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EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (K. NASIR, SECTION EDITOR)

Cardio-Obstetrics: the Next Frontier in Cardiovascular Disease Prevention

Aarti Thakkar[1] · Tigist Hailu[1] · Roger S. Blumenthal[1] · Seth S. Martin[1] · Colleen M. Harrington[2] · Doreen DeFaria Yeh[3] · Katharine A. French[4] · Garima Sharma[1]

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Abstract

Purpose of Review Internationally, cardiovascular disease (CVD) is the leading cause of death in women. With risk factors for CVD continuing to rise, early identification and management of chronic diseases such as hypertension, diabetes, and obstructive sleep apnea is necessary for prevention. Pregnancy is a natural stress test for women with risk factors who may be predisposed to CVD and offers a unique opportunity to not only recognize disease but also implement effective and long-lasting strategies for prevention.

Recent Findings Prevention begins before pregnancy, as preconception screening, counseling, and optimization of chronic diseases can improve maternal and fetal outcomes. Throughout pregnancy, women should maintain close follow-up, continued reevaluation of risk factors, with counseling when necessary. Continued healthcare engagement during the "fourth trimester," 3 months following delivery, allows clinicians to continue monitoring the evolution of chronic diseases, encourage ongoing lifestyle counseling, and connect women with primary care and appropriate specialists if needed. Unfortunately, this postpartum period represents a major care gap, as a significant proportion of most women do not attend their scheduled visits. Social determinants of health including decreased access to care and economic instability lead to increased risk factors throughout pregnancy but particularly play a role in poor compliance with postpartum follow-up. The use of telemedicine clinics and remote monitoring may prove to be effective interventions, bridging the gap between physicians and patients and improving follow-up for at-risk women.

Summary While many clinicians are beginning to understand the impact of CVD on women, screening and prevention strategies are not often implemented until much later in life. Pregnancy creates an opportunity to begin engaging women in cardiovascular protective strategies before the development of the disease.

Keywords Cardio-Obstetrics · Prevention · Cardiovascular disease · Telemedicine · Postpartum care

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✉ Garima Sharma
gsharma8@jhmi.edu

[1] Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Blalock 559, 600 N. Wolfe Street, Baltimore, MD 21287, USA

[2] Division of Cardiovascular Medicine, University of Massachusetts Memorial Healthcare, Worcester, MA, USA

[3] Division of Cardiology, Adult Congenital Heart Disease Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[4] Lifespan Cardiovascular Institute, Division of Cardiology, Warren Alpert School of Medicine, Brown University, Providence, RI, USA

Introduction

CVD is the leading cause of pregnancy-related maternal mortality in the USA [1, 2]. Through extraordinary efforts worldwide, global maternal mortality has been decreasing steadily over the past few decades [3–6]; however, the proportion of direct and indirect maternal mortality due to CVD is on the rise [7, 8]. The rise of CVD has been particularly notable in developed countries such as the USA, which has seen an increase in maternal mortality in recent years [5, 6]. Most concerning about the rising trend is that an estimated two-thirds of CVD-related pregnancy deaths are thought to be preventable, indicating a significant lapse in surveillance and implementation of prevention strategies [9].

Pregnant women are at particular risk for CVD complications as every organ system undergoes physiologic and anatomic stress not only while fostering the growing fetus but also during the process of labor and childbirth [10]. During pregnancy and labor, cardiac output can increase by approximately 30 to 50% as a result of increased stroke volume and heart rate [10–12]. Many women are able to undergo this stress without significant residual effects; however, this natural "stress test" can enhance CVD in women who have underlying risk factors leading to serious complications [10].

The risk of CVD has only intensified in recent years as more women are becoming pregnant later in life and traditional risk factors such as chronic hypertension, diabetes, obesity, and smoking are on the rise [13, 14]. As demonstrated in Fig. 1 below, such risk factors can increase a women's risk for adverse pregnancy outcomes (APOs), including preterm birth, gestational diabetes mellitus, preeclampsia, gestational hypertension, small-for-gestational-age infant, and placental abruption, which are associated with increased CVD risk later in life [15, 16]. Specifically, APOs increase a women's risk of indirect maternal adverse events such as arrhythmias, heart failure, peripartum cardiomyopathy, valvular disorders, cerebrovascular accidents (CVA), and coronary artery disease (CAD) [7, 16, 17••].

The rising trends in CVD risk factors and specific preventative care strategies before, during, and after pregnancy will be the focus of our discussion below. As CVD remains the leading cause of death for women across age groups, pregnancy offers a window of opportunity for risk evaluation, stratification, and implementation of primary and secondary prevention strategies as women are more engaged with the healthcare system.

Trends of Cardiovascular Risk Factors

Chronic hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, and sleep apnea are all risk factors for APOs and cardiovascular diseases in reproductive age women [10, 15, 16]. Understanding the definitions, prevalence, and associated risks of each can help women and clinicians make informed decisions about their care.

