Recognizing (and hopefully responding to) TB during Pregnancy

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Barbara J Seaworth M.D. has no disclosures to note.

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity
I would like to dedicate this presentation to the memory of this beautiful young woman, mother of 4 who died way too soon, 1/29/2022, from a disease that is preventable and curable.
TB in Pregnancy, Labor and Puerperium

Read in section on Obstetrics, Southern Medical Association 54th MTG 1950; Reese and Martin

• The “old view” Young, 1926
  • “For the virgin no marriage for the married no pregnancy for the pregnant no confinement for the mother no suckling”

• Reported opinions had changed.

• CXR mandatory when TB suspected.

• TB little effect on fertility unless marked debility or genital TB

• Pregnancy has little effect on the evolution of TB, especially of TB under treatment.

• **Puerperium and few months following, women are very vulnerable to effects of TB**

• Be on guard against anemia in the pregnant tuberculous woman.
Still a Lot to Do and Learn in 2023

• Data on prevalence of LTBI and TB disease during pregnancy

• Strategies to identify and treat those at risk of progression during pregnancy

• Expectation that treatment during pregnancy improves outcomes for moms and infants.

• Good information about the safety, efficacy and dosing of medications during pregnancy, postpartum period and lactation

• Switch from “automatic exclusion” of pregnancy to “expectation” that pregnant patients should be “included in research” unless definite safety/contraindication exists.
Prevalence of TB Disease

• TB Prevalence:
  • -- in HIV negative women in South Africa 2010/100,000 (Grounder et al, J Acquir Immune Defic Syndr, 2001)
  • -- in South Africa 6880/100,00 HIV positive (Grounder et al, J Acquir Immune Defic Syndr, 2001)
  • -- in HIV infected women in high incidence countries 0.8-11%
  • -- in UK in 2009 reported as 4.2/100,000. (Knight et al, BJOG 2009)
  • -- in a TB tertiary hospital in India: 10-year experience; prevalence of 1.16/1000 deliveries (Chopra et al Tropical Doctor 2017)

• Pregnancy status not routinely collected in most countries
• Estimated the number of pregnant women with active TB for 217 countries
  • Used country-level estimates of population, distribution of population by age/sex/crude birth rate/est. prevalence of active TB and case notification data by age/sex

• Estimate: 216,500 active TB cases in pregnancy globally in 2011.
  • Greatest burden: WHO African region with 89,400 cases
  • SE Asian: 67,500 cases

• CXR estimated to detect up to 114,100 additional cases than smear alone
• Xpert estimated to detect 120,300 TB more

Clicking the Update link notes: no update 2/14/2023
What do we know about TB rates in Pregnancy?
(total # of cases, rate/1,000 pregnant women % of global burden)

- 200,000 women/year
- Likely underestimate

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean (95% uncertainty range)</th>
<th>Rate per 1000 pregnant women (95% uncertainty range)</th>
<th>Percentage of global burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>All countries combined</td>
<td>216 500 (192 100–247 000)</td>
<td>2.1 (1.8–2.4)</td>
<td>--</td>
</tr>
<tr>
<td>African Region</td>
<td>89 400 (74 200–110 500)</td>
<td>3.6 (3.0–4.5)</td>
<td>41%</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>4800 (3900–6000)</td>
<td>0.4 (0.3–0.5)</td>
<td>2%</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td>28 500 (19 700–41 900)</td>
<td>2.3 (1.6–3.4)</td>
<td>13%</td>
</tr>
<tr>
<td>European Region</td>
<td>4900 (3800–6300)</td>
<td>0.6 (0.5–0.8)</td>
<td>2%</td>
</tr>
<tr>
<td>South-East Asia Region</td>
<td>67 500 (52 000–87 100)</td>
<td>2.4 (1.9–3.1)</td>
<td>31%</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>21 400 (19 400–23 700)</td>
<td>1.1 (1.0–1.2)</td>
<td>10%</td>
</tr>
</tbody>
</table>

Table 2: Total number of active tuberculosis cases in pregnant women, rate per 1000 pregnant women and percentage of global burden by WHO region and combined

Sugarman *The Lancet* 2014
Fig. 2.1.5 Global estimates of TB incidence numbers and case notifications disaggregated by age and sex (female in purple; male in green), 2021

Regional estimates of the distribution of TB cases by age and sex are shown in Fig. 2.1.6.
The latest year for which WHO has published estimates of global deaths by cause remains 2019, when TB was the top cause of death from a single infectious agent and the 13th leading cause of death worldwide (Fig. 2.2.3). In 2020 and 2021, it is anticipated that TB will rank second as a cause of death from a single infectious agent, after COVID-19 (3).
Prevalence of LTBI in Pregnancy in U.S.

• U.S. prevalence not known with certainty
  • Assumed to be like estimated LTBI prevalence in women in U.S. population (4.4%)

• Substantially higher in foreign-born populations
  • Varies with country of origin

• Impact of refugee/immigrant status
  • Stress, malnutrition,
  • Congregate settings prior to destination
• Retrospectively evaluated all reported cases of TB diagnosed during pregnancy to 6 months postpartum in Israel’s Northern Health District 2002-2012

• Active TB diagnosed in 6 patients
  • All HIV negative; 2 immigrants
  • Average incidence during period 3.9/100,000 pregnancies similar to general population
  • Diagnosis delayed for 3 – 7 months
• **Asked Question:** Does Pregnancy Increase Risk of TB?
  - Or is increased risk due to higher occurrence of TB in high-risk groups?

• Used U.K. General Practice Research Database to identify cohort to investigate epidemiology of TB in pregnancy
  - All women with pregnancies occurring 1996-2008
    - Included all stillbirths, terminations and miscarriages.

• Retrospective cohort study; nested self-controlled case series (SCCS) analysis
  - Women in this analysis, TB could have occurred before, during or after pregnancy

• 177 TB events occurred during the study
  - 44 occurred during pregnancy/postpartum
  - 8 (1\(^{st}\)), 7 (2\(^{nd}\)), 7 (3\(^{rd}\)) and 22 (PP)
Self Controlled Case Series

Individual with an event (TB) and an exposure (pregnancy)

Compares the incidence of the event (TB) during the exposure time with the respective incidence in a “control time”

Risk in same person during a “risk” period with “non-risk” period.

Exposure time: pregnancy and 6 months postpartum

Control time: no pregnancy

Controls for all non-time dependent confounds of TB such as country of origin or ethnicity.

Excluded 6 months prior to pregnancy in calculating background risk.

