



# Prevention Starts in the Womb: Opportunities for Addressing Cardiovascular Risk Factors During Pregnancy and Beyond

## REVIEW

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## ABSTRACT

Early identification and mitigation of sex-specific cardiovascular disease risk factors is a potential trajectory-changing strategy to improve lifelong cardiovascular health in women. These sex-specific risk factors include adverse pregnancy outcomes, polycystic ovarian syndrome, and premature menopause. We start by discussing the impact and management of risk factors for adverse pregnancy outcomes as an upstream intervention for cardiovascular disease risk reduction and then address the long-term effect and mitigation of sex-specific risk factors for cardiovascular disease.

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## INTRODUCTION

Pregnancy is often described as “nature’s stress test” because it challenges maternal lipid, carbohydrate, and vascular homeostasis and can unmask underlying cardiovascular dysfunction. Thus, it offers a unique window into a woman’s future cardiovascular health and is an opportunity for early assessment and management of cardiovascular disease (CVD) risk factors. Traditional cardiovascular risk factors such as hypertension, dyslipidemia, and obesity increase the risk for adverse pregnancy outcomes (APOs),<sup>1-4</sup> which include (1) preeclampsia (5% incidence in the United States<sup>5</sup>), (2) gestational hypertension/other hypertensive diseases of pregnancy (HDP) and gestational diabetes mellitus (GDM; 5.4% incidence<sup>6</sup>), (3) preterm birth (PTB; 10% incidence<sup>7</sup>), (4) small-for-gestational-age infant (SGA; 10% incidence<sup>8</sup>), (5) placental abruption (1% incidence<sup>9</sup>), (6) ischemic stroke (0.04% incidence<sup>10</sup>), and (7) maternal and neonatal mortality, among other complications of pregnancy. Conversely, APOs and other sex-specific diseases, such as polycystic ovarian syndrome (PCOS) and premature menopause,<sup>11</sup> are also associated with higher risks of CVD.<sup>12,13</sup> Therefore, upstream identification and mitigation of risk factors for APOs are also important. In this review, we discuss both the impact and management of risk factors for APOs and the long-term effects and mitigation of sex-specific risk factors for overall cardiovascular health.

## IMPACT AND MANAGEMENT OF TRADITIONAL CVD RISK FACTORS DURING PREGNANCY

Cardiovascular disease is the primary cause of pregnancy-related mortality in the United States.<sup>14</sup> This is partly due to the rising prevalence of traditional CVD risk factors including hypertension, obesity, and dyslipidemia.<sup>15,16</sup>

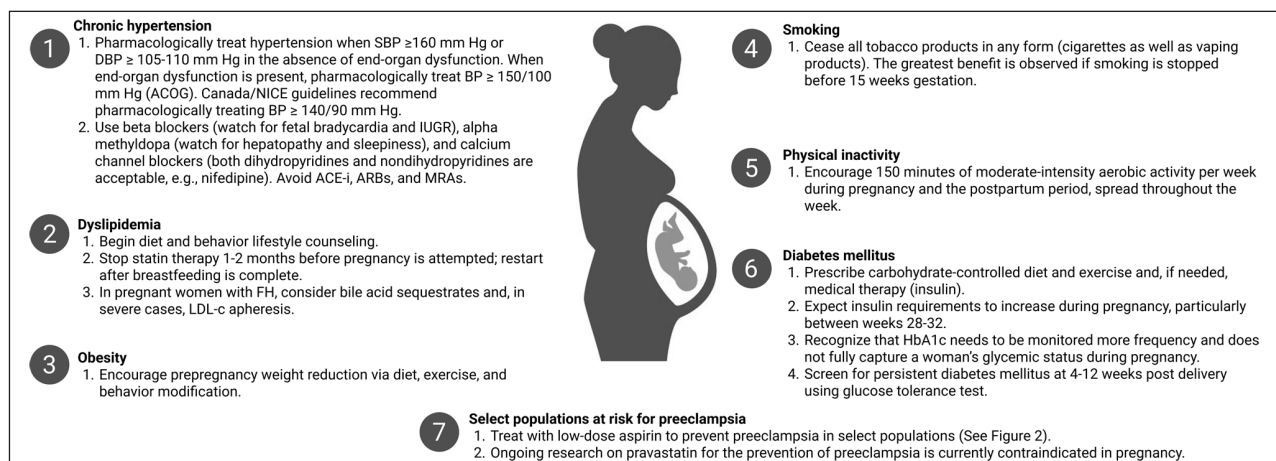
Worse pregnancy outcomes are especially pervasive in rural and racial minority communities. For example, the rate of prepregnancy hypertension has doubled in rural women in the past decade, and there are also higher rates of obesity, diabetes, and tobacco use in these vulnerable populations.<sup>17-19</sup> Furthermore, many maternal risk factors also are associated with a higher relative risk of poor cardiovascular health in offspring during adolescence, potentially perpetuating poor cardiovascular health within these communities.<sup>20</sup> Recognizing and managing these risk factors is a critical component of APO risk reduction and maternal and fetal cardiovascular care optimization (*Figure 1*).

