Medical Update:
Diagnosis and Management of Tuberculosis in the Pregnant Patient
December 15, 2010

Sponsored by
Global Tuberculosis Institute

Objectives

At the end of this seminar, participants will be able to:

• Apply the recommended standards for diagnosis of latent TB infection and active TB disease in pregnant women

• Describe the treatment and management of latent TB infection and active TB disease in pregnant women

• Explain the importance of counseling TB patients of child bearing age on appropriate family planning strategies

• Describe post-partum management of patients diagnosed with latent TB infection and active TB disease during pregnancy
Faculty

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Columbia University College of Physicians and Surgeons
New York, New York

E. Jane Carter, MD
Associate Professor of Medicine, Brown University
Senior Consultant, Rhode Island TB Clinic
Providence, Rhode Island

Agenda

Welcome and Overview - Lee Reichman, MD, MPH
Medical Management of TB Infection and Disease in Pregnant Patients - Chia-Ling Nhan-Chang, MD, MS
Case Presentation – E. Jane Carter, MD
Questions and Discussion
MEDICAL UPDATE:

DIAGNOSIS AND MANAGEMENT OF TUBERCULOSIS IN THE PREGNANT PATIENT

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Disclosure

- No financial conflicts
Tuberculosis in Pregnancy

- Tuberculosis in Reproductive Aged Women
- Prenatal care in the United States
- Screening guidelines
- Signs and symptoms of TB in pregnancy
- Treatment guidelines
- Postpartum care and breastfeeding
- Family planning strategies
- Deficits in research
Tuberculosis in Pregnancy

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Tuberculosis: Global

- Over 900 million women worldwide have TB
- Men more likely to become infected, but women much more likely to progress to active disease
- In reproductive age women (15-44yo), TB contributes to 9% of all deaths
  - HIV/AIDS 3%
  - Heart disease 3%
  - 1 million deaths/year
Tuberculosis: Global

- The majority of those infected with M. Tuberculosis do not have active disease
- Untreated, approximately 10% of infected patients will develop active TB
  - First 1 to 2 years after the primary infection
- Worldwide, TB kills more women each year than any other infection
- Avoidance or lack of access to medical care may contribute to the underreporting of TB in women

Tuberculosis: US cases

<table>
<thead>
<tr>
<th>Year</th>
<th>Tuberculosis Cases</th>
<th>Tuberculosis Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Rate</td>
</tr>
<tr>
<td>1990</td>
<td>25,701</td>
<td>10.3</td>
</tr>
<tr>
<td>1991</td>
<td>26,283</td>
<td>10.4</td>
</tr>
<tr>
<td>1992</td>
<td>26,873</td>
<td>10.4</td>
</tr>
<tr>
<td>1993</td>
<td>25,107</td>
<td>9.7</td>
</tr>
<tr>
<td>1994</td>
<td>24,205</td>
<td>9.2</td>
</tr>
<tr>
<td>1995</td>
<td>22,728</td>
<td>8.6</td>
</tr>
<tr>
<td>1996</td>
<td>21,210</td>
<td>7.9</td>
</tr>
<tr>
<td>1997</td>
<td>19,751</td>
<td>7.2</td>
</tr>
<tr>
<td>1998</td>
<td>18,287</td>
<td>6.6</td>
</tr>
<tr>
<td>1999</td>
<td>17,501</td>
<td>6.3</td>
</tr>
<tr>
<td>2000</td>
<td>15,639</td>
<td>5.8</td>
</tr>
<tr>
<td>2001</td>
<td>15,945</td>
<td>5.8</td>
</tr>
<tr>
<td>2002</td>
<td>15,059</td>
<td>5.2</td>
</tr>
<tr>
<td>2003</td>
<td>14,830</td>
<td>5.1</td>
</tr>
<tr>
<td>2004</td>
<td>14,499</td>
<td>4.9</td>
</tr>
<tr>
<td>2005</td>
<td>14,094</td>
<td>4.8</td>
</tr>
<tr>
<td>2006</td>
<td>13,734</td>
<td>4.6</td>
</tr>
<tr>
<td>2007</td>
<td>13,280</td>
<td>4.4</td>
</tr>
<tr>
<td>2008</td>
<td>12,000</td>
<td>4.2</td>
</tr>
<tr>
<td>2009</td>
<td>11,645</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Adapted from www.cdc.gov/tb/statistics/reports/2009/pdf/Table1.pdf
Tuberculosis: US cases

Reported TB Cases by Age Group, United States, 2009

- >65 yrs (20%)
- 15-24 yrs (11%)
- 25-44 yrs (34%)
- 45-64 yrs (30%)
- <15 yrs (6%)


Tuberculosis: Reproductive Age

Reported TB Cases by Age Group, United States, 2009

- >65 yrs (20%)
- 15-24 yrs (11%)
- 25-44 yrs (34%)
- 45-64 yrs (30%)
- <15 yrs (6%)

>50%

**US-born vs Foreign-born**

![Graph showing number of TB cases in U.S.-born vs Foreign-born Persons United States, 1993–2009](image)

*Updated as of July 1, 2010.