177 pregnant women with TB

192,801 pregnant women

Figure 1. Schematic of (4) study populations and (B) exposure times for cohort and self-controlled case series studies. The schematic in B provides an overview for censoring and risk periods used in the cohort study as well as the self-controlled case series study. Exp = exposure; SCCS = self-controlled case series; TB = tuberculosis.
TB Rates in Pregnancy and Postpartum UK

Significant Increased Rate

- Outside Pregnancy: 9.1/100,000
- Pregnancy and Postpartum: 15.4/100,000
- Postpartum (180 days): 19.2/100,000

Risk not significantly higher during pregnancy
- Pregnancy: 1.29
- Postpartum: 1.95

IRR significantly higher in postpartum period

Testing for LTBI during Pregnancy: TST vs IGRA

Kaplan et al., *J Acquir Immune Defic Syndr* 2022

![Graph showing prevalence of LTBI among pregnant women by HIV status](image)

**Proportion positive (%) (95% CI)**

- **Overall**: 35.8% (32.3-39.3)
- **HIV+**: 37.0% (31.5-42.5)
- **HIV-**: 34.5% (33.2-35.8)

**Figure 2.**

Prevalence of latent tuberculosis infection by TST and QFT-Plus among pregnant women by HIV status.

Abbreviations: LTBI, latent tuberculosis infection; QFT-Plus, QuantiFERON TB Gold Plus; TST, tuberculin skin test.

TST positive defined as ≥5 mm induration for women living with HIV (HIV+) and ≥10 mm induration if HIV negative.

**Figure 1.**

TST and IGRA perform differently in pregnant women with and without HIV.

Proportion of positive QFT and TST tests among HIV Infected women in Western Kenya by peripartum stage

Marhad, J Int AIDS Soc  March 2020
“With few exceptions, radiation exposure through radiography, CT scan or nuclear medicine imaging techniques is at a dose much lower than the exposure associated with fetal harm.”
• Ultrasonography and MRI are not associated with risk and are imaging techniques of choice for pregnant patient

• With few exceptions, radiation exposure through radiographic, computed tomography (CT) scan or nuclear medicine imaging techniques is at a dose much lower than the exposure associated with fetal harm.

<table>
<thead>
<tr>
<th>Low- to moderate-dose examinations (0.1–10 mGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiography</td>
</tr>
<tr>
<td>Abdominal radiography</td>
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<tr>
<td>Lumbar spine radiography</td>
</tr>
<tr>
<td>Intravenous pyelography</td>
</tr>
<tr>
<td>Double-contrast barium enema</td>
</tr>
<tr>
<td>CT</td>
</tr>
<tr>
<td>Chest CT or CT pulmonary angiography</td>
</tr>
<tr>
<td>Limited CT pelvimetry (single axial section through the femoral heads)</td>
</tr>
<tr>
<td>Nuclear medicine</td>
</tr>
<tr>
<td>Low-dose perfusion scintigraphy</td>
</tr>
<tr>
<td>Technetium-99m bone scintigraphy</td>
</tr>
<tr>
<td>Pulmonary digital subtraction angiography</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Higher-dose examinations (10–50 mGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal CT</td>
</tr>
<tr>
<td>Pelvic CT</td>
</tr>
<tr>
<td>$^{18}$F PET/CT whole-body scintigraphy</td>
</tr>
</tbody>
</table>

• Limit use of gadolinium contrast with MRI; it may be used as a contrast agent only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome.

• Breastfeeding should not be interrupted
Case Report

TST 35 mm at time of incarceration –
  CXR negative, asymptomatic
  First trimester of pregnancy
  Plan to treat LTBI postpartum

HIV negative

No known exposure but prior incarceration and no prior reported TST results
  Could she be a converter?

How Should She be Managed?
Should treatment of LTBI be Expanded during Pregnancy?

Should it at least be studied?

Equitable access to TB prevention is a human right

Everyone has a #RightToPreventTB

How about the pregnant diabetic?

Two significant risk factors more prevalent in immigrant/refugee populations we are not even discussing

Social Circumstance

Persons who have a hx of being homeless or incarcerated or of being employed in a facility where these persons reside may have an increased risk of exposure to infectious TB

The USPSTF recommends testing and treating persons with these risk factors.

INH and rifamycin are considered safe

All regimens except 3HP can be used.

Rifampin monotherapy offers shortest and most tolerable option
Deciding When to Treat LTBI During Pregnancy

Groups Who Should be Given High Priority for Latent TB Infection Treatment include:

- People with a positive TB blood test (interferon-gamma release assay or IGRA).
- People with a tuberculin skin test (TST) reaction of 5 or more millimeters who are:
  - HIV-infected persons.
  - Recent contacts to a patient with active TB disease.
  - Persons with fibrotic changes on chest radiograph consistent with old TB.
  - Organ transplant recipients.
  - Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of ≥15 mg/day of prednisone for 1 month or longer, taking TNF-α antagonists).
- People with a TST reaction of 10 or more millimeters who are:
  - From countries where TB is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala, or other countries with high rates of TB. (Of note, people born in Canada, Australia, New Zealand, or Western and Northern European countries are not considered at high risk for TB infection, unless they spent time in a country with a high rate of TB.)
  - Injection drug users.
  - Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities).
  - Mycobacteriology laboratory personnel.
What the CDC Recommends During Pregnancy:

TEST THESE

• Those at high risk for developing TB disease
  • Persons recently infected with TB
  • Persons with medical conditions that weaken the immune system

TREAT THESE

• Most can have treatment for LTBI delayed until 2-3 months post-partum
  • Why not - MOST SHOULD BE TREATED?

• For those at high risk for progression from LTBI to disease – especially recent contacts – treatment should not be delayed
What WHO Recommends during Pregnancy

• WHO End TB Strategy recommends improving access to testing and treatment of LTBI to prevent progression to active disease.

• **Pregnancy is not an established risk factor for LTBI**, neither the WHO’s guidelines nor most national guidelines in low-incidence countries stipulate systemic screening for LTBI in pregnant populations.

• WHO recommends TB Symptom Screen to rule-out TB
  • Early data from India suggested high negative predictive value in HIV infected postpartum women (CID 2011)
    • Cough, fever, night sweats or weight loss had a 99.3% negative predicted value in 799 women
  • Newer prospective data from multiple sub-Saharan African countries suggest performance lower during pregnancy
Those at Risk for Progression to TB Disease during Pregnancy Who Should be Considered For LTBI Treatment During Pregnancy Include:

- HIV infected
- Recent contacts
  - This likely includes many refugee populations including Afghani, Haitian, Cuban, Ukrainian and others due to crowding, social unrest leading to disruption of TB services in country of origin

- Those with immune suppression or on immunosuppressant medications
  - This likely includes some refugee populations immune suppressed by stress, malnutrition and poor living conditions.

