Management of Ischemic Heart Disease in Pregnancy

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Abstract

Purpose of Review Cardiovascular disease is an escalating cause of maternal morbidity and mortality. Women are at risk for acute myocardial infarction (MI), and more are living with risk factors for ischemic heart disease (IHD). The purpose of this review is to describe the evaluation and management of women at risk for and diagnosed with IHD in pregnancy.

Recent Findings Pregnancy can provoke MI which has been estimated as occurring in 1.5–10/100,000 deliveries or 1/12,400 hospitalizations, with a high inpatient mortality rate of approximately 5–7%. An invasive strategy may or may not be preferred, but fetal radiation exposure is less of a concern in comparison to maternal mortality. Common medications used to treat IHD may be continued successfully during pregnancy and lactation, including aspirin, which has an emerging role in pregnancy to prevent preeclampsia, preterm labor, and maternal mortality. Hemodynamics can be modulated during pregnancy, labor, and postpartum to mitigate risk for acute decompensation in women with IHD.

Summary Cardiologists can successfully manage IHD in pregnancy with obstetric partners and should engage women in a lifetime of cardiovascular care.

Keywords Pregnancy · Heart · Cardiac · Ischemia · Maternal mortality · Secondary prevention

Introduction

Cardiovascular disease, already the major cause of death in the USA, is a rising cause of maternal morbidity and mortality, responsible for over 1/3 of deaths [1••]. Non-Hispanic black and Native American/Alaska Native women have the highest all-cause maternal mortality in the USA, 3.3- and 2.5-fold that of non-Hispanic white women [1••]. Analysis of pregnancy-related deaths indicates these groups are disproportionately affected by multiple factors which contribute to worse outcomes. These include less access to medical care, inadequate insurance coverage, lack of provider training or continuity, limitations in their built environment leading to poor housing or transportation, and less health education [1••]. In response, obstetricians and cardiologists across professional societies have galvanized to address, evaluate, and manage risk, advocating for improved research, education, and treatment to avert tragic outcomes in young women, which has family and community-wide impact [2, 3•]. The aim of this review is to summarize current knowledge relating to the management of ischemic heart disease in pregnancy (Fig. 1) and where there are urgent opportunities for interdisciplinary endeavors.

