

## Where are the Recommendations on Healthy Lifestyle and Cardiovascular Disease Prevention for Pregnant Women?

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From the practical point of view, there is still a large knowledge gap relating to how to effectively prevent, diagnose, and treat cardiovascular risk factors and cardiovascular disease and its complications in pregnant women.<sup>1</sup> In many countries, both cardiologists and obstetricians are still afraid to treat such cases owing to a lack of knowledge, data (in most of the available studies, pregnancy is one of the most important exclusion criteria), and practical guidelines. In consequence, most of the existing guidelines still base their recommendations on expert opinion and/or relatively small cohort studies of short duration and mainly focus on the treatment of existing diseases such as coronary heart disease, arrhythmias, thromboembolic diseases, aortic and valvular disease, congenital heart diseases, and/or cardiomyopathies or heart failure.<sup>1,2</sup> Moreover, in most of the existing guidelines, especially in Europe,<sup>1</sup> there is no information on the effective management of cardiovascular risk factors and effective methods of prevention of cardiovascular disease (CVD) during pregnancy. This is especially important now as there is an increasing trend towards more and more women becoming pregnant at an older age.<sup>3</sup> In busy obstetrical centers, including the one I represent, it is now common to see pregnant women at the age of  $\geq 45$  years and even  $\geq 50$  years. Therefore, the analysis presented by Dr. Perak and colleagues on pregnant women  $< 45$  years does not, in fact, reflect the current age trends and therefore misses (probably because of a paucity of pregnant women aged  $> 45$  years in their study) the most challenging group of pregnant women with respect to the prevention and management of CVD.<sup>4</sup>

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These pregnancies in the late reproductive years might be expected to be associated with an increasing prevalence of cardiovascular risk factors, especially diabetes mellitus, hypertension, and obesity.<sup>5</sup> Because of this fact, as well as because of a general increase in unhealthy behaviors in the population (significant increase of underweight and obesity, low level of physical exercise, increase of smoking for some age ranges, especially in young women, and unhealthy diet—often with an inappropriate approach to weight loss), effective prevention of CVD by ameliorating cardiovascular risk factors is the most crucial current issue.<sup>6–8</sup> It is critically important because aside from the treatment of gestational hypertension (occurring in as many as 7–10% of all pregnancies) and diabetes mellitus,<sup>1</sup> there are no recommendations on healthy diet for pregnant women, no clear data on optimal physical activity (which should be individualized and fitted for the pregnancy trimester [T]), and there is a complete lack of knowledge on how to prevent and manage lipid disorders (the existing obstetrical guidelines do not even make any recommendations for lipid monitoring), which may be a significant risk factor for complications both for the mother (preeclampsia, stillbirth, recurrent pregnancy loss), and for the child (preterm delivery or intrauterine growth restriction).<sup>1,2,9</sup>

### Gestation as a Risk Factor?

Pregnancy induces changes in the cardiovascular system in order to meet the increased metabolic demands of the mother and fetus.<sup>1,2</sup> Therefore, knowledge of the risks associated with CVDs before and during pregnancy, and their optimal management is of critical importance. However, data about the prevalence and incidence of pregnancy-related heart disease are still limited from most parts of the world, and especially from the less developed countries (middle- and low-income countries), where there are no existing registries, and where digitalization of health records is limited.<sup>1</sup> As mentioned above, age may be one of the most important nonmodifiable risk factors of cardiovascular complications for pregnant women; especially considering that according to the World Atlas, the highest mean age at first birth in some countries, including Greece, Australia, and Italy may be

>30 years (30.3–31.2).<sup>3</sup> However, it seems that this relatively mild increase in maternal age does not fully explain the observed increase in CVD during pregnancy; therefore, it seems that other co-existing, mainly modified risk factors play a more important role.<sup>1–3</sup>

