with lower risk for thrombosis	If OHSS develops, consider initiating prophylactic anticoagulation If active VTE develops, strongly consider pausing ART and treatment	MFM, hematologist, cardiologist with expertise in cardio-obstetrics
IHD	Continuation, or discontinuation, of antiplatelet agents should be individualized on the basis of patient risk and factoring in REI center protocol Statin can be continued through ART Consider discontinuing teratogenic medications (Table 3) if considering immediate conception with fresh embryo transfer If symptoms of IHD occur, consider cardiovascular imaging with both stress echocardiogram and echocardiogram; if results are abnormal, pursue additional work-up as per established guidelines before pursuing ART	Decision to resume antiplatelet medication made in conjunction with REI specialist	MFM, cardiologist with expertise in cardio-obstetrics
Stroke	Continuation, or discontinuation, of antiplatelet agents should be individualized on the basis of patient risk and factoring in REI center protocol Consider discontinuing teratogenic medications if considering immediate conception with fresh embryo transfer	Decision to resume antiplatelet medication made in conjunction with REI specialist	MFM, neurologist
Cardiomyopathy	Ensure up-to-date imaging of baseline LVEF before any ART; if LVEF <30%, the patient may still be a candidate for oocyte retrieval, but pregnancy is contraindicated Diuretics can be continued through ART Consider discontinuing teratogenic medications if considering immediate conception with fresh embryo transfer If known dilated cardiomyopathy, consider genetic testing to determine need for pregenetic diagnosis Consider antagonist protocols to reduce likelihood of OHSS and recommend single embryo transfer	Monitor for signs or symptoms of heart failure during ART If patient has signs or symptoms of acute decompensated heart failure or worsening ejection fraction during ART, treat patient as per established guidelines and pause any further ART	MFM, cardiologist with expertise in cardio-obstetrics, advanced heart failure cardiologist
Valvular heart disease	Ensure up-to-date imaging assessment of valve function before ART In patients with prosthetic valves, if evidence of valve dysfunction is present, pursue work-up as per established guidelines before pursuing ART In mWHO IV valve disease, the patient may still be a candidate for oocyte retrieval, but pregnancy is contraindicated For patients with prosthetic heart valves, based on individual patient risk for valve thrombosis and after discussion with the REI specialist, warfarin may be safe to continue during gamete retrieval Continuation, or discontinuation, of anticoagulation should be individualized on the basis of patient risk and factoring in REI center protocol	Decision to resume anticoagulation made in conjunction with REI specialist	MFM, cardiologist with expertise in cardio-obstetrics
Congenital heart disease	Ensure up-to-date imaging assessment of systemic ventricular function Depending on imaging findings, the patient may be mWHO IV for pregnancy, in which case pregnancy is contraindicated, but oocyte retrieval may not be Identify and repair hemodynamically important cardiac lesions If feasible, consider performing ART procedures in a hospital-based, monitored setting with multidisciplinary collaboration Congenital heart disease with valvular disease: see row on valvular heart disease	Monitor volume status and adjust medications, particularly systemic anticoagulation, before and after oocyte retrieval	MFM, congenital heart disease specialist

(*Continued*)

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Table 2. Continued

Cardiovascular disease	Pre-ART considerations	Monitoring during ART	Consultants
Essential hypertension	Optimization of BP to goal of SBP <130 mm Hg and DBP <80 mm Hg consistently, as per ACC/AHA guidelines[45] Consider discontinuing or changing ACEs or ARBs before ART if considering immediate conception with fresh embryo transfer; if plans for frozen embryo transfer, ACEs or ARBs should be discontinued before planned transfer	Close monitoring of blood pressure throughout ART, particularly with frozen embryo transfer given possible risk for hypertensive disorders of pregnancy Treatment of blood pressure during pregnancy as per published ACOG guidelines[46]	MFM or obstetrician, primary care or cardiologist with expertise in cardio-obstetrics
Hyperlipidemia	All medications for hyperlipidemia can be continued through gamete retrieval Consider changing or discontinuing statin if considering immediate conception fresh embryo transfer For patients with elevated risk for ASCVD (ie, FH), consider continuing statin depending on ASCVD risk	No specific monitoring during ART recommended	MFM, lipid specialist (particularly for patients with FH), cardiologist with expertise in cardio-obstetrics

