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Pregnancy as a Window to Future Health

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Cardiovascular disease (CVD) is the leading cause of mortality among women in the United States and developed countries.[1] Women on average experience CVD mortality about 10 years later than men.[1] However, women experience a higher fatality rate following a first myocardial infarction, and despite an overall decline in the CVD death rate in the United States, the rate of decline has been slower for women compared with men. In addition, the death rate is 70% higher in African-American women compared with White women.[2] Two-thirds of coronary heart disease sudden deaths occur in women with no previous symptoms, compared with one-half of sudden deaths in men. It is now evident that this excess mortality is due in part to an increased death rate among premenopausal women, although little is known regarding coronary artery disease among this group.[3] From 1995 to 2014, myocardial infarction (MI) hospitalizations increased in young women but not in men; relative to men, young women with MI had a higher comorbidity index and a lesser likelihood of being managed with guideline-based medications.[4] Also, young women hospitalized for MI have relatively more comorbidities and inpatient mortality[5] and poorer health status 1 year later.[6] High rates of overweight/obesity (~55%) and elevated blood pressure (BP) in young women likely contribute to this disparity.[7,8] There is also evidence that hypertriglyceridemia, low high-density lipoprotein cholesterol, hyperinsulinemia, inflammation, central adiposity, and hypertension are more strongly related to heart disease risk among women compared with men.[8,9] Women's risk for CVD increases after menopause, although indistinguishable from aging; however, risk factors that are elevated premenopause increase proportionally postmenopause.[10] Thus detection of elevated risk during reproductive years may provide a critical opportunity to delay or prevent onset of CVD in women.

Healthy pregnancy requires profound maternal vascular, immune, and metabolic adaptations to support placentation and fetal growth (discussed in detail in Chapters 8 and 10). It is now well established that an impaired ability to mount these adaptations contributes to adverse pregnancy outcomes (APOs) such as preeclampsia, preterm birth, fetal growth restriction, stillbirth, and gestational diabetes mellitus (GDM). Indeed, pregnancy now can be viewed as a "stress test" of these systems, with APOs being a harbinger of excess cardiometabolic risk and CVD morbidity and mortality (Fig. 72.1A). Leveraging this possibility may help mitigate this high-risk trajectory and delay or prevent CVD in women (see Fig. 72.1B), and new guidelines identify women with APOs as a high-risk group for CVD.[11]

Accumulation of Cardiovascular Disease Risk Across the Life Course

CVD in women is a life course disease, with risk accumulating in young adulthood that is independently related to CVD later in life.[12] By 45 years of age, only 7.1% of women have no cardiovascular risk factors and 40% have one major risk factor such as hypertension, high cholesterol, or smoking.[13] Even a relatively low risk factor burden is associated with significant excess CVD risk across a woman's lifetime. It is unknown how women accumulate CVD risk in their reproductive years and how pregnancy factors, such as gestational weight gain, may be related to APOs and to later-life CVD. It is hypothesized that APOs may be the first manifestation of an occult predisposition to CVD.

Hypertension

Hypertension is common in women, accounts for a significant proportion of CVD, and often goes undetected. Early detection of hypertension is critical, as treatment is widely available, inexpensive, and cardioprotective. Yet, up to 38% of stage 2 hypertension goes undetected before 40 years of age.[14] Hypertension contributes to more CVD events in women relative to men (32% versus 19% of CVD events are attributable to hypertension, $P = .02$; Fig. 72.2).[15] Short of hypertension, the accumulation of modest BP elevations over young adulthood is linked to atherosclerosis, coronary calcification, and higher left ventricular mass.[16–18] The prevalence of hypertension during the reproductive years has doubled due to the newest guidelines that define stage 1 hypertension as blood pressure above 130/80 mm Hg, and young adults (younger than age 40) with stage 1 or stage 2 hypertension have excess risk for CVD events later in life.[19–21] Notably, recent analyses reveal that BP trajectories in women evaluated over the life course in a sex-stratified fashion increase more rapidly than in men, beginning as early as in the third decade of life.[22] These findings have implications for later-life cardiac and vascular diseases that often present differently in women compared with men. Women also have evidence of impaired coronary flow reserve, a marker of target-organ damage that may precede coronary artery disease.[23] As noted by the Institute of Medicine (now named the National Academy of Medicine), optimizing BP in younger populations has tremendous opportunity to prevent premature morbidity and mortality.[24] Pregnancy care is (mostly) universally accessible, and the access to care available during pregnancy may not be paralleled again until 65 years of age. Over 80% of women in the United States bear a child.[25] Pregnancy is a unique opportunity to assess CVD risk in women.

Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy (preeclampsia, gestational hypertension) are common pregnancy complications, affecting 5% to 7% of births and up to 15% of women, with major

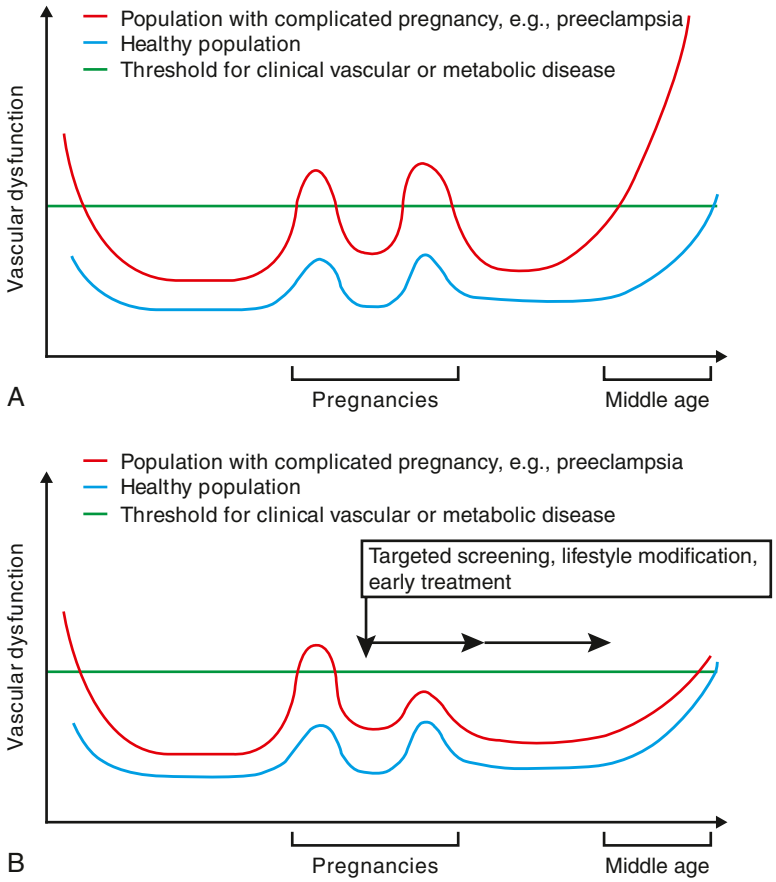

Figure 72.1 Pregnancy is a "stress test" that can reveal subclinical trajectories and identify new opportunities for chronic disease prevention. (A) Women at high risk for future cardiovascular disease are identifiable during pregnancy, at which point subclinical vascular risk may become clinically evident. (B) The risk revealed by pregnancy can be used to target high-risk women for screening and early intervention by lifestyle modification and treatment, altering their chronic disease trajectory as they enter midlife. (*Data from Rich-Edwards JW, McElrath TF, Karumanchi SA, Seely EW. Breathing life into the lifecourse approach: pregnancy history and cardiovascular disease in women.* Hypertension. *2010;56:331–334; Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening?* BMJ. *2002;325:157–160.*)

long-term implications.[26] Epidemiologic evidence linking data for individual women across decades has firmly established a link between the development of hypertension during pregnancy and an elevated risk for hypertension, CVD, and renal disease later in life.[27] Risk ratios for these outcomes are about twofold higher in women with preeclampsia and as high as eightfold for early-onset preeclampsia requiring delivery before 34 weeks' gestation.[27] Also, chronic hypertension 2 to 7 years after hypertensive disorders of pregnancy (HDP) in a first pregnancy is detected in 36.5% of affected women compared to 17.0% in women with uncomplicated pregnancies.[28] Rates of hypertension are as high as 50% following early-onset preeclampsia, 39% after gestational hypertension, and 25% following late-onset preeclampsia.[29] By comparison, stage 2 hypertension rates in women with normotensive term births are very low (<4%) 2 to 5 years after delivery.[30] Many factors are dysregulated in women with prior preeclampsia, including lipids, inflammatory markers, endothelial function, and thrombotic markers.[31–34] In addition, left ventricular diastolic dysfunction, asymptomatic heart failure, and left ventricular remodeling have been detected up to a decade postpregnancy in women with preeclampsia.[35,36] Indeed, women with preeclampsia have a higher risk for CVD (coronary artery disease [CAD], cerebrovascular disease, peripheral vascular disease, heart failure, or revascularization procedures) within 5 years after delivery, suggesting that short- and long-term cardiovascular sequelae are high.[37] The American Heart Association (AHA) identifies a history of hypertension in pregnancy to be an established risk factor for CVD.[11,38] An important observation is that the relative risk for CVD associated with preeclampsia compared with normotensive pregnancies appears to diminish in the years after menopause. It is unknown whether this is caused by increasing absolute risks in all women (those with and without a history of preeclampsia) and thus smaller risk differences may still reveal a large burden of disease in older women. More research is needed to study the very-long-term links between pregnancy history and CVD and to determine whether HDP may help predict CVD risk beyond traditional risk factors.