Hypertension Chronic hypertension, or preexisting hypertension, is defined by systolic blood pressure (SBP) ≥140 and/or diastolic blood pressure (DBP) ≥ 90 mmHg before 20 weeks of gestation or having an elevated blood pressure that persists after 12 weeks or more postpartum [18]. A study by Bateman et al of over 50 million women reported that the prevalence of chronic hypertension in the USA grew from 0.9 in 1995–1996 to 1.5% in 2007–2008 [19]. Another cross-sectional analysis demonstrated almost a 13-fold increase in

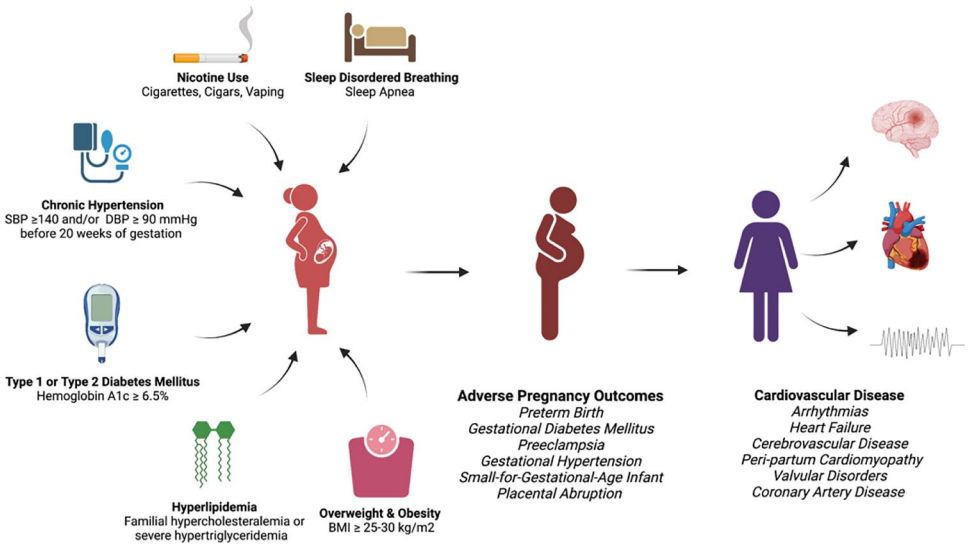

Fig. 1 Traditional risk factors in pregnancy. Legend: *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *BMI*, body mass index. Figure created via BioRender.com

the prevalence of chronic hypertension since 1970, closely correlated with increasing maternal age [13]. While older maternal age is a risk factor for chronic hypertension, the rate of the disease has been increasing across all age groups [20]. Women with congenital heart defects (CHD) such as aortic coarctation are also at increased risk of preexisting hypertension and thus pregnancy-related hypertensive complications [21].

Further analysis by Cameron et al. has demonstrated that women from rural communities in the USA have a higher prevalence of preexisting hypertension than women from urban communities [22]. The rural-urban gap is compounded by other social determinants of health including racial inequity, poor health literacy, food insecurity, and economic instability, all of which are correlated with increased APOs [23]. Women with chronic hypertension are at increased risk for poor maternal and fetal outcomes [18, 19, 24]. Bateman et al. demonstrated that women with chronic hypertension are at increased risk for several adverse outcomes including preeclampsia (odds ratio [OR] 10.07; 95% confidence interval [CI] 9.68–10.48), pulmonary edema (OR 9.26; 95% CI 6.67–12.85), stillbirth (OR 2.31; 95% CI 2.11–2.53), and poor fetal growth (OR 3.00; 95% CI 2.83–3.19) [19]. This study went on to show that having concomitant comorbidities such as gestational diabetes or chronic renal disease further increased the risk of APOs [19]. A meta-analysis of 55 studies found that women with chronic hypertension have a relative risk of 7.7 (95% CI 5.7–10.1) for preeclampsia and a relative risk for preterm delivery and neonatal admission of 2.7 (95% CI 1.9 to 3.6) and 3.2 (95% CI 2.2 to 4.4), respectively [24].

Diabetes Mellitus Approximately, 90% of diabetes cases during pregnancy are the result of gestational diabetes; however, pregestational diabetes due to type 1 and type 2 diabetes are increasing [25]. Compared to gestational diabetes, type 1 and type 2 diabetes in pregnancy have greater maternal and fetal risk, particularly when uncontrolled [26, 27]. Poor glucose control particularly during early pregnancy can lead to congenital malformations, spontaneous abortion, and stillbirths [28]. Neonates are at increased risk of a number of complications including hypoglycemia, macrosomia, respiratory distress, and hyperbilirubinemia amongst others [29]. Children born to women with diabetes are at risk of becoming obese or developing diabetes later in life [30]. Pregnancy can also lead to APOs such as preeclampsia, which can further exacerbate known diabetes complications such as retinopathy and nephropathy [25, 31, 32]. Women with pregestational diabetes are at increased risk for acute myocardial infarction and symptomatic coronary artery disease during pregnancy, particularly those with comorbidities such as nephropathy and hypertension [33, 34].