**Tuberculosis in Pregnancy**

- Historically, women with tuberculosis were offered termination of pregnancy.
- Contemporary studies show that women with pulmonary TB who are treated appropriately do **not** have:
  - Increased rates of maternal complications
  - Neonatal complications

http://memory.loc.gov/ammem/wpaposters/wpahome.html
Vertical Transmission

- **M. tuberculosis** identified in:
  - Amniotic fluid
  - Placenta (granuloma)
- **Congenital tuberculosis** could be transmitted:
  - Fetal aspiration of infected amniotic fluid
  - Direct hematogenous spread though the placenta
- **Identification of TB granulomas in the placenta may reflect only maternal disease and not congenital tuberculosis**

Vertical Transmission

- There is a higher incidence of congenital TB in women who have extrapulmonary TB
- 15% of neonates sampled in first 3 weeks of life had TB bacilli
- TB in HIV+ pregnant women may increase risk of HIV in-utero transmission
  - 19% in-utero infection rate among 42 HIV/TB pregnant women compared to 5-10% in HIV

Pillay CID 1999, Pillay Lancet ID 2004; DeCock 2000

Active TB in pregnancy

- Higher prevalence than expected in epidemic communities
  - New York City 1985-1992
    - Kings County Hospital and Saint Vincent’s Hospital
    - 16 cases of active TB
      - 10 pulmonary TB
      - 2 meningal TB
      - 1 mediastinal
      - 1 renal
      - 1 gastrointestinal
      - 1 pleural

Extrapulmonary TB

- Extrapulmonary TB are associated with adverse maternal and neonatal outcomes

In a report on the outcomes of 33 women with extrapulmonary TB:
- 1983-1993
- 29/33 were treated
  - Majority isoniazid, rifampin, and ethambutol for nine months
  - Compared with 132 healthy pregnant women


Extrapulmonary TB: Complications

<table>
<thead>
<tr>
<th>Extrapulmonary Site</th>
<th>Number of patients (%)</th>
<th>Clinical Presentation</th>
<th>Method of Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph nodes</td>
<td>12 (36)</td>
<td>Cervical lymphadenopathy, cold abscess and sinus discharge</td>
<td>Fine-needle or surgical biopsy</td>
</tr>
<tr>
<td>Intestines</td>
<td>9 (27)</td>
<td>Subacute intestinal obstruction</td>
<td>Laparatomy or fine-needle biopsy</td>
</tr>
<tr>
<td>Kidney</td>
<td>2 (6)</td>
<td>Perinephric abscess</td>
<td>Intravenous pyelography</td>
</tr>
<tr>
<td>Meninges</td>
<td>2 (6)</td>
<td>Fever and altered sensorium</td>
<td>Cerebrospinal fluid analysis</td>
</tr>
<tr>
<td>Endometrium</td>
<td>1 (3)</td>
<td>Primary infertility</td>
<td>Endometrial biopsy</td>
</tr>
</tbody>
</table>

Extrapulmonary tuberculosis that is confined to the lymph nodes has no effect on obstetrical outcomes.
Extrapulmonary TB: 
Methods of Diagnosis


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lymph-Node TB</th>
<th>Other extra-pulmonary sites</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of gestation (weeks)</td>
<td>38.9±1.5</td>
<td>38.6±2.1</td>
<td>38.8±1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Mean birth weight (g)</td>
<td>2894±430</td>
<td>2617±540</td>
<td>2868±498</td>
<td>0.04</td>
</tr>
<tr>
<td>Prematurity</td>
<td>1 (8%)</td>
<td>2 (10%)</td>
<td>10 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>1 (8%)</td>
<td>7 (33%)</td>
<td>14 (11%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Apgar score ≤6 at 1 minute</td>
<td>1 (8%)</td>
<td>4 (19%)</td>
<td>4 (3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>0</td>
<td>2 (10%)</td>
<td>2 (2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>0</td>
<td>2 (10%)</td>
<td>2 (2%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Low Birth Weight

- Neonatal Complications:
  - Respiratory distress syndrome
  - Intraventricular hemorrhage (IVH)
  - Patent ductus arteriosus
  - Necrotizing enterocolitis
  - Retinopathy of prematurity

- Adult Complications:
  - Hypertension
  - Type 2 (adult-onset) diabetes
  - Heart disease
  - birth were 10 times more likely to have metabolic syndrome

March of Dimes
Impact of Concurrent HIV and TB

Tuberculosis in Pregnancy

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Pregnancy in the US

- 6.4+ million pregnancies in 2005
  - 49-65% are unintended
  - 4.14 million live births
  - 1.21 million induced abortions
  - 1.06 million fetal losses


http://memory.loc.gov/ammem/wpaposters/wpahome.html
Weight Gain in Pregnancy

<table>
<thead>
<tr>
<th>Prepregnancy BMI</th>
<th>Total Weight Gain</th>
<th>Rates of Weight Gain*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range in kg</td>
<td>Range in lbs</td>
</tr>
<tr>
<td>Underweight (&lt; 18.5 kg/m²)</td>
<td>12.5-18</td>
<td>28-40</td>
</tr>
<tr>
<td>Normal weight (18.5-24.9 kg/m²)</td>
<td>11.5-16</td>
<td>25-35</td>
</tr>
<tr>
<td>Overweight (25.0-29.9 kg/m²)</td>
<td>7-11.5</td>
<td>15-25</td>
</tr>
<tr>
<td>Obese (≥ 30.0 kg/m²)</td>
<td>5-9</td>
<td>11-20</td>
</tr>
</tbody>
</table>

* Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997).

