TB infection in pregnancy: Novel insights into immunology and prevention

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Objectives

Epidemiology

Immunology of TB and pregnancy

TB prevention in pregnancy
What is the burden of TB in pregnancy?
Global TB incidence by sex, 2021

- Female: 3.4 million
- Male: 5.9 million

WHO Global TB Report, 2022
Global estimate of TB in pregnancy

<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>48,000 (39,000–60,000)</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>49,000 (38,000–63,000)</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

Based on total population, crude birth rate, age distribution, TB case notification by age/sex

Sugarman, Lancet Global Health 2014
TB Incidence in US- or Canadian- vs. foreign-born persons, 1993-2021

- US CDC TB Report, 2022
- Tuberculosis Surveillance in Canada Summary Report, 2010-2020
TB Rates, by Age and Sex:
United States, 2022
Canada, 2020

- US CDC TB Report, 2022
- Tuberculosis Surveillance in Canada Summary Report, 2020
Risk of TB in Pregnancy

UK Cohort: 1996-2008
• 192,801 women
• 177 TB events:
  • Postpartum 15.4 vs. 9.1 per 100,000 PY

Swedish cohort: 2005-2013
• 649,342 women
• 553 TB events:
  • Postpartum: 17 vs. 9 per 100,000 PY

IRR 1.95
Postpartum TB

Immune changes during pregnancy increase risk of disease

- Increased risk of malaria, listeria
- Increased severity of flu, varicella, Covid-19

Figure adapted from Kourtis NEJM 2014
Immunology of TB infection

CD4$^+$ T cells release IFN-γ, TNF-α

IFN-γ, TNF-α stimulate macrophages

Adapted from Griffiths, Nat Med Review 2010
Clue #1: Latent TB tests perform differently during pregnancy

Pai, Lancet 2004, ¹ Mathad, AJRCCM 2016 & PLOS One 2014; ³ LaCourse, JA
Clue #2: IGRA and IFN-γ responses change with stages of pregnancy

- IGRA+ responses:
  - HIV+ ANC: 100%
  - HIV+ L&D: 61%
  - HIV+ 6m: 0%
  - HIV-ANC: 100%
  - HIV- L&D: 77%
  - HIV- 6m: 90%

- IGRA- responses:
  - HIV+ ANC: 0%
  - HIV+ L&D: 14%
  - HIV+ 6m: 0%
  - HIV-ANC: 0%
  - HIV- L&D: 16%
  - HIV- 6m: 10%

- IGRA indet responses:
  - HIV+ ANC: 0%
  - HIV+ L&D: 24%
  - HIV+ 6m: 0%
  - HIV-ANC: 0%
  - HIV- L&D: 0%
  - HIV- 6m: 7%
Clue #3: Cellular responses change in the 3rd trimester

1. Mtb-specific CD4+ T-cell responses diminish third trimester

2. Mtb-specific T Effector memory cells diminish third trimester

3. Non-specific CD4+ T-cell activation increases third trimester

Black circle: HIV-
Gold triangle or circle: PLHIV

Saha, J Infect Dis 2022

Courtesy of Sylvia LaCourse, University of Washington
Putting it all together

| The **frequency of MTB-specific T-cell subtypes decreases** as pregnancy progresses. |
| Non-specific CD4+ T-cell activation increases in 3rd trimester; this has been associated with progression in other populations. |
| Cellular and cytokine changes correlate with the longitudinal changes in IGRA responses during pregnancy. |
| **But does this result in TB progression?** |
Unique gene sets diagnose and predict postpartum TB

- Diagnostic model: ITSN1 and LONRF1. Involved in adaptive and innate immunity.

Neither involve IFN pathways.

Mathad, Clin Infect Dis 2022
TB prevention in pregnancy
Case presentation

35 yo pregnant female with HIV from India presenting for first antenatal visit. IGRA is positive.

How would you manage this patient?
# Recommendations for TB prevention regimens

<table>
<thead>
<tr>
<th>Priority</th>
<th>Regimen</th>
<th>Recommendation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>2 months of weekly INH + RPT (3HP)</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Preferred</td>
<td>4 months daily RIF (4R)</td>
<td>Strong</td>
<td>Moderate (HIV negative)</td>
</tr>
<tr>
<td>Preferred</td>
<td>3 months daily INH + RIF (3HR)</td>
<td>Conditional</td>
<td>Very low (HIV negative)</td>
</tr>
<tr>
<td>Alternative</td>
<td>6 months daily INH (6H)</td>
<td>Strong</td>
<td>Moderate (HIV negative)</td>
</tr>
<tr>
<td>Alternative</td>
<td>9 months daily INH (9H)</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*Guidelines for the Treatment of Latent Tuberculosis Infection, MMWR 2020*
Is IPT safe in pregnancy?