Dyslipidemia Between 1999 and 2008, approximately 18–22% of reproductive-age women in the USA were reported to have abnormally elevated triglycerides levels [35]. During pregnancy, all plasma lipids including triglycerides, total cholesterol, and low-density lipoprotein-c (LDL-C) rise [36]. The greatest increase is typically seen in triglycerides, which can increase as much as double or triple prepregnancy levels [36]. Overall, these physiologic changes are thought to be nonatherogenic as they quickly normalize after delivery [36, 37]. However, the rise in triglycerides also has a corresponding decrease in LDL-C size creating particles that may be especially atherogenic although this is debated [38, 39]. Fetal effects of hyperlipidemia include premature birth, low birth weight, and later in life, increased risk of atherogenesis [40].

Obesity The proportion of women who are overweight (body mass index [BMI] $\geq$ 25 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2) has increased globally from 29.8 (CI 29.3–30.2%) in 1980 to 38.0% (CI 37.5–38.5%) in 2013 [41]. The Center for Disease Control (CDC) reports that in the USA, the number of women who were obese prior to pregnancy rose from 26.1 in 2016 to 29% in 2019; a trend that was consistent across all age groups [42]. In the USA, African American and Native American women have higher rates of obesity at 34.7% and 36.4%, respectively, compared to White women at 23.7% [43]. Obesity and excessive weight gain during pregnancy have not only been associated with increased risk of APOs (preeclampsia, gestational diabetes) [44] but also maternal mortality [45] during pregnancy. Increased neonatal and infant mortality, as well as CHDs in the fetus [46, 47], have also been associated with a higher maternal BMI [48]. The effects of maternal obesity during pregnancy extend beyond the peripartum period and have been associated with long-term complications such as major cardiovascular events (MACE), including death, myocardial infarction, stroke, and peripheral artery disease, compared to mothers with normal BMI [49].

Smoking In the USA, the prevalence of cigarette smoking during pregnancy has decreased from 9.2 in 2010 to 6.9% in 2017; though, smoking prevalence remains high among young women between ages 20 and 24 [50]. Unfortunately, e-cigarette use among pregnant women has recently increased drastically, particularly among young women [51]. In this analysis by Obisesan et al., 50% of women reported concurrent cigarette use [51]. Smoking cigarettes and the use of other nicotine-containing products during pregnancy is associated with an increased risk of stillbirth [52], preterm birth, and low-birth-weight deliveries [53]. Children whose mothers smoked are also at increased risk of asthma [54] and childhood obesity as they get older [55, 56].

Sleep Apnea Sleep-disordered breathing (SDB) and more concerning, obstructive sleep apnea (OSA), is a common complication of pregnancy characterized by intermittent upper airway obstruction and resultant desaturation, frequent awakenings from sleep with increased systemic arterial pressures [57]. A systematic review of 33 studies estimates the global prevalence to be approximately 15% (95% CI 12–18%) [58]. OSA has been shown to increase in prevalence across gestation, with the highest prevalence in the third trimester [59]. Pregnant women with a history of type 2 diabetes, hypertension, obesity, CHDs, and increasing maternal age are at risk of developing OSA [59, 60]. The development of OSA further increases the risk of cesarian delivery, gestational hypertension, preeclampsia, and preterm delivery [61–63]. Maternal OSA also has a two-fold increased risk of low birth weight and small for gestational age infants [64]. OSA during pregnancy also has prolonged morbidity and leads to an increased risk of pulmonary embolism (OR 5.4; 95% 2.3–8.9), cardiomyopathy (OR 9.0; 95% CI 7.5–10.9), and congestive heart failure (OR 8.9; 95% CI 7.5–10.7) [65].

Preventive Care and Counseling Before and During Pregnancy

Pre-conception CVD Risk Evaluation Many nonpregnant women do not know the health risks associated with pregnancy [66]. While women and providers recognize the importance of establishing regular prenatal care; preconception care is not routinely sought out or offered. Preconception counseling should be offered to all reproductive-age women whether the patient is actively planning a pregnancy or not [67]. However, women with CVD risk factors should receive prepregnancy counseling by specialized multidisciplinary cardio-obstetrics teams [68, 69]. Referrals to specialized cardio-obstetrics teams for individual risk analysis and shared decision-making should be placed at least 6 months prior to planned conception [68]. Preconception counseling offers the opportunity for screening, primary CVD prevention, and optimization of chronic health conditions prior to conception, which can prove vital in improving maternal, fetal, and later childhood outcomes [70•]. Nutritional surveys and medication reconciliation with regard to pregnancy can improve control of CVD and reduce the risk of teratogenicity effects prior to conception. As risk factors change over time, each should be reevaluated as needed prior to conception and throughout pregnancy. Recommendations for the management of CVD risk factors throughout all stages of pregnancy are summarized in Table 1 below.