## CHRONIC HYPERTENSION

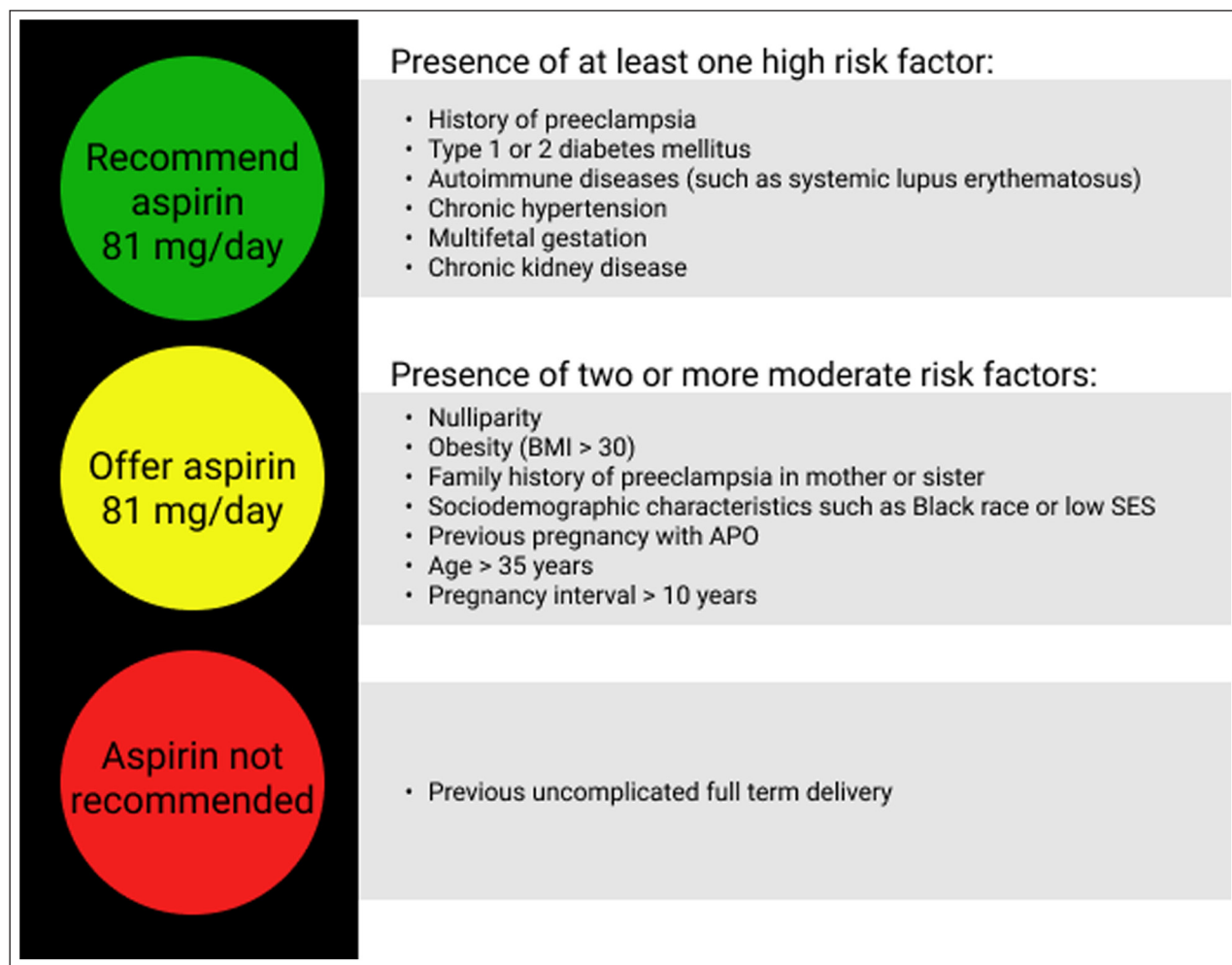
Chronic hypertension (CH) in pregnancy is defined by a systolic blood pressure (SBP)  $\geq$  140 mm Hg and/or diastolic blood pressure (DBP)  $\geq$  90 mm Hg before pregnancy or 20 weeks of gestation.<sup>2</sup> Women with CH are at increased risk for APOs, particularly preeclampsia (*Figure 2*). A meta-analysis of 55 studies found relative risks (RR) of 7.7 for superimposed preeclampsia (95% CI, 5.7–10.1), 2.7 for PTB (95% CI, 1.9–3.6), and 1.3 for cesarean section (95% CI, 1.1–1.5).<sup>21</sup> Women with CH also are more likely to experience pregnancies complicated by poor fetal growth (OR 3.0; 95% CI, 2.8–3.2)<sup>1</sup> and placental abruption (RR 2.4; 95% CI, 2.3–2.5).<sup>2</sup> Notably, women with CH who develop preeclampsia are at even higher risk for other APOs and often develop preeclampsia earlier than those without CH.<sup>2</sup> Finally, women with CH are at higher risk of cerebrovascular complications (OR 5.4; 95% CI, 4.3–6.9).<sup>1</sup>

## MANAGEMENT OF CHRONIC HYPERTENSION DURING PREGNANCY

Although the American College of Cardiology (ACC) and the American Heart Association (AHA) have well-established



**Figure 1** Management of adverse pregnancy outcome risk factors. SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure; ACOG: American College of Gynecologists; NICE: National Institute for Health and Care Excellence; ACE-i: angiotensin-converting enzyme inhibitor; ARBs: angiotensin receptor blockers; MRAs: mineralocorticoid receptor antagonists FH: familial hypercholesterolemia; LDL-c: low-density lipoprotein cholesterol; HbA1c: hemoglobin A1c.



**Figure 2** Aspirin use in the prevention of preeclampsia. SLE: systemic lupus erythematosus; BMI: body mass index; SES: socioeconomic status; APO: adverse pregnancy outcomes.

guidelines for the management of chronic hypertension in nonpregnant individuals, optimal goal ranges for blood pressure management during pregnancy are highly debated. Overly aggressive blood pressure control may decrease fetoplacental perfusion.<sup>2</sup> A 2011 Cochrane review of two studies including 256 women found that tight blood pressure control was associated with a higher risk of hospital admission (RR 2.53; 95% CI, 1.14–5.63) without differences in severe preeclampsia or fetal growth restriction.<sup>22</sup> A subsequent Cochrane review of 31 trials including 3,485 women with mild-to-moderate hypertension during pregnancy (SBP 140–169 mm Hg and DBP 90–109 mm Hg) found that treatment reduced risk of severe maternal hypertension—defined as SBP  $\geq$  170 mm Hg and/or DBP  $\geq$  110 mm Hg on two consecutive occasions 15 minutes apart (RR 0.49 in 20 trials; 95% CI, 0.40–0.60)—but did not significantly reduce the risk of APOs (including preeclampsia, fetal/neonatal death/miscarriage, SGA, and PTB).<sup>23</sup>

On the other hand, the Control of Hypertension in Pregnancy Study (CHIPS) randomized women with CH or gestational hypertension to “tight” or “less tight” control (target DBP 85 vs 100 mm Hg, respectively) and found that “tight control” was protective against severe maternal hypertension; in addition, a post-hoc

analysis found that severe hypertension was a risk marker for APOs, independent of blood pressure control or preeclampsia.<sup>24</sup> Post-hoc analysis also found that “less tight” blood pressure control appeared to result in a lower incidence of SGA babies (OR 0.66; 95% CI, 0.44–1.00).<sup>25</sup>

Based on these studies, the American College of Obstetrics and Gynecology (ACOG) recommends pharmacological treatment only for severe hypertension in pregnancy (SBP  $\geq$  160 mm Hg or DBP  $\geq$  105–110 mm Hg) in the absence of end-organ dysfunction. In the presence of end-organ dysfunction, antihypertensives are recommended at a blood pressure  $\geq$  150/100 mm Hg. Additionally, ACOG recommends discontinuing antihypertensives in women with mild CH (140–160/90–110 mm Hg) during pregnancy.<sup>26</sup> In contrast, influenced by the CHIPS data, Canada and UK guidelines both recommend treating blood pressure  $\geq$  140/90 mm Hg in pregnant women with hypertension.<sup>27,28</sup> The ongoing CHAP trial (Chronic Hypertension and Pregnancy Project) hopes to address this question more definitively.<sup>25</sup>

Recommended antihypertensive medications during pregnancy include beta blockers, alpha methyldopa, and calcium channel blockers.<sup>29</sup> Labetalol is the preferred beta blocker, although metoprolol is an acceptable alternative.<sup>30</sup>

When using beta blockers, careful fetal monitoring is advised because of associated fetal bradycardia and intrauterine growth restriction.<sup>29,31</sup> For calcium channel blockers, both dihydropyridines and nondihydropyridines are acceptable, though nifedipine is most commonly used.<sup>29,32</sup> Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are strongly contraindicated during pregnancy due to risk for fetal abnormalities.<sup>29,31</sup>

## DYSLIPIDEMIA

Triglycerides, total cholesterol, and low-density lipoprotein-c (LDL-C) increase during pregnancy and drop following delivery.<sup>33,34</sup> Physiologic changes in total cholesterol and triglycerides are thought to be nonatherogenic. However, pregnancy is also associated with an increased proportion of smaller, denser LDL-C particles that may be more atherogenic, with higher concentrations correlating with an increased risk of CVD later in life.<sup>34</sup> Elevated levels of lipids in predisposed women carry increased risk for APOs.<sup>33,34</sup>

