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New Insights into the Relationship between Viral Infection and Pregnancy Complications

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Abstract

A recent study by McDonnold and co-investigators published in the *American Journal of Obstetrics and Gynecology* reports an association between human papillomavirus (HPV) infection and preeclampsia. The investigation was based on the hypothesis that HPV trophoblast infection results in failed trophoblast invasion, and placental dysfunction and hypoxia. The findings from this study along with previous data addressing the relationship between viral infection and obstetrical complications highlight the relevance of viral infection during pregnancy. A better understanding of mechanisms via which virus leads to pregnancy complications will drive us closer to finding a strategy to prevent adverse outcomes.

Keywords

Complication; infection; pregnancy; virus

Opinion

A growing body of evidence links viral infection with complications of pregnancy,[1–8] such as preterm labor and preeclampsia,[9,10] although the mechanisms of disease are poorly understood.

Over decades, the association between bacterial and viral infections and preeclampsia has been assessed.[11–14] The evidence that links infection with preeclampsia is the following: (i) microorganisms and their products can exert a direct effect on trophoblasts and alter trophoblast invasion and deep pla-centation;[15–17] (ii) infectious agents can induce atherosclerotic-like changes in the placental vessels;[18–21] and (iii) microbial products can induce an exaggerated maternal systemic inflammatory response.[22–26]

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Preeclampsia is diagnosed by the combined presence of hypertension and proteinuria in preg-nancy.[27–31] Placental ischemia and hypoxia have been implicated and thought to result from a disorder of deep placentation.[32,33] However, the precise mechanism responsible for this has not been elucidated.

Recently, we described a mouse model of viral infection during pregnancy consisting of the injection of the murine herpes virus-68 (MHV-68) early in pregnancy.[34] Using such model, we demonstrated that MHV68 is able to infect the trophoblast and decidua although with no apparent effect on the pregnancy.[34] However, MHV68 infection of the placenta induces vascular changes characterized by the presence of edema in the placenta and fetus. Furthermore, we showed that viral infection of the placenta modifies the immune response to bacterial products by breaking the normal 'tolerance' to LPS and exacerbating the inflammatory response, which then leads to preterm labor.[34,35] Based on these observations, we proposed a 'double-hit hypothesis' where a viral infection sensitizes the placenta/decidua unit to bacterial products.

Several reports demonstrate that human papillomavirus (HPV) is able to infect the human placenta, syncytiotrophoblasts being the dominant cellular tar-get,[36] and that trophoblast transfected with HPV-16 oncogenes leads to increased apoptosis and failure to adhere to endometrial cell line HEC.[37,38] These findings suggest that as with other viruses, such as adeno-associated virus or cytomegalovirus,[12,13,16] HPV may also lead to inadequate or failed trophoblast invasion and obstetrical complications related to placental dysfunction.

Our model may explain some of the findings described in a recent study published in the February issue of *American Journal of Obstetrics and Gynecology*, entitled 'High risk human papillomavirus at entry to prenatal care and risk of preeclampsia' by McDonnold and colleagues.[39] The study reports an association between HPV infection and preeclampsia.[39] The investigation was based on the hypothesis that HPV trophoblast infection results in failed trophoblast invasion, and placental dysfunction and hypoxia. To explore a link between HPV infection and defective trophoblast invasion, they conducted a retrospective cohort study comparing the prevalence of preeclampsia between a high-risk human papillomavirus (HR-HPV) unexposed group, defined as pregnant women who had two or more normal Papanicolaou (PAP) smears within 3 years, and an exposed group with the presence of abnormal pap smear results including LSIL, HSIL, ASCUS r/o HSIL, and ASUS with positive HR-HPV. The authors found a higher rate of preeclampsia in women exposed to HPV than in the unexposed group (10.19 versus 4.94%; $P = 0.04$).

The findings from this study along with previous data addressing the relationship between HPV infection and obstetrical complications, such as *in vitro* fertilization failure or spontaneous abortion,[40–42] preterm labor,[43] and preterm premature rupture of the membranes,[44] provide important information to help us to understand the relevance of viral infection during pregnancy.

We have proposed in the past that viral infection of the placenta may lead to substantial changes in the trophoblast physiology.[45] These changes may be associated with the ability of the placenta to modulate the maternal immune system, interact with the maternal blood

vessels, and protect the fetus from additional infections.[34,35,46] Such functional changes in the trophoblast due to viral infection may lead to either pregnancy failure or the development of preeclampsia. In our animal model, a murine form of herpes virus, MHV68, was not only able to infect the trophoblast, but also induced significant changes in the capacity of the trophoblast to respond to additional danger signals.[35] By injecting lipopolysaccharide (LPS) (at a dose shown to have almost no effect on pregnancy outcome) into pregnant mice that were pre-exposed to MHV68, we were able to demonstrate that viral infection modulates the capacity of the trophoblast to elicit increased inflammatory mediators such as IL-6, G-CSF, and MCP-1 in response to LPS. The novel concept is that a viral infection in the placenta triggers an exaggerated immune response to bacteria and may apply to the mechanism by which HR-HPV infection causes PE or even other adverse outcomes such as preterm labor.

