Autoimmune Disorders in Pregnancy

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Systemic Lupus Erythematosus

- 90% cases are in women
- Prevalence of 1/500 in childbearing age
- Mortality has changed dramatically over the years
  - 1950s: 5 year survival was 50%
  - 1990s: 10 year survival is 90-95%

SLE: Criteria for Diagnosis

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers - painless
- Arthritis - 2+ joints
- Serositis
- Renal disorder
- CNS disorder
- Hematological disorder
- Immunological disorder – anti-DNA, anti-Smith, false positive VDRL
- ANA antibody

SLE: Criteria for Diagnosis

- At least 4 criteria needed, either serially or simultaneously
- 98% specificity and 97% sensitivity
- Renal involvement in 50% of cases
- Involvement of brain, lungs, kidney or heart worsens prognosis

Autoantibodies in SLE

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Frequency</th>
<th>Clinical Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-nuclear (ANA)</td>
<td>95%</td>
<td>Not specific for SLE</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>70%</td>
<td>Clinical activity, renal</td>
</tr>
<tr>
<td>Anti-Smith</td>
<td>30%</td>
<td>Specific for lupus</td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>40%</td>
<td>MCTD, lupus</td>
</tr>
</tbody>
</table>

Related to Diagnosis

Autoantibodies in SLE

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Frequency</th>
<th>Clinical Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Ro (SSA)</td>
<td>30%</td>
<td>Sjogren’s Syndrome, Neonatal lupus, Congenital heart block</td>
</tr>
<tr>
<td>Anti-LA (SSB)</td>
<td>10%</td>
<td>Sjogren’s Syndrome, Neonatal lupus, Congenital heart block</td>
</tr>
<tr>
<td>Anticardiolipin</td>
<td>50%</td>
<td>APS, thrombosis, IUGR, fetal death, PET</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>26%</td>
<td>IUGR, fetal death, PET</td>
</tr>
</tbody>
</table>

Related to Outcome

Questions in SLE and Pregnancy

1) Does pregnancy influence the course of SLE?
2) Does SLE influence the course of pregnancy?
3) Does SLE affect the fetus?
4) What medications can be used in pregnancy?
1) Effect of Pregnancy on SLE
2) Effect of SLE on Pregnancy

- Maternal and fetal outcomes related to major end organ involvement and autoantibodies

- Poorer prognosis with:
  - CNS involvement
  - Renal involvement
  - Hypertension
  - APS
  - SSA / SSB antibody

Question 1
Effect of Pregnancy on SLE

- In general, most women do well during pregnancy.

- No real consensus on incidence of SLE flares (9% - 74%)

- Controversy explained by different definitions of flare, patient selection and clinical implications of activity.

- Flares can occur in any trimester as well as postpartum.

- ±90% of flares are mild to moderate, requiring 4-20 mg additional Prednisone.

1) Maternal Outcomes - LPCH

<table>
<thead>
<tr>
<th>All Pregnancies (N=63)</th>
<th>New Onset of SLE (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Outcomes</td>
<td>Number (%)</td>
</tr>
<tr>
<td>Flare during Pregnancy</td>
<td>42 (68)</td>
</tr>
<tr>
<td>Mild to Moderate Flare</td>
<td>30 (71)</td>
</tr>
<tr>
<td>Severe Flare</td>
<td>12 (29)</td>
</tr>
</tbody>
</table>

1) Effect of Pregnancy on SLE

- ±10% of flares are severe, requiring ≥20 mg additional Prednisone

- Overall, exacerbations are common, but usually mild and manageable with changes in medications

- Most important predictor of flares
  Disease activity at conception

- If SLE is active at conception, flare is more likely
1) Organ System Involvement in Flares

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Preg. Pts. % N=37</th>
<th>Non Preg. Pts. % N=185</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculo skeletal</td>
<td>35</td>
<td>58</td>
<td>YES</td>
</tr>
<tr>
<td>Neurologic</td>
<td>4</td>
<td>21</td>
<td>YES</td>
</tr>
<tr>
<td>Renal</td>
<td>43</td>
<td>22</td>
<td>YES</td>
</tr>
<tr>
<td>Hematologic</td>
<td>38</td>
<td>17</td>
<td>YES</td>
</tr>
</tbody>
</table>

Constitutional, Dermatologic, Serositis, and Pulmonary - no diff.

