Pregnancy's effects on cardiovascular health: A woman's first "cardiac stress test"

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The effects of pregnancy on a woman's heart, especially with respect to her changing lipid profile and her risk for developing gestational diabetes mellitus or pre-eclampsia, can sometimes predict her future cardiovascular (CV) status. As such, the state of pregnancy may serve as a "cardiac stress test" that can warn her healthcare provider about potential CV problems that perhaps can be forestalled or mitigated.

KEY WORDS: **pregnancy, lipid profile, gestational diabetes, pre-eclampsia, cardiovascular disease**

After becoming pregnant, a woman is likely to focus on the health of her growing fetus; she may not necessarily consider the effects of pregnancy on her *own* health, except in terms of how it may affect her future child. In essence, though, pregnancy can have a profound effect on a woman's health and may, in fact, be her first "cardiac stress test." Even an otherwise healthy woman experiences a rise in total cholesterol (TC), triglycerides (TG), and possibly blood pressure (BP) during pregnancy. A woman who gains excessive weight or makes poor lifestyle choices during pregnancy can heighten the metabolic changes already occurring and place her at risk for developing gestational diabetes mellitus (GDM) or pre-eclampsia. These events may not only jeopardize the pregnancy outcome but may also increase the woman's risk for developing cardiovascular disease (CVD) in the future.

A woman's CV status during pregnancy gives her healthcare provider (HCP) a glimpse into how her body may react, both in the short term and in the long term, when she is under major physical stress. The onset of GDM or hypertension (HTN; a sign of pre-eclampsia) during pregnancy may provide HCPs with a unique opportunity to identify young women who may be at increased risk for develop-

ing CVD in the future.[1] Of note, the positive association of GDM and pre-eclampsia with post-pregnancy CV risk may be due largely to pre-pregnancy risk factors such as obesity, dyslipidemia, and HTN, rather than reflecting a direct influence of the pregnancy complication.[1] But these pre-pregnancy risk factors may not become clinically apparent until a pregnancy places its own particular stresses on the heart.

Normal metabolic changes during pregnancy

During pregnancy, maternal metabolism adapts to benefit the growth and development of the fetus.[2] This process can be divided into two phases: Phase 1 comprises the first and second trimesters and phase 2 comprises the third trimester. During phase 1, fetal energy demands are limited, but maternal visceral fat stores increase. This latter effect is attributable in part to maternal behavioral changes, including hyperphagia, and increased adipose tissue lipogenesis. Also during phase 1, insulin sensitivity is normal or slightly improved, with normal peripheral sensitivity to insulin and normal hepatic basal glucose production.[2] In the midst of this metabolic environment, pregnancy-related endocrine changes (e.g., rising levels of estrogen, progesterone, and cortisol) favor lipogenesis and accumulation of fat.[2]

During phase 2 of pregnancy, the anabolic state switches to a catabolic state.[2] Increasing insulin resistance results in increased hormone-sensitive lipase activity and decreased lipoprotein lipase activity, which in turn result in a marked increase in lipolysis rates and increased delivery of free fatty acids to the liver. The free fatty acids are channeled into hepatic TG synthesis and increased secretion of very-low-density lipoproteins (VLDL).[2] At a similar time, estradiol acts to increase hepatic VLDL production, promote apolipoprotein A1 (Apo A1) production, and reduce hepatic lipase activity, resulting in increased production of high-density lipoproteins (HDL).[2]

