MEDICAL UPDATE:

DIAGNOSIS AND MANAGEMENT OF TUBERCULOSIS IN THE PREGNANT PATIENT

WEBINAR: December 15, 2010

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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

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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%

- 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

Tuberculosis cases and deaths per 100,000 population

<table>
<thead>
<tr>
<th>Year</th>
<th>US-born Cases</th>
<th>Percentage Change</th>
<th>US-born Deaths</th>
<th>Percentage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>14,636</td>
<td>-2.4%</td>
<td>1,186</td>
<td>22.1%</td>
</tr>
<tr>
<td>1994</td>
<td>14,636</td>
<td>0.0%</td>
<td>1,186</td>
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<td>2001</td>
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<tr>
<td>2002</td>
<td>14,636</td>
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<tr>
<td>2003</td>
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</table>

US-born vs Foreign-born


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

Vertical Transmission

- *M. tuberculosis* identified in:
  - Amniotic fluid
  - Placenta (granulomas)
  - Autopsy in neonates
- Identification of TB granulomas in the placenta may reflect only maternal disease and not congenital tuberculosis

References:

Vertical Transmission

- Tuberculosis could be transmitted antepartum:
  - Fetal aspiration of infected amniotic fluid
  - Direct hematogenous spread through the placenta
- Intrapartum
  - Aspiration/ingestion of infected amniotic fluid or genital secretions
- Postpartum
  - Inhalation/ingestion of respiratory droplets


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
  - ? Either vertical or horizontal transmission


Vertical Transmission

- 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
    - Patients who have access to HAART have perinatal transmission of <1%

De Cock et al. JAMA 2000;283:1175-82

What are the risks?

http://memory.loc.gov/ammem/epaposters/epahome.html
Tuberculosis in Pregnancy

- **Latent TB:**
  - No increased risk to fetus in utero
  - Postpartum risk of developing active TB

- **Active TB:**
  - Complications are controversial

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 meningeal TB
    - 1 mediastinal
    - 1 renal
    - 1 gastrointestinal
    - 1 pleural

Extrapulmonary TB

- Extrapulmonary TB are associated with adverse maternal and neonatal outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Pulmonary Tuberculosis in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>35</td>
</tr>
<tr>
<td>Origin</td>
<td>Mexico</td>
</tr>
<tr>
<td>Prematurity</td>
<td>↑</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>↑</td>
</tr>
<tr>
<td>IUGR</td>
<td>←→</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>↑</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>N/A</td>
</tr>
<tr>
<td>Medical complications</td>
<td>←→</td>
</tr>
</tbody>
</table>

*Cases to be related to prematurity

Bejerkedal T et al. Scand J Respir Dis 1975;36:244

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, abdominal mass, ascites</td>
<td>Laparotomy or fine-needle or endoscopic biopsy</td>
</tr>
<tr>
<td>Skeleton</td>
<td>7 (21)</td>
<td>Chronic progressive backache, paraplegia, and dorsolumbar kyphoscoliosis</td>
<td>Radiography of bones and joints</td>
</tr>
<tr>
<td>Kidney</td>
<td>2 (6)</td>
<td>Fever of unknown origin and perinephric abscess</td>
<td>Urinalysis and 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>38.8±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

Impact of Concurrent HIV and TB

March of Dimes

National Library of Medicine
Impact of Concurrent HIV and TB

- Maternal outcomes
  - Increased maternal deaths (Zambia, Durban, Malawi)
    - Secondary to TB, pneumonia, meningitis
  - Lower CD4 counts (compared with TB or HIV alone)
  - Higher antenatal admissions for complications

- Fetal outcomes
  - Increased perinatal death
  - Increased prematurity
  - Increased low birthweight
  - Increased SGA
  - Increased TB and HIV transmission to infant

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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

- Approximately 23% of all pregnant women are uninsured

Pregnancy in the US

- Uninsured pregnant women:
  - Less likely to seek prenatal care in the first trimester
  - Less likely to receive the optimal number of visits during their pregnancy

- 31% higher likelihood of experiencing an adverse health outcome after giving birth

- Universal Prenatal Care Assistance Program (PCAP) is underutilized
  - Patient awareness
  - Undocumented immigrants afraid of deportation


www.acog.org
Prenatal Visits

- **Visits**
  - <28 weeks: q 4 weeks
  - 28 -36 weeks: q 2 weeks
  - >36 weeks: q week

- **Ultrasound**
  - First trimester (genetic screen 11-13 weeks)
  - Second trimester anatomy scan (17-23 weeks)
  - Third trimester scans only if chronic disease or Size ≠ Date

