Recognizing
(and hopefully responding to)
TB during Pregnancy

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Heartland National TB

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.

She did not die of Covid-19!

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

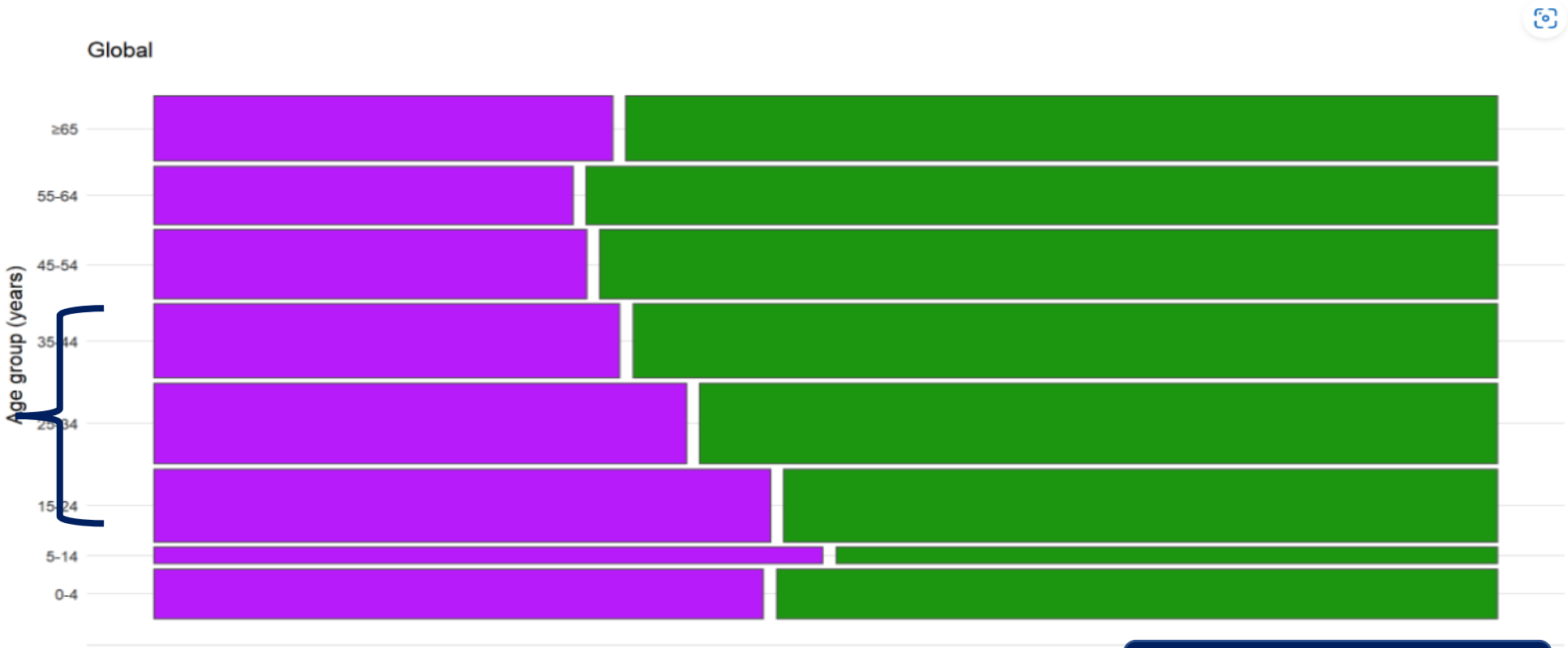
	Mean (95% uncertainty range)	Rate per 1000 pregnant women (95% uncertainty range)	Percentage of global burden
All countries combined	216 500 (192 100–247 000)	2·1 (1·8–2·4)	--
African Region	89 400 (74 200–110 500)	3·6 (3·0–4·5)	41%
Region of the Americas	4800 (3900–6000)	0·4 (0·3–0·5)	2%
Eastern Mediterranean Region	28 500 (19 700–41 900)	2·3 (1·6–3·4)	13%
European Region	4900 (3800–6300)	0·6 (0·5–0·8)	2%
South-East Asia Region	67 500 (52 000–87 100)	2·4 (1·9–3·1)	31%
Western Pacific Region	21 400 (19 400–23 700)	1·1 (1·0–1·2)	10%

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

TB Mortality in HIV negative

Fig. 2.2.2 Global distribution of estimated TB mortality in HIV-negative people by age group and sex (female in purple; male in green), 2021



Global TB Report 2022

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*).

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?

Is risk of progression to TB disease increased in pregnancy?

