

# Specific Guidance for Women Embarking on Pregnancy with Cardiovascular Diseases -Precautionary Measures for Avoidance of Complications by Utilization of Multidisciplinary Team Strategy -A Review

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## ABSTRACT

Having reviewed the different significant etiopathogenesis and role of different antiobesity agents, comprehensively, role of adipocytokines in Heart failure with preserved ejection fraction (HFpEF) HFpEF and HF with reduced( $<40\%$ ) ejection fraction(HFrEF), role of SGLT2 Inhibitors beyond Glycosuria in controlling obesity, NAFLD Treatment, Pancreatic  $\beta$  Cell Protection Besides Therapy for Diabetes Mellitus, CVOT and Renoprotection including MACE withSGLT2 Inhibitors molecular modes Implicated in Diastolic Impairment in early HFpEF and HFrEF, and epigenetics modifications in diabetic cardiomyopathy(DbCM),with Role of SGLT2 Inhibitors and GLP-1RA in therapy of DbCM here we have concentrated on the plethora of persons with manifestation in the form of cardiovascular disease (CVD) possesses the capability of gaining advantages from the accessibility of assisted reproductive technologies (ARTs) regarding generating family building. Utilization of this for such population needs to be in lieu of underlying infertility, a requirement for fertility preservation conducted prior to disease inimicality or heart transplant, a genetic cardiac disorder they deemed to prevent passing to offspring, or the requirement of utilization of a gestational surrogate in the scenario of (CV) contraindications to pregnancy. CVD presentation is in the form of a spectrum, from mild as well as frequent diseases that possess least challenges to maternal health at the time of pregnancy to robust in addition to sparse diseases with a high risk of morbidity, along with maternal mortality if ART or pregnancy is embarked upon. In this review, here we detail the properties of variable CVD from the vision of the patient who is in the age with reproduction embarking on ART. Classification of the imperative steps in the pre-ART assessment from the multidisciplinary team, detail risk stratification prior to ART treatment as well as plausible subsequent pregnancy, in addition to yield corroborator dependent recommendations on the care of such patients at the time of the in vitro fertilization and embryo transfer(IVF-ET) cycles.

**Keywords:** Cardiovascular Disease (CVD), Assisted Reproductive Technologies, Multidisciplinary Team, Pregnancy

## Introduction

Cardiovascular disease (CVD), whether congenital or acquired, is an escalatingly frequent comorbidity met by we reproductive endocrinology & Infertility specialist (REI) in the fertility scenario. Advancements in congenital heart disease (CHD) management have drastically escalated survival for patients, so that maximum are alive by the reproductive-aged years [1]. In the meantime, tendency of postponed childbearing has escalated the incidence of acquired cardiac situations influencing patients undergoing

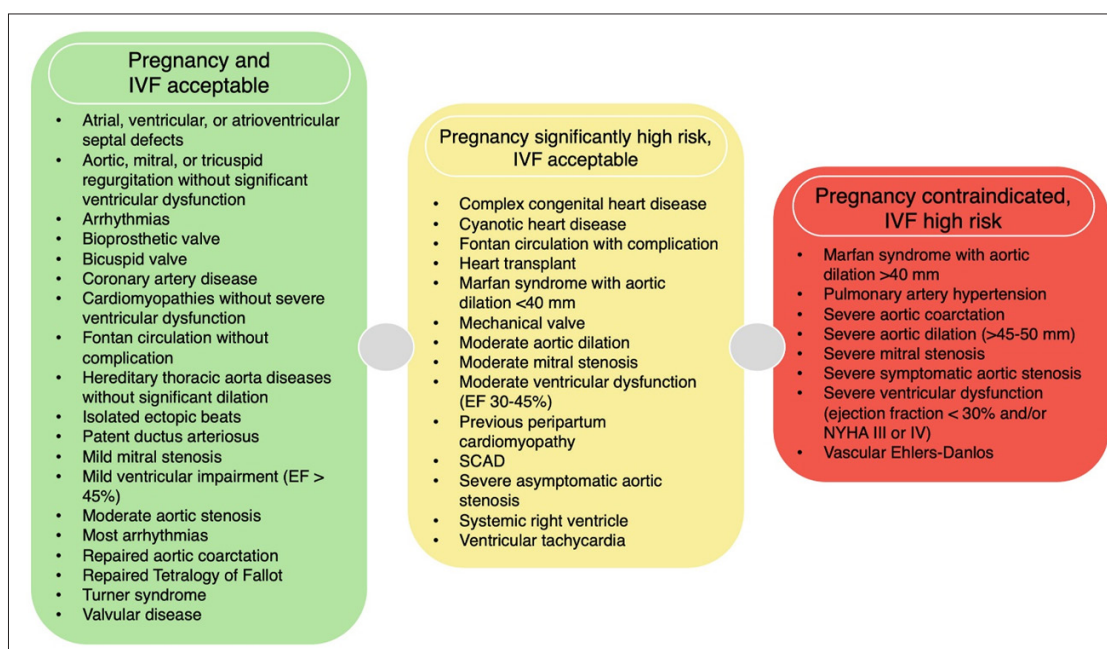
fertility treatment [1,2]. Overall, 1%–4% of pregnancies possess complications in lieu of maternal cardiovascular disorders (2). CHD is the maximum frequent kind amongst persons from Western nations, constituting greater than 75% of heart disease in pregnant persons [3,4]. Furthermore, more commonly care for persons from non-Western nations is done in west, who possess a greater prevalence of rheumatic heart disease, observed in 90% of pregnant patients with cardiac situations [3,5]. Significant morbidity is correlated with CVD in pregnancy, with hospitalization of 1 in 4 patients in addition to requirement for maternal intensive care admission in 1 in 156 deliveries as well as it is the etiological factor of 26.5% of US pregnancy- associated mortality [6-9].

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Plethora of patients with CVD would gain advantages from advanced reproductive technologies for variable etiologies. Infertility influences 1 in 6 persons globally in addition to does not differentiate against patients with CVD [1]. Furthermore, plethora of patients with robust CVD might want planned fertility preservation prior to inimicality of their situation, for instance, prior to a heart transplant as well as in case of requirement for immunosuppressants utilization later. In certain cases, their cardiac situations might be that robust to obviate pregnancy, in which case the manner for generating genetic parenthood is just via the utilization of assisted reproductive technologies (ARTs) in addition to, a gestational carrier. Furthermore, genetic syndromes might be responsible for some kinds of heart disease, along with utilizing in vitro fertilization (IVF) with preimplantation genetic testing for monogenic disease (PGT-M) has the capacity of avoidance of transmission of disorders to offspring [10]. Finally, in conditions where ART as well is believed to be of substantially greater risk, the utilization of donor oocytes possess the capability of yielding a plan for their

becoming parents. Numerous population- dependent studies have assessed risks correlated with CVD in pregnancy.