Weight Gain in Pregnancy

<table>
<thead>
<tr>
<th>Prepregnancy BMI</th>
<th>Total Weight Gain</th>
<th>Rates of Weight Gain&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range in kg</td>
<td>Mean (range in kg/week)</td>
</tr>
<tr>
<td></td>
<td>Range in lbs</td>
<td>Mean (range in lb/week)</td>
</tr>
<tr>
<td>Normal weight (&lt;25.3 kg/m²)</td>
<td>11.5-16.5</td>
<td>0.42 (0.30-0.60)</td>
</tr>
<tr>
<td>Overweight (25.3-29.9 kg/m²)</td>
<td>16-21</td>
<td>0.46 (0.32-0.61)</td>
</tr>
<tr>
<td>Obese (≥30 kg/m²)</td>
<td>21-30</td>
<td>0.37 (0.25-0.55)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Calculations assume 0.42 kg (0.9 lbs) weight gain in the first trimester (based on Singer et al., 1994; Adams et al., 1997; Catalano 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 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

**Screening/Testing Methods**

- 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 was to be highly effective
  - Resulted in high PPD read and treatment compliance
  - 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

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[Image](http://memory.loc.gov/ammem/wpaposters/wpahome.html)
Screening: Tuberculin Skin Test

- The tuberculin skin test (TST) with Mantoux technique 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

<table>
<thead>
<tr>
<th>Induration (mm)</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 5</td>
<td>HIV infection</td>
</tr>
<tr>
<td></td>
<td>Close contact of active contagious case</td>
</tr>
<tr>
<td></td>
<td>Abnormal chest x-ray with radiographic changes consistent with old TB</td>
</tr>
<tr>
<td></td>
<td>BCG vaccination</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy, organ transplantation, glucocorticoid treatment</td>
</tr>
<tr>
<td>≥ 10</td>
<td>Persons with clinical conditions that increase the risk of reactivation:</td>
</tr>
<tr>
<td></td>
<td>Silicosis, chronic renal failure requiring dialysis, diabetes mellitus,</td>
</tr>
<tr>
<td></td>
<td>Some malignancies (leukemia, lymphoma, carcinoma of the head, neck, or lung)</td>
</tr>
<tr>
<td></td>
<td>Underweight (≤10% ideal body weight), malnourished (jejunoileal bypass)</td>
</tr>
<tr>
<td></td>
<td>Injection-drug users</td>
</tr>
<tr>
<td></td>
<td>Children less than 2 y of age</td>
</tr>
<tr>
<td></td>
<td>Foreign-born from countries with high incidence of TB (HBC's)</td>
</tr>
<tr>
<td></td>
<td>Residents and employees in high-risk settings, such as prisons, jails, healthcare facilities, mycobacteriology labs, and homeless shelters</td>
</tr>
<tr>
<td>≥ 15</td>
<td>Healthy US-born persons with low likelihood of true TB infection</td>
</tr>
</tbody>
</table>

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
- 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,
  - True screening rate may be as low as 84% owing to phlebotomy failure or clotted specimens

Interferon-Gamma Release Assays

- The US Food and Drug Administration has approved the use of the QuantiFERON®-TB Gold (QFT-GIT) assay
  - Particularly in patients 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
Interferon-Gamma Release Assays: In Pregnancy

Use of the QuantiFERON®-TB Gold Assay in Pregnant Patients

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®-TB Gold assay is 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”

Interferon-Gamma Release Assays

333 women tested (cryopreserved blood)
- 52 (15.6%) had indeterminate IGRA results
- 281 women with interpretable results

CONCLUSION:
- “Positive IGRA results for HIV-1-infected pregnant women were associated with postpartum active tuberculosis and mortality among mothers and their infants.”

Interferon-Gamma Release Assays

120 (42.7%) Positive
- Associated with a 4.5-fold increased risk of active tuberculosis (aHR 4.5; 95% CI, 1.1-18.0)
- In with with CD4 cell count, <250 cells/µL, positive IGRA results were associated with increased:
  - Maternal mortality (aHR 3.5; 95% CI, 1.02-12.1)
  - Maternal active TB or mortality (aHR 5.2; 95% CI, 1.7-15.6)
  - Infant active TB or mortality (aHR 3.0; 95% CI, 1.0-8.9)

CONCLUSION:
- “Positive IGRA results for HIV-1-infected pregnant women were associated with postpartum active tuberculosis and mortality among mothers and their infants.”
After a Positive Screening Test

- Chest X-Ray
- Reassess for evidence of active TB
- Encourage family to be screened