- Those incarcerated, living in homeless shelters or congregate settings or who are employed there.
  - LTBI in pregnancy in this situation is at definite risk of progression
In 1993 the FDA recommended: including pregnant women in clinical trials of any medication likely to be used in pregnancy

Merkatz. NEJM 1993;329:292-6

....we are making a few gains but these are slow and painfully inadequate

If we had the research and knew more management of the pregnant women with a TST of 35 who was recently incarcerated would be clearer
Research in Pregnant and Lactating Women

• 2018 US FDA draft guidance outlines prerequisites for “reasonable” and ethically justifiable” inclusion of pregnant women in:
  • Premarketing studies – if adequate nonclinical data plus established safety in nonpregnant women and no alternate means to extrapolate efficacy and/or assess safety.
    • Generally, Phase I and II trials in should be nonpregnant women of reproductive age
  • Inclusion in Phase III and IV based on clear risks and benefits assessment
  • Critical trial components include
    • PK data with minimum requirements (gestational age at enrollment, gestational timing/duration of drug exposure, pregnancy outcomes, obstetrical care meeting recognized standards and follow up safety data among infants of moms with exposure
  • Capture pregnancy outcomes among women who become pregnant while participating in therapeutic trial.
    • Reconsent with option to continue unless teratogenicity known or suspected
Trial designs for TB Preventive Therapy in Pregnant and Lactating women

- Systemically excluded from the > 12 Phase III and post marketing clinical studies

- IMPAACT P1078: 1st randomized placebo-controlled trial to assess safety and optimal timing of IPT in HIV-infected in high TB burden settings
  - evaluated antepartum vs deferred postpartum IPT

- IMPAACT P2001: PK and safety of 3 months of weekly INH and rifapentine (3HP)

- IMPAACT Concept 5021: safety, tolerability, optimal timing and PK of 3HP versus 1 month of daily INH and rifapentine (1HP)

- Next step – Global Registry

LaCourse, et al; JAIDS Sept 2019

91% completion

- Search through May 2019 for RCT and non-randomized studies where IPT given to pregnant women

**Results:**

- Increased risk of hepatotoxicity among pregnant women given IPT compared to no IPT. **RR 1.64**

- Four looked at IPT vs no IPT in HIV infected pregnant women
  - 1 Adverse pregnancy outcomes OR 1.51
  - 3 Showed a protective effect
INH preventive therapy in HIV-infected pregnant and postpartum women “APRISE Trial”

- Double blind placebo controlled, randomized, pregnant HIV infected
- INH preventive treatment x 28 weeks; F/U x 48 wks.
  - Immediate group – initiate during pregnancy – (≥ 14 ≤ 24 wks. // ≥ 24 ≤ 34 wks.)
  - Deferred group – initiate at week 12 postpartum
- 956 women enrolled, mean CD4 493, all but 1 receiving ART (85% efavirenz)
- TB in 6; (3 each group); all during postpartum period. None in infants

**Conclusions:**
- Initiation of INH PT during pregnancy was noninferior to initiation during postpartum with respect to maternal treatment-related adverse events
- However greater incidence of adverse pregnancy outcomes in immediate group than in deferred group without any additional benefit with respect to risk of TB or maternal or infant death is cause for concern.
INH preventive therapy in HIV-infected pregnant and postpartum women

Gupta et al, NEJM 2019

Figure S3. Post-Hoc Analysis of Adverse Pregnancy Outcomes by Treatment Arm and Gestational Age Stratum

This stratified gestational age analysis was post-hoc and not adjusted for multiple comparisons. Adverse pregnancy outcome was a composite of low birth weight (<2500 g), preterm delivery (<37 weeks of gestation according to the Ballard examination, when available, or obstetrical estimate), spontaneous abortion (<20 weeks of gestation), stillbirth (<20 weeks of gestation), or major congenital anomaly (according to the Metropolitan Atlanta Congenital Defects Program of the US Centers for Disease Control and Prevention)².
INH preventive therapy in HIV-infected pregnant and postpartum women

Gupta et al, NEJM 2109

Liver Toxicity:
- Not all associated with INH
- All on efavirenz

6.6% grade 3 or higher liver toxicity
- 4 symptomatic, all during postpartum period

2 deaths likely due to INH induced liver failure, 1 each group, but occurred in postpartum period
- 2 others died of liver failure but never received INH, ART recently started
- 2 deaths not associated with liver disease (bacterial sepsis, pneumonia)
Composite Adverse Pregnancy Outcome: observed in 33% of INH exposed vs 18% INH-unexposed. INH exposure starting in 1st trimester was associated with increased adverse pregnancy outcomes, none statistically significant.

<table>
<thead>
<tr>
<th>Composite Adverse Pregnancy Event</th>
<th>INH-exposed during pregnancy N=39</th>
<th>INH-unexposed during pregnancy N=69</th>
<th>Unadjusted OR (95% CI)</th>
<th>OR adjusted for covariates at study entry (95% CI)</th>
<th>OR adjusted for covariates proximal to pregnancy outcome (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Birth</td>
<td>Yes</td>
<td>23 (59%)</td>
<td>70 (79%)</td>
<td>2.56 (1.13, 5.79)</td>
<td>2.97 (1.26, 7.02)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>16 (41%)</td>
<td>19 (21%)</td>
<td></td>
<td>1.87 (0.75, 4.69)</td>
</tr>
<tr>
<td>Spontaneous abortion &lt;20 wks</td>
<td>Yes</td>
<td>12 (31%)</td>
<td>13 (15%)</td>
<td>2.80 (0.97, 5.38)</td>
<td>2.63 (1.06, 6.53)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3 (8%)</td>
<td>3 (3%)</td>
<td></td>
<td>1.73 (0.67, 4.50)</td>
</tr>
<tr>
<td>Elective abortion</td>
<td>Yes</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>12 (31%)</td>
<td>21 (24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm Birth &lt;37 weeks in live births</td>
<td>Yes</td>
<td>3 (14%)</td>
<td>7 (13%)</td>
<td>1.02 (0.24, 4.35)</td>
<td>Not obtained(^1)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>19 (86%)</td>
<td>45 (87%)</td>
<td></td>
<td>Not obtained(^2)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>1</td>
<td>18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) OR adjusted for age, BMI, CD4, HIV RNA, TB treatment, smoking status, and alcohol consumption.

\(^2\) OR adjusted for age, BMI, CD4, HIV RNA, TB treatment, smoking status, alcohol consumption, and maternal and infant antenatal care.
Pregnancy in Women with HIV in a TB Preventive Therapy (TPT) Trial

Singh et al J AIDS Dec 2022

• Evaluated pregnancy outcomes in 216/896 who conceived on study

• Randomized trial of 4 TPT regimens in S. African adults with HIV
  • ART not available until 2004, In all arms < ¼ started ART


• Pregnancy exclusion; treatment stopped in all but INH arm
  • 34 became pregnant while taking TB Preventive Therapy (TPT),
Pregnancy outcomes in 34 who became pregnant while taking TPT

- 50% mom/baby healthy
- 6 (18%) elective abortion
- 3 (9%) spontaneous abortion (1-3 HR, 2-INHc)
- 1 (3%) premature birth
- 2 (6%) neonatal deaths (1-3 HR, 1-INH)

Table 4: Delivery Outcomes for Pregnancies Occurring During Study Treatment by Arm

<table>
<thead>
<tr>
<th>Count of Delivery</th>
<th>Delivery Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy</td>
</tr>
<tr>
<td>3HP</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>3HR</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>6H</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>H-cont</td>
<td>12 (38.2%)</td>
</tr>
<tr>
<td>Grand total</td>
<td>17 (50.0%)</td>
</tr>
</tbody>
</table>

