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Reproductive Health and Cardiovascular Disease (G Sharma, Section Editor)

Management Considerations for Lipid Disorders During Pregnancy

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Abstract

Purpose of review Dyslipidemias including familial hypercholesterolemia and elevated lipoprotein (a) are not uncommon in young women who may desire pregnancy. In all women, abnormal lipid metabolism has been linked to adverse outcomes during pregnancy, including hypertensive disease of pregnancy, gestational diabetes mellitus, and preterm birth. Optimal management of dyslipidemias in pregnant women remains undefined, as statins are contraindicated in this group.
Recent findings Recent literature questions this traditional avoidance of statins, however, as well as explores their potential benefit in pre-eclampsia specifically.
Summary In this review, the arsenal of nutrition, bile acid resins, omega-3 fatty acids, and low-density lipoprotein cholesterol apheresis is explored, as are newer therapies like mipomersen and proprotein convertase subtilisin/kexin type 9 inhibitors, for the management of dyslipidemias during pregnancy.

Introduction

Cardiovascular disease (CVD) remains the leading cause of death for women in the USA [1]. Women as compared to men carry unique risk beyond traditional CVD risk factors, stemming from conditions such as

early menarche, hypertensive disease of pregnancy (HDOP), systemic lupus erythematosus, and depression [2]. Both traditional and sex-specific CVD risk factors need attention, especially during the reproductive years, to improve outcomes for women. Abnormal lipids are particularly problematic for women: one epidemiologic study showed that dyslipidemia (assessed by apolipoprotein B to A1 ratio) was found to explain 47% of the population attributable risk of myocardial infarction in women [3]. Clinicians undertreat dyslipidemias generally, and managing dyslipidemias in patients who are pregnant or planning to become pregnant becomes even more paramount as abnormalities here have been associated with increased maternal and fetal morbidity [4–9]. Recent data shows there is a gap with respect to both screening for dyslipidemias and knowledge of dyslipidemia as a CVD risk factor in pregnant women, especially non-Hispanic Black pregnant women [10]. In this review, we discuss the best clinical management of dyslipidemias, including familial hypercholesterolemia (FH) and elevated lipoprotein (a) [Lp(a)], during pregnancy.

Dyslipidemias and adverse pregnancy outcomes

Cardiologists, obstetricians, and primary care providers must understand the importance of recognizing and treating dyslipidemias in pregnant women, from preconception counseling through post-pregnancy follow-up (Fig. 1). In normal pregnancy, maternal lipids rise to play essential roles in fetal growth and development [11]. Total plasma cholesterol and low-density lipoprotein cholesterol (LDL-C) levels increase by about 50%, while high-density lipoprotein cholesterol (HDL-C) levels increase by about 30% [12, 13]. Triglyceride (TG) levels can increase up to fourfold [13]. Immediately after delivery, these elevations begin to resolve, though it can take up to 6 weeks for LDL-C levels to return to baseline [12]. For this reason, the American College of Obstetrics and Gynecology actually recommends against checking screening lipids during pregnancy, though testing at 6 weeks postpartum is acceptable for a woman who has never been screened [14].

Pregnancy in the context of underlying dyslipidemias has been associated with poor outcomes. Dyslipidemias in the first trimester confer significant risk for HDOP: one study found that elevated total cholesterol (> 231.7 mg/dL) was associated with pre-eclampsia, while another linked elevated LDL-C levels with pregnancy-induced hypertension and gestational DM [8, 15]. A large meta-analysis showed elevated total cholesterol, non-HDL-C, and TG levels throughout pregnancy in women who ultimately developed pre-eclampsia as compared to women with normal blood pressures [5]. Both FH and elevated Lp(a) levels may increase risk for