Diagnostic Imaging in Pregnancy

- 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

Diagnostic Imaging in Pregnancy

<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>Mammoagrapy</td>
<td>7-20 mrad</td>
</tr>
<tr>
<td>Intravenous pyelography</td>
<td>2-1 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 pelivimetry (low exposure technique)</td>
<td>250 mrad</td>
</tr>
</tbody>
</table>

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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<td>Abdominal film (single view)</td>
<td>100 mrad</td>
</tr>
<tr>
<td>Full film pelvis view</td>
<td>100 mrad</td>
</tr>
<tr>
<td>Fluoroscopy</td>
<td>0.25 mrad</td>
</tr>
<tr>
<td>Mammography</td>
<td>7-20 mrad</td>
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<tr>
<td>X-ray of abdomen and lumbar spine</td>
<td>3.5 rad</td>
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X-Ray in Pregnancy

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

Testing in Pregnancy: Cultures

- 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 (those who are unable to provide sputum)
  - 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

Testing in Pregnancy: Cultures

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<td>Meninges</td>
<td>Cerebrospinal fluid analysis</td>
</tr>
<tr>
<td>Endometrium</td>
<td>Endometrial biopsy</td>
</tr>
</tbody>
</table>


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
    - Anyplex MDR TB test: detect the mutations of drug-resistant genes to rifampicin, (INH), and inhA promoter; (Seegene, Korea)
- 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 Masquerader"

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

**Presenting symptoms**

Numerous case reports of extrapulmonary presentations in pregnancy have been described in literature:

- Symptoms of TB have significant overlap with symptoms of pregnancy
  - Fatigue, malaise, anorexia, nausea/vomiting, weight loss and generalized abdominal or back discomfort
  - A dull pain in the retrosternal intrascapular area has been noted to be associated with worsening with swallowing
- 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

**Genital, Urinary and Peritoneal TB**

- Perineal abscesses
- Degenerating leiomyomata
- Ascites
- Nausea and vomiting
- Back pain
- Neurologic deficits
- Paraplegia

**Meningeal and Spinal TB**

- Of note, extrapulmonary TB has presented during pregnancy as:
Tuberculosis in Pregnancy

- Tuberculosis in Reproductive Aged Women
- Prenatal care in the United States
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Latent TB in Pregnancy

- Post-partum treatment
- Exceptions:
  - 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

Latent TB in Pregnancy: Why wait?

- Fear of tetatogenicity and toxicity to the fetus
- Low risk of latent TB to mother and fetus during the pregnancy
- The postponement of treatment to the postpartum period may result in delay and loss of follow-up for a large number of patients

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

**Why wait? “It’s too expensive”**

- Cost-Effectiveness:
  - Markov decision-analysis model comparing antenatal to postpartum INH treatment strategies
  - Assumptions:
    - INH started at 20 weeks gestation for 6 months
    - 67% completion rate
    - 0.1% serious hepatitis
    - 0 fetal deaths from hepatitis
  - Showed an overall marginal increase in life expectancy despite an increased risk of side effects in the antenatal treatment group

---

**Cost-Analysis**

Table 1: Markov model for LTBI (source: Boggess KA et al. Obstet Gynecol. 2000;96(5 Pt 1):757–762)

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Markov Decision-Analyses</th>
<th>Antenatal</th>
<th>Postnatal</th>
<th>Total Marital</th>
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**Cost-Analysis**

Table 2: Markov model for LTBI (source: Boggess KA et al. Obstet Gynecol. 2000;96(5 Pt 1):757–762)

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</tr>
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Cost-Analysis

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

Active TB in Pregnancy

- Treat! Treat! Treat!
- Maternal and fetal benefits outweigh any potential harm to fetus
- Beware of organogenesis in early first trimester

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>Isoniazid</td>
<td>Latent TB: 300 mg/day for 9 months.</td>
<td>Hepatic dysfunction, Hepatitis</td>
<td>Pregnancy risk factor – C, Breastfeeding – Probably safe</td>
</tr>
<tr>
<td></td>
<td>Active TB: 5 mg/kg per day for 9 months.</td>
<td>Peripheral neuropathy, Skin reactions</td>
<td>Crosses placenta, Teratogenic in animal studies in high doses</td>
</tr>
<tr>
<td></td>
<td>*Take with 25 mg Pyridoxine per day</td>
<td>Anemia, thrombocytopenia, CNS symptoms</td>
<td>No teratogenic effect in humans identified</td>
</tr>
</tbody>
</table>