Testing for LTBI during Pregnancy; TST vs IGRA

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

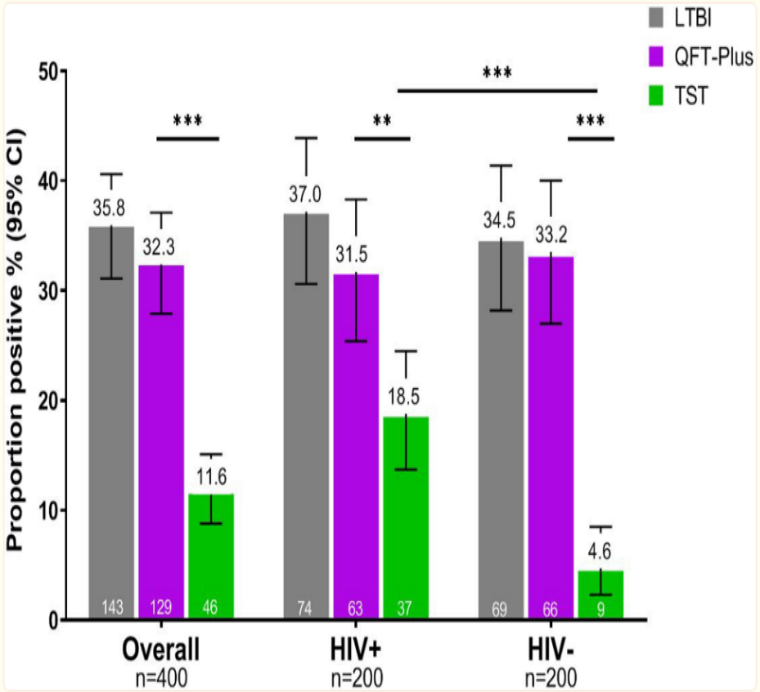


Figure 2.

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 ≥10mm induration if HIV negative

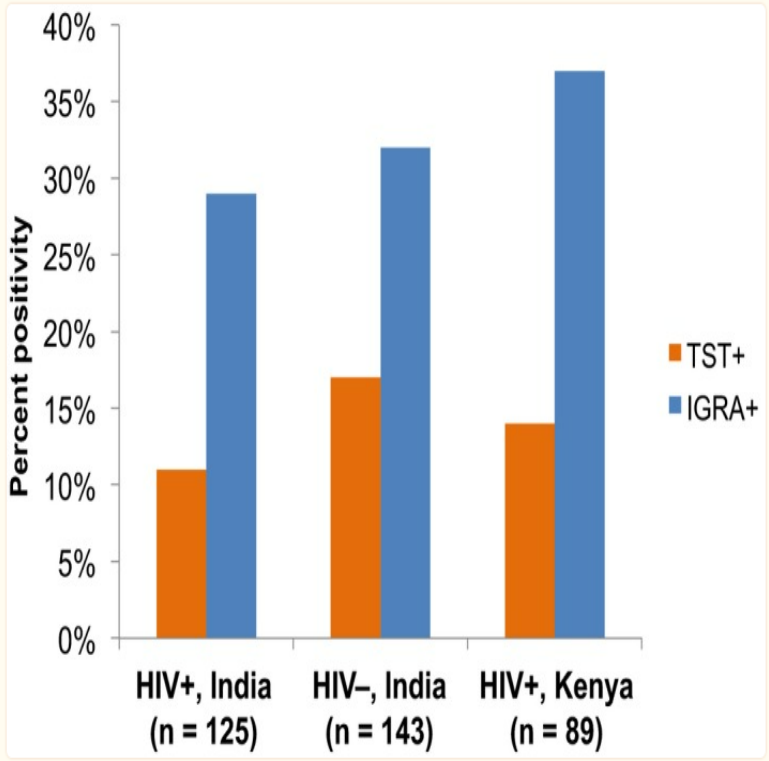
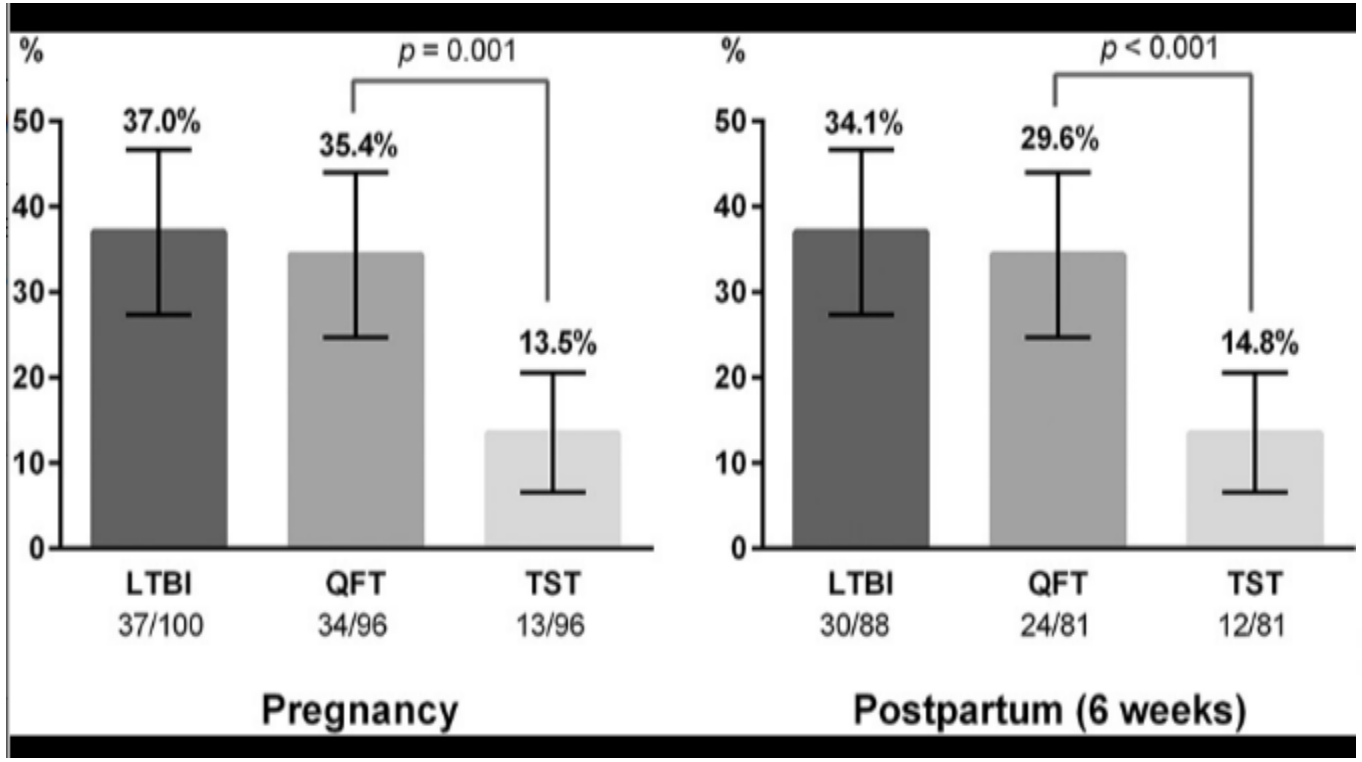