Hypertension Guidelines tend to have more liberal thresholds than the general population due to concerns for decreased fetoplacental perfusion with more aggressive blood pressure control as well as data demonstrating the increased risk of hospitalization without increased risk of other adverse effects for mothers with more tightly controlled blood pressures [18, 72]. Women with chronic hypertension taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs) should be switched to another medication at least 1 month prior to attempting to conceive [71]. If found to be pregnant while taking ACE inhibitors or ARBs, these medications should be discontinued within 2 days due to the risk of congenital abnormalities.

The American College of Cardiology (ACC) and American Heart Association (AHA) hypertension guidelines explicitly lay out treatment thresholds for hypertension in the general population with goal SBP < 120 and DBP < 80 mm Hg [73]. However, current guidelines for the management of hypertension in pregnancy do not currently take into account the AHA/ACC guidelines and are conflicting across societies due to limited and disputing data regarding the efficacy of strict blood pressure control [18, 74–77].

The European Society of Cardiology (ESC) recommends treatment for chronic hypertension when SBP ≥ 150 mm Hg or DBP ≥ 95 mm Hg [76]. However, these targets are lower for individuals with gestational hypertension or evidence of preeclampsia with target blood pressure thresholds of SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg [76]. These recommendations stem from the results of the Control of Hypertension in Pregnancy Study (CHIPS), which demonstrated that tighter control of blood pressure was more protective of severe maternal hypertension [78]. A further post hoc analysis of this study demonstrated that for those with less tight control, the development of severe hypertension was a particular risk factor for adverse maternal outcomes [79] The current treatment thresholds are outlined in Table 2 below.

A meta-analysis examining the use of anti-hypertensives for women with mild to moderate hypertension (SBP 140–169 and DBP 90–109) by Abalos et al. further demonstrated that pharmaceutical management with beta-blockers and calcium-channel blockers reduced the risk of maternal development of severe hypertension [81]. However, the data regarding poor neonatal and fetal outcomes and the development of maternal complications was inconclusive [81]. The Chronic Hypertension and Pregnancy (CHAP) trial is a recently published, multi-center, randomized, open-label trial which demonstrated that a treatment threshold of 140/90 for pregnant women with chronic hypertension led to a reduction of preeclampsia, preterm birth, neonatal fetal harm and death [82]. While previous ACOG guidelines recommended a treatment threshold of SBP ≥ 160 mm Hg or DBP ≥ 105-110 mm Hg, in April 2022, ACOG revised their guidelines to reflect the results of the CHAP trial and

Table 1 Summary of recommendations for the management of CVD risk factors throughout pregnancy

	Prenatal	Antenatal	Postnatal
Chronic hypertension	SBP 120–160 mm Hg and DBP 80–110 mm Hg*		SBP < 150 mm Hg and DBP < 100 mm Hg
	First-line oral: labetalol, nifedipine, methyldopa *Second-line oral:* hydralazine and HCTZ *Contraindicated:* ACE-I, ARB (should be discontinued prior to or as soon as aware of pregnancy)		Follow up within 72 hrs if developed severe HTN during pregnancy Follow up within 7–10 days if developed other HDP during pregnancy
Diabetes mellitus	Goal A1c <6.5%	Fasting BG <95 mg/DL and 1hr BG postprandial <140 mg/dL or 2 hr BG postprandial <120 mg/dL Aspirin 81 mg initiated at 12 weeks of gestation until delivery	Women with a history of GDM should be screened for type 1 or 2 DM using the 75-g OGTT at 4–12 weeks postpartum
	First-line: insulin, metformin *Contraindicated:* all oral hypoglycemics other than metformin should be discontinued prior to or as soon as aware of the pregnancy		
Dyslipidemia	Total cholesterol < 200 mg/dL HDL > 60 mg/dL LDL < 100 mg/dL Triglycerides <150 mg/dL	Women with a history of GDM should be screened for type 1 or 2 DM using the 75-g OGTT at 4–12 weeks postpartum	Women with FH or GDM should receive regular lipid screening
	First-line: omega-3 fatty acids and bile sequestrants *Contraindicated:* Statins, niacin, fibrates, and ezetimibe should all be discontinued at least 4 weeks prior to discontinuation of contraception		Antihyperlipidemic medications should be held until the cessation of breastfeeding
Obesity	BMI screening Weight loss counseling	IOM guidelines for weight gain based on initial BMI	
Smoking	Cessation and abstinence from all nicotine products		
Sleep apnea	Regular screening should be continued throughout pregnancy CPAP for the treatment of OSA		

