

SUSCEPTIBILITY TO SERIOUS VIRAL DISEASE IN PREGNANCY – A PROBLEM OF IMMUNE REGULATION?

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ABSTRACT

The current swine-origin H1N1 pandemic has highlighted the fact that pregnant patients are susceptible to serious disease or life-threatening complications following acute viral infections such as pandemic influenza, varicella and hepatitis E virus, whereas chronic viral infections such as human papillomavirus and cytomegalovirus often reactivate during pregnancy. The increased susceptibility to particular viral infections is probably due to pregnancy-induced tolerance, which is necessary to allow placentation, without rejection, and is yet poorly characterised. The recently identified T-cell subset, T regulatory cells (Tregs) may provide a new research target to understand pregnancy-associated tolerance and increased susceptibility to viral infections.

The increased morbidity and mortality of the current pandemic swine-origin H1N1 influenza in pregnancy has highlighted the difference in susceptibility to certain viral diseases associated with pregnancy.

Pregnant women with serious disease have been over-represented in the recent swine-origin H1N1 influenza outbreak in the USA, with the hospitalisation rate about 0.32 per 100 000 pregnant women compared to 0.076 per 100 000 for the population at risk.¹ A very high proportion of pregnant women among those who died of pandemic influenza has also been observed in the subsequent southern hemisphere outbreaks such as in Australia² and South Africa. Although seasonal influenza is usually associated with an increased risk in pregnant women, the increase in case-fatality associated with pregnancy was more pronounced during previous pandemics and especially during the 1918-1919 pandemic.³ Mechanical reasons, such as the decrease in effective tidal volume associated with third-trimester pregnancy may partially explain the increased risk of death due to influenza pneumonia as pregnancy progresses. However, it does not explain the significantly increased risk of cardiopulmonary events during seasonal influenza from as early as week 21.⁴ Also, mechanical factors or the increased cardiac output do not account for the particular pathology observed in some pregnant patients during influenza pandemics, including the current one, where patients presented with viral pneumonia⁵ and acute respiratory distress syndrome.⁶ Pregnant patients also tend to present with more severe disease during influenza pandemics than during seasonal influenza epidemics,⁵ where most patients hospitalised had other co-morbid conditions.⁷

Life-threatening viral pneumonia is an unexpected finding in the current pandemic since the 2009 H1N1 influenza strain is not particularly virulent.^{8,9} However, this strain, being new to humankind, differs from seasonal influenza, in that there are no cross-reacting antibodies, from prior influenza exposures. It appears that an aberrant immune response towards a primary viral infection may exacerbate severity and increase the case fatality rate during pandemic influenza. Similarly primary infection with varicella zoster virus during pregnancy is associated with a risk of pneumonia as high as 10%.¹⁰ Measles has also been associated with pneumonitis in pregnant patients.¹¹ Hepatitis E virus (HEV) infection has been associated with an increased risk of death in pregnant women¹² with mortality higher than 25% in some outbreaks¹³ whereas the usual case fatality rate is less than 0.1%.¹⁴ Increased susceptibility during pregnancy is also observed for chronic or persisting viral infections. Genital warts often increase in pregnancy to such an extent that they can cause obstructive labour;^{15,16} this may be due to tolerance towards human papillomaviruses associated with genital warts. Human cytomegalovirus (HCMV) is normally controlled by cellular immunity but as pregnancy progresses HCMV-specific cellular immunity is suppressed, explaining the frequency of HCMV reactivation found in pregnant patients.^{17,18} Asymptomatic reactivation and excretion of human polyomaviruses have also been found to be related to a decreased cellular immune response in pregnant women.^{19,20} Furthermore, emerging viral diseases may also show increased mortality in pregnant women, as has been observed for severe acute respiratory syndrome (SARS).³

Pregnancy is characterised by tolerance towards the fetus and placenta, which allows growth of this 'foreign' tissue without rejection. How the immune system adapts to maintain placentation without rejection and how this results in an increased susceptibility to viral infections are not clearly understood. The increased oestrogen and progesterone levels may suppress humoral immunity during pregnancy, inhibiting B-cell production in the bone marrow.²¹ However since cellular immunity is extremely critical in the defence against most viral infections, tolerance probably lies at the level of cellular immunity. The ineffective immune response towards viral infections during gestation was previously ascribed to a shift in T-helper (Th) cells from Th-1 to Th-2 cytokine expression profiles.^{14,22} However, although the Th-bias was found in circulating immune cells,²² it has not been shown to be involved in rejection at placental level. Rather placentation is characterised by 'controlled inflammation' on the level of the innate immune system with HLA-C antigens expressed on trophoblast cells, interacting with natural killer cells.²³ In addition, a recently identified subset of T-lymphocytes, T regulatory cells (Tregs) may play an important role in pregnancy associated tolerance,²⁴ and low Treg levels may be associated with pregnancy loss in humans and laboratory animals.²⁵ The role of Tregs has been characterised in chronic infections such as HIV, hepatitis C virus and Epstein-Barr virus (EBV)²⁶ but data on their role in acute viral disease are lacking. A decreased pathogen clearance by the cellular immune system, induced by Tregs during pregnancy,

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may explain the increased severity of particular viral diseases in pregnancy. In some individuals pregnancy-associated immune-suppression or tolerance may unmask susceptibility, whether genetic or acquired, to particular infectious diseases. In most other healthy pregnant individuals, however, the redundancy of the immune system probably provides sufficient protection against serious viral disease despite the suppressive effects of pregnancy.