Figure 1

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

Marhad, *J Int AIDS Soc* March 2020

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



Marhad, *J Int AIDS Soc* March 2020

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG COMMITTEE OPINION

Number 723 • October 2017

(Replaces Committee Opinion Number 656, February 2016)

Committee on Obstetric Practice

This document is endorsed by the American College of Radiology and the American Institute of Ultrasound in Medicine. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Member contributors included Joshua Copel, MD; Yasser El-Sayed, MD; R. Phillips Heine, MD; and Kurt R. Wharton, MD. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

INTERIM UPDATE: This Committee Opinion is updated as highlighted to reflect a limited, focused change in the language and supporting evidence regarding exposure to magnetic resonance imaging and gadolinium during pregnancy.

Table 3. Fetal Radiation Doses Associated With Common Radiologic Examinations ⇦

Type of Examination	Fetal Dose* (mGy)
Very low-dose examinations (<0.1 mGy)	
Cervical spine radiography (anteroposterior and lateral views)	<0.001
Head or neck CT	0.001–0.01
Radiography of any extremity	<0.001
Mammography (two views)	0.001–0.01
Chest radiography (two views)	0.0005–0.01
Low- to moderate-dose examinations (0.1–10 mGy)	
CT	
Chest CT or CT pulmonary angiography	0.01–0.66

"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. "

Risk of Tuberculosis in Pregnancy

A National, Primary Care–based Cohort and Self-controlled Case Series Study

Dominik Zenner[1], Michelle E. Kruijshaar[1], Nick Andrews[1], and Ibrahim Abubakar[1,2]