The Amsterdam Born Children and their Development cohort study discovered a linear association between elevated maternal triglyceride levels in early pregnancy and pregnancy-induced hypertension (OR 1.6; 95% CI, 1.1–2.3), preeclampsia (OR 1.69; 95% CI, 1.1–2.6), and induced PTB (OR 1.69; 95% CI, 1.2–2.5).<sup>4</sup> Additionally, the Coronary Artery Risk Development in Young Adults study found an independent correlation between prepregnancy total cholesterol levels that were either low (< 156 mg/dL) or high (> 195 mg/dL) with PTB. Based on these results, low prepregnancy cholesterol may be a marker of poor nutritional status or a baseline inflammatory state that leads to PTB-inducing cascade, whereas high prepregnancy cholesterol represents a “proatherogenic phenotype” with increased risk of PTB.<sup>35</sup>

## MANAGEMENT OF DYSLIPIDEMIA DURING PREGNANCY

Behavioral and lifestyle counseling are the cornerstones of management for dyslipidemia in pregnancy.<sup>34,36,37</sup> Drug therapy is limited because of concerns for teratogenicity, with current guidelines recommending against the use of many drugs during pregnancy and lactation.<sup>33,34,36,37</sup> In particular, the 2018 AHA Cholesterol Guidelines recommend stopping statin therapy 1 to 2 months before conception and restarting after cessation of breastfeeding.<sup>37</sup> Despite these recommendations, ongoing trials are evaluating pravastatin in pregnant women to prevent preeclampsia, because hydrophilic statins such as pravastatin or rosuvastatin are potentially less associated with fetal malformations than lipophilic statins such as simvastatin or atorvastatin.<sup>37,38</sup>

Other medications, including ezetimibe, niacin, and fibrates, are similarly associated with teratogenicity and are thus contraindicated during pregnancy.<sup>33</sup> Proprotein convertase subtilisin/kexin type 9 serine protease inhibitors have not been tested for safety during pregnancy and are not currently approved during pregnancy.<sup>33</sup> Safe therapies are limited to bile acid sequestrants and LDL-C apheresis, both of which are only approved in women with severe familial hypercholesterolemia.<sup>33,39</sup>

## OBESITY

There is growing evidence linking obesity (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) with a multitude of APOs.<sup>3</sup> A subgroup of women with obesity enrolled in the Cardiac Disease in Pregnancy (CARPREG II) study had a higher risk of experiencing a cardiac event (OR 1.7; 95% CI, 1.0–2.7) or preeclampsia (8% vs. 2%;  $P = .001$ ) compared with women of normal weight.<sup>40</sup> Obese women were more likely to present with heart failure in pregnancy (8% vs 3%;  $P = .02$ ) compared with normal-weight women (BMI 18.5–24.9 kg/m<sup>2</sup>). Risk of maternal mortality also has been linked to increasing BMI. A population-based case-control study in France found that overweight women (BMI 25–29.9 kg/m<sup>2</sup>) had an OR of 1.7 (95% CI, 1.3–2.2) for maternal death, and those with class 2 to 3 obesity (BMI  $\geq 35$  kg/m<sup>2</sup>) had an OR of 3.4 (95% CI, 2.2–5.3), compared with those who have normal BMI.<sup>41</sup>

Obesity was also associated with an increased risk of fetal complications such as PTB (19% vs 10%;  $P = .05$ ) and respiratory distress syndrome (8% vs. 3%;  $P = .02$ ).<sup>40</sup> Women who were overweight but not obese also had higher rates of infant mortality than women with normal weight.<sup>42</sup> Finally, maternal obesity portends long-term risks for offspring, including an increased risk of metabolic syndrome and childhood obesity, even after adjustment for complications such as GDM.<sup>3</sup>

## MANAGEMENT OF OBESITY IN PREGNANCY

To mitigate obesity-related complications of pregnancy, clinical guidelines from ACOG and the National Institute for Health and Care Excellence recommend weight-related screening and preconception care.<sup>3</sup> Obese women who have even small weight reductions before pregnancy have improved pregnancy outcomes.<sup>3</sup> Overweight and obese women should also receive counseling on the increased risks of pregnancy complications and should be encouraged to engage in prepregnancy weight reduction via diet, exercise, and behavior modification.<sup>3,43</sup>

## PHYSICAL INACTIVITY

In pregnancy, physical inactivity is an independent risk factor for maternal obesity and related pregnancy complications, including GDM.<sup>44,45</sup> Moreover, aerobic

exercise has been associated with positive pregnancy outcomes such as less gestational weight gain and lower incidences of GDM, gestational hypertension, PTB, and cesarean delivery.<sup>45,46</sup> Pregnant women should continue to or initiate safe physical exercise in the absence of obstetric or medical contraindications.

The US Department of Health and Human Services Physical Activity Guidelines recommend at least 150 minutes of moderate-intensity aerobic activity per week during pregnancy and the postpartum period, spread throughout the week.<sup>47</sup> Examples of such aerobic activities include walking, stationary cycling, dancing, water aerobics, and use of resistance exercises.<sup>45,46</sup>

## SMOKING

Cigarette smoking is associated with many APOs.<sup>48</sup> Active smoking is associated with increased risk of miscarriage (RR 1.23; 95% CI, 1.2–1.3)<sup>49</sup> and stillbirth (RR 1.5; 95% CI, 1.4–1.5).<sup>50</sup> Maternal smoking also has a dose-dependent relationship with obesity and short stature in adult daughters; in fact, 61% of offspring of heavier smokers ( $\geq 10$  cigarettes/day) and 37% of light smokers ( $< 10$  cigarettes/day) are more likely to be obese than the daughters of nonsmokers.<sup>51</sup> It should be noted that harmful effects on pregnancy also occur with the use of other nicotine products, including vaping products with nicotine or nicotine salts.<sup>48</sup> Smoking cessation at any point in gestation is beneficial to the pregnant woman and her fetus, although the greatest benefit occurs with smoking cessation prior to 15 weeks of gestation.<sup>48</sup> Thus, cessation of all tobacco products should be strongly encouraged as early as possible.

To accomplish this, the most recent US Preventive Services Task Force (USPSTF) Guidelines recommend behavioral interventions because current evidence was determined to be insufficient to assess the balance of benefits and harms of pharmacotherapy (eg, nicotine replacement therapy) for tobacco cessation in pregnant women.<sup>52</sup> Trials that do exist for nicotine replacement therapy show inconsistent data,<sup>48,52</sup> with most trending towards benefit, although some trials were terminated early due to concerns from data/safety monitoring committees.<sup>48</sup> The USPSTF also identified no strong evidence base to support varenicline and bupropion, other commonly used pharmacologic agents in nonpregnant patients, during pregnancy.<sup>52</sup>

## DIABETES MELLITUS

Pregnancy in healthy women is associated with a component of insulin resistance, which may be needed to deliver adequate nutrition to the developing fetus. Insulin resistance rises throughout pregnancy, peaks in the third trimester, and returns to prepregnancy levels after delivery.<sup>53</sup> However, frank diabetes (or prediabetes) is deleterious to the fetus and associated with APOs.<sup>54,55</sup> Women who develop GDM are almost twice as likely to develop postpartum diabetes.<sup>55,56</sup> Pregnant women with preconception type 1 or type 2 diabetes have become more prevalent in recent years<sup>54</sup> and have a significantly

higher risk of preeclampsia<sup>53,57</sup> and acute myocardial infarction during pregnancy.<sup>58</sup>