Future advances in our understanding of the innate immune system and the complex interaction of different classes of T-lymphocytes may further elucidate the effects of pregnancy on susceptibility to viral infections – with the ultimate aim being to identify and timeously treat those who are at risk of serious disease.

Declaration of conflict of interest

The author declares no conflict of interest.

REFERENCES

- Jamieson DJ, Honein MA, Rasmussen SA, *et al.* H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009; **374**: 451-458.
- Sweet M. Pandemic lessons from Australia. *BMJ* 2009; **339**: b3317.
- Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. *Emerg Infect Dis* 2006; **12**: 1638-1643.
- Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol* 1998; **148**: 1094-1102.
- Hardy JM, Azarowicz EN, Mannini A, Medearis DN Jr, Cooke RE. The effect of Asian influenza on the outcome of pregnancy, Baltimore, 1957-1958. *Am J Public Health Nations Health* 1961; **51**: 1182-1188.
- Novel influenza A (H1N1) virus infections in three pregnant women – United States, April-May 2009. *MMWR Morb Mortal Wkly Rep* 2009; **58**: 497-500.
- Hartert TV, Neuzil KM, Shintani AK, *et al.* Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. *Am J Obstet Gynecol* 2003; **189**: 1705-1712.
- Neumann G, Noda T, Kawaoka Y. Emergence and pandemic potential of swine-origin H1N1 influenza virus. *Nature* 2009; **459**: 931-939.
- Munster VJ, de Wit E, van den Brand JM, *et al.* Pathogenesis and transmission of swine-origin 2009 A (H1N1) influenza virus in ferrets. *Science* 2009; **325**: 481-483.
- Paryani SG, Arvin AM. Intrauterine infection with varicella-zoster virus after maternal varicella. *N Engl J Med* 1986; **314**: 1542-1546.
- Arya SC, Agarwal N. Measles during pregnancy including neonates. *J Infect* 2005; **51**: 340-341.
- Sharapov MB, Favorov MO, Yashina TL, *et al.* Acute viral hepatitis morbidity and mortality associated with hepatitis E virus infection: Uzbekistan surveillance data. *BMC Infect Dis* 2009; **9**: 35.
- Aggarwal R, Krawczynski K. Hepatitis E: an overview and recent advances in clinical and laboratory research. *J Gastroenterol Hepatol* 2000; **15**: 9-20.
- Navaneethan U, Al Mohajer M, Shata MT. Hepatitis E and pregnancy: understanding the pathogenesis. *Liver Int* 2008; **28**: 1190-1199.
- Michiels I, Tjalma WA. The rapid development of a giant condylo-ma acuminatum (Buschke-Lowenstein tumor) during pregnancy. *Acta Obstet Gynecol Scand* 2007; **86**: 762-763.
- Morrison EA, Gammon MD, Goldberg GL, Vermund SH, Burk RD. Pregnancy and cervical infection with human papillomaviruses. *Int J Gynaecol Obstet* 1996; **54**: 125-130.
- Tanaka A, Hirota K, Takahashi K, Numazaki Y. Suppression of cell mediated immunity to cytomegalovirus and tuberculin in pregnancy employing the leukocyte migration inhibition test. *Microbiol Immunol* 1983; **27**: 937-943.
- Agatsuma Y, Fitzpatrick P, Lele A, Kaul A, Ogra PL. Cell-mediated immunity to cytomegalovirus in pregnant women. *Am J Reprod Immunol* 1981; **1**: 174-179.
- Coleman DV, Gardner SD, Mulholland C, *et al.* Human polyomavirus in pregnancy. A model for the study of defence mechanisms to virus reactivation. *Clin Exp Immunol* 1983; **53**: 289-296.
- Kalvatchev Z, Slavov S, Shtereva M, Savova S. Reactivation of Polyomavirus hominis 1 (BKV) during pregnancy and the risk of mother-to-child transmission. *J Clin Virol* 2008; **43**: 328-329.
- Medina KL, Smithson G, Kincade PW. Suppression of B lymphopoiesis during normal pregnancy. *J Exp Med* 1993; **178**: 1507-1515.
- Vince GS, Johnson PM. Is there a Th2 bias in human pregnancy? *J Reprod Immunol* 1996; **32**: 101-104.
- Sargent IL, Borzychowski AM, Redman CW. NK cells and human pregnancy -an inflammatory view. *Trends Immunol* 2006; **27**: 399-404.
- Guerin LR, Prins JR, Robertson SA. Regulatory T-cells and immune tolerance in pregnancy: a new target for infertility treatment? *Hum Reprod Update* 2009; **15**: 517-535.
- Saito S, Shima T, Nakashima A, Shiozaki A, Ito M, Sasaki Y. What is the role of regulatory T cells in the success of implantation and early pregnancy? *J Assist Reprod Genet* 2007; **24**: 379-386.
- Joosten SA, Ottenhoff TH. Human CD4 and CD8 regulatory T cells in infectious diseases and vaccination. *Hum Immunol* 2008; **69**: 760-770.

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