HIV+ pregnant women: 14-34 weeks gestation

Arm A: Immediate IPT

Arm B: Deferred IPT

Systematic Review

Which one do you believe?

Gupta, NEJM 2019

Hamada, Eur Respir J 2020
Is IPT safe postpartum?

**TB APPRISE:**
- Increased hepatotoxicity postpartum (7.2% vs. 6.2%, \( p=0.56 \))
- Increased ALT in both arms at 12 weeks postpartum

*Gupta, NEJM 2019*
What about 3HP?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Preganancies Exposed to Study Drugs</th>
<th>All Reported Pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3HP (n = 31)</td>
<td>9H (n = 56)</td>
</tr>
<tr>
<td>Live birth, n (%)</td>
<td>20 (65)</td>
<td>41 (73)</td>
</tr>
<tr>
<td>Elective abortion, n (%)</td>
<td>7 (23)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Fetal loss (all are spontaneous abortion &lt;20 wk), n (%)</td>
<td>4 (13)*</td>
<td>8 (14)*</td>
</tr>
<tr>
<td>Fetal loss, n (%) 95% CI of individual proportion</td>
<td>4/31 (13) (4–30)</td>
<td>8/56 (14) (6–26)</td>
</tr>
</tbody>
</table>

Infant outcomes

| Congenital anomalies, n (%) | 0†                               | 2 (5)‡                         | 2 (3)‡                         | 1 (3)††               | 2 (4)††               | 3 (3)††               |
| Congenital anomalies, n (%) | 0/20 (0) (0–17)                   | 2/41 (5) (1–17)                | 2/61 (3) (0–11)                | 1/37 (3) (0–14)       | 2/56 (4) (0–12)       | 3/93 (3) (1–9)       |

Moro, Annals ATS 2018
<table>
<thead>
<tr>
<th></th>
<th>Mothers</th>
<th>Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2nd trim.</strong></td>
<td><strong>Cohort 1: Screening Visit</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enrollment visit (Intensive PK, n=25)</td>
<td></td>
</tr>
<tr>
<td><strong>3rd trim.</strong></td>
<td>Weekly Visits with DOT for 10 weeks</td>
<td><strong>Cohort 2: Screening Visit</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enrollment visit (Intensive PK n=25)</td>
</tr>
<tr>
<td>Postpartum</td>
<td>Week 11 visit (Sparse PK with last dose)</td>
<td>Weekly Visits with DOT for 10 weeks</td>
</tr>
<tr>
<td></td>
<td>Monthly visits until 24 weeks postpartum</td>
<td>Week 11 visit (Sparse PK with last dose)</td>
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<td></td>
<td></td>
<td>Monthly visits until 24 weeks postpartum</td>
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</tbody>
</table>

**IMPAACT 2001: Safety and PK of 3HP in pregnancy**

Mathad Clin Infect Dis 2021
Clearance in pregnant people with HIV was 30% HIGHER than without HIV.

Postpartum clearance was 28% HIGHER in participants without, but not with HIV.

NO dose change required for RPT in pregnant or postpartum women.
DOLPHIN Moms

Safety and tolerability of 1HP and 3HP with pharmacokinetics of dolutegravir in pregnant people with HIV

Regimens
Arm 1: 1HP + DTG (BID)
Arm 2: 3HP + DTG (BID)

Primary Outcomes
Arm 1 vs Arm 2

1st trimester 2nd trimester 3rd trimester Postpartum

Delivery 12 & 24 wk PP

Pregnancy outcomes assessed Maternal and infant outcomes assessed

PK

Randomize

1HP

3HP

PK

PK

Composite maternal safety, pregnancy, and infant outcomes
Conclusions

4R remains the safest option for TB prevention in pregnancy except for:
- People with HIV or on other medications that interact with rifampin
- People with liver abnormalities or bleeding risks

Best options for TB prevention in pregnant people with HIV remain unknown.
- INH may increase risk of adverse pregnancy outcomes
- 3HP has promising but inadequate safety data
What are the gaps?

- Epidemiology
- PK and safety
  - LTBI
  - DRTB
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