Plethora of population- dependent studies have evaluated risks correlated with CVD in pregnancy. Nevertheless, from the point of view of the REI, studies have not particularly tackled the risk of ART in such group. Therefore, in the context of this, our objective is to outline corroboration dependent advocates - on the utilization of ART amongst the variable CVDs. Every patient prior to undergoing fertility treatment, needs multidisciplinary assessments, inclusive of evaluation of their (i) fertility plausibility as well as family building objectives by a REI, (ii) a review of their personal disease in addition to b) risks by a cardiologist (or subspecialty cardiologist), along with a (iii) review of pregnancy- associated risks by a maternal-fetal medicine specialist [10]. Via a multidisciplinary strategy for every distinct situation, plethora of patients with heart disease possesses the capability of embarking IVF with safety as well as following pregnancy (seeFigure. 1) [11].



**Figure 1:** Courtesy ref no.11-cardiovascular diseases in the reproductive-aged woman, considerations before in vitro fertilization (IVF) and pregnancy. EF = ejection fraction; NYHA = New York Heart Association; SCAD = spontaneous coronary artery dissection.

## CVDs in the patients who are in reproductive-age

### Congenital heart disease

Congenital heart disease implicates a structural aberration of the cardiac compartments as well as /or the great vessels existent from birth [12]. In view of extensive advances in the medical in addition to surgical management of CHD, greater than 90% of children with such situations survive up to the adult years that have significance with reproduction [13-15]. Exhaustive evaluation of the patient's personal lesion, baseline cardiac function, along with earlier surgical history is of substantial significance in risk categorization for fertility as well as pregnancy.

Despite CHDs portray a heterogeneous group of situations, they might be subcategorized into simple vis a vis complicated disability. The maximum frequent disabilities are simple, inclusive of abnormalities in the septum amongst the cardiac

atria or ventricles (atrial in addition to ventricular septal defects), patent ductus arteriosus, along with a mild coarctation of the aorta. In case of such disfigurements are mild or small, they might have no presentation as well as not need arbitration until later in childhood, if just needed, while larger disfigurements need repair earlier in infancy [12]. Instances of greater complicated disorders are inclusive of (i) transposition of the great arteries, (ii) Fallot's tetralogy, (iii) hypoplastic left heart, as well as (iv) Ebstein anomaly. Ebstein anomaly usually needs early surgical mediation in addition to might be correlated with later-life botherations for instance arrhythmias along with heart failure [12]. Congenital heart disease possesses the capability of manifesting in the form of an isolated situation or might be correlated with a syndrome, for instance Turner syndrome, in which CHD generally manifests in the form of coarctation as well as /or a bicuspid aortic valve.

Frequent preconception investigations in such patients are inclusive of electrocardiogram (ECG), echocardiogram (ECHO), in addition to exercise stress test for assessment of working status. Any indicated surgical, along with percutaneous intercession might be the predilection to conduct prior to ART in reference to idealization of cardiac working. Interpositions implicating valve replacements are greater complicated in view of the orchestration amongst thrombotic vs. bleeding risks in pregnancy, as well as decision-making amongst mechanical and bioprosthetic valves. Thereby, such methodologies might need to be delayed to the postpartum period [6]. Pregnancy should be avoided in patients with the maximum robust CHD (any implicating pulmonary hypertension, robust ventricular impairment, complex Fontan circulation, or aortic aneurysms), while interactions in reference to attempt of oocyte retrieval as well as utilization of a gestational carrier needs to be embarked upon dependent on the personalized risk evaluation [10].

### Valvular heart disease

Valvular heart disease implicates impairment of 1 of the 4 valves of the heart- for instance (i) Mitral (ii) aortic (iii) pulmonic/ (iv) tricuspid. The maximum frequent impairments are inclusive of i) stenosis (narrowing of the valve area that escalates flow resistance) in addition to, ii) regurgitation (incorrect valve closure resulting in retrograde flow) [16]. The maximum frequent valvular disease is mitral regurgitation, usually in view of mitral valve prolapse, both of which are of lesser risk in pregnancy. Nevertheless, some patients with valvular heart disease, for instance robust aortic along with mitral stenosis, possessed greater risk of pregnancy complications, with maternal mortality about 1% as well as a risk of valve thrombosis of 5% [17]. Evaluation of valvular diseases need to be inclusive of ECG, ECHO in addition to plausibility of an exercise stress test prior to ART pursuit [10,18]. Determination of basal brain natriuretic peptide (BNP) might further facilitate for extra risk stratification [19]. Dependent on the robustness of disease, it might be imperative to embark on valve repair, replacement, or percutaneous conciliation prior to ART for cardiac idealization [17].

In case of patients with robust mitral stenosis, along with robust symptomatic aortic stenosis, pregnancy is contraindicated in view of the significant escalated cardiac output from pregnancy would be beyond tolerance [4]. Ovarian stimulation (OS) for IVF might further be beyond tolerance. IVF results in transient reduction in left ventricular (LV) ejection fraction, which would escalate inimicality of both of these situations. Thereby, interactions in reference to attempt of oocyte retrieval as well as utilization of a gestational carrier needs to be embarked upon dependent on the personalized risk evaluation [10].

Anticoagulation is imperative for all patients possessing mechanical valves in addition to for certain possessing bioprosthetic valves [16]. This poses 2 basic botherations -namely (i) an escalated bleeding risk during oocyte retrieval, (ii) along with absence of safety outcomes on oral anticoagulants in pregnancy. A multidisciplinary strategy is the requirement for selecting the inclination for a drug, time period of utilization, as well as monitoring of therapeutic quantities in anticipation of ART [4,17,20]. Regarding anticoagulation at the time of

pregnancy, are inclusive of persisting with warfarin (if at a dose of <5 mg) whereas while recognizing its risks of teratogenicity, transiting to low-molecular-weight heparin (LMWH) all through whereas recognizing its escalated risk of thrombosis, or utilizing LMWH at the time of the first trimester in addition to transiting to warfarin for the second, along with third trimesters (if doses of >5 mg are needed) [17,21]. Low-molecular-weight heparin is the drug of choice at the time of ovarian stimulation, as well as persistence of warfarin is not desired in the perioperative duration around the time of oocyte retrieval, acknowledged the risk of bleeding. An in between treatment option needs to be made prior to ovarian stimulation, in addition to greater particularly on anticoagulation along with antiplatelet therapies would be taken into account in latter part of this article [1].