Although the observation reported by McDonnold and colleagues presents a very important association,[39] additional issues remain to be addressed. First, 10.4% of women with normal PAP smears were found to have latent HPV infection, of which 32%were HPV 16 or 18 according to the meta-analysis by de Sanjosé et al.[47] This indicates that a patient with a normal PAP smear cannot be considered HPV negative. However, the control group in this study was pregnant women with normal cervical cytology *per se* without HPV testing, which may have falsely categorized patients with latent HPV infection into the HR-HPV unexposed group. Second, of 58.4% (329 of 563) of women with ASCUS excluded from the study, a substantial number (unknown) were excluded due to absent HR-HPV testing, which may represent a potential bias. Racicot et al. has shown that viral infection of the cervix increases the susceptibility to ascending infection,[7] and HPV may not have been the primary causative agent, but rather a contributing factor to other coexisting bacteria or virus. Third, it should not be ignored that periconceptional HPV infection can also occur through infected seminal fluid or sperm.[40] Thus, paternal HPV infection status should also be considered. The clinical evidence delineating the relationship between HPV infection and adverse pregnancy outcome emphasizes that although HPV by itself may not be detrimental, it can place the pregnancy at risk of complications, such as PE or preterm labor.

In summary, the potential mechanisms of action to explain these clinical observations could be due to viral effect on trophoblast function. Viral infection of trophoblast might result in: (i) suboptimal trophoblast invasion or (ii) hypersensitivity to bacteria or other viral infections due to changes in the normal immune modulatory role of the trophoblast (Fig. 1).

By exploring and defining the role of viruses in the development of adverse pregnancy outcomes, we may be closer to finding a strategy to prevent adverse outcomes.

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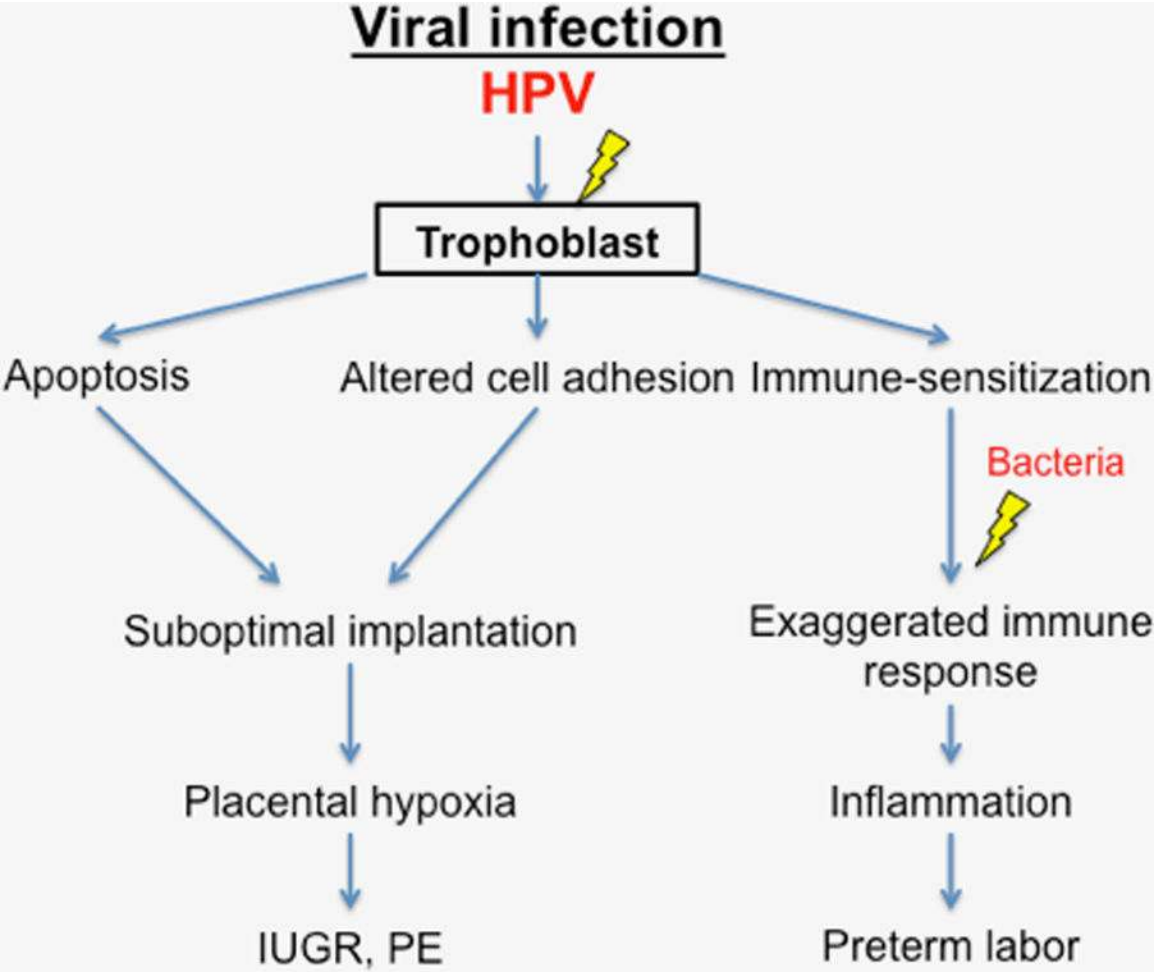

Figure 1.
Potential effect of viral infection on trophoblast function leading to pregnancy complications. HPV, human papilloma virus; IUGR, intrauterine growth restriction; PE, preeclampsia.