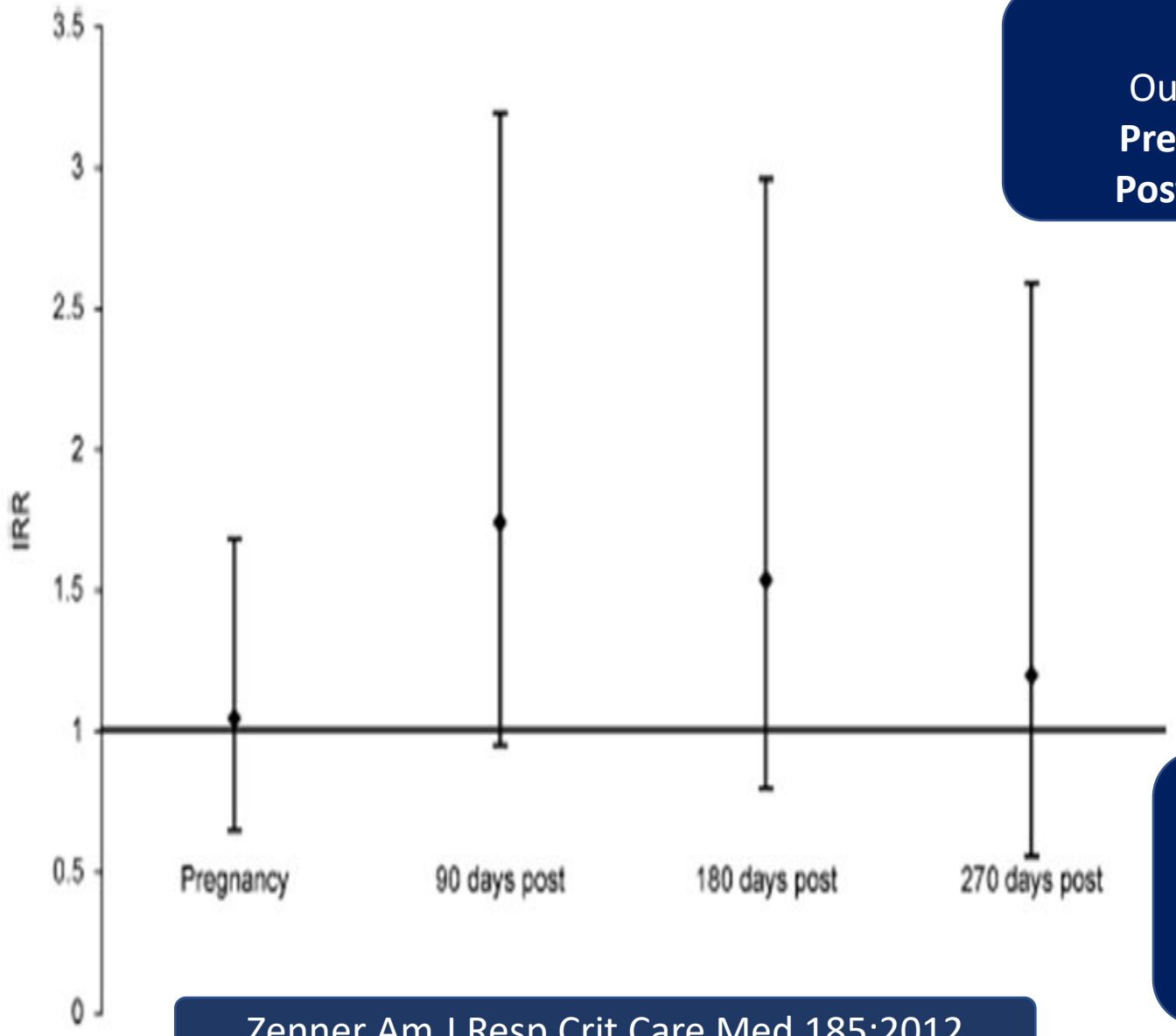
[1]Health Protection Agency, Health Protection Services Colindale, London; and [2]Biomedical and Clinical Sciences Research Institute, Norwich Medical School, University of East Anglia, Norwich, United Kingdom

Am J Respir Crit Care Med 2012

- *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
  - 44/177 TB events occurred during pregnancy/postpartum
    - 8 (1st), 7 (2nd), 7 (3rd) and 22 (PP)

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**

Figure 2. Adjusted incidence rate ratios for various time periods. Shown are the adjusted incidence rate ratios for various pregnancy and postpartum periods from the self-controlled case series model (adjusted for age and period). *Bars* denote 95% confidence intervals. Reference is the time outside of pregnancy (IRR 1), denoted by the *x* axis line. IRR = incidence rate ratio.

IRR significantly higher in postpartum period
risk not significantly higher during pregnancy
Pregnancy 1.29
Postpartum 1.95

Zenner Am J Resp Crit Care Med 185:2012

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.

Accessed 2/9/2023; Deciding When to Treat Latent TB Infection | TB | CDC

Last reviewed 4/8/2016

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

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

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 and inclusion in Phase III TB trials**

INH preventive therapy in HIV-infected pregnant and postpartum women "APRISE Trial"