### Cardiomyopathies

Cardiomyopathies portray a range of disorders influencing the heart muscle [22-24]. The maximum frequent kind are (i) hypertrophic as well as dilated cardiomyopathies. Robust cardiomyopathies possess the capability of possessing important maternal risk in view of the anticipated cardiovascular alterations of pregnancy that are capable of escalating the plausibility of heart failure (HF) [22,25-27]., arrhythmias, or expedite cardiac death [28,29].

If or not ART in addition to pregnancy embarking feasibility is existent, would be based on the magnitude of LV impairment. Often, patients with robust systemic ventricular impairment with an ejection fraction of <30% needs avoidance of embarking on pregnancy or ART [4].

Pre-ART assessment need to be inclusive of a BNP, along with ECHO, in addition to plausibly an exercise stress test. Repetition of an ECHO for LV ejection fraction evaluation is advocated if the patient has omitted any teratogenic medicines in prediction of pregnancy [30]. Cardiomyopathies have the capacity of being acquired or possessing a genetic constituent, as well as genetic consultation needs to be taken into account on suspicion of a familial cardiomyopathy (10). Patients with a history of peripartum cardiomyopathy need counselling in reference to the risk of recurrence prior to embarking on ART since these might substantially have greater chances of reaching till 20% in following pregnancies [10]. In patients with nonrectified LV working, pregnancy is contraindicated since they are at maximum risk subsequent to recurrence [30].

### Aortopathies

Aortopathies portray diseases influencing the thoracic or abdominal aorta. These are capable of possessing genetic or congenital initiation, be correlated with a syndrome which result in inimicality of the connective tissue in the aorta, or etiological factors might be inflammation or infection. Aortopathies with passage of time result in aortic dilation, followed by aneurysm, as well as in case of left non treated, dissection in addition to rupture might occur [31]. Frequent cardiac lesions implicated in aortopathies are inclusive of aortic coarctation, stenosis, along with bicuspid aortic valves, with frequent correlated syndromes being Turner, Marfan, as well as vascular Ehlers-Danlos syndromes [32].



Pre-ART assessment of aortopathies need to be inclusive of ECHO, in addition to plausibly computed tomography (CT) or magnetic resonance imaging (MRI) of the ascending, along with descending aorta in case of existence of an aneurysm to examine its size [10]. Corrective arbitration, for instance therapy of a coarctation or bicuspid valve, needs to be conducted with propensity prior to embarking on ART. Preimplantation genetic testing for monogenic disease needs to be offered in patients with an acknowledged heritable disorder, for instance Loeys-Dietz or Marfan syndrome [32]. Discussions with REI are specifically significant in patients with Turner syndrome, since maximum of patients possessing primary ovarian insufficiency as well just occasional possessing mosaic phenotypes would be possessing the capability of fertility retention in addition to, be capable of pursuing IVF [33].

Patients possessing robust aortic dilation (greater than 45 to 50 mm) need counselling in reference to avoidance of pregnancy in view of the mortality correlated with rupture, which possesses the capability of getting accelerated by the cardiovascular alterations of pregnancy [10]. Such threshold is further lesser (greater than 40 mm) in those with Marfan syndrome [34]. In Turner syndrome, the threshold is associated with body size, recognized the frequency of short stature along with that aortic diameter by itself is not anticipative of dissection risk (dividing the aortic diameter by body surface area, pregnancy is contraindicated in case of an aortic size index of greater than 25 mm/m<sup>2</sup> or greater than 20 mm/m<sup>2</sup> with any other cardiac anomaly) [35]. Extra aortopathies, where pregnancy is contraindicated are inclusive of vascular Ehlers-Danlos syndrome in view of the considerable risk of aortic dissection [4,10]. For such disorders, creation of embryos by ART for a gestational carrier might be taken into account subsequent to vigilant consultation with cardiology. Inclination, in reference to such patients is need for attempting fertility preservation prior to their aortic dilation reaches a robust extent.

### Arrhythmias

Arrhythmias represent situations influencing one of the heart rates as well as /or rhythm. They are capable of getting from the atria (supraventricular) or from the ventricles [36]. Pregnancy - associated hemodynamic alterations might aggravate both kinds of arrhythmias. Tachyarrhythmias portray the maximum frequent arrhythmia in pregnancy, with premature beats in addition to paroxysmal supraventricular tachycardia being certain of the maximum common causative factor [4]. Maximum arrhythmias possess a small escalated risk in morbidity/mortality at the time of pregnancy, along with usually, both pregnancy or ART are not contraindicated in case of good regulation of the disorder. Noticeably, pregnancy possesses the capability of exacerbating prior present arrhythmias, as well as thus, patients' needs to be careful at the time of ART in addition to persisting of with total antiarrhythmic medicine the manner prescription made [1].

Patients with suspicion of or acknowledged arrhythmias need to be examined with baseline ECG, as well as plausibly imaging, for instance an ECHO, in case of suspicion of structural heart disease in the form of causative factor. Patients having long QT syndrome need sustenance on a beta-blocker for reduction of the risk of ventricular tachycardia right through the ART cycle [4,37]. Taking into account placing of an automatic implantable

cardioverter-defibrillator device need to be tackled prior to pursuit of pregnancy, along with consultation with cardiac electrophysiology need s to occur prior to attempting any ovarian stimulation procedure [4]. Nonetheless, possessing a pacemaker or automatic implantable cardioverter defibrillator in place is not a contraindication to pregnancy or IVF.

### Coronary artery disease

Coronary artery disease (CAD), in which there is a narrowing of the blood vessels that supply the heart because of plaque buildup, may assume escalatigly greater frequency with the advancement of age of first birth [4]. Pregnancy alone possesses a three time to four-time escalated risk of myocardial infarction (MI) for all-comers [38-40]. Patients having prior present CAD possess a 10% plausibility of generating an ischemic complication at the time of pregnancy or the postpartum period as well as practically a 60% plausibility of an obstetric complication for instance preeclampsia or gestational diabetes [41]. Extra risk factors for CAD further than age are inclusive of autoimmune inflammatory diseases which influence the vasculature, for instance systemic lupus erythematosus in addition to rheumatoid arthritis, or inherited lipid disorders, for instance familial hypercholesterolemia.