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Lupus and Pregnancy: Eleven Year Experience at a Single Center

Yasser Y. El-Sayed, M.D., Erika J. Lu, B.A., Mark C. Genovese, M.D., R. Elaine Lambert, M.D., Usha Chitkara, M.D., and Maurice L. Druzin, M.D.

The Department of Obstetrics and Gynecology

The Department of Medicine

Stanford University Medical Center

Submitted 2002

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1) Pregnancy Outcome CNS Lupus

- 4 patients with 5 pregnancies
- 3 patients CNS symptoms in 1st and 2nd trimester
- 2 patients severe CNS exacerbation post partum
- 1 maternal death 2 years later
- 2 neonatal deaths at 26 weeks – severe IUGR

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1) Summary

- Women with CNS lupus are at high risk for pregnancy complications.
- CNS lupus appears to represent an especially severe manifestation of SLE, with greater maternal and fetal risks than other end-organ involvement.
- These risks may exist whether or not there are active CNS symptoms in pregnancy.
1) Effect of Pregnancy on SLE

Lupus Nephropathy

- If in remission – patient will do well
- 50% will develop hypertension
- 8-30% will have *transient* and reversible worsening of renal function

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Question 2

Effect of SLE on Pregnancy

Increased incidence of maternal / fetal complications:

- Hypertension
- Gestational diabetes
- Placental Insufficiency Syndromes +/- APS – Secondary
  - Preeclampsia *
  - Intrauterine growth restriction
  - Preterm delivery
  - Fetal death

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1) Pregnancy Following Renal Transplantation


<table>
<thead>
<tr>
<th>SLE – n 36</th>
<th>Non-SLE – n 274</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies</td>
<td>60</td>
</tr>
<tr>
<td>Live Births</td>
<td>77%</td>
</tr>
<tr>
<td>Pregnancy Loss</td>
<td>17%</td>
</tr>
<tr>
<td>TAB</td>
<td>10%</td>
</tr>
</tbody>
</table>

Incidence of hypertension, GDM and c-section *lower in SLE* than non-SLE transplant group.
2) Predictors of Maternal Outcomes - LPCH

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Outcome (RR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Preeclampsia</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3.2 (1.2-8.6)</td>
</tr>
</tbody>
</table>

Chakravarty et al

2) International Consensus Statement on Preliminary Criteria for the Classification of the Antiphospholipid Syndrome

ACOG Practice Bulletin #68
November 2005

2) Antiphospholipid Antibody Syndrome (APS)

- Clinical Criteria
  - Fetal loss: 3+ before 10 wks, or unexplained after 10 wks
  - Obstetrical: placental insufficiency, IUGR, early preeclampsia (< 34 wks)
  - Thrombosis: clinical episodes of venous, arterial or small vessel

- Laboratory Criteria
  - Anticardiolipin antibodies: IgG or IgM isotype in medium-high titers
  - Lupus anticoagulant: Prolonged aPTT, dilute RVVT, kaolin clotting time
  - Dilute PT

  2 or more occasions, 6 weeks apart

- Occurs in 25% of patients with SLE - Secondary

- Increased risk for spontaneous loss, fetal demise and thrombosis

- Decidual vasculopathy, placental infarction, early onset preeclampsia, fetal growth restriction
2) APS

- Postpartum syndrome - autoimmune exacerbation
  - Fever
  - Pulmonary infiltrates
  - Pleural effusions
  - ± Renal insuff., pulm. H/T, thrombosis

