Autoimmune Disorders in Pregnancy

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Presenter Disclosure

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Learning Objectives

• Review the normal changes of the immune system in pregnancy and compare to the pathophysiology of autoimmune disorders

• Discuss the maternal management of the more common autoimmune disorders in pregnancy

• Discuss the antenatal monitoring strategies to optimize perinatal outcome depending on the type of autoimmune disorder present
Autoimmune Disorders in Pregnancy

• Autoimmunity vs. autoimmune disease
  • Autoimmunity- immune response against self
    • May show autoantibodies without clinical disease (e.g.- positive ANA but no signs of SLE)
      • Positive ANA can be positive years prior to clinical dx of SLE
    • Autoimmune dz- pathogenic autoimmunity that leads to overt pathology of organs or organ-systems.

• Difficult to assign specific diagnosis
  • May take 12 months of follow-up
  • Explains the category of “undifferentiated” disease

• Female and non-Caucasian preponderance
  • 8:1 to 10:1 depending on the disease (Sjogren’s- 10:1)
  • SLE higher incidence in African American women (4:1)
Autoimmune Disorders in Pregnancy

Types of Autoimmune Disorders

• Organ-Specific
  • Single tissue or organ is targeted
  • Can have multiple organ-specific autoimmune disease
  • E.g.- Type 1 DM, autoimmune hepatitis, thyroiditis

• System-specific (older name- collagen vascular disease)
  • Multiple organs of the same or different systems are affected by the same autoantibodies
  • E.g.- SLE, Sjogren’s Syndrome, Scleroderma
Maternal Immune System Concepts

- Medawar theory (1952)
  - Addresses the unique immunology of maternal-fetal interface for first time
  - Described the fetal allograft analogy wherein the fetus is viewed as semi-allogeneic because it is partly made up of paternal antigens and therefore foreign to maternal immune system yet evades rejection of the maternal immune system
Maternal Immune System Concepts

• Maternal-placental tolerance
  • Embryo divides into inner cell mass (fetus) and external trophoectoderm (placenta)
  • Trophoblasts directly interact with maternal uterine cells/immune system
  • Somehow the trophoblasts can avoid immune rejection
  • Fetus has paternal major histocompatibility complex (MHC) antigens expressed
    • Not on trophoblasts
Types of Immune Response

Innate Immunity

• Involves phagocytic cells
  • Macrophages and granulocytes

• Express pattern recognition receptors (PRR)
  • Detect conserved pathogen-derived sequences on microbes

• Several actions
  • Produce inflammatory cytokines, release degradative enzymes, induce phagocytosis

• Primer for the adaptive immune response
Types of Immune Response

Adaptive Immunity

- Receives phagocytic material from innate system
- Humoral and Cellular responses
  - Antibody production (humoral)
  - Cell lysis with T lymphocytes
  - Release cytokines
- Memory attribute
  - Will remember the foreign antigenic material so that can respond even more vigorously to subsequent exposure
Types of Immune Response

Adaptive Immunity

- **CYTOKINES**
  - Can be proinflammatory or anti-inflammatory
  - T helper cell differentiation
  - Both types - counter-regulatory effects
    - Th1 cells proinflammatory
      - IL-2, interferon -Y which induce a cytotoxic response
    - Th2 cells anti-inflammatory
      - IL-4, IL-6, IL-10 involved in antibody production
REASONS FOR IMMUNE PROTECTION OF THE PREGNANCY

• Placenta as mechanical barrier
• Suppression of maternal immune system
• Absence of MHC class I molecules on trophoblasts
• Local and systemic cytokine shifts
• Local immune suppression mediated by Fas/Fas ligand (FasL) system
REASONS FOR IMMUNE PROTECTION OF THE PREGNANCY

• Placenta - mechanical barrier (up to 1980s)
  • Physical barrier to maternal immune cells
  • Studies showed bidirectionality of cells between placenta and uterus
    • Fetal cells shown in maternal tissue years after pregnancy

• Suppression of maternal immune system
  • Pregnancy somehow reduces maternal immune response
  • Studies show no effect on antiviral immunity
  • Also not supported by woman’s survival in hostile environments in some cultures
REASONS FOR IMMUNE PROTECTION OF THE PREGNANCY

Cytokine Shift

• Relates to the different phases of implantation/placentation

• Divided into 3 phases
  • Correlate with the trimesters of pregnancy
  • First- proinflammatory
  • Second- anti-inflammatory
  • Third- proinflammatory
REASONS FOR IMMUNE PROTECTION OF THE PREGNANCY

_Cytokine Shift_

• First phase
  • Trophoblasts break through endometrium causing tissue damage and stimulating immune response
  • Removal of damaged cells and cellular repair needed
  • Maternal symptoms in first trimester partially due to this immune response
REASONS FOR IMMUNE PROTECTION OF THE PREGNANCY

