Women and Tb: Impact of Gender

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Talk Outline

• Epidemiology
• Gender Issues in TB Control
• Issues in Low Incidence, High Resource Countries (Focus on Canada and US)
  – Screening
  – Treatment
Epidemiology Global 2013

Global
- 9 million TB cases
- 3,697,499 TB cases notified
- 1.1 Million in PLWAs
- 1.5 Million people died
- 360,000 of deaths in patients with TB/HIV

Women
- 3.3 million
- 1,427,151 TB Cases notified
- 510,000 women died with TB
- 180,000 of deaths were in women with TB/HIV
- 550,000 children with TB
- 80,000 children without HIV died of their TB

WHO Global TB Report 2014
Sex differences in Infection

- Annual infection rates consistent across many studies in various sites
- M=F until about age 14 then M>F
- Hypothesis:
  - ? After 14 men have more external exposures then women
  - ? TST is less sensitive in women

Sex Differences in Notification rates
Influences of country incidence

Figure 2  Shift in age and sex patterns of tuberculosis notification rates. England and Wales, 1952 and 1970.

Figure 3  Tuberculosis notification rates for Tanzania (cases/100 000), 1989–1991.

Do women of child bearing years have higher rates of progression to disease?

- Biology
- Recent exposure leading to progression
- Timing of interaction with the health care system

Male: Female Notifications 2013

<table>
<thead>
<tr>
<th>Region</th>
<th>M:F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>1.6</td>
</tr>
<tr>
<td>Africa</td>
<td>1.4</td>
</tr>
<tr>
<td>The Americas</td>
<td>1.7</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>1</td>
</tr>
<tr>
<td>Europe</td>
<td>1.9</td>
</tr>
<tr>
<td>South East Asia</td>
<td>1.5</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>2.2</td>
</tr>
</tbody>
</table>

The HIV epidemic is affecting the notification ratios as well. In high HIV and TB incidence countries, the rates of F TB notification are increasing and approaching M notification rates (HIV and TB both are diseases of age 15-34 – reproductive years for F).

As a result, most research looking at gender differences appears to be focuses on LIC/MIC countries where HIV and TB have a high intersection.
Tb in High burden areas

• Reduction of tuberculosis (TB) transmission, morbidity and mortality relies largely on intensified case finding, with consequent early initiation of adequate treatment

• Screening and diagnosis still remains a challenge in resource limited settings especially among women due to:
  – Pregnancy
  – Poverty and low women empowerment
  – Higher burden of HIV infection among women
    • In Kenya women have a higher (6.4%) prevalence of HIV compared to men (4.4%)
## Gender Imbalance (in notification rates) caused by?

### Socioeconomic
- Restricted access to Health care
- Traditional beliefs
- Greater reliance on less qualified (less expensive) health providers
- Stigmatization

### Biologic
- Higher rates of contributing co-morbidities in men
  - Alcoholism
  - Cigarette Smoking
- Influence of pregnancy and child bearing in women
  - Biologic differences (change in symptoms?)
  - Health Care Access – for example radiography use
Evidence for biologic or non biologic basis?

• Rwanda – case control study
  – Women more likely to be HIV infected, more likely to be smear negative or have EPTB and more likely to die during treatment of smear positive disease (Int J TB Lung Dis 15 (6):776-781, 2011)

• Malawi-review of 2 years country register data
  – Women less likely to submit sputa and less likely to be smear positive (Int J TB Lung Dis 4 (9):882-4, 2000)
Most information has focused on Pregnancy and the Post Partum state

• ? Due to fact that women are in care at this time
  – Prenatal care
  – PMTC programs

• ? Biologic differences during pregnancy that influence care
  – Th1 proinflammatory responses are suppressed in pregnancy = masking of symptoms, increased susceptibility of new infection or progression to disease
  – Postpartum Th1 suppression reverses (similar to IRIS) which may exacerbate sx
Risk of TB in Pregnancy