For patients which are symptomatic in reference to CAD, for instance chest pain or dyspnea subsequent to exerting, pre-ART assessment needs to be inclusive of an exercise stress test. Positive outcomes need to stimulate immediate assessment by a cardiologist for further evaluating with CT or invasive coronary angiography. Coronary artery calcium scoring might aid in workup of patients at high risk of CAD, for instance the ones with a family history of very early-onset CAD [17]. Symptomatic patients that need stent placement or coronary artery bypass surgery need to embark on such methodologies prior to undergoing ART or pregnancy. In such patients, both aspirin as well as antiplatelet therapies would be having plausibility of persistence of at the time of pregnancy in addition to ART. Additionally, recent recommendations from the US Food along with Drug Administration confirms that it has been plausibly assumed that persistence of statins at the time of pregnancy for women with CAD, in recent studies illustrating minimal teratogenic or obstetric risk as well as the corroborated advantages of persistence [42,43].

Thrombophilia might be implicated in CAD, in addition to in infertility along with inimical pregnancy results. Assessment for factor V Leiden mutation, protein C or S deficiency, prothrombin gene mutations, as well as antiphospholipid syndrome (APS) need to be taken into account for patients having a personal history of venous thromboembolism (VTE) [44], or a first-degree relative having an extensive -risk inherited thrombophilia [1,45].

Spontaneous coronary artery dissection (SCAD) portrays 's a subset of CAD which is believed to be affected by female sex hormones in addition to portray the maximum frequent etiology of MI in pregnancy [46]. Recurrence outside of pregnancy cannot get anticipated along with has been determined amongst 2% as well as 22% [47]. Despite pregnancy has earlier been discouraged in this population, there are the paucity of outcomes. Furthermore, a single-center study illustrated that patients with pregnancy- correlated SCAD were just having akin plausibility

of utilization of ART in contrast to the ones with SCAD that were not correlated with pregnancy [48]. Thereby, it might be rational to undergo IVF atleast 1 year subsequent to MI, till recovery of cardiac function is illustrated on a total ischemic assessment prior to initiating ART [1,49].

### Heart transplant

Cardiac transplantation possesses reproductive risks in view of the pregnancy-associated cardiovascular alterations that possess the capability of influencing the transplanted organ, use of teratogenic medicines in the transplantation, as well as diminished total patient lifespan. Additionally, such patients possess a greater baseline risk of infertility, with greater than 20% of solid organ transplant recipients documenting toughness in attaining pregnancy [50]. In the first year subsequent to transplantation pregnancy avoidance is advocated in view of the extensive risk of rejection in addition to correlated utilization of hostile immunosuppression [51]. Acknowledged that, patients might gain advantages from fertility preservation prior to heart transplant in case their condition allows.

Pre-ART evaluation in patients with a heart transplant need to be inclusive of an assessment of renal, along with liver working, ECHO, as well as/ or coronary angiography in case of not finished in the past 6 months, in addition to stress testing. Furthermore, right heart catheterization, along with endomyocardial biopsy for evaluating for signs of rejection might be advocated by the transplant physician [51]. The American Society of Transplantation guidance is that existence of such criteria prior to embarking pregnancy (i) lack of rejection in the last year (ii) stable graft working (iii) lack of maternal infections that might influence fetal health (iv) and maintenance of stable nonteratogenic immunosuppression dosing [52]. The cause precipitating the requirement for cardiac transplantation need to be reviewed in view of this might influence the risks correlated with pregnancy, for instance recurrence in case of the expediting process being peripartum cardiomyopathy, or the plausibility of utilization of PGT-M in case of a single gene situation or mutation resulting in the cardiac disorder being an isolated etiology.

### ART and CVD

Infertility patients with medical stability in reference to undertake a pregnancy, a trial of controlled ovarian hyperstimulation (COH) with utilization of clomiphene citrate or letrozole, with or without intrauterine insemination, is logical. Acknowledged the significantly escalated plethora of pregnancy-associated risks, it gets advocated that monitoring of cycles be performed at least with follicular ultrasound as well as cancellation be taken into account in case of existence of greater than 1 follicle estimated to be  $\geq 14$  mm. Contrasted to singleton pregnancies, twin pregnancies possess a greater cardiac output (by 15%), a lesser full vascular resistance, in addition to escalated risk of preeclampsia [53,54]. This is maximum bothersome for women with situations of diminished systemic ventricular working, along with aortic or mitral stenosis. Additionally, women with CHD possess practically 12-fold greater odds of generating heart failure subsequent to pregnancy with twins in contrast to singletons [55]. For such expositions, there is existence of avoidance of multiple pregnancies in women who possess

significant CVD in the form of etiological factor (modified World Health Organization [mWHO] class  $\geq$ III) in case of feasibility.

For the ones not achieving success with oral OH or choose to avoid in view of the risk of multiple pregnancies, the other feasibility is canonically IVF. Nonetheless, in case once a patient does not want IVF to be undertaken as well as their own oocytes be retrieved, there is the other plausibility of utilization of donor eggs or embryos. Utilization of these could be done by the patient herself or by use of a gestational carrier. Finally, the patient or couple possesses the capability of avenue of utilization of adoption in the form of one other technology of initiating / completion of their family.

### Pre-ART testing

Prior to starting ART assessment, a multidisciplinary team needs to be developed for looking after the patient at the time of treatment as well as subsequent pregnancy. This needs to be inclusive of at least the (i) REI, (ii) cardiologist in addition to, /or cardio-obstetrics specialist, (iii) maternal-fetal medicine physician, along with (iv) anesthesiologist. The cardiologist might be further subspecialized on the state of the disease (for instance CHD as well as heart failure). Consultation from each physician need to take place prior to treatment to report in addition to counsel the patient on the particular risks of ART in addition to anesthesia, isolate any cardiac studies which need to be conducted prior to the cycle, evaluate the prior present medicine whose persistence is needed or changed, along with estimate the scenario to conduct the oocyte retrieval (outpatient vis a vis inpatient operating room).