Gestational Diabetes Mellitus

Nearly one-half of women with GDM, which affects roughly 5% of pregnancies, will develop type 2 diabetes mellitus (T2DM) in the 10 years after pregnancy.[39,40] A meta-analysis of 675,455 women reported that women with a history of GDM have seven times the risk for later diabetes compared with women without GDM.[40] Type 2 diabetes is a potent CVD risk factor, especially among women.[41] Based on these associations, it would be

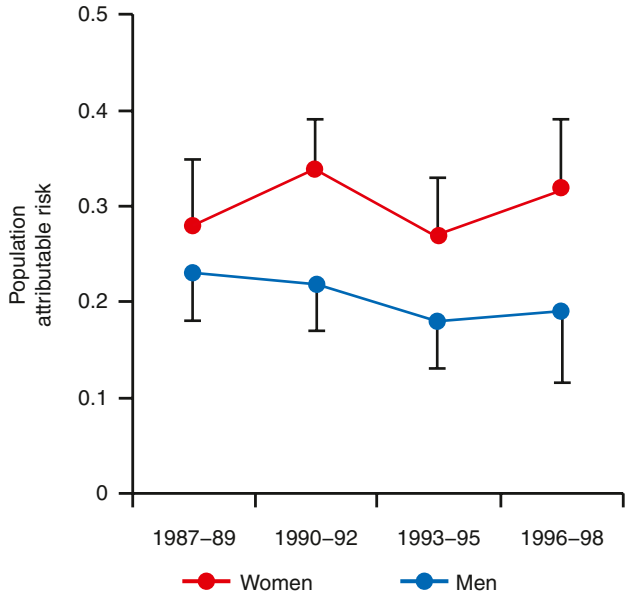

Figure 72.2 Cardiovascular disease risk attributable to hypertension in men and in women. Estimates of the 10-year cardiovascular disease risk attributable to hypertension across four examination years in women *(red)* and men *(blue)*. (*Data from Cheng S, Claggett B, Correia AW* et al. *Temporal trends in the population attributable risk for cardiovascular disease: the atherosclerosis risk in communities study.* Circulation. *2014;130:820–828.*)

expected that GDM history would be associated with increased risk for CVD events. Indeed, several studies confirm a 50% to 85% higher CVD risk in women with GDM,[42–44] and the AHA considers a history of GDM to be a CVD risk factor.[11] Although much of this association was thought to be explained by the development of T2DM in women with a history of GDM, recent work indicates that CVD risk and presence of coronary artery calcification are higher in women with GDM even among those who do not progress to T2DM.[44–46] Despite these data, excess CVD risk attributable to GDM could potentially be avoided by preventing the development of T2DM or hypertension in this group.

Preterm Birth

Although early delivery (<37 weeks' gestation) is the leading cause of neonatal and childhood mortality and morbidity, it was thought until recently to be unrelated to later-life maternal health. There is now consistent epidemiologic evidence across multiple cohorts that women with preterm births have about a twofold excess risk for CVD compared with women with term births.[47] In studies that have distinguished spontaneous and medically indicated preterm births, preterm births linked to hypertension are associated with very high CVD risk (eightfold higher compared with normotensive term births).[48] Evidence is accumulating that spontaneous preterm births, early preterm births, and recurrent preterm births are also associated with excess CVD risk.[49,50] Of note, the duration of pregnancy, even at term, predicts long-term coronary heart disease and stroke mortality.[51] Little is known about mechanisms linking preterm birth to later CVD, and although metabolic and placental dysregulation and elevated blood pressure may be implicated, traditional CVD risk factors do not explain the detected associations raising the possibility of novel factors.[52–57]

