Infertility Treatment and Cardiovascular Disease

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Increasing numbers of women seek assisted reproductive techniques (ART) in worldwide , they are frequently older and may have pre-existing cardiovascular risk factors and morbidities

In parallel with these fertility trends is an increase in the prevalence of cardiovascular risk factors among expectant mothers, with chronic hypertension affecting approximately 5% of pregnancies and diabetes affecting approximately 2%.

Polycystic ovarian syndrome (PCOS), one the most common causes of female-factor infertility, affecting about 15% of females of childbearing age, is strongly linked with metabolic syndrome.

Furthermore, recent evidence suggest that endometriosis, a gynaecologic condition that affects up to 11% of females of childbearing age, and present in 30%-50% of females with infertility, may also be associated with increased risk of cardiovascular disease (CVD).

Moreover, 0.2% to 4% of pregnancies are complicated by pre-existing acquired or congenital heart disease.

It is conceivable that use of ART poses additional cardiac and metabolic stress during pregnancy, due to marked fluctuations in endogenous estrogen

The importance of pre-ART counselling and health optimization must therefore be emphasised. Though generally safe, use of infertility treatment, in particular IVF, has been associated with severe maternal complications, including pre-eclampsia and other hypertensive disorders of pregnancy (HDPs), as well as obstetrical hemorrhage and complications due to abnormal placentation.

An improved understanding of the potential additional effects of infertility treatments in at-risk individuals, regarding both perinatal outcomes and longer-term CVD, is needed to ensure safe reproduction and pregnancy.

Infertility and Infertility Treatment Considerations Among Individuals With Congenital and Acquired Heart Diseases

The prevalence of female infertility is likely to be similar among individuals with heart disease and the general population.

However, severity of infertility has been evaluated as a potential marker of increased cardiovascular risk. A population-based study in Ontario showed that receipt of infertility treatment not resulting in pregnancy (ie, unsuccessful treatment) was associated with a 19% increased risk of a composite cardiovascular outcome over 8 years compared with those who had a live birth after treatment.

Infertility and adult congenital heart disease

Certain syndromes that include congenital cardiac defects are associated with infertility:

For example, menstrual irregularities have been described in pregnant individuals after Fontan palliation.

The most common and well understood syndrome associated with infertility and congenital heart conditions is Turner syndrome. Because the majority of individuals with Turner syndrome have premature ovarian insufficiency, it is highly unlikely for these individuals to conceive without reproductive assistance.

Turner syndrome is considered to be high risk because of associated aortopathies and metabolic issues. As such, appropriate pre-IVF care in patients with Turner syndrome includes:

cross-sectional imaging of the aortic root and aortic valve

Pregnancy, and therefore IVF, is contraindicated if the aortic size index exceeds 25 mm/m2, because the risk of dissection during pregnancy in these cases approaches 10%.

Prepregnancy aortic root repair can be considered if the aortic diameter is 20-24 mm/m2.36 Individuals with Turner syndrome should also be counselled about the risk of gestational diabetes, and they require monitoring for the development or worsening of hypertension in pregnancy.

Association between polycystic ovarian syndrome and cardiovascular disease

PCOS is a heterogeneous disorder characterised by oligoanovulation, hyperandrogenism, and insulin resistance. Because obesity and metabolic syndrome commonly coexist with PCOS, it is typically recommended to screen all individuals with PCOS for type 2 DM, HTN, and DLP, which, if present, are typically managed with lifestyle approaches as well as insulin sensitisers and statins.

Over the long term, studies have indicated a 3-fold increase in the risk of type 2 DM and an approximately 1.5-fold increased risk of chronic HTN and CVD among individuals with PCOS compared with unaffected individuals.

Individuals with PCOS attempting to conceive are initially treated with the aromatase inhibitor letrozole, which has shown superiority over clomiphene citrate in inducing ovulation and achieving live births.

If ovulation induction approaches are not successful →

IVF is the next step along with intensive ovarian stimulation approaches, which puts patients at high risk of ovarian hyperstimulation syndrome, a potentially life-threatening complication of infertility treatment (characterised by ovarian enlargement, widespread endothelial injury, and third spacing).

Once pregnant, persons with PCOS experience an increased risk of a variety of complications, such as miscarriage, preterm birth, gestational diabetes, and HDPs.

Association between endometriosis and cardiovascular disease

Endometriosis is another condition that is strongly linked with infertility as well as poor cardiometabolic health.

affects up to 15% of reproductive-age females.

pregnancy outcomes depend on the severity of disease.

Several observational studies have suggested an increased risk of CVD in individuals with endometriosis.

