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Dyslipidemia management in women of reproductive potential: An expert clinical consensus from the national lipid association

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Abstract: Cardiovascular disease (CVD) is the leading cause of death among women and its incidence has been increasing recently, particularly among younger women. Across major professional society guidelines, dyslipidemia management remains a central tenet for atherosclerotic CVD prevention for both women and men. Despite this, women, particularly young women, who are candidates for statin therapy are less likely to be treated and less likely to achieve their recommended therapeutic objectives for low-density lipoprotein cholesterol (LDL-C) levels. Elevated LDL-C and triglycerides are the two most common dyslipidemias that should be addressed during pregnancy due to the increased risk for adverse pregnancy outcomes, such as preeclampsia, gestational diabetes mellitus, and pre-term delivery, as well as pancreatitis in the presence of severe hypertriglyceridemia. In this National Lipid Association

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Expert Clinical Consensus, we review the roles of nutrition, physical activity, and pharmacotherapy as strategies to address elevated levels of LDL-C and/or triglycerides among women of reproductive age. We include a special focus on points to consider during the shared decision-making discussion regarding pharmacotherapy for dyslipidemia during preconception planning, pregnancy, and lactation.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in women.[1] Alarmingly, CVD rates are increasing among younger women ≤ 55 yr.[2–4] Increased rates of disease track with a worrisome trend of an increasing prevalence of CVD risk factors among young adults over the past decade.[5,6] Given the overwhelming evidence from genetic, observational, and interventional studies that low-density lipoprotein cholesterol (LDL-C) and other apolipoprotein B (apoB)-containing particles are causally related to atherosclerotic CVD (ASCVD) pathogenesis,[7] lipid management remains a central tenet for ASCVD prevention across major professional society guidelines.[8,9] Despite this, female patients, particularly young women, are less likely to be treated with statin therapy and less likely to achieve their LDL-C therapeutic targets based on their calculated risk for CVD.[10,11] Primary prevention and early intervention strategies to alleviate modifiable CVD risk factors are effective strategies to mitigate CVD risk.

Notably, the CV health (CVH) of pregnant women is declining in the United States (U.S.) with less than 1 in 10 pregnant women having high or optimal CVH.[12] One of the biggest risk factors for an adverse pregnancy outcome is starting a pregnancy with suboptimal CVH. Thus, improving the CVH in reproductive age adolescent and young women should be a high priority for the health of the mother and her offspring.[13,14] Optimizing dyslipidemia diagnosis and management in women of reproductive potential can play a large role in mitigating CV risk in pregnancy and beyond. Women with high pre-pregnancy levels of total cholesterol (TC), LDL-C, and triglycerides (TG) are more likely to develop an adverse pregnancy outcome, such as preeclampsia, gestational diabetes mellitus (GDM), and/or a pre-term delivery.[15–17]

In this National Lipid Association (NLA) Expert Clinical Consensus, we review the approach to lipid management among women of reproductive age, with a special focus on consideration of pharmacologic treatment of dyslipidemia during preconception planning, pregnancy, and lactation.

Preconception planning

Who should be screened for lipid and lipoprotein disorders pre-pregnancy?

The 2018 American Heart Association (AHA)/American College of Cardiology (ACC)/ Multisociety Guideline on the Management of Blood Cholesterol (Blood Cholesterol Guideline) recommends lipoprotein lipid screening starting at age 20 for all adults, which includes women of reproductive age, if they have not received screening during the recommended pediatric age group with age-specific normal levels. There are no specific guidelines regarding when to screen women before pregnancy.[8,9] Screening for lipid disorders before pregnancy can help identify women at risk for ASCVD and provide opportunities for optimal maternal and fetal health outcomes with appropriate interventions. Women at risk include those with advanced maternal age, those with prior adverse pregnancy outcomes (e.g., hypertensive disorders, preeclampsia, GDM, delivery of a preterm or low-birth-weight infant, and a history of placental abruption and/or a stillbirth), those with a personal or family history of lipid disorders or premature ASCVD, and/or those with pre-existing medical conditions (e.g., chronic hypertension [HTN], obesity, diabetes, and/or polycystic ovary syndrome [PCOS]).[8,9,18] Screening for lipid disorders should be a shared decision between the patient and her primary healthcare team after the benefits and risks of screening and treatment are explained.

What effect does pregnancy have on lipid and lipoprotein levels?

The levels of major lipoproteins and lipids increase steadily during pregnancy and peak near term. TC, LDL-C, TG, and lipoprotein(a) [Lp(a)] all rise during pregnancy; therefore, it is recommended that women with a known lipid disorder have a consultation with a lipid specialist prior to pregnancy.[19,20] Cholesterol levels can increase 25–50 % in pregnancy. In uncomplicated or ''normal'' pregnancies, neither TC nor TG concentrations exceed 250 mg/dL at any time during pregnancy (Fig. 1).[20,21] Over the three months postpartum, the level of major lipoproteins and lipids declines toward pre-pregnancy levels.[22] The increase in lipoprotein and lipid levels during pregnancy ensures the availability of fuel for fetal development, and circulating levels reflect increasing insulin resistance for the mother as her pregnancy progresses through term.[23] Because of increased insulin resistance during pregnancy, along with other conditions like gluconeogenesis, about 6–9 % of pregnant women develop GDM. Women with GDM and/or preeclampsia often have elevated TG levels pre-pregnancy. TG levels in women with GDM may exceed 300 mg/dL and increase as pregnancy progresses.[23]

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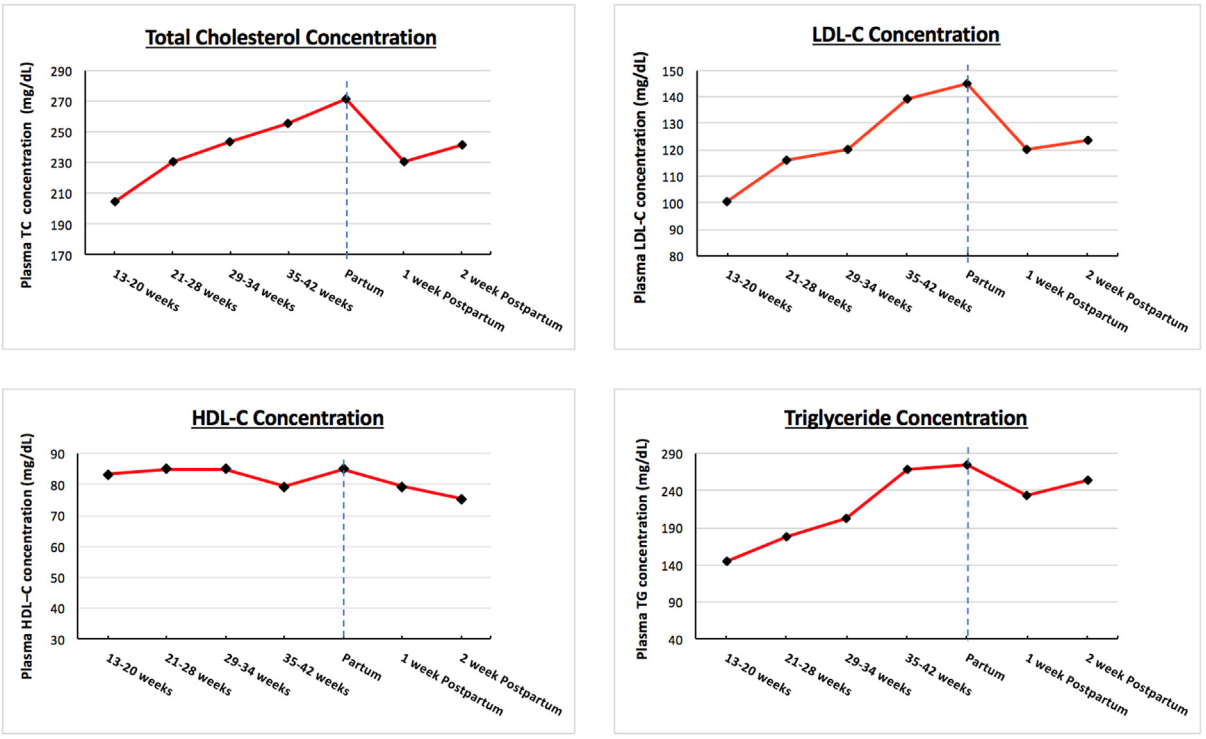

Fig. 1 Lipoprotein lipid levels before, during, and after pregnancy. Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG=triglycerides. Figure depicts mean levels of TC, LDL-C, HDL-C, and TG during pregnancy and early post-partum period. Data obtained by averaging 2.5th and 97thpercentiles for each category. Adapted from Klajnbard A et al., Clin Chem Lab Med. 2010.[20]