Thus, the article by Dr. Perak et al based on National Health and Nutrition Examination Surveys data is indeed a unique and important analysis, despite all the obvious limitations. The authors aimed to characterize cardiovascular health (CVH), as defined by the American Heart Association and to compare CVH in pregnant and nonpregnant women aged 20 to 44 years.<sup>4</sup> The main aim of introduction of the American Heart Association CVH index was to improve CVH in the United States by 20% by 2020 and to enable further improvement thereafter.<sup>10,11</sup> The 7 CVH metrics include diet, physical activity, nonsmoking, body mass index, blood pressure, total cholesterol (TC), and fasting glucose, and it has been shown that better CVH metrics are associated with CVD-free longevity and other positive health outcomes in nonpregnant adults.<sup>4,10,11</sup>

I would like to congratulate the authors for the fact that they have attempted to characterize CVH for the first time for pregnant women. This was not an easy task, especially considering that some of the parameters are still based on expert recommendations.<sup>4</sup> Considering 4 health behaviors, there is obviously no doubt as to the smoking/nonsmoking status, but physical activity certainly requires much more attention; it is difficult to quantify and should be more extensively adjusted, taking into account the gestational age and concomitant diseases (not only cardiovascular, but other pregnancy-related and/or rheumatological diseases). Therefore, more work should be carried out by experts collaborating to optimize the recommended values for pregnant women. Moreover, owing to the status of pregnancy, physical activity is sometimes contraindicated, as it might be in the case of high risk of miscarriage or preterm delivery. Therefore, the analysis by Perak et al should only have included healthy pregnant women, whereas the authors appear to have included all consecutive pregnant women, as they did not describe any exclusion criteria.<sup>4,12</sup>

One of the most debatable issues is the most healthy diet for pregnant women. It is essential that we have some dietary recommendations for healthy pregnant women, as well for pregnant women with complications. The problem is that, while general recommendations have been made by the US Food and Drug Administration,<sup>13</sup> in most cases these appear to be an attempt to apply the dietary guidelines for nonpregnant women to define a healthy diet in pregnancy. Because of the lack of clear guidelines for a healthy diet during pregnancy, the results obtained by the authors with respect to CVH parameters are not surprising—only 0.1% of the investigated pregnant women had ideal diets, and as

many as 80.5% had a poor diet.<sup>4</sup> Furthermore, we might expect to observe increasing numbers of cases of pregnant women in our clinical practice who are adhering to unhealthy restricted diets, including high-protein, or low-fat or low-carbohydrate/high protein diets, instead of well-balanced diets,<sup>14</sup> which are critically important both for the mother as well as for the growing fetus. Therefore, there is a great need for clear guidelines on the definition of healthy diet for pregnant women, and thus both the 2020 Dietary Guidelines for Americans as well as the International Lipid Expert Panel 2020 recommendations on healthy diet are eagerly anticipated.<sup>4</sup>

Of the investigated CVH health factors, the most debatable is plasma TC. During the end of the second and especially during the third trimester (which is sometimes referred to as the “hyperlipidemic period”), TC increases are common (even by as much as 50%), and an even more substantial increase (2.5 times) in triglycerides can be seen. This is associated with a smaller increase in low-density lipoprotein cholesterol, by ≈30–40%.<sup>15</sup> Such changes are associated with the hormonal changes both from the maternal and the fetal side—in T1 and T2, progesterone level increases, and consequently increased appetite, weight gain, and fat deposition can occur. In T2 and T3 estrogen levels increase, resulting in increased secretion of triglyceride-rich lipoproteins, increased lipogenesis, and suppressed activity of hepatic lipase. This causes triglyceride enrichment of low-density lipoprotein and high-density lipoprotein. Finally, in the same trimesters, we observe an increase in human placental lactogen and consequently, peripheral insulin resistance with suppressed plasma lipoprotein lipase activity, enhanced plasma cholesterol ester transfer protein activity, and enhanced free fatty acid flux to the liver.<sup>16</sup> Therefore, because of these physiological changes we cannot use the same values of healthy lifestyle for TC for pregnant and nonpregnant women. There have been some attempts to define reference values of lipids during pregnancy (eg, with values <300 mg/dL [7.75 mmol/L] in T2 and even <350 mg/dL [9 mmol/L] in T3); however, further studies are required before these values can be confirmed.<sup>17</sup> Based on the data from other studies, and clinical experience, it seems that these reference values should be lower with <250 mg/dL (6.5 mmol/L) in T2 and <300 mg/dL (7.75 mmol/L) in T3.<sup>4,15,16</sup> Thus, the reference values used by the authors (<200 mg/dL/5.2 mmol/L for ideal TC levels) seem to be far too low, and it is probably the reason that only 38.9% of pregnant women had ideal levels of TC in comparison to nonpregnant ones (67.2%). The data on the distribution of TC across the trimesters confirmed this, because in T1 there were >80% pregnant women with ideal levels of cholesterol and in T3, <16%.<sup>4</sup> The diagnosis and management of lipid disorders during pregnancy is an important problem, there are no recommendations to help, and knowledge and evidence is