Fetal Growth Abnormalities

Fetal undergrowth and overgrowth have long-term consequences for the newborn and can be markers of excess maternal CVD risk. The association between macrosomia (birthweight >4000 g) and later maternal CVD risk appears to be due largely to GDM and related T2DM morbidity.[58] In contrast, impaired fetal growth, typically characterized as <10th percentile for gestational age in population studies (and covered in depth in Chapter 44), is associated with excess maternal CVD risk. In high-income countries such as the United States, fetal growth impairment in singleton gestations is due largely to placental factors, including preeclampsia, that compromise the maternal-fetal interface and maternal vascular disease. Fetal growth restriction has been related to about a twofold excess CVD risk in mothers.[59,60] It is very difficult to disentangle the effects of impaired fetal growth from underlying maternal hypertensive disorders and preterm delivery. For example, even modest elevations in blood pressure that remain within the normotensive range are linked to impaired fetal growth.[61] Thus occult maternal vascular impairments may link growth restriction to later maternal CVD, although more work is needed to isolate the particular mechanisms. A prospective US cohort of 4500 women followed 2 to 7 years after a first birth detected no blood pressure elevations among women who had delivered infants with birth weights <5th percentile accounting for gestational age, suggesting that normotensive growth restriction may be a fetal risk factor but perhaps not a maternal risk factor. Alternatively, normotensive growth restriction may be associated with accelerated atherosclerosis but not hypertension, and longer maternal follow-up can help disentangle these overlapping yet often distinct pathophysiologies.[28]

Parity, First Birth, and Last Birth

Many studies investigated the association between parity—the number of deliveries a woman has—and maternal CVD risk.[62–64] The largest report a *J*-shaped association, with lowest risk generally at two children, the mode for most Western populations.[65] Compared with bearing two children, nulliparity is associated with a small increase in CVD risk, on the order of 10%, and having more than four children is associated with a roughly 60% increased CVD risk. As discussed elsewhere,[66] such a pattern is unlikely to indicate that pregnancy per se increases CVD risk. The number of children a woman bears is socially patterned, dependent on her partnership status, her socioeconomic position, and her access to contraception and abortion services. These factors are themselves likely to be associated with CVD risk; thus bearing fewer or more children than average may reflect a burden of other CVD risk factors. The fact that men who have fathered four or more children also have increased CVD risk[67,68] suggests that the association between high parity and later CVD may result from shared socioeconomic or behavioral risk factors associated with rearing large families.

The modest increased CVD risk with nulliparity or primiparity—the "hook" in the *J*-shaped association—may reflect subclinical vascular and metabolic antecedents that are related to low fertility and complicated pregnancy. Women who bear fewer than two children—the societal norm—may more often have primary or secondary infertility. Furthermore, the excess CVD risk associated with pregnancy complications such as preeclampsia or preterm birth is strongest, although not limited to, last births.[51,69,70] Women with severe pregnancy

complications may be advised against further pregnancies. Parents whose offspring suffer health problems as a result of prematurity or growth restriction may also choose to limit family size. Thus the "hook" of the *J*-shaped association between parity and CVD may be driven by prepregnancy CVD risk factors that affect fertility and pregnancy outcomes.

How to Leverage Pregnancy to Improve the Health of Women and Infants

Despite advancements in management, CVD remains a significant cause of morbidity and mortality. This is particularly true in women, who often present with atypical symptoms and are frequently misdiagnosed and undertreated. Women are more likely to have nonobstructive CAD, yet their mortality remains significantly elevated.[71] This has been attributed in part to the increased recognition of coronary microvascular dysfunction and other coronary-related and non–coronary-related disorders that contribute to ischemia and related adverse cardiovascular outcomes in these patients.[72] Along these same lines, as diagnosis remains challenging in this population, so does risk stratification. Risk stratification has traditionally been insensitive in women, as existing risk scores tend to categorize most women as low risk. This has led to a move toward more sex-specific risk stratification with inclusion of alternative markers such as high-sensitivity C-reactive protein (hsCRP) in the Reynolds risk score[73] or inclusion of stroke in the American College of Cardiology (ACC)/AHA atherosclerotic cardiovascular disease (ASCVD) risk score.[74] However, another area that has remained underappreciated is the potential predictive value of a history of APOs. These conditions often occur in young otherwise healthy women who, under the "stress test" of pregnancy, demonstrate future tendencies toward metabolic and cardiovascular conditions such as hypertension and diabetes (see Fig. 72.1).