Cytokine Shift

• Second phase
  • Period of fetal growth/development
  • Proinflammatory state replaced by anti-inflammatory state
  • Maternal symptoms decrease

• Third Phase
  • Occurs near end of third trimester
  • Influx of immune cells into myometrium restarting the proinflammatory state
    • Promotes contractions, expulsion of baby and placenta
Maternal Immune System
Rethinking its Role
(Redefining Medawar Hypothesis)

• Immune system functions differently towards pregnancy compared to typical concerns in transplantation

• Much of maternal immune system works in concert with pregnancy, not against it
  • Involved in supportive roles towards the pregnancy
  • Probably related to semi-allograft tissue with changes to protect against an immune response towards the paternal-derived fetal cells
Maternal Immune System Concepts

• Much more to the story than graft-host interaction
• Maternal immune system can have protective/nurturing effect on pregnancy
• Fetoplacental unit not a passive entity
  • Trophoblast response, FIRS
• Maternal inflammation can have long-term effect on fetal development
Systemic Lupus Erythematosus (SLE) in Pregnancy

• Occurs in approx. 1 per 1000 pregnancies

• Multisystem autoimmune disease
  • Skin, kidneys, liver, CNS, immune system, hematologic
  • Result of immune-mediated tissue damage
  • Involvement of pathologic activation of complement system

• Maternal Complications- usually involves flare
  • Lupus flare- increased symptoms, decreased complement
  • Risk dependent on presence of flare within 6 months of conception
    • No flare- 8% risk, flare within 6mos – 58% risk
    • Developing active flare – Risk of pregnancy loss – 40%
**SLE in Pregnancy**

**Maternal Effects**

- **Active flare - Lupus nephritis**
  - Strong predictor of pregnancy outcome
  - Active nephritis in pregnancy - 2-3x increased risk for pregnancy loss or preterm birth
    - Preterm birth secondary to severe pre-eclampsia

- **Thrombocytopenia**
  - Can be SLE-induced or secondary to antiphospholipid syndrome (APS)
  - Not easily distinguished even in the presence of APS-antibodies
  - If APS related then also increased risk for thrombosis
SLE in Pregnancy
Antiphospholipid Syndrome

• Lab criteria: at least one must be present
  • Lupus anticoagulant- positive
  • Anticardiolipin Ab- IgM and IgG medium/high positive
  • Beta-2 glycoprotein-1 Ab- IgM and IgG >99th percentile (usually medium/high positive)

• Clinical criteria: at least one must be present
  • Vascular thrombosis- arterial or venous, any size vessel
  • Unexplained fetal death at or beyond 10wks
  • Unexplained fetal losses x 3 < 10 wks with chromosomal abnormalities excluded
  • Preterm delivery < 34 wks due to pre-eclampsia or placental insufficiency (IUGR)
SLE in Pregnancy

Antiphospholipid Syndrome

- Thrombosis- 40% risk with SLE and APS present
- Pregnancy morbidity- mechanism not well understood
  - Pregnancy loss, pre-eclampsia, placental insufficiency, preterm birth
  - Management depends on history of thrombosis or the type of pregnancy complication
  - Hx of thrombosis and APS- Heparin (prophylactic + aspirin (81mg))
  - Any of the co-morbidities present with antibodies- prophylactic heparin indicated antepartum and postpartum
  - Tx: Low molecular weight heparin preferred- less side effects
  - Antibodies without any clinical history- anticoagulation may not be indicated
SLE in Pregnancy

Neonatal Effects

• Neonatal Lupus Syndrome - always transient
  • Photosensitive rash, thrombocytopenia, hepatitis, hemolytic anemia
  • Usually with high maternal SSA or SSB titers
    • Types of anti-nuclear antibodies

• Long-term risks
  • Some studies suggest children of SLE moms may be at increased risk for SLE later in life
    • Probably genetic component involved
  • Congenital heart block - usually permanent when develops
    • In presence of maternal SSA or SSB antibodies
SLE in Pregnancy

Congenital Heart Block

• 1/3 patients with SLE have SSA or SSB antibodies
• Approx. 1-3% risk for affected child with no history
• Increases to 25-30% risk of CHB with one affected child
• Highest risk between 18-28 weeks gestation
• Dexamethasone given if signs of CHB- poorly effective
• Latest recommendation: weekly monitoring of fetal PR Interval with ultrasound if SSA or SSB positive
  • Suggested to monitor until 28 weeks
    • In our practice- monitor from 17 weeks until delivery
    • Reason: once in CHB- will not reverse in most cases
  • PR interval abnormally increased- suggest 1st deg. heart block
    • Dexamethasone is recommended to prevent progression to complete heart block
Sjogren’s Syndrome (SS) in Pregnancy