ACC indicates American College of Cardiology; ACE, angiotensin-converting enzyme; ACOG, American College of Obstetricians and Gynecologists; AHA, American Heart Association; ARB, angiotensin receptor blocker; ART, assisted reproductive technology; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; DBP, diastolic blood pressure; FH, familial hypercholesterolemia; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MFM, maternal–fetal medicine; mWHO, modified Word Health Organization; OHSS, ovarian hyperstimulation syndrome; REI, reproductive endocrinology and infertility; SBP, systolic blood pressure; and VTE, venous thromboembolism.

be considered by the multidisciplinary team. In most centers, procedures for fertility therapy are done in an office setting. However, for individuals with CVD, performing these procedures in a hospital setting with adequate cardiovascular and anesthesia support may be preferrable.

RISK ASSOCIATED WITH ART IN INDIVIDUALS WITH CVD OR WITH RISK FACTORS FOR CVD

The following section will focus on counseling before and management during ART. Counseling for individuals with CVD before and management during pregnancy has been discussed previously.[38] Data on outcomes after ART for specific cardiac diseases are limited to small single-center studies, limiting the ability to draw generalizable conclusions and highlighting the need for more data in this field.

Venous Thromboembolism

ART increases the risk for thromboembolism above the baseline risk for pregnancy, and the risk of VTE is higher for patients with a history of VTE. For all women with previous VTE or thrombophilia, clinicians should discuss the elevated risk of VTE with ART.[14,48] Clinicians should approach ART with a goal of using protocols with a lower risk for thrombosis and consider initiating prophylactic anticoagulation in women who develop OHSS to prevent VTE.[49] Among those patients in whom thromboprophylaxis is indicated at the start of pregnancy as outlined in recent guidelines,[49] thromboprophylaxis should be initiated at the start of ovarian gonadotropin stimulation, and discussions should occur in concert with the REI specialist on when to hold anticoagulation for oocyte retrieval (Table 2).[49]

Atherosclerotic CVD

Ischemic Heart Disease

In small retrospective studies of individuals with CVD undergoing ART, few had ischemic heart disease, limiting the ability to draw meaningful conclusions.[50–52] For women with ischemic heart disease in whom thrombosis from thrombophilias (such as Factor V Leiden mutation or protein C and S deficiency causing myocardial infarction with nonobstructive coronaries) was the cause of ischemia, counseling before ART should include discussions on risk for thromboembolism. For those on antiplatelet therapy, clinicians should discuss the elevated risk of bleeding with some ART procedures. Given the elevated risk of bleeding with TVOR, the timing of TVOR and decisions on when to continue or hold antiplatelet therapy should be made in concert with the patient's REI clinician to balance risks of bleeding with those of thrombotic complications (Tables 2 and 3).

Cerebrovascular Accident

No specific data on ART outcomes among women with history of stroke are available. Risk reduction strategies should focus on reducing the risk of hypertension and thrombosis during ART and pregnancy (Table 2). Considerations regarding antiplatelet therapy are similar to those in ischemic heart disease.

Spontaneous Coronary Artery Dissection

Hormones, both endogenous and exogenous, have been implicated in the pathophysiology of spontaneous coronary artery dissection (SCAD), although their exact role in SCAD pathophysiology is unclear.

Available data on ART use in individuals with CVD do not include individuals with a history of SCAD.[50–52] Data

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Table 3. Safety of Commonly Prescribed Cardiovascular Medications During Gamete Retrieval and Embryo Transfer With or Without Immediate Pregnancy

Medications	Safety during gamete retrieval	Safety during embryo transfer	Safety in pregnancy*
Amiodarone	O	X†	X
Verapamil	O	O	O
Diltiazem	O	O	O
Amlodipine	O	O	O
Nifedipine	O	O	O
Metoprolol and carvedilol	O	O	O
Atenolol	O	X	X
Renin-angiotensin-aldosterone system inhibitors	O	X	X
Aldosterone antagonists	O	X	X
Statins	O	O	–
Direct oral anticoagulants	O‡	X	X
Warfarin	O‡	X§	–§
Unfractionated heparin	O‡	O‡	O
Enoxaparin	O‡	O‡	O
Aspirin	O‡	O‡	O
Clopidogrel	O‡	O‡	O
Prasugrel	O‡	–	–
Ticagrelor	O‡	–	–
Endothelin receptor antagonists	O	X	X

Data on medication use are limited, and recommendations may change with accruing data. Refer to Halpern et al[44] for additional information on medication safety during pregnancy. O, safe to continue; X, contraindicated; –, limited data/to be used with caution.