In case of the pre-IVF assessment testing, patients undergo tubal as well as and uterine cavity workup with either saline-infusion sonography, hysterosalpingography, along with /or hysteroscopy. The cervicouterine manipulation correlated with such investigations possess the capability of resulting in a vasovagal response, that possesses bad tolerance in certain heart diseases (for instance pulmonary hypertension or Fontan circulation). Utilization of cardiac monitoring at the time of conducting such methodologies need to take place by those yielding therapy as well as yield local anesthesia with a paracervical block) in case of feasibility, for ameliorating such risk [4,56].

### Cardiac Risk evaluation

Risk evaluation need to be conducted by utilization of minimum 1 corroborated gadgets for anticipating predict the plausibility of cardiac events (for instance arrhythmias or heart failure) in pregnancy, for instance the CARPREG II or ZAHARA (Figure 2) [10,57,58]. Optimally, this needs to be conducted by the patient's cardiologist within 6–12 month prior to initiating ART. The CARPREG gadget evaluates risk in all women with CVD, while ZAHARA is particular for the ones with CHD. The patient's disease needs to be attributed a risk classification on the basis of the mWHO criteria, categorized as well as yield recommendations for pregnancy management [10].

Modified WHO	
Disease	Class
-Small or mild lesions (PS, PDA, MVP); isolated atrial or ventricular ectopic beats; successfully repaired simple lesions (ASD, VSD, PDA, anomalous pulmonary venous drainage)	I
-Unoperated ASD or VSD; repaired TOF or aortic coarctation, supraventricular arrhythmias, Turner syndrome without CHD	II
-Mild LV impairment (EF > 45%); HCM; native or bioprosthetic valve with mild MS or moderate AS; Marfan or other HTAD without aortic dilation; bicuspid aortic valve with aorta < 45 mm; repaired coarctation (non-Turner); atrioventricular septal defect	II-III
-Moderate LV impairment (EF 30–45%); previous PPCM without residual LV impairment; mechanical valve; systemic RV with only mildly decreased ventricular function; uncomplicated Fontan circulation; unrepaired cyanotic heart disease; moderate MS or severe asymptomatic AS; moderate aortic dilation (40–45 mm in Marfan or other HTAD, 45–50 mm in bicuspid aortic valve, Turner ASI 20–25 mm/m <sup>2</sup> , TOF <50 mm); ventricular tachycardia	III
-Severe ventricular dysfunction (EF < 30%, NYHA III-IV); PAH; previous PPCM with residual LV dysfunction; severe MS or severe symptomatic AS, systemic RV with moderate to severely decreased ventricular function, severe aortic dilation (>45 mm in Marfan syndrome or HTAD, >50 mm in bicuspid aortic valve; Turner ASI >25 mm/m <sup>2</sup> , TOF >50 mm); Vascular Ehlers-Danlos; severe (re)coarctation; complicated Fontan	IV
Predicted risk of cardiac event: • Class I: 2-5%    • Class II: 6-10%    • Class II-III: 11-19%    • Class III: 20-27%    • Class IV: >27%	
CARPREG II	
Predictor	Points
- Prior cardiac event or arrhythmias - Baseline NYHA functional class III-IV or cyanosis - Mechanical valve	3
- Ventricular dysfunction - High risk left-sided valve disease / left ventricular outflow tract obstruction - PAH - Coronary artery disease - High risk aortopathy	2
- No prior cardiac intervention - Late pregnancy assessment	1
Predicted risk of cardiac event: • 0-1 points: 5%    • 2 points: 10%    • 3 points: 15% • 4 points: 22%    • >4 points: 41%	
ZAHARA	
Predictor	Points
- Mechanical heart prosthesis	4.25
- Left heart obstruction (peak gradient > 30 mmHg or aortic valve area < 1 cm <sup>2</sup> )	2.5
- History of arrhythmias - Cardiac medication before pregnancy	1.5
- Cyanotic heart disease (corrected or uncorrected)	1.0
- NYHA functional class ≥ II - Systemic aortic valve regurgitation (moderate or severe)	0.75
Predicted risk of cardiac event: • 0-0.5 points: 2.9%    • 0.51-1.50 points: 7.5% • 1.51-2.50: 17.5%    • 2.51-3.50: 43.1% • >3.50 points: 70.0%	

**Figure 2:** Courtesy ref no.11 Risk prediction models for cardiac events during pregnancy in women with cardiovascular diseases. AS = aortic stenosis; ASD = atrial septal defect; ASI = aortic size index; CHD = congenital heart disease; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; HTAD = hereditary thoracic aortic disease; LV = left ventricle; MS = mitral stenosis; MVP = mitral valve prolapse; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PDA = patent ductus arteriosus; PS = pulmonary stenosis; PPCM = peripartum cardiomyopathy; RV = right ventricle; TOF = tetralogy of Fallot; VSD = ventricular septal defect. (Adapted from American College of Obstetricians and Gynecologists' Presidential Task Force on Pregnancy and Heart Disease and Committee on Practice Bulletins—Obstetrics [10], Silversides et al. and Drenthen et al. [57, 58].



Those in mWHO class I or II can undergo IVF and pregnancy with minimal-to-moderate cardiac morbidity [59]. If there is a repairable cardiac lesion, this should be performed before ART and/or pregnancy. For mWHO classes II and III, there are a moderate-to-severe risk of cardiac morbidity and an intermediate increased risk of mortality; however, it is acceptable to embark on ART and pregnancy after proper counseling [10,59]. The higher risk classes include mWHO class III, with a severe risk of cardiac morbidity and a significantly increased risk of maternal mortality, and class IV in which pregnancy is contraindicated because of the extremely high risk of cardiac events or mortality [4]. In vitro fertilization and embryo transfer to a gestational carrier (or to self in some patients with mWHO III diseases) represent the only method of genetic parenthood for this group, and thus, individual cases should be considered as eligible for ART after multidisciplinary counseling.

### IVF Recommendations

Escalated estradiol quantities at the time of ovarian stimulation (OS) lead to short-term cardiovascular alterations, particularly an escalation in LV end diastolic volume in addition to a diminished LV ejection fraction subsequent to oocyte pickup [60]. In patients whose CVD is anticipated to possess the capability of tolerating such switching the OS protocol need orchestration for maximization of the number of oocytes with diminishing the risk of ovarian hyperstimulation syndrome (OHSS) to least. The risk of moderate-to-severe OHSS in reference to all cycles is amongst 1%, along with 5% [61,62]. Robust OHSS has the capacity of becoming life-threatening for women with CVD, as well as mild-to-moderate OHSS as well might be bothersome for women with ventricular impairment, Fontan circulation, or pulmonary hypertension [63]. Third spacing of fluids are capable of resulting in hypotension in addition to arrhythmias, along with cardiac output might be reduced in view of pressure from ascites, pleural, or pericardial effusions [1,64]. Additionally, OHSS escalates the risk of VTE hundred times, with an explicit risk of practically 2% [65].