Rifampin

- 3 months
- Latent TB: 600 mg/day for 3 months
- Active TB: 10 mg/kg per day
- Or 15 mg/kg 3 times a week
- Hepatic dysfunction, Hepatitis, Skin reactions, Gastrointestinal upset, Anemia, and thrombocytopenia
- Fever, Flu-like symptoms
- Pregnancy risk factor – C, Breastfeeding – Compatible
- Crosses placenta, Teratogenic in animal studies in high doses
- No teratogenic effect in humans identified
- Associated with neonatal hemolytic anemia. Recommend vitamin K to neonate at birth

Optic neuritis, Decreased color discrimination, Skin reactions, Gastrointestinal upset

Pyrazinamide

- Active TB: 25 mg/kg per day (max 2 gm)
- Or 50 mg/kg 3 times a week
- Hepatic dysfunction, Hepatitis, Gastrointestinal upset, Arthralgia, Myalgia, Malaise, Gout
- Pregnancy risk factor – 7C, Breastfeeding – Probably safe
- Limited data, Not used US
- No animal studies
- No teratogenic effect in humans identified

GG Briggs et al. Drugs in pregnancy and lactation: Eighth Ed. Lippincott Williams & Wilkins
Second Line Agents (MDR-TB, XDR-TB)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Maternal Effects</th>
<th>Pregnancy Risk Factor</th>
<th>Pregnancy Effects</th>
</tr>
</thead>
</table>
| Fluoroquinolones          | Effects (oral) Only, nausea, vomiting, insomnia, confusion, somnolence, fever, headache | -4                    | Pregnancy risk factor:  
|                           | and loss of taste and smell, elevation of liver enzymes                           |                       | > Damage articular cartilage and juvenile arthritis     |
|                           |                                                                             |                       | Human exposure during the first trimester: > No        |
|                           |                                                                             |                       | musculoskeletal but a trend for higher rate of medical|
|                           |                                                                             |                       | abortions                                             |
| Amoxicillin-clavulanic acid| Effects (oral) Only, nausea, vomiting, rash, urticaria, alopecia, pruritus, vaginal| B                    | Breastfeeding - Enters breast milk/use with caution    |
|                           |                                                                             |                       | There are no data on the use of clavulanic acid in    |
|                           |                                                                             |                       | early pregnancy                                         |
|                           |                                                                             |                       | 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      |
| Paraaminosalicylic acid   | Effects (oral) Only, nausea, vomiting, rash, pruritus, alopecia, pruritus, vaginal| C                    | Breastfeeding - Enters breast milk/not recommended     |
|                           |                                                                             |                       | Collaborative Perinatal Project identified 43 women   |
|                           |                                                                             |                       | who had been exposed to the drug in the first trimester|
|                           |                                                                             |                       | with 5 babies showing various malformations.          |

Medications Not Used

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pregnancy Risk Factor</th>
<th>Pregnancy Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>D</td>
<td>1:6 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>

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 Take with Pyridoxine</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Liver function testing</td>
<td>Turns secretions orange Take on an empty stomach</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Check color vision and acuity</td>
<td>Unilateral ophth exam</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Liver function testing</td>
<td>L orc acid</td>
</tr>
</tbody>
</table>

Monitor Weight Gain

KM Rasmussen and AL Yaktine, Editors; Institute of Medicine, 2009
**Tuberculosis in Pregnancy**

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**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

**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

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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 with breast-feeding
- Progestin-only “mini” pill
  - Typical use: 92 %
  - Preferred method with breast-feeding
- 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
    - Fertility returns rapidly after removal of the rod
    - Pregnancies have been reported postmarketing
      - Manufacturer: 0.38 pregnancies/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: 97-98%
- Cervical Cap
  - Typical use: 94%
- 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 (i.e., not providing food or other liquid to the infant)
  - She is amenorrheic
  - Typical use: 95%
- Vasectomy
  - Typical use: 99%

Infertility

- 1% and 10% of women with infertility have genital TB
- Genitourinary TB is usually caused by reactivation:
  - ≤ 2 years following the primary infection by *M. tuberculosis*
  - Hematogenous or gastrointestinal spread

Infertility

- Women (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

Infertility

- Lead to salpingitis & impairment of cilia
  - Overcome with artificial reproductive technology (ART)
- May be of concern in the future if undiagnosed
  - Presentation when immuno-compromised

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Research

- Evaluation of drug safety and pharmacokinetics in pregnancy
  - PZA
- 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®-TB rapid testing
  - Large scale for compliance
  - Non-cryopreserved blood
  - At delivery to late presenting women
    - Similar to Rapid HIV