Gupta et al, NEJM 2109

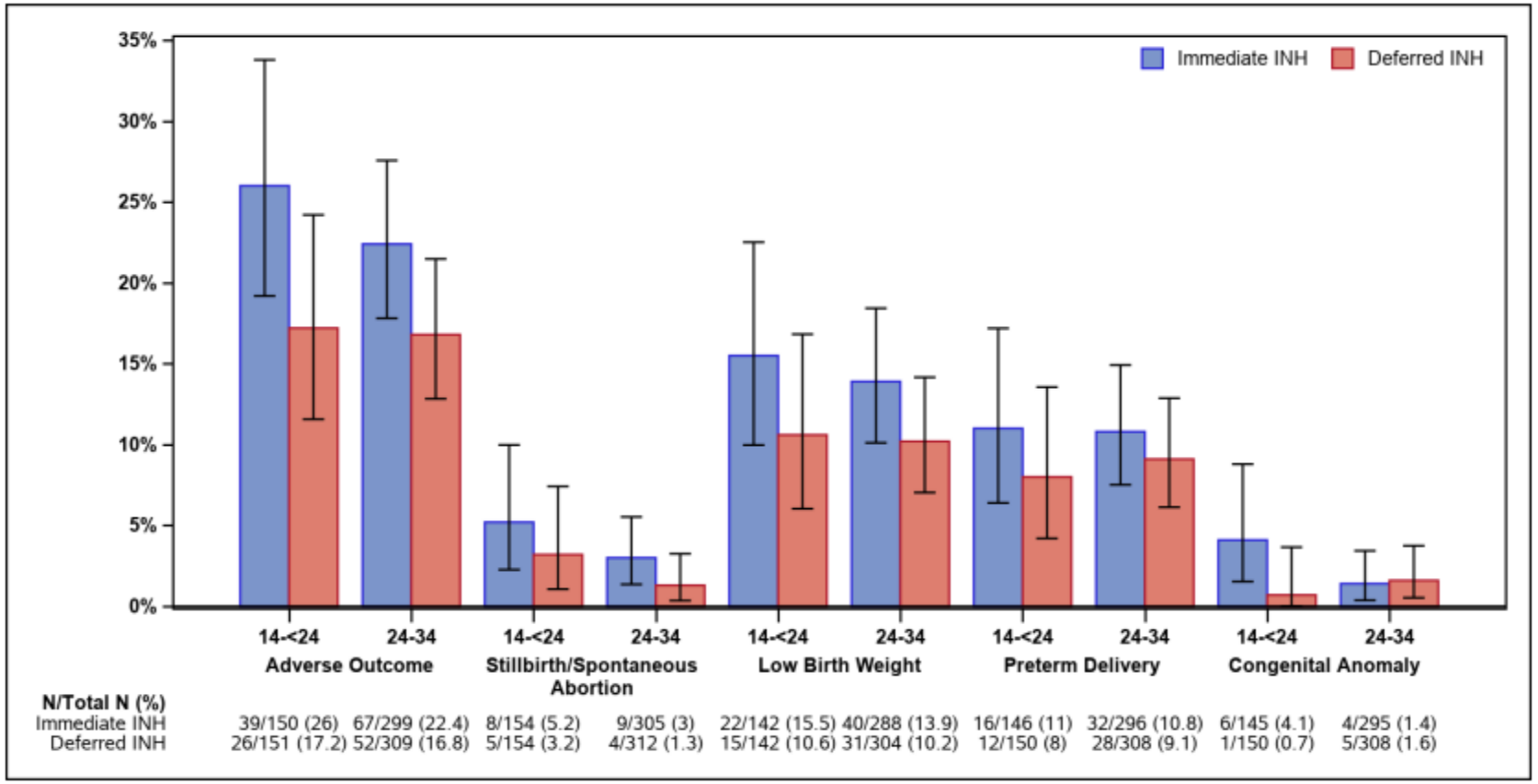
- Double blind placebo controlled, randomized, pregnant HIV infected
- INH preventive treatment x 28 weeks; F/U x 48 wks.
  - **Immediate group** – initiate during pregnancy – (≥ 14 ≤ 24 wks. // ≥ 24 ≤ 34 wks.)
  - **Deferred group** – initiate at week 12 postpartum
  - 956 women enrolled, mean CD4 493, 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



N/Total N (%)	Adverse Outcome 14-<24	Adverse Outcome 24-34	Stillbirth/Spontaneous Abortion 14-<24	Stillbirth/Spontaneous Abortion 24-34	Low Birth Weight 14-<24	Low Birth Weight 24-34	Preterm Delivery 14-<24	Preterm Delivery 24-34	Congenital Anomaly 14-<24	Congenital Anomaly 24-34
Immediate INH	39/150 (26)	67/299 (22.4)	8/154 (5.2)	9/305 (3)	22/142 (15.5)	40/288 (13.9)	16/146 (11)	32/296 (10.8)	6/145 (4.1)	4/295 (1.4)
Deferred INH	26/151 (17.2)	52/309 (16.8)	5/154 (3.2)	4/312 (1.3)	15/142 (10.6)	31/304 (10.2)	12/150 (8)	28/308 (9.1)	1/150 (0.7)	5/308 (1.6)

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)[1].