limited. It is very surprising that management of hyperlipidemia was not a part of the recent European Society of Cardiology guidelines for the management of CVD during pregnancy,<sup>1</sup> with almost no recommendations on prevention in general. This issue is of critical importance, especially as, in busy centers, we are likely to see patients with severe hypercholesterolemia, including familial hypercholesterolemia, as well as severe hypertriglyceridemia with pancreatitis during pregnancy, which is a life-threatening condition.

## Mother-Offspring Continuous Risk

The authors have demonstrated that among pregnant women, CVH was far from optimal: only 4.6% had high CVH, 60.6% moderate CVH, and 34.8% had low CVH. Compared with nonpregnant women, the distribution of CVH scores was lower overall among pregnant women. This was especially true in the case of parameters where ongoing debate exists around their definition during pregnancy, ie, healthy diet (however, there were no significant differences), physical activity, and cholesterol level. There were also differences in comparison of ideal CVH metrics across the trimesters of pregnancy; total CVH scores were lower in later trimesters, and the prevalence of high CVH was 6.4% in T1, even 15.0% in T2, and only 2.9% in T3. This was probably driven mainly by cholesterol and physical activity (where attainment of the ideal metric decreased from 32.4% to 24%).<sup>4</sup>

Finally, it is important to emphasize the phenomenon of continuous mother-fetus-newborn cardiovascular risk. There are some studies available showing that the risk of developing atherosclerosis (and its complications) in a child is enhanced by significant progression of maternal atherosclerosis during pregnancy.<sup>1,18–20</sup> Gestation is also increasingly recognized as a critical period for the possible development of offspring CVD risk (eg, maternal obesity in pregnancy has been associated with CVD risk factors in child, including elevated blood pressure, abnormal lipid levels, and insulin resistance, as well as higher increase of CVD events, and premature all-cause mortality).<sup>4,18–20</sup> In the FELIC study (Fate of Early Lesions in Children), the authors observed that maternal hypercholesterolemia during pregnancy induced significant changes in the fetal aorta that determined the long-term susceptibility of children to fatty-streak formation and subsequent atherosclerosis.<sup>20</sup> Therefore, it is vitally important to carefully monitor not only healthy lifestyle parameters but also gynecological (preeclampsia, preterm delivery, recurrent pregnancy loss or intrauterine growth restriction) and cardiovascular outcomes (both subclinical and clinical atherosclerosis progression as well CVD outcomes). This is the main problem of this analysis, as we only have data on CVH metrics, without any indication as to how these metrics relate to outcomes in this population.

Were such data available, this would enable the categorization of pregnant women into groups at high, moderate, or low risk of CVD according to the evaluated parameters. Without this, it is difficult to make any direct conclusions on the long-term implications for healthcare systems for pregnant women in the United States and worldwide. This necessitates a “call to action” to design an observational study with continuous monitoring (to avoid the limitations of such studies such as the National Health and Nutrition Examination Surveys) of healthy lifestyle parameters in order to make definitive recommendations on their values for pregnant women and then to have the opportunity for long-term follow-up, in order to link them with the risk factors (hypertension, diabetes mellitus) and cardiovascular complications observed in the mother after delivery and in children and adolescents.

In conclusion, clear and practical recommendations for CVD prevention in pregnant women are urgently required. Additionally, the time is right to consider the coordination of care for pregnant women within multidisciplinary teams. This is the only approach that can provide the level of diagnosis and treatment that is required for pregnant women at high risk of CVD.

## Disclosures

None.

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