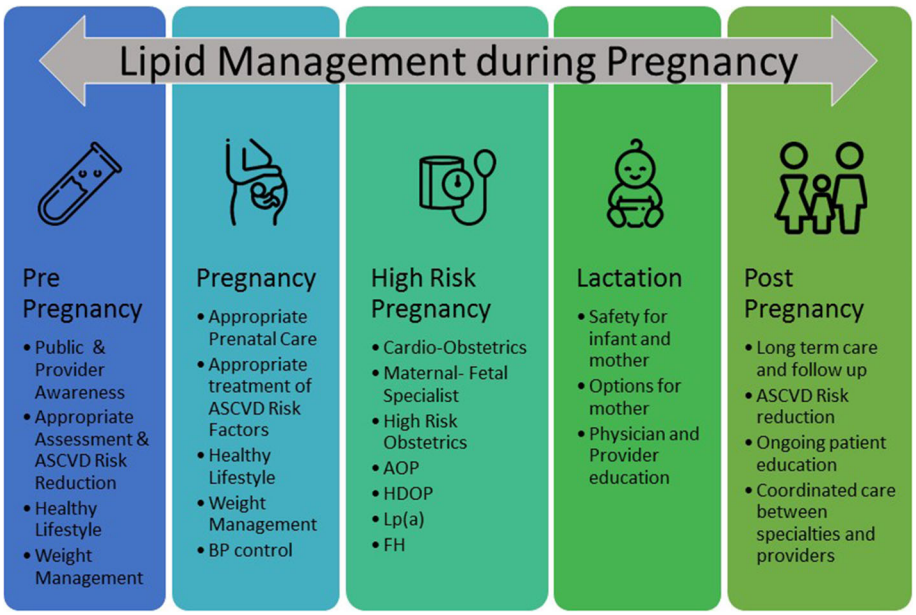

Fig. 1. Management of dyslipidemias in pregnant women from preconception counseling through post-pregnancy follow-up.

pre-eclampsia as well, though the data are less consistent for the latter [16, 17].

A study of about 4000 women from the Amsterdam Born Children and their Development (ABCD) cohort showed that elevated maternal TG levels early in pregnancy were associated with HDOP, specifically pregnancy-induced hypertension and pre-eclampsia, as well as preterm birth and large for gestational age infants [6]. Elevated TG levels have been associated with the presence of gestational DM as well [18]. The multicenter, observational, longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) study analyzed prepregnancy cardiometabolic risk profiles and found that low levels of HDL-C in women without a family history of DM, in addition to abnormal fasting glucose and insulin levels, was associated with the development of gestational DM [7].

With respect to other adverse pregnancy outcomes, a meta-analysis of over 13,000 pregnant women showed that dyslipidemias are generally associated with preterm births, with a pooled odds ratio of 1.68 [9]. Broken down, the odds ratio for preterm births for women with increased total cholesterol was 1.71, with increased TG was 1.55, and with low HDL-C was 1.33 [9]. Finally, it is worth noting that maternal dyslipidemias may have effects that persist beyond birth, as one study found that women with elevated LDL-C levels early in pregnancy have children whose LDL-C levels are elevated as well when measured between 6 and 13 years of age [19].

There are several proposed pathophysiologic mechanisms to explain these adverse maternal and fetal outcomes seen in gestating women with dyslipidemias. In women with abnormal lipid metabolism, oxidative stress and impaired defense may lead to damaged vascular endothelium and, ultimately, pre-eclampsia [16]. The high circulating levels of fibrinogen in pregnant women can increase blood viscosity and adversely affect circulation to maternal organs [16]. For the fetus, dyslipidemias are associated with atherosclerosis, vascular resistance, and endothelial dysfunction, potentially compromising placental blood flow and resulting in intrauterine growth restriction [16, 20]. Atherosclerosis and hypercoagulability can lead to spiral artery thrombosis and placental insufficiency and placental infarction [21•]. Additionally, slow flow due to viscosity in umbilical vessels can increase the risk of stunted fetal development [16].

Specific high-risk dyslipidemias in pregnancy

Familial hypercholesterolemia

Familial hypercholesterolemia is one of the most common congenital lipid disorders, with a prevalence of about 1 in 500 for the heterozygous variant [22]. It is known to be associated with earlier onset and more extensive coronary artery disease [23]. Several different genetic mutations are known to cause FH; all affect LDL-C metabolism, most commonly at the level of the LDL-C receptor [24]. The National Lipid Association Expert Panel on Familial Hypercholesterolemia recommends screening adults with an LDL-C level greater than or equal to 190 mg/dL and children with an LDL-C level greater than or equal to 160 mg/dL for FH [22].