Nutrition and lifestyle considerations for Dyslipidemia during the reproductive years

A healthful lifestyle is the foundation for the prevention and management of ASCVD, and one of the key components of a healthful lifestyle is a cardioprotective dietary pattern.[8,9,18,24–26] Although there are several recommended dietary patterns, such as the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and healthful vegetarian (including vegan), there are similarities among them. The recommended dietary patterns are aligned with food-based guidance from several scientific and professional organizations and are nutritionally adequate. All of the recommended dietary patterns include the following components that are associated with improved health outcomes: whole, unprocessed, or minimally processed foods, including fruits and vegetables, whole grains; healthful protein sources, such as fish and seafood, plant-based proteins (e.g., nuts, seeds, legumes/pulses), and lower fat animal proteins (meats, poultry, dairy, eggs); and non-tropical, liquid plant oils (e.g., olive, peanut, sunflower, and soybean) in place of solid fats (e.g., butter, lard, and coconut oil). The recommended dietary patterns all emphasize a low intake of foods with high amounts of saturated fatty acids and *trans* fatty acids and highly processed foods, including processed meats, refined grains, and foods/beverages with added sugars and salt.[8,9,18,24–26] Additionally, high diet quality is emphasized in each of the recommended dietary patterns.[27] All women should be encouraged to consume a cardioprotective dietary pattern throughout their lifespan and receive support on personalizing their food choices. For women who have dyslipidemia, personalized counseling is recommended to optimally implement appropriate nutrition interventions of proven efficacy.[8,9,24–26,28]

What is the evidence for effective nutrition interventions for managing dyslipidemias in women of reproductive years?

The most important way to manage dyslipidemia for any individual is to practice a healthful lifestyle throughout the lifespan, including consuming a cardioprotective dietary pattern.[8,9,18,24–26,28] Although there are no nutrition guidelines for managing dyslipidemia specifically for women during pregnancy and lactation, the previous section highlighted at-risk women who should be screened for dyslipidemia. The evidence-based nutrition interventions recommended for any individual with dyslipidemia are appropriate for women with dyslipidemia during pregnancy and lactation (Tables 1 and 2).

During a woman's reproductive years, healthful eating habits are important to reduce the risk of pregnancy-related conditions that increase the risk for ASCVD later in life, as well as to promote the health of her offspring.[26] The authors of a systematic review reported that dietary patterns before and during pregnancy that are higher in vegetables, fruits, whole grains, nuts, legumes, fish, and vegetable oils and lower in processed meat and refined grains are asso-

Table 1 Potential causes and the effective lifestyle interventions for elevated LDL-C levels[18,24,25,28]

Potential Causes	Effective Lifestyle Interventions
Dietary pattern • Positive energy balance • High SFA intake • High TFA intake • High dietary cholesterol intake **Genetics** **Diseases/disorders/altered metabolic states** • Anorexia nervosa • Autoimmune disorders • Chronic kidney disease • HIV infection • Hypothyroidism • Menopause transition with declining estrogen levels • Nephrotic syndrome • Metabolic liver disease • Polycystic ovary syndrome • Pregnancy • Increased adiposity	**Nutrition interventions** • Follow a recommended healthful dietary pattern • Moderate total fat intake (30–35 % TDE • Saturated fat intake <7 % TDE • Replace SFAs with UFAs, primarily PUFAs • Avoid TFAs • Reduce dietary cholesterol intake (200–300 mg/day) • Increase viscous soluble fiber intake (≥10 g/day) • Consider supplementation of plant sterols/stanols 2 g/day • Implement the "portfolio dietary approach": increased intake of viscous soluble fiber, soy protein, plant sterols/stanols, and nuts **Increase physical activity:** generally, 200–300 min/week of moderate or higher intensity**Reduce excessive body fat**

Abbreviations: HIV=human immunodeficiency virus; PUFAs = polyunsaturated fatty acids; SFAs = saturated fatty acids; TDE = total daily energy; TFAs = *trans* fatty acids; UFAs = unsaturated fatty acids

ciated with reduced risk of GDM and hypertensive disorders of pregnancy, including preeclampsia.[29] For example, a Mediterranean-style dietary pattern, which is also recommended for lipid management, has been associated with a reduced risk of preeclampsia.[30]

Familial hypercholesterolemia (FH) and severe hypertriglyceridemia are the most common dyslipidemias that should be addressed during pregnancy.[22] The nutrition interventions for managing FH and hypertriglyceridemia during pregnancy are the same as for non-pregnant women. The nutrition interventions for FH and hypertriglyceridemia for all adults are discussed in detail in the NLA Clinical Perspective, "Nutrition Interventions for Adults with Dyslipidemia"[24] and summarized in Tables 1 **and** 2. Women with severe hypertriglyceridemia, especially if TG levels are ≥1000 mg/dL, or familial chylomicronemia syndrome (FCS), a rare genetic form of severe hypertriglyceridemia, have a higher risk of complications during pregnancy, especially acute pancreatitis (discussed below).[31] Implementing nutrition interventions for managing severe hypertriglyceridemia during pregnancy requires careful consideration for the needs of both the mother and fetus and should be provided by a multidisciplinary team that includes a registered dietitian nutritionist (RDN).[31] Initially, a very-low-fat (≤5 % total daily energy) diet should be recommended to resolve chylomicronemia and reduce the risk of pancreatitis, with TG levels closely monitored. Once TG levels are <750 mg/dL, individualization of the diet based on underlying causal factors is essential. For patients without FCS, dietary fat may be cautiously liberalized, although some patients may require a diet with <20 % total daily energy from fat to maintain TG levels <750 mg/dL.[24,31] After pregnancy, the nutrition intervention should be further individualized based on the TG level to allow for a lower or moderate fat intake in patients without FCS.[24] Patients with FCS will require a very-low-fat diet (<15–20 g/d) for life.[24,31,32]

For those who must maintain a very-low-fat diet, adequate intake of essential fatty acids (i.e., linoleic acid and α-linolenic acid) should be encouraged.[24,31,32] Additionally, because caloric requirements during pregnancy increase and low-fat diets may be hypocaloric, some women may benefit from supplementation with medium-chain TG (MCT) oil to increase calories and adjust the macronutrient distribution of the diet.[24,31,32] Medical-grade MCT oil should be used to ensure it contains only capric and caprylic fatty acids.[24,32] Other nutrition interventions for women with severe hypertriglyceridemia and/or FCS include maintaining adequate hydration and electrolyte balance and balancing caloric intake to achieve appropriate gestational weight gain (GWG). Use of omega-3 fatty acids has shown inconsistent effects on lowering TG levels in patients with FCS and, if used, the fat content needs to be considered as part of the total daily fat intake.[32] Counseling from an RDN is strongly recommended to educate women with severe hypertriglyceridemia during pregnancy on how to balance a low-fat diet with high-quality carbohydrate foods within their caloric requirements.[24,31,32] For women with FCS, regular monitoring of TG levels, nutrition intervention adjustment, and treatment with a multidisciplinary team, including an RDN, is essential before, during, and after pregnancy.[32]

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Table 2 Potential causes and the effective lifestyle interventions for hypertriglyceridemia[18,23–25,28,43]

Potential Causes			
Dietary habits	• Positive energy balance • High glycemic load • Excess alcohol		
Genetics	• Polygenic disorders • Monogenic disorders, e.g., familial chylomicronemia syndrome		
Diseases/disorders/altered metabolic states	• Autoimmune disorders • Chronic kidney disease • Diabetes, metabolic syndrome/insulin resistance • HIV infection • Hypothyroidism • Nephrotic syndrome • Menopause transition with declining estrogen levels • Overweight and obesity • Polycystic ovary syndrome • Pregnancy (especially third trimester)		
Summary of Nutrition Interventions for Different Levels of Elevated Triglycerides*			
Nutrition interventions based on shared decision-making	**TG <500 mg/dL**	**TG 500–749 mg/dL**	**TG≥750 mg/dL**
Added sugars (foods and beverages)	Reduce	Markedly reduce	Eliminate
Total fat (% total daily energy)	25–35 %	**Individualize**†	**Individualize**†‡
Alcohol	Restrict	Abstain completely	Abstain completely
Aerobic activity	≥150 min/week of moderate-intensity or 75 min/week of vigorous-intensity aerobic activity (or equivalent)		
Reduce adiposity	Recommended weight loss goal is 5–10 % for patients with increased adiposity		

Abbreviation: TG = triglycerides

*Because there are various underlying causes of hypertriglyceridemia, it is critical to individualize nutrition interventions, especially carbohydrate and fat intake, and monitor the TG response to those interventions to ensure the recommended nutrition interventions have the desired effects. This is particularly in patients with TG levels ≥750 mg/dL.[24]

†The ACC[43] and the NLA[24] have published nutrition recommendations for managing hypertriglyceridemia, including details on features of healthful dietary patterns that meet nutrition recommendations for hypertriglyceridemia based on triglyceride elevation and presence of chylomicronemia., ‡‡Initially, a very-low-fat (≤5 % total daily energy) diet should be recommended to resolve chylomicronemia and reduce the risk of pancreatitis, with TG levels closely monitored. Once TG levels are <750 mg/dL, individualization of the diet based on underlying causal factors is essential. For patients without FCS, dietary fat may be cautiously liberalized, although some patients may require a diet with <20 % total daily energy from fat to maintain TG levels <750 mg/dL. After pregnancy, the nutrition intervention should be further individualized based on the TG level to allow for a lower or moderate fat intake in patients without FCS.[24] Patients with FCS will require a very-low-fat diet (<15–20 g/d) for life.[24,31,32]

What is the evidence for the effect of physical activity on dyslipidemias in women of reproductive years?