- Catastrophic APS
  - Accelerated coagulation vasculopathy
  - High mortality

2) Treatment of APS – Level C

ACOG #68

- Prophylactic regimens: *fetal losses but no thrombotic events*
  - Heparin and low-dose aspirin daily and 6 wks post-partum
    - Standard heparin
      - 7,500-10,000U q 12 hrs in 1st trimester; 10,000U q 12hrs in 2nd and 3rd trimesters
    - Low molecular weight heparin
      - Lovenox (enoxaparin) 30mg q 12hrs or Fragmin (dalteparin) 5,000U q 12hrs

- Antenatal monitoring for IUGR

Placental Pathology in Systemic Lupus Erythematosus: A prospective study


- Objectives: distinguish between the effect of SLE and antiphospholipid antibody (APLA) on outcome and placental pathologic conditions in pregnant patients with SLE
Conclusions

- Decidual vasculopathy/coagulopathy
  - mediate APLA-related and
  - much of SLE-related deleterious effect on the placenta and gestational outcome

- Presence of APLA largely, but not invariably, predicts fetal death

- APLA-independent chronic villitis may represent a second mechanism of SLE-related change

Question 3

Effect of SLE on the Fetus

- Increased rates adverse outcomes:
  - PPROM
  - Preterm birth
  - IUGR
  - Pregnancy loss: early and late

- Neonatal Lupus

3) Effect of SLE on the Fetus

- Adverse outcomes more likely if:
  - End organ disease: renal, pulmonary, CNS
  - Active disease at conception
  - Presence of Anti-Ro and Anti-La antibodies – SSA or SSB antibodies
  - Presence of antiphospholipid antibodies

3) Fetal Outcomes - LPCH

<table>
<thead>
<tr>
<th>Fetal Outcomes</th>
<th>ALL PREGNANCIES (N=63)</th>
<th>NEW ONSET SLE (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Loss, 1st trimester</td>
<td>6 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Elective Termination</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Premature (&lt;37 weeks GA)</td>
<td>29 (54)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>GA 32-37 weeks</td>
<td>25 (46)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>GA 28-32 weeks</td>
<td>2 (4)</td>
<td>0</td>
</tr>
<tr>
<td>GA &lt;28 weeks</td>
<td>2 (4)</td>
<td>1 (25)</td>
</tr>
</tbody>
</table>

Chakravarty et al
3) Fetal Outcomes – LPCH

<table>
<thead>
<tr>
<th>Fetal Outcomes</th>
<th>ALL PREGNANCIES (N=63)</th>
<th>NEW ONSET SLE (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
</tr>
<tr>
<td>Birth weight (g)*</td>
<td>2505 (771)*</td>
<td>1995 (1114)*</td>
</tr>
<tr>
<td>IUGR</td>
<td>5 (9)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>1 minute APGAR &lt;7</td>
<td>13 (48)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>5 minute APGAR &lt;7</td>
<td>3 (6)</td>
<td>0</td>
</tr>
<tr>
<td>NICU Admission</td>
<td>31 (57)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>1 (2)</td>
<td>1 (25)</td>
</tr>
</tbody>
</table>

* Mean (SD)

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3) Clinical Predictors of Prematurity and Preeclampsia in the SLE Pregnancy - LPCH

- **Premature Delivery**
  - Severe flare (RR 1.96, 95% CI 1.13-3.40)
  - Anti-hypertensives at conception (RR 1.83, 95% CI 1.23-2.73)
  - Prednisone at conception (RR 1.77, 95% CI 1.07-2.94)
- **Preeclampsia**
  - Thrombocytopenia (RR 3.2, 95% CI 1.2-8.6)

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3) Neonatal Lupus

- Correlated with transplacental passage of Anti-Ro (SS-A) and Anti-La (SS-B)
- 14-16 weeks
- Occurs in 10% of patients with these antibodies
- Most cases are cutaneous lupus (transient neonatal rash) and thrombocytopenia

