The Immune System in Pregnancy: A Unique Complexity

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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 dose a viral infection affect the fetus and the pregnancy outcome ?
- Are prophylaxis and treatment appropriate and beneficial for pregnant women ?

- 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 .

Are pregnant women more susceptible to infectious disease threats?

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%; marcophages : 20-25% ; dentritic cells : 1.7%
    - During 1st trimester , accumulate around the invading trophoblast cell .
    - No NK cell →trophoblast cell can't reach the EM vascularity→termination of pregnancy . (Hanna, 2006)
    - dentritic cells ↓ → prevent blastocyst implantation and decidual formation . (Birnbertg, 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.

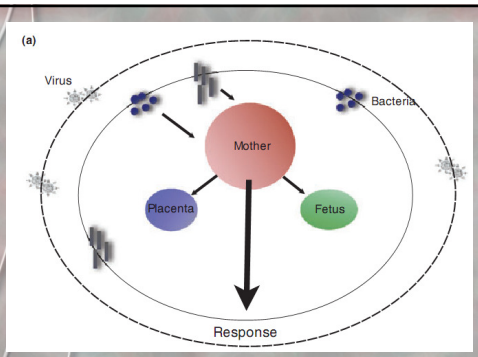
  Instead, is a modulation of the immune system which leads to differential response depending not only on the microorganisms, but on the stages of the pregnancy.

"classical concept" vs recent concept

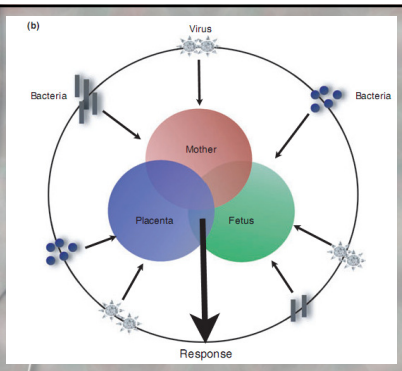
- Over 50 yrs ago , Sir Peter Medawar proposed ….
  - Fetus is a semi-allograft , not rejected by the maternal immune system .
  - Fetus might escape maternal immune surveillance.
  - The placenta is an allograft expressing paternal proteins → should be rejected.
- Now , the placenta is thought of more 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.



- Old model : the maternal immune system as the major player in responses to the fetus and microorganism.
- Fetal responses are considered limited.



- New integrational model : the fetal-placental immune response and the maternal immune system are integrated.

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 .
- Need a pro-inflammatory environment to promotes 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 ??

- Viral infection during pregnancy→
  - Cross placenta → reach the fetus →fetal death, miscarriage, major congenital anomalies

    or

    No placental transmission →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 . (Mor G, 2008)
- Fetal and maternal cells move in the two direction . (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 →affect the immunological response of the mother → affect the pregnancy outcome.
  - Placental infection → produce inflammatory cytokines →activate maternal immune system → placental damage , abortion or preterm labor . (Koga, 2009)
  - Placental viral infection → mild inflammatory response →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 non-active immunological organs , 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
    - Amnial study (Cardenas,2009): placental viral infection , no virus reach the fetus → cause fetal inflammatory response similar in FIRS.
  - FIRS increases the future risk for autism, schizophrenia, neurosensorial deficits and pyschosis .
  - Pro-inflammatory cytokines may cause fetal ventriculomegaly and hemorrhages
  - The response may predispose to disease in adulthood.

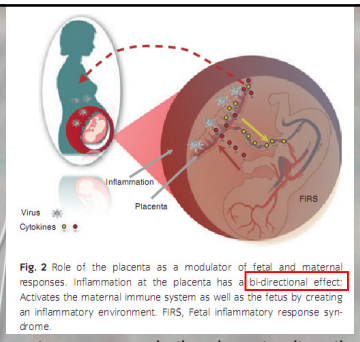


Fig. 2 Role of the placenta as a modulator of fetal and maternal responses. Inflammation at the placenta has a bi-directional effect: Activates the maternal immune system as well as the fetus by creating an inflammatory environment. FIRS, Fetal inflammatory response syndrome.

- 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 → 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 →help early detection and prevention of damage.

Thank you !