Supplementary Appendix

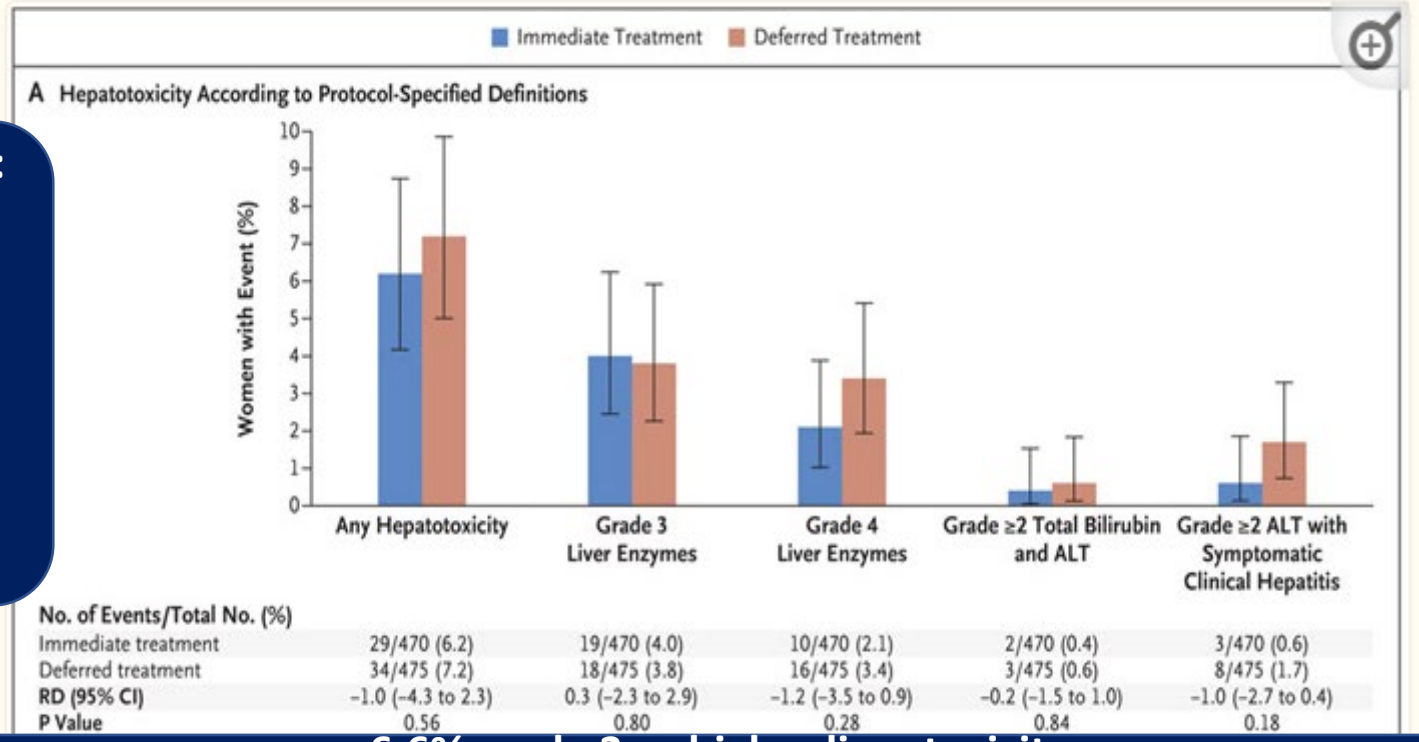
INH preventive therapy in HIV-infected pregnant and postpartum women

Gupta et al, NEJM 2109

Liver Toxicity:

Not all associated with INH

All on efavirenz



No. of Events/Total No. (%)					
Immediate treatment	29/470 (6.2)	19/470 (4.0)	10/470 (2.1)	2/470 (0.4)	3/470 (0.6)
Deferred treatment	34/475 (7.2)	18/475 (3.8)	16/475 (3.4)	3/475 (0.6)	8/475 (1.7)
RD (95% CI)	−1.0 (−4.3 to 2.3)	0.3 (−2.3 to 2.9)	−1.2 (−3.5 to 0.9)	−0.2 (−1.5 to 1.0)	−1.0 (−2.7 to 0.4)
P Value	0.56	0.80	0.28	0.84	0.18

6.6% grade 3 or higher liver toxicity

4 symptomatic, all during postpartum period

2 deaths likely due to INH induced liver failure, I 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)

Exposure to LTBI Treatment during Pregnancy The PREVENT TB and the iAdhere Trials

Moro et al, Annals ATS May 2018

- 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 %

Clinical Infectious Diseases

MAJOR ARTICLE

Pharmacokinetics and Safety of 3 Months of Weekly Rifapentine and Isoniazid for Tuberculosis Prevention in Pregnant Women

Mathad et al, *CID* July 2021

- 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.

Table 3. Recommendations for Regimens to Treat Latent Tuberculosis Infection

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

* 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)

Source: Adapted from Sterling TR, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep.* 2020 Feb 14;69(1):1-11.