The management of diabetes in pregnancy includes a carbohydrate-controlled diet, exercise, and medical therapy to achieve euglycemia.<sup>59</sup> Insulin is the preferred medical treatment for patients who are not adequately controlled by diet and exercise, and providers should expect insulin requirements to increase during pregnancy, particularly between 28 and 32 weeks gestation.<sup>55</sup> Given the increased red blood cell turnover and the physiologic changes of pregnancy, HbA1c needs to be monitored more frequently, and even then it may not fully capture a woman's glycemic status during this time.<sup>55,59</sup> Finally, women with GDM should be tested for persistent diabetes mellitus for 4 to 12 weeks after delivery using an oral glucose tolerance test.<sup>59</sup>

## ADDITIONAL STRATEGIES TO MITIGATE RISK FACTORS DURING PREGNANCY

Low-dose aspirin reduces the risk of APOs in women who are at increased risk for preeclampsia. A 2019 Cochrane Review of 77 trials found an 18% reduction in proteinuric preeclampsia (RR 0.82; 95% CI, 0.77–0.88), fetal or neonatal death (RR 0.85; 95% CI, 0.76–0.95; 14% risk reduction), PTB (RR 0.91; 95% CI, 0.87–0.95; 9% risk reduction), and SGA babies (RR 0.84; 95% CI, 0.76–0.92).<sup>60</sup> However, antiplatelet agents made little or no difference in the risk of HELLP syndrome, severe maternal morbidity, or admission to a newborn special care unit.<sup>60</sup> Similarly, the USPSTF performed a systematic review and found that low-dose aspirin reduced the risk for preeclampsia by 24%, PTB by 14%, and intrauterine growth restriction by 20%.<sup>61</sup>

Thus, both USPSTF and ACOG recommend the prophylactic use of low-dose aspirin (81 mg/d) between 12 and 16 weeks gestation in women with the preeclampsia risk factors noted in *Figure 1*.<sup>61</sup> In addition to optimal control of the above risk factors, aspirin in at-risk women and prepregnancy weight loss in obese and overweight women, there are also several therapies under investigation, including statins. Although they are classified as pregnancy category X by the FDA,<sup>62</sup> several prospective human studies (NCT03648970, NCT01717586) are investigating the role of pravastatin in preeclampsia prevention and treatment and should have results in the next few years.<sup>63,64</sup>

## LONG-TERM EFFECT OF SEX-SPECIFIC RISK FACTORS ON CARDIOVASCULAR HEALTH

### ADVERSE PREGNANCY OUTCOMES

Adverse pregnancy outcomes result in short-term complications during pregnancy and are strongly associated with an increased long-term risk for CVD such as heart failure, coronary artery disease, and stroke

(**Figure 3**).<sup>12</sup> In particular, preeclampsia predicts increased CVD risk before the emergence of traditional CVD risk factors.<sup>65</sup> Compared with women with uncomplicated pregnancy, women who have had preeclampsia have a four-fold increased risk of heart failure and a two-fold increased risk of coronary artery disease, heart failure, stroke, and CVD death.<sup>66</sup> Preeclampsia and preterm birth are also associated with an increased risk of CVD-related death, with OR 1.73 (95% CI, 1.46–2.06) and 1.93 (95% CI, 1.83–2.03) respectively.<sup>12</sup> Women with gestational hypertension or GDM are 67% more likely to have subsequent CVD compared to women without these adverse pregnancy outcomes.<sup>12</sup> In addition, women who have had HDP are more likely to develop chronic hypertension after pregnancy.<sup>67</sup> Finally, pregnancy loss is also associated with greater odds of future CVD even after adjustment for CVD risk factors.<sup>68</sup> For these reasons, APOs such as preeclampsia and preterm delivery are now considered risk-enhancing factors in the assessment of atherosclerotic risk to guide statin therapy for asymptomatic women at intermediate risk of atherosclerotic cardiovascular disease.<sup>69</sup>

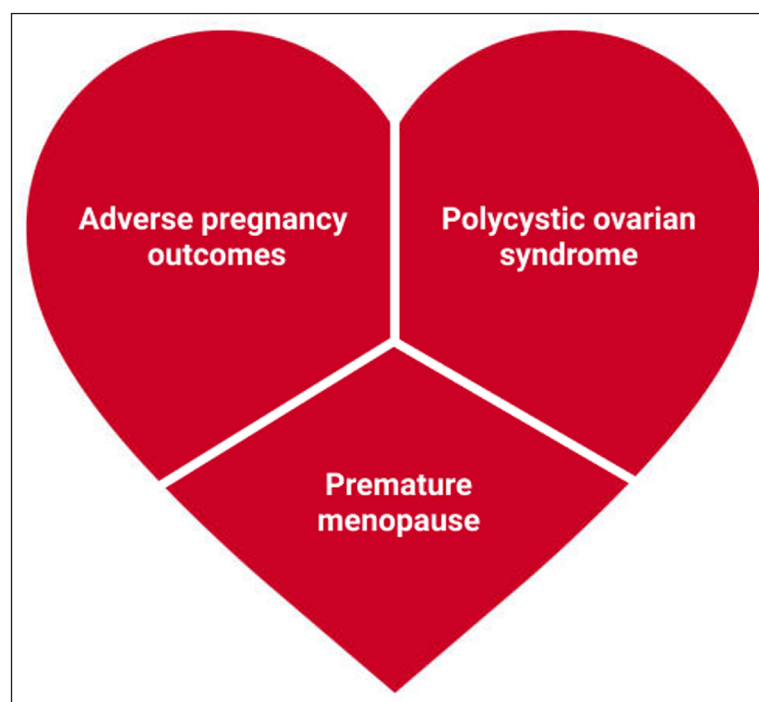
### **POLYCYSTIC OVARIAN SYNDROME**

PCOS presents during a woman's reproductive years and contributes to subfertility, APOs, and potentially higher rates of CVD.<sup>70–72</sup> PCOS is associated with a higher prevalence of central adiposity, insulin resistance, dyslipidemia, hypertension, obstructive sleep apnea, metabolic syndrome, and obstructive sleep apnea.<sup>73–75</sup> In pregnancy, women with PCOS have higher rates of GDM

(OR 2.8; 95% CI, 1.9–4.1) and HDP (OR 4.1; 95% CI, 2.8–6.0).<sup>70</sup> Notably, PCOS appears to be an independent risk factor for GDM and preeclampsia even after controlling for obesity, multiple pregnancy, and low parity.<sup>74</sup>

Women with PCOS have a higher prevalence of subclinical CVD as measured by coronary artery calcium, carotid intima-media thickness, and endothelial function via flow-mediated brachial artery dilatation.<sup>72</sup> However, the degree of CVD in women with PCOS is unclear, and studies have demonstrated mixed findings. A recent study of 60,574 women with PCOS in the Danish Registry Cohort found a 19% higher risk of developing CVD compared with women who did not have PCOS when adjusted for age and obstetric and social risk factors.<sup>76</sup>

However, when stratified by age, women with PCOS aged 50 and older did not have a higher cardiovascular risk, while women in their 30s and 40s with PCOS trended towards being at greater risk of CVD compared with those without PCOS. The diminishing difference in older women may be due to the confounding positive association between age and CVD risk factors.<sup>76</sup> Accounting for this confounding, other studies have suggested that the absolute risk conferred by PCOS is negligible, although certain phenotypes of women with PCOS are at higher risk.<sup>71</sup> More well-designed trials are needed to assess the true risk of CVD due to PCOS and guide risk stratification. Until then, we advocate that PCOS be treated as a significant risk factor for CVD regardless of BMI, with aggressive treatment of comorbid conditions such as diabetes and hyperlipidemia.