Singh et al J AIDS Dec 2022
Exposure to LTBI Treatment during Pregnancy
The PREVENT TB and the iAdhere Trials

• Both looked at 12 weeks of once weekly INH and rifapentine (3 HP)
  • Prevent TB: compared 3 HP to 9 months of INH (9H)
  • iAdhere: compared adherence in those with DOT vs self-administered 3 HP

• Those pregnant or planning pregnancy were excluded
  • If pregnancy occurred treatment with 3 HP stopped; option to go to INH
  • 31 pregnancies exposed to 3 HP
  • 56 pregnancies exposed to (9H)
Exposure to LTBI Treatment during Pregnancy
The PREVENT TB and the iAdhere Trials

Moro et al, *Annals ATS* May 2018

3 HP
- Fetal Loss (all < 20 wks)
  - 4/31 (13%)
- Congenital abnormalities (live births)
  - 0/20

9 H
- Fetal Loss (all < 20 wks)
  - 8/56 (14%)
- Congenital abnormalities (live births)
  - 2/41 (5%)

Conclusions:
Among reported pregnancies – No unexpected fetal loss or congenital anomalies
No reports of maternal death, fetal death or neonatal/post-neonatal death
One INH recipient had hepatotoxicity

U.S. estimates: Fetal loss 17%  Congenital Anomalies 3%
Effectiveness and Safety of anti-TB drugs

Reviewed studies showed no significant association between child abnormality and mother’s exposure to anti-TB drugs

Small number of AE encountered

- 2 cases drug induced hepatitis
- 2 cases PZA allergy
- 1 severe N/V which led to termination of pregnancy
- 2 sensorineural deafness (streptomycin not used in these)
What do we know about drugs in pregnancy?

Population Pharmacokinetics of INH, PZA and Ethambutol in Pregnant SA Women with TB/HIV
Abdelwahab et al. *Antimicrobial Agents and Chemotherapy*, March 2020

Those participating in Tshepiso a prospective cohort study in SA underwent sparse PK sampling at > 36 weeks and 7 weeks post partum.

No significant differences seen during pregnancy versus postpartum in Area under curve (AUC) 0-24 hours.

No significant differences in maximum concentration during pregnancy versus postpartum.
• IMPAACT 2001 – Phase I/II trial evaluating the pharmacokinetics and safety of 3 HP among pregnant women with Indications for TB preventative therapy.
  • 50 participants; 20 HIV positive on efavirenz based ART and 30 HIV uninfected

Among women without HIV, clearance of rifapentine was 28% lower during pregnancy than postpartum. In pregnant women with HIV, clearance was 30% higher than women without HIV; clearance did not change significantly between pregnancy and postpartum. Pregnancy did not impact INH pharmacokinetics. No drug-related serious adverse events, treatment discontinuations or TB cases in women or infants.

Conclusion: 3 HP does not require dose adjustment in pregnancy. RPT clearance is higher among women with HIV, but all women achieved exposures of RPT and INH associated with successful TB prevention. Data support proceeding with larger safety-focused studies of 3 HP in pregnancy.
Clinical Pharmacokinetics and Pharmacodynamics of Antitubercular Drugs in Pregnancy
Shiu et al, European Journal of Drug Metabolism and Pharmacokinetics 2021

• Qualitative review of anti-tuberculous drugs during pregnancy

• Utilized searches in Medline, PubMed, Embase and Google Scholar from inception to 8/13/2020

• Pregnancy does not appear to have an extensive impact on the PK of most first line or second line agents. Most data were collected in late-stage pregnancy without high quality controls.
### Table 3. Recommendations for Regimens to Treat Latent Tuberculosis Infection

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Priority Rank</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>3HP: 3 months of isoniazid and rifapentine once weekly</td>
<td>Preferred</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>4R: 4 months of rifampin daily</td>
<td>Preferred</td>
<td>Strong</td>
<td>Moderate (HIV-negative)*</td>
</tr>
<tr>
<td>3HR: 3 months of isoniazid and rifampin daily</td>
<td>Preferred</td>
<td>Conditional</td>
<td>Very low (HIV-negative) Low (HIV-positive)</td>
</tr>
<tr>
<td>6H: 6 months of isoniazid daily or twice weekly</td>
<td>Alternative</td>
<td>Strong^ Conditional</td>
<td>Moderate (HIV-negative) Moderate (HIV-positive)</td>
</tr>
<tr>
<td>9H: 9 months of isoniazid daily or twice weekly</td>
<td>Alternative</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

* No evidence reported in persons with HIV infection.

^ Strong recommendation for persons unable to take a preferred regimen (e.g., because of drug intolerability or drug-drug interactions)

Third Trimester – out on ankle monitor and working in pawn shop

• Fatigue
• Tachycardia
• Increasing anemia despite iron supplementation
• Decreasing albumin
• No weight gain last 2 months, then slight weight loss
• Headache 2 weeks prior to delivery
Delays Associated with Adverse Outcomes
Early Diagnosis and Treatment – Vital

Diagnostic Delays
• Late presentations
  • Symptoms TB mimic those of pregnancy
    • Fatigue, Anorexia
    • Lean body weight loss
      • May be attributed to N/V of pregnancy or masked by weigh gain of pregnancy itself
    • Cough < 60%
    • Fever < 30%
  • Conservative approach to diagnosis

Treatment Delays
• Associated with poorer outcomes for mother and fetus
• More pronounced in women of minority ethnic background
• More common in recent arrivals from high prevalence areas.
• Concern regarding safety of TB drugs
Clinical Presentation of pulmonary TB
Yadav et al, 2021 *Indian J of Tuberculosis*

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Group 1 N = 15 (%)</th>
<th>Group 2 (Low risk Pregnant patients) N = 191 (%)</th>
<th>P value and significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>15 (100%)</td>
<td>4 (2.09%)</td>
<td>p = 0.001 HS</td>
</tr>
<tr>
<td>Chest pain</td>
<td>12 (80%)</td>
<td>2 (1.04%)</td>
<td>p = 0.01 SIG</td>
</tr>
<tr>
<td>Expectoration</td>
<td>15 (100%)</td>
<td>3 (1.57%)</td>
<td>p = 0.001 HS</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>5 (33.3%)</td>
<td>0</td>
<td>p = 0.02 SIG</td>
</tr>
<tr>
<td>Fever</td>
<td>14 (93.3%)</td>
<td>6 (3.14%)</td>
<td>p = 0.03 SIG</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13 (86.6%)</td>
<td>3 (1.57%)</td>
<td>p = 0.01 SIG</td>
</tr>
<tr>
<td>Loss of weight</td>
<td>12 (80%)</td>
<td>4 (2.09%)</td>
<td>p = 0.02 SIG</td>
</tr>
</tbody>
</table>
Prevalence and Clinical Characteristics of Pulmonary TB Among Pregnant and Post-Partum Women

