The Immune System in Pregnancy: A Unique Complexity


Fellow 洪雅珊
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Introduction

• Viral and bacterial pandemics threaten the general population.
• Children and pregnant women may be at a higher risk and more susceptible to or more severely affected by infectious diseases.

Are pregnant women more susceptible to infectious disease threats?

• How does a viral infection affect the fetus and the pregnancy outcome?
• Are prophylaxis and treatment appropriate and beneficial for pregnant women?

Are pregnant women more susceptible to infectious disease threats?

• The concept of immunology of pregnancy as an organ transplantation have complicated the field and delayed the development of new guidelines with clinical implications.
• Aim
  – To evaluate many of the “classical concepts” to define new approaches of the immunology of pregnancy.

Immune system in pregnancy

• Innate immune systems
  – Surveillance, recognition, response to microorganism
  – High numbers of immune cells in human decidua: macrophages, NK cells, regulatory T cells
  – NK cells: 70%, macrophages: 20-25%, dendritic cells: 1.7%
  • During 1st trimester, accumulate around the invading trophoblast cell.
  • No NK cell/trophoblast cell can’t reach the EM vascularly-termination of pregnancy (Hanna, 2006)
  • Dendritic cells → prevent blastocyst implantation and decidual formation (Birnberg, 2007)
• Adaptive immune system
  – B cells are absent
  – T lymphocytes constitute about 3-10% of the decidual immune cells.

• uNK cells are critical for trophoblast invasion in the uterus.
  • uDC
    – necessary for decidual formation
    – may affect the angiogenic response
    – With T cell responses to the fetal "allograft," starkly contrast with their prominent role in organ transplant rejection. (Collins, 2009)

• The fetal-maternal immune interaction is more complex than the transplant allograft!!!

• The presence of immune cells at the implantation site is not associated with a response to the "foreign" fetus, but to facilitate and protect the pregnancy.

• The immune system is not suppressed, but is active, functional and is carefully controlled.

Is the systemic immunity of the mother suppressed?

• During pregnancy, the maternal immune system
  – reinforced network of recognition and communication
  – trafficking and repair
  – alarm if necessary
  – maintain the well-being of the mother and the fetus.

• The fetal immunity provide a developing active immune system, modify the way the mother responds to the environment.

• Pregnancy is a unique immune condition that is modulated, but not suppressed.

• Pregnancy should not imply more susceptibility to infectious diseases. Instead, is a modulation of the immune system which leads to differential response depending not only on the microorganisms, but on the stages of the pregnancy.
"classical concept" vs recent concept

- Over 50 yrs ago, Sir Peter Medawar proposed ....
  - Fetus is a semi-allograft, not rejected by the maternal immune system.
  - Fetus might escape maternal immune surveillance.
  - The placenta is an allograft expressing paternal proteins should be rejected.
- Now, the placenta is thought of more than a transplanted organ.
- The trophoblast and the maternal immune system have established a cooperative status help the success of the pregnancy.

'A new paradigm " is proposed ...

- The immunological response of the mother to microorganisms which will be determined and influenced by the presence and responses from the fetal/placental unit.
- Immunology of pregnancy the combination of signals and responses originated from the maternal immune system and the fetal-placental immune system.
- The signals originated in the placenta will modulate the way the maternal immune system behaves.

Cytokine shift

- Numerous studies attempts to prove
  - pregnancy is an anti-inflammatory condition.
  - Shift in the types of cytokines lead to abortion or pregnancy complications.
  - But numerous studies against this notion.
- In reality, pregnancy has 3 distinct immunological phases and can be symbolized by how the pregnant women feels.

The first phase

- Blastocyst implanted on the epithelial lining damage the EM tissue to invade trophoblast replaced the EM form maternal blood vessels adequate placental-fetal blood supply.
- An inflammatory environment is required repair and remove cells
- Mother feels sick to adapt the fetus (hormonal changes and other factors)
- The first trimester is a pro-inflammatory phase.
The second phase
• A period of rapid fetal growth and development.
• The mother, placenta and the fetus are symbiotics
• An anti-inflammatory status.
• Optimal time for the mother
  – No nausea, fever as she did in the first stage

The last phase
• The fetus has completed its development
• The mother needs to deliver the baby → parturition!
  – An influx of immune cells into the myometrium to promote recrudescence of an inflammatory process.
•需 a pro-inflammatory environment to promote uterine contractions, expulsion of the baby and rejection of the placenta.
• Pregnancy is a pro-inflammatory and anti-inflammatory condition, depending upon the stage of gestation.