BJOG An International Journal of Obstetrics and Gynaecology
Royal College of Obstetricians & Gynaecologists
Systematic Review

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

- Treatment in 1st trimester vs 2nd/3rd
  - **No preterm births** (0/9) treated in 1st trimester
    - 33% (4/12) in 2nd and 3rd trimesters
  - **No cases of perinatal death** (0/9) treated in 1st trimester
    - Perinatal death 23% (3/13) treated in 2nd and 3rd trimester
  - **No low birth weight** infants (0/23) when treated in 1st trimester
    - 61% (33/54) low birth weight when treated in 2nd and 3rd trimester
  - Fewer complications in mothers
    - 29% treated in 1st trimester vs 60% treated in 2nd and 3rd trimester

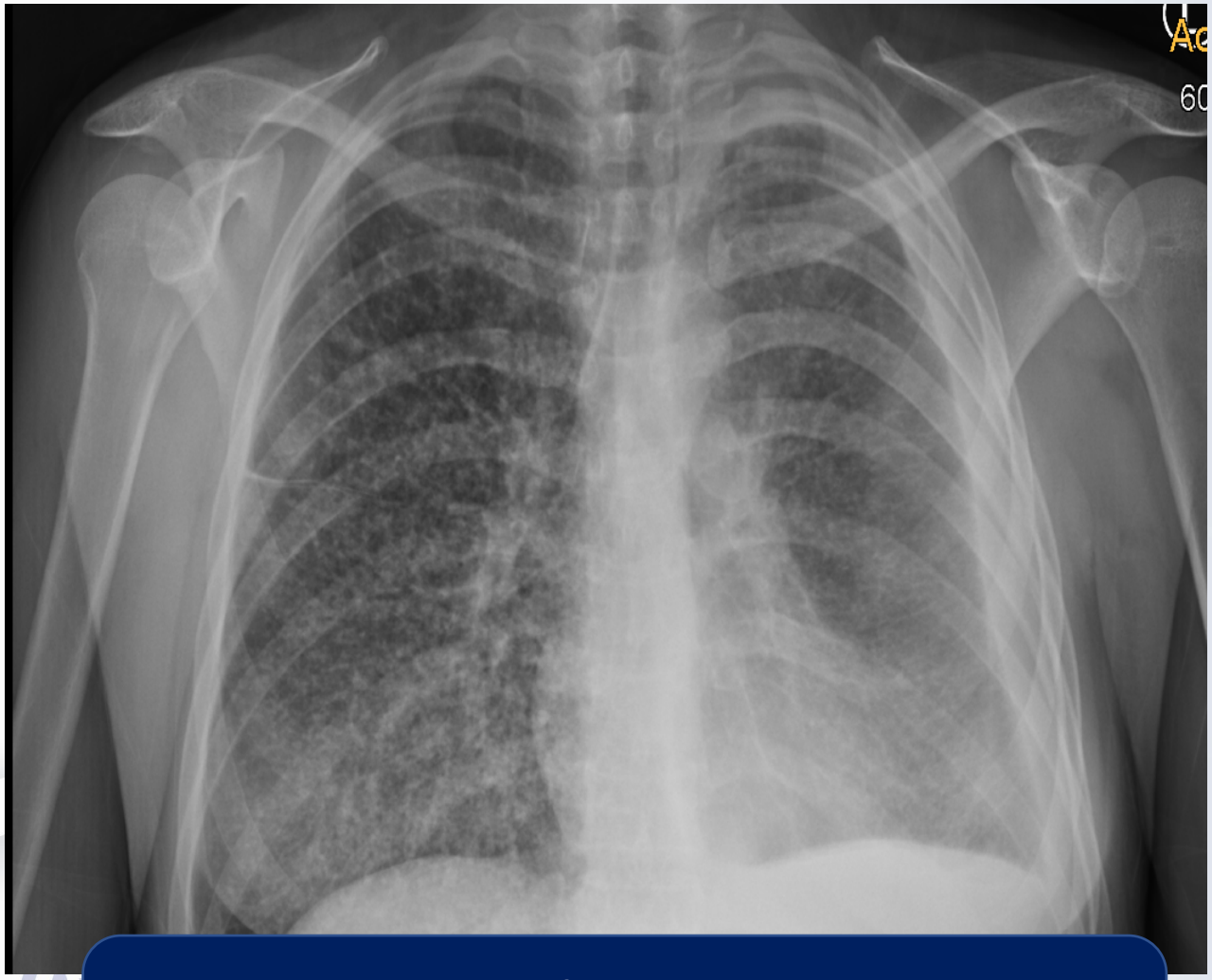
Outcomes better when treatment is early AND disease is limited.