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Fig. 1 **a** Highlights of the management of women with ischemic heart disease (IHD) in pregnancy. ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor inhibitor, MI = myocardial infarction. [1]From ref. 4. **b** Composition of the Cardio-Obstetrics Heart Team at our institution. Cardiology representation is most frequently from general/imaging and adult congenital heart disease. Additional services are involved depending on maternal need
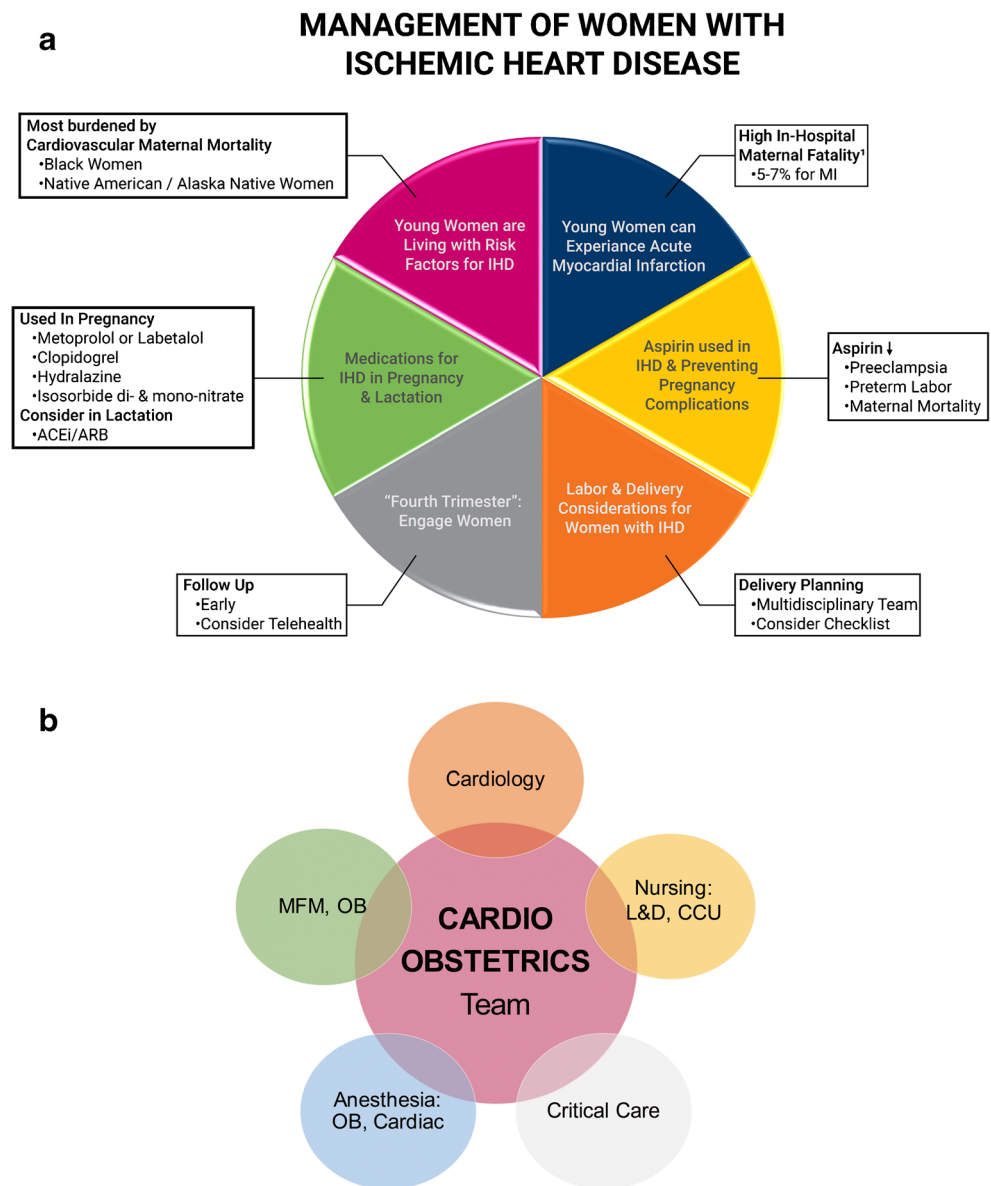
More Women in Their Reproductive Years Are Living with Risk Factors for Ischemic Heart Disease

While cardiovascular disease (CVD) has declined across the population, there has been a paradoxical rise in women of reproductive age, with less awareness of risk factors in women of color [5, 6]. More young women in the USA are living with obesity, hypertension, and diabetes, a classic trifecta of risk factors for ischemic heart disease (IHD). Physicians must be attuned to this evidence and routinely estimate risk and screening for overt disease in young women. Obstetric and pre-conception care encounters are occasions for global assessment that will affect women beyond the three trimesters of pregnancy. These are moments for anticipatory guidance about

cardiovascular health which can influence and engage women in care for a lifetime.

A broad scope of risk factors for IHD in women of reproductive age must be considered. Sex-specific CVD risk factors are under-evaluated at physician visits [7]. In the general population, for adults 20–39 with low-to-borderline 10-year risk assessment, periodic monitoring (every 4–6 years) is recommended [8]. However, not all risk factors, like female-preponderant or female-specific risk factors, are considered by widely used scoring calculators like the Atherosclerotic Cardiovascular Disease (ASCVD) Risk Algorithm or Framingham 10-year risk score [9, 10]. More frequent monitoring might be useful with increasing risk factors, but at present, specific recommendations for women are lacking, thus relying on obstetricians, cardiologists, and other physicians to tailor care.

With regard to women of reproductive age, physicians may take into account advanced maternal age, obesity, physical inactivity, undiagnosed hypertension, metabolic (thyroid, polycystic ovarian syndrome, diabetes) and rheumatic disorders (lupus and rheumatoid arthritis), race-ethnic, immigration, and socioeconomic characteristics, psychosocial stress (domestic violence, depression), symptoms of untreated sleep apnea, and substance use. This is in addition to classical biomarkers like elevated serum total, low density lipoprotein (LDL) cholesterol, triglycerides, and potentially lipoprotein (a), as well as low serum high density lipoprotein (HDL) cholesterol, prothrombotic factors, and inflammation [11, 12]. Use of estrogen-containing contraceptives must be evaluated, as high estrogen, > 50 μg, increases risk of myocardial infarction (MI) and stroke, 1.6–1.7-fold, respectively [13].