For ASCVD prevention and overall health, it is recommended that adults accumulate at least 150 minutes/week of moderate- to vigorous-intensity physical activity, as well as resistance exercises two times/week.[8,18,28,33] The evidence-based physical activity interventions recommended for any individual with dyslipidemia would also be appropriate for women with dyslipidemia and include: 1) a minimum quantity of 150 min/week of moderate to higher intensity aerobic activity to decrease TG levels; and 2) >2000 kcal/week of energy expenditure (generally 200 to 300 min/week) of moderate or higher intensity activity to enhance the effects of lowering TG, as well as reduce LDL-C levels and excess adiposity.[23] European guidelines for the management of dyslipidemias recommend that people with dyslipidemia participate in ≥30 min/day of moderate to vigorous physical activity, even if they do not have overweight or obesity.[28]

During pregnancy, physical activity can be safe for generally healthy women, and women with uncomplicated pregnancies should be encouraged to participate in aerobic and strength-training activities before, during, and after pregnancy.[33–35] A thorough clinical evaluation should be conducted before recommending an exercise program to ensure there is not a medical reason to avoid physical activity, and she should be monitored during the progress of the pregnancy.[33,34] Clinicians should be familiar with contraindications for exercising during pregnancy (gestational hypertension, pre-eclampsia, ruptured membranes, incompetent cervix, bleeding in the second or third trimester, multiple gestation at risk for premature labor, placenta previa, and premature labor).[34–36] Women should be educated on how to adjust their physical activity regimens during pregnancy to address the normal anatomic and physiologic changes and fetal re-

Fig. 2 Physical activity guidelines for women during pregnancy and postpartum*. *A thorough clinical evaluation should be conducted before recommending an exercise program to ensure that a woman does not have a medical reason to avoid physical activity and she should be monitored during the progress of the pregnancy.[33,35,36]

quirements.[33–35] Physical activity during pregnancy can confer many benefits, including reducing the risk of excessive GWG, GDM, symptoms of postpartum depression,[33–35,37] and the management of dyslipidemia as described above. Furthermore, physical activity during pregnancy increases cardiorespiratory fitness without increasing the risk of negative pregnancy outcomes, such as low birth weight, preterm delivery, or early pregnancy loss,[33-35] and limited evidence has suggested an inverse relationship between physical activity and risk of preeclampsia, gestational HTN, and antenatal anxiety and depressive symptoms.[37] Physical activity during the postpartum period (first year after delivery) may improve the mother's cardiorespiratory fitness and decrease symptoms of postpartum depression.[33,34] Several professional organizations have provided physical activity guidelines for women during pregnancy and the postpartum period, which would also be appropriate for pregnant and postpartum women with dyslipidemia (Fig. 2).[33–35] Additional details about the characteristics of a safe and effective exercise regimen in pregnancy are provided by the American College of Obstetricians and Gynecologists (ACOG) and the Canadian guideline for physical activity throughout pregnancy.[34,35]

What is an appropriate caloric intake and weight gain during pregnancy in women with dyslipidemias?

Maintaining a healthy body composition is important for any individual for overall health and ASCVD prevention. Women who gain excessive weight before or during pregnancy are more likely to have abnormal lipid profiles.[23] Excess adiposity can contribute to elevated levels of TG, as well as apoB-containing lipoproteins, in some individuals.[24] Additionally, women who gain weight outside the recommended ranges during pregnancy may experience various adverse maternal outcomes, including increased risk for pregnancy-associated HTN, GDM, complications during labor and delivery, and postpartum weight retention and subsequent maternal obesity.[38]

The Institute of Medicine (IOM) published recommendations for appropriate weight gain during pregnancy

Table 3 Weight gain recommendations for pregnancy.[38]

Pre-pregnancy Weight Category	BMI	Range of Total Weight Gain (lb)	Rates of Weekly Weight Gain* in the Second and Third Trimesters (mean range, lb/wk)
Underweight	<18.5	28–40	1.0 (1.0–1.3)
Normal weight	18.5–24.9	25–35	1.0 (0.8–1.0)
Overweight	25–29.9	15–25	0.6 (0.5–0.7)
Obese	≥30	11–20	0.5 (0.4–0.6)

*Calculations assume a 1.1 to 4.4 lb weight gain in the first trimester.
Abbreviations: BMI = body mass index

Table 4 Estimated calorie needs during pregnancy and lactation for women with a healthy pre-pregnancy weight.[a 40]

Stage of Pregnancy or Lactation	Estimated Increase in Calories/Day Compared to Pre-pregnancy Needs
Pregnancy: 1st trimester	↑ 0 calories
Pregnancy: 2nd trimester	↑ 340 calories
Pregnancy: 3rd trimester	↑ 452 calories
Lactation: 1st 6 months	↑ 330 calories[b]
Lactation: 2nd 6 months	↑ 400 calories[c]

[a]These estimates apply to women with a healthy pre-pregnancy weight. Women with a pre-pregnancy weight that is considered overweight or obese should consult their healthcare provider for guidance regarding appropriate caloric intake during pregnancy and lactation.
[b]The estimated energy requirements for the first six months of lactation is calculated by adding 500 calories/day to pre-pregnancy needs to account for the energy needed for milk production during this time period, then subtracting 170 calories/day to account for weight loss in the first six months postpartum.
[c]The estimated energy requirements for the second six months of lactation is calculated by adding 400 calories/day to pre-pregnancy needs to account for the energy needed for milk production during this time period. Weight stability is assumed after six months postpartum.

(Table 3). Some clinicians believe the weight gain during pregnancy recommended by the IOM is too high, especially for women with overweight or obesity.[39] Other concerns include that the high weight gain recommendations do not address concerns related to postpartum weight retention and do not differentiate between degrees of obesity, especially for women with severe obesity.[39] The ACOG emphasizes the importance of discussing appropriate weight gain and nutrition and physical activity recommendations at the initial pregnancy visit and periodically throughout the pregnancy. Additionally, ACOG recommends individualized care and clinical judgment when facilitating appropriate weight gain in a woman with overweight or obesity who is gaining less weight, or wishes to gain less weight, than recommended by the IOM but whose fetus is growing appropriately.[39]

To encourage a woman to gain an appropriate amount of weight during pregnancy, it is important to educate her about her caloric needs during pregnancy and lactation. The estimated caloric needs during the first trimester of pregnancy generally do not increase above pre-pregnancy requirements. Additional calories needed for the later trimesters of pregnancy and during lactation are approximately 300 to 400 additional calories per day (Table 4). However, the appropriate caloric intake for a pregnant woman may be influenced by many factors, including pre-pregnancy weight status, GWG, and multiple pregnancies. As shown in Table 3, women with overweight or obesity have lower recommended weight gain during pregnancy, which may affect caloric needs.[40] Thus, as with other lifestyle interventions, the caloric needs of a woman during pregnancy and lactation should be individualized.

What are recommendations for reducing excess adiposity post-partum in women with dyslipidemias?