These differences in cytokines may reflect the sensitivity to infectious diseases.
• For examples…
  – Malaria: high risk during the first half of the pregnancy, risk declines during the second half.
  – Lassa fever: high rate of case-fatality in the 3rd trimester.
  – In general, pregnant women are resistant to viral infection including HIV.

Active protection of the trophoblast against viral infection
• Trophoblast
  – Cellular unit of the placenta
  – Recognize the microorganism
  – Initiates immune response
  – Produce anti-microbial peptides → active protection
    • Anti-microbial human β-defensin 1 and 3
    • Secretory leukocyte protease inhibitor → inducer of bacterial lysis
    • IFN-β
    • TLR-3, TLR-7, TLR-8, TLR-9
  – Response at the maternal-fetal interface → placenta prevents transmission of viral infection to the fetus.

The placenta represents an active immunological organ, capable of recognizing and responding to pathogens.

How a viral infection affects the fetus and the pregnancy outcome??

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How a viral infection affects the fetus and the pregnancy outcome??
• Viral infection during pregnancy
  – Cross placenta \(\rightarrow\) reach the fetus \(\rightarrow\) fetal death, miscarriage, major congenital anomalies
  – No placental transmission \(\rightarrow\) fetus was adversely affected by the maternal response
  – Some may be asymptomatic, half of all preterm deliveries have histologic evidence of inflammation of the placenta.
  – Only a fraction of fetuses demonstrable congenital infection.
  – Placenta may have a potent immune-regulatory interface protecting the fetus from systemic infection.

• The placenta functions as a regulator of the trafficking rather than as a barrier. \(\text{(Mor G, 2008)}\)

• Fetal and maternal cells move in the two direction. \(\text{(Stevens, 2004; Mold, 2008)}\)

• Although viral infections are common during pregnancy, transplacental passage and fetal infection appear to be the exception rather than the rule!

• The type of response initiated in the placenta \(\rightarrow\) affect the immunological response of the mother \(\rightarrow\) affect the pregnancy outcome.
  – Placental infection \(\rightarrow\) produce inflammatory cytokines \(\rightarrow\) activate maternal immune system \(\rightarrow\) placental damage, abortion or preterm labor. \(\text{(Koga, 2009)}\)
  – Placental viral infection \(\rightarrow\) mild inflammatory response \(\rightarrow\) not terminate the pregnancy, but activate the immune system of the mother and the fetus.

• Possible consequence after activation of immune system
  – Sensitize the mother to other microorganisms, increase the risk of pregnant women to infection
  – Promote an inflammatory response in the fetus, even though there is no viral transmission.

Key points …
• In the past, the placenta and the fetus was thought as \(\text{immunologically dead organ} \rightarrow\) only the action of the maternal immune system.

• Now, the placenta and the fetus represent an additional immunological organ which affects the global response of the mother to microbial infections.

Mother-Placenta-Fetus: a complex response to infection
• Fetal inflammatory response syndrome (FIRS)
  – Absence of cultivable microorganism
  – High circulating levels of inflammatory cytokines in fetus, affect the CNS and circulatory system
  – Animal study \(\text{(Cardenas, 2009)}\): placental viral infection, no virus reach the fetus \(\rightarrow\) cause fetal inflammatory response similar in FIRS.
  – FIRS increases the future risk for autism, schizophrenia, neurosensorial deficits and psychosis.
  – Pro-inflammatory cytokines may cause fetal ventriculomegaly and hemorrhages
  – The response may predispose to disease in adulthood.
An inflammatory response in the placenta alters the cytokine balance in the fetus, may affect the normal development of the fetal immune system leading to anomalous responses during childhood or later in life.

Are prophylaxis and treatment appropriate and beneficial for pregnant women?

New pathogens will continue to increase.

- It is important to know the placenta response to the pathogen, because
  - Some microorganisms may not directly affect the pregnancy but could "sensitize" the mother and the fetus to additional pathogens.
- Prophylaxis is required, and the earlier the better.
- Risk-benefit of vaccination during all stages of pregnancy should be carefully evaluated!!

Conclusion

- Placental immune response affect the pregnant women's susceptibility to and severity of certain infectious diseases.
- The generalization of pregnancy as a condition of general immune suppression or increase risk is misleading and prevents the determination of adequate guidelines for treating pregnant women during pandemics.

Next steps we need to do ....

- Evaluate the interaction of each specific pathogen with the fetal/placental unit and its responses to design the adequate prophylaxis or therapy.
- Evaluate the presence of maternal viral infection prenatally to prevent long-term adverse outcomes
- Develop useful biomarkers for viral infections during pregnancy to help early detection and prevention of damage.

Thank you!