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

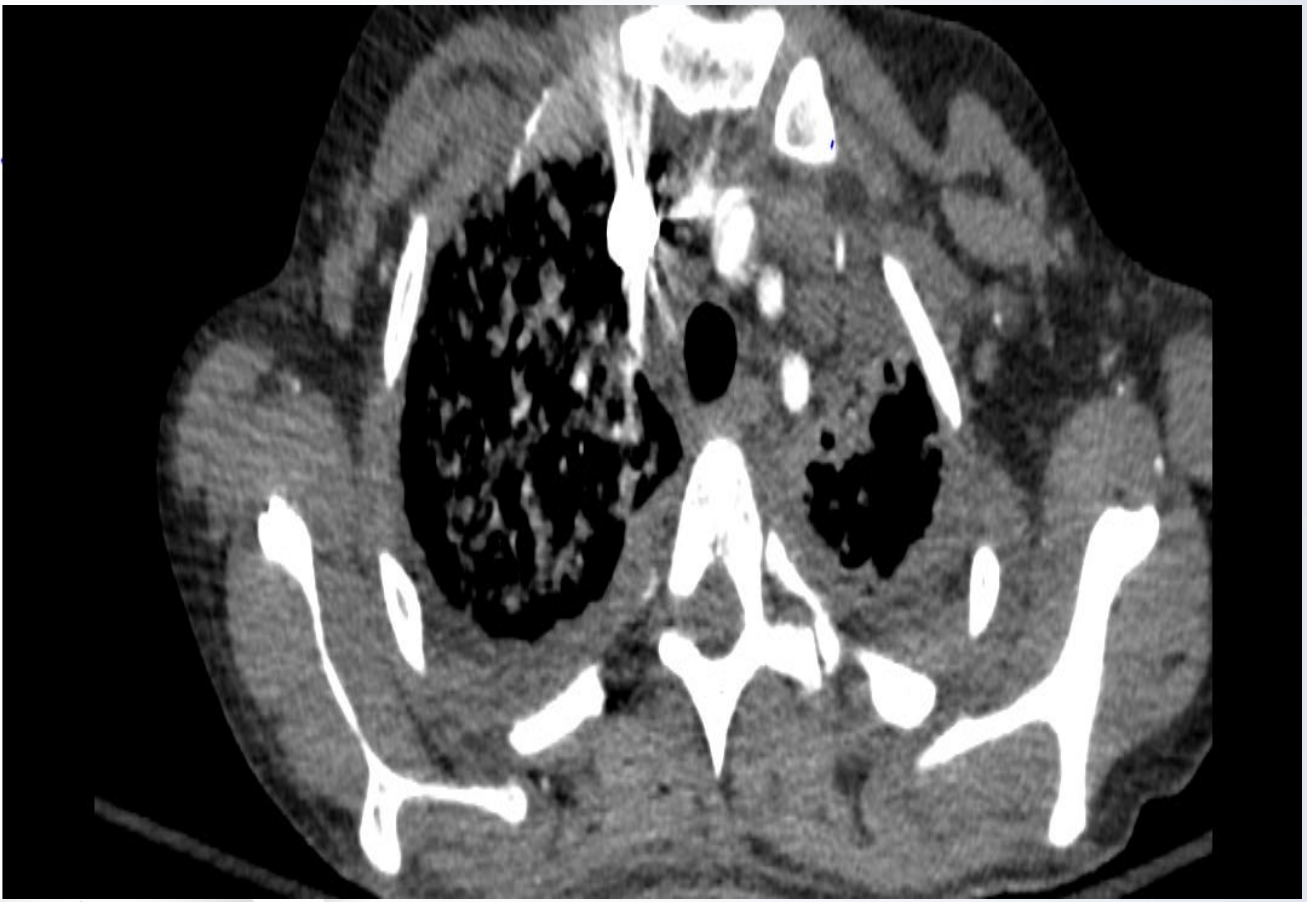
Postpartum



7 ½ weeks post partum
CXR interpreted bilateral nodular infiltrates

- **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
  - 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?**

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

Table 2. Manifestations and proposed pathogenic basis of pathogens or clinical conditions exacerbated during the postpartum period.

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

CID 2007:45 Singh and Perfect

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"

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.

Cheng et al *Eur J Clin Microbiol Infect Dis* 2003, (Review of Literature 1966-2002)

Open Forum Infectious Diseases
MAJOR ARTICLE

Pregnancy-Related Tuberculous Meningitis and Immune Reconstitution Inflammatory Syndrome: A Case Series and Systematic Review

Katelyn A. Pastick,[1,2] Enock Kagimu,[3] Joanna Dobbin,[4] Kenneth Ssebambulidde,[3] Jane Gakuru,[3] Jack Milln,[5,6] Betty Nakabuye,[7,8] David B. Meya,[3] David R. Boulware,[2] Fiona V. Cresswell,[6,9] and Nathan C. Bahr[10]

October 2022

- **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**

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's risk with pregnancy was never captured by surveillance

NEVER COUNTED!