nancy in type 2 diabetic women. Maternal weight gain and the rate of caesarean deliveries were lower in type 2 diabetes. Gestational age at birth was significantly higher and the rate of large infants for gestational age lower in infants of women with type 2 diabetes. The rates of perinatal mortality and major congenital malformations were comparable in both groups. First-trimester A1C in type 2 and type 1 diabetic mothers with perinatal mortality was 9.9 and 8.1 ± 1.2%, respectively. Among pregnancies complicated by major congenital malformations, first-trimester A1C was >7% in 84% of women with type 1 diabetes and only in one woman (16.7%) with type 2 diabetes ($P = 0.006$). Neonatal distress respiratory syndrome was more frequent in infants of mothers with type 1 diabetes.

In our study, pregnancy outcomes in type 2 diabetic women were, if anything, similar to those with type 1 diabetes. In fact, women with type 2 diabetes had lower rates of large infants for gestational age, neonatal respiratory distress syndrome, and caesarean delivery.

As in some of the studies available, we found no significant differences in perinatal mortality or major congenital malformations between women with type 2 and type 1 diabetes (1–2). However, the results of five recent publications (3–7) suggest that type 2 diabetes could even represent a higher risk of perinatal mortality or congenital malformations than that conferred by type 1 diabetes. Similar rates of preconceptional care in women with type 1 and type 2 diabetes in our study could explain this discrepancy, as could the fact that gestational age at first visit to the clinic was comparable in both type 1 and type 2 diabetic women who did not undergo preconceptional care.

In our study, congenital malformations in type 2 diabetes were not related to poor first-trimester metabolic control in most cases. The concurrence in women with type 2 diabetes of factors other than glycemic control, such as obesity and older age, may account for this finding (8).

In conclusion, our study shows that pregnancy outcomes in type 2 diabetes are better than in type 1 diabetes when type 2 diabetic women receive as much intensified medical treatment during preconception and pregnancy as that given to type 1 diabetic women.

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COMMENTS AND RESPONSES

Glucose Abnormalities in Patients With Hepatitis C Virus Infection: Epidemiology and Pathogenesis

Response to Lecube et al.

We read with great interest the review article by Lecube et al. (1) on the pathogenic factors specifically linking hepatitis C virus (HCV) infection and glucose abnormalities. After analyzing the different mechanisms by which HCV is thought to contribute to the development of type 2 diabetes, Lecube et al. focus their attention on the role of proinflammatory cytokines, in particular tumor necrosis factor (TNF)-α and interleukin-6. They suggest that the activation of the TNF-α system in HCV-infected patients, which has been directly related to insulin resistance in their recent study (2), could be related to the T-helper (Th)1 immune response observed in the course of HCV infection. Accordingly, as shown in Fig. 1 of their review article, the activation of the TNF-α system following the Th1 immune-mediated response is central to the pathogenesis of both liver fibrosis and insulin resistance associated with HCV infection.

However, an apparent paradox is raised by an attempt to fit such interpretation with well-acquired data and the most recent evidence from literature. Indeed, a vigorous Th1 cytokine response has been classically observed in patients who clear their HCV infection, either spontaneously (3) or in response to antiviral treatment (4,5). By contrast, recent studies have demonstrated that insulin resistance is independently associated with a poor response to antiviral therapy in HCV patients (6,7), consistent with previous observations on the lower success rate of interferon alone or interferon plus ribavirin in obese and diabetic patients. Therefore, it is difficult to understand how an increased Th1 immune response, which is protective in relation to viral clearance, can be, at the same time, the major determinant of insulin resistance and responsible for a poor response to antiviral treatment.

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Glucose Abnormalities in Patients With Hepatitis C Virus Infection: Epidemiology and Pathogenesis

Response to Gentilucci et al.

We thank Gentilucci et al. (1) for their comments on our articles (2,3) regarding the pathogenic mechanisms of diabetes in patients with hepatitis C virus (HCV) infection. The authors question why an increased T-helper (Th)1 immune response can be simultaneously the major determinant of insulin resistance and responsible for a poor response to antiviral treatment. This question is based on the statement that Th1 immunoresponse favors HCV clearance. However, although a vigorous Th1 response could play an essential role in spontaneous viral clearance, this is not so evident after interferon treatment. It should be noted that in sustained responders, pretreatment intrahepatic mRNA levels of γ-interferon and tumor necrosis factor-α were lower than in nonsustained responders (4). In addition, a lower Th2 response during antiviral treatment (specifically a decrease in interleukin [IL]-10 rather than an increase of Th1) has been associated with a long-term virological response (5,6). Tsai et al. (7) and Eckels et al. (8) demonstrated that in vitro cytokine responses to recombinant HCV antigens were confined to IL-4 and IL-10 and proposed that such Th2 predominance might be conductive to viral persistence. Furthermore, Masaki et al. (9) reported that a lower Th1/Th2 ratio before interferon therapy may favor long-term virological response in patients with chronic hepatitis C. In addition, activation of naïve B-cells via CD81 has been involved in the immunological response triggered by HCV (10). Therefore, the immune mechanisms involved in the clearance of HCV after interferon therapy are complex and are far from being elucidated.

Low-grade inflammation mediated by activated innate immunity is an underlying pathogenic mechanism of insulin resistance and type 2 diabetes. Apart from the impairment of immune response, there is a cluster of alterations associated with insulin resistance such as obesity, ageing, hypertriglyceridemia, liver esteatosis, and fibrosis; these alterations are also risk factors for nonresponse to antiviral treatment. It has recently been demonstrated (11) that hyperinsulinemia blocks the inhibition of HCV virus replication by interferon. Therefore, it seems that there is a vicious circle in which insulin resistance facilitates the persistence of HCV and, alternatively, HCV favors insulin resistance.

Altogether, one can depict a complex scenario in which Th1 response is only one more of the actors. Future studies are needed to not only confirm that insulin resistance and type 2 diabetes are poor response predictors of antiviral treatment but also to unravel the mechanisms involved.

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