The focus during pregnancy should be on appropriate weight gain for a woman of any body weight. Once a woman is post-partum, if she has excess adiposity, a shared decision-making conversation is appropriate to determine whether she is ready and able to address lifestyle changes to reduce excess adiposity and improve her lipid and lipoprotein levels, if dyslipidemia is present. Achieving a 5–10 % weight loss, if appropriate, may lower TG levels by approximately 20 %, LDL-C levels by up to 15 %, and is associated with an increase in high-density lipoprotein cholesterol of 8–10 %.[41,42] The results of some studies suggest that reducing excess adiposity can promote a 10–20 % TG reduction, although a TG reduction up to 70 % may be achieved in some individuals.[43] It is important to recognize that some individuals with severe hypertriglyceridemia may not have excess adiposity, but rather a genetic disorder, such as FCS.[24,43] Therefore, individualizing nutrition and lifestyle therapies for each patient through behavioral counseling is essential (see next section). The beneficial effect on lipid/lipoprotein levels has been maintained with long-term sustained weight loss (2–3 yr) but has not been consistent over longer periods despite maintained weight loss. Therefore, other interventions

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should be considered for longer term to maintain the benefits of lowering lipid/lipoprotein levels.[44]

The nutrition and physical activity recommendations discussed previously can promote reduced excess adiposity in the post-partum period, and the behavior counseling strategies discussed below can increase the likelihood of success. However, in patients with overweight or obesity and adiposity-related comorbidities who have not achieved adequate reduction in excess adiposity with intensive lifestyle interventions alone, pharmacotherapy with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) or dual agonists can be an effective strategy for long-term weight management.[45] The use of these medications has been shown to improve cardiometabolic risk factors, including favorable changes in the lipid and lipoproteins associated with reduction of excess adiposity. The U.S. Food and Drug Administration (FDA) has recently approved both semaglutide (a GLP-1 RA) and tirzepatide (a dual glucose-dependent insulintropic polypeptide/GLP-1 RA) for the indication of chronic weight management; these agents can confer weight loss in the range of 12–20 %. Liraglutide (an older GLP-1 RA) is also FDA approved for weight management but confers less weight reduction (~8 %). It should be noted that these GLP-1 RA agents are contraindicated in pregnancy and should be discontinued at least two months before pregnancy.[46] It is also unknown whether these agents are excreted into human milk and, therefore, should not be used during lactation.[47]

What behavioral and counseling methods have been shown to promote successful lifestyle changes during the reproductive years?

Making and maintaining lifestyle changes can be challenging. Several professional organizations recommend shared decision-making and a team-based approach to implement strategies to reduce ASCVD risk, which includes dyslipidemia management.[8,9,18,25,28] The U.S. Preventive Services Task Force (USPSTF) concluded with moderate certainty that intensive counseling interventions to facilitate healthful dietary practices and physical activity in adults with CVD risk have a moderate net benefit on CVD risk factors[48] and a small net benefit in those without CVD risk.[49] Adults with CVD risk who received behavioral interventions achieved significant reductions in blood pressure, TC and LDL-C levels, body mass index (BMI), weight, and waist circumference and had fewer CV events (e.g., myocardial infarction, stroke, or incidence of peripheral artery disease).[50,51] Additionally, behavioral counseling to promote healthful dietary and/or physical activity habits in adults without CVD risk was associated with significant improvements in blood pressure, LDL-C levels, weight, BMI, and waist circumference.[49] Based on this evidence, the USPSTF recommends offering or referring adults with CVD risk factors, e.g., HTN, dyslipidemia, and/or the metabolic syndrome (MetSyn), or an estimated 10-year CVD risk ≥7.5 % to behavioral counseling interventions to facilitate healthful nutrition practices and physical activity.[49–52]

Behavior counseling characteristics identified by the USPSTF that promote healthful GWG in pregnant adolescent and adult patients are summarized in Table 5. Counseling and structured behavioral interventions (i.e., including an activity and/or dietary component) to limit GWG were associated with decreased risk of GDM, emergency cesarean delivery, macrosomia, and large for gestational age. GWG interventions were also associated with modest reductions in mean GWG and decreased likelihood of exceeding recommendations for GWG.[53]

The European Society of Cardiology/European Atherosclerosis Society have discussed strategies to facilitate healthful lifestyle changes in patients,[28] and the AHA has published a Science Advisory that provides lifestyle-related behavior change counseling strategies, including the use of the 5A Model framework, that healthcare professionals can use with patients at CVD risk and during every clinical visit[54] (Fig. 3). Additionally, the AHA published a Science Advisory on special considerations for healthful lifestyle practices across the lifespan, which includes a discussion of the use of the 5A Model framework for behavioral counseling in primary care to counsel women during their reproductive years on lifestyle behavior change for CVD risk reduction in both the mother and child[55] (Fig. 3). For nutrition interventions specifically, it is recommended to refer patients to an RDN for medical nutrition therapy (MNT) to address dyslipidemia.[9,24,43,56] RDNs can provide MNT for patients with hypertriglyceridemia, FH, FCS, and other dyslipidemias and cardiometabolic risk factors, as well as facilitate education and understanding of dietary and lifestyle practices for ASCVD prevention, overall.[24,43,54]

What is the recommendation for fish consumption for pregnant and lactating women to decrease the risk of mercury poisoning?

It is well known that the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), support fetal development.[57] Dietary recommendations for women who plan to become pregnant or who are pregnant or lactating include consuming at least 8 ounces and up to 12 ounces of a variety of seafood per week due to the favorable effects on cognitive development in young children. The FDA and the U.S. Environmental Protection Agency (EPA) provided joint advice for seafood consumption by pregnant and lactating women to limit their methylmercury exposure. Overconsumption of methylmercury during pregnancy can have negative effects on the developing fetus and can also be harmful to the brain and nervous system of pregnant and lactating women. Based on advice from the FDA and EPA, depending on body weight, women should choose seafood lowest in methylmercury.[40] Additionally, certain species of seafood (e.g., shark, swordfish, king mackerel) should be avoided during pregnancy. More information is available

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Table 5 Effective behavioral counseling interventions to promote healthy gestational weight gain in pregnant adolescent and adult patients[53]

Content	Individual focus on nutrition, physical activity, or lifestyle and behavioral change or multiple components, most commonly including active/supervised exercise or counseling about diet and physical activity
When to start/stop	Generally started at the end of the first trimester or the beginning of the second trimester and ended prior to delivery
Duration and intensity	• Varied from 15 to 120 minutes • Consisted of <2 contacts to ≥12 contacts
Who delivered the intervention	Highly diverse and included clinicians, registered dietitian nutritionists, qualified fitness specialists, physiotherapists, and health coaches across different settings (e.g., local community fitness centers)
How the intervention was delivered	Delivery methods included individual or group counseling that was delivered in person, by computer/Internet, or by telephone calls

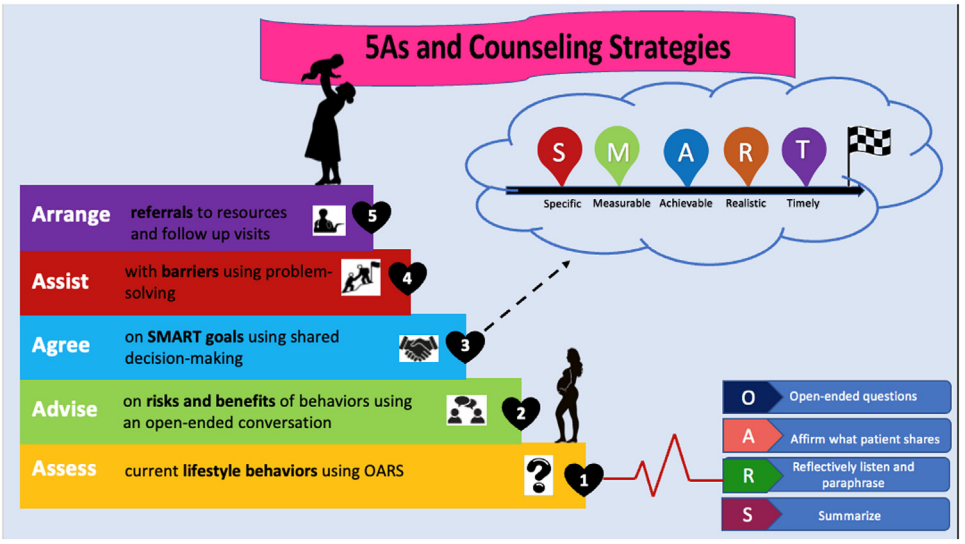

Fig. 3 5As and counseling strategies to implement throughout pregnancy*. *Strategies to promote successful lifestyle changes in patients with dyslipidemia and other cardiovascular disease risk factors.[28,54,55]

on the FDA or EPA websites at FDA.gov/fishadvice and EPA.gov/fishadvice.[40]

What is the recommendation for the use of omega-3 fatty acid supplementation for pregnant and lactating women?

Omega-3 fatty acid dietary supplements are reasonable alternatives for women who are unable or unwilling to eat seafood to ensure adequate intake of EPA and DHA. However, dietary supplements are very loosely regulated by the FDA, and the FDA is not authorized to approve dietary supplements for safety and effectiveness before they are marketed to consumers.[58] Careful selection of high-quality supplements is advised, and consumers should be educated about purchasing supplements with the "USP Verified Mark." This ensures that the supplement has been produced using the FDA's current Good Manufacturing Practices, contains the ingredients listed on the label, does not contain harmful substances, and will dissolve once taken.[59] The exact dosing of omega-3 fatty acid supplements to promote maternal and fetal health remains controversial as many professional organizations recommend 200–300 mg daily, but higher doses (up to 1000 mg/day) of DHA were found to be superior compared to 200 mg/day in reducing early preterm birth[57] with no increased risk of adverse effects for the mother.

