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

ARTICLES | VOLUME 2, ISSUE 12, E710-E716, DECEMBER 2014

Tuberculosis in pregnancy: an estimate of the global burden of disease

Jordan Sugarman, BSc • Charlotte Colvin, PhD • Allisyn C Moran, PhD • Dr Olivia Oxlade, PhD

THE LANCET Global Health

Open Access • Published: December, 2014 • DOI: https://doi.org/10.1016/S2214-109X(14)70330-4 •

2014

- 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
  - 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

	Maternity care access indicator	
	Antenatal care services (at least one antenatal care visit)	Labour and delivery services (births attended by skilled health personnel)
Smear microscopy		
Smear positive	85 000	62 600
Smear negative	0	0
Total	85 000	62 600
Chest radiography		
Smear positive	80 000	58 900
Smear negative	34 200	25 600
Total	114 100	84 500
Xpert MTB/RIF		
Smear positive	83 300	61 400
Smear negative	37 000	27 600
Total	120 300	89 000

Table 5: **Number of active tuberculosis cases detected with different diagnostic tests in pregnant women—all countries combined**

120 300 active tuberculosis cases in antenatal care settings and 89 000 in labour and delivery settings. Chest radiography was estimated to detect a similar number of cases: 114 100 and 84 500 respectively.

What do we know about TB rates in Pregnancy?
(total # of cases, rate/1,000 pregnant women % of global burden)

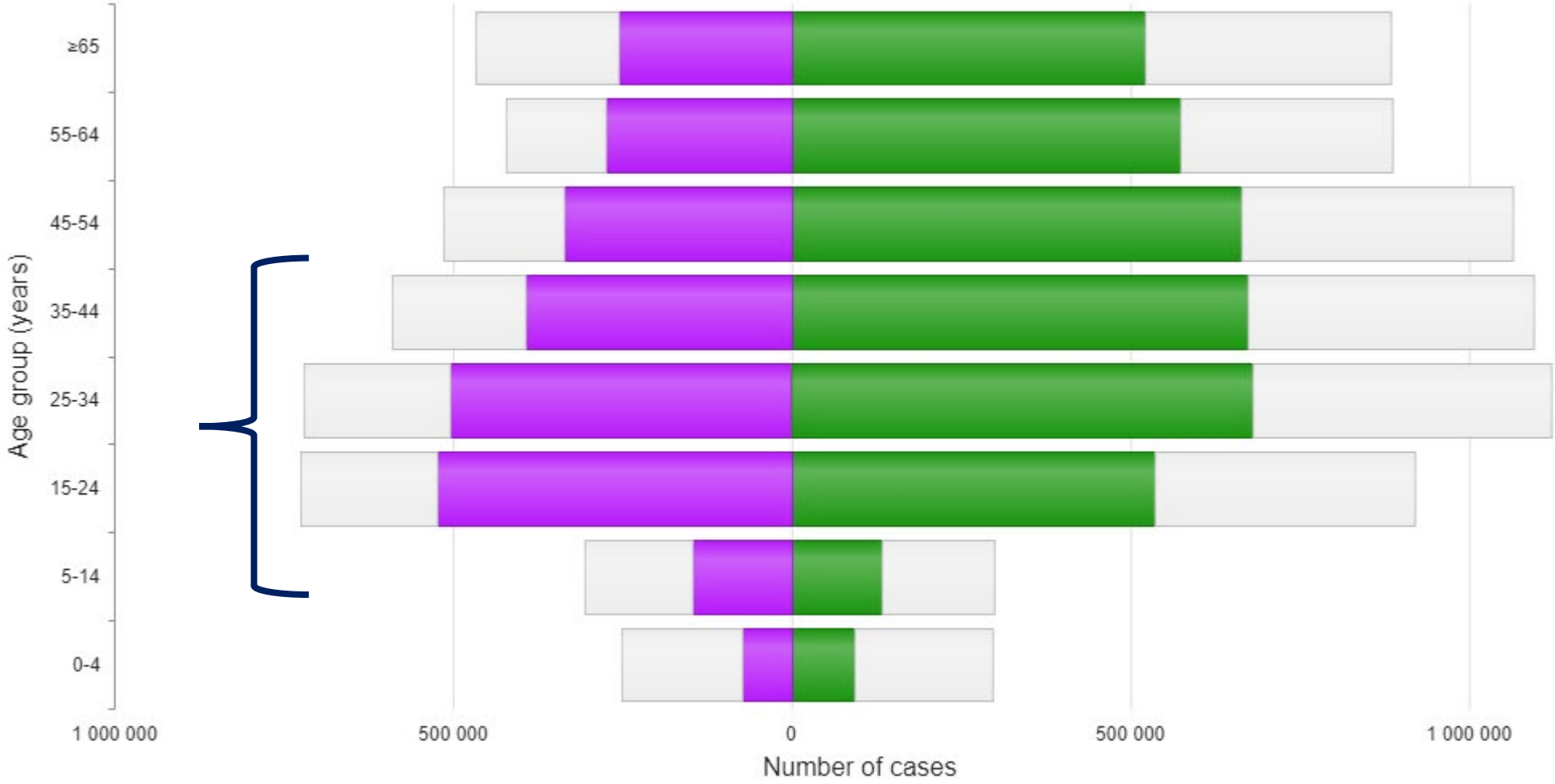
- 200,000 women/year
- Likely underestimate