3) Neonatal Lupus

- Dermatology Online Journal Vol. 12 Number 7 2006 Robles et al
3) Neonatal Lupus

- Neonatal lupus did not correlate with the titer of anti-Ro antibodies
- Two neonatal lupus children with congenital heart block were born to mothers not previously known to have SLE


3) Congenital Heart Block

- Most serious manifestation of neonatal lupus
- Diffuse myocarditis and fibrosis in the region between the AV node and bundle of His
- Cardiac lesion is permanent; pacemaker needed


3) Neonatal Lupus

- Incidence is <3%
- 1/3 affected infants die within 3 years
- 15% recurrence risk if affected sibling
- Therapy does not normalize conduction

3) Neonatal Lupus

- Life-threatening neonatal lupus is **rare** in mothers known to have SLE.
- Prophylactic therapy is therefore **not** indicated in these women.

Lockshin, Bonta, Elkon, Druzin et al.
Neonatal Lupus Risk to Newborns of Mothers With SLE.
Arthritis Rheum 31:697, 1988

A New Therapeutic Approach to the Fetus With Congenital Complete Heart Block: Preemptive, Targeted Therapy With Dexamethasone

Therapy of established CCHB in the fetus has resulted in improved survival but persistence of heart block.

Morbidity of heart block → sudden death → pacemaker

Ref: Rosenthal D, Druzin ML, Dubin A et al. Obstet Gynecol 1998; 92(4); p689-91

Case

- 35 y.o. g 2, p 1, with Sjogren Syndrome and a previous pregnancy complicated by CCHB + pacemaker
- Intensive fetal monitoring with echocardiography was employed
- Early evidence of myocardial dysfunction and dysrhythmia was found

Dexamethasone therapy was initiated
- Dysfunction and dysrhythmia resolved
- Pregnancy went to term without further complication
- Neonate- 1° heart block up to 3/12 -Rx steroids

**Conclusion:** A new and successful strategy to identify very early signs of myocardial disease in a fetus at high risk of congenital complete heart block, enabling targeted, preemptive therapy.
**Congenital Heart Block**

*The Stanford University Protocol*

Fetal echocardiographic screening of Anti-SSA/Ro and/or Anti-SSB/La positive patients to detect impending heart block

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**Screening Protocol for Patients with Anti-SSA/Ro and/or Anti-SSB/La Antibodies**

- Maternal anti-SSA/Ro and/or anti-SSB/La antibodies
  
  Fetal echocardiogram at 16, 18, 20, 22, 24, 27 and 30 weeks
  
  Abnormal echocardiograms
  
  Administer dexamethasone 4 mg qD
  
  Neonatal antibody screening and steroid treatment if indicated

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**Results**

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled to date</td>
<td>23</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Previously affected pregnancy</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Average number echocardiograms per patient</td>
<td>5.33</td>
<td>N/A</td>
</tr>
<tr>
<td>Incidence of CHB (95% CI: 0 to 0.13)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abnormalities seen of echocardiogram</td>
<td>1 mild tricuspid regurgitation 1 rhabdomyoma</td>
<td>N/A</td>
</tr>
<tr>
<td>Structural cardiac anomalies</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Number of patients receiving prophylactic steroids</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cases of neonatal lupus</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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**2006 - New Protocol**

Serial AVCT measurements for fetuses that are exposed to maternal anti-Ro/La antibodies at the following gestational ages:

- 18, 20, 21, 22, and 24 weeks

Réf: Jaeggi E et al. JVCS 2005
2008 - Scheduling Guidelines for Fetal Echocardiograms

Lucile Packard Children’s Hospital at Stanford

Theresa Tacy, MD
Associate Professor of Pediatrics
Lucile Salter Packard Children’s Hospital
Stanford University Medical Center

Maternal Lupus
16-24 weeks

For Maternal Lupus, every other week from 16-24 weeks, then once per month 26 weeks to term.

