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VIRAL INFECTION

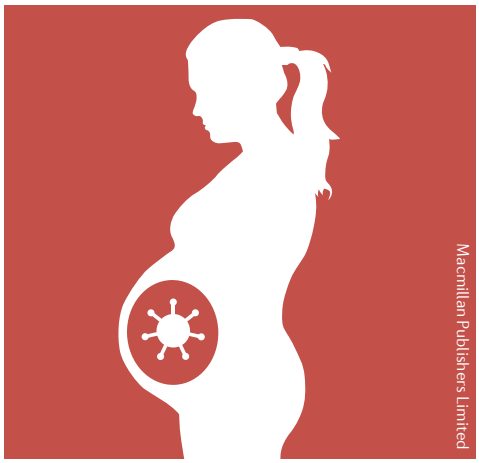
The mother of all viruses

> pregnancy may lead to the emergence of more virulent strains of influenza

Pregnant women are particularly vulnerable to influenza virus infection during pandemics; although this is thought to be due to suppression of the maternal immune system during pregnancy, the mechanisms involved are poorly defined. Engels *et al.* now report that pregnant mice develop weaker antiviral immune responses in the lungs than non-pregnant mice following infection with a pandemic strain of H1N1 influenza virus. Strikingly, this leads to the emergence of virus variants that show increased virulence even in non-pregnant animals.

Previous work examining influenza virus infection in pregnant mice used syngenically mated mice. To more accurately model human pregnancy (in which the fetus expresses allogenic paternal antigens), the authors mated C57BL/6 female mice with BALB/c males and infected pregnant females with the 2009 pandemic (pH1N1) strain of influenza virus. Of note, mortality was higher in these pregnant females after pH1N1 infection than in pregnant C57BL/6 mice that had been syngenically mated, whereas non-pregnant C57BL/6 mice all survived infection with pH1N1. Non-pregnant mice and surviving syngenically mated pregnant mice fully recovered from pH1N1 infection by day 14, but allogenically mated pregnant mice showed increased and prolonged weight loss following pH1N1 infection. By contrast, infection with a seasonal strain of influenza virus did not cause mortality or significant weight loss in non-pregnant mice or in either group of pregnant mice, even at very high infection doses.

For the rest of their study the authors used allogenically mated pregnant mice and found that, compared with non-pregnant controls, these animals showed reduced expression of interferon (IFN)-stimulated genes (ISGs) and had lower levels of IFNα, IFNγ, interleukin-6 and tumour necrosis factor in the lungs following infection with pH1N1. Furthermore, infected pregnant mice showed reduced expression of co-stimulatory molecules on antigen-presenting cell populations in the lungs. Experiments using mice with a $CD11c^+$ cell-restricted deficiency in the progesterone receptor suggested that the pregnancy hormone progesterone was at least partly responsible for suppressing innate immune responses to pH1N1. Pregnant mice also showed suppressed virus-specific antibody responses and reduced $CD8^+$ T cell recruitment to the lungs following pH1N1 infection. Although pregnant mice had higher frequencies of virus-specific $CD8^+$ T cells than non-pregnant mice following pH1N1 infection, *in vivo* killing assays showed that



$CD8^+$ T cells from pregnant mice had reduced cytotoxicity against virus-peptide loaded target cells. Adoptive transfer of virus-specific $CD8^+$ T cells from non-pregnant mice to pregnant mice did not improve survival rates in response to pH1N1 infection, but did improve recovery from infection in surviving pregnant animals.

Overall, these results suggested that the immune response to influenza virus is suppressed during pregnancy, and the authors reasoned that failure to rapidly clear pH1N1 influenza virus may lead to the emergence of novel virus variants. To assess this, they sequenced viral RNA genomes isolated from the lungs of pregnant and non-pregnant pH1N1-infected mice. They found that mutation frequencies were increased in viruses obtained from pregnant mice; in particular, viruses isolated from pregnant mice had a high frequency of a specific mutation in the non-structural gene-encoded protein NS1 that was found to further supress the maternal IFN response. Notably, when the authors infected mice with a recombinant pH1N1 influenza virus containing this NS1 mutation, the virus strain induced increased mortality and morbidity compared with the parental H1N1 influenza virus, even in non-pregnant animals.

These findings have important clinical implications as they indicate that pregnancy may lead to the emergence of more virulent strains of influenza virus; they also highlight the importance of effective vaccination programmes for pregnant women.

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ORIGINAL ARTICLE Engels, G. *et al.* Pregnancy-related immune adaptation promotes the emergence of highly virulent H1N1 influenza virus strains in allogenically pregnant mice. *Cell Host Microbe* **21**, 321–333 (2017)