	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

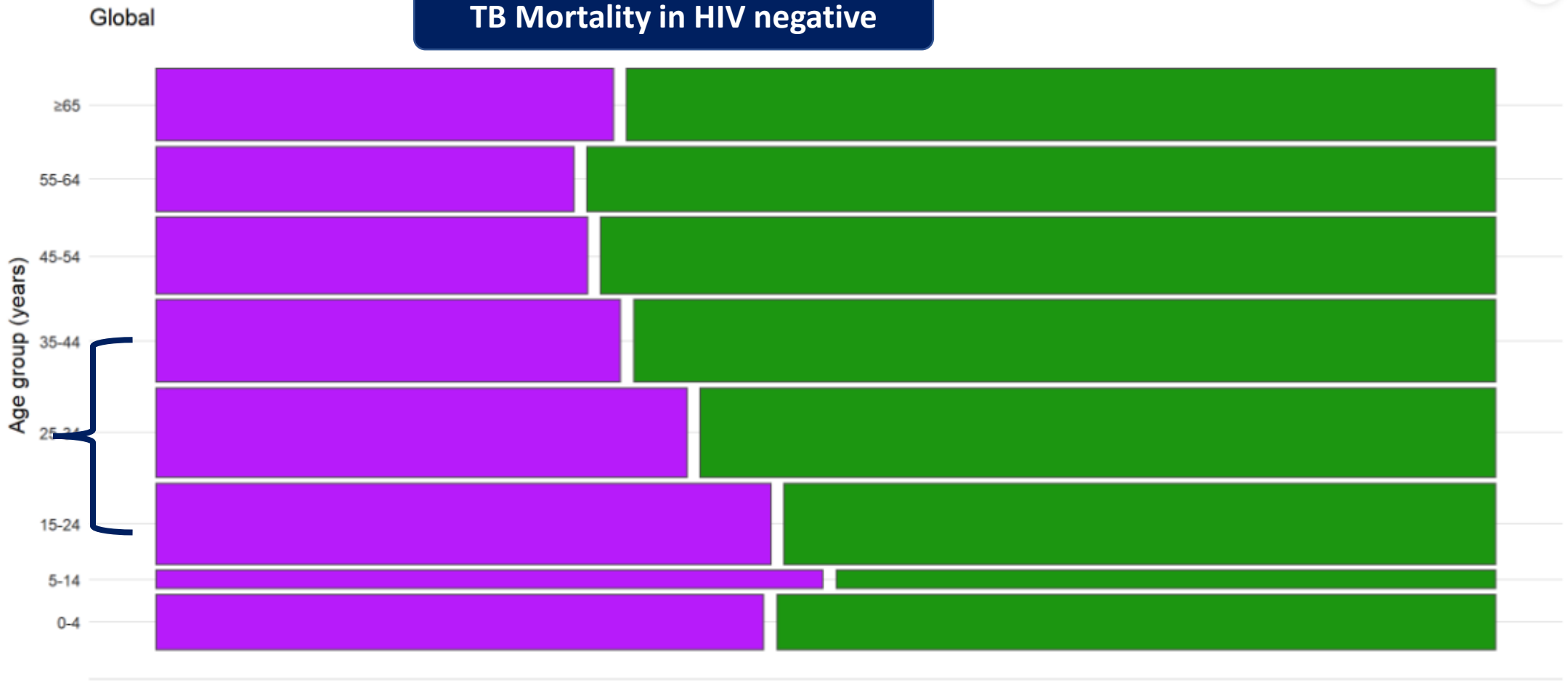
Sugarman *the Lancet* 2014

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**.

TB Mortality in HIV negative



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*).

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

> Isr Med Assoc J. 2015 Jun;17(6):346-50.

Tuberculosis during Pregnancy in Northern Israel, 2002–2012: Epidemiology and Clinical Practices

Hashem Bishara, Noam Goldstein, Marwan Hakim, Olga Vinitsky, Danit Shechter-Amram, Daniel Weiler-Ravell

- 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

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

Risk of TB in Pregnancy

Zenner, *Am J Resp Crit Care Med* 2012

Self Controlled Case Series

Individual with an **event (TB)**

177

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.