**Figure 3** Sex-specific cardiovascular risk factors in women.

## PREMATURE MENOPAUSE

The postmenopausal state is a well-established risk factor for CVD.<sup>77</sup> Premature menopause and primary ovarian failure, now termed primary ovarian insufficiency (POI), is the depletion or dysfunction of ovarian follicles with cessation of menses before age 40.<sup>78</sup> Similarly, women with the cessation of menstruation before age 45 are considered to have early-onset menopause. Early loss of residual ovarian follicles and consequent estrogen deficiency results in a cascade of negative downstream cardiovascular effects.<sup>78</sup> In particular, estrogen deficiency is associated with less-compliant blood vessels and endothelial dysfunction due to activation of the renin-angiotensin-aldosterone system.<sup>77</sup> Estrogen deficiency also leads to adverse lipid metabolism and atherosclerotic plaque development.<sup>78</sup>

Unsurprisingly, women with POI have an increased risk of CVD and mortality.<sup>77,78</sup> A 2020 cohort study of 144,260 postmenopausal women in the UK found that menopause before age 40 was associated with increased risk (HR 1.4; 95% CI, 1.2–1.6) for a composite outcome that included CAD, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism after adjustment for conventional CVD risk factors and the use of menopausal hormone therapy.<sup>79</sup> A meta-analysis of 32 observational studies found that women with premature menopause (age < 40 years) had an increased risk of CAD (RR 1.5; 95% CI, 1.3–1.8).<sup>77</sup> In addition, women who underwent menopause between ages 50 to 54 years versus at age 50 and younger had a decreased risk of fatal coronary heart disease (RR 0.87; 95% CI, 0.80–0.96). A 2019 pooled analysis of individual patient data from 15 observational studies found that women with premature and early menopause (age < 40 vs < 45, respectively) had a significantly increased risk of a nonfatal CVD event before age 60, with HR 1.6 (95% CI, 1.4–1.7) and 1.3 (95% CI, 1.2–1.4), respectively, compared to women with natural menopause (age 50–51).<sup>80</sup>

## MANAGEMENT OF PREMATURE MENOPAUSE

Based on these and other data, recent updates to the ACC/AHA cholesterol guidelines include premature menopause (prior to age 40) as a risk enhancer and warrant stronger consideration for statin therapy.<sup>37</sup> In addition, unless there is an absolute contraindication to taking estrogen therapy, ACOG recommends hormone therapy in women with POI until the average age of natural menopause (age 50–51).<sup>78</sup> In women with POI, hormone therapy improves endothelial dysfunction

and blood pressure, although the results from the Women's Health Initiative trials related to menopause therapy are not fully applicable to women with POI in terms of cardiovascular risk-to-benefit assessment.<sup>78</sup> More studies are needed to assess the direct impact of hormone therapy in women with POI on incident cardiovascular events. At the time of writing, evidence is insufficient to support hormone therapy for the sole purpose of preventing CVD in the absence of premature menopause.

## CONCLUSION

Cardiovascular disease remains the leading cause of death for women, necessitating early and active intervention. The peripartum period has the potential to serve as a catalyst for behavior change because women may be more receptive to making lifestyle changes before, after, and during pregnancy.<sup>65,64</sup> Recognizing and mitigating risk factors for APOs has the added benefit of also improving risk-factor profiles for long-term CVD and should be a goal of care. Finally, screening for both traditional and sex-specific cardiovascular risk factors by all providers—primary care physicians, obstetricians/gynecologists, and cardiologists—offers an upstream, potentially trajectory-changing strategy to optimize long-term cardiovascular health in women.

## KEY POINTS

- In addition to screening for traditional cardiovascular risk factors, all providers caring for women should screen for sex-specific risk factors such as adverse pregnancy outcomes, polycystic ovarian syndrome, and premature menopause.
- Traditional cardiovascular risk factors such as chronic hypertension, dyslipidemia, obesity, smoking, physical inactivity, and diabetes increase the risk for adverse pregnancy outcomes.
- Risk from sex-specific cardiovascular risk factors can be mitigated with early detection and intervention.
- Pregnancy is an opportune time to identify women who are at risk for future cardiovascular disease, intervene early, and not only improve pregnancy outcomes but also improve long-term cardiovascular health.

## COMPETING INTERESTS

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## REFERENCES

- Bateman BT, Bansil P, Hernandez-Diaz S, Mhyre JM, Callaghan WM, Kuklina EV.** Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. *Am J Obstet Gynecol.* 2012 Feb;206(2):134.e1. doi: [10.1016/j.ajog.2011.10.878](https://doi.org/10.1016/j.ajog.2011.10.878)
- Seely EW, Ecker J.** Chronic hypertension in pregnancy. *Circulation.* 2014 Mar 18;129(11):1254-61. doi: [10.1161/CIRCULATIONAHA.113.003904](https://doi.org/10.1161/CIRCULATIONAHA.113.003904)
- ACOG [Internet].** Washington, DC: American College of Obstetricians and Gynecologists; c2021. Catalano PM, Koutrouvelis GO. Obesity in Pregnancy; 2013 [cited 2021 Aug 12]. Available from: <https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2015/12/obesity-in-pregnancy>
- Vrijkotte TGM, Krukziener N, Hutten BA, Vollebregt KC, Van Eijsden M, Twickler MB.** Maternal lipid profile during early pregnancy and pregnancy complications and outcomes: the ABCD study. *J Clin Endocrinol Metab.* 2012 Nov;97(11):3917-25. doi: [10.1210/jc.2012-1295](https://doi.org/10.1210/jc.2012-1295)
- AHRQ [Internet].** Rockville, MD: Agency for Healthcare Research and Quality; c2021. Fingar KR, Mabry-Hernandez I, Ngo-Metzger Q, Wolff T, Steiner CA, Elixhauser A. Delivery Hospitalizations Involving Preeclampsia and Eclampsia, 2005-2014. 2017 Apr [cited 2021 Aug 12]; Available from: <https://hcup-us.ahrq.gov/reports/statbriefs/sb222-Preeclampsia-Eclampsia-Delivery-Trends.jsp>
- H-CUP [Internet].** Rockville, MD: Agency for Healthcare Research and Quality; c2021. Wier LM, Witt E, Burgess J, Elixhauser A. Statistical Brief #102; Hospitalizations Related to Diabetes in Pregnancy; 2010 Dec [cited 2021 Aug 12]. Available from: <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb102.pdf>
- CDC [Internet].** Atlanta, GA: Centers for Disease Control and Prevention; c2021. Martin JA, Hamilton BE, Osterman MJK. Births in the United States; Data from the National Vital Statistics System. 2019 Jul [cited 2021 Aug 12]; Available from: <https://www.cdc.gov/nchs/products/databriefs/db346.htm>
- CDC [Internet].** Atlanta, GA: Centers for Disease Control and Prevention; c2021. QuickStats: Percentage of Small-for-Gestational-Age Births By Race and Hispanic Ethnicity in the United States; 2008 Dec 19 [cited 2021 Aug 12]. Available from: <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5750a5.htm>
- H-CUP [Internet].** Rockville, MD: Agency for Healthcare Research and Quality; c2021. Elixhauser A, Wier LM. Complicating Conditions of Pregnancy and Childbirth, 2008; HCUP Statistical Brief #113; 2011 May [cited 2021 Aug 12]. Available from: <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb113.jsp>
- Elgendy IY, Bukhari S, Barakat AF, Pepine CJ, Lindley KJ, Miller EC.** American College of Cardiology Cardiovascular Disease in Women Committee. Maternal Stroke: A Call for Action. *Circulation.* 2021 Feb 16;143(7):727-738. doi: [10.1161/CIRCULATIONAHA.120.051460](https://doi.org/10.1161/CIRCULATIONAHA.120.051460)
- Cho L, Davis M, Elgendy I,** et al. Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020 May 26;75(20):2602-2618. doi: [10.1016/j.jacc.2020.03.060](https://doi.org/10.1016/j.jacc.2020.03.060)
- Grandi SM, Filion KB, Yoon S,** et al. Cardiovascular Disease-Related Morbidity and Mortality in Women with a History of Pregnancy Complications. *Circulation.* 2019 Feb 19;139(8):1069-1079. doi: [10.1161/CIRCULATIONAHA.118.036748](https://doi.org/10.1161/CIRCULATIONAHA.118.036748)
- Brown HL, Warner JJ, Gianos E,** et al. Promoting risk identification and reduction of cardiovascular disease in women through collaboration with obstetricians and gynecologists: A presidential advisory from the American Heart Association and the American College of Obstetricians and Gynecologists. *Circulation.* 2018 Jun 12;137(24):e843-e852. doi: [10.1161/CIR.0000000000000582](https://doi.org/10.1161/CIR.0000000000000582)
- Creanga AA, Syverson C, Seed K, Callaghan WM.** Pregnancy-Related Mortality in the United States, 2011-2013. *Obstet Gynecol.* 2017 Aug;130(2):366-373. doi: [10.1097/AOG.0000000000002114](https://doi.org/10.1097/AOG.0000000000002114)
- Ananth CV, Duzyj CM, Yadava S, Schwebel M, Tita ATN, Joseph KS.** Changes in the prevalence of chronic hypertension in Pregnancy, United States, 1970 to 2010. *Hypertension.* 2019 Nov;74(5):1089-1095. doi: [10.1161/HYPERTENSIONAHA.119.12968](https://doi.org/10.1161/HYPERTENSIONAHA.119.12968)