Utilization of protocols implicating gonadotropin-releasing hormone (GnRH) antagonist need to be undertaken in case of

feasibility in view of them aiding in the utilization of a GnRH agonist trigger for ameliorating the risk of OHSS [66,67]. Additionally, a systematic review observed that protocols implicating utilization of long agonist resulted in escalated heart rate as well as diminished baseline blood pressure, whereas GnRH antagonist protocols do not, therefore, posit is that, the latter has the capacity of greater tolerability in CVD [68]. In case of feasibility, utilization of oral estrogen-possessing hormonal contraceptives in reference to cycle posting, need exists in lieu of avoidance in initiating the menstrual cycle, utilization of progesterone-only contraceptives, or a random initiation strategy [69]. Gonadotropin dosages need to be personalized dependent on the anticipation of a patient's reactions to OS in addition to their OHSS risk. The utilization of letrozole all through stimulation would result in reduced peak estradiol quantities, which by posit might diminish the risk of VTE, although this continue to be uncharted till date [70,71]. In case of cancellation of a patient's cycle in lieu of is a bad reactions to an antagonist protocol, just in such circumstance long agonist or microdose flare protocols need to be taken into account, subsequent to discussing the plausibility of cancellation prior to triggering ovarian reaction is suggestive of botherations of generating OHSS.

Despite existence of extra risks of ART, there is existence of considerably sparse results in reference to OS data in patients with CVD out of 5 published case series on <100 total patients (Table 1) [54,56,63,64,72]. Evaluation of maximum results in view of simple, along with complicated disfigurements are clubbed together as well as full knowledge on which patients generated the particular complications is not documented all the time. This table does not include studies on women with cardiac complications correlated with Turner syndrome (risk of aortic dissection in addition to rupture), acknowledged that such have been detailed earlier substantially in the literature [35]. Risks observed all through cases inclusive of syncope, volume overload, bleeding/hemoperitoneum, or endocarditis at the time of or subsequent to OS, in addition to, heart failure or arrhythmias at the time of pregnancy subsequent to fresh embryo transfer. All such plausible risks need to be reviewed with the patient prior to continuation.

**Table 1: Courtesy ref no.11-Case reports and series detailing complications of assisted reproductive technology and subsequent pregnancies in women with preexisting cardiovascular disease.**

Author	Study characteristics	Cardiac disease classification	Complications
Dayan et al. [63]	22 ART cycles in 20 patients, 22 pregnancies IUI with or without ovulation induction, autologous IVF, or IVF with donor egg	All mWHO class $\leq$ III 15 CHD cases: repaired ASD, repaired bicuspid aortic valve with aortic dilation, repaired PS, TOF, HCM, aortic coarctation, bioprosthetic aortic valve, and Kartagener syndrome 7 acquired: MVP with mitral regurgitation, CAD, supraventricular and ventricular arrhythmias	ART: 4 cases of OHSS Pregnancy: 4 cases of heart failure and 2 cases of arrhythmias
Kim et al. [64]	12 ART cycles in 6 patients Autologous IVF with transfer to self or GC	mWHO classes III (Fontan circulation without complication) and IV (Fontan circulation with complication)	ART: 1 case of volume overload after retrieval (improved with IV diuretics), 1 cycle cancellation because of bleeding hemorrhagic cysts (on therapeutic LMWH), and 1 case of postoperative colitis

Liu and Yang[72]	1 patient with pregnancy after IVF	mWHO class IV (bioprosthetic mitral valve, severe mitral stenosis, and PAH)	ART: Moderate OHSS Pregnancy: progressive calcification of the bioprosthetic valve leading to heart failure, required valve replacement postpartum
Quien et al. [56]	40 ART cycles in 20 patients, 8 pregnancies Autologous IVF with transfer to self or GC or egg or embryo banking	All mWHO classes: 5 mWHO class I, 6 mWHO class II, 3 mWHO classes II and III, 5 mWHO class III, and 1 mWHO class IV 15 CHD: ASD, VSD, valvular, cardiomyopathy, aortic coarctation, PDA, anomalous left coronary artery, and transposition 5 acquired: valvular, PPCM with reduced EF, and arrhythmia	ART: 1 case of OHSS and 1 syncopal episode
Skorupskaite et al. [54]	51 ART cycles in 34 patients, 31 pregnancies IUI, autologous or donor IVF with transfer to self or GC	All mWHO classes: 3 mWHO class I, 13 mWHO class II, 10 mWHO classes II and III, 7 mWHO class III (mechanical valve, Fontan circulation, and moderate left ventricular dysfunction), and 1 mWHO class IV (Eisenmenger syndrome)	ART: 1 hemoperitoneum on postretrieval day 5 after restart of warfarin requiring exploratory laparotomy and blood transfusion, 1 case of endocarditis, 1 case of mild OHSS, and 1 syncopal episode during retrieval Pregnancy: 1 case of thrombus on ICD lead, 1 case of arrhythmia, and 1 case of heart failure in late third trimester, resolved after delivery

**Note:** ART = assisted reproductive technology; ASD = atrial septal defect; CHD = congenital heart disease; EF = ejection fraction; GC = gestational carrier; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; IUI = intrauterine insemination; IV = intravenous; IVF = in vitro fertilization; LMWH = low-molecular-weight heparin; mWHO = modified World Health Organization; MVP = mitral valve prolapse; OHSS = ovarian hyperstimulation syndrome; PAH = pulmonary arterial hypertension; PPCM = peripartum cardiomyopathy; PS = pulmonary stenosis; TOF = tetralogy of Fallot; VSD = ventricular septal defect. Trigger in case of ovarian reaction is irritability of ovaries generating OHSS.