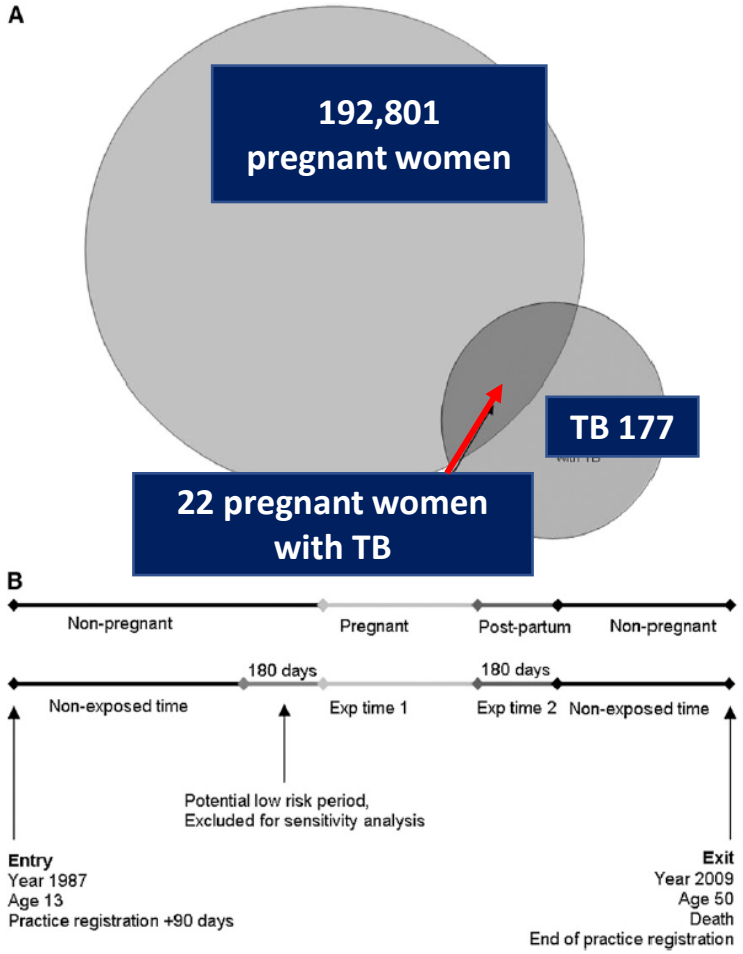
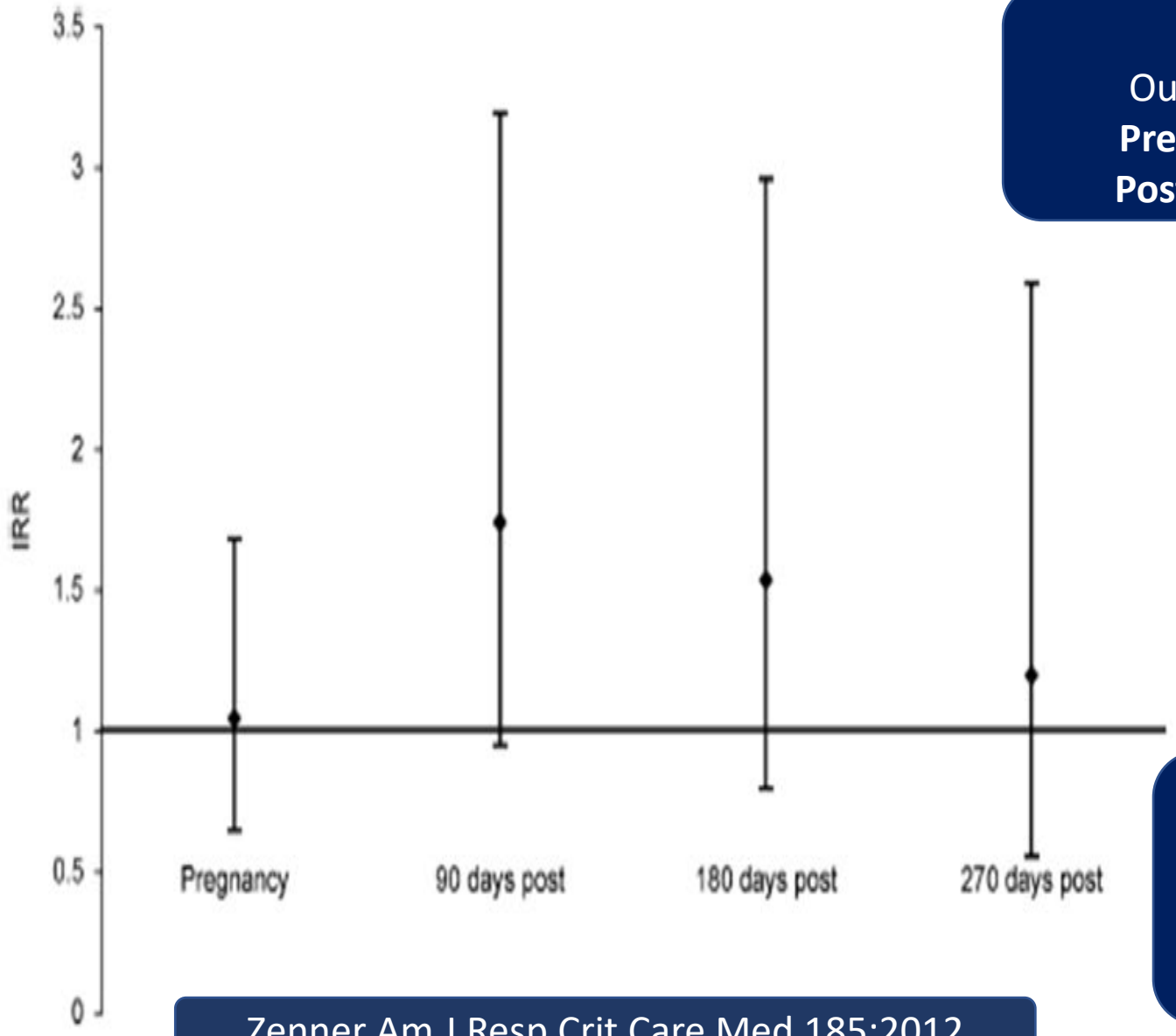


Figure 1. Schematic of (*A*) study populations and (*B*) exposure times for cohort and self-controlled case series studies. The schematic in *B* provides an overview for censoring and risk periods used in the cohort study as well as the self-controlled case series study. Exp = exposure; SCCS = self-controlled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