Cardiometabolic profile during the reproductive years

What is the connection between hypertriglyceridemia and abnormal glucometabolic state and when should we screen lipoproteins/lipids?

Although genetics play a major role in blood levels of lipoproteins/lipids, cardiometabolic disease, which is largely influenced by lifestyle, appears to be a driving force for many dyslipidemias. The rising prevalence of obesity and MetSyn has led to significant increases in the prevalence of dyslipidemias throughout multiple stages of a woman's lifespan and is additionally influenced by hormonal changes during one's lifetime. Obesity can worsen outcomes based on its

association with insulin resistance, an increased inflammatory state, and impaired endothelial function. Abnormal glucometabolic states represented by diabetes, prediabetes, and MetSyn (often associated with PCOS) can lead to increased TG levels as excess glucose in the liver drives fatty acid and TG synthesis providing yet another mechanism for increased CVD risk.[23]

In addition to the pregnancy period, the pre-pregnancy period is crucial for several reasons. Pre-pregnancy dyslipidemia, including elevated TC, LDL-C, and TG, is associated with increased risk of developing preeclampsia during pregnancy.[15–17] Conception rates also appear to be highly connected to the cardiometabolic state with MetSyn noted to be associated with decreased rates of conception, whereas interventions addressing lifestyle and reducing excess adiposity were associated with improved success rates.[60] In prior retrospective analyses, assisted reproductive technologies (ART) have been shown to be associated with increased risk of preeclampsia, perinatal mortality, preterm birth, and small for gestational age births, even when compared to age-matched controls.[61,62] The increased event rate in this population may be associated with underlying cardiometabolic disease associated with infertility, rather than the ART itself. An analysis of data from a large registry did not find excess CVD risk among women who underwent ART,[63] although there may be differences in CVD risk regarding the type of ART used, such as frozen versus fresh embryo transfer.[64] Of note, for most women undergoing egg harvesting, statin therapy can be continued, but is usually discontinued one to two months before attempting conception, unless a woman is at very high ASCVD risk where it may be continued, as discussed in a section below.

How do we treat an abnormal cardiometabolic state if linked to hypertriglyceridemia?

If the glucometabolic state is the driver of the TG disorder, improvement in glycemic control and reducing excess adiposity can potentially fully address hypertriglyceridemia. In cases of a severe genetic predisposition, such as FCS, a very-low-fat diet is also required to maintain TG levels <500 mg/dL, as discussed previously. Lifestyle interventions, including exercise and a healthful eating plan individualized based on underlying causal factors, are the first line of treatment for all TG disorders, as described in an NLA Clinical Perspective.[24]

What are the secondary causes of hypertriglyceridemia that can be targeted?

Secondary causes of hypertriglyceridemia include medical conditions (e.g., poorly controlled diabetes, renal disease), medications (e.g., estrogens, protease inhibitor therapies, thiazide diuretics, and cardio-selective beta blockers), metabolic disorders (e.g., overweight/obesity, MetSyn/insulin resistance), and unhealthful dietary/lifestyle practices (e.g., high intakes of alcohol, added sugars, and refined starches, and physical inactivity)[9,24,43] (Table 2). Secondary causes of hypertriglyceridemia should be considered in its management and addressed to reduce the risk of both ASCVD and pancreatitis. When secondary causes and lifestyle have been addressed but TG levels remain ≥500 mg/dL, prescription omega-3 fatty acids and fibrates are effective treatments for lowering TG to reduce the risk of pancreatitis.[9,18,25,43,65]

Should lipids be checked pre-pregnancy to allow a woman to alter her lifestyle to improve her TG level? When should pharmacotherapy be considered?

Estrogen-induced high TG levels are likely a result of increased hepatic very-low-density-lipoprotein (VLDL) synthesis and decreased lipoprotein lipase (LPL) activity.[65] These estrogen effects can compound a genetic predisposition for lower LPL levels and result in drastic acute changes of TG levels in pregnancy, menopause, or in the setting of menopausal hormone therapy. Awareness of a woman's baseline lipids in early adulthood is recommended by dyslipidemia management guidelines, as well as earlier in women with a family history of a genetic lipid disorder.[23] It is also imperative to check lipid levels prior to pregnancy to keep both the mother and fetus safe especially considering the physiologic increase in all lipoproteins that occur during pregnancy.[66] Depending on the level of TG prior to pregnancy, dietary habits and physical activity may be adequate to reduce and control TG levels during pregnancy.

What is the treatment for acute severe elevations in TG during pregnancy?

In order to prevent pancreatitis caused by persistent chylomicronemia, when TG levels are ≥750 mg/dL the patient should receive counseling for a very-low-fat diet (≤5 % total daily energy intake), initially hypocaloric if appropriate, over 1-4 weeks or longer.[24] This is especially true if risk of imminent pancreatitis is high (TG ≥2000 mg/dL). Pharmacologically, prescription omega-3 fatty acids would be the first line in therapy (Fig. 4), with fibrates also being classified as safe after the first trimester.[31] If symptoms of pancreatitis occur or if further escalation of TG is evident, hospitalization with a supervised fasting state can quickly lower TG levels, with insulin-dextrose infusion and/or plasmapheresis used for more extreme cases.[31] TG-lowering therapies that can be used during pregnancy are summarized in Fig. 4. Nutrition interventions for elevated triglycerides are summarized in Table 2 and are provided in detail in the NLA Clinical Perspective, "Nutrition Interventions for Adults with Dyslipidemia."[24]

What is the risk of hypertriglyceridemic pancreatitis in pregnancy?

High TG levels in pregnancy do not pose an immediate ASCVD risk; however, high TG can contribute to the devel-

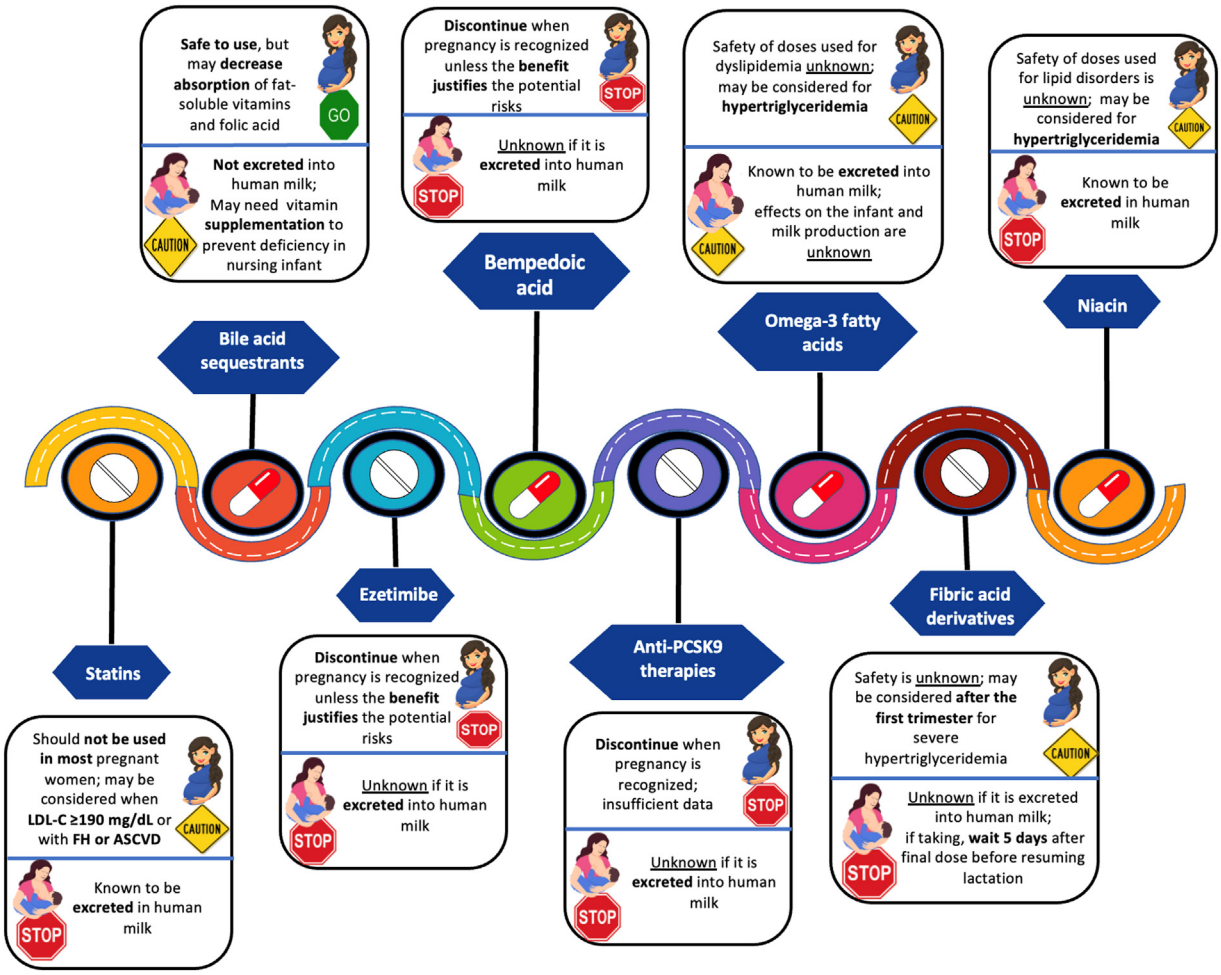

Fig. 4 Safety profile of lipid-lowering pharmacotherapies in pregnancy and lactation. Abbreviations: ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolemia; LDL-C = Low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9