Adapting Recommendations for Detection of Risk

Although GDM and HDP are now included in CVD risk stratification guidelines for women,[2] other adverse pregnancy conditions are becoming more widely recognized.[11] In addition, CV risk calculators such as the Framingham risk score, Reynolds risk score, and 2013 ASCVD calculator do not incorporate these adverse pregnancy conditions, leading to potential underestimation of lifetime CV risk in women.[73–75] A major reason for the lack of sufficient evidence to incorporate these adverse pregnancy conditions into risk calculators is that the large population registries able to link pregnancy history to CV events lack data on traditional risk factors, such as cholesterol levels, required as input for the risk calculators. Furthermore, most large cohorts that follow women to collect data on these cardiovascular risk factors have failed to collect information regarding their history of pregnancy complications. In part, this is caused by questions about the accuracy of maternal recall of pregnancy complications. For example, an initial review evaluating maternal recall of hypertensive disorders in pregnancy demonstrated relatively poor accuracy.[76] However, women recall GDM, infant birth weight, and length of gestation much more accurately (92% sensitivity, and correlations ranging from 0.95 to 0.85).[77] Thus maternal recall of these common pregnancy complications may prove useful to screen for CVD risk. Indeed, a recent very large, multiethnic cohort of women who are more densely phenotyped, with longer-term follow-up and APO adjudication from the Women's Health Initiative, convincingly showed that HDP and low birth weight are independently associated with future CVD in women after adjustment for established risk factors and other APOs, suggesting that this risk enhancement should be incorporated into a new ASCVD risk score for women.[78] Accordingly, research is needed to determine whether incorporation of reliably reported pregnancy history data will improve CV risk scoring systems for women. Early evidence using older age cohorts have yielded null prediction benefit,[79] and critical next steps are outlined in Box 72.1. Further, should these ASCVD scores be useful for detection and treatment, it will behoove us to mandate coding of APOs in the electronic health record (EHR), which currently is not done. Specifically, medical and surgical history are mandatory elements in the EHR, while pregnancy history is not. Policy action is needed to (1) add pregnancy or APO history to required EHR fields in medical and surgical history, (2) identify and enter APOs into the EHR at the time of delivery, (3) increase access to APO EHR history by clinicians and continuity of care systems over women's life courses, and (4) calculate ASCVD risk scores adding APO history to improve CVD in women.[80] In the meantime, women with a history of adverse pregnancy conditions may benefit from additional or more frequent CV risk stratification, including annual screening of blood pressure, lipids, and fasting glucose. Women with preeclampsia or gestational hypertension should follow up with a physician for a blood pressure check within 1 week of delivery, and women with GDM should have repeat glucose testing at 6 weeks postpartum.[81] Health systems should consider including CV screening in the obstetrics and gynecology practice, perhaps using advanced practice providers, such as nurse practitioners or physician assistants, and/or referral to primary care providers for additional screening and treatment. Some clinical centers have launched follow-up care protocols dedicated to women with APOs, and a joint statement from ACOG and AHA highlights the critical need for care coordination and appropriate handoffs.[82] There has also been a call for dedicated training in cardio-obstetrics.[83] These may be the first steps toward a best-practice model to leverage pregnancy history to screen women for emerging CVD risk postpartum.

Noninvasive measures of subclinical atherosclerosis (such as carotid intimal-media thickness [CIMT] and coronary artery calcium [CAC] scoring), endothelial dysfunction (brachial artery testing, peripheral arterial tonometry), or inflammation

BOX 72.1 NEXT STEPS NEEDED TO TRANSLATE TO IMPROVED CVD HEALTH FOR WOMEN

- Use adverse pregnancy outcomes as a "clinometric" score, similar to the Apgar score, to identify near-term at-risk women.
- Add adverse pregnancy outcomes as risk factors in existing CVD risk scores for longer-term at-risk women.
- Add standard adverse pregnancy outcomes and CVD risk score reporting into the electronic health record in women.
- Deploy the EHR to improve risk detection and treatment for women.