- Cohort series with case control
- All pregnancies in General Practitioner Data base in England over 12 years
- 192,801 women with a total of 264,136 pregnancies
- 177 TB events – 22 during pregnancy and 22 during 180 days postpartum
  - Incident rate ratios 1.29 pregnancy and 1.95 postpartum
  - Administrative, immunologic or medical factors

Zinner AJRCCM 185(7):779-784;2012
TB Case Rates by Age Group and Sex, United States, 2013

Cases per 100,000

- Under 5
- 5 - 14
- 15 - 24
- 25 - 44
- 45 - 64
- ≥65

Male
Female

CDC logo
What are the pragmatic issues of concern?

• Screening
  – LTBI
  – TB Disease

• Treatment
  – Tolerability
  – Side Effects

• Breastfeeding
• Infant evaluation

• Recommended

• Disease RX always indicated
• Well tolerated

• Reasonable data
• Good data re Protection
• How extensive the evaluation should be is the ?.
Screening for LTBI In Pregnancy

- CDC, ACOG, Canadian Guidelines suggest screening for LTBI as targeted testing
  - Those at risk: FB, contact to active, HIV, co-morbid disease that predisposes to TB
- TST or IGRA – screening thresholds do not change
- CXR for those who are found to have LTBI or are symptomatic
- Barrier in low burden countries is awareness of term “those at risk”
LTBI Treatment in Pregnancy

- Risk factors for side effects appear to be elevated
  - Concomitant factors in and postpartum period
  - (An Aside- risk may be elevated in women outside of that time frame as well)
- Treatment should not be deferred until the postpartum period if high risk (new conversion, HIV infected)
  - Interpretation of other high risk is left open ended
# Liver and Pregnancy

## Table 2. Characteristics of Liver Diseases in Pregnancy.*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Symptoms</th>
<th>Jaundice</th>
<th>Trimester</th>
<th>Incidence in Pregnancy</th>
<th>Laboratory Values†</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis gravidarum</td>
<td>Nausea, vomiting</td>
<td>Mild</td>
<td>1 or 2</td>
<td>0.3–1.0%</td>
<td>Bilirubin &lt;4 mg/dl, ALT &lt;200 U/liter</td>
<td>Low birth weight</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>Pruritus</td>
<td></td>
<td>2 or 3</td>
<td>0.1–0.2% in U.S.</td>
<td>Bilirubin &lt;6 mg/dl, ALT &lt;500 U/liter, increased bile acids</td>
<td>Stillbirth, prematurity, bleeding, fetal mortality 3.5%</td>
</tr>
<tr>
<td>Biliary tract disease</td>
<td>Right-upper-quadrant pain, nausea, vomiting, fever</td>
<td>With CBD obstruction</td>
<td>Any Unknown</td>
<td></td>
<td>If CBD stone, increased bilirubin and GGT</td>
<td>Unknown</td>
</tr>
<tr>
<td>Drug-induced hepatitis</td>
<td>None or nausea, vomiting, pruritus</td>
<td>Early (in cholestatic hepatitis)</td>
<td>Any Unknown</td>
<td></td>
<td>Variable</td>
<td>Unknown</td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>Upper abdominal pain, nausea, vomiting, confusion late in disease</td>
<td>Common</td>
<td>3</td>
<td>0.008%</td>
<td>ALT &lt;500 U/liter, low glucose, DIC in &gt;78%, increased bilirubin and ammonia late in disease</td>
<td>Increased maternal mortality (≈20%) and fetal mortality (13–18%)</td>
</tr>
<tr>
<td>Preeclampsia and eclampsia</td>
<td>Upper abdominal pain, edema, hypertension, mental-status changes</td>
<td>Late, 5–14%</td>
<td>2 or 3</td>
<td>5–10%</td>
<td>ALT &lt;500 U/liter (unless infarction), proteinuria, DIC in 7%</td>
<td>Increased maternal mortality (~1%)</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>Upper abdominal pain, nausea, vomiting, malaise</td>
<td>Late, 5–14%</td>
<td>3</td>
<td>0.1% (4–12% of women with preeclampsia)</td>
<td>ALT &lt;500 U/liter, platelets &lt;100,000/ mm³, hemolysis, increased LDH, DIC in 20–40%</td>
<td>Increased maternal mortality (1–3%) and fetal mortality (35%)</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>Nausea, vomiting, fever</td>
<td>Common</td>
<td>Any</td>
<td>Same as general population</td>
<td>ALT greatly increased (&gt;500 U/liter), increased bilirubin, DIC rare</td>
<td>Maternal mortality increased with hepatitis E</td>
</tr>
</tbody>
</table>