opment of adverse pregnancy outcomes. Acute pancreatitis is the most serious consequence of high TG levels in pregnancy. Pancreatitis has been estimated to occur in approximately 1 in 3000 pregnancies. Up to 30 % of cases in large series are ascribed to hypertriglyceridemia, which leads to more severe pancreatitis than the more common pancreatitis due to gallstones or biliary disease. In fact, acute pancreatitis in pregnancy can be extremely dangerous to both mother and fetus with mortality rates for each noted to be as high as 3.3 % and 11.6 %, respectively.[67]

Pharmacologic therapies

What is the new classification system of pregnancy and lactation risk for medications?

In 2015, the FDA implemented the Pregnancy and Lactation Labeling Rule to modify the requirements for pregnancy and lactation labeling.[68] The most notable change was the removal of the pregnancy letter categories of A, B, C, D, and X, in favor of providing standardized information to better assist healthcare professionals in assessing the risk and benefit of medications in pregnant women and lactating mothers. Furthermore, it provides information to be used for patient counseling (subsections 8.1 *Pregnancy* and 8.2 *Lactation)*, and includes available information on pregnancy registries, a background statement of risk, fetal risk summary, clinical considerations, and any available human or animal data. A new subsection, 8.3 *Females and Males of Reproductive Potential,* was added to the labeling to provide guidance on the need for pregnancy testing, contraception recommendations, and infertility information as it relates to the medication.

It should be noted that, in July 2021, the FDA removed the strongest label warning regarding statins in pregnancy.[69] Although most women generally should stop statins prior to pregnancy, this label change allows more flexibility for treatment options in pregnant women, particularly those at highest ASCVD risk, as part of shared decision-making.

Which lipid-lowering medications are effective and safe during pregnancy and lactation, and what are the data that supports risk of teratogenicity?

Statins: Statin use is generally avoided in women attempting conception and during pregnancy. Available evidence

suggests that statins are likely not teratogenic; however, the data remain limited. For example, a recent systematic review of 16 studies found no clear relationship with statin use during pregnancy and congenital abnormalities.[70] Most of the studies involved statin exposure during the first trimester; however, the length of statin exposure could not be accurately determined. The authors did not make conclusions about possible differences in teratogenic effects between lipophilic versus hydrophilic statin exposure. The authors believed that the quality of the evidence was not conclusive to support that statins are safe in pregnancy, and they suggested that statins not be used during the first trimester when major teratogenic risk is highest.[70]

The results of two studies examining the effects of statin exposure in pregnant women with FH did not demonstrate an increased risk of teratogenic effects; however, these studies included small numbers of pregnant women exposed to statins.[71,72] Low-dose pravastatin (10–20 mg daily) does not appear to be teratogenic when given during the second trimester to women at risk for preeclampsia. There were no differences in the rates of congenital malformations, fetal death, or infant death in the treatment and the placebo groups in two small studies.[73,74] In fact, statins are being investigated for their potential for the prevention of preeclampsia as seen in animal models.[75] In a recent meta-analysis of 1,570 pregnant women who received pravastatin or placebo, pravastatin treatment reduced the incidence of preeclampsia by 61 % and premature birth by 45 %, along with a 45 % reduction in intrauterine growth retardation (IUGR) in the treated group and a 77 % reduction in the need for neonatal intensive care unit admissions.[76] Another multicenter randomized placebo controlled trial assigned 1,120 women with singleton pregnancies to pravastatin 20 mg daily vs. placebo.[77] The use of pravastatin did not reduce the incidence of delivery with pre-eclampsia. A larger randomized clinical trial is on-going (NCT03944512) to evaluate whether pravastatin given at 12-17 weeks gestation can reduce preeclampsia in women at high risk for that outcome. This trial will be informative in providing additional insight regarding the safety of statin therapy during pregnancy, as well as its potential benefits in the pregnant population.

Since the removal of the contraindication for using statins during pregnancy in July 2021 by the FDA,[78] statins may now be considered in selected high-risk women, such as those with a history of ASCVD, homozygous FH (HoFH), or severe heterozygous FH. The FDA encourages using patient-clinician shared decision-making, which includes a discussion of the benefits and potential risks of continuing statin therapy during pregnancy in those selected high-risk women. Breastfeeding while taking statin therapy is not recommended for most women because statins may be present in human milk in small amounts.[79]

Bile acid sequestrants (BAS): BAS (colestipol, colesevelam, and cholestyramine) are not absorbed systemically, thus making them a safer option for lowering LDL-C levels during pregnancy and lactation.[80] However, BAS can bind with fat-soluble vitamins (A,D,E, and K) and folic acid, which are important for fetal and maternal health, and other medications that may be important for fetal and maternal health (e.g., levothyroxine).[81] The potential to impair fat-soluble vitamin and folic acid absorption may also adversely affect milk production in the lactating mother; however, the lack of systemic absorption limits the potential for BAS to impair vitamin absorption in the infant. BAS may also increase TG levels, which could be problematic as TG levels rise during pregnancy and peak during the third trimester. The rise in TG level can be significantly greater when the fasting TG level is $\geq$300 mg/dL and in the presence of GDM.[82] Overall, colesevelam appears to be better tolerated than cholestyramine and colestipol.

Anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) therapies: The PCSK9 monoclonal antibodies (mAbs), alirocumab and evolocumab, as well as the small interfering RNA drug targeting PCSK9 (inclisiran), have not been evaluated for safety during pregnancy and, therefore, are contraindicated at this time. However, data from animal studies suggest PCSK9 may play a role in neural tube development.[83] Therefore, therapies targeting PCSK9 during pregnancy could increase the risk of neural tube defects; however, this finding has not been further substantiated. In general, mAbs are known to minimally cross the placenta during the first trimester but do cross the placenta in increasing amounts in the second and third trimesters. Given their longer half-life and ability of mAbs to cross the placenta, it is recommended to stop PCSK9-mAb 3 months before conception. There is no specific information regarding the use of PCSK9-mAbs during lactation; however, while human immunoglobulin G (IgG) is present in human milk, it is believed that minimal human milk IgG antibodies enter neonatal and infant circulation. As such, it is advisable to avoid PCSK9-mAbs during lactation.[84,85]

Bempedoic acid: There are currently no available data on the use of bempedoic acid in pregnant women; however, teratogenic effects have not been observed in animal studies.[86] It is recommended to discontinue bempedoic acid 1-2 months prior to conception or when pregnancy is recognized given the lack of available human data unless the benefits to the mother outweigh the risks to the fetus. It is unknown if bempedoic acid is found in human milk, therefore, its use is not recommended in lactating mothers.[86]

Omega-3 fatty acids: The safety of using prescription-only omega-3 fatty acids in pregnant women to treat lipid disorders remains unclear; however, case reports suggest this can be a safe and effective strategy to manage severely elevated TG levels.[87] The available results from animal studies are mixed and there have been no human studies. Omega-3 fatty acids are detected in human milk; however, there are no data on the effects of supplementation on the infant. Given the effects of omega-3 fatty acids on infants is currently unknown, omega-3 fatty acids should be used with caution during lactation.