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

Testing for LTBI during Pregnancy; TST vs IGRA

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

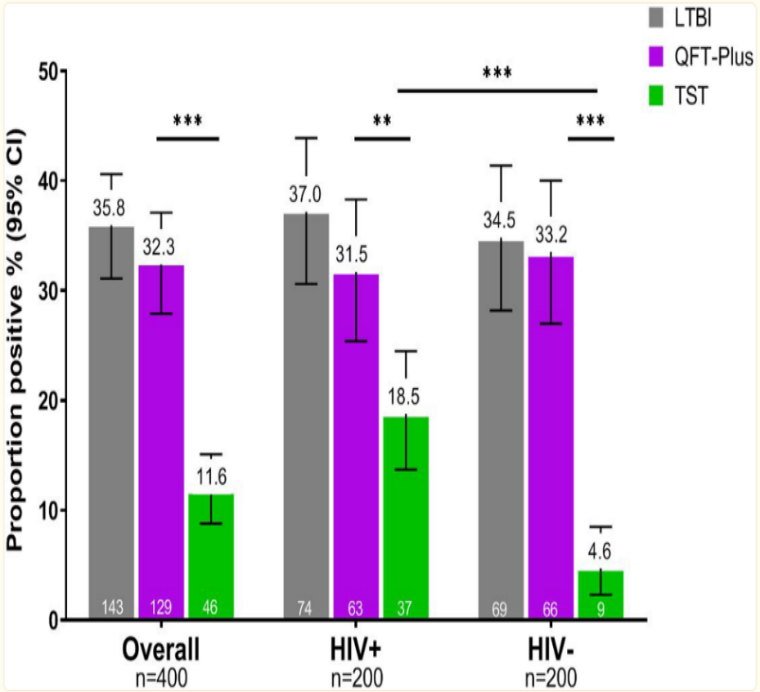


Figure 2.

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

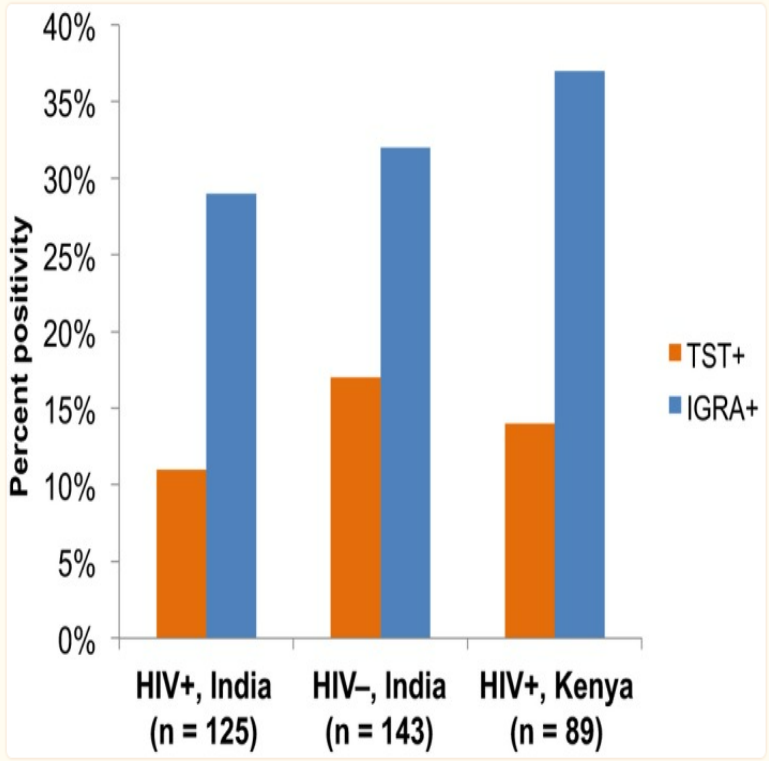
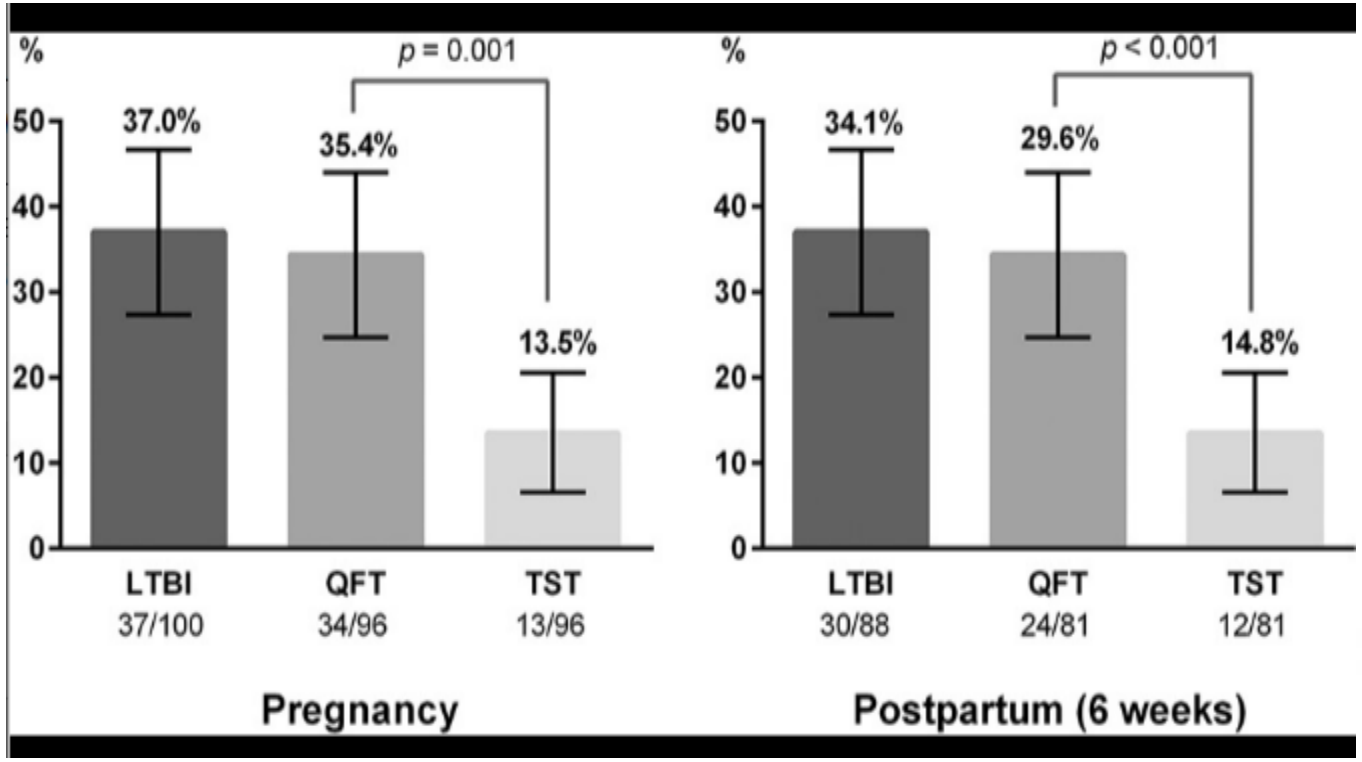