Legend: *ACE-I*, angiotensin-converting enzyme inhibitors; *ARB*, angiotensin-II receptor blockers; *BG*, blood glucose; *BMI*, body mass index; *CPAP*, continuous positive airway pressure; *DM*, diabetes mellitus; *FH*, familial hypercholesterolemia; *GDM*, gestational diabetes mellitus; *HCTZ*, hydrochlorothiazide; *HDL*, high-density lipoprotein; *HDP*, hypertensive disorders of pregnancy; *IOM*, Institute of Medicine; *LDL*, low-density lipoprotein; *mg/dL*, milligram per deciliter

*Blood pressure thresholds based on ACOG guidelines for chronic hypertension without evidence of end organ. Guidelines may vary on treatment thresholds

Table 2 Treatment thresholds for hypertensive disorders of pregnancy

Treatment thresholds by guideline				
	ISSHP [75] 2018	ACOG [82, 83] 2022	ESC [76] 2018	NICE [74] 2019
Gestational hypertension	SBP ≥ 140 mm Hg or DBP ≥ 90 mmHg	None	SBP ≥ 140 mm Hg or DBP ≥ 90 mmHg	SBP ≥ 150 mm Hg or DBP ≥ 100 mmHg
Chronic HTN without organ damage	SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg	SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg	SBP ≥ 150 mm Hg or DBP ≥ 95 mmHg	
Preeclampsia Chronic hypertension with preeclampsia	SBP ≥ 160 mm Hg or DBP ≥ 90 mm Hg	SBP ≥ 140 mm Hg or DBP ≥ 90 mmHg	SBP ≥ 140 mm Hg or DBP ≥ 90 mmHg	
Treatment goal	**SBP 110–140 and DBP 80–85 mmHg**	**None specified**	**None specified**	**SBP < 150 and DBP < 80–100**

Legend: *ISSHP*, International Society for the Study of Hypertension in Pregnancy; *ACOG*, American College of Obstetricians and Gynecologists; *ESC*, European Society of Cardiology; *NICE*, National Institute for Health and Care Excellence; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure

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currently recommends a treatment threshold of 140/90 mm Hg for women with chronic hypertension. [83].

Common first-line outpatient anti-hypertensives with demonstrated safety in pregnant women are beta-blockers, specifically labetalols (initial dose 100–200 mg twice daily, increasing as needed to 800 mg every 8 to 12 h for a maximum 2400 mg per day), dihydropyridine calcium-channel blockers such as extended-release nifedipine (30–60 mg daily, maximum 120 mg per day) and methyldopa (250 mg twice or three times daily, to maximum dose 3000 mg per day) [18, 84]. Hydralazine or diuretics such as hydrochlorothiazide can be considered a second-line agent [18, 85]. In the acute inpatient setting, severe hypertension should be managed with intravenous (IV) or intramuscular (IM) therapy. ACOG recommends using IV labetalol (initial dose of 10–20 mg, followed by 20 to 80 mg every 10 to 30 min, for a maximum cumulative dose of 300 mg), IV or IM hydralazine (initial dose of 5 mg, then 5–10 mg every 20–40 min, for a maximum cumulative dose of 20 mg), or immediate-release oral nifedipine (initial dose of 10–20 mg, repeat as needed in 20 min then in 2–6 h for a maximum cumulative dose of 180 mg) [77].

Diabetes Mellitus The American Diabetic Association (ADA) recommends that women should be counseled on strict maintenance of glycemic control for a target hemoglobin A1c <6.5% prior to conception [86]. NICE guidelines recommend that any woman with A1c above 10% should be advised to avoid pregnancy due to fetal and neonatal risks [87]. Early in pregnancy, women have increased insulin sensitivity and lower insulin requirements; however, this reverses and peaks during the second and early third trimester, after which it stabilizes [88]. During pregnancy, ACOG [25] and ADA [85] recommend the following glucose targets (as much as safely possible) for type 1 and 2 diabetes as well as gestational diabetes:

- Fasting <95 mg/dL (5.3 mmol/L) and either
- One-hour postprandial <140 mg/dL (7.8 mmol/L) or
- Two-hour postprandial <120 mg/dL (6.7 mmol/L)

Tight control with A1c <6.5% has been shown to have the lowest rate of congenital defects and other adverse fetal outcomes during pregnancy [26, 27, 85]. If strict maintenance <6.5% is unsafe due to the risk of hypoglycemia, the A1c goal can be liberalized to <7% [26, 84]. Due to frequent red-cell turnover during pregnancy, A1c is more variable, requiring more frequent monitoring [25]. The management of diabetes involves both pharmacologic and nonpharmacologic therapy, including a carbohydrate-controlled diet and regular exercise [89]. With regard to pharmacologic therapy, insulin is the preferred therapy for the management of type 1 and type 2 diabetes [84]. Insulin requirements should be monitored closely due to rapid shifts in insulin resistance during pregnancy. There are limited data on the effectiveness and risk of adverse effects for most oral hypoglycemic agents; however, recent data suggest metformin may be used safely in pregnancy [25, 90]. Given that diabetes in pregnancy leads to an increased risk of preeclampsia, low-dose aspirin at 81 mg/day should be initiated at 12 weeks of gestation, ideally prior to 16 weeks and continued until delivery [25, 85].