Women with both heterozygous and homozygous FH do have successful pregnancies [21, 25, 26]. Women with heterozygous FH, compared to women with normal lipid metabolism, show similar relative increases in their LDL-C and TG levels during pregnancy, though the absolute magnitude of these lipoprotein levels is higher [26]. Women with heterozygous FH also show significantly higher apolipoprotein B levels in pregnancy [26]. Another study demonstrated that women with heterozygous FH show "larger net procoagulant activity" as compared to a reference group of women without FH, thereby potentially increasing their risk of cardiovascular disease even more [27]. In FH, increased

levels of hemostatic and inflammatory factors may cross the placental barrier, potentially raising the risk of thrombosis for the fetus [20]. Interestingly, a registry study of over 1000 women with heterozygous FH in Norway revealed no increased risk of premature birth, low birth weight, nor congenital abnormalities with this disease [21•]. These authors did find that HDOP, specifically pregnancy-induced hypertension, was associated with all three of these adverse outcomes and that age was associated with premature birth, too [21•].

For women with FH who are planning to become pregnant, expert recommendations include preconception counseling and cessation of potentially teratogenic lipid agents, including statins, ezetimibe, and niacin, 4 weeks before conception, or as soon as pregnancy status is realized in cases of unintended pregnancies [22]. Optimal management during pregnancy remains unclear. The one therapeutic class of medications that can be safely continued throughout pregnancy, bile acid resins, do not appear to adequately treat LDL-C levels in women with FH [28]. Some newer studies in which women have taken pravastatin during pregnancy show interesting results, suggesting a reduction in pre-eclampsia with no increased risk of major congenital abnormalities [29, 30•].

Elevated lipoprotein (a)

Lipoprotein (a) is a genetic abnormality defined as an LDL-C particle with an attached apolipoprotein (a) [31]. Elevated levels have been shown to be associated with premature coronary artery disease [32]. Proposed mechanisms of action reference its pro-thrombotic, pro-inflammatory, and pro-atherogenic properties [33]. Women appear to be at increased risk for having elevated (≥ 50 mg/dL) Lp(a) levels as compared to men [34]. With respect to Lp(a) and pregnancy, levels rise during pregnancy, peaking at 35 weeks gestation and falling after delivery [35]. Possible physiologic explanations for this observation include Lp(a) serving as an "acute-phase protein" in response to lipid changes and their associated endothelial dysfunction, and/or that Lp(a) aids in producing steroid hormones, during pregnancy [17]. Intrauterine growth restriction and spontaneous abortion have been linked to elevated Lp(a) levels as well, albeit inconsistently [17]. Ultimately, data on Lp(a) levels and pregnancy outcomes are limited, and the relationship between Lp(a) and pre-eclampsia specifically remains unanswered [17].

Lipid treatment considerations in pregnancy

Reassuringly, there are many opportunities to intervene in the management of dyslipidemias during pregnancy (Fig. 2). Statins, the traditional mainstay for treating dyslipidemias, are contraindicated in women who are pregnant and/or lactating, according to the *Journal of the American College of Cardiology* [36]. The American College of Obstetrics and Gynecology also recommends against taking a statin during pregnancy [14]. Other pharmacologic options including ezetimibe, fibrates, and niacin are generally avoided based on adverse outcomes in animal studies [16].

Fig. 2. Treatment considerations for dyslipidemias in pregnancy.

Accordingly, management of dyslipidemias during pregnancy is composed primarily of nutrition, bile acid resins, and omega-3 fatty acids. Recent data questions this avoidance of statins during pregnancy as well as queries their potential benefit in the management of pre-eclampsia [29, 30•]. Finally, we explore the use of plasma apheresis as a treatment modality for extremely high levels of LDL-C, such as in women with homozygous FH, and briefly touch on emerging therapies which may be applicable to this patient population [16, 37].

Healthy diet and lifestyle

A healthy diet and lifestyle remain a core part of preventing and managing dyslipidemias in all children and adults [38]. Key dietary studies reveal:

- A randomized, controlled trial of a low-cholesterol, low-saturated fat diet during pregnancy showed improved maternal total cholesterol and LDL-C levels as well as fewer preterm births [39].
- One case report showed that a low-fat diet, in addition to omega-3 fatty acids and glycemic control, led to an "uneventful pregnancy" in a woman with hypertriglyceridemia [40].

- In pregnant women with heterozygous FH, a cholesterol-free diet lowered LDL-C levels by 33%, while a low-cholesterol diet lowered LDL-C levels by 14% [41].