*Pregnancy is defined as a positive pregnancy test up until delivery.

†For patients with recurrent or persistent supraventricular tachycardia or ventricular tachycardia, refractory to other medical therapy or ablation and already taking amiodarone, discuss risks and benefits of discontinuing amiodarone with electrophysiologist.[47]

‡Recommend deferral to anticoagulation or antithrombotic therapy protocols as defined by individual REI centers.

§Consider continuing in certain populations (eg, patients with mechanical valves, after factoring in individual patient's risk/benefit ratio for bleeding or thrombosis).

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on SCAD after fertility therapy[53] or hormones used in fertility therapy[54] are limited to case reports or single-center studies.[55] In a single-center study of patients with SCAD, individuals with pregnancy-associated SCAD had similar rates of ART use compared with patients whose SCAD was not associated with pregnancy (9% pregnancy-associated SCAD versus 4% nonpregnancy-associated SCAD).[55]

Because of concerns regarding the role of sex hormones in the pathophysiology of SCAD, exogenous exposure to systemically absorbed estrogen or progesterone is generally avoided in patients with a history of SCAD.[56] In patients with a history of SCAD, there are potential risks to hormonal stimulation protocols used in ART.[57] Although the data on rates of recurrent SCAD during pregnancy are limited, individuals with a history of SCAD are generally counseled against future pregnancies.[58] Thus, given the potential risk with ART and pregnancy, patients with a history of SCAD should be counseled on all possible family-building options, including use of donor oocytes and a gestational carrier.[57] Counseling should include avoiding unplanned pregnancies, and those with a history of SCAD who become pregnant should be managed by a multidisciplinary team.[57]

Cardiomyopathy

Known complications of ART, such as OHSS with its accompanying fluid shifts and thromboembolic events, bleeding complications, and adverse reactions to anesthesia, may be poorly tolerated in individuals with cardiomyopathy, especially those with substantial ventricular dysfunction.[48] Multifetal gestations are associated with increased hemodynamic stress during pregnancy that could worsen preexisting ventricular dysfunction or lead to cardiac complications such as heart failure.[38,50] A single-center retrospective case-control study included 20 patients with CVD undergoing ART, 4 of whom had cardiomyopathy: 3 with congenital cardiomyopathy and 1 with acquired cardiomyopathy. There were no cardiovascular complications among these individuals.[51] A retrospective case review of 34 patients with CVD receiving ART included 1 patient with restrictive cardiomyopathy, who delivered at 36 weeks of gestation because of symptomatic heart failure.[52]

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Individuals with cardiomyopathy contemplating ART should be counseled on the known risks of ART and the possibility of greater hemodynamic compromise given their left ventricular systolic dysfunction. In those with left ventricular systolic dysfunction, it is reasonable to avoid multiembryo transfers to minimize the hemodynamic load of pregnancy. Individuals with dilated cardiomyopathy may want to consider genetic testing, pregenetic diagnosis, or both before oocyte fertilization. Management before ART should include counseling on risk for pregnancy, assessment of left ventricular systolic function, and optimization of volume status before any procedures (Table 2).

Heart Transplant Recipients

Limited data on ART in heart transplant exists and current recommendations are driven by expert consensus.[59] Patients should be counseled that the safety of ART in the transplant population is not known.

A multidisciplinary team including transplant cardiology and reproductive endocrinology should counsel patients on risks of graft dysfunction or rejection, infection, teratogenicity of immunosuppression therapy, maternal life expectancy, and early delivery or miscarriage.[59–61] ART and pregnancy should be deferred for at least 1 year after transplant with demonstration of stable graft function on a stable immunosuppression regimen.[59,61,62] Given the risk of multiple gestation with ART, which may further increase the already elevated risk of preeclampsia in patients who have received a heart transplant, single embryo transfer is recommended.[60] OHSS should be carefully monitored for in patients who have received a heart transplant given the potential for reduced tolerance of hemodynamic shifts and risk of thrombotic events (Table 2).[59,61] Rates of rejection during pregnancy and in the postpartum period in individuals with heart transplant range from 7% to 9%.[60,63] Thus, individuals should also expect more frequent surveillance of graft function given concern for risk of rejection during pregnancy.[59,61] Given the concern for rejection, counseling should include discussion of all family-building options, including use of a gestational carrier. Left ventricular assist devices are considered a contraindication to pregnancy on the basis of expert consensus and thus ART cannot be recommended.[59]