CVD, Cardiovascular disease; *EHR,* electronic health record.

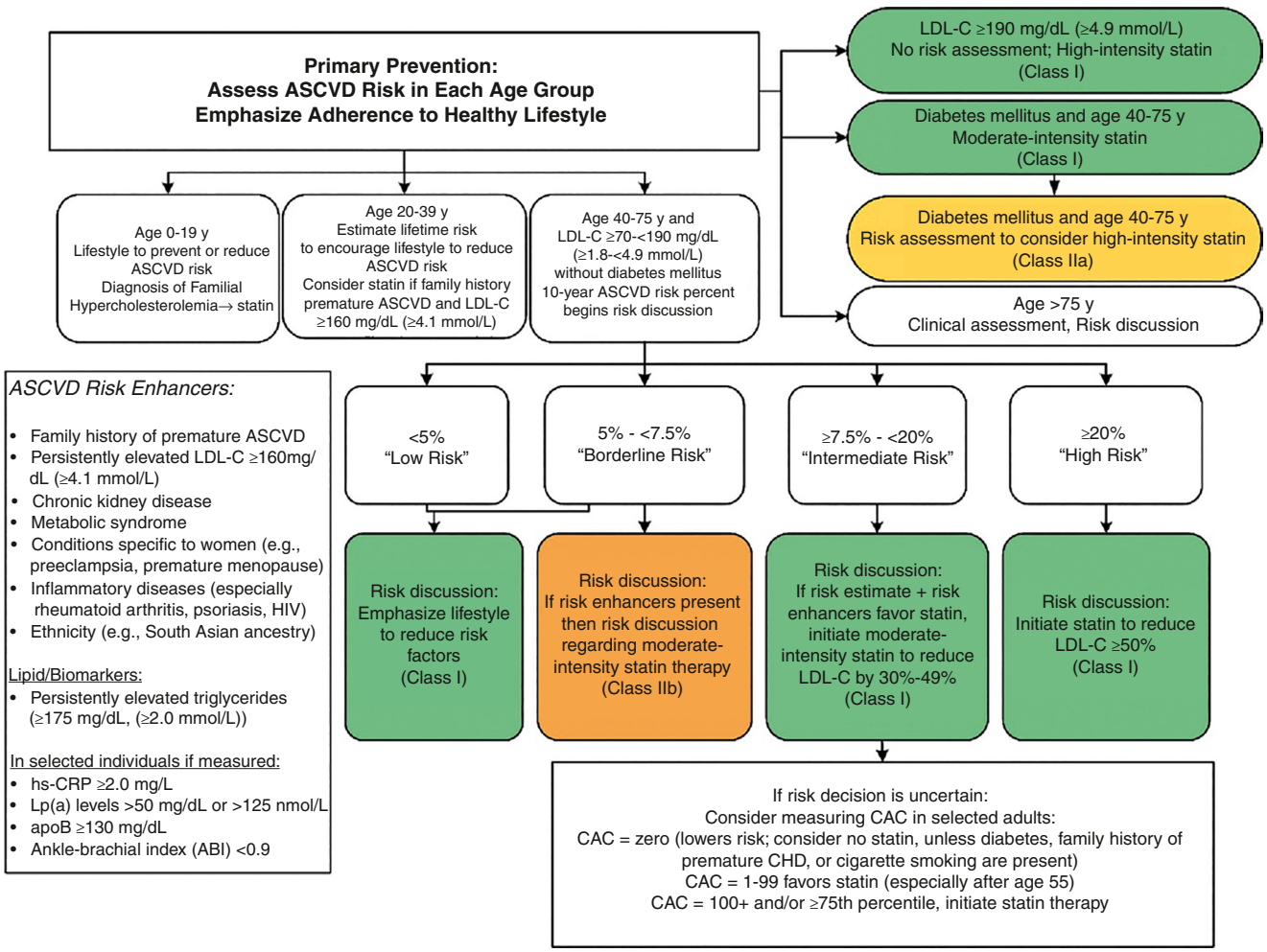

Figure 72.3 Guideline on cardiovascular disease prevention in women. (*Reprinted with permission from Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* Circulation. *2019;140:e596–e646. © 2019 American Heart Association, Inc.*)

(hsCRP) may play a role in risk stratification of women with the highest-risk adverse pregnancy conditions, such as those with early preeclampsia, but research trials are needed to demonstrate that these measures will improve CV outcomes.