Evidence indicates the importance of reproductive history in the full CVD risk assessment of women. The total number of lifetime ovulations matters with respect to a woman's risk of MI; the more lifetime ovulations, the higher the risk. IHD risk decreases with older age at menarche. In a study of the National Health and Nutrition Examinations Survey (NHANES), for each 1-year delay in menarche, there was a 17% increase in the odds of having ideal cardiovascular health [14]. In a small prospective cohort, IHD risk rose with older age at first birth (age-adjusted relative risk ratio (RR) 2.90 for ages 33–43 as compared with 25–29 years) and later age at last birth (age-adjusted RR 3.79 for ages ≥40 as compared with 35–39 years) [15]. In a large prospective Japanese study, a U-shaped association between parity and CVD mortality was described [16]. For women with ≥3 deliveries, older maternal age ≥28 years at first delivery was associated with a 1.2- to 1.5-fold increase in CVD mortality [16]. With respect to the postpartum period, there is mixed evidence on the effects of lactation on cardiovascular health. Some studies indicate that longer breastfeeding may be associated with reduced odds of maternal metabolic syndrome, but a recent systematic review was inconclusive, potentially due to between-study heterogeneity [17].

Nulliparity has been identified as a long-term risk factor for cardiovascular disease, but studies do not usually distinguish if this is due to women's life choices or infertility, per se. Polycystic ovarian syndrome, but not necessarily all-cause infertility, has been associated with cardiovascular risk and diabetes [18]. Premature ovarian failure, recurrent miscarriage, or early menopause contributes a 1.5- to 1.9-fold increased risk of MI [15]. While ovulation-inducing agents used in reproductive endocrine treatments of infertility have not been shown to increase the risk of cancer, the relationship between fertility medications and MI is understudied [19]. An infrequent complication from infertility treatment, ovarian hyperstimulation syndrome (OSH), leads to increased vascular permeability, inflammation, and hypercoagulability. It has been associated with stroke and acute MI [20]. Individuals with predisposition to CVD or preexisting cardiovascular conditions may be at greater risk of MI with OSH.

A woman's obstetric history is a window to her cardiovascular future. Lifetime prevalence of hypertension and diabetes are predicted by hypertensive disease of pregnancy (gestational hypertension, preeclampsia/eclampsia), diabetes of pregnancy (both pre-gestational and gestational), and adverse pregnancy outcomes (placental abruption, fetal demise, intrauterine growth restriction (IUGR)). The total contribution of mild-to-moderately elevated risk factors should be considered as describing a fuller picture of the pregnant patient, with the view towards establishing an intrapartum and long-term plan for interval monitoring. A cardio-obstetric or similar heart team approach is useful in assessing and monitoring at-risk pregnant patients, and recommended for those with overt CVD, like preexisting IHD [3•, 21, 22].

Pregnancy is a physiologic stress test, with increased demand to the cardiovascular system from doubling of blood volume and cardiac output and weight carrying [23]. Distinguishing between normal pregnancy and occult heart disease can therefore be challenging, and screening with electrocardiogram (EKG) and echocardiography may yield normal studies. However, in a study of maternal mortality in California, cardiovascular disease, primarily cardiomyopathy, was detected in 25% of women who died and retrospective screening of abnormal signs and symptoms revealed that 88% of cases could have been identified using an algorithmic approach [24, 25]. The Centers for Disease Control and Prevention estimates 60% of maternal deaths as preventable [1••]. While the optimal threshold for screening of women without a prior diagnosis of IHD requires further investigation, physicians may consider EKG, echocardiography, and referral to cardiology for pregnant women with abnormal vital signs, like hypoxia, hypertension, tachycardia >100 bpm, or unexpected changes in their exercise tolerance [24]. For women with a diagnosis of IHD, risk stratification scores for adverse outcomes from cardiac disease in pregnancy, like CARPREG, ZAHARA, or WHO, ascribe higher risk to worse New York Heart Association Class and left ventricular ejection fraction, but in the newer CARPREG II, women with a prior diagnosis of IHD also receive points for a diagnosis of CAD [26••]. Women with CAD alone had higher odds of adverse cardiac events in pregnancy, OR 3.0 (95% CI 1.1–7.6); hence, scoring tools may be useful for pre-pregnancy risk stratification as well as patient counseling [26••]. Obesity also portends a poor prognosis [4].

