MATERNAL TB AND NEONATAL IMPLICATIONS

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Child and Adolescent TB Working Group
Hyderabad, India

30 October, 2019
CC: fever

HPI: 8 day old male born in Taiwan at 37 weeks gest.
  - Fever for 2 days
  - No respiratory or GI symptoms
  - No known sick contacts

Exam: T 39°C, other vitals stable
  - Clear lungs, no HSM

Labs:
  - WBC 17,500/uL
  - CRP 7.3 mg/dL
  - CSF and all cultures negative

A/P: Sepsis -> Cefotaxime/ampicillin

Yeh, Frontiers Pediatrics 2019
Exam: still febrile
  - Abdominal distention

Labs:
  - HSV, EBV, CMV, Hep
  - CRP 14.4 mg/dL

CXR:

Plan: Change abx to Vanc/Ceftazidime

Yeh, Frontiers Pediatrics 2019
**HOSPITAL COURSE: CONT’D**

- **Day 6**: CT with R pleural effusion
  - Parents refused drainage

- **Day 11**: Parents allow gastric lavage -> 1/3 with few AFB

- **Day 15**: CT c/a/p with patchy consolidation in RUL, multiple bilateral pulmonary nodules, splenic and hepatic nodules
  - Treatment: INH, RIF, PZA
  - Cultures ultimately grow DS TB

**Delay in diagnosis:**
- ✔ Reluctance for invasive procedures
- ✔ Symptoms overlap with sepsis

_Yeh, Frontiers Pediatrics 2019_
## CONGENITAL TB

### Diagnostic criteria for congenital\(^1\):
Proven TB lesions with...
- In the first week of life, OR
- Primary hepatic complex or caseating granulomas in the liver, OR
- TB infection in placenta or maternal genital tract, OR
- Contact investigation excludes postnatal transmission

### Published cases in English: <350
- 80% in Asia

<table>
<thead>
<tr>
<th>Signs &amp; Symptoms(^2)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>64%</td>
</tr>
<tr>
<td>Resp. distress</td>
<td>64%</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>65%</td>
</tr>
<tr>
<td>Lethargy/irritable</td>
<td>40%</td>
</tr>
<tr>
<td>Poor feeding</td>
<td>39%</td>
</tr>
<tr>
<td>Cough</td>
<td>35%</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>25%</td>
</tr>
<tr>
<td>Pale</td>
<td>25%</td>
</tr>
<tr>
<td>Abd. Distention</td>
<td>22%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>20%</td>
</tr>
</tbody>
</table>

\(^1\)Cantwell NEJM 1994; \(^2\)Peng Pedi Pulm 2011
NEONATAL TB DIAGNOSIS

- 80% have abnormal chest imaging\(^1\)
  - 50% miliary or nodular

- AFB/culture/PCR
  - 75% yield if from early AM gastric aspirate\(^2\)

- Mortality remains HIGH\(^1\)
  - 53% before 1994
  - 34% post 1994

\(^{1}\) Peng, Pedi Pulm 2011; Starke Pediatrics 1989
75% of mothers who transmit TB to their babies DON’T KNOW IT

Mortality of infants born to mothers with TB was 2.2x higher if mothers were asymptomatic

### NEONATES GET TB FROM THEIR MOMS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average onset age (days)</td>
<td>20.7 ± 20.2</td>
</tr>
<tr>
<td>Median</td>
<td>15</td>
</tr>
<tr>
<td>Maternal TB</td>
<td>157 (92%)</td>
</tr>
<tr>
<td>Prepartum</td>
<td>36 (22%)</td>
</tr>
<tr>
<td>Postpartum</td>
<td>121 (77%)</td>
</tr>
</tbody>
</table>

Maternal TB type

- Miliary: 53
- Genital or placenta: 45
- TB pleurisy: 22
- TB meningitis: 12
- Infiltrative pulmonary TB: 22
- Unknown/Other: 8

Peng, Pedi Pulm 2011; Yeh Frontiers Pedi 2019
Mother developed dry cough at 1 week postpartum, weakness

Day 24 postpartum: altered mental status
  - AFTER baby was diagnosed!