Prevention in Premenopausal and Postmenopausal Women

US guidelines indicate that in the general population,[19] pharmacologic treatment should be initiated when blood pressure is 150/90 mm Hg or higher in adults 60 years of age and older, 140/90 mm Hg in adults, or 130/80 mm Hg in adults with an estimated ASCVD 10-year risk >10%. In patients with diabetes, chronic kidney disease, post–kidney transplant, heart failure, ischemic heart disease, post-stroke, or peripheral arterial disease, pharmacologic therapy should be started at 130/80 mm Hg. Initial antihypertensive treatment should include a thiazide diuretic, calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker in the general non-Black population or a thiazide diuretic or calcium channel blocker in the general Black population. If the target blood pressure is not reached within 1 month after initiating therapy, the dosage of the initial medication should be increased or a second medication should be added. The ACOG Task Force recommends that women with a history of preeclampsia and preterm birth or recurrent preeclampsia should have annual assessment of their lipid profile, blood pressure, body mass index, and fasting blood glucose.[84] These women should also receive preventive CV counseling including diet, exercise, and smoking cessation.

All women, regardless of ASCVD risk score, benefit from lifestyle and risk factor modification to reduce their overall risk, and this should be part of the therapeutic plan. Certainly, in those with a high-risk ASCVD risk score (≥10%), the first part of the treatment plan must be addressing lifestyle and ASCVD risk factors before initiation of any low-dose aspirin and statin therapy. In addition, guidelines recommend that a discussion of the potential for benefit versus the potential for adverse effects of statin therapy be undertaken. It should include an informed patient preference so that she can decide whether aspirin and a statin should be given.

Lifestyle and weight management guidelines that were presented and published simultaneously with cholesterol guidelines focus on how lifestyle changes can improve ASCVD risk factors and help in weight management.[85] The risk