Dyslipidemia Dyslipidemia is particularly associated with APOs such as gestational diabetes and preeclampsia when triglyceride levels exceed 250 mg/dL [40]. Women with

familial hypercholesterolemia (FH) and severe hypertriglyceridemia are at particularly high risk during pregnancy as there are few options for the management of dyslipidemia in pregnancy [37, 91]. Statin therapy (HMG-CoA reductase inhibitors), niacin, fibrates, and ezetimibe are all contraindicated due to evidence of teratogenicity [90]. When women are ready to conceive, guidelines recommend women discontinue statin therapy at least 4 weeks prior to discontinuing contraceptives and should continue holding it until after she has stopped breastfeeding [90, 91]. Of note, statin use, while still strongly discouraged in pregnancy, is being reevaluated as there is emerging data that hydrophilic statins (pravastatin, rosuvastatin) may not be associated with fetal malformations as seen in lipophilic statins (simvastatin, atorvastatin) [92]. For women at very high risk for CVD, The United States Food and Drug Administration (FDA) no longer lists statins as strictly contraindicated in pregnancy; however, as the data evolve, the decision to start or remain on statin therapy should be made after patient-centered risk versus benefit discussion [93].

Reproductive age women taking contraindicated medications should receive preconception counseling regarding the side effects of these medications and should be recommended to use contraceptives. If a woman discovers she is pregnant while on these medications, the medications should be stopped immediately [91]. Proprotein convertase subtilisin/kexin type 9 serine protease (PCSK-9) inhibitors have not been studied in pregnancy. However, an observational pregnancy exposure registry for evolocumab is currently underway [94]. Omega-3 fatty acids [37] and bile acid sequestrants [90] are the only two medications, which have been reported as safe during pregnancy. Thus, behavioral counseling regarding diet and exercise is crucial for additional risk mitigation. For women with FH and significant atherosclerotic disease, LDL apheresis can be considered during pregnancy [95].

Obesity To prevent obesity-related complications, ACOG and the National Institute for Health and Clinical Excellence (NICE) guidelines recommend regular weight counseling including both diet and exercise for all women, particularly prior to pregnancy as any amount of weight loss can improve maternal and fetal outcomes [96, 97]. ACOG specifically recommends 150 min of moderate-intensity aerobic activity weekly for pregnant women; however, women should talk to their doctors if they have a specific cardiac condition that may require a tailored exercise plan [98]. ACOG further recommends an initial assessment of BMI during pregnancy and the use of the Institute of Medicine (IOM) guidelines on weight gain to prevent increasing complications [99]. The United States Preventative Services Task Force (USPSTF) released a systematic review concluding that behavioral counseling interventions by primary physicians for obesity and reducing excessive weight gain had a moderate benefit, reducing the incidence of gestational diabetes, emergency cesarian section delivery, and infant macrosomia (level B recommendation) [43]. One limitation in such reviews is the heterogeneity of behavioral interventions in terms of length and intensity of engagement [43].

Smoking ACOG and the USPSTF recommend regular screening for tobacco use beginning with the initial visit, ideally preconceptual regular smoking cessation counseling and behavioral interventions for all women throughout pregnancy [56, 100]. The greatest advantage of smoking cessation occurs before 15 weeks of gestation; however, cessation at any point in pregnancy has benefits [101]. Women should be warned that all nicotine products including vaping, e-cigarettes, lozenges, gum, and hookahs, can all have harmful effects on the mother and fetus [56]. There are limited data regarding the risk versus benefit of nicotine replacement therapy for pregnant women [102]. However, as nicotine has known harmful effects, nicotine replacement therapy (NRT) should only be considered after a thorough discussion between patient and clinician [56]. Currently, other pharmacologic options such as varenicline and bupropion, appear to be safe in pregnancy; however current data are limited [103, 104].

Sleep Apnea OSA and SDB are currently underdiagnosed and undertreated in pregnant women [65]. Current validated screening models for OSA including the Berlin Questionnaire and Epworth Sleepiness Scale have been shown to be poor predictors in pregnant women [103]. Facco et al. created a four-variable model, which includes frequent snoring, age, chronic hypertension, and BMI; which had higher sensitivity (88%) and specificity (86%) in identifying SDB in pregnant women [105]. Continuous positive airway pressure (CPAP) is the mainstay of treatment for mild to severe OSA as it reverses airway obstruction thus improving oxygenation and blood pressure [106].