Lipid profile changes during pregnancy

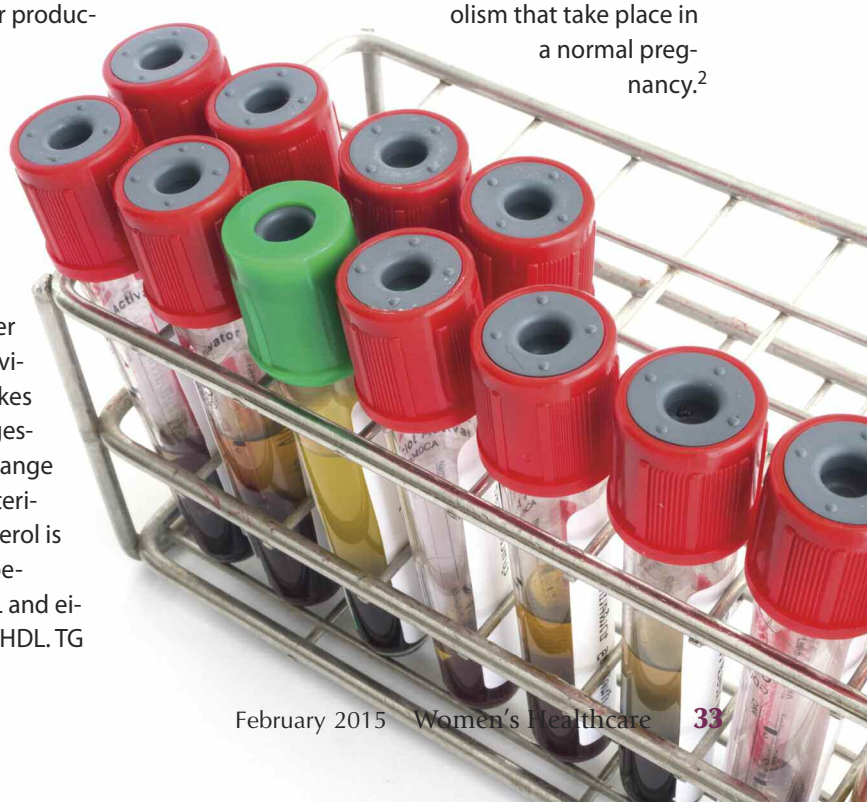
Plasma lipid concentrations rise markedly as pregnancy advances.[2] For example, plasma TC and TG concentrations climb by 25%-50% and 200%-400%, respectively. The increase in TG is due mainly to that of VLDL-TG, which rises threefold between the end of the first trimester and late pregnancy. VLDL is composed of two fractions, VLDL1, which is secreted by the liver to supply tissues with TG fatty acids in the post-absorption state, and VLDL2, which is a major precursor of the cholesterol-transporting particles intermediate-density lipoprotein and low-density lipoprotein (LDL). As plasma TG increase with advancing gestation, VLDL1 and VLDL2 increase by an average of fourfold.

The abundance of VLDL-TG is caused by their enhanced liver production and delayed lipolysis in the presence of increased cholesterol ester transfer protein activity, which takes place mid-gestation. Exchange of TG for esterified cholesterol is facilitated between VLDL and either LDL or HDL. TG accumulate in the lipoprotein fractions of higher densities, LDL and HDL.[3] By the third trimester, most women have a lipid profile that would be considered highly atherogenic in the non-pregnant state.[4,5]

In a normal pregnancy, HDL cholesterol (HDL-C) levels are elevated by the end of the first trimester and peak at the end of the second trimester (total rise, about 40%).[2] The increase in HDL-C is due mainly to increasing estrogen concentrations, which promote Apo A1 production and reduce hepatic lipase activity. In the latter phase of pregnancy, elevated TG adversely affect LDL composition, causing a shift to small dense particles, which are more atherogenic. LDL-C concentrations rise by about 70% during a normal pregnancy. After delivery, women can expect their lipid values to return to normal in 4 weeks to 3 months.

Effects of exaggerated lipid alterations: Gestational diabetes and pre-eclampsia

Additional maternal metabolic stresses such as obesity and other risk factors for DM may exacerbate the alterations in lipoprotein metabolism that take place in a normal pregnancy.[2]



For example, obese pregnant women, versus their leaner counterparts, have higher serum TG and VLDL-C levels and lower HDL-C levels.[2] This dysregulation of maternal lipid metabolism may predispose them to GDM and pre-eclampsia.

Gestational diabetes mellitus

Gestational diabetes mellitus is defined as any degree of glucose intolerance that is first detected during pregnancy.[2] Four percent to 9% of pregnancies are affected by GDM. In a normal pregnancy, the normal progression of insulin resistance is compensated by increased insulin secretion by the pancreas' beta cells. Women with GDM have an imbalance between insulin resistance and insulin secretion capacity, resulting in increased circulating glucose levels. A recent study showed that, during the first trimester of pregnancy, women who had relatively lower levels of adiponectin, an adipokine suspected of having insulin-sensitizing properties, were more likely to develop increased insulin resistance and GDM.[6]

Pre-eclampsia

This condition, which is characterized by elevated BP and, in most cases, large amounts of protein in the urine, affects 2%-4% of pregnancies.[2] Although the cause and the pathogenesis of pre-eclampsia have not been definitively established, the hyperlipidemia of normal pregnancy (i.e., the elevated TC and TG) becomes more extreme in women who develop pre-eclampsia. The exaggerated rise in TG leads to increased production of small dense LDL (almost 3 times the level seen in normal pregnancy) and reduced HDL-C. This lipid profile may contribute to endothelial dysfunction.