Valvular Heart Disease

Data on ART outcomes in patients with substantial valvular heart disease are limited, with little data on prosthetic valves.[50–52] A retrospective case review included 2 patients with mechanical valves: 1 aortic and 1 mitral. The patient with the aortic mechanical valve had major abdominal bleeding requiring blood transfusion 5 days after TVOR when warfarin was restarted.[52] A retrospective single-center study including 5 patients with valvular disease, 1 with a mechanical aortic valve, reported no cardiovascular complications.[51]

Counseling should be tailored to the individual patient, with the pathogenesis of valve disease, severity of valve disease, and presence of a prosthetic valve factored into the risk assessment. The decision whether or not to continue warfarin during gamete retrieval must be tailored for each individual patient and made in conjunction with the REI specialist (Tables 2 and 3).

Congenital Heart Disease

With >90% of children born with congenital heart disease surviving to adulthood, the number reaching childbearing age has increased substantially.[7,64,65] A majority of women with congenital heart disease can become pregnant without difficulty, but a number of conditions can compromise fertility, including Fontan single ventricles and unrepaired cyanotic heart disease.[66,67] For individuals with conditions that affect fertility, alternatives such as ART may be sought. Studies dedicated to risk stratification for pregnancy in congenital heart disease have been conducted,[38,41,43,65,68] but less is known about the risk of ART in congenital heart disease.

Available data derive from small, retrospective studies in patients with CVD, including only a subset of modified Word Health Organization II through IV congenital heart disease, who have undergone ART with varying levels of hormonal stimulation.[50–52] In these studies, individuals with congenital heart disease had higher rates of cardiovascular complications, such as heart failure, arrhythmias, and thrombosis, which is similar to what has been observed in pregnancies conceived without ART.[38,43,50–52] One of the early studies was based on older ART approaches associated with higher rates of complications, such as OHSS.[50] Together, these small studies found occurrence of preeclampsia, miscarriage, and fetal prematurity to be higher than in pregnancies with ART in patients without congenital heart disease, with an inconsistent increased risk of OHSS, and no reported maternal deaths.[50–52]

Individuals with single ventricle anomalies who have undergone Fontan palliation represent a unique subset of patients with congenital heart disease.[69] There is a high incidence of infertility in these patients.[66,67] For those who do conceive, evidence is limited and based primarily on retrospective studies, with a majority of patients having single morphologic left ventricles.[69–71] In general, well-selected patients who have undergone Fontan palliation who are followed closely in a center with adult congenital heart disease and maternal–fetal medicine expertise have no reported maternal deaths, but high rates of morbidity are observed, largely due to arrhythmia (8%–11%) and heart failure (4%–14%).[70,71]

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Given the limitations of Fontan circulation, cardiac output may not be augmented to a level necessary to sustain pregnancy. Rate of miscarriage is high (upwards of 50%), with a higher proportion occurring in those with cyanosis.[69,70] For pregnancies that are carried to live birth, neonatal complications are common, and include preterm birth, small for gestational age newborns, and intrauterine growth restriction.[70,71] The effect of older maternal age and extracardiac complications associated with Fontan circulation, including Fontan-associated liver disease, renal dysfunction, and chronic venous stasis, are not known. Furthermore, long-term effects of pregnancy on Fontan circulation are also not known.[69] ART may be considered but poses some risk, with OHSS being of particular concern given inherent susceptibility of Fontan circulation to thrombosis and volume shifts.[69] Use of techniques to minimize risks of OHSS,[13] assessing for euvolemia before ovarian stimulation, and initiation of thromboprophylaxis if indicated by established guidelines[49] is recommended. One small series including 6 patients who received Fontan palliation suggested that oocyte stimulation and retrieval using prophylactic systemic anticoagulation can be done safely, but acknowledged that more data are needed.[72]

Caution must be exercised when applying current, limited data on ART risk in CVD broadly to the congenital heart disease population, particularly those with moderate to high-risk lesions.[50–52] Evaluation before ART must be done by an adult congenital heart disease specialist, as advocated for by current guidelines.[73] This provides an opportunity to optimize the patient's cardiovascular status and ensure it is not of prohibitive risk before ART, allowing for appropriate counseling regarding risks of carrying a pregnancy versus consideration of a gestational carrier. Given the overlap of congenital heart disease with acquired cardiovascular conditions, such as valvular heart disease, ventricular dysfunction or heart failure, and arrhythmia, recommendations regarding pre-ART counseling and risk assessment from these sections may be applicable for the patient with congenital heart disease. For individuals with congenital heart disease classified as intermediate to substantially increased risk of maternal mortality and moderate to severe risk of maternal morbidity (modified Word Health Organization II/III or III), performing ART procedures in a monitored setting with multidisciplinary collaboration should be considered (Table 2).