Generational Effects of CVD The risk of poor maternal CVD health on maternal and fetal mortality has been well-established. More recently, researchers have also sought to understand the long-term effects of uncontrolled CVD as the offspring of these mothers get older [107]. A study by Perak et al. characterized baseline maternal CVD health at 28 weeks of gestation by combining individual characteristics of BMI, blood pressure, total cholesterol, abnormal glucose, and smoking [108]. The results of this cohort study found that better maternal health was significantly associated with better cardiovascular health for their offspring during adolescence [109].

Preventive Care and Counseling Postpartum

Women with preexisting conditions including chronic hypertension, diabetes, sleep apnea, dyslipidemia, diabetes, and obesity are at increased risk of APOs and subsequently increased risk of developing cardiovascular disease in their lifetime. Thus, regular follow-up, screening, and care coordination during the postpartum "fourth trimester" is crucial for any woman with CVD risk factors or APOs. The 3 months after delivery offer an opportunity for continuity of care and reinforcement of appropriate primary and secondary prevention strategies.

Postpartum Clinics and Telemedicine All women are encouraged to reach out to their obstetrician-gynecologists within the first 3 weeks postpartum to establish an initial assessment of individual needs [110]. However, as opposed to a single encounter, ACOG's Presidential Task Force on Redefining Postpartum Care encourages regular longitudinal follow-up as needed, particularly for chronic diseases, lactation difficulty, or mental health concerns [111]. These visits allow the opportunity to counsel women with pregnancies complicated by APOs about their increased risk of recurrence in future pregnancies as well as overall increased risk of cardiovascular diseases. ACOG recommends a comprehensive visit within 3 months postpartum. [108].

Comprehensive postpartum care encompasses many domains including a woman's physical, social, and psychological health, infant care, as well as chronic disease management and health maintenance [108]. With many pregnancies complicated by the rising prevalence of chronic cardiovascular risk factors and increasing maternal age, the AHA and ACOG have supported the use of multidisciplinary care by cardiologists and obstetricians [10]. A review by Jowell et al. found that referrals to transitional clinics within 0 to 6 months postdelivery improved patient education, lifestyle modifications, and appropriate specialty care referrals when necessary [109]. Referrals to specialized adult congenital disease clinics for women with CHD have also demonstrated a mortality benefit [110].

Unfortunately, an estimated 40% of women do not currently attend their postpartum visits [108]. A systemic review by Jones et al. observed that non-Hispanic White, Asian, and non-Black race/ethnicities were associated with increased follow-up rates [112]. Medicaid coverage, Medicaid eligibility, and less than a high-school education were all negative predictors of follow-up [111]. Targeted interventions improve follow-up, and care coordination may be instrumental in the prevention of further cardiovascular disease. For example, the use of telemedicine during the postpartum period is beneficial, particularly for women with limited access to transportation.

Telemedicine has shown benefits in helping women maintain breastfeeding exclusivity, manage postpartum depression, and continued blood pressure monitoring [113, 114, 115•, 116]. A feasibility study conducted by Hoppe et al. found that remote blood pressure monitoring allowed for early identification and treatment of severe hypertension and reduced readmission rates [116, 117]. As telemedicine is becoming more accessible after the COVID-19 pandemic, its use in the management of hypertensive disorders of pregnancy (HDP) in the fourth trimester is promising and may improve access to women who are unable to receive care due to time and resource constraints [118]. Telemedicine can also help bridge the gap in social determinants of health by improving health literacy and reducing the cost burden of frequent follow-up [23].

Establishing postnatal follow-up paves the way for further interventions to improve cardiovascular risk including pharmacotherapy, intensive lifestyle management, and patient and clinician education, particularly with regard to future pregnancy planning and risk of CVD [17, 109]. Further studies and interventions specifically addressing disparities in access to care across socioeconomic and racial groups are needed to change the face of postpartum care. At the health systems level, increased advocacy is needed to expand Medicare coverage and access to comprehensive care for women who lose access at 60 days postpartum [70]. The AHA in particular has been working to increase its advocacy efforts with regard to Medicaid expansion, strengthening telehealth infrastructure, and increased care coordination to mitigate the impact of the social determinants of health [70].

Preeclampsia and Chronic Hypertension For women who required antihypertensives for any HDP, the AHA recommends early blood pressure surveillance during the first 1–2 weeks postpartum for goal blood pressure SBP < 150 mm Hg and DBP < 100 mm Hg [68]. ACOG similarly recommends that all women who developed HDP should have follow-up within this same time period of 7–10 days; with earlier follow-up within 72 h after delivery for women who developed severe hypertension [119]. Approximately half of the postpartum strokes occur in the first 10 days after discharge [107]. The recommended treatment of severe-range blood pressures includes IV labetalol or hydralazine or rapid onset nifedipine, with corresponding oral agents for maintenance of blood pressure [120]. Both nifedipine and labetalol are considered compatible with breastfeeding [121, 122]. Other medication classes including non-dihydropyridine calcium channel blockers such as verapamil and certain ACE-inhibitors, such as captopril and enalapril have also been used in postpartum hypertensive management [68, 117]. The use of furosemide, a diuretic, has shown effectiveness in early blood pressure control when used in conjunction with other antihypertensive agents [123].