16. **Wild R, Weedin EA, Wilson D.** Dyslipidemia in Pregnancy. *Endocrinol Metab Clin North Am.* 2016 Mar;45(1):55-63. doi: [10.1016/j.ecl.2015.09.004](https://doi.org/10.1016/j.ecl.2015.09.004)
17. **Harrington RA, Califf RM, Balamurugan A,** et al. Call to Action: Rural health: A Presidential Advisory From the American Heart Association and American Stroke Association. *Circulation.* 2020 Mar 10;141(10):e615-e644. doi: [10.1161/CIR.0000000000000753](https://doi.org/10.1161/CIR.0000000000000753)
18. **Cameron NA, Molsberry R, Pierce JB,** et al. Pre-Pregnancy Hypertension Among Women in Rural and Urban Areas of the United States. *J Am Coll Cardiol.* 2020 Dec 1;76(22):2611-2619. doi: [10.1016/j.jacc.2020.09.601](https://doi.org/10.1016/j.jacc.2020.09.601)
19. **Shahul S, Tung A, Minhaj M,** et al. Racial disparities in comorbidities, complications, and maternal and fetal outcomes in women with preeclampsia/eclampsia. *Hypertens Pregnancy.* 2015 Oct 2;34(4):506-515. doi: [10.3109/10641955.2015.1090581](https://doi.org/10.3109/10641955.2015.1090581)
20. **Perak AM, Lancki N, Kuang A.** HAPO Follow-Up Study Cooperative Research Group. Associations of Maternal Cardiovascular Health in Pregnancy With Offspring Cardiovascular Health in Early Adolescence. *JAMA.* 2021 Feb 16;325(7):658-668. doi: [10.1001/jama.2021.0247](https://doi.org/10.1001/jama.2021.0247)
21. **Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC.** Chronic hypertension and pregnancy outcomes: Systematic review and meta-analysis. *BMJ.* 2014 Apr 15;348. g2301. doi: [10.1136/bmj.g2301](https://doi.org/10.1136/bmj.g2301)
22. **Nabhan AF, Elsedawy MM.** Tight control of mild-moderate pre-existing or non-proteinuric gestational hypertension. *The Cochrane Database of Systematic Reviews.* 2011 Jul 6; (7):CD006907. DOI: <https://doi.org/10.1002/14651858.CD006907.pub2>
23. **Abalos E, Duley L, Steyn DW, Gialdini C.** Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev.* 2018 Oct 1;10(10):CD002252. doi: [10.1002/14651858.CD002252.pub4](https://doi.org/10.1002/14651858.CD002252.pub4)
24. **Sinkey RG, Oparil S.** Lower blood pressure thresholds raise the bar in pregnancy. *Circ Res.* 2019 Jul 5;125(2):195-197. doi: [10.1161/CIRCRESAHA.119.315384](https://doi.org/10.1161/CIRCRESAHA.119.315384)
25. **Tita ATN, Sibai BM, Oparil S.** Less-Tight versus Tight Control of Hypertension in Pregnancy. *New Engl J Med.* 2015 Jun 11;372(24):2366-7. doi: [10.1056/NEJMc1503870](https://doi.org/10.1056/NEJMc1503870)
26. **American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics.** ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. *Obstet Gynecol.* 2019 Jan;133(1):e26-e50. doi: [10.1097/AOG.0000000000003020](https://doi.org/10.1097/AOG.0000000000003020)
27. **Butalia S, Audibert F, Côté AM,** et al. Hypertension Canada's 2018 Guidelines for the Management of Hypertension in Pregnancy. *Can J Cardiol.* 2018 May;34(5):526-531. doi: [10.1016/j.cjca.2018.02.021](https://doi.org/10.1016/j.cjca.2018.02.021)
28. **Webster K, Fishburn S, Maresh M, Findlay SC, Chappell LC.** Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. *BMJ.* 2019 Sep 9; 366:l5119. doi: [10.1136/bmj.l5119](https://doi.org/10.1136/bmj.l5119)
29. **Mehta LS, Warnes CA, Bradley E,** et al.; American Heart Association Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Stroke Council. Cardiovascular Considerations in Caring for Pregnant Patients: A Scientific Statement From the American Heart Association. *Circulation.* 2020 Jun 9;141(23):e884-e903. doi: [10.1161/CIR.0000000000000772](https://doi.org/10.1161/CIR.0000000000000772)
30. **Bateman BT, Heide-Jørgensen U, Einarsdóttir K,** et al. -Blocker Use in Pregnancy and the Risk for Congenital Malformations: An International Cohort Study. *Ann Intern Med.* 2018 Nov 20;169(10):665-673. doi: [10.7326/M18-0338](https://doi.org/10.7326/M18-0338)
31. **Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U.** Peripartum Cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020 Jan 21;75(2):207-221. doi: [10.1016/j.jacc.2019.11.014](https://doi.org/10.1016/j.jacc.2019.11.014)
32. **Easterling T, Mundle S, Bracken H,** et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. *Lancet.* 2019 Sep 21;394(10203):1011-1021. doi: [10.1016/S0140-6736\(19\)31282-6](https://doi.org/10.1016/S0140-6736(19)31282-6)
33. **ACC.org [Internet].** Washington, DC: American College of Cardiology; c2021. Lundberg GP, Mehta LS. Familial Hypercholesterolemia and Pregnancy; 2018 May 14 [cited 2021 Aug 27]. Available from: <https://www.acc.org/latest-in-cardiology/articles/2018/05/10/13/51/familial-hypercholesterolemia-and-pregnancy>
34. **ACC.org [Internet].** Washington, DC: American College of Cardiology; c2021. Mukherjee M. Dyslipidemia in Pregnancy; 2014 May 19 [cited 2021 Aug 27]. Available from: <https://www.acc.org/latest-in-cardiology/articles/2014/07/18/16/08/dyslipidemia-in-pregnancy>.
35. **Chen Q, Chen H, Xi F,** et al. Association between maternal blood lipids levels during pregnancy and risk of small-for-gestational-age infants. *Sci Rep.* 2020 Nov 16;10(1):19865. doi: [10.1038/s41598-020-76845-1](https://doi.org/10.1038/s41598-020-76845-1)
36. **ACOG.org [Internet].** Washington, DC: American College of Obstetricians and Gynecologists; 2021. Christopher BA, Pagidipati NJ. Evaluation and Management of Lipid Disorders; 2019 Mar [cited 2021 Aug 27]. Available from: <https://www.acog.org/clinical/journals-and-publications/clinical-updates/2019/03/evaluation-and-management-of-lipid-disorders>
37. **Grundy SM, Stone NJ, Bailey AL,** et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2019 Jun 18;139(25):e1082-e1143. doi: [10.1161/CIR.0000000000000625](https://doi.org/10.1161/CIR.0000000000000625)
38. **Morton S, Thangaratinam S.** Statins in pregnancy. *Curr Opin Obstet Gynecol.* 2013 Dec;25(6):433-40. doi: [10.1097/GCO.0000000000000026](https://doi.org/10.1097/GCO.0000000000000026)