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Screening Strategy

- Unique time period in non US-born women
- Many non US-born women first access health care during pregnancy
  - Ideal time period to reach out to the family and community and provide screening and care to immigrant population


Screening Strategy

- CDC and American Congress of Obstetricians and Gynecologists (ACOG)
  - Women with HIV infection
  - Close contact with individuals known or suspected to have tuberculosis
  - Medical risk factors known to increase risk of disease if infected
    - Lymphoma
    - Diabetes mellitus
    - Chronic renal failure
    - Immunosuppression/chronic steroid use
    - Low BMI
  - Born in country with high tuberculosis prevalence (HBC’s)
  - Medically underserved, low socioeconomic status
  - Alcoholism
  - Intravenous drug use
  - Residents of long-term care facility
    - Correctional institutions
    - Mental institutions
    - Nursing homes and facilities
  - Health care professional working in high risk health care facilities

CDC
ACOG Committee Health Opinion, Number 452, December 2009
Screening Strategy

- Universal screening programs:
  - Programs in the setting of prenatal care clinics may be more effective than risk based programs
  - In a New York City clinic setting with a large immigrant population universal screening to be highly effective
    - Resulted in high treatment compliance rates
    - Hispanic and US-born women were less likely to be compliant
    - Asian women more likely to be compliant
    - Universal screening strategy also identified LTBI in 11.1% of US-born women
    - Compliance PP and chest X-ray was lower when compared with non US-born women


Screening/Testing Methods

http://memory.loc.gov/ammem/wpaposters/wpahome.html
Screening: Tuberculin Skin Test

- The tuberculin skin test (TST) is the preferred tool to identify patients with LTBI
  - It has been validated for use in pregnant women
- Stimulate a T lymphocyte-mediated delayed type hypersensitivity response
  - Sensitization to mycobacterial antigens
  - Measurable cutaneous irritation 2 to 12 weeks after exposure

CDC, ACOG

Screening: Tuberculin Skin Test

- Mantoux technique
  - Purified protein derivative (PPD) of tuberculin material
  - Intradermal injection on the inner surface of the forearm
  - 5 tuberculin units (0.1 mL)

CDC, ACOG
## Screening: Tuberculin Skin Test

<table>
<thead>
<tr>
<th>Induration (mm)</th>
<th>Risk factor</th>
</tr>
</thead>
</table>
| ≥5             | *HIV infection*  
|                | *Close contact of active contagious case*  
|                | *Abnormal chest x-ray with radiographic changes consistent with old TB*  
|                | *Immunosuppressed patients: TNF-alpha inhibitors, chemotherapy, organ transplantation, glucocorticoid treatment* |
| ≥10            | *Persons with clinical conditions that increase the risk of reactivation: Silicosis, chronic renal failure requiring dialysis, diabetes mellitus, Some malignancies (leukemias, lymphomas, carcinoma of the head, neck, or lung)*  
|                | *Underweight (10% ideal body weight), malnuritioned (jejunoileal bypass)*  
|                | *Injection drug users*  
|                | *Children less than 4 y of age*  
|                | *Foreign born from countries with high incidence of TB (HBC’s)*  
|                | *Residents and employees in high risk settings, such as prisons, jails, healthcare facilities, mycobacteriology labs, and homeless shelters* |
| ≥15            | *Healthy US born persons with low likelihood of true TB infection* |

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**Interferon-Gamma Release Assays**

- **Interferon-gamma release assays (IGRAs)**
  - Detection of cell-mediated immune response
  - A single specimen of whole blood is stimulated in vitro to antigens that are unique to *M. tuberculosis*.
  - T-cell mediated release of interferon gamma (IFN-gamma) is then measured using a sensitive enzyme-linked immunoassay
**Interferon-Gamma Release Assays**

- **Provides diagnostic accuracy:**
  - In large multi-ethnic populations
  - Not affected by:
    - A history of BCG vaccine
    - Prior infection with nontuberculous mycobacteria

- **Theoretical compliance is 100% of patients,**
  - although the true screening rate may be as low as 84% owing to phlebotomy failure or clotted specimens

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**Interferon-Gamma Release Assays**

- The US Food and Drug Administration has approved the use of the QuantiFERON-TB Gold In-Tube (QFT-GIT) assay
  - Particularly in patient exposed to BCG vaccine

- Supported by the CDC as the primary screening tool for LTBI
  - May be used in all circumstances for which the Mantoux TST is indicated

*CDC, FDA*
Interferon-Gamma Release Assays: In Pregnancy

Chehab BM. Et al. KJM 2010; 3(2):24-30

- 152 women between ages 18 and 45
  - HIV negative
  - Concordant results between the tests were shown in 131 subjects (86.2%)
    - Pregnant women, 91.2% had concordant results
    - Non-pregnant women, 76% had concordant results
    - Significantly more discordant results occurred in non-pregnant women (p<.022).