Women in Their Reproductive Years and in Pregnancy Can Experience Acute Myocardial Infarction

The rate of acute myocardial infarction (MI) in women of reproductive age was <100/100,000 patient-years for ages 30–39, rising to >100/100,000 over the age of 45 years, in a

study of the National Inpatient Sample (NIS), with black women having a higher rate of MI than white women [27]. Young women as a group had higher in-hospital mortality than men and longer length of stay [27]. There is up to a 4-fold higher risk of MI during pregnancy and while MI is a rare event, it is associated with a high in-hospital mortality rate [28•]. Risk of MI in pregnancy was estimated at 3–10/100,000 deliveries or 1/12,400 hospitalizations in the NIS and the in-hospital maternal fatality rate was astoundingly high at 4.5–5.1% and up to 7.3% in a California-based cohort [28•, 29, 30].

Hypercoagulability is a frequent etiology of MI in women of reproductive age, from antiphospholipid syndrome and protein S and factor XII deficiencies. In a small series, mechanisms of MI in pregnancy were most often spontaneous coronary artery dissection (SCAD), followed by atherosclerosis and, less often, stress (takotsubo) cardiomyopathy or non-iatrogenic coronary spasm [31]. Less common are embolization or ischemia from coronary artery anomalies. Mortality from ST elevation MI (STEMI) was not significantly different than non-STEMI (NSTEMI) and NSTEMI accounted for most cases. In the NIS, slightly less than half of MI in pregnancy occurred antepartum or during labor and delivery (L&D) [28•]. Older maternal age, tobacco use, hypertension, diabetes mellitus, and thrombophilia were independent risk factors. Approximately half of MI cases were managed invasively, and of those, >3/4 underwent percutaneous coronary intervention while <1/4 underwent coronary artery bypass grafting. Invasive management was associated with lower in-hospital mortality than medical management with an adjusted odds ratio (OR) of 0.17 (95% CI, 0.07–0.42) [28•].

The 2018 European Society of Cardiology guidelines for the management of cardiovascular disease in pregnancy give coronary angiography and PCI a Class I recommendation, Level of evidence (LOE) C for STEMI and invasive management for NSTEMI with high risk features a Class IIa, LOE C recommendation [21]. When do the benefits of an invasive strategy in pregnant women outweigh potential risks? Besides STEMI, cardiologists might consider an invasive strategy for hemodynamic instability, when a left anterior descending or left main culprit is likely, and when no alternative diagnosis is suspected. Invasive diagnosis can change management and while radiation exposure in pregnancy should be minimized, maternal health must be prioritized. A case report of PCI in pregnancy reported an estimated fetal absorbed dose = 0.79 milliGray (mGy), modeled retrospectively. By comparison, a chest X-ray has an estimated fetal absorbed dose of 0.1–0.9 mGy [32]. For perspective, doses of 50 mGy increase fetal loss within the first 2 weeks of pregnancy and the risk of congenital abnormality increases at doses >150 mGy, well above what might be expected from a single cardiac catheterization [33]. Technical choices such as radial artery access, using 4-Fr catheters and 5-Fr guides; ensuring coaxial

injection and lowering the injection rate; collimation; placing lead under the patient; and saving fluoroscopy images rather than using higher radiation dose cine acquisition are strategies interventional cardiologists can use to help mitigate risk to pregnant women undergoing catheterization. Pregnant women should be positioned with a slight leftwards tilt to relieve pressure on the inferior vena cava to increase filling to the right heart and avoid syncope. This position is especially important in emergent cases when cardiopulmonary resuscitation (CPR) must be performed. If CPR duration is longer than 5 min, emergent bedside evacuation of the uterus by an obstetrician is recommended for maternal survival [34].