History of Arrhythmia

Women with CVD have increased risk of de novo arrhythmia during pregnancy, and pregnancy may aggravate preexisting arrhythmias.[41,47] Whether use of ART further increases risk of arrhythmias above this already increased risk is not known. Available data do not include enough patients with a history of arrhythmia before ART to draw any meaningful conclusions.[50–52] Patients who develop arrhythmias during pregnancy should be managed according to existing guidelines and expert consensus statements.[38,47]

Risk Factors for Atherosclerotic CVD

Individuals who pursue ART are likely to be older and have higher rates of atherosclerotic CVD (ASCVD) risk factors compared with individuals who do not undergo ART.[3] Before initiating ART, individuals with ASCVD risk factors should undergo medical optimization and receive counseling on medication changes to occur before, and known cardiovascular risks associated with, ART. Oocyte retrieval and pregnancy is rarely contraindicated in individuals with risk factors for, but no manifest, ASCVD.

Established guidelines exist on the management of preexisting diabetes and hypertension before and during ART, and have been discussed previously.[74] ART is well tolerated by individuals with type 2 diabetes, although few studies have investigated the effect of ovarian stimulation on glucose control. Medications used for ovarian suppression and stimulation affect cardiovascular hemodynamics, with the former causing a small increase in blood pressure and peripheral vascular resistance and the latter lowering both.[75] These hemodynamic changes during ART are unlikely to be clinically substantial in individuals with hypertension. Preexisting hypertension is a major risk factor for developing preeclampsia during pregnancy. In addition, ART is associated with an elevated risk of hypertensive disorders of pregnancy.[24–26] Individuals with preexisting hypertension who pursue ART should be counseled on their elevated risk for preeclampsia and receive close blood pressure monitoring, and may benefit from aspirin therapy as advocated for in current guidelines.[45,46,76]

Hyperlipidemia

Several small studies have investigated changes in blood lipid levels in response to ovarian stimulation. Triglyceride levels increase in the 2-week period after ovarian stimulation, although changes in total cholesterol and low-density lipoprotein cholesterol vary by treatment protocol and study population.[77,78] Levels of lipoprotein(a), a low-density lipoprotein that is an independent risk factor for ASCVD, also increase after ovarian stimulation, and return to baseline in those who do not conceive.[77,79] The clinical significance of these changes during ART are not well studied, but the cumulative effects may be greater with multiple attempts, particularly if lipid-lowering medications are interrupted.

Familial hypercholesterolemia is an autosomal dominant genetic disorder that affects 1 in 200 individuals, causes substantial elevation in low-density lipoprotein cholesterol levels, and is associated with premature ASCVD. Individuals with familial hypercholesterolemia

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experience substantial elevations in low-density lipoprotein cholesterol levels during pregnancy, but changes during ART have not been well described.[80] Individuals with familial hypercholesterolemia should undergo multidisciplinary management by a lipidologist or cardiologist and REI specialist before and during ART.

Statins may be continued during ART, although the decision to continue statin use through pregnancy should be made between the patient and the physician, factoring in individual risk for ASCVD events. Rates of lipid screening in individuals of reproductive age are suboptimal. Lipid screening before ART or during the first trimester of pregnancy may be an opportunity to identify individuals with severe lipid disorders.[81] Individuals with hypertriglyceridemia, in particular familial hypertriglyceridemia, should have serial lipid panels given risk of elevated triglycerides with ART and pregnancy and be monitored for signs and symptoms of pancreatitis.

PSYCHOLOGICAL HEALTH SUPPORT DURING ART

Infertility can have a negative psychological effect and is often associated with feelings of anxiety, depression, and guilt, particularly when coping with being unable to fulfill hopes of parenthood.[82,83] Some who have experienced infertility continue to have negative psychological effects even after conceiving and delivering a child.[83] Infertility can also be a considerable stressor on partnership and can negatively affect the partner who is not undergoing ART.[84] Thus, both partners must be supported throughout this process.