The risk of coronary disease and other cardiovascular conditions were 1.8-fold higher in a population with laparoscopically confirmed endometriosis compared with unaffected individuals.

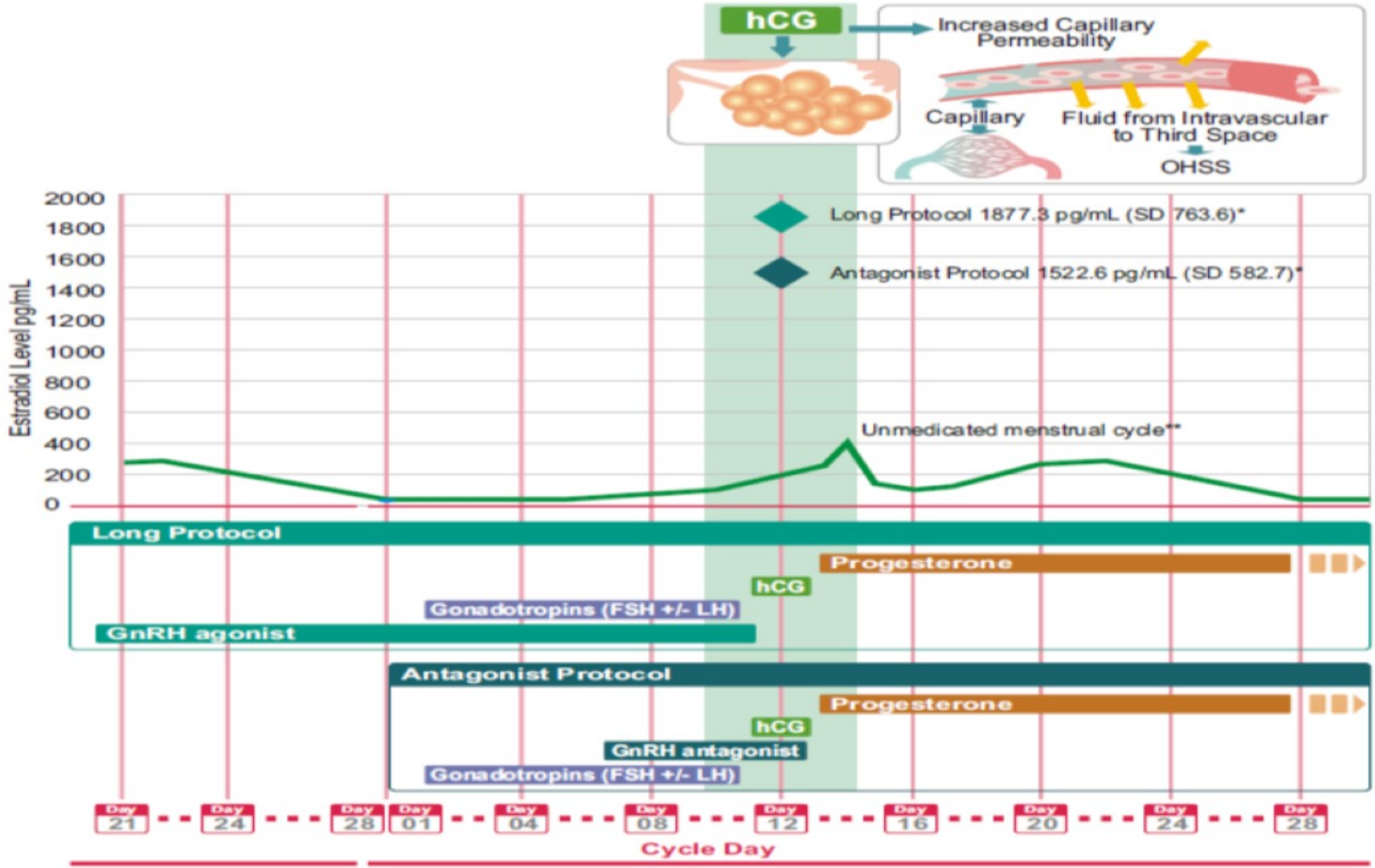
IVF protocols

It is likely that the pre-IVF strategies for oocyte maturation have important implications for individuals with CVD, as these often result in supraphysiologic levels of circulating estrogen and dramatic fluid shifts.

Oocyte maturation may rely on endogenous triggers, so-called "natural-cycle" IVF. although the success rate with this technique is relatively low given the low number of follicles that are produced in a given cycle.