Pharmacologic treatments in pregnancy

Bile acid resins

Colesevelam, colestipol, and cholestyramine are bile acid sequestrants commonly used to treat hypercholesterolemia. They work by limiting the absorption of cholesterol from the gut and can reduce LDL-C levels between 10 and 60% [42]. They are safe to administer during pregnancy because of their low systemic absorption. Common side effects from bile acid resins include constipation, stomach pain, and bloating [42]. Unfortunately, many pregnant women already suffer from constipation, thereby limiting the utility of this class of drugs in this population. Another potentially serious side effect is decreased absorption of fat-soluble vitamins, which could adversely affect fetal development [36]. Bile acid resins should not be used in patients with elevated TG levels [42].

Omega-3 fatty acids

Omega-3 fatty acids are another mainstay of treatment for dyslipidemias. They can be useful in the treatment of severely elevated TG levels, as levels over 1000 mg/dL carry a significant risk of pancreatitis [16]. Patients with familial hypertriglyceridemia as well as Frederickson class I and V dyslipidemias are most at risk, and the goal with treatment is to reduce TG levels to below 885 mg/dL in these patients [16]. Omega-3 fatty acids are safe in pregnant women and have actually been shown, in direct comparison to n-6 polyunsaturated fatty acids, to result in improved maternal lipid profiles [43]. Even in pregnant women without dyslipidemias, omega-3 fatty acids are recommended through dietary intake or supplementation as they aid in fetal brain and eye development [44].

Statins in pregnancy

As previously noted, statins are currently contraindicated during pregnancy and lactation. In fact, an American Heart Association Scientific Statement on abnormal lipids in adolescents cautions on the need for abstinence or contraception for people taking a statin [45]. Some older data implicates teratogenic effects, including congenital central nervous system abnormalities and limb deficiencies, with statin use, especially early in pregnancy; however, published case series are inconsistent regarding this association [46–48]. As one group of authors point out, there may be confounding effects from concurrent obesity and DM, which are often associated with statin use, in these cases [47]. Indeed, a cohort study of more than a thousand women showed that the higher prevalence of congenital malformations noted in children born to women who took statins during their first trimester of pregnancy was accounted for by controlling for confounders including DM [49•]. Interestingly, lipophilic statins like simvastatin and atorvastatin seem to be more problematic than hydrophilic statins like pravastatin [46, 48].

A recent systematic review did not show any relationship between statin use during pregnancy and congenital abnormalities [50]. More recent observational data suggests there is a risk of premature birth, but not birth defects, with statin use [36]. The previously mentioned registry study of women with heterozygous FH did not show any apparent increased risk of adverse outcomes with statin use, though interpretation is limited by the small number of women [16] who were taking a statin [21•]. Similarly, in a smaller study of women with homozygous FH, of whom 18 were on statins at some point during their pregnancy and/or immediately after delivery, there was not a clearly increased risk of miscarriage, low birth weight, nor congenital birth defects in that group [25]. There was an observed but statistically insignificant increase in elective c-sections in women who had received a statin [25]. These authors recommend stopping a statin 1 month prior to conception and restarting it in the second trimester for women with homozygous FH [25]. Extrapolation of both of these latter findings to larger audiences is limited by the small number of women studied as well as the observational modality.

Statins to reduce pre-eclampsia

There may be a role for statins in the prevention of pre-eclampsia given their anti-inflammatory, anti-thrombotic pleiotropic effects [29, 51]. Pravastatin in particular demonstrates hepatoselectivity with a short half-life and limited placental transfer, making it an ideal drug for exploration [52]. Basic science studies show that pravastatin decreases biomarkers associated with endothelial dysfunction and improves nitric oxide synthesis [53, 54]. A pilot study in humans showed that pravastatin is safe to administer, with an observed decrease in the incidence of pre-eclampsia among a group of women at high risk for the disease [30•]. In women with early onset pre-eclampsia, though, pravastatin was not shown to improve biomarkers, raising the question of ideal timing [55]. Ultimately, while early data is promising, larger trials are needed to confidently integrate this therapy into regular prenatal care [52].