• Lymphocytic infiltration of epithelial cells of various tissues leading to immune complexes or B-cell hyperactivity
  • Female predominance
• Primary SS- immune complexes in salivary and tear glands- leads to oral/ocular dryness
• Secondary SS- systemic or found with other autoimmune diseases (e.g.- SLE)
  • Can lead to immune complex deposition within tissues
    • Nephritis, obstructive bronchiolitis, cholangitis
  • Can lead to B-cell hyperactivity
    • Glomerulonephritis, neuropathy, B-cell lymphoma
Sjogren’s Syndrome (SS) in Pregnancy

• Maternal morbidity - usually uncomplicated
  • Depends on underlying disease state - primary vs. secondary

• Fetal/neonatal morbidity
  • Mainly secondary to presence of SSA and SSB antibodies
  • SSA - 60-80% of pts, SSB - 30-40% of pts.
    • SSB is never present unless SSA is present in Sjogren’s Synd.
  • SSA and SSB antibodies have affinity for specific fetal myocardial antigens and epitopes
  • If SSA OR SSB positive then should follow recommendations discussed previously concerning fetal monitoring of heart rhythm
Scleroderma (Systemic Sclerosis) in Pregnancy

• Uncommon disease of unknown cause and variable presentation
  • Hallmarks: autoimmunity, inflammation, pathologic alteration of small blood vessels, interstitial and vascular fibrosis in the skin and internal organs

• Connective tissue disease affecting skin and internal organs
  • Chronic inflammation with variable degrees of collagen accumulation (fibrosis)
  • Obliterative vasculopathy of various organs
  • Treatment- organ-specific but no therapy available for the disease systemically
Systemic Sclerosis in Pregnancy

- Data limited since Systemic Sclerosis usually develops after childbearing years
- Course depends on disease present prior to pregnancy
  - Based on amount of small-vessel disease present
- Scleroderma renal crisis
  - 2-3% of Scleroderma pregnancies
  - Can be indistinguishable from severe pre-eclampsia/HELLP
  - Delivery sometimes indicated due to acute renal failure
  - ACE inhibitors indicated postpartum but has fetal effects antepartum
- Increased risk for IUGR/placental insufficiency
  - Low-dose ASA should be considered, antenatal monitoring of growth and weekly antenatal testing in the third trimester
Rheumatoid Arthritis in Pregnancy

• Systemic autoimmune disease with chronic inflammation of joints and other structures
• Female predominant - 3:1
• Pregnancy morbidity
  • Antepartum - usual improvement of arthritic symptoms - approx. 75% of patients
  • Postpartum - higher risk for flare
  • Glucocorticoids can be used either antepartum or postpartum for flares
    • Small amount of medication will cross placenta
    • Small increased risk for IUGR
      • Consider monitoring fetal growth
      • Weekly testing based on growth pattern
Takayasu Arteritis in Pregnancy

- Immune arteritis causing inflammation of the aorta, major branches and pulmonary arteries
- Female predominance- 6-8:1
  - Early age onset (< 30y/o), more common Asian women (1 in 3000 in Japan), 2.6/million in the U.S.
- Organ involvement- cardiac, lungs, aorta, kidneys
  - Cardiac- 6-16% with coronary artery disease, heart failure
  - Aorta- increased risk for aneurysms
  - Lungs- pulmonary hypertension
- Pregnancy morbidity- based on maternal disease
  - Comarmond(2015)- studied 142 pregnancies- pre- and post-dx
  - Pre-eclampsia(24%), preterm delivery(8%), IUGR/fetal demise (5%)
Antenatal Fetal Monitoring Strategies

• Consider fetal growth assessment throughout pregnancy regardless of the type of disorder

• First Trimester
  • Antiphospholipid Ab, SSA/SSB titers, anti-dsDNA, complement (C3, C4, CH50), ANA titer
    • Serial ANA titers not necessary unless concern for flare
    • Consider SSA and SSB with ANA positive regardless of SLE dx
  • 24-urine for protein and creatinine clearance if underlying risk for vasculopathy (i.e. not necessary for RA)

• Third Trimester- depends on whether risk increased for vasculopathy (i.e. can affect placental function)
  • Weekly NST starting at 32-34 weeks until delivery
  • Mode of delivery based on obstetrical indications

• Timing of delivery- variable based on maternal/fetal status
Autoimmune Disorders in Pregnancy

Summary

• Maternal immune system in healthy state is very adaptive and supportive to the allogeneic fetus

• Important to be aware of the various autoimmune disorders due to the predominance in women

• SLE in pregnancy should be monitored closely as any flare can impact the pregnancy in terms of placental function and delivery timing

• SSA and SSB should be checked with certain disorders (SLE, Sjogren’s, Scleroderma) due to risk of CHB

• Antenatal monitoring important to optimize fetal outcome