Because of the stigma associated with infertility, those undergoing ART may not seek support from their usual network of family and friends. Online peer support groups can help by establishing a greater sense of community.[85] Many clinicians have recognized the importance of having embedded mental health services to provide patient-centered care.

KNOWLEDGE GAPS

Although the use of ART continues to rise, knowledge gaps persist. Data are sparse overall on outcomes after ART in those with CVD.[50–52] Data on rates of infertility may not consider ART accessibility to individuals from different racial or ethnic groups or members of the LGBTQIA+ (lesbian, gay, bisexual, transgender, queer/questioning, intersex, asexual, and other gender identities and sexual orientations) community, and much less is known on the effects of ART in these populations. Multicenter, prospective studies and large, multinational databases with the dedicated purpose of assessing the cardiovascular effects of ART, both long and short term, are needed. These studies must focus on both those at risk for, and with a broad range of, CVDs, and explore how the effect of ART varies with socioeconomic status, race and ethnicity, age, and CVD burden.

CONCLUSION

The use of ART is growing. The cardiovascular clinician must be aware of the known risks of ART in individuals with CVD and be comfortable with counseling patients on those risks. This need will grow as the population of patients with CVD expands to younger individuals and an increasing number of patients with congenital heart disease survive into adulthood. Previous studies have made inroads to identify risks of ART in individuals with CVD and risk for future CVD after ART; more data are needed to guide patients appropriately in shared decision-making surrounding fertility.

ARTICLE INFORMATION

The views expressed in this manuscript are those of the authors and do not necessarily reflect the official policy of the Department of Defense or the US government.

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on August 9, 2024, and the American Heart Association Executive Committee on September 23, 2024. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com

The American Heart Association requests that this document be cited as follows: Mauricio R, Sharma G, Lewey J, Tompkins R, Plowden T, Rexrode K, Canobbio M, Skowronski J, Hameed A, Silversides C, Reynolds H, Vaught A; on behalf of the American Heart Association Cardiovascular Disease & Stroke in Women and Underrepresented Populations Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and Council on Lifelong Congenital Heart Disease and Heart Health in the Young. Assessing and addressing cardiovascular and obstetric risks in patients undergoing assisted reproductive technology: a scientific statement from the American Heart Association. *Circulation*. 2024;150:e•••–e•••. doi: 10.1161/CIR.0000000000001292

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Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Rina Mauricio	University of Texas Southwestern	None	None	None	None	None	None	None
Arthur Vaught	Johns Hopkins University	None	None	None	None	None	None	None
Mary Canobbio	UCLA School of Nursing	None	None	None	None	None	None	None
Afshan Hameed	University of California, Irvine Medical Center	None	None	None	None	None	None	None
Jennifer Lewey	University of Pennsylvania Perelman School of Medicine	None	None	None	None	None	None	None
Torie Plowden	Uniformed Services University of the Health Sciences	None	None	None	None	None	None	None
Kathryn Rexrode	Brigham and Women's Hospital, Harvard Medical School	None	None	None	None	None	None	None
Harmony Reynolds	New York University Grossman School of Medicine	American Heart Association (funding)*; National Institutes of Health (funding)*; Abbott Vascular (donation of optical coherence tomography catheters)*; Biotelemetry (donation of telemetry monitors for an unrelated research study)*	None	None	None	None	Heartflow*	None
Garima Sharma	Inova Heart and Vascular Institute	None	None	None	None	None	None	None
Candice Silversides	Mount Sinai Hospital (Canada)	None	None	None	None	None	None	None
Jenna Skowronski	University of Pittsburgh Medical Center	None	None	None	None	None	None	None
Rose Tompkins	Cedars-Sinai Smidt Heart Institute	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

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Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Ildiko Agoston	UT Health San Antonio	None	None	None	None	None	None	None
Jennifer F. Kawwass	Emory	None	None	None	None	None	None	None
Kathryn J. Lindley	Vanderbilt University	None	None	None	None	None	None	None
Amy Sarma	Massachusetts General Hospital	CRICO*; AHA*	None	None	None	None	None	None
Keri Shafer	Boston Children's Hospital	None	None	None	None	None	None	None

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