Interventional procedures: LDL-C apheresis in pregnancy

LDL-C apheresis has been shown to be a safe, effective treatment option for pregnant women with dyslipidemias [16, 37]. Specifically for pregnant women with FH, the National Lipid Association cites LDL-C apheresis as an option for homozygous FH or for "significant atherosclerotic disease" [22]. Recent data show that apheresis continues to be employed in women with homozygous FH [56–58]. Although not specifically studied in pregnant women, there is also some support for the use of LDL-C apheresis in patients with heterozygous FH already on medical/dietary therapy with LDL-C levels above 300 mg/dL (or 200 mg/dL and known coronary disease) [59].

This invasive treatment option can also be used to treat patients with elevated TG and elevated Lp(a) levels, though this latter data is limited, based mostly on cases [16]. Therapeutic apheresis has a clear role in pregnant patients who are at risk for pancreatitis [16, 60]. It has been used in pregnant women to treat acute pancreatitis and has been shown to be a reasonable alternative to total parenteral nutrition [16]. Another case report comments on the use of plasmapheresis for pancreatitis with miscarriage and preterm birth [61]. On the

other hand, some data indicate hypertriglyceridemia-induced acute pancreatitis in pregnant women can be managed without apheresis, instead relying on insulin, heparin, and supportive care including hospitalization [62]. In women with hypertriglyceridemia at risk for or with pancreatitis, heparin and/or insulin infusions can stimulate lipoprotein lipase activity, thereby mitigating elevated TG levels [61, 63]. The available data indicate earlier treatment is generally better and also note that delivery may be an option for women who are near term, as TG levels subsequently decline [16].

A single apheresis session can reduce LDL-C levels by 60%, TG levels by 20–50%, and Lp(a) levels by 43–64% [37]. LDL-C apheresis also has some anti-inflammatory effects and can improve quality of life for patients [25]. Although there are no clear contraindications to LDL-C apheresis, significant hypertriglyceridemia resulting in high density plasma may make apheresis less efficacious [37]. Additionally, fibrinogen and/or other clotting factors may be removed with apheresis, possibly explaining the observed improvement in endothelial function that can be seen after apheresis [37, 64]. With respect to adverse side effects from LDL-C apheresis, HDL-C can be removed during the process, and clinicians should monitor for apoferritin deficiency [16, 59].

Emerging therapies for consideration in pregnancy

Newer options for treating dyslipidemias in pregnancy, including mipomersen and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, remain undefined in terms of their utility in pregnant women [25]. Mipomersen is an mRNA antisense inhibitor that targets apolipoprotein B and has been shown to consistently lower LDL-C levels [65]. It is FDA approved to treat homozygous FH in the USA and may be a treatment option for pregnant women with FH according to the National Lipid Association [66]. Regarding PCSK9 inhibitors, these drugs inhibit the breakdown of LDL-C receptors, leading to significantly lower circulating LDL-C levels and reduced major adverse cardiac events [67, 68]. In one case report of an unplanned pregnancy, a woman remained on her PCSK9 inhibitor through the first 8 weeks of gestation [25]. Other studies show that PCSK9 inhibitors can cross the placenta but do not cause adverse fetal development in animals [25, 69]. At this time, PCSK9 inhibitors are not routinely used in pregnant women, though registry data collection is ongoing. Lomitapide, a microsomal TG transfer protein inhibitor, is teratogenic and therefore not a treatment option for dyslipidemias in pregnant women [25].

Longer term management post-pregnancy

Women with dyslipidemias are at increased risk for complicated pregnancies, and women with complicated pregnancies, including HDOP (gestational hypertension and pre-eclampsia) and gestational DM, are at increased risk for subsequent cardiovascular disease [70]. Data about long-term outcomes for this group of patients is emerging. HDOP has been shown to be an independent factor for 10-year risk of CVD [71]. And, a recent study showed that women with HDOP and current hypertension have more structurally abnormal hearts 10 years after pregnancy as compared to women without HDOP [72]. Similarly, gestational diabetes has been found to be associated with increased incidence of

CVD even after 10 years [73]. As we continue to learn more about these diseases, it will be increasingly vital to diagnose and treat dyslipidemias in pregnant women early to help prevent these long-term adverse effects.

Compliance with Ethical Standards

Conflict of Interest
Lakshmi S. Tummala declares no conflict of interest. Akanksha Agrawal declares no conflict of interest. Gina Lundberg declares no conflict of interest.

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

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