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Spontaneous Preterm Labor and Cardiovascular Disease Risk: One Step Closer to a Better Understanding

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Currently four pregnancy complications, gestational diabetes, hypertensive disorders in pregnancy, preterm delivery, and delivery of a small for gestational age (SGA) infant, are recognized as cardiovascular disease (CVD) risk factors.¹ Incorporating a history of gestational diabetes or hypertensive disorders in pregnancy has been shown to improve CVD risk prediction in women.² The relationship between gestational diabetes or hypertensive disorders in pregnancy and CVD is believed to be explained, at least in part, by the atherogenic inflammation and oxidative stress that often accompany obesity.³ Indeed, overweight/obese women are 2–6 times more likely to develop gestational diabetes and 2–3 times more likely to develop hypertensive disorders in pregnancy in comparison to normal weight women.⁵ Women with a history of these complications are more likely to develop hypertension or type 2 diabetes.⁶ Despite substantial evidence linking these risk factors to CVD, a lack of modifying treatments for these risk factors may limit their use in CVD risk assessment and management.

Preterm delivery has also been associated with maternal overweight or obesity.⁷ In a meta-analysis of 39 studies, however, associations remained statistically significant only for medically indicated preterm labor, and no statistically significant associations were found for spontaneous preterm labor.⁷ Moreover, overweight and class I obesity of the first degree emerged as protective factors for spontaneous preterm labor. In the case-controlled study by Bartha et al.⁸ in this issue of the *Journal of Women's Health*, women with spontaneous preterm labor were matched with women without preterm labor. The study showed that women with spontaneous preterm labor had significantly lower prepregnancy body mass index (BMI). During the third trimester, they had higher levels of interleukin-6 (IL-6) and lower levels of myeloperoxidase. Most noteworthy, these women had lower levels of total cholesterol, lower levels of high-density lipoprotein cholesterol (HDL-C), and a higher total cholesterol/HDL-C ratio. Thus, except for low HDL-C levels, women in this study did not fit the traditional CVD risk profile associated with high BMI. Nevertheless, they had

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increased levels of IL-6 and decreased levels of HDL-C, which are recognized biomarkers of inflammation and oxidative stress.^{9,10}

Certainly, the study by Bartha et al.⁸ brings us one step closer to understanding the changes in lipid profile and inflammatory biomarkers among women with spontaneous preterm labor. Their findings on low total cholesterol during the third trimester are not surprising. Low total cholesterol may be an indicator of malnutrition, and low prepregnancy total cholesterol is a risk factor for spontaneous preterm labor.¹¹ The results on HDL-C from the study by Bartha et al. are difficult to interpret, as studies describing HDL-C levels among women with complicated pregnancy are scant. In a recently published study, low HDL-C levels measured in the middle of pregnancy were not associated with spontaneous preterm labor.¹² Future studies among women with spontaneous preterm labor are needed to confirm whether HDL-C levels fail to increase in the first trimester, as happens in a normal pregnancy,¹³ or decrease in the third trimester of pregnancy.

Increased levels of IL-6 reported in the study by Bartha et al.⁸ among women with spontaneous preterm labor are consistent with the inflammation hypothesis of spontaneous preterm labor. IL-6 is the key proinflammatory cytokine that upregulates the synthesis and secretion of C-reactive protein (CRP), an acute-phase reactant.⁹ Both of these biomarkers were found to be associated with spontaneous preterm labor¹⁴ and are recognized as CVD risk factors.¹⁵ Nevertheless, it is not known if a poor diet before and during pregnancy increases susceptibility to infections or initiates inflammation or if a genetic predisposition to inflammation puts women with low BMI at risk for spontaneous preterm labor as well as CVD. Although CRP was found to be more responsive to changes in diet in women with low BMI compared to women with normal or high BMI,¹⁶ interventional studies correcting poor nutritional status failed to prevent preterm birth.¹⁷ It also should be noted that in comparison to women with gestational weight gain within the normal range, women with very low gestational weight gain have a higher risk for spontaneous preterm labor regardless of prepregnancy BMI.¹⁸ Moreover, severely thin mothers with very low gestational weight gain are at the greatest risk for spontaneous preterm birth.

This study prompts several questions. Do women with low BMI and history of spontaneous preterm labor have increased risk for CVD? Do they have an increased CVD risk even if they have low total cholesterol? Do they have low total cholesterol and high HDL-C before or after pregnancy? Does low gestational weight gain put them at the highest risk for CVD?

Until we have a better understanding of how and to what degree inflammation, susceptibility to infection, and malnutrition play a role in spontaneous preterm labor and atherogenesis, it would be challenging to develop evidence-based clinical recommendations for management of CVD risk factors among women with a history of spontaneous preterm labor.

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