In a given patient, this may change to weekly imaging or even more frequently, and we will guide the scheduling desk accordingly.

Transplacental Fetal Treatment Improves the Outcome of Prenatally Diagnosed Complete Atrioventricular Block without Structural Heart Disease

- 37 consecutive cases of fetal CAVB were studied since 1990.
- Mean age at diagnosis was 25.6 +/- 5.2 EGA
- 33 Patients (92%) – CAVB was associated with maternal anti-Ro/La autoantibodies

Overall 22 Fetuses were treated
- 21 – Dexamethasone
- 9 – B-stimulation
- Mean 7.5 +/- 4.5 weeks
The 21 patients treated with dexamethasone had a 1 year survival rate of 90% compared with 46% without glucocorticoid therapy (P<0.02).

**Conclusion**

A standardized treatment approach, including transplacental fetal administration of dexamethasone and B-stimulation at heart rates < 55 bpm, reduced the morbidity and improved the outcome of isolated fetal CAVB.

**Question 4**

What medications can be used in pregnancy?

**Answer:** Most of the medications used when you are not pregnant, with some exceptions.

**4) SLE Medications**

- **Cyclophosphamide, Methotrexate and Cell Cept**
  - Teratogenic and should be avoided
- **Azathioprine:**
  - Generally considered safe
  - Some association with IUGR, although unclear if disease related vs drug effect
  - Induces chromosome breaks – disappear as infant grows
4) Cell Cept – Mycophenolate Mofetil

Pregnancy: Teratogenic Effects: Pregnancy

Category D

4) Cell Cept - MMF

Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant woman. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations:

- external ear
- other facial abnormalities including cleft lip, palate
- anomalies of the distal limbs
- heart, esophagus and kidney

In the National Transplantation Pregnancy Registry (NTPR) Data on 33 MMF-exposed pregnancies in 24 transplant patients

There were 15 spontaneous abortions (45%) and 18 live-born infants

Four of these 18 infants had structural malformations (22%).

4) SLE Medications

- Prednisone
  - Generally considered safe
  - Facial clefts in animal studies
  - Higher doses: risk for gestational diabetes
  - If used daily/regularly, high dose IV steroids
  - Should be administered during labor and delivery
4) SLE Medications

- **Heparin**
  - Extensive safety record in pregnancy
  - Medication of choice for anticoagulation
  - Risk for osteoporosis and thrombocytopenia
  - Low risk for HIT in pregnancy

- **Aspirin**
  - Low dose aspirin – 81mg
  - Considered safe
  - Discontinue close to delivery due to risk of hemorrhage in the neonate

**Plaquenil ~ 1990-2000**

A Randomized Study of the Effect of Withdrawing Hydroxychloroquine Sulfate in Systemic Lupus Erythematosus

The Canadian Hydroxychloroquine Study Group

**Results**

- The relative risk of a clinical flare-up was 2.5 times higher (95 percent confidence interval, 1.08 to 5.58) in the patients taking placebo than in those continuing to take hydroxychloroquine (16 of 22 patients vs. 9 of 25 had flare-ups), and the time to a flare-up was shorter ($P = 0.02$)

4) Summary 2000 – present

- Flares of SLE disease have been documented when these agents are discontinued.

- Flares of SLE disease activity are known to be detrimental to pregnancy outcome in patients with SLE.