Nguenha et al, Int J Tuberc Lung Dis 2022

- Cross sectional TB prevalence study among pregnant and post-partum women (9/2016 – 3/2018, Mozambique)
  - 10 women diagnosed with active TB (5 + culture, 3 Xpert +)
  - All Rx
  - Symptoms not common

- Ante-natal Clinic Patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>ALL n (%)</th>
<th>NO TB n (%)</th>
<th>TB 10 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough-YES</td>
<td>143 (7.22%)</td>
<td>139 (7.06)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Fever -Yes</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>54 (2.73)</td>
<td>52 (2.64)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>30 (1.52)</td>
<td>28 (1.42)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>67 (3.38)</td>
<td>63 (3.2)</td>
<td>4 (40)</td>
</tr>
</tbody>
</table>
37-year-old pregnant Afghani immigrant referred for follow-up screening after U.S. entry

Treatment for Tb x 6 months in Afghanistan

Told – she’d always have problems

Initial eval:
  Negative T-Spot
  + Xpert –
  No INH or rifampin resistance by pyrosequencing
  Culture no growth

Marked clinical improvement:
  Decreased cough/shoulder pain
  Resolution of anemia and low albumin

Delivered healthy infant 11/25/2020
• **Maternal Treatment Outcomes in Pregnancy**

  • **Initial systematic review:** 14 Studies; 375 pregnant women with TB

    • 332/375 – **cured** with documented culture conversion

    • **Maternal mortality:** 25 died during treatment
      • 11 TB meningitis
      • 11 MDR TB
      • 2 ARDS
      • 1 non- TB – massive pulmonary embolism

    • **Other adverse outcomes:**
      • 4 treatment failures
      • 4 residual functional defect
      • 7 treatment terminations due to Aes
      • 3 lost to follow up
• Pregnancy Outcomes

• Initial systematic review: 14 Studies; 375 pregnant women with TB
  • 332 live births
    • 4 died shortly after birth due to prematurity and pneumonia
    • 2 HIV positive
    • 1 active TB
    • 2 LTBI
    • 50 low birth weight
    • 7 growth restrictions
  
  • 18 not born alive
    • 11 terminations (more frequent in HIV infected women)
    • 1 therapeutic abortion
    • 3 miscarriages
    • 3 stillbirths
Systematic review and meta-analysis

- 13 studies through December 2015
  - Included if cohort of pregnant women with TB and pregnant women without TB as control
  - Pregnancy outcomes data included.
  - Included 3384 pregnant women with TB; 119,448 without TB

- **Site:** pulmonary 72%, Unknown 22%, extrapulmonary 5.8%, 3 patients with both pulmonary and extrapulmonary

- Only 7 HIV +

- **Timing** of diagnosis
  - prior to pregnancy - 73%
  - 1<sup>st</sup> trimester - 11%
  - 2<sup>nd</sup> trimester - 12%
  - 3<sup>rd</sup> trimester or postpartum - 4%
### Maternal deaths

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>P value</th>
<th>% weight</th>
<th>TB affected</th>
<th>Total affected</th>
<th>R-weighted total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. Jana, 1994</td>
<td>Subtotal (P = 0.7%, P = 0.714)</td>
<td></td>
<td>0.42</td>
<td>0.42</td>
<td>116,068,285</td>
<td>46</td>
</tr>
<tr>
<td>Ricardo-Figueira-Damian, 1998</td>
<td>Anemia</td>
<td></td>
<td>0.98</td>
<td>0.98</td>
<td>13,487,079</td>
<td>21</td>
</tr>
<tr>
<td>T-Shirted, 1975</td>
<td>Maternal Mortality</td>
<td></td>
<td>4.75</td>
<td>4.75</td>
<td>17,488,249</td>
<td>32</td>
</tr>
<tr>
<td>N. Jana, 1994</td>
<td>Maternal Mortality</td>
<td></td>
<td>0.35</td>
<td>0.35</td>
<td>19,747,057</td>
<td>36</td>
</tr>
<tr>
<td>N. Jana, 1994</td>
<td>Maternal Mortality</td>
<td></td>
<td>3.25</td>
<td>3.25</td>
<td>24,840</td>
<td>34</td>
</tr>
<tr>
<td>P.J. Kavango, 2004</td>
<td>Maternal Mortality</td>
<td></td>
<td>50.0</td>
<td>50.0</td>
<td>25,045,000</td>
<td>100</td>
</tr>
</tbody>
</table>

### Anemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>P value</th>
<th>% weight</th>
<th>TB affected</th>
<th>Total affected</th>
<th>R-weighted total</th>
</tr>
</thead>
<tbody>
<tr>
<td>V. Pranoviuski, 2003</td>
<td>C-section Delivery</td>
<td>0.96</td>
<td>0.96</td>
<td>20,889</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>P.J. Kavango, 2004</td>
<td>C-section Delivery</td>
<td>0.96</td>
<td>0.96</td>
<td>20,889</td>
<td>50</td>
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<td>C-section Delivery</td>
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<td>0.96</td>
<td>0.96</td>
<td>20,889</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>T-Shirted, 1975</td>
<td>Subtotal (P = 29.8%, P = 0.241)</td>
<td></td>
<td>0.96</td>
<td>0.96</td>
<td>20,889</td>
<td>50</td>
</tr>
</tbody>
</table>

### Miscarriage

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>P value</th>
<th>% weight</th>
<th>TB affected</th>
<th>Total affected</th>
<th>R-weighted total</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.J. Kavango, 2004</td>
<td>Subtotal (P = 81.3%, P = 0.036)</td>
<td></td>
<td>0.96</td>
<td>0.96</td>
<td>20,889</td>
<td>50</td>
</tr>
</tbody>
</table>

### Notes:
- weights are from random effects analysis.
- November 2016
Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis

S Sobhy, ZOE Babiker, J Zamora, KS Khan, H Kunst

First published: 11 November 2016 | https://doi.org/10.1111/1471-0528.14408 | Citations: 63

**Perinatal deaths**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Authors</th>
<th>Country</th>
<th>Total</th>
<th>Gestational age</th>
<th>% Active TB/ % Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ricarda Figueras, Damien</td>
<td>2001</td>
<td>93</td>
<td>75</td>
<td>9</td>
<td>75.2% (68, 72, 03)</td>
<td>15.27</td>
</tr>
<tr>
<td>N. Jana, 1994</td>
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<td>13</td>
<td>9</td>
<td>75.2% (68, 72, 03)</td>
<td>15.27</td>
</tr>
<tr>
<td>P. A. Kagwa, 2003</td>
<td>99</td>
<td>93</td>
<td>3</td>
<td>9</td>
<td>75.2% (68, 72, 03)</td>
<td>15.27</td>
</tr>
<tr>
<td>T. Djerenaci, 1975</td>
<td>79</td>
<td>93</td>
<td>3</td>
<td>9</td>
<td>75.2% (68, 72, 03)</td>
<td>15.27</td>
</tr>
<tr>
<td>Total (n = 53.7%, p = 0.044)</td>
<td>79</td>
<td>93</td>
<td>3</td>
<td>9</td>
<td>75.2% (68, 72, 03)</td>
<td>15.27</td>
</tr>
</tbody>
</table>