- Conclusion:
  - Quantiferon are accurate to use in pregnant women
  - “The decision to use either test in pregnant women should be based mainly on the compliance of the patient to return to have the TST read”

Chehab BM. Et al. KJM 2010; 3(2):24-30
American College of radiology and American Congress of Obstetricians and Gynecologists

- "No single diagnostic x-ray results in radiation exposure to a degree that threatens the developing preembryo, embryo, or fetus."

ACOG Committee Opinion. Number 299, September 2004
Brent RL. Semin Oncol. 1989;16:347-68

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<table>
<thead>
<tr>
<th>Procedure</th>
<th>Fetal exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray (2 views)</td>
<td>0.02-0.02 mrad</td>
</tr>
<tr>
<td>Abdominal film (single view)</td>
<td>100 mrad</td>
</tr>
<tr>
<td>Hip film (single view)</td>
<td>200 mrad</td>
</tr>
<tr>
<td>Mammography</td>
<td>7-20 mrad</td>
</tr>
<tr>
<td>Intravenous pyelography</td>
<td>≥ 1 rad</td>
</tr>
<tr>
<td>Barium enema or small bowel series</td>
<td>2-4 rad</td>
</tr>
<tr>
<td>CT scan of head or chest</td>
<td>&lt;1 rad</td>
</tr>
<tr>
<td>CT scan of abdomen and lumbar spine</td>
<td>3.5 rad</td>
</tr>
<tr>
<td>CT pelvimetry (low exposure technique)</td>
<td>250 mrad</td>
</tr>
</tbody>
</table>
Diagnostic Imaging in Pregnancy

- 1-2 rad = 1.5-2.0 fold increase the risk of leukemia
  - 1 in 2,000 of leukemia exposed to ionizing radiation
  - 1 in 3,000 background rate

- 100 rad = 40% risk of mental retardation
- 150 rad = 60% risk of mental retardation

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<tr>
<td>Hip film (single view)</td>
<td>200 mrad</td>
</tr>
<tr>
<td>Fluoroscopy</td>
<td>7-20 mrad</td>
</tr>
<tr>
<td>Intravenous pyelography</td>
<td>5-1 rad</td>
</tr>
<tr>
<td>UpperGI series or small bowel</td>
<td>2-4 rad</td>
</tr>
<tr>
<td>CT scan of head or chest</td>
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</tr>
</tbody>
</table>


X-Ray in Pregnancy

- Informed consent
- Double lead shielding of abdomen
- After 15 weeks


Testing in Pregnancy:

- Culture
  - The gold standard for the diagnosis of pulmonary TB
  - Take 2 to 10 weeks
- Method:
  - Three sputum specimens
  - Sputum induction with inhalation of hypertonic saline or bronchoscopy
  - (Individuals who are
  - An acid-fast bacillus stain (AFB) on a smear immediately.
    - Approximately 50% to 80% of patients with pulmonary tuberculosis will have positive sputum smears.
  - Susceptibility testing should be conducted on the first positive culture

Testing in Pregnancy: Cultures

- Other sources for culture:
  - Early morning gastric aspirate
  - Pleural fluid
  - Blood or the body fluid
  - Tissue biopsy from the organ of clinical suspicion

<table>
<thead>
<tr>
<th>Extrapulmonary Site</th>
<th>Method of Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph nodes</td>
<td>Fine-needle or surgical biopsy</td>
</tr>
<tr>
<td>Intestines</td>
<td>Laparotomy or fine-needle or endoscopic biopsy</td>
</tr>
<tr>
<td>Skeleton</td>
<td>Radiography of bones and joints</td>
</tr>
<tr>
<td>Kidney</td>
<td>Urinalysis and intravenous pyelography</td>
</tr>
<tr>
<td>Meninges</td>
<td>Cerebrospinal fluid analysis</td>
</tr>
<tr>
<td>Endometrium</td>
<td>Endometrial biopsy</td>
</tr>
</tbody>
</table>

Testing in Pregnancy

- Rapid Assay
  - 2 to 7 hour turnaround time
  - Nucleic acid amplification technology (NAAT)
  - RNA-based
    - Gen-Probe MTD: Gen-Probe Incorporated, San Diego, CA
  - DNA PCR based
    - Amplicor Mycobacterium tuberculosis test: Roche Diagnostic Systems, Inc., Branchburg, NJ
- The sensitivity and specificity of the rapid assays have mixed reviews; therefore, these tests support but do not replace the standard culture
- NAAT results may remain positive for months after treatment due to the presence of dead mycobacterium


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Signs & Symptoms

“Great Masquerador”

Signs

- The clinical presentation of TB in pregnancy is similar to that of nonpregnant women
  - Fever
  - Cough
  - Night sweats
  - Anorexia
  - Weight loss
  - General malaise
  - Weakness
- May have fewer of the typical TB symptoms
- 20-67% of pregnant patients with pulmonary TB unaware of their disease and without significant symptoms
- Pulmonary signs and symptoms are present in only one-third of the patients
Extrapulmonary TB: Common Sites

- Lymph glands
- Pleura
- Genito-urinary tract:
  - Women: uterus and fallopian tubes
  - Men: Epididymis
  - Both sexes: renal and bladder
- Skeletal (both bones and joints)
- Meninges
- Bowel and/or peritoneum
- Pericardium
- Skin