- It is our opinion that these drugs should not be discontinued during pregnancy in a patient with lupus, particularly when the known terminal elimination half life is 1 to 2 months.
4) Summary
2000 - present

- Hydroxychloroquine relatively **safe** in pregnancy
- No long term effects noted
- Appropriate **therapy** for control of disease important
- Recommend continuation of HCQ

LPCH

<table>
<thead>
<tr>
<th></th>
<th>Discontinued Medication Pre-conceptionally (n = 5)</th>
<th>Discontinued Medication at first OB visit (n = 11)</th>
<th>Continued Medication (n = 2)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/Moderate SLE Flare</td>
<td>2 (40%)</td>
<td>6 (55%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Severe SLE Flare</td>
<td>0</td>
<td>2 (18%)</td>
<td>0</td>
</tr>
<tr>
<td>PET</td>
<td>0</td>
<td>3 (27%)</td>
<td>0</td>
</tr>
<tr>
<td>PPROM</td>
<td>0</td>
<td>4 (36%)</td>
<td>0</td>
</tr>
<tr>
<td>PTD (&gt;33wks)</td>
<td>0</td>
<td>7 (64%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*one patient lost to follow-up
Chakravarty et al.

4) Treatment of SLE

- **Medication to maintain remission**
- Low dose aspirin ± low dose heparin for APS
- Full anticoagulation if history of thrombotic event

Most Important Objective: Preconceptional Counseling

- **Discuss**
  - Contraception
  - Risks
  - Medication changes
  - Laboratory evaluation
  - Timing of Pregnancy

- **Goal**
  - Pregnancy when SLE in remission
Management in Pregnancy

- Co-management between OB and Rheumatology specialists
- Visits every 2-4 weeks
- Ultrasounds every 4 weeks
- Monthly laboratory evaluations
- Fetal antenatal surveillance ≥ 30-32 weeks
- Treatment of disease activity and/or complications

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that disproportionately affects women.

Although the peak incidence of RA occurs around the age of menopause, many women develop RA during the childbearing years with estimated delivery rates among RA patients in the United States ranging from 800 to 2,100 annually.

This makes the safety of pregnancy from a maternal and fetal perspective an important clinical question.

Historically, disease activity was thought to improve during pregnancy and little attention was paid to the impact of rheumatoid arthritis on pregnancy outcomes.

RA has on pregnancy outcomes, several authors have observed disproportionately high rates of adverse pregnancy outcomes including low birth weight and prematurity.

This has been postulated to be related to the effect of systemic inflammation during pregnancy.
However, the majority of recent data on pregnancy outcomes of patients with RA come from large administrative databases in different countries and have not necessarily controlled for the impact of disease activity or medication use.

The aim of the current study was to describe the outcomes of pregnancies complicated by maternal RA and evaluate potential associations between disease characteristics, medication use, and pregnancy outcomes.

Materials and Methods

We conducted an institutional review board approved retrospective review of all pregnancies complicated by RA delivered at our institution between June 2001 and June 2009.

We searched all records with diagnosis codes of RA and pregnancy. Those patients with mixed connective tissue disease or other autoimmune diagnoses were excluded.

Confirmation of the diagnosis was made with review of rheumatology notes when available, and otherwise by review of the obstetrical notes by a rheumatologist (EFC) for the purposes of this study.

Materials and Methods

All subjects had a diagnosis of RA prior to conception.

Data collection included obstetrical history, rheumatologic disease characteristics, medication use, and pregnancy outcomes.

Pregnancies that did not result in delivery including therapeutic pregnancy terminations or spontaneous abortions prior to 20 weeks gestational age were not captured in our dataset and therefore not evaluated.

Materials and Methods

A patient was considered to have active disease at conception if she had musculoskeletal complaints typical of RA at her first medical visit during pregnancy to either her obstetrician or rheumatologist.

Given the retrospective nature of our study, clinically significant disease flare was defined conservatively as symptoms that required an increase in prednisone use, immunosuppressant medication use, or hospitalization for musculoskeletal complaints.