Labs:
  - HIV neg
  - Renal failure
  - Liver failure
  - AFB+, PCR for MTB+

Treatment: RIPE
  - Died 3 days later
IMMUNE CHANGES MASK SYMPTOMS

<table>
<thead>
<tr>
<th>First trimester</th>
<th>Second trimester</th>
<th>Third trimester</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monocytes and phagocytosis</td>
<td>Monocytes and phagocytosis</td>
<td>Dendritic cells</td>
<td>Monocytes and phagocytosis</td>
</tr>
<tr>
<td>Polymorphonuclear cells</td>
<td>Polymorphonuclear cells</td>
<td>α-Defensins</td>
<td>Polymorphonuclear cells</td>
</tr>
<tr>
<td>Regulatory T cells</td>
<td>Regulatory T cells</td>
<td>CD4+ T cells</td>
<td>Regulatory T cells</td>
</tr>
<tr>
<td>CD8+ T cells</td>
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<td>CD8+ T cells</td>
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<tr>
<td>B cells</td>
<td>B cells</td>
<td>B cells</td>
<td>B cells</td>
</tr>
<tr>
<td>Natural killer cells</td>
<td>Natural killer cells</td>
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</tr>
<tr>
<td>Cytotoxicity</td>
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- Increased risk of malaria, listeria
- Increased severity of flu, varicella

Figure adapted from Kourtis NEJM 2014
PREGNANCY AND INFANT OUTCOMES

Pregnancy
- Pre-eclampsia & eclampsia (2 fold)
- Vaginal bleeding (2 fold)
- Hospitalization (12 fold)
- Miscarriage (10 fold)
- Mortality
  - 25 fold for HIV-uninfected
  - 37 fold for HIV-infected

Infant
- Low birth weight (2 fold)
- Lower Apgar scores
- Prematurity (2 fold)
- Small for gestational age (2 fold)
- Infant HIV (2 fold)
- Congenital TB (rare)
- Infant mortality (3.4 fold)

Jana NEJM 1999; Pillay Lancet 2000; Khan AIDS 2001; Gupta JID 2011; Mathad CID 2012
## TREATMENT OF PULMONARY TB IN PREGNANCY

<table>
<thead>
<tr>
<th></th>
<th>HIV negative</th>
<th>HIV positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Burden</strong>¹</td>
<td>INH 5mg/kg/d x 9 mo RIF 10mg/kg/d x 9mo EMB wt-based x 2 mo B6 25mg/d x 9 mo</td>
<td>INH 5 mg/kg/d x 6 mo RIF 10 mg/kg/d x 6 mo EMB 15mg/kg/d x 2 mo PZA 25mg/kg/d x 2 mo B6 10-25mg/d x 6 mo</td>
</tr>
<tr>
<td><strong>High Burden</strong>²</td>
<td>INH 300 mg/d x 6 mo RIF 600 mg/d x 6 mo EMB wt-based x 2mo PZA wt-based x 2 mo B6 25mg/d x 6 mo</td>
<td>INH 5 mg/kg/d x 6 mo RIF 10 mg/kg/d x 6 mo EMB 15mg/kg/d x 2 mo PZA 25mg/kg/d x 2 mo B6 10-25mg/d x 6 mo</td>
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**DIFFERENCE IN PZA guidance**

**NO MDR-TB guidelines**

¹ CDC, ATS, IDSA guidelines; ² WHO, British thoracic Society, RNTCP and IUATLD guidelines
BREASTFEEDING?