39. **Goldberg AC, Hopkins PN, Toth PP**, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011 Jun;5(3 Suppl):S1-8. doi: [10.1016/j.jacl.2011.04.003](https://doi.org/10.1016/j.jacl.2011.04.003)
40. **Pfaller B, Siu SC, D'Souza R**, et al. Impact of Obesity on Outcomes of Pregnancy in Women With Heart Disease. *J Am Coll Cardiol*. 2021 Mar 16;77(10):1317-1326. doi: [10.1016/j.jacc.2021.01.010](https://doi.org/10.1016/j.jacc.2021.01.010)
41. **Saucedo M, Esteves-Pereira AP, Pencolé L**, et al. Understanding maternal mortality in women with obesity and the role of care they receive: a national case-control study. *Int J Obes (Lond)*. 2021 Jan;45(1):258-265. doi: [10.1038/s41366-020-00691-4](https://doi.org/10.1038/s41366-020-00691-4)
42. **Ely DM, Gregory ECW, Drake P**. Infant Mortality by Maternal Prepregnancy Body Mass Index: United States, 2017-2018. *Natl Vital Stat Rep*. 2020 Aug;69(9):1-11. PMID: 22054916
43. **Denison F, Aedla N, Keag O**, et al. Care of Women with Obesity in Pregnancy: Green-top Guideline No. 72. *BJOG*. 2019 Feb;126(3):e62-e106. doi: [10.1111/1471-0528.15386](https://doi.org/10.1111/1471-0528.15386)
44. **Artal R**. The role of exercise in reducing the risks of gestational diabetes mellitus in obese women. *Best Pract Res Clin Obstet Gynaecol*. 2015 Jan;29(1):123-32. doi: [10.1016/j.bpobgyn.2014.05.013](https://doi.org/10.1016/j.bpobgyn.2014.05.013)
45. **ACOG.org [Internet]**. Washington, DC: American College of Obstetricians and Gynecologists; 2021. Birchner ML, Gyamfi-Bannerman C. Physical Activity and Exercise During Pregnancy and the Postpartum Period; 2020 Apr [cited 2021 Aug 27]. Available from: <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/04/physical-activity-and-exercise-during-pregnancy-and-the-postpartum-period>
46. **Berghella V, Saccone G**. Exercise in pregnancy! *Am J Obstet Gynecol*. 2017 Apr;216(4):335-337. doi: [10.1016/j.ajog.2017.01.023](https://doi.org/10.1016/j.ajog.2017.01.023)
47. **Health.gov [Internet]**. Washington, DC: US Department of Health and Human Services; c2021. Physical Activity Guidelines for Americans: 2nd edition; 2019 Sep [cited 2021 Aug 27]. Available from: [https://health.gov/sites/default/files/2019-09/Physical\\_Activity\\_Guidelines\\_2nd\\_edition.pdf](https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf)
48. **ACOG.org [Internet]**. Washington, DC: American College of Obstetricians and Gynecologists; 2021. Valent AM, Choby B. Tobacco and Nicotine Cessation During Pregnancy; 2020 May [cited 2021 Aug 27]. Available from: <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/05/tobacco-and-nicotine-cessation-during-pregnancy>
49. **Pineles BL, Park E, Samet JM**. Systematic review and meta-analysis of miscarriage and maternal exposure to tobacco smoke during pregnancy. *Am J Epidemiol*. 2014 Apr 1;179(7):807-23. doi: [10.1093/aje/kwv301](https://doi.org/10.1093/aje/kwv301)
50. **Pineles BL, Hsu S, Park E, Samet JM**. Systematic Review and Meta-Analyses of Perinatal Death and Maternal Exposure to Tobacco Smoke During Pregnancy. *Am J Epidemiol*. 2016 Jul 15;184(2):87-97. doi: [10.1093/aje/kwv301](https://doi.org/10.1093/aje/kwv301)
51. **Maessen SE, Ahlsson F, Lundgren M, Cutfield WS, Derraik JGB**. Maternal smoking early in pregnancy is associated with increased risk of short stature and obesity in adult daughters. *Sci Rep*. 2019 Mar 12;9(1):4290. doi: [10.1038/s41598-019-39006-7](https://doi.org/10.1038/s41598-019-39006-7)
52. **US Preventive Services Task Force [Internet]**. Rockville, MD: US Preventive Services Task Force; c2021. Tobacco Smoking Cessation in Adults, Including Pregnant Persons: Intervention; 2021 Jan 19 [cited 2021 Aug 27]; Available from: <https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions#fullrecommendationstart>
53. **Parretti E, Lapolla A, Dalfrà MG**, et al. Preeclampsia in lean normotensive normotolerant pregnant women can be predicted by simple insulin sensitivity indexes. *Hypertension*. 2006 Mar;47(3):449-53. doi: [10.1161/01.HYP.0000205122.47333.7f](https://doi.org/10.1161/01.HYP.0000205122.47333.7f)
54. **Peng TY, Ehrlich SF, Crites Y**, et al. Trends and racial and ethnic disparities in the prevalence of pregestational type 1 and type 2 diabetes in Northern California: 1996-2014. *Am J Obstet Gynecol*. 2017 Feb;216(2):177.e1-177.e8. doi: [10.1016/j.ajog.2016.10.007](https://doi.org/10.1016/j.ajog.2016.10.007)
55. **ACOG.org [Internet]**. Washington, DC: American College of Obstetricians and Gynecologists; 2021. Pregestational Diabetes Mellitus; 2018 Dec [cited 2021 Aug 27]. Available from: <https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/12/pregestational-diabetes-mellitus>
56. **Bentley-Lewis R, Powe C, Ankers E, Wenger J, Ecker J, Thadhani R**. Effect of race/ethnicity on hypertension risk subsequent to gestational diabetes mellitus. *Am J Cardiol*. 2014 Apr 15;113(8):1364-70. doi: [10.1016/j.amjcard.2014.01.411](https://doi.org/10.1016/j.amjcard.2014.01.411)
57. **Phipps EA, Thadhani R, Benzing T, Karumanchi SA**. Preeclampsia: pathogenesis, novel diagnostics and therapies. *Nat Rev Nephrol*. 2019 May;15(5):275-289. doi: [10.1038/s41581-019-0119-6](https://doi.org/10.1038/s41581-019-0119-6)
58. **James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER**. Acute myocardial infarction in pregnancy: a United States population-based study. *Circulation*. 2006 Mar 28;113(12):1564-71. doi: [10.1161/CIRCULATIONAHA.105.576751](https://doi.org/10.1161/CIRCULATIONAHA.105.576751)
59. **American Diabetes Association**. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018 Jan;41(Suppl 1):S137-S143. doi: [10.2337/dc18-S013](https://doi.org/10.2337/dc18-S013)
60. **Duley L, Meher S, Hunter KE, Seidler AL, Askie LM**. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev*. 2019 Oct 30;2019(10):CD004659. doi: [10.1002/14651858.CD004659.pub3](https://doi.org/10.1002/14651858.CD004659.pub3)
61. **LeFevre ML**. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014 Dec 2;161(11):819-26. doi: [10.7326/M14-1884](https://doi.org/10.7326/M14-1884)