Extrapulmonary TB: Presenting symptoms

- A dull pain in the retrosternal intrascapular area has been noted to be associated with worsening with swallowing
- Numerous case reports of extrapulmonary presentations in pregnancy have been described in literature:
  - Symptoms of TB have significant overlap with symptoms of pregnancy, including fatigue, malaise, anorexia, nausea/vomiting, weight loss and generalized abdominal or back discomfort
  - Of note, extrapulmonary TB has presented during pregnancy as perineal abscesses, degenerating leiomyomata, and ascites in women complaining of abdominal and lower back pain presenting with symptoms initially thought to be pregnancy related. In addition, meningeal and spinal TB have been described in numerous case reports with presenting symptoms ranging from nausea and vomiting, back pain, neurologic deficits to paraplegia in cases of severe cervical TB (Pott's disease).
- TB is misdiagnosed frequently, leading to a delay of treatment
  - Particularly in developed countries
- Differential diagnosis of women with both common and rare symptoms should include TB
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Latent TB – High Risk

- Women with HIV
- Women with close recent contact with a patient with active TB
- Women who have had a skin test conversion within the last 2 years.
### Treatment - 1st Line Agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Maternal Effects</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong></td>
<td>Latent TB*: 300 mg per day for 9 months</td>
<td>Hepatic dysfunction</td>
<td>Pregnancy risk factor – C</td>
</tr>
<tr>
<td></td>
<td>Active TB*: 5 mg/kg per day</td>
<td>Hepatitis</td>
<td>Breastfeeding – Probably safe</td>
</tr>
<tr>
<td></td>
<td>After 2 mo: 15 mg/kg, twice a week</td>
<td>Gastrointestinal upset</td>
<td>Crosses placenta</td>
</tr>
<tr>
<td></td>
<td>* Take with 25mg Pyridoxine per day</td>
<td>Skin reactions</td>
<td>Embryocidal in rat and rabbit studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anemia, thrombocytopenia</td>
<td>No teratogenic effect in humans identified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNS symptoms</td>
<td></td>
</tr>
<tr>
<td><strong>Rifampin</strong></td>
<td>Latent TB: 10 mg/kg (maximum 600 mg) per day in patients who are not</td>
<td>Hepatic dysfunction</td>
<td>Pregnancy risk factor – C</td>
</tr>
<tr>
<td>2 months</td>
<td>taking Isoniazid</td>
<td>Hepatitis</td>
<td>Breastfeeding – Compatible</td>
</tr>
<tr>
<td></td>
<td>Active TB: 10 mg/kg (maximum 600 mg) per day</td>
<td>Gastrointestinal upset</td>
<td>Crosses placenta</td>
</tr>
<tr>
<td></td>
<td>Or 15 mg/kg 3 times a week</td>
<td>Anemia, thrombocytopenia</td>
<td>Teratogenic in rat and mice studies in high doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever</td>
<td>No teratogenic effect in humans identified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flu-like symptoms</td>
<td>Associated with neonatal hemolytic anemia. Recommend vitamin K to neonate at birth</td>
</tr>
</tbody>
</table>

**Ethambutol**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Maternal Effects</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latent TB with HIV: 15 mg/kg per day</td>
<td>Optic neuritis</td>
<td>Pregnancy risk factor – C</td>
</tr>
<tr>
<td></td>
<td>Active TB: 15 mg/kg per day</td>
<td>Decreased color discrimination</td>
<td>Breastfeeding – Compatible</td>
</tr>
<tr>
<td></td>
<td>30 mg/kg per day for meningeval TB 30-50 mg/kg 2-3 times a week</td>
<td>Skin reactions</td>
<td>Crosses placenta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal upset</td>
<td>Teratogenic in animal studies in high doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No teratogenic effect in humans identified</td>
</tr>
</tbody>
</table>

**Pyrazinamide**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Maternal Effects</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active TB: 25 mg/kg (maximum 2gm) per day</td>
<td>Hepatic dysfunction</td>
<td>Pregnancy risk factor – C</td>
</tr>
<tr>
<td></td>
<td>30 mg/kg 3 times a week</td>
<td>Hepatitis</td>
<td>Breastfeeding – Probably safe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal upset</td>
<td>Limited data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anthaigia, Myalgia, Malaize, Gout</td>
<td>No animal studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No teratogenic effect in humans reported</td>
</tr>
</tbody>
</table>
# Second Line Agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Maternal Effects</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td>Pregnancy risk factor – C, Breastfeeding -</td>
</tr>
<tr>
<td>Ciprofloxacin 500mg twice daily or ofloxacin 400 mg/day as part of a multiple drug regimen</td>
<td>Cipro crosses placenta and found in breast milk</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Animal studies -&gt; damage articular cartilage and juvenile arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Human exposure during the first trimester -&gt; no musculoskeletal but a trend for higher rate of medical abortion</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td></td>
<td>Pregnancy risk factor – B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>There are no data on the use of clavulanic acid in early pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In the second and third trimester, this has been used as antibacterial prophylaxis in preventing infection following premature rupture of membranes with an increased incidence of necrotizing enterocolitis</td>
</tr>
<tr>
<td>Paraaminosalicylic acid</td>
<td>10-30% Gastrointestinal effects</td>
<td>Pregnancy risk factor – C</td>
</tr>
<tr>
<td></td>
<td>5-10% hypersensitivity rash</td>
<td>Collaborative Perinatal Project identified 43 women who had been exposed to the drug in the first trimester with 5 babies showing various malformations. A subsequent study identified an inconsistent association with limb and ear abnormalities</td>
</tr>
</tbody>
</table>