Complicating the picture, factors released from the placenta enhance peripheral lipolysis, which is already being stimulated by hormone-sensitive lipase, resulting in an increased flux of free fatty acids to the liver. These free fatty acids are channeled primarily into hepatic TG synthesis, resulting in increased secretion of TG-rich lipoproteins. Accumulation of TG occurs in the hepatocyte when this pathway is saturated. Increased concentrations of VLDL1 in the circulation drive production of atherogenic lipoproteins. This pathway plays a role in the formation of lipid-laden macrophages (foam cells) in the spiral arteries of the decidua basalis and may be involved in enhanced placental production of the pro-inflammatory mediators in pre-eclampsia.

Use of lipid-lowering medications during pregnancy

Women with previously diagnosed hyperlipidemia who become pregnant while taking a statin should stop this treatment immediately.[7,8] Statins are Category X medications; that is, they are contraindicated in pregnant women, with positive evidence of serious fetal abnormalities in animals. As Category C agents, fibrates (e.g., gemfibrozil, fenofibrate), ezetimibe, niacin, and prescription omega-3-acid ethyl esters are also to be avoided in pregnancy; animal studies have shown adverse fetal effects. The bile acid sequestrant cholestyramine is designated Category C, but colesevelam, a Category B bile acid sequestrant, can be used safely in pregnancy. This agent has been reported to lower LDL-C by about 15%.[7]

Beneficial effects of breastfeeding on maternal lipid profiles

A woman's body continues to change after she gives birth. All women should be encouraged to breastfeed exclusively for the first 6 months of life.[9] As stated earlier, during gestation, visceral fat accumulates and insulin resistance and lipid and TG levels rise. These changes appear to reverse more quickly, and more completely, with lactation.[10] Data from several large cohort studies suggest that breastfeeding has beneficial effects on adiposity, lipids, and glucose homeostasis.[10] Researchers have found protective associations between duration of breastfeeding and incidence of hyperlipidemia, HTN, type 2 DM, the metabolic syndrome, and myocardial infarction (MI).[11]

During pregnancy, dramatic changes occur in a woman's physiology as she accommodates the demands of "metabolizing for two." These changes both support the developing fetus and allow for accumulation of energy stores in anticipation of lactation. This accumulation is characterized by well-described increases in visceral fat, insulin production, insulin resistance, and circulating lipid levels. After birth, lactation is thought to play a central role in mobilizing these accumulated fat stores and resetting maternal metabolism, thereby reducing maternal risk for metabolic disease. The longer a woman lactates, the more completely she off-loads these accumulated stores. Conversely, when a woman does not lactate, adverse metabolic changes persist for a longer period of time, increasing her disease risk.[11]

Effects of GDM and pre-eclampsia on mothers' future health

Women with a history of gestational glycosuria or GDM are likely to have higher levels of fasting glucose and insulin many years after the pregnancy.[12] Nearly 50% of women with

a history of GDM go on to develop type 2 DM within 10 years. Nearly two decades after pregnancy, women with a history of gestational HTN or pre-eclampsia, compared with women who were normotensive during pregnancy, have elevated body mass index (BMI), waist circumference, and BP.

Women with a history of pre-eclampsia, versus those without pre-eclampsia, are twice as likely to develop CVD (e.g., coronary heart disease, MI, heart failure).[13] These women are also more likely to develop CVD earlier in life. Although pre-eclampsia is a CVD risk factor that cannot necessarily be modified, pregnant women can help prevent pre-eclampsia in the first place by limiting weight gain. Women with a history of pre-eclampsia should take extra care to control other CVD risk factors (e.g., high LDL-C, low HDL-C, HTN) as they age.

In the Avon Longitudinal Study of Parents and Children, researchers studied the associations of *pregnancy diabetes mellitus* (pre-gestational DM, GDM, and glycosuria) and *hypertensive disorders of pregnancy* (HDP; gestational HTN and pre-eclampsia) with a wide range of CV risk factors measured 18 years post-pregnancy (mean age at outcome assessment, 48 years) in a prospective cohort of more than 3,000 women.[12] Pregnancy DM was associated with higher glucose concentrations 18 years post-pregnancy, even when potential confounders, including pre-pregnancy BMI, were controlled for. In addition, pregnancy DM was associated with higher glucose; GDM and glycosuria were associated with higher insulin and pro-insulin; and glycosuria was associated with higher TG levels. Both gestational HTN and pre-eclampsia were associated with a greater number of CV risk factors 18 years post-pregnancy: higher BMI, waist circumference, systolic and diastolic BP, insulin, pro-insulin, and TG, and lower HDL-C.