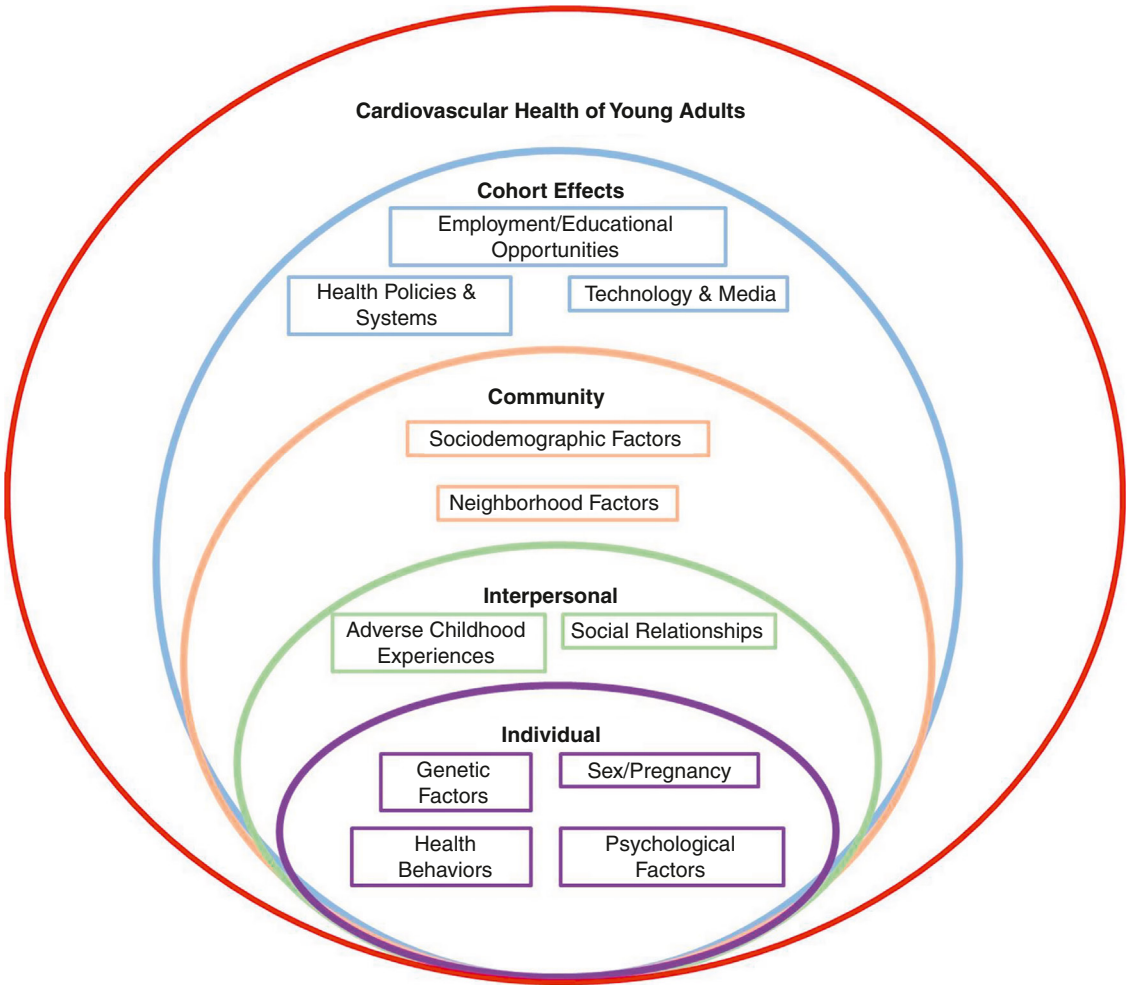

Figure 72.4 Multilevel influences on adult cardiovascular health. (*Used with the permission of John Wiley & Sons, Inc., Holly C. Gooding. Journal of the American Heart Association. Challenges and Opportunities for the Prevention and Treatment of Cardiovascular Disease Among Young Adults: Report From a National Heart, Lung, and Blood Institute Working Group, 2020, Volume: 9, Issue: 19, DOI: (10.1161/JAHA.120.016115).*)

assessment guideline offers a lifetime risk estimator that is crucial for women to understand their long-term risk and to motivate lifestyle changes to improve ASCVD risk, particularly when their short-term risk is low yet lifetime risk is high.[85] This was expressly to be used in those 20 to 59 years of age to enhance the discussion for improvement in risk factors through lifestyle optimization. Cholesterol guidelines have made lifestyle an integral part of the risk discussion.[85] Moreover, the follow-up of lipid values on fixed statin doses still requires periodic low-density lipoprotein cholesterol to determine both adequacy and adherence to therapy. Figure 72.3 depicts guidelines for CVD prevention in women.

Diagnosis and Treatment in Women With Prior Adverse Pregnancy Outcomes

Pregnancy is a time of significant hemodynamic and physiologic adaptations. Impairments in these processes may first become apparent as pregnancy complications that can serve as indicators of future risk. In addition, it is well established that the offspring of women with pregnancy complications such as GDM are at risk for development of diabetes or CVD later in life. Thus familial aggregation of adverse consequences stemming from pregnancy complications may lead to intergenerational risk for chronic conditions. In recent years, the ACC, AHA, and European Society of Cardiology (ESC) have incorporated assessment of APOs in recommendations regarding CV risk assessment.[85] Obstetric history should be included in every assessment of a female patient, and future studies should focus on integration of these risks into a scoring system to better risk-stratify these women. This is particularly important in young women who otherwise have few comorbidities but may be at increased yet unrecognized risk. The evidence presented here indicates that pregnancy can be a window into occult CVD risk and also identifies the need for more research. In addition, work in this area highlights the importance of clinical recognition of these conditions and potential for future risk modification.

Next Steps

To enhance the promotion of cardiovascular health among young adults 18 to 39 years old, the medical and broader public health community must understand the biological, interpersonal, and behavioral features of this life stage. Therefore the National Heart, Lung, and Blood Institute, with support from the Office of Behavioral and Social Science Research, convened a

2–day workshop in Bethesda, Maryland, in September 2017 to identify research challenges and opportunities related to the cardiovascular health of young adults. The multilevel factors required to translate the aforementioned evidence to improved health for women and their families are summarized in Fig. 72.4.[86]

Key Points

- Healthy pregnancy requires profound maternal vascular, immune, and metabolic adaptations to support placentation and fetal growth.
- It is well established that an impaired ability to mount these adaptations contributes to adverse pregnancy outcomes.
- Pregnancy can be viewed as a "stress test," with adverse pregnancy outcomes being a harbinger of excess CVD risk.
- Future investigation is examining the role of pregnancy in unmasking CVD risk and/or causing CVD risk.

A full reference list is available online at ExpertConsult.com.

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