EDITORIAL

Determinants of C-reactive protein concentrations in pregnant women with type 1 diabetes

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The study by Gutaj et al[1] describes the changes in high-sensitive C-reactive protein (hs-CRP) over the course of pregnancy in a group of patients with type 1 diabetes patients at a mean age of 29 ±4 years, of whom the majority had normal body weight at conception. The authors found that hs-CRP levels, a well-established and reliable inflammatory marker, doubles between the first and second trimesters and then stabilizes at an elevated level. They also found that the increase in hs-CRP levels correlates with maternal body mass index (not, as they wrote, with obesity as none of the studied women were obese) and indices of insulin resistance.

Elevated hs-CRP levels are a sign of subclinical inflammation, which is a common and well-described finding in patients with obesity and type 2 diabetes.[2] Nowadays, it is well known that visceral adipose tissue, apart from being an energy store, is also a highly metabolically active organ that has multiple endocrine functions, some of which are yet to be discovered. Visceral fat is a source of numerous cytokines, now called adipokines, whose possible task is to preserve redundant energy in the body and provide information to other organs (including the brain) on, for example, how big the energy storage is. Adipokines are also potent inflammatory mediators and signs of subclinical inflammation such as elevated plasma interleukin 6 or interleukin 1β levels. Along with increased inflammatory markers, higher plasma levels of adhesins, sE-selectin, thrombomodulin, and other endothelial dysfunction molecules are also found.[3,4] Subclinical inflammation leads to a gradual increase in insulin resistance, and if this occurs in a patient with low reserve of insulin-producing β cells then this chain of events leads to sustained hyperglycemia and eventually type 2 diabetes.[5]

This brief description of the pathogenesis of type 2 diabetes, as it is understood today, contains all the complexity of metabolic derangements found in patients with type 2 diabetes. Of note, the whole science of visceral fat started in mid-1990s, with the discovery of leptin, the first identified specific adipokine.[6]

With the current knowledge on the inflammatory effect of adipose tissue, the findings reported by Gutaj et al[1] are not surprising. The results of their study clearly show that patients with type 1 diabetes, including those who become pregnant, are not free from the consequences of accumulating fat and increased insulin resistance. Interestingly, with the fetal development, subclinical inflammation apparently increases, which is reflected by elevated hs-CRP levels. However, as it often happens, the results of the study provoke more questions than they provide anwsers.

First, it is unclear whether the increased inflammation in pregnant women with type 1 diabetes has any significant clinical consequences, be it during the perinatal period or later in the course of the disease. Subclinical inflammation in recent years has been identified as a mechanism responsible for the progression of various diseases, from cancer to joint and skin lesions.[7-9] In type 2 diabetes, elevated hs-CRP levels have been associated with the increased risk of developing macrovascular complications.[10] Also, it has been shown that individuals with elevated hs-CRP levels derive a significant benefit from statin use.[11] However, vascular complications of diabetes develop over the years, and this mechanism is unlikely to be related to unfavorable perinatal outcomes. It is also obvious from the study by Gutaj et al[1] that the increase in hs-CRP levels was not related to the increase in blood glucose because in fact glucose control considerably improved in study participants as hemoglobin A_{1c} was reduced from a mean level of 6.5% to 5.6% between the first and second trimesters. This finding, namely, an inverse correlation between blood glucose and

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plasma hs-CRP levels, makes it clear that subclinical inflammation is linked to the amount of accumulated fat, and not to the eventual efficacy of intrinsic glucose regulation.

Secondly, pregnancy is known to be associated with a slight decrease in insulin sensitivity; however, it is striking how closely subclinical inflammation is related to this change in tissue responsivity to insulin action. For that instance, it is a little unfortunate that the study did not include healthy pregnant women matched for age and body weight as controls because this would provide more data on the sole effect of type 1 diabetes on hs-CRP levels in pregnancy. As the authors pointed out in the Introduction section,[1] the reports on changes in CRP levels in healthy pregnant women are conflicting.

Thirdly, and interestingly, the study results show how pregnancy makes type 1 diabetes by changing the features of type 2 diabetes, namely, increased insulin resistance and subclinical inflammation. When an individual is diagnosed with diabetes, it is necessary to identify the type of diabetes in the large majority of cases.

Type 1 diabetes is an autoimmune disease resulting from the autodestruction of insulin-secreting β cells. It usually affects younger and lean people, has dramatic onset, and frequently leads to ketoacidosis. In type 1 diabetes, insulin secretion is severely impaired, and in the course of the disease, it wanes almost entirely, while insulin action remains unaffected.

Type 2 diabetes is a complication of overweight, with apparent insulin resistance and secretory failure (but never absolute) β cells. In this type of the disease, both insulin production and action are ineffective.

Differentiating between the type of diabetes is crucial for the choice of treatment. Type 1 diabetes requires intensive insulin therapy, while type 2 diabetes is best treated with weight loss and several oral agents. However, in some cases the decision on insulin type cannot be made on the basis of clinical observation, and specific tests have to be performed, such as assessing the presence of islet cell autoantibodies. As the lifespan increases and our knowledge on the pathogenesis of diabetes becomes more profound, it is more and more difficult to tell the type of diabetes at first assessment. In particular, the number of patients with both features of autoimmune reaction against β cells and features of insulin resistance is increasing, which poses a challenge in diabetes care, and results in usually futile attempts to improve glucose control by combining insulin and metformin in type 1 diabetes patients with overweight or obesity. The patients described by Gutaj et al[1] constitute yet another group of individuals in whom glucose intolerance may be caused by 2 types of factors. Fortunately, therapeutic decisions in pregnancy are simple, and the treatment may comprise only diet and insulin.

In summary, the study by Gutaj et al[1] helps understand the effect of pregnancy on subclinical inflammation related to insulin resistance in patients with type 1 diabetes. However, the clinical importance of this finding is yet to be demonstrated.

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