

Why is influenza virus more risky for pregnant women?

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To the editor:

Pregnancy results in altered immune responses to infectious diseases and an increased risk of severe disease caused by many pathogens. Recently, it has been shown that pregnant women are at an increased risk of severe disease and complications from pandemic H1N1 influenza virus (H1N1 2009) [1,2]. Because of concerns about the severity of disease during pregnancy, the US Centers for Disease Control and Prevention (CDC) have implemented enhanced surveillance for pandemic H1N1 influenza virus infections in pregnant women in the USA. During previous seasonal influenza epidemics [3,4] and pandemics, pregnant women had increased morbidity and mortality from influenza infection compared to women who were not pregnant. For this reason, the WHO advises early antiviral treatment for suspected or confirmed pandemic influenza illness. Although it is known that pregnant women are transiently immunodepressed, it is unclear why this category, during a widespread outbreak, showed a greater susceptibility to pandemic influenza virus infection and was at increased risk of hospitalization and death [5–7]. Is it possible that the hormonal modifications during pregnancy could change the cell membrane receptors and make cells more susceptible to viral infection? It has been shown that sialic acid may be altered in pregnancy. Some data have demonstrated that the amount of sialic acid in serum and, probably, on cell membranes is elevated during pregnancy, in particular at the end of the second trimester (14–19 weeks) and in the third trimester (29–40 weeks) [8]. Moreover, quantitative alterations in relative amounts of sialic acid have been observed in oligosaccharide structures of amniotic fluid glycoconjugates in correspondence with the gestation period. An increased sialic acid content at 21 and 40 weeks of pregnancy has also been found in saliva [9]. A correlation exists between an increased risk of complications attributable to influenza at different weeks of gestation (with odds ratios of 1.06 during weeks 1–7, 2.52 (1.74–3.65) during weeks 21–26,

and 4.67 during weeks 37–42) and an increased level of sialic acid [9]. It appears, moreover, that both types of sialic acid linkages, α 2,6 or α 2,3 to Gal, may be present on pregnancy-associated molecules [10]. Whether sex hormones influence the enzymatic activities of sialyltransferases and/or sialidases that control serum sialic acid levels is unknown. The increase in total serum sialic acid may reflect increased sialylation of glycoproteins or glycolipids attributable to increased sialyltransferase activity and/or increased secretion of sialic acid from cell membranes attributable to elevated sialidase activity. Thus, increased level of sialic acid in serum and, probably, on cell receptors should enhance the avidity of the binding and the number of interactions between human influenza virions and the cell surface, producing a greater amount of virus. Experimental data have also shown that MDCK-SIAT1 cells engineered by transfection with human CMP-*N*-acetylneuraminate β -galactoside α -2,6-sialyltransferase and expressing enhanced α -2,6-linked receptor levels contribute to a higher recovery rate for human influenza viruses than in MDCK [11]. It is likely that a higher amount of sialic acid in blood might correspond with a greater presence of this receptor on the cell membranes, thus facilitating the infection by promoting early events of the virus replicative cycle and reducing the time required to establish infection. On the other hand, increased levels of cell-free sialic acid could theoretically inhibit virus attachment to epithelial cells blocking the initial interaction of a virus with host cell receptors and preventing viral infection. However, this is questionable, because subtype specificity and strain variance may play a critical role in determining the ability of sialic acid molecules to inhibit binding [12]. Consequently, this feature would support the hypothesis that a change in the level of sialic acid during pregnancy could be an important factor contributing to an increased risk of severe complications in pregnant women infected with influenza virus. Furthermore, increased levels of sialic acid have been associated with multiple medical and

non-medical conditions besides pregnancy, including cancer, diabetes, and chronic renal failure [13], as well as the ageing process; thus, it would be interesting to analyse this parameter also in these categories of subjects to evaluate the role of this factor during influenza epidemics.

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