---

# Medications Not Used

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>Pregnancy risk factor – D</td>
</tr>
<tr>
<td></td>
<td>1 in 6 risk of hearing impairment and irreversible congenital deafness in offspring of women who were treated with streptomycin in pregnancy (any trimester)</td>
</tr>
</tbody>
</table>

Scheinhorn DJ et al. West J Med. 1977 Sep;127(3):196-8
## Monitoring in Pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Monitoring</th>
<th>Special Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Liver function testing</td>
<td>Antacids reduce absorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Take with Pyridoxine</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Liver function testing</td>
<td>Turns secretions orange</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Take on an empty stomach</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Check color vision and acuity</td>
<td>Unilateral opho exam</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Liver function testing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uric Acid</td>
<td></td>
</tr>
</tbody>
</table>

### Why wait?

- The postponement of treatment to the postpartum period may result in delay and loss of follow-up for a large number of patients

---

Why wait?
“It’s too expensive”

- Cost-Effectiveness:
  - Markov decision-analysis model comparing antenatal to postpartum INH treatment strategies
  - Showed an overall marginal increase in life expectancy despite an increased risk of side effects in the antenatal treatment group

**Cost-Analysis**

**Table 2. Predicted Cases of Tuberculosis Within the Cohort, Cases Secondary to Horizontal Transmission, Cases of Fetal and Neonatal Hepatitis, and Discounted and Undiscounted Total Costs and Life Expectancy**

<table>
<thead>
<tr>
<th>Assumptions and Biology</th>
<th>Cases of TB per 10,000 within the cohort</th>
<th>Additional cases secondary to horizontal transmission</th>
<th>Total TB cases prevented vs. no treatment</th>
<th>Cases of INH-related hepatitis</th>
<th>Undiscounted total cost ($)</th>
<th>Total cost discounted at 3% annually ($)</th>
<th>Life expectancy discounted at 3% annually (y)</th>
<th>Incremental cost ($/k-year saved) (discounted) ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-fertility rate 7%,</td>
<td>1400</td>
<td>748</td>
<td>2148</td>
<td>1004</td>
<td>2.7 million</td>
<td>2.7 million</td>
<td>79.1 million</td>
<td>15.9 million</td>
</tr>
<tr>
<td>ages 18-34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipartment</td>
<td>1796</td>
<td>1289</td>
<td>3085</td>
<td>1004</td>
<td>2.7 million</td>
<td>2.7 million</td>
<td>79.1 million</td>
<td>15.9 million</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>500</td>
<td>1289</td>
<td>3085</td>
<td>1004</td>
<td>2.7 million</td>
<td>2.7 million</td>
<td>79.1 million</td>
<td>15.9 million</td>
</tr>
<tr>
<td>Undiscounted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discounted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cost-Analysis

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<th>Total TB cases prevented vs. no treatment</th>
<th>Cases of HBV-related hepatitis deaths</th>
<th>Undiscounted total TB (B)</th>
<th>Undiscounted life-expectancy (A)</th>
<th>Life expectancy discounted at 3% annually (C)</th>
<th>Life expectancy discounted at 3% annually (D)</th>
<th>Incremental cost/savings (discounted) (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-fertility rate 7%, age 18-54</td>
<td>Antepartum</td>
<td>1485</td>
<td>1344</td>
<td>4880</td>
<td>9</td>
<td>280</td>
<td>2</td>
<td>35.9 million</td>
<td>57.1</td>
</tr>
<tr>
<td></td>
<td>Prepartum</td>
<td>1789</td>
<td>2247</td>
<td>3039</td>
<td>42</td>
<td>90</td>
<td>0.9</td>
<td>30.6 million</td>
<td>52.1</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>57.1</td>
<td>57.1</td>
<td>57.1</td>
<td>57.1</td>
<td>57.1</td>
<td>57.1</td>
<td>57.1</td>
<td>57.1</td>
</tr>
<tr>
<td>Cost-fertility rate 4%, age 18-54</td>
<td>Antepartum</td>
<td>1425</td>
<td>1312</td>
<td>4394</td>
<td>0.9</td>
<td>200</td>
<td>2</td>
<td>28.1 million</td>
<td>57.2</td>
</tr>
<tr>
<td></td>
<td>Prepartum</td>
<td>1789</td>
<td>2247</td>
<td>3039</td>
<td>1.2</td>
<td>90</td>
<td>0.9</td>
<td>20.2 million</td>
<td>52.2</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>57.2</td>
<td>57.2</td>
<td>57.2</td>
<td>57.2</td>
<td>57.2</td>
<td>57.2</td>
<td>57.2</td>
<td>57.2</td>
</tr>
</tbody>
</table>

TB = tuberculosis, PSH = deceased.