"Disease activity during pregnancy" was defined as a composite variable of either active disease at conception or RA flare during pregnancy.
Materials and Methods

- Pregnancy outcomes of interest included:
  - Preterm delivery
  - Preterm premature rupture of membranes
  - Pre-eclampsia
  - Fetal demise
  - Birth weight
  - Congenital malformations
  - Neonatal intensive care unit (NICU) admission

- A composite outcome of neonatal morbidity was defined as:
  - Intrauterine fetal demise
  - Small for gestational age at the time of delivery
  - Neonatal intensive care unit admission

Long term outcomes of patients or affected infants were not available.

- Fisher’s exact tests were used to calculate odds ratios and 2-tailed student’s t-tests were performed to examine differences between groups. A p-value of ≤ 0.05 was considered statistically significant.

Results

- We reviewed the available medical records of 40 women with RA who delivered at our institution between June, 2001 and June, 2009.
- Six of these women had two deliveries during the study period the our cohort.
- Baseline characteristics are described in Table 1.
- Eight of the women had juvenile RA.
- Rheumatoid factor status was not available for all patients, but was documented to be positive at some time point for 86% (12/14) of patients who had available data.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at delivery (years)</td>
<td>32.6 +/- 6</td>
</tr>
<tr>
<td>Race / Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic, White</td>
<td>40% (21/56)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>36% (14/41)</td>
</tr>
<tr>
<td>Asian</td>
<td>22% (10/46)</td>
</tr>
<tr>
<td>Black</td>
<td>2% (1/46)</td>
</tr>
<tr>
<td>Gravida</td>
<td>2.3 +/- 2.06</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>48% (20/42)</td>
</tr>
<tr>
<td>Length of RA diagnosis (years)</td>
<td>8.2 +/- 7.16 (range 1-30)</td>
</tr>
</tbody>
</table>

Baseline Characteristics, Table 1
Medication Use During Pregnancy

- Seventy percent (32/46) of pregnancies began with women using anti-rheumatic medications near the time of conception (Table 2).

- Prednisone (25/42, 60%) and hydroxychloroquine (plaquenil) (12/42, 29%) were the most commonly used agents, followed by methotrexate (5/42, 12%), leflunomide (2/42, 5%), tumor necrosis factor inhibitors (5/42, 12%) and anakinra (1/42).

- Plaquenil was discontinued in 7/12 women. Those who continued plaquenil delivered between 2006 and 2009. Those women who had their plaquenil discontinued delivered between 2001 and 2009. With the exception of prednisone and plaquenil, the majority of medications were stopped secondary to pregnancy.

Table 2

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of women using the medication near the time of conception</th>
<th>Number of women who discontinued the medication because of pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Plaquenil</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Infliximab</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Anakinra</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Medication use near conception. Table 2.

Disease Activity During Pregnancy

- In the majority of cases, disease modifying anti-rheumatic drug therapy was discontinued after conception, but in the first trimester (7/9).

- In one case, pregnancy was not recognized until 20 weeks gestation: adalimumab was discontinued immediately upon diagnosis of pregnancy.

- No congenital anomalies were observed in the exposed infant at birth.

- 24% of women had active RA at conception as assessed by musculoskeletal complaints at the first medical visit after conception (Table 3).

- The majority (53.3%, 24/45) of patients experienced a disease flare during pregnancy with flares more common in the first and second trimesters.

- 70% of patients required prednisone during pregnancy to control signs and symptoms of underlying disease. While disease flare and prednisone use were common, the majority of the flares were mild and treated with prednisone alone.
Women who had medications discontinued secondary to pregnancy had a higher rate of disease flare than those who did not have medication changes (71% vs. 45%). This difference, however, did not reach statistical significance (OR 2.96, 95% CI 0.66-15.87).

Pregnancy Outcomes

- Obstetrical outcomes of pregnancies complicated by maternal RA are shown in Table 4.
- There was a single intra-uterine fetal demise at 26+2/7 weeks gestation that was presumed to be secondary to an umbilical cord accident and not related to underlying maternal RA.
- One pregnancy was terminated at 23 weeks of gestation secondary to severe growth restriction and oligohydramnios.
  - Her evaluation revealed no etiology for her poor outcome. She had a normal thrombophilia evaluation, and autopsy revealed a small, but otherwise normal fetus and placenta.