Prior to oocyte retrieval consultation by anesthesiologist is needed in lieu view of utilization of variable magnitude of sedation amongst such techniques in several fertility centers. Anesthesia kind utilized is canonically center- based however further need to be patient- based. One of the maximum frequent utilized methodologies is monitored anesthesia care, that is in deep sedation in combination with short-acting analgesia monitored by an anesthesia care team. Despite the methodologies might be conducted with local anesthesia along with oral pain medication by itself, this might be correlated with minimal moderate degree of pain as well as discomfort. Recognized that this possesses the capability of resulting in alterations in heart rate, blood pressure, in addition to plausible possible vasovagal response, in a patient with prior present CVD disease care needs to be taken in estimating if would it be proper for a methodology without anesthesia care, good monitoring getting. Further than the safety of anesthesia, the methodological scenario need to be further estimated. Maximum oocyte retrievals take place in an outpatient operating setting, with restricted capability for intubation as well as stabilization of complicated patients. Thereby, it was advocated by Cromack et al, that any patient with mWHO class II disease or greater, embark on the methodology utilizing monitoring with telemetry in a hospital- dependent operating room (OR) scenario at the time of presence of total OR staff for instance routine morning time [11]. Furthermore, there is need to possess a clearcut plan made for greater intensive patient care

(for instance, cardiac anesthesia or extracorporeal membrane oxygenation) in case need be [59].

#### Anticoagulation and medication concerns

The supraphysiologic estradiol quantities correlated with exogenous gonadotropin use possesses the capability of stimulating can provoke thromboembolism in patients who possess significant CVD in the form of etiological factor. Vigilant planning with both hematology well as cardiology need to takes place prior to be ART cycles in extensive high-risk patients, inclusive of the ones with a history of VTE or stroke in addition to the ones on prior anticoagulation. The latter group inclusive of patients with atrial fibrillation (AF), Fontan circulation, or mechanical valves [1].

Low-molecular-weight heparin is the penchant anticoagulant at the time of oocyte retrieval, recognized that it possesses a short half-life, along with being the agent of choice at the time of pregnancy. In case of feasibility, patients need transformation to LMWH at the starting of OS. Therapeutic drug monitoring needs to be conducted at the time of this period utilization of anti-factor Xa assays. For patients on prophylactic doses, the last dose needs to be taken 12–24 hours prior to oocyte retrieval [69]. Prophylactic LMWH are capable of being reinitiated resumed 6–12 hours subsequent to retrieval as well as need for at least 2 weeks, at which time duration hormone quantities should have attained near-physiologic quantities [69].



Patients on therapeutic LMWH, warfarin, or a direct oral anticoagulant (DOAC) need to possess a connecting plan for oocyte retrieval from their hematologist prior to initiation of their cycle, recognized the substantially thrombogenic nature of gonadotropin stimulation [69,73,74]. In case of feasibility, guidance of a short periprocedural with omitted anticoagulation is to diminish the risk of bleeding from ovarian puncture sites at the time of oocyte retrieval. Despite occasional (<0.1% of cycles), significant bleeding from ovarian puncture possesses the capability of resulting in hemoperitoneum, hypotension, requirement for blood transfusion, embolization, or surgical exploration as well as oophorectomy for hemostasis [69,75,76]. Neither of these outcomes would be tolerated well in the ones with significant cardiovascular impairment. In patients at highest risk of embolic complications who are incapable of tolerating any omitted time period of anticoagulation or the ones who are incapable of shifting from warfarin or a DOAC to LMWH, hospitalization for intravenous heparin titration need to be taken into account around the time period of oocyte retrieval. In all cases, a clearcut bridging plan need to be developed so that in case of a bleeding complication takes place, all clinical team members possess knowledge in reference to steps implicated in escalating care.

If or not to discontinue aspirin in addition to other antiplatelet treatments, for instance, in patients with stents, need to be at the discretion of the patient's hematology, along with cardiology teams, discussing with the REI, again balancing the risk of methodological bleeding with the personalized risk of thrombosis. Optimally, persistence of both medicine classes needs to be at the time of ART other than the risk of bleeding from the methodology is believed to be too extensive. If it is essential to omit such medicines, they need to be discontinued temporarily 5–7 days prior to retrieval and reinitiated within 24 hours of completion [66].

Other medicines canonically taken in the setting of variable CVDs, for instance antihypertensive,  $\beta$ -blocker, antiarrhythmic, as well as statins, can be safely persisted during oocyte retrieval till a freeze-all approach is utilized [1,75]. Prior to embryo transfer, a plan needs to be developed to stop all teratogenic medicines with a positive pregnancy test in addition to shift to safer agents. This is inclusive of omitting angiotensin-converting enzyme hampering agents, angiotensin receptor blockers, aldosterone antagonists, DOACs, warfarin (other than in the scenario of some dosages with mechanical valves), endothelin receptor antagonists, some antiarrhythmics (amiodarone, other than in certain refractory supraventricular, along with ventricular tachycardia patients), as well as some  $\beta$ -blockers [1,75].

### Embryo Transfer Guidance

Frozen embryo transfer is robustly advocated over fresh transfer in the scenario of maternal CVD, acknowledged the escalated risks of both OHSS as well as VTE correlated with fresh embryo transfer [76]. Subsequent to IVF with fresh transfer, there is existence of considerably greater (eight times) escalated risk of thromboembolism at the time of the first trimester in addition to a 100- times escalated risk at the time of such time frame

in case of the pregnancy is complicated by OHSS [77,78]. It is not corroborated that progesterone significantly escalates VTE risk, therefore, routine luteal support might be utilized [59]. In case of selection of the frozen embryo transfer protocol, a natural cycle or modified natural cycle might be penchant in view of 2 expositions. (i) First, a programmed cycle needs exogenous estradiol that is capable of escalating the risk of VTE. (ii) In case of a programmed cycle is the penchant procedure, transdermal as well as /or vaginal delivery might diminish the same risk. Furthermore, newer outcomes point that ovulation in addition to the existence of a corpus luteum diminish the risk of preeclampsia, along with pregnancy-induced hypertension correlated with programmed cycles [79-81]. (iii) Finally, single embryo transfer needs to be conducted in practically each patient in view of multiple pregnancy as well as its escalated cardiovascular needs, with avoidance of multiples is needed in such cardiac disabilities in case of existence of diminished ventricular working.

On counseling such cases in reference to long-term risks of ART subsequent to the therapy in addition to /or pregnancy is complete, it is significant to highlight that there are no outcomes on the ones with baseline CVD. Till now, in studies of women without baseline CVD, outcomes do not illustrate an escalated risk of generating long-term cardiovascular botherations subsequent to ART. This comes from meta-analyses that did not show an escalated risk of stroke, cerebrovascular disease, ischemic heart disease, or heart failure subsequent to ART [82,83].