Figure 1

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. "

Diagnostic Imaging During Pregnancy and Lactation
American College of Obstetricians and Gynecologists' Committee on Obstetric Practice 2017

- 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.

Low- to moderate-dose examinations (0.1–10 mGy)	
Radiography	
Abdominal radiography	0.1–3.0
Lumbar spine radiography	1.0–10
Intravenous pyelography	5–10
Double-contrast barium enema	1.0–20
CT	
Chest CT or CT pulmonary angiography	0.01–0.66
Limited CT pelvimetry (single axial section through the femoral heads)	<1
Nuclear medicine	
Low-dose perfusion scintigraphy	0.1–0.5
Technetium-99m bone scintigraphy	4–5
Pulmonary digital subtraction angiography	0.5
Higher-dose examinations (10–50 mGy)	
Abdominal CT	1.3–35
Pelvic CT	10–50
^{18}F PET/CT whole-body scintigraphy	10–50

- 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

Radiographics 2012; 237: 897-911

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?

#RightToPreventTB

How about the pregnant diabetic?
Two significant risk factors more prevalent in immigrant/refugee populations we are not even discussing

A GUIDE FOR HEALTH CARE PROVIDERS AND PUBLIC HEALTH PROGRAMS

Testing and Treatment of Latent Tuberculosis Infection in the United States: Clinical Recommendations

2021

A SECTION OF NTCA
National Society of Tuberculosis Clinicians

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.

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

What WHO Recommends during Pregnancy

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

BUT

- **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 date 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