62. **Ma'ayeh M, Rood KM, Kniss D, Costantine MM.** Novel Interventions for the Prevention of Preeclampsia. *Curr Hypertens Rep.* 2020 Feb 12;22(2):17. doi: [10.1007/s11906-020-1026-8](https://doi.org/10.1007/s11906-020-1026-8)
63. **ClinicalTrials.gov [Internet].** Bethesda, MD: US National Library of Medicine; c2021. Indonesia Pravastatin to Prevent Preeclampsia Study (INOVASIA); 2018 Aug 28 [cited 2021 Aug 27]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03648970>
64. **ClinicalTrials.gov [Internet].** Bethesda, MD: US National Library of Medicine; c2021. Pravastatin for Prevention of Preeclampsia (Statin); 2020 Oct 27 [cited 2021 Aug 27]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01717586>
65. **Seely EW, Celi AC, Chausmer J,** et al. Cardiovascular Health After Preeclampsia: Patient and Provider Perspective. *J Womens Health (Larchmt).* 2021 Mar;30(3):305-313. doi: [10.1089/jwh.2020.8384](https://doi.org/10.1089/jwh.2020.8384)
66. **Wu P, Haththotuwa R, Kwok CS,** et al. Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Qual Outcomes.* 2017 Feb;10(2):e003497. doi: [10.1161/CIRCOUTCOMES.116.003497](https://doi.org/10.1161/CIRCOUTCOMES.116.003497)
67. **Benschop L, Duvekot JJ, Roeters Van Lennep JE.** Future risk of cardiovascular disease risk factors and events in women after a hypertensive disorder of pregnancy. *Heart.* 2019 Aug;105(16):1273-1278. doi: [10.1136/heartjnl-2018-313453](https://doi.org/10.1136/heartjnl-2018-313453)
68. **Hall PS, Nah G, Vittinghoff E,** et al. Relation of Pregnancy Loss to Risk of Cardiovascular Disease in Parous Postmenopausal Women (From the Women's Health Initiative). *Am J Cardiol.* 2019 May 15;123(10):1620-1625. doi: [10.1016/j.amjcard.2019.02.012](https://doi.org/10.1016/j.amjcard.2019.02.012)
69. **Arnett DK, Blumenthal RS, Albert MA,** et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019 Sep 10;74(10):1376-1414. doi: [10.1016/j.jacc.2019.03.009](https://doi.org/10.1016/j.jacc.2019.03.009)
70. **Kjerulff LE, Sanchez-Ramos L, Duffy D.** Pregnancy outcomes in women with polycystic ovary syndrome: a metaanalysis. *Am J Obstet Gynecol.* 2011 Jun;204(6):558.e1-6. doi: [10.1016/j.ajog.2011.03.021](https://doi.org/10.1016/j.ajog.2011.03.021)
71. **Carmina E, Lobo RA.** Is There Really Increased Cardiovascular Morbidity in Women with Polycystic Ovary Syndrome? *J Womens Health (Larchmt).* 2018 Nov;27(11):1385-1388. doi: [10.1089/jwh.2018.7162](https://doi.org/10.1089/jwh.2018.7162)
72. **Osibogun O, Ogunmoroti O, Michos ED.** Polycystic ovary syndrome and cardiometabolic risk: Opportunities for cardiovascular disease prevention. *Trends Cardiovasc Med.* 2020 Oct;30(7):399-404. doi: [10.1016/j.tcm.2019.08.010](https://doi.org/10.1016/j.tcm.2019.08.010)
73. **Guzick DS.** Cardiovascular Risk in PCOS. *J Clin Endocrinol Metab.* 2004 Aug;89(8):3694-5. doi: [10.1210/jc.2004-1136](https://doi.org/10.1210/jc.2004-1136)
74. **ACOG.org [Internet].** Washington, DC: American College of Obstetricians and Gynecologists; 2021. Hoeger K, Vitek W. Polycystic Ovary Syndrome; 2016 Jul [cited 2021 Aug 27]. Available from: <https://www.acog.org/clinical/journals-and-publications/clinical-updates/2016/07/polycystic-ovary-syndrome>
75. **Mehta JL, Mcsweeney J,** editors. Gender Differences in the Pathogenesis and Management of Heart Disease. Switzerland: Springer International Publishing; 2018. 359. doi: [10.1007/978-3-319-71135-5](https://doi.org/10.1007/978-3-319-71135-5)
76. **Oliver-Williams C, Vassard D, Pinborg A, Schmidt L.** Risk of cardiovascular disease for women with polycystic ovary syndrome: results from a national Danish registry cohort study. *Eur J Prev Cardiol.* 2020 Aug 2;2047487320939674. doi: [10.1177/2047487320939674](https://doi.org/10.1177/2047487320939674)
77. **Muka T, Oliver-Williams C, Kunutsor S,** et al. Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis. *JAMA Cardiol.* 2016 Oct 1;1(7):767-776. doi: [10.1001/jamacardio.2016.2415](https://doi.org/10.1001/jamacardio.2016.2415)
78. **ACOG.org [Internet].** Washington, DC: American College of Obstetricians and Gynecologists; 2021. Primary Ovarian Insufficiency in Adolescents and Young Women; 2014 Jul [cited 2021 Aug 27]. Available from: <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2014/07/primary-ovarian-insufficiency-in-adolescents-and-young-women>
79. **Honigberg MC, Zekavat SM, Aragam K,** et al. Association of Premature Natural and Surgical Menopause With Incident Cardiovascular Disease. *JAMA.* 2019 Dec 24;322(24):2411-2421. doi: [10.1001/jama.2019.19191](https://doi.org/10.1001/jama.2019.19191)
80. **Zhu D, Chung HF, Dobson AJ,** et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *Lancet Public Health.* 2019 Nov;4(11):e553-e564. doi: [10.1016/S2468-2667\(19\)30155-024](https://doi.org/10.1016/S2468-2667(19)30155-024)

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