- Antepartum treatment was the least expensive.
- At 1% rate of case-fatality:
  - Antepartum treatment resulted in a marginal increase in life expectancy
- At 0.1% rate of case-fatality:
  - Antepartum treatment become the least advantageous strategy

Post-partum compliance

- Compliance with post-partum treatment:
  - In a San Francisco clinic population
    - 42% compliance with a follow-up visit in their TB clinic
    - 18% overall treatment completion rate among
  - Reasons for non-compliance:
    - lack of treatment referral (31%)
    - failure to keep referral appointment (18%)
    - nonadherence with prescribed treatment (35%)


Important Strategy:

- Current approach strategy for LTBI:
  - Referral for treatment
  - Aggressive follow-up on the part of the prenatal care provider
  - Involvement of cultural case managers
  - Directly observed preventive therapy programs

Tuberculosis in Pregnancy

• Tuberculosis in Reproductive Aged Women
• Prenatal care in the United States
• Screening guidelines
• Signs and symptoms of TB in pregnancy
• Treatment guidelines
• Postpartum care and breastfeeding
• Family planning strategies
• Deficits in research

Breastfeeding

▪ Breastfeeding is the preferred method of feeding for newborns and infants
▪ The ACOG recommends that exclusive breastfeeding be continued until the infant is 6 months old

ACOG Committee Opinion. Number 361 • February 2007
Breastfeeding

- Breast milk does not contain tuberculosis bacilli

- TB is a respiratory disease transmitted by aerosol droplets
  - Concern for horizontal transmission

Breastfeeding

- Latent TB:
  - No contraindication to breastfeeding

- Active TB:
  - Highest risk periods for transmission from mother to baby
  - Close respiratory proximity to the baby.
  - A mother with newly diagnosed untreated active disease should be separated from her infant to prevent respiratory exposure/transmission, regardless of mode of infant feeding.
  - Resume her breast-feeding after anti-TB medications have begun and negative sputum cultures are documented.
Breastfeeding: Exceptions

- Exceptions are women:
  - Who take street drugs or do not control alcohol use
  - Have an infant with galactosemia
  - Infected with human immunodeficiency virus (HIV) or human T-cell lymphotropic virus type I or type II
  - Active untreated tuberculosis
  - Active Varicella
  - Active herpes simplex virus with breast lesions

Postpartum Period

- Family planning strategies should be initiated during prenatal care
  - Give information about methods and services that will help them meet their reproductive goals
- Options include:
  - Nonhormonal methods
  - Hormonal methods
  - Lactational amenorrhea method

ACOG Committee Opinion. Number 361 • February 2007
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Contraception
Surgical Contraception

- Bilateral Tubal ligation
  - Post-partum mini-laparotomy
  - During cesarean delivery
  - Laparoscopic
- Bilateral Tubal occlusion
  - Essure
Hormonal Contraception

- Pills
  - Typical use: 92%
  - Not contra-indicated in breast-feeding
- Progestin-only “mini” pill
  - Typical use: 92%
- Transdermal Patch
  - Typical use: 92%
- Vaginal contraceptive ring “Nuvaring”
  - Typical use: 92%
Hormonal Contraception

- **Implants:**
  - Implanon (subcutaneous)
    - Typical use: 99%
    - Single-rod progestin implant
    - Contraception is provided for 3 years
    - Protection from pregnancy occurs within 24 hours of insertion
    - Fertility returns rapidly after removal of the rod.
    - Pregnancies have been reported postmarketing
      - The manufacturer cites 0.38 pregnancies per 100 women-years of use.
  - Mirena (intrauterine)
    - Typical use: 99%
    - Intrauterine Levonorgestrel device
    - Approved for 5 years of use
    - Benefit of decreased menstrual flow or amenorrhea

Other forms of Contraception

- **Condoms**
  - Male
    - Typical use: 85%
  - Female
    - Typical use: 79%
- **Copper IUD**
  - Approved for 10 years of use
  - Typical use: 97-99%
- **Cervical Cap**
  - Typical use: 84%
- **Spermicides**
  - Typical use: 78-90%
- **Withdrawal method**
  - Not reliable: 73-80%
- **Amenorrhea method**
  - The woman is less than six months postpartum
  - She is breastfeeding exclusively (ie, not providing food or other liquid to the infant)
  - She is amenorrheic
    - Typical use: 95%
- **Vasectomy**
  - Typical use: 99%
■ 1% and 10% of women with infertility have genital TB
■ Women undergoing (Cohort of 420 women) undergoing diagnostic laparoscopy for infertility:
  ▫ PCR of peritoneal fluid and biopsy specimens identified evidence of TB in 5.7%
■ Women with nongenital tuberculosis and genital tuberculosis frequently have menstrual disorders:
  ▫ Amenorrhea
  ▫ Oligomenorrhea


■ Overcome with artificial reproductive technology (ART)
■ May be of concern in the future if undiagnosed
  ▫ Presentation when immuno-compromised
Tuberculosis in Pregnancy

- Tuberculosis in Reproductive Aged Women
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Research

- Evaluation of drug safety and pharmacokinetics
- Assessment of drug resistance
  - Emerging drug resistance during pregnancy or the postpartum period
- Clinical outcomes of treated extrapulmonary TB
Research

- **Cost-Analysis**
  - Antepartum versus postpartum treatment
    - Adherence
    - HIV-1 infected women

- **Use of Quantiferon rapid testing**
  - Large scale for compliance
  - At delivery to late presenting women