**Low birth weight**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Authors</th>
<th>Country</th>
<th>Total</th>
<th>% Active TB/ % Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ricarda Figueras, Damien</td>
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<td>93</td>
<td>75</td>
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</tr>
<tr>
<td>N. Jana, 1994</td>
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<td>9</td>
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<tr>
<td>T. Djerenaci, 1975</td>
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<td>93</td>
<td>3</td>
<td>9</td>
<td>75.2% (68, 72, 03)</td>
</tr>
<tr>
<td>Total (n = 53.7%, p = 0.044)</td>
<td>79</td>
<td>93</td>
<td>3</td>
<td>9</td>
<td>75.2% (68, 72, 03)</td>
</tr>
</tbody>
</table>

**Pre-term birth**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Authors</th>
<th>Country</th>
<th>Total</th>
<th>% Active TB/ % Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ricarda Figueras, Damien</td>
<td>2001</td>
<td>93</td>
<td>75</td>
<td>9</td>
<td>75.2% (68, 72, 03)</td>
</tr>
<tr>
<td>N. Jana, 1994</td>
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<td>93</td>
<td>13</td>
<td>9</td>
<td>75.2% (68, 72, 03)</td>
</tr>
<tr>
<td>P. A. Kagwa, 2003</td>
<td>99</td>
<td>93</td>
<td>3</td>
<td>9</td>
<td>75.2% (68, 72, 03)</td>
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<tr>
<td>T. Djerenaci, 1975</td>
<td>79</td>
<td>93</td>
<td>3</td>
<td>9</td>
<td>75.2% (68, 72, 03)</td>
</tr>
<tr>
<td>Total (n = 55.5%, p = 0.001)</td>
<td>79</td>
<td>93</td>
<td>3</td>
<td>9</td>
<td>75.2% (68, 72, 03)</td>
</tr>
</tbody>
</table>

**Active TB Poorer Outcomes**

<table>
<thead>
<tr>
<th>NOTE: weights are from random effects analysis</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000012</td>
<td>4.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Treatment in 1\textsuperscript{st} trimester vs 2\textsuperscript{nd}/3\textsuperscript{rd} trimester
  • No preterm births (0/9) treated in 1\textsuperscript{st} trimester
    • 33\% (4/12) in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimesters
  • No cases of perinatal death (0/9) treated in 1\textsuperscript{st} trimester
    • Perinatal death 23\% (3/13) treated in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester
  • No low birth weight infants (0/23) when treated in 1\textsuperscript{st} trimester
    • 61\% (33/54) low birth weight when treated in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester
  • Fewer complications in mothers
    • 29\% treated in 1\textsuperscript{st} trimester vs 60\% treated in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester

Outcomes better when treatment is early AND disease is limited.
Poor Obstetric and Infant Outcomes in Human Immunodeficiency Virus-Infected Pregnant Women with TB in SA: The Tshepiso Study. Salazar-Austin et al, *Clinical Inf Dis*, 2017

- Prospective cohort study of HIV infected pregnant women with or without TB (Jan 2011 – Jan 2014)
  - 80 case patients and 155 controls
  - **Infants of moms with HIV and TB** –
    - Higher risk of **Low Birth Weight** (20.8 vs 10.7 %)
    - Prolonged hospitalization at birth (51 vs 16%)
    - Infant death (66 vs 7 deaths/1000)
    - TB disease despite appropriate maternal therapy and infant TB preventive therapy

- **Obstetric Outcomes in co-infected woman:**
  - Higher risks of maternal hospitalization 25 vs 11 %
  - Preeclampsia .5 vs 0.7 %

- Similar rates of case 68.8% patients and controls 63.2% receiving ART

- No difference in birth outcomes including liver births, stillbirths, and spontaneous abortion

- 7 of the “controls” were identified with + cultures – subclinical TB
  (Rickman et al. *Int J Tuberc Lung Dis* 2020)

- **Screening/case finding is important in these high incident TB communities with high HIV rates.**
Obstetrics outcome in pulmonary tuberculosis

Vikas Yadav a, J.B. Sharma b,*, Alka Kriplani b, Neerja Bhatla b, Garima Kachhawa b, Reeta Mahey b, Rajesh Kumari b

a Department of Obstetrics and Gynecology, SMS&R, G. NOIDA, UP, India
b Department of Obstetrics and Gynecology, AIIMS, New Delhi, India

Table 2 – Obstetric complications and mode of delivery in two groups.

<table>
<thead>
<tr>
<th>S.NO</th>
<th>OUTCOME</th>
<th>Group 1 N = 15 (%)</th>
<th>Group 2 (Low risk Pregnant patients) N = 191 (%)</th>
<th>P value and significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pulmonary TB group</td>
<td>Low risk Pregnant patients</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>OBSTETRIC EVENTS:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PIH</td>
<td>2 (13.33)</td>
<td>15 (7.85)</td>
<td>P &gt; 0.05 NS</td>
</tr>
<tr>
<td></td>
<td>Oligohydramnios</td>
<td>0</td>
<td>3 (1.57)</td>
<td>P &gt; 0.05 NS</td>
</tr>
<tr>
<td></td>
<td>GDM</td>
<td>5 (33.33)</td>
<td>17 (8.9)</td>
<td>P &gt; 0.05 NS</td>
</tr>
<tr>
<td></td>
<td>PROM</td>
<td>8 (53.33)</td>
<td>4 (2.09)</td>
<td>P = 0.024 SIG</td>
</tr>
<tr>
<td></td>
<td>ICP</td>
<td>2 (13.33)</td>
<td>8 (4.18)</td>
<td>P &gt; 0.05 NS</td>
</tr>
<tr>
<td></td>
<td>Preterm labor</td>
<td>8 (53.33)</td>
<td>17 (8.9)</td>
<td>P &lt; 0.02 SIG</td>
</tr>
<tr>
<td></td>
<td>Post partum complication</td>
<td>2 (13.33)</td>
<td>2 (1.04)</td>
<td>P &gt; 0.05 NS</td>
</tr>
<tr>
<td></td>
<td>Need for blood transfusion (antepartum or intrapartum)</td>
<td>0</td>
<td>1 (0.05)</td>
<td>P &gt; 0.05 NS</td>
</tr>
</tbody>
</table>

GDM: Gestational diabetes mellitus.
APH: Antepartum hemorrhage.
PROM: Premature rupture of membrane.
ICP: Intrahepatic cholestasis of pregnancy.