Noninvasive testing may not provide additional risk stratification, may be non-diagnostic, or may delay care for MI in pregnancy. Echocardiography is useful in assessing wall motion abnormalities which may aide in decision-making but can be limited by poor windows. Computed tomography angiography requires a heart rate <100 bpm, weight <350–400 lbs (usual table limit), 100–150 mL of contrast, and radiation dose of 1–2 mSV, and if positive, cardiac catheterization may still be recommended. Conversely, there may be equipoise for an invasive strategy when EKG changes are equivocal or normal or co-morbidities make the procedure riskier, like renal dysfunction or contrast dye allergy. Additionally, the frequency of complications during invasive catheterization has been reported as higher in pregnant women than might be expected for non-pregnant patients, including emergent coronary artery bypass grafting (CABG) for iatrogenic dissection [31]. Thus, a thorough informed consent discussion and shared decision-making with patients are important, as is an interdisciplinary team approach involving obstetricians, interventional cardiologists, and other physicians.

Pregnancy increases vessel fragility, and this may contribute to SCAD, in which a false lumen results from disruption of the coronary tunica media [35]. Two pathophysiologies have been proposed: the "inside-out" and "outside-in" models. The former is thought to begin with an intimal tear from shear stress, with blood penetrating the internal elastic lamina to accumulate in the tunica media, the latter resulting from bleeding of the vasa vasorum and medial hemorrhage [36]. The Saw classification groups SCAD into four types based on angiographic appearance: Type 1 (29–48%), characterized by a linear flap with contrast dye staining; Type 2 (52–67%), a long smooth stenosis; Type 3 (0–3.9%), a short, focal stenosis, like atherosclerosis; and Type 4, an acute total occlusion [37]. SCAD can be a manifestation of fibromuscular dysplasia, a diffuse disorder of small and medium arteries characterized by disorganized architecture of the arterial wall [38]. Individuals presenting with SCAD should undergo evaluation of the cerebral, renal, and thoracic vasculature to rule out this disorder [38].

Treatment options for SCAD are medical therapy, balloon angioplasty, percutaneous coronary intervention (PCI), and/or

CABG. Selection depends on hemodynamic stability, ischemia, and SCAD classification. For non-flow limiting dissection, medical management, especially beta-blockers, is generally preferred as the vessel wall commonly heals [39]. Dissection can propagate and extended inpatient monitoring has been suggested for this reason [39]. With increasing obstruction to flow and active ischemia, balloon angioplasty and/or PCI may be preferred or necessary when the patient is unstable [39]. Low-pressure cutting balloon angioplasty may be useful to fenestrate the dissection flap and has been described in case series and reports [40]. If PCI is desired, the interventionalist might consider stenting the distal and proximal ends of the dissection and then the mid-section, if a dual stent strategy is required to cover the entire length of the lesion, so as not to propagate the dissection down the vessel [41]. Intravascular imaging during cardiac catheterization with optical coherence tomography (OCT) or intravascular ultrasound (IVUS) may be useful in distinguishing SCAD from atherosclerosis, particularly the Type III variety. The risk of passing catheters through an abnormal vessel and a larger-volume injection in the case of OCT should be weighed against information gained. Dissected vessels may be challenging to size by visual estimation alone which might contribute to the high in-stent restenosis and thrombosis rates reported in PCI for SCAD [39]. Intravascular image-guided PCI for atherosclerosis generally leads to increased minimal luminal stent area from better stent sizing, more frequent post-dilation and less in-stent restenosis [42]. It is not clear if this is also true in PCI for SCAD but is a hypothesis for study. CABG for left main or multivessel disease is rare during pregnancy but has been documented [28•]. It is generally avoided as placental perfusion may be poor during bypass, leading to fetal bradycardia, hypoxia, or acidemia [43]. Nonetheless, maternal survival must be prioritized.