As noted in Table 4, we had an unexpectedly high preterm birth rate of 28%.

- Spontaneous preterm births include women with preterm premature rupture of membranes (P-PROM) and spontaneous preterm labor.
- All of the women with P-PROM did take prednisone at some point during pregnancy.
- Among the indicated preterm births, 2 were secondary to pre-eclampsia and the other was secondary to IUGR and oligohydramnios of one twin along with preterm contractions in a woman with a history of a prior laparoscopic myomectomy.
Table 4

<table>
<thead>
<tr>
<th>Genitalia of Delivery</th>
<th>27.14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navel (cm)</td>
<td>17 (5.4)</td>
</tr>
<tr>
<td>Genitalia (cm)</td>
<td>17 (5.4)</td>
</tr>
<tr>
<td>Cervix (cm)</td>
<td>27 (9.3)</td>
</tr>
<tr>
<td>Navel Height (cm)</td>
<td>27 (9.3)</td>
</tr>
<tr>
<td>Average Genital Age of Delivery (weeks)</td>
<td>21.64</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>4 (8.8)</td>
</tr>
<tr>
<td>Induced</td>
<td>20 (11)</td>
</tr>
<tr>
<td>NR U/S/Abortion</td>
<td>27 (12.4)</td>
</tr>
<tr>
<td>Small for Gestational Age</td>
<td>18 (10)</td>
</tr>
</tbody>
</table>

*Includes an IUFD at 26 weeks and one termination due secondary to oligohydramnios and IUFD at 26 weeks.
**26 infants = 16 premedicated + 1 IUFD + 4 sets of twins.
***16 infants = 4 premedicated + 1 IUFD + 10 sets of twins.

- To capture the adverse perinatal outcomes of the pregnancies complicated by severe, early IUGR and the 26 week IUFD, we created a composite outcome of neonatal morbidity.
- This outcome was considered positive if the pregnancy was complicated by IUFD, small for gestational age at the time of delivery, or neonatal intensive care unit admission.
- We examined whether prednisone use, disease activity during pregnancy, or discontinuation of medication use may be associated with neonatal morbidity. None of these factors were significantly associated with an increased risk of neonatal morbidity.

Congenital Anomalies

- Congenital anomalies were identified in 6 (13%) pregnancies. Table 5 outlines all abnormalities and associated medications taken during pregnancy.
- Only two anomalies were observed infants with antenatal exposure to potential teratogens:
  - Patent ductus arteriosis in an infant exposed to methotrexate
  - Acquired bilateral non-accommodative estropia diagnosed at 10 months of age in an infant with early exposure to leflunomide.

Congenital Anomalies

Neither of these conditions has been associated with methotrexate or leflunomide exposure in the past. Although the numbers are small, there does not appear to be a pattern of congenital anomalies associated with any medication exposure during pregnancy in this cohort.
Table 5

<table>
<thead>
<tr>
<th>Abnormality Noted at Birth</th>
<th>Maternal Medication Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inguinal Hernia</td>
<td>Prednisone, Hydrocortisol</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Prednisone, Lovenox, Estrogen, Progesterone, Dexamethasone</td>
</tr>
<tr>
<td>Suwko-Wiedmann Syndrome</td>
<td>Prednisone, Aspirin, Synthroid</td>
</tr>
<tr>
<td>Bilateral Non-Acouplomatic Esotropia (acquired) diagnosed at 10 months of age</td>
<td>Leflunomide</td>
</tr>
<tr>
<td>Intrauterine growth restriction, oligohydramnios (Pregnancy terminated at 23 weeks)</td>
<td>Anakinra</td>
</tr>
</tbody>
</table>

Fetal Anomalies and Maternal Medication use, Table 5

Thank you