Gestational age at delivery  
26-39 weeks  
29 -41 weeks

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/
30-year-old from South America who presented with intractable N/V

- 10 weeks pregnant – twins,
  - Weight 48kg
- RUL cavity
- + T Spot, HIV negative
- Normal LFTs, Hct 33, A1C 5.3
- Sputum Xpert +
- No rifampin resistance

- Prior treatment in Peru
- 9/15-10/19/22

- Meds: **Rifampin 450**, INH 300mg, ethambutol 800, B6 50mg

**Concerns:**

- Risk of liver toxicity
- One month later... now early 2\textsuperscript{nd} trimester
  - rash and AST/ALT > 5 times upper limit of normal
  - unlikely due to anti-emetics (promethazine; ondansetron)
- Intractable N/V will not allow adequate treatment of TB
  - NO PZA as would increase N/V
  - No contraindication to PZA if tolerated
- Gestational diabetes and impact on TB and pregnancy

- **Retrospective study** on
  - pregnant and age matched non-pregnant women receiving treatment for active TB at 4 hospitals in Western Sweden between 1992-2017
    - 40 pregnant women/95 non-pregnant

- **Frequency of severe liver toxicity (LFTs > 5 x upper normal)**
  - 40% pregnant vs 6% non-pregnant

- **Temporary drug withdrawal due to elevated LFTs**
  - 40% vs 9.5%
36 Weeks
Spontaneous Premature Rupture of Membranes

• Afebrile, Hb 7.8, platelet 653,000

• Delivered healthy infant without problems
  • 5 pounds 5 ounces

• Reported erythema and pain of R breast x 1 week
  • Required surgical drainage – 2 deep pockets identified
    • 3 x 3.3 x 4.4 cm and 6.9 x 2.5 x 2.2 cm
    • Large amount purulent material
    • Wound left open
  • Routine cultures negative – etiology not identified
Postpartum

- **3 weeks** post partum again incarcerated
- **now TST 00 mm (1st trimester 35 mm)**
- Multiple documented visits to medical
  - Fatigue, night sweats, SOB,
  - Tachycardia (110 +)
  - Lab – anemia (Hb 6.8), low albumin
- **6 weeks** post partum sick call visit
  - Referred to ER – SOB, Tachycardia, Fever, Cough
    - **COVID negative**
- **7 ½ weeks** post partum continued symptoms, more cough Fever 103
  - Referred to ER – **COVID positive (1/3/2022)**
    - Treated with steroids, returned to jail
Disseminated TB 13 weeks Postpartum

- **13 weeks post partum:** 1/23/2022 Admit
  - 4 days increased fever, SOB, O2 sat < 84%, pulse 140,
  - 10/10 chest pain, diarrhea, abdominal pain
  - Intermittently incontinent stool/urine
  - Anemic Hb 8.4, albumin 1.8, alk phosph 1,381, ALT 56
  - QFT +, sputum and urine 4+ AFB positive
    - Later Sputum, urine and blood culture + MTB
  - RIPE 1/26/2022
  - Arrested 1/26/2022; next morning blown pupils
  - MRI, transtentorial herniation of brain
  - **Expired 1/29/2022**

- **MTB involved:** Lungs, lymph nodes, brain, adrenals, peritoneum - ascites, kidneys, heart (ejection fraction 35% c/w myocarditis) bone marrow

- Unmasking IRIS
- How sick did she need to get for TB diagnosis?
Breast Abscess (13 weeks post op) shortly before her death...

She breastfed infant until her return to jail.
Immune Events with non-HIV IRIS in Pregnancy

Pregnancy

Delivery

Immune Reconstitution

Clinical Symptoms of IRIS

Response

Time

Unmasking TB

Paradoxical Reaction?
Tuberculosis one of the infectious diseases most often exacerbated in postpartum period

<table>
<thead>
<tr>
<th>Pathogen or clinical condition</th>
<th>Usual clinical manifestations</th>
<th>Proposed pathogenic basis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Pulmonary infiltrates, meningitis, CNS lesions, osteoarticular infection</td>
<td>Reactivation of endogenous foci presenting as symptomatic foci triggered by inflammatory responses during the postpartum period</td>
<td>[36–44, 93]</td>
</tr>
<tr>
<td><em>Mycobacterium leprae</em></td>
<td>Skin lesions and neuritis caused by tuberculoid leprosy</td>
<td>Increased cellular immunity and reversal reactions associated with Th1</td>
<td>[3]</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Meningitis, CNS lesions, pulmonary nodules and/or infiltrates, soft-tissue or osteoarticular infection</td>
<td>Symptomatic disease due to Th2 and Th1 reversal during the postpartum period</td>
<td>[59–61]</td>
</tr>
<tr>
<td><em>Coccidioides immitis</em></td>
<td>Disseminated infection, particularly during the third trimester and postpartum period</td>
<td>Hormonal modulation of cellular immunity, proinflammatory responses during the postpartum period</td>
<td>[62, 63, 65]</td>
</tr>
<tr>
<td><strong>Virus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis virus</td>
<td>Increased levels of aminotransferases and HCV RNA or HBV DNA in chronic carriers of HCV or HBV</td>
<td>Restoration of virus-specific cellular immune responses and paradoxical viral replication</td>
<td>[81, 82]</td>
</tr>
<tr>
<td>Herpes virus</td>
<td>Herpes simplex virus endometritis, higher frequency of cytomegalovirus excretion</td>
<td>Reversal of pregnancy-related suppression of nonspecific mitogenic and virus-specific lymphocyte responses</td>
<td>[88, 91]</td>
</tr>
</tbody>
</table>
Peripartum TB as a Form of Immunorestitution Disease

Peripartum TB: “acute deterioration or worsening of clinical symptoms of pre-existing TB during pregnancy or onset of clinical symptoms attributable to MTB within 1 month of delivery”

Assess clinical spectrum of peripartum TB from perspective of Immunorestitution disease

29 patients with peripartum TB

- 27 (93.1%) extra-pulmonary; 20/27 (60%) CNS
- 22/29 (75.9%) No symptoms during pregnancy, None HIV +

Median time from delivery to onset of symptoms 4 days
- 8/14 with clinical history noted had significant fever

Treatment delay 27 days – overall recovery 34.5%
- 11 (38%) died; 4 (13.8%) residual functional deficits.

Identified 8 cases of TB meningitis in HIV + women
  - screened during meningitis clinical trials Uganda 2018-22

Systematic review of literature 1970-7/2022 - 40 cases

48 Combined cases
  - 50% diagnosed postpartum;
    - 23/48 (50%) initial onset in pregnancy
    - 9/24 (38%) worsening of symptoms/relapse post partum
  
• Diagnosis missed/delayed 33%
• Maternal mortality 23% - of survivors 30% residual defects
• Fetal/neonatal mortality 30%

Most in HIV negative except 8 cases in this study
Normal CSF cell count does not exclude CNS TB or TB Meningitis

<table>
<thead>
<tr>
<th>CSF Parameters</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening pressure, mm H2O (normal &lt;250)</td>
<td>NA</td>
<td>400</td>
<td>15</td>
<td>200</td>
<td>80</td>
<td>280</td>
<td>70</td>
<td>170</td>
</tr>
<tr>
<td>White blood cells, cells/μL</td>
<td>625 (83% lymphocytes)</td>
<td>275 (78% lymphocytes)</td>
<td>165 (85% lymphocytes)</td>
<td>310 (85% lymphocytes)</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>635 (83% lymphocytes)</td>
</tr>
<tr>
<td>Protein, mg/dL</td>
<td>187</td>
<td>147</td>
<td>103</td>
<td>184</td>
<td>90</td>
<td>79</td>
<td>29</td>
<td>138</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>NA</td>
<td>&lt;1.1</td>
<td>&lt;1.1</td>
<td>&lt;1.1</td>
<td>45</td>
<td>Unknown</td>
<td>59</td>
<td>Low</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>NA</td>
<td>12.3</td>
<td>NA</td>
<td>NA</td>
<td>2.2</td>
<td>Unknown</td>
<td>2.4</td>
<td>5.5</td>
</tr>
<tr>
<td>AFB stain</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CSF GeneXpert</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>(trace)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MTB/RIF Ultra</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urine GeneXpert MTB/ RIF Ultra</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urine LAM</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+/−</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CSF culture</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: =, negative; +, positive; AFB, acid-fast bacilli; CSF, cerebrospinal fluid; LAM, lipoarabinomannan; NA, not performed or not available.