- Breast feeding allowed if on 1st line
  - **NOT** recommended with rifabutin or fluoroquinolones
  - *No evidence for other DR medications*

- If mother suspected of having TB, separate from infant\(^1\)
  - Can resume when smear negative (after 2-3 weeks of treatment), or infant started on TB treatment
  - Baby should get INH (3-6 months) + BCG

*WHO 1998*
# TREATMENT OF LTBI IN PREGNANCY

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<tr>
<td><strong>Low burden</strong></td>
<td><strong>INH 300mg + Vit B6 (10-25mg) daily for 6-9 mos(^1,2)</strong></td>
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<tr>
<td>Defer until postpartum, unless recent household contact</td>
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</tr>
<tr>
<td><strong>High burden</strong></td>
<td><strong>INH 300mg + Vit B6 (10-25mg) daily for 6-9 mos(^1,2)</strong></td>
</tr>
<tr>
<td>No official guidance</td>
<td></td>
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\(^1\) CDC 2013, \(^2\) WHO 2010
956 HIV+ pregnant women from 8 countries
- Randomized to immediate versus deferred (12 wk PP) IPT

Gupta A, NEJM 2019
### P2001: 3HP IN PREGNANT/POSTPARTUM WOMEN

<table>
<thead>
<tr>
<th><strong>2nd trimester</strong></th>
<th><strong>3rd trimester</strong></th>
<th><strong>Postpartum</strong></th>
<th><strong>Infants</strong></th>
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<tr>
<td><strong>Cohort 1:</strong> Screening Visit</td>
<td></td>
<td></td>
<td><strong>Newborn visit (within 3d)</strong></td>
</tr>
<tr>
<td><strong>Enrollment Visit (Intensive PK, n=25)</strong></td>
<td><strong>Cohort 2:</strong> Screening Visit</td>
<td></td>
<td><strong>Monthly visits (until 24 wks)</strong></td>
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<tr>
<td><strong>Weekly Visits with DOT dosing for 11 weeks</strong></td>
<td><strong>Enrollment Visit (Intensive PK, n=25)</strong></td>
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<td><strong>Study exit visit</strong></td>
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<td><strong>Last dose visit (week 12 visit) with Sparse PK sampling</strong></td>
<td><strong>Weekly Visits with DOT dosing for 11 weeks</strong></td>
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<td><strong>Monthly visits until 24 weeks postpartum</strong></td>
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- **Interim analysis when n=12**

Study visit

Monthly visits until 24 weeks postpartum

Last dose visit (week 12 visit) with Sparse PK sampling

*Note: DOT (Direct Observation Therapy) dosing for 11 weeks.*
**IMPAACT 2025: 1HP VS. 3HP IN PREGNANT VS. POSTPARTUM WOMEN**

**Regimens**
- Arm 1: 1HP Antepartum
- Arm 2: 3HP Antepartum
- Arm 3: 1HP Postpartum
- Arm 4: 3HP Postpartum

**Primary Outcomes***
- Arm 1 vs Arm 2
- Arm 3 vs Arm 4

- Composite: Maternal safety (including all-cause mortality), pregnancy outcomes (Arm 1 vs Arm 2 only), Rx discontinuation

**Outcomes assessed**
- PP, postpartum; HP, Isoniazid and rifapentine; TPT, Tuberculosis preventive therapy; Rx, treatment
# WHAT WE NEED

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<th>Neonatal</th>
<th>Maternal</th>
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<td>Better screening guidelines</td>
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<td>Diagnostics (POC)</td>
<td>Diagnostics- POC and improved sensitivity</td>
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<tr>
<td>Evidence-based treatment guidelines (DS and DR)</td>
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<td>PK studies from breast milk</td>
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- Better screening guidelines
- Diagnostics (POC)
- Evidence-based treatment guidelines (DS and DR)
- PK studies from breast milk
- Better screening guidelines
- Diagnostics- POC and improved sensitivity
- Evidence-based treatment guidelines (DR, PZA)
Maternal and child lung health working group

- Thursday, October 31 @ 7:45am
- Room: MR G.03 & G.04

Other sessions:

- Friday, November 1
  - TB preventive therapy: Is it safe and how should we implement it?
    - 10:30-12: Room: MR G01 & G02
  - TB in pregnancy: optimising diagnosis and treatment
    - 12:15-1:15, Eposter area 2

- Saturday, November 2
  - Confronting the crisis: emerging research in maternal-child TB
    - 10:30-12, Room G05&G06
  - Meet the Expert, IPT in Mothers and children: Yael Hirsch-Moverman, Jyoti Mathad
    - 12:15-1:15, MR 2.03&2.04