Aspirin Is Beneficial in the Treatment of Ischemic Heart Disease and Prevention of Preeclampsia in Pregnancy

Aspirin is safe and effective in women for the prevention and treatment of MI and ischemic stroke, but aspirin also has a unique and emerging role in pregnancy [44, 45]. Use of 81–162 mg of daily oral aspirin after the 9th week of pregnancy is salutorious for the placenta by improving invasion of the uterine spiral arteries and reduces placental vascular resistance [46]. Women with CVD are more likely to have fetal growth abnormalities due to placental insufficiency or fetal demise [47]. As a result of improved placental health, at-risk women on aspirin initiated between 6 and 13 weeks of pregnancy have less early-onset preeclampsia, preterm labor, and mortality around the time of delivery [48, 49••]. Aspirin may also prevent recurrent miscarriage in women with antiphospholipid antibodies [50]. It is recommended for women with a combination of risk factors, including obesity and hypertension, for example, but also socioeconomic disadvantage and African American race-ethnicity [51•]. Cardiologists should be aware of the dual importance of aspirin in pregnancy for women with IHD.

Labor and Delivery Considerations for Women with Ischemic Heart Disease

Delivery planning should be multidisciplinary for women with CVD (Fig. 1b). At our institution, cardio-obstetrics team meetings most often include representatives from Maternal Fetal Medicine (MFM), Cardiology (including Adult Congenital Heart Disease), Internal Medicine/Critical Care, L&D plus Cardiac Intensive Care Unit (CICU) Nursing, and Obstetric Anesthesia. A heart team approach is recommended by consensus [21]. A standardized approach is helpful in organizing data and communicating the plan, and can be incorporated into the electronic medical record to inform stakeholders [22]. The team reviews cardiac studies and discusses concerns and contingencies during labor and delivery to decide the timing and mode of delivery, location (L&D vs. CICU), and monitoring. The pregnant patient with IHD should be stabilized and medically optimized prior to delivery. MFM physicians recommend planned delivery between 37 and 39 weeks when the fetus is full term to avoid preeclampsia and better control circumstances of L&D [52].

Avoiding preeclampsia from prolonged pregnancy, avoiding high afterload, reducing cardiac workload, and controlling tachycardia, as well as lowering volume and oxygen demand, are paramount in women with IHD, particularly in the second and third trimesters when cardiac output peaks [53]. A vaginal delivery is usually ideal and safe in the stable patient with IHD, but avoiding Valsalva and pain control should be considered to decrease left ventricular wall stress and demand ischemia. The patient may require operative assisted vaginal delivery, assistance in the second stage of labor with vacuum or forceps, or in certain cases, expedited delivery with Cesarean (C) section. Besides maternal indications, there can be obstetric indications for C-section which are not foreseeable. Therefore, in the delivery planning process, the cardio-obstetric team must review risks associated with the maternal cardiac stress of a surgical procedure.

Continuous maternal and fetal monitoring, maternal oxygen saturation, and telemetry are required during L&D for women with IHD. Of note, this requires cardiac nursing to be available on the L&D floor, as obstetric nurses are not often trained to interpret EKGs and may have less familiarity with advanced cardiac life support. Maternal implantable cardioverter defibrillators (ICDs) should be turned off and automatic external defibrillator pads placed on the chest with

continuous monitoring from the device in case of arrhythmia. Medications, like beta-blockers, calcium channel antagonists, and intravenous nitroglycerin, should be readily available to treat cardiac ischemia during labor and are commonly located on L&D floors. Importantly, some common obstetric vaso-constrictors should be avoided, like methergine, neostigmine, epinephrine, and other vasopressors.

Neuraxial anesthesia is preferred for pain relief of vaginal and C-section deliveries. Hypotension due to anesthesia can be avoided with careful obstetric technique, lower-dose anes-thesia, slower induction, and intravenous fluid administration. However, spinal hematomas are a risk for those patients on anti-platelet or anti-coagulants. It is generally preferred that thienopyridines and anti-coagulants be ceased ahead of labor to prevent this complication [54]. General anesthesia is more commonly used for patients who are fully anti-coagulated and require emergent delivery where there is no time for reversal.

The placenta is delivered during the third stage of labor immediately after the neonate is born. Release of blood back into the circulation from the involuting uterus and release of pressure on the inferior vena cava is equivalent to a large-volume bolus which may provoke acute congestive heart fail-ure in some women. Diuretics, venodilation with nitrates, an-tihypertensives, and continuing anesthesia are strategies to decrease acute volume return.