More commonly, exogenous hormones are used to trigger oocyte maturation through controlled ovarian stimulation ("stimulated-cycle" IVF)

There are 2 predominant controlled ovarian stimulation protocols that require careful consideration in a patient with preexisting heart disease:


hCG
Increased Capillary Permeability
Capillary
Fluid from Intravascular to Third Space
OHSS
Estradiol Level pg/mL
2000
1800
1600
1400
1200
1000
800
600
400
200
0
Long Protocol 1877.3 pg/mL (SD 763.6)*
Antagonist Protocol 1522.6 pg/mL (SD 582.7)*
Unmedicated menstrual cycle**
Long Protocol
Progesterone
hCG
Gonadotropins (FSH +/- LH)
GnRH agonist
Antagonist Protocol
Progesterone
hCG
GnRH antagonist
Gonadotropins (FSH +/- LH)
Day 21
Day 24
Day 28
Day 01
Day 04
Day 08
Day 12
Day 16
Day 20
Day 24
Day 28
Cycle Day

-The main rationale for choosing an antagonist protocol is to diminish the risk of OHSS. The modestly lower clinical pregnancy rate associated with GnRH antagonists, however, may result in repeated implantation failure and may thus subject the patient to repeated rounds of controlled ovarian stimulation.

-The final step in the long protocol is to stimulate follicular growth and oocyte maturation with the use of exogenous FSH, resulting in a surge in estradiol.

-short protocols skip the down-regulation phase and begin immediately with the administration of FSH along with GnRH agonist.

-In both long and short protocols, human chorionic gonadotropin is administered for the final maturation of the oocytes and oocyte extraction.

Cardiovascular concerns of ovarian stimulation and IVF

Process of controlled ovarian stimulation may result in:

- endothelial dysfunction and subsequent capillary leak syndrome
- marked activation of the renin-angiotensin system during periods of elevated estradiol in ovarian stimulation
- a direct association between the rise in prorenin and number of follicles stimulated.

OHSS can be potentially devastating in patients with cardiovascular conditions such as VHD or cardiomyopathy because they may be unable to tolerate the increased preload.

The incidence of moderate to severe OHSS has been reported to range from 3% - 8% of the individuals undergoing controlled ovarian stimulation in the general population and increases to 10%-20% among individuals who require more intensive stimulation approaches, such as those with PCOS.

While comparison of different protocols has not been studied in patients with CVD, using approaches that minimise risk for OHSS is likely to be safest.

The ESC statement about pregnancy and heart disease recommends consideration for natural-cycle IVF or controlled ovarian stimulation with careful monitoring with the use of GnRH antagonists and low-dose FSH.

Infertility treatment is contraindicated in patients with modified WHO class IV heart disease, because pregnancy is not advised in these individuals:

- PAH
- LVEF < 30%
- Previous PPCM with any residual left ventricular impairment
- Severe MS
- Severe symptomatic AS
- Severe aortic dilation (>45mm in Marfan syndrome or other HTAD, >50mm in BAV, Turner syndrome ASI>25 mm/m2, TOF>50mm)
- Severe (re)coarctation
- Fontan with any complication
- Systemic RV with moderate-severe decreased function

Other considerations for individuals with preexisting heart disease undergoing controlled ovarian stimulation and oocyte retrieval include periprocedural anticoagulation management for individuals with mechanical heart valves or atrial fibrillation.

In most but not all jurisdictions, elective single-embryo transfer is the preferred approach to avoid health risks due to multiple gestation. Multiple-gestation pregnancy is associated with increased metabolic and cardiovascular demands and should be avoided in most individuals with CVD.

Cardiovascular and pregnancy Outcomes After Infertility Treatment

Pregnancy is considered a cardiovascular stress test.

Stroke volume and heart rate increase to achieve a plasma volume and cardiac output increase by approximately 50% by the third trimester.

Cardiac output in twin pregnancies increases by another 20% compared with singleton pregnancies.

These changes intensify during labour and delivery during uterine contractions, expulsive efforts, pain, stress, and blood loss.

Cardiac output increases by 15% during labour and up to 80% in the early postpartum period, with persistent altered cardiovascular reserve for up to 6 months after delivery.

These physiologic demands of pregnancy are more difficult to tolerate with preexisting CVD and may result in cardiovascular decompensation, including arrhythmias, congestive heart failure, systemic thromboembolism, stroke, endocarditis, and death.

Pregnancy outcomes of infertility treatment among individuals with CVD

Outcomes of infertility treatments in pregnant individuals with preexisting CVD are poorly described.