Fibric acid derivatives: The fibric acid derivatives, gemfibrozil and fenofibrate, are indicated for use in patients with severely elevated TG levels. While there are limited human

data regarding the safety of fibric acid derivatives in pregnant women, including development of gallstones during pregnancy, several case reports have reported no adverse effects on the fetus.[9,18,25,43,88] Fenofibrate is present in rat milk and is presumed to be likely present in human milk; therefore, lactating women should not breastfeed during treatment with fenofibrate. In a lactating woman taking fenofibrate, it is recommended to wait five days after the final dose before resuming breastfeeding.[88–91]

Nicotinic acid (niacin): There is a lack of both animal and human studies that examined the use of niacin in pregnancy; however, there is evidence to suggest niacin supplementation may reduce the risk of congenital malformations in mice.[92] Of course, this evidence has not been translated to humans, and pregnant women should not take niacin by supplement or prescription. Niacin is excreted into human milk; however, the amount of exposure to the infant is unknown. Therefore, lactating women should avoid niacin use while lactating. Given the lack of CVD benefit and potential increased risk, niacin is no longer used as a treatment for lipid management for ASCVD prevention.[9,18,28]

Apheresis*:* Lipoprotein apheresis is also approved during pregnancy and considered safe for very high-risk women with known significant ASCVD or HoFH. Apheresis is effective not only in lowering LDL-C levels but also removes Lp(a) and downregulates adhesion molecules and inflammatory cytokines.[93,94] It is performed once every one to two weeks. Different methods of apheresis exist, such as immunoadsorption, dextran sulfate adsorption, and double plasma filtration, which are all effective and depend on institutional preference.[95]

With the increasing complexity of lipid management during pregnancy, referral to a lipid specialist may be considered to assist with assessment and management of women with dyslipidemia.

What counseling should be provided to a woman who is considered for treatment with lipid-lowering therapies and is not planning a pregnancy?

In women with dyslipidemia who are considered for primary prevention of ASCVD, counseling should occur in the context of a clinician–patient risk discussion. This risk discussion should include:

- Estimation of 10-year risk for ASCVD using the Pooled Cohort Equations or the 10- and 30- year risk of CVD (ASCVD and heart failure) using the PREVENT score[96];
- Presence of risk-enhancing factors with special attention to female-specific factors, e.g., pregnancy-associated complications and premature menopause, as well as female-predominant conditions, such as autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus);
- Assessment of atherosclerotic burden via coronary artery calcium scoring if risk is uncertain or if more refined risk stratification is desired;
- Potential benefits of lifestyle and statin therapies (or other lipid-lowering therapies as needed);
- Potential adverse effects of drug therapies and drug-drug interactions;
- Clarifying any misconceptions or concerns the patient may have;
- Cost considerations; and
- Patient preferences and values.[9]

Although the 2018 AHA/ACC/Multisociety Blood Cholesterol Guideline recommends considering statin therapy at a 10-yr risk of ≥7.5 %,[9] taking a statin is not an absolute recommendation. However, if a woman has a diagnosis of severe primary hyperlipidemia (LDL-C ≥ 190 mg/dL), diabetes, or clinical ASCVD, statin therapy is strongly recommended (class I recommendation).[9] The presence of a risk-enhancing condition would also favor the initiation of statin therapy among those at borderline or intermediate risk. A coronary artery calcium score can be performed if risk is uncertain to refine risk estimation and guide shared decision-making. These recommendations were applied to individuals aged 40–75 yr of age. For women who require a statin, in addition to the clinician-patient discussion points listed above, women should be educated on what to do if they believe they are having a statin-related adverse effect, as well as the use of effective and safe methods of birth control. However, if a woman finds that she becomes pregnant, most women should stop statin therapy during pregnancy unless the benefits clearly outweigh the risks.[22]

What counseling should be provided to a woman who is considering pregnancy (or is currently pregnant) and is treated with lipid-lowering therapies?

Women with ASCVD or at high risk for ASCVD should receive counseling on the potential maternal and fetal risks of lipid-lowering therapies before conceiving.[22] A woman who takes lipid-lowering therapies should be counseled to discuss plans for pregnancy with her clinician two to three months before attempting pregnancy, so that changes can be made to the drug therapy regimen, if necessary. Important aspects for counseling related to specific lipid-lowering agents are summarized in Fig. 4**.** Counseling for specific drug classes and apheresis is described below.

Statins

- Women at high ASCVD risk, such as those with HoFH, severe heterozygous FH, or with prior CV events, along with their clinicians, should make individual decisions about benefits and risks of statin use during pregnancy. If the statin is initially discontinued, a

woman may consider using pravastatin after the first trimester when organogenesis is completed.
- Women not at high risk for ASCVD who take a statin should stop the statin one to two months prior to attempting pregnancy or immediately when pregnancy is first discovered.
- Women should avoid breastfeeding while taking a statin. If a woman prefers to breastfeed, the statin should be stopped until breastfeeding ends.69
- Limiting the duration of breast-feeding should also be discussed, so that lipid-lowering drug therapies can be re-instituted.97

Ezetimibe, PCSK9 mAbs, inclisiran, bempedoic acid, niacin, fibrates, and prescription high-dose omega-3 fatty acids

- There are no data to support the safety of these agents in pregnant and lactating women.[98]
- Clinicians should carefully evaluate benefit versus risk or avoid these agents entirely.

Bile acid sequestrants

- BAS are safe to take during pregnancy and lactation.
- Women should be informed of side effects and receive education on ways to prevent constipation and other gastrointestinal side effects.
- Because BAS may reduce the absorption of fat-soluble vitamins, folic acid, and other medications, women should take vitamins and other medications (e.g., levothyroxine) at least two hours before or four to six hours after taking BAS.
- As BAS can increase TG levels, these agents should not be used in women with hypertriglyceridemia. Rather, women with hypertriglyceridemia should be counseled on lifestyle interventions (dietary changes, exercise) to reduce elevated TG levels.

Apheresis

- Lipoprotein apheresis may be used for pregnant and lactating women with HoFH with or without ASCVD.
- Counseling should include the expensive, time-consuming, and invasive nature of lipoprotein apheresis.

What birth control methods are recommended for women of child-bearing age with dyslipidemia?

For women with FH or hypertriglyceridemia, oral contraceptives, transdermal patches, intra-uterine devices, and barrier methods may be used as contraceptive methods. Due to increased risk of thrombosis, estrogen-containing contraceptives should be avoided in women who use tobacco, especially those older than 35 yr of age. Estrogen-based therapies should also be avoided in women with severe hypertriglyceridemia. In women with established CVD or at high risk of CVD, long-acting reversible contraception, such as intrauterine devices and subdermal implants are preferred given their safety and efficacy.[99]

The impact of estrogen-progestin combinations on lipoprotein and lipid levels varies. Estrogen decreases LDL-C levels and increases TG levels in a dose-related response; however, estradiol valerate and the low doses of ethinyl estradiol ($\leq$35 mcg) used in currently available oral contraceptives impact lipid levels less than previously available oral contraceptives.[100] The androgenic progestins, levonorgestrel and norgestrel, may increase LDL-C and TG levels.[101] Although the results of several studies that evaluated the impact of estrogen-progestin containing contraceptives on lipoprotein and lipid parameters demonstrated non-significant changes in LDL-C and TG levels or on-treatment values within normal range, the clinician should keep in mind that these studies were of short duration and included women without a history of very high LDL-C levels or hypertriglyceridemia.[101,102] Therefore, clinicians should evaluate lipoprotein and lipid values before and periodically after initiating oral or transdermal contraception, especially in women with a history of very high LDL-C levels or hypertriglyceridemia.

FH during the reproductive years

What is the risk to women with FH during pregnancy and to the child of a mother with FH?

FH is an often underdiagnosed genetic condition characterized by lifelong severe hypercholesterolemia and a greatly increased ASCVD risk. Heterozygous FH is present in nearly 1 in 250 individuals with an increased prevalence in some ethnic groups. Patients with an FH phenotype typically have an LDL-C level >190 mg/dL, although many will have lower levels, especially in young adulthood, and a 10-20-fold higher risk of ASCVD.[103,104] If left untreated, 30 % of women with FH will have a myocardial infarction before age 60.[105] It should be noted that there is no "female-advantage" in the setting of FH, and women with FH who are sub-optimally treated have the same early onset of ASCVD as their male counterparts.[103,104,106–108] HoFH is uncommon with a prevalence of 1:250,000- 360,000. Individuals with HoFH often have LDL-C levels $\geq$400 mg/dL and develop ASCVD as early as childhood.[109]

Management of FH during reproductive years poses unique challenges that require consideration. Plasma cholesterol levels consistently rise by 25–50 % with pregnancy. This corresponds to a higher absolute rise in plasma lipoprotein and lipid levels in patients with FH.[110,111] It is hypothesized that hypercholesterolemia may promote atherosclerosis of the uteroplacental arteries eventually leading to placental infarctions and oxidative stress to the mother's vascular endothelium, predisposing her to preeclampsia.[112,113] Ma-

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ternal hypercholesterolemia also predisposes the newborn to develop atherosclerosis.[114] Women with HoFH are at a particularly increased risk of ASCVD events during pregnancy. Case reports describe rapid worsening of CVD and acute coronary syndrome events in patients with HoFH.[97]

What is the best way to control lipids in a non-pregnant woman with FH during her reproductive years?