To combat both acute and long-term effects of HDP, Harrington et al. highlighted the importance of disease education, anticipatory guidance, and blood pressure monitoring prior to discharge from the hospital [116]. Women with HDP, particularly preeclampsia, have an increased risk of hypertension, CAD, stroke, VT, and CVD-related mortality both in the short (less than 10 years) and long term (greater than 10 years) [124, 125]. However, many women are unaware of this relationship, and thus may be less inclined to seek care after delivery. Counseling women on self-assessments with home blood pressure cuffs can also help women become more engaged in their health and follow-up [117].

Given the increased risk of future CVD, the AHA recommends contraception counseling to all women with HDP, as well as other APOs, to help women optimize risk factors prior to future pregnancies [68]. The type of contraception should be decided based on individual risk factors and comorbidities so as to not increase a woman's risk of venous thromboembolism [68]. For women with HDP, in the long term, screening for chronic hypertension and BMI should occur twice during the first postpartum year and then spaced to annual check-ins [126, 127]. Hemoglobin A1c levels, fasting glucose, and lipid profiles should be assessed at 3 to 6 months after delivery then annually [128]. Despite its recognition as a risk-enhancing factor, there are no validated tools predicting the risk of CVD in women who develop HDP [129]. The development of such tools may be useful to help guide clinicians on the next steps in the management and follow-up recommendations.

Diabetes Insulin sensitivity increases shortly after delivery, thus women should be warned to pay close attention to glucose readings and respective insulin requirements to reduce the risk of hypoglycemia [84]. Any woman with a recent history of gestational diabetes mellitus (GDM) should be screened 4–12 weeks postpartum using the 75-g oral glucose tolerance test as this can uncover an underlying previous unknown history of type 1 or type 2 diabetes [25, 85]. If found to have prediabetes, patients should receive intensive lifestyle counseling as there is a high risk of conversion to type 2 diabetes. Screening for prediabetes and type 2 diabetes should be continued in these women every 3 years [130]. All women with a history of diabetes should be counseled on contraceptive use to better plan for glycemic control prior to pregnancy.

Dyslipidemia Screening for postpartum dyslipidemia is not recommended in current guidelines. However, women with a previous history of elevated cholesterol, familial hypercholesterolemia, or those who develop GDM during pregnancy are at increased risk of chronic dyslipidemia and should receive regular screening postpartum [128, 129]. Age greater than 35 years, elevated SBP before labor, A1c > 5.1%, and LDL-C > 3.56 mmol/L (137.6 mg/dL) in the second trimester have also been associated with an increased prevalence of postpartum dyslipidemia [130].

Smoking As many as half of the women who quit smoking during pregnancy relapse within the 6 months after delivery placing themselves and their child again at risk [131]. One systematic review found that being younger, multiparous, less well educated, experiencing higher stress and anxiety, not breastfeeding, and living with a partner who smoked was the most common predictor of relapse [132]. Thus, continued counseling and identification of triggers and risk factors for relapse is of particular importance during the third trimester and should be carried out during the postpartum visits.

Sleep Apnea While the majority of women will see their OSA resolve within the first 2 to 3 months postpartum, preliminary results by Street et al. suggest that approximately 20% of women will have persistent symptoms at 6 to 8 months [133]. These results reinforce the need for women diagnosed with OSA during pregnancy to be reevaluated postpartum. The management of OSA in the postpartum period should be continued use of CPAP to reduce long-term cardiovascular risk.

Conclusion

Cardiovascular risk factors including chronic hypertension, diabetes, sleep apnea, dyslipidemia, diabetes, and obesity have been increasing steadily over the past few decades, particularly in women of reproductive age. Each of these risk factors increases a woman's risk for the development of APOs and higher maternal morbidity and mortality and poor fetal outcomes. Unfortunately, the compounding adverse events further increase a woman's lifetime risk of cardiovascular disease beginning immediately after delivery. Women from rural areas, with limited access to care, poor insurance coverage, and lower socioeconomic status are at particularly high risk of developing cardiovascular risk factors and eventual diseases.

Primary prevention and risk mitigation of cardiovascular risk factors should begin prior to conception and be maintained throughout pregnancy. Continued follow-up in the fourth trimester, 3 months after delivery, can help with early identification of CVD; however, many women do not attend their postpartum visits. Health system interventions including improved care coordination, patient education, and increased digital health infrastructure can improve access to care and risk mitigation during this crucial time period. Appropriate disease screening and management can greatly improve outcomes for mother and baby throughout

pregnancy and lead to overall decreased mortality from cardiovascular disease.

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Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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