*Positive Fuji LAM, negative Alere LAM
An Opportunity Mostly Missed - Update of U.S. TB Surveillance - 2020

- Previous update was in 2009
- One of the New Questions Added
- Is the Patient Pregnant? (Yes/No/Unknown)

My patient risk with pregnancy was never captured by surveillance

NEVER COUNTED!
What about Her Baby?

- Child seen at 13 weeks of age
  - Normal exam
  - Normal CXR
  - **TST + 11 mm induration**
  - Elevated platelet count > 600,000
  - Elevated CRP

- Referred to hospital and additional evaluation showed normal CT scan and negative LP

- Now what – continue RIPE?

- Remember she was breast fed for nearly a month with mom with breast abscess
Female Genital Tract TB and Infertility
Muneer et al, *Nature Reviews Urology* 2019

- Female genital tract TB occurs through both haematogenous and lymphatic spread of NTB
  - All female reproductive organs are at risk
  - Endometrium and fallopian tubes most frequently involved.
  - Diagnosis delayed, presentation often primary infertility
  - Often asymptomatic or chronic pelvic pain due to adhesions


- Treatment if findings to support PRIOR to IVF!
IVF with Embryo Transfer (ET) in GU TB

• Several series depict poor outcomes for moms/infants due to disseminated/congenital TB

• Often TB is occult and reactivates after IVF-ET
  • Vascular permeability increases which can lead to hematogenous disseminated and extrapulmonary TB
  • Presents with rapid progression and poor prognosis – high fever, abnormal CXR
  • Spontaneous abortions most common at 12 – 16 weeks after ET due to severe TB toxemia and chorioamnionitis

Coexistence of primary infertility, untreated prior pulmonary TB and fallopian tube obstruction – high risk of TB dissemination in setting of IVF-ET
Screening and referral algorithm for patients with TB-risk factors. AST = Antimicrobial susceptibility test, CXR = chest radiographs; IGRA = interferon-gamma release assay; MDR = multidrug-resistant tuberculosis; PCR = polymerase chain reaction; PPD = purified protein derivative; TB = tuberculosis; TST = tuberculin skin test

Association of *in vitro* fertilization with maternal and perinatal outcomes among pregnant women with active tuberculosis: A retrospective hospital-based cohort study

Xia et al, *Frontiers in Public Health*, 2022

Retrospective analysis of 80 pregnant women with TB hospitalized at Shanghai Public Health Clinical Center June 2014 – November 2020.

Analyze maternal and perinatal outcomes in active TB after IVF versus normal pregnancy.

- 80 women with TB and pregnancy
  - 28/80 (35%) received IVF-ET
  - 52/80 (65%) spontaneous pregnancy

- Symptoms develop earlier in IVF group

- Symptoms began several weeks after progesterone stopped at week 8 – 10
  - Authors note this is a “Clear Intervention Point” at which to screen for TB after IVF treatment.
    - Week 8 - 22
### Association between IVF status and maternal outcomes among TB in pregnancy

<table>
<thead>
<tr>
<th></th>
<th>IVF-TB (n = 28)</th>
<th>Non-IVF-TB (n = 52)</th>
<th>OR*</th>
<th>95% CI</th>
<th>P-value (crude)</th>
<th>adjusted OR**</th>
<th>95% CI</th>
<th>P-value (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric complications (%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>13 (46.4)</td>
<td>1 (1.9)</td>
<td>44.2</td>
<td>5.3–366.0</td>
<td>&lt;0.001</td>
<td>47.6</td>
<td>5.2–439.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Maternal criticality</td>
<td>6 (21.4)</td>
<td>1 (2.0)</td>
<td>13.9</td>
<td>1.6–122.4</td>
<td>0.007</td>
<td>28.3</td>
<td>1.9–171.2</td>
<td>0.015</td>
</tr>
<tr>
<td>Preecclampsia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>TB outcomes (%)</td>
<td></td>
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<td></td>
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<tr>
<td>Fever &gt; 38.2°C</td>
<td>26 (92.9)</td>
<td>27 (51.9)</td>
<td>12</td>
<td>2.6–56.0</td>
<td>&lt;0.001</td>
<td>16.7</td>
<td>3.2–87.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Cough</td>
<td>21 (75.0)</td>
<td>30 (57.7)</td>
<td>2.2</td>
<td>0.8–6.1</td>
<td>0.149</td>
<td>2.3</td>
<td>0.8–6.7</td>
<td>0.135</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1 (3.6)</td>
<td>19 (36.5)</td>
<td>0.06</td>
<td>0.01–0.51</td>
<td>0.001</td>
<td>0.05</td>
<td>0.01–0.42</td>
<td>0.006</td>
</tr>
<tr>
<td>Miliary TB</td>
<td>89% vs 13.5%</td>
<td></td>
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</tr>
<tr>
<td>TB Meningitis</td>
<td>32% vs 7.7%</td>
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</tr>
</tbody>
</table>

*Odds ratio for IVF treatment vs. no IVF treatment by univariate analysis; **Multivariate regression was applied after adjusting for age, delay in diagnosis, and culture result.

### Association between IVF status and perinatal outcomes among TB in pregnancy

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<th>P-value (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>64 vs 28%</td>
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<td></td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>46 vs 11.5%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*Odds ratio for IVF treatment vs. no IVF treatment by univariate analysis; **Multivariate regression was applied after adjusting for age, delay in diagnosis, culture result, and induced abortion according to the patient's will. These data came from medical records or telephone review conducted at least 1 year after delivery.
• Prospective cohort trial to determine if infertile women with prior pulmonary TB detected on CXR have LTBI and whether LTBI affects IVF-ET outcomes

• Plan to analyze relationship between LTBI and pregnancy outcomes following IVF-ET in patients with untreated prior PTB

Previously analyzed 14,254 infertile patients who underwent IVF in 2017; 1,487 had pulmonary TB on CXR. 1,239 (81.8%) did not receive TB treatment. Untreated prior PTB group had significantly lower clinical pregnancy and live birth rates than the non-PPTB group.