A 2014 case series reported outcomes of 22 pregnancies in 20 patients with CVD who used infertility treatment to conceive from the Pregnancy and Heart Disease Program in Toronto. Among this sample, 73% of pregnancies resulted in at least 1 complication, including cardiac outcomes (arrhythmia, congestive heart failure), obstetrical outcomes (postpartum hemorrhage, antepartum hemorrhage, preeclampsia, abruption), and fetal and neonatal outcomes (neonatal death, preterm birth, respiratory distress, small for gestational age). A diagnosis of ovarian hyperstimulation syndrome was reported in 4 patients

Short- and long-term cardiovascular implications of infertility treatments

While it is known that individuals who are pregnant with the help of ART are at greater risk of experiencing pregnancy complications such as preeclampsia and preterm birth, it is unclear whether use of infertility treatment independently affects longer-term CVD.

HDPs have been consistently linked with ART. HDPs include gestational hypertension, preeclampsia, and the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, which together complicate up to 10% of pregnancies in the general population.

The risk of HDPs appears to be increased among pregnant individuals who have conceived with the use of ART, in particular among those with additional risk factors for HDPs, such as obesity.

A recent systematic review of 85 cohort studies found that IVF increased the risk of HDPs in both singleton pregnancies and multiple pregnancies. This risk was particularly high among frozen embryo transfers (FET) and oocyte-donation pregnancies.

Pregnancy is a known risk factor for venous thromboembolism (VTE), with an estimated incidence of 1-2 per 1000 pregnancies.

Receipt of infertility treatment has been shown to further increase the risk of pregnancy-associated VTE.

A systematic review of 21 studies revealed a 2-fold increase in the risk of antepartum VTE in ART-exposed pregnant individuals compared with unexposed women, especially if OHSS was present.

The risk of PTE has also been reported to be higher after unsuccessful ART cycles compared with successful ART, highlighting the importance of studying individuals who receive controlled ovarian stimulation, and not only those who become pregnant through ART.

Long-term data on thromboembolic risk after exposure to ART are lacking, although one study demonstrated no increased risk of VTE over a median follow-up of 9.7 years.

A systematic review of long-term cardiovascular outcomes after ART including 6 studies reported no increased risk of cardiovascular morbidity or death among individuals previously exposed to infertility treatment compared with unexposed individuals when pooling data from 4 studies. There were insufficient data on the development of HTN or DM after ART in this review. That review showed a possible signal toward increased risk of stroke that warrants further study

Antithrombotic Therapy During ART Pregnancy

The US Preventive Task Force and other bodies recommend :

use of low-dose ASA for the prevention of preeclampsia in pregnant individuals at high risk for this disorder, starting at 11 weeks' gestation.

This recommendation is based on high-level evidence demonstrating a consistent reduction in overall rate of preeclampsia with the use of ASA ranging from 50-150 mg nightly when initiated before 16 weeks.

A recent large randomised trial using a validated algorithm to identify pregnant persons at high risk for preterm preeclampsia revealed 62% reduction in preterm (onset before 37 weeks' gestation) preeclampsia in those randomised to receive 150 mg ASA daily compared with placebo.

Although clinical risk factors alone are known to be poorly predictive of preeclampsia, risk factors prompting prescription of ASA noted in these guidelines include chronic HTN, obesity, CKD, advanced female age, twin gestation, antiphospholipid syndrome, and a history of preeclampsia.

ASA use is not universally recommended for the purpose of improving clinical pregnancy live birth or reducing the rate of miscarriage, because this approach has not been consistently found to be effective and may cause harm due to bleeding during oocyte retrieval.

Individuals with CVD planning IVF who are on secondary prevention of CVD with 81 mg oral ASA daily may be advised to discontinue for a period of 5-7 days before oocyte retrieval and then resume.

Indications for ASA for secondary CVD prevention is not different in a person with and without infertility treatment. Most clinical guidelines do not mention infertility treatment as a risk factor warranting prophylaxis with ASA to prevent preeclampsia. ASA is typically recommended in those who use ART and have additional risk factors for preeclampsia or according to the validated algorithm that combines clinical risk factors with first-trimester biomarkers, placental biomarkers, and uterine artery Doppler.

Anticoagulation

Despite the high thrombotic risk in persons who use ART, the absolute risk of VTE in all comers who use ART is estimated to be 1% or lower.

Prophylaxis with LMWH is recommended when the estimated risk of pregnancy-associated VTE in pregnancy exceeds 1%, such as :

among individuals who undergo ART complicated by severe OHSS or among individuals with other risk factors for VTE.

There is a lack of formal guidance on prophylactic anticoagulation in individuals with CVD undergoing ART.

Individuals with a preexisting indication for therapeutic anticoagulation should continue during infertility treatment as well as during pregnancy.

Health care providers should withhold anticoagulation during oocyte retrieval and initiate periprocedural bridging if required.

Thanks for your attention