These results suggest that pre-eclampsia, relative to GDM, is a stronger marker of future CVD; in the study, pre-eclampsia was associated with a greater number of CV risk factors, whereas GDM was linked to greater glycemia later in life.[12] The results also suggest that the mechanisms underlying these associations are different; in the study, pregnancy DM and HDP were associated with different CV risk factors. Therefore, how a woman fares during pregnancy may serve as an early cardiac stress test revealing future CVD risk.

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Clinical recommendations

Pre-conception

HCPs should advise women aged 20 years or older who are considering pregnancy and who have not had a lipid profile in the past 5 years to have this screening.[14] Women whose lipid values are outside the normal range should institute lifestyle changes and, if necessary, medication to normalize their values before trying to become pregnant. Women with a cholesterol disorder such as familial hypercholesterolemia (FH), an autosomal dominant disorder, should be counseled on the risk of pregnancy to their own health, as well as the chance of passing on the disorder to future children.[15] A woman with heterozygous FH has a 50% chance of passing on the mutated gene to each child. A woman with homozygous FH, a much more severe form of FH than heterozygous FH, will definitely pass on a copy of the mutated gene—and, therefore, at least heterozygous FH, to her children. HCPs should counsel women using a statin, fibrate, or ezetimibe who are trying to become pregnant (or who learn that they are pregnant) to stop the medication immediately and contact the HCP who prescribed it.

During pregnancy

Women who are pregnant must be counseled on the proper amount of weight they should gain and be given nutrition recommendations. Moderate aerobic exercise (150 minutes/week) is safe and appropriate for most pregnant women. Women who have been inactive, are obese, or have other CVD risk factors should consult with their HCP to determine the level of exercise and monitoring they need.

Women whose lipid values are highly elevated at the beginning of pregnancy (e.g., TC >300 mg/dL, LDL-C >190 mg/dL, TG >500 mg/dL) should have their lipid profiles checked monthly. They should follow a diet designed for their lipid abnormality. For example, women with elevated TG should follow a low-fat, carbohydrate-controlled diet.[14]

Pregnant women should be counseled on recommended weight gain based on their pre-pregnancy BMI: a total of 11-20 lb if they were obese before pregnancy and 15-25 lb if they were overweight before pregnancy.[16] The goal is to reduce DM and CVD risk in both mother and child.

After delivery

Breastfeeding is recommended to boost infants' immune systems and aid in maternal weight loss, which

can also help lower mothers' TC and TG values. In addition, breastfeeding leads to increased maternal insulin sensitivity. Lipid profiles should be ordered every 3 months for women whose lipid values were elevated during pregnancy. Like pregnant women, breastfeeding women should delay use of cholesterol-lowering agents, again with the exception of colesevelam. Statins, fibrates, ezetimibe, and niacin are not recommended for use by nursing mothers. At 6 months post-delivery, women whose LDL-C is >190 mg/dL and/or whose TG are >500 mg/dL 6 months postpartum should give strong consideration to stopping breastfeeding so that they can take cholesterol-lowering medication to reduce CV risk.

Conclusion

Attention to a woman's CV health pre-conception, during pregnancy, and postpartum allows HCPs to identify risk factors, encourage heart-healthy behaviors, and use pharmacotherapy effectively and safely when needed to treat dyslipidemia. This care can help reduce the risk for CVD in women as they age.

The courses of women's pregnancies may provide HCPs with insight into their future CV health. Identifying dysglycemic pregnancies will simultaneously identify women who are at increased subsequent cardiometabolic risk.[17] Women who have or who have had pre-eclampsia, versus those who have not, are twice as likely to develop CVD (e.g., coronary heart disease, MI, heart failure). When a dysglycemic pregnancy or pre-eclampsia is detected, HCPs have the opportunity to go beyond managing the condition during pregnancy to attenuating the risk for future CVD with targeted intervention. Heart health belongs in all women's healthcare, including throughout the reproductive years.

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