Medications for the Treatment of Ischemic Heart Disease Can Be Used in Pregnancy and Women Who Breastfeed

There may be hesitancy or unfamiliarity regarding medica-tions to treat IHD during pregnancy. Some of the medications cardiologists are accustomed to using in non-pregnant patients can be initiated or continued in pregnancy and breastfeeding [55]. In addition to aspirin, which has dual roles, clopidogrel is used in pregnancy for patients needing dual anti-platelet ther-apy. Ticagrelor and prasugrel have less data and are not usu-ally preferred for this reason. There is concern for statin use in pregnancy, as HMG-coA reductase inhibitors could affect em-bryogenesis with case reports on limb defects and severe cen-tral nervous system anomalies [56]. Metoprolol is well known for its benefits in IHD, and twice-daily dosing of metoprolol succinate might be preferable given a higher metabolic rate in pregnancy, although unproven. However, beta-blockers can be associated with IUGR; thus, fetal growth must be moni-tored. As IUGR is more frequent in women with CVD due to worse placental health, it may be difficult to distinguish be-tween placental versus medication effects on the fetus. Labetalol and methyldopa are frequently used antihyperten-sives, but so are hydralazine and isosorbide, often favored for heart failure with reduced ejection fraction, particularly due to benefit in African Americans. Angiotensin-converting enzyme inhibitors are not used during pregnancy to avoid damage to fetal kidneys, but enalapril is often used in breastfeeding when the neonate is not premature [57]. The website https://www.reprotox.org/ is a resource for cardiologists and obstetricians needing updated information on use of medications in pregnancy and lactation.

The "Fourth Trimester": an Opportunity to Prevent or Capture Acute Decompensation and Engage in Lifelong Cardiac Care

The postpartum period is characterized by rapid reversal of pregnancy physiology, both immediately and over the subse-quent 3 months. Postpartum preeclampsia, a sudden rise in blood pressure associated with pulmonary edema, stroke, or seizure, in addition to postpartum cardiomyopathy, may ap-pear during this period. Routine follow-up for healthy women is commonly at 6 weeks postpartum, but for women with IHD or at higher risk, it may be useful to schedule follow-up in the first week, either in-person or by telehealth visit with home blood pressure or even oxygen saturation monitoring. Symptoms of shortness of breath, chest discomfort, or new-onset hypertension >140/90 mmHg should trigger referral to the emergency department, for example [24]. In one study, women at risk for severe postpartum hypertension were followed via telehealth for remote blood pressure monitoring, of which, 16% developed severe hypertension post discharge from L&D and 53% at 6 weeks postpartum [58]. The advan-tages of telehealth for women with CVD is an area for future investigation.

Postpartum, cardiologists should ensure that women of re-productive age with IHD are referred for contraceptive counseling. For women with IHD, non-hormonal or progesterone-alone contraception avoids exposure to the prothrombotic effects of estrogen. There is a wide array of methods from which women may select, grouped into revers-ible and non-reversible methods. Long-acting reversible con-traception (LARC) includes the non-hormonal copper intra-uterine device (IUD), progesterone-containing IUD (Liletta, AbbVie, Inc., Chicago, IL), medroxyprogesterone acetate subcutaneous injection (Depo-Provera, Pfizer, Inc. New York, NY), or implant (Nexplanon, Merck & Co., Inc., Kenilworth, NJ). Tubal ligation, IUD placement, or subcuta-neous implant can be performed immediately postpartum. Barrier methods (diaphragm, female/male condoms) or progesterone-alone oral contraception ("minipill") are other options. Progesterone-containing products are compatible with breastfeeding and not considered to decrease milk supply [59]. Suppressing menses with progesterone-containing IUDs may be particularly useful for women in which menorrhagia and/or pregnancy can be life-threatening, such as those requir-ing dual anti-platelet therapy or anticoagulation due to

mechanical valves or left ventricular assist devices. A plan for long-term retention in cardiac care should be established.

Conclusions

Cardiologists must be informed about the management of IHD in pregnancy in an era of rising US maternal mortality and morbidity. Cardiologists bring a wealth of expertise to partner effectively with obstetricians and others, for the benefit of women during and after pregnancy. Reducing the burden of cardiovascular disease risk factors in young women, especially women of color, using best practices to treat acute myocardial infarction in pregnancy, and retaining high-risk women in lifelong cardiac care, are areas for continued research and education to curb this alarming trend.

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Declarations

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