Women with FH who are of childbearing age should receive individualized pre-pregnancy counseling and contraceptive advice (see sections above). It should be noted that estrogen-containing contraceptives are contraindicated in patients with HoFH and/or ASCVD due to thrombotic risk. Recent data show that women with FH can have an off-statin period of up to 14 yr during their childbearing years, which increases their risk of developing ASCVD. It is important to minimize time off statin therapy to reduce morbidity in these high-risk women.[115] For women with FH planning pregnancy, management with an interdisciplinary team with expertise in FH (i.e., lipid specialists) should be considered. Patients with FH should be encouraged to adopt a healthful dietary pattern, including a reduced intake of foods high in saturated fatty acids and dietary cholesterol before, during, and after pregnancy (see sections above and Table 1). Similarly, the aim should be to achieve adequate control of LDL-C levels with guideline-recommended pharmacotherapy before pregnancy. Given that inclisiran is almost entirely cleared from the circulation within 24 h, but the lipoprotein lowering effect may last ~6 mon, this may provide a unique opportunity in this setting with dosing spaced immediately before and right after pregnancy. However, data on the benefits and risks of inclisiran use during pregnancy are needed. Lipoprotein apheresis is the most effective LDL-C-lowering therapy in pregnancy. It can reduce LDL-C levels by 25–30 % and reduces ASCVD risk.[116,117] Authors of case reports describe the use of lipoprotein apheresis safely during pregnancy in patients with HoFH.[97,118]

Women at high risk for ASCVD during the reproductive years

What constitutes high ASCVD risk in young women during the reproductive years?

ASCVD is driven by CV risk factors. Standard risk factors, such as age, sex, race, apoB-containing lipoprotein levels, blood pressure, diabetes, and smoking status, are well documented.[8] Emerging metrics, including elevated Lp(a), and inflammatory makers, such as high sensitivity C-reactive protein, are also likely markers of risk.[119] For most individuals, advancing age is the most important driver of ASCVD risk; however, for some young individuals, the presence of a single severe risk factor leads to high CV risk that must be addressed. The most common single severe risk factor that drives ASCVD risk in young patients is heterozygous FH.

How to treat dyslipidemia in a pregnant patient with a history of clinical ASCVD?

In patients with a history of clinical ASCVD, dyslipidemia must be treated aggressively in order to prevent recurrent events and adverse pregnancy outcomes. Given our recent understanding of the relative safety of certain lipid-lowering agents during pregnancy, the risk-benefit assessment will favor continuing lipid-lowering therapy during pregnancy in many patients with ASCVD (Fig. 4).[22]

Prevention of ASCVD in high-risk patients requires lifelong vigilance, including during vulnerable time periods, such as the reproductive years. Defining strategies that protect the health of the mother and fetus is imperative and further research is necessary to define optimal strategies.

Elevated Lipoprotein(a) during the reproductive years

What are special considerations during pregnancy in patients with elevated Lp(a)?

An elevated Lp(a) level is considered an independent and causal risk factor for ASCVD.[120] An elevated level (≥50 mg/dL or 125 nmol/L) often warrants intensifying the management of other ASCVD risk factors.[24] Limited data exist on the role of elevated Lp(a) during pregnancy; however, it is thought that elevated Lp(a) may be associated with an increased risk of adverse pregnancy outcomes, such as preeclampsia.[121–124] Lp(a) levels are thought to increase during the second and third trimester of pregnancy and fall to pre-pregnancy levels within six months post-delivery.[125,126] There are currently no approved pharmacologic interventions for Lp(a) reduction and dietary interventions minimally alter Lp(a) levels.[24] Although recommendations for elevated Lp(a) levels in non-pregnant women include intensifying lipid-lowering therapies to reduce vascular risk, in pregnant women, existing recommendations emphasize stopping lipid-lowering therapy approximately two months before anticipated conception, withholding it throughout pregnancy and lactation, and restarting it as indicated after cessation of lactation. As discussed previously, in most pregnancies, the focus should remain on optimizing lifestyle habits, and pharmacologic therapy should be considered in individuals who are at a substantially increased risk.

Women with pre-eclampsia and recurrent pregnancy loss have been shown to have increased Lp(a) levels; however, no causal associations have been identified.[121,127,128] Presently, there is no clear role of Lp(a) in normal or complicated pregnancies and there are not sufficient data to support the routine use of aspirin during pregnancy in women with elevated Lp(a) in the absence of other risk factors, although aspirin

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is used in pregnancy for women at high risk for preeclampsia.[129]

What are the fetal risks with elevated Lp(a)?

Currently, there are no known risks to the fetus in women with elevated Lp(a). Limited data on the association of elevated Lp(a) levels with IUGR have shown no difference in Lp(a) levels in women who experienced IUGR versus those who did not.[130]

Long term Dyslipidemia management during the reproductive years

What does the fourth trimester of pregnancy imply for ASCVD risk factor reduction in women with dyslipidemia?

After childbirth, most women in the U.S. are not scheduled for follow-up care until six weeks, and this visit is poorly attended.[131] Many new mothers feel unprepared for the common health issues they encounter and are uncertain of whom to contact. To improve care, the fourth trimester concept was coined[131,132] and refers to the 12 weeks after delivery as the key time to address contraception, mental health, CV risk factors, and identify potential postpartum complications. Key issues that need to be addressed include: 1) the intense focus on women's health prenatally is unbalanced by infrequent and late postpartum care; 2) medical practice guidelines often do not align with women's experiences and constraints; 3) validation of women as experts on their infants and elevating their strengths as mothers is necessary to achieve health goals; and 4) mothers need comprehensive care, which is difficult to provide because of numerous system constraints.[131] Maternal health issues in the fourth trimester intersect and can compound. Enhanced collaboration among healthcare professionals may improve the focus of clinical interactions to address interrelated health issues most important to women. The field of cardio-obstetrics has emerged in response to the rising rates of maternal morbidity and mortality related to CVD during pregnancy.[133]

What is appropriate long-term management and coordination of care for women with dyslipidemia?

Women of childbearing age with or at risk for ASCVD should receive appropriate counseling regarding maternal and fetal risks of pregnancy, medical optimization, and contraception advice. A multidisciplinary cardio-obstetrics team should ensure appropriate monitoring during pregnancy, a plan for labor and delivery, and ensure close follow-up during the postpartum period when CVD complications remain common. The hemodynamic changes throughout pregnancy and during labor and delivery should be considered in managing specific types of CVD. Women with adverse pregnancy outcomes are at increased risk of long-term CVD and should receive appropriate education and longitudinal follow-up.[132,134] Differing models for primary and specialty follow-up are proposed to assure proper primary and secondary prevention of CVD.[135–147] Given the burden and impact of CVD on women in our society, the entire medical community must work to establish feasible practice and referral patterns for assessment and treatment of CVD risk factors.[134,148]

Conclusions

In summary, all women of reproductive potential should have a baseline lipid panel as part of ASCVD risk screening, as pre-pregnancy dyslipidemia and an adverse cardiometabolic risk profile are associated with adverse pregnancy outcomes. Pregnancy involves timely counseling around dyslipidemia management. A patient-clinician discussion and shared decision-making are essential for determining appropriate lifestyle interventions and pharmacotherapy for women with dyslipidemia. Delays in treatments in women of reproductive potential affect their long-term ASCVD risk. It is imperative to minimize time off treatment for women at high ASCVD risk, such as those with FH.

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There was no funding for this project.

Conflicts of interest

During the past 24 months, **Dave L. Dixon** received research funding from Boehringer Ingelheim as a principal investigator; **Erin D. Michos** received honoraria as a consultant/advisor from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifescience, Esperion, Medtronic, Merck, Novartis, Novo Nordisk, NewAmsterdam Pharma, and Pfizer; **Karol Watson** received honoraria as a consultant/advisor/speaker from Amarin, Amgen, Boehringer Ingelheim, Eli Lilly, and Esperion; and **Robert Wild** maintained a research contract for lipid measurement with Boston Heart and Quest Diagnostics.

Anandita Agarwala, Kim K. Birtcher, Lynne T. Braun, Eugenia Gianos, Carol F. Kirkpatrick, Laxmi S. Mehta, Priyamvada Pillai, and Priyanka Satish have nothing to disclose.

CRediT authorship contribution statement

Anandita Agarwala: Writing – original draft, Writing – review & editing. **Dave L. Dixon:** Writing – original draft. **Eugenia Gianos:** Writing – original draft. **Carol F. Kirkpatrick:** Writing – original draft. **Erin D. Michos:** Writing – original draft. **Priyanka Satish:** Writing – original draft. **Kim K. Birtcher:** Writing – original draft. **Lynne T. Braun:**

Writing – original draft. **Priyamvada Pillai:** Writing – original draft. **Karol Watson:** Writing – original draft. **Robert Wild:** Writing – original draft. **Laxmi S. Mehta:** Writing – original draft.

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