Acknowledgements

- **Lee Reichman, MD MPH**
  - Executive Director
  - Professor of Medicine, Preventive Medicine and Community Health
  - NJ Medical School Global Tuberculosis Institute, Newark, NJ

- **Rajita Bhavaraju, MPH, CHES**
  - Training and Consultation Specialist
  - NJ Medical School Global Tuberculosis Institute, Newark NJ

- **Theodore Jones, MD**
  - Interim Chair
  - Department of Obstetrics and Gynecology
  - Wayne State University, Detroit, MI
Case Discussion:
TB in Pregnancy

December 15, 2010

E. Jane Carter, M.D.
Day of Referral

- 28 year old female referred to ENT for evaluation of progressive hoarseness
- Laryngoscopy demonstrated diffuse inflammation and granulomas
- Prescription given for steroids for inflammatory laryngitis
- She was pregnant – ENT immediately called OB to discuss case

History Related to ENT

- 29 weeks pregnant with twins
- 1st Trimester: Significant heartburn, GERD and vomiting
- Vomiting resolved but GERD continued
- Hoarseness started at same time but has progressed to the point she can only whisper
- “Everything started with pregnancy.”
Why was TB clinic called?

- ENT called OB-GYN to discuss not only unusual differential but to inform about prednisone use
- OB noted the following history
  - Patient had a +TST performed in 1st trimester of pregnancy
  - Appointment to RISE clinic on non-urgent basis for LTBI had been scheduled but had not occurred yet
- The phone call between the two MDs raised possibility of TB laryngitis
- ENT called TB clinic – same day appointment given

Why was she TST-ed?

- Born in India
- In the US 18 months
- Husband on a work visa
  - She is accompanying family
  - No screening performed previously
- TST performed as targeted testing strategy as part of the package of prenatal care
Back to the case –
now at TB clinic

- No fevers, hemoptysis, or other constitutional findings
- Pre-pregnancy weight 103, now 116
- Family reports “Not eating enough”
- Maybe a little cough
- PMH: none
- Meds: Zantac, prenatal vitamins

Work up at TB clinic

- Physical examination was unremarkable
  - Appeared tired but well
  - Afebrile
  - Gravid uterus
- HIV negative (already performed as part of prenatal care)
- CXR performed
- Sputum requested for AFB smears
- Prednisone treatment held
Minimal streaky infiltrate RUL

Next day

- Sputum was smear positive - rare
Treatment

- Regimen: Isoniazid, Rifampin, Ethambutol and B6
  - Pyrazinamide deleted due to pregnancy
    - Used throughout the world but not graded by FDA for safety in pregnancy
    - Commits to longer course but regimen is still appropriate to prevent emergence of resistance

Public Health

- Quarantine initiated
- Plans needed to be made for ongoing OB care
  - No isolation room at private OB office
    - Last appointment of the day with patient masked
  - Testing required at the obstetrical hospital
    - Hospital notified; masking of patient; expedited appointments
Clinical Course

- Tolerated medications without difficulty
- Started gaining weight
  - 22 pounds in 8 weeks
- DST returned fully susceptible
  - Ethambutol dropped
- Sputum collection every 2 weeks
  - Sputum smear conversion occurred at 4 weeks into treatment

IC Plan: Obstetrical Hospital

- Unclear if she would be non-contagious (culture negative) prior to delivery
- Plan designed by TB Clinic and approved by Infection Control at hospital
  - Private isolation room
  - Staff with PRP
  - No visiting to the newborn nursery
  - Placenta examined for granuloma
  - Window prophylaxis for babies if no disease noted
  - Husband no restrictions (CXR clear)
Outcomes - 1

- Mom scheduled for c-section but went into labor 3 weeks early
- She was smear negative but not culture negative
- Placenta showed no granulomas
- Babies placed on window prophylaxis so they can re-unite with mom

Outcomes - 2

- Mom’s cultures - taken 10 days prior to delivery. Eventually demonstrated no growth (no longer any risk of contagion)
- Babies taken off IPT at 6 weeks when this information discovered
- TST in babies at 12 weeks were both 0 mm
- Dad was not ignored
  - TST 15 mm at time of wife’s diagnosis
  - INH therapy simultaneous to Mom’s treatment
Outcomes - 3

- Mom finishing her medications without difficulty
  - DOT
  - 9 month treatment course (no PZA)
- Voice returned to near normal at 4 months into therapy

Lessons Learned - 1

- Targeted testing strategies for LTBI can easily be incorporated into prenatal care

- In the era of declining TB rates in the US, diagnosis of disease requires awareness of at risk populations
  - Think TB!
Lessons Learned - 2

- TB treatment in pregnancy is not only safe for mother and child but critically necessary for good outcomes
- Communication/cooperation between services is a critical component for good TB care
  - ENT-OB and then ENT-OB-TB Clinic
  - TB Clinic-Infection Control-OB
- Unusual presentation for TB laryngitis

Last lesson in TB control: Constant education is necessary!

- Despite detailed instructions to the OB hospital,
  - Father was made to wear a mask throughout admission (assumption was that he was also contagious!)
  - Staff wore N95 respirators throughout admission though “standard” infection control would have let her out of quarantine
  - Hospital originally charged patient for all her isolation facilities after health insurance denied charge due to “lack of medical necessity”
Questions or Comments?