*ALT denotes alanine aminotransferase, CBD common bile duct, GGT γ-glutamyl transpeptidase, DIC disseminated intravascular coagulation, and LDH lactate dehydrogenase.
†To convert bilirubin values to micromoles per liter, multiply by 17.1.

Knox NEJM 335 (8):569-576;1996
Screening for Active Disease

• In HIV TB high incidence countries, screening for active disease involves collection of sputa for cough any duration, fever, weight loss
  – Absence of sx have a negative predictive value of 90-97%; Positive predictive value is low

• In LIC, screening for TB disease is dictated by symptomatic women with a history of risk factors
  – No published data regarding efficacy of screening practices
Treatment of TB Disease in Pregnancy

• Treatment of TB Disease varies little with pregnancy
• PZA not approved in the US in pregnant women but used in the remainder of the world
• Canada suggests PZA use in severe cases
• Pyridoxine (B6) should be given although little data to support increased neuropathy in pregnancy
Breastfeeding

• Breastfeeding does not transmit TB
  • No documented cases of transmission from breast milk
• Formula fed infants remain at high risk of infection
• Anti-tuberculous drugs cross into breast milk in small amounts
  – Serum level no more than 20% of the therapeutic level for INH
    • Less than 11% for others
  – No toxic effects reported
  – No indication to advise mom to “pump and dump”

Breastfeeding

• The issue is not transmission of the organism through breast milk but rather the proximity of the mother to baby during feeding in the case of a mother who is infectious (smear positive)

• CDC = On first line ATT and no longer infectious

• WHO = smear negative
Public Health

PROPHYLACTIC ISONIAZID
PROTECTION OF INFANTS IN A TUBERCULOSIS HOSPITAL

B. A. DORMER
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M.B. Cape Town
MEDICAL OFFICER

J. A. SWART
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S. R. VIDOR
M.B. Cape Town
MEDICAL OFFICER

KING GEORGE V HOSPITAL, DURBAN, SOUTH AFRICA

The Lancet. 1959

Some of our mothers with their babies.
Study Summary

• Treatment – 10/1955 to 1/1959
  – Child kept in crib next to mom’s bedside
  – 30 bed open ward, all women with active pulmonary TB
  – Infants given INH twice daily
  – Breastfed
  – No special precautions taken to prevent infection
    • “mothers are allowed to fondle their children as much as they wish”
  – Infants PPDs monthly, CXRs twice monthly

• Outcomes
  – 101 pregnancies, 103 live births
  – 2 stillborn, 3 died within 3 weeks
  – 98 healthy
    • 4 became PPD positive (mom’s not giving INH)
Separation

• “INH therapy for newborns has been so effective that separation of mother and infant is no longer considered mandatory”

• Separation should occur only if
  – the mother is ill enough to require hospitalization
  – if she has been or is expected to become nonadherent to her treatment
  – if she is thought to be infected with a drug-resistant strain of *M. tuberculosis*
Summary

• The true incidence of TB in women is unclear
  – Influenced by biology, access or other factors?
• Because TB is primarily a disease of young adults; thus, much of the information about TB and women focus on the intersection between pregnancy/PP and TB
• TB remains a leading cause of death in women of childbearing years