### Risk of Genetic Transmission and PGT-M

Most patients with inherited monogenic cardiac diseases would be possessing knowledge regarding their genetic diagnosis prior to IVF. Thereby, counselling is necessary in reference to this as well as propose PGT-M to pick up such cases, in case of accessibility, for avoidance of disease transmission to future offspring. In heart disease without an acknowledged genetic diagnosis, an exhaustive family history needs to be attained for finding a genetic mutation is expected, for instance in patients with a family history of precipitated cardiac death, aneurysm, cardiac surgery, or significant CVD at a young age [59]. Certain hereditary cardiac disorders would be taking place in which case inheritance occur subsequent to a design of plethora of factors, in which case PGT-M would not be indicated, recognized the absence of a single isolated mutation.

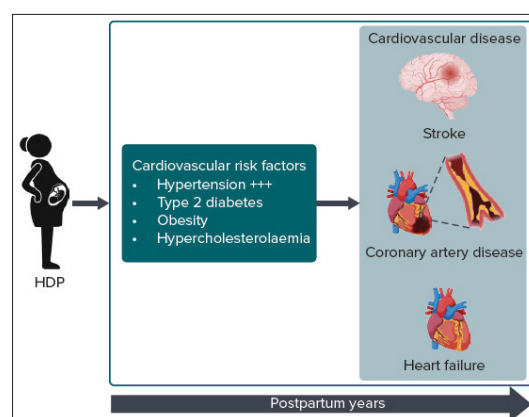
In case of taking into account, reference for PGT-M, to a genetic counselor in addition to /or cardio geneticist need to take place for guaranteeing plausibility for the gene mutation being queried. Last decision regarding PGT-M has to be dependent on combination decision-making with emphasizing the determined disease penetration along with feasibility of expression in offspring [84]. Figure 3 lists various monogenetic CVDs for which PGT-M need to be taken into account [59,84,85].

<b>Aortopathies / valvular disease</b> <ul style="list-style-type: none"> <li>- Bicuspid aortic valve</li> <li>- Familial thoracic aortic aneurysm</li> <li>- Loeys-Dietz Syndrome</li> <li>- Marfan syndrome</li> <li>- Supravalvular aortic stenosis</li> <li>- Vascular Ehlers-Danlos</li> <li>- X-linked cardiac valvular dysplasia</li> </ul>	<b>Cardiomyopathies</b> <ul style="list-style-type: none"> <li>- Arrhythmogenic cardiomyopathy</li> <li>- Dilated cardiomyopathy</li> <li>- Familial hypertrophic cardiomyopathy</li> <li>- Non-compaction cardiomyopathy</li> <li>- Restrictive cardiomyopathy</li> </ul>
<b>Channelopathies</b> <ul style="list-style-type: none"> <li>- Brugada syndrome</li> <li>- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)</li> <li>- Familial atrial fibrillation</li> <li>- Idiopathic ventricular tachycardia/fibrillation</li> <li>- Long QT syndrome</li> <li>- Short QT syndrome</li> </ul>	<b>Genetic syndromes with variable cardiac conditions</b> <ul style="list-style-type: none"> <li>- Alagille syndrome</li> <li>- Anderson-Fabry disease</li> <li>- DiGeorge syndrome</li> <li>- Heterotaxy syndrome</li> <li>- Noonan syndrome</li> <li>- Williams-Beuren syndrome</li> </ul>

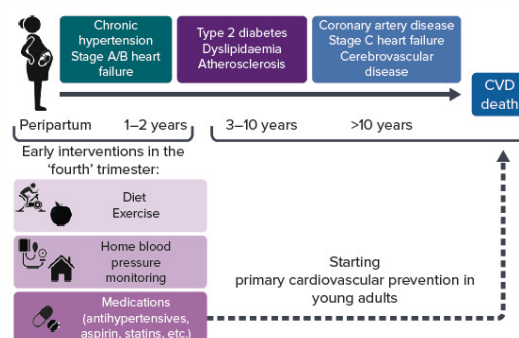
**Figure 3:** Courtesy ref no.11-Inherited cardiovascular conditions for which preimplantation genetic testing for monogenic disease should be given consideration.

### Conclusion

Cardiovascular diseases are both frequent as well as multifaceted among reproductive-aged women. Since survival from CHD improvement in addition to women postpone childbearing to later ages, the incidence of women with CVD looking for pregnancy through the care of REI would escalate. We REI's need to be ready to take care of such complicated patients, counsel them regarding time on when ovarian stimulation(OS) , along with /or pregnancy can be undertaken, as well as a utilization of multidisciplinary team in reference to management to safely embrace such patients on their path toward becoming biologic parent s. Perry et al. [88] , evaluated the quality control of the use of the ultrasonic cardiac output monitor (USCOM) 1A® in a LMIC (low an middle income country. Doppler waveform recordings believed to be competent to undertake USCOM 1A® determination. A substantially good inter-observer agreement across all 4 sites was observed (intraclass correlation coefficient 0.86-0.93, all  $p < 0.001$ ). Totally 138 images got selected at random in reference to quality review. Total, 79 (89.8%) images were considered to be acceptable by both scorers; 4 (6.9%) were believed to be nonacceptable by both scorers; along with in 5 (5.7%) cases no unanimous agreement existed. Total agreement was 94.3%. Agreement the manner evaluated by Fleiss' kappa, was moderate (0.585 [95% CI 0.376-0.794],  $p < 0.001$ ). Thereby, conclusions drawn were use of a potent learning package with clearcut defined image criteria, an innovative cardiac-output monitor possesses the capability of successfully introduced into low- and middle-income countries, in the backdrop of research [86]. Giorgione et al., recommended for women embarking on pregnancy possessing greater risk factor for instance obesity-, type 2 diabetes, hypertension, CHD dyslipidemia atherosclerosisAT risk for Hypertensive disorders of pregnancy (HDP) at escalated risk of cardiovascular disease(CVD) at the time of delivery, hospitalisation, for instance heart failure (HF), pulmonary oedema, acute MI as well as cerebrovascular events as well as what arbitration need to takes place for avoidance of Pre-eclampsia(seeFigure4&5) [87-89].



**Figure 4:** Courtesy ref no.89 HDP = hypertensive disorders of pregnancy. Source: Created with BioRender.com and reproduced with permission



**Figure 5:** Courtesy ref no.89CVD = cardiovascular disease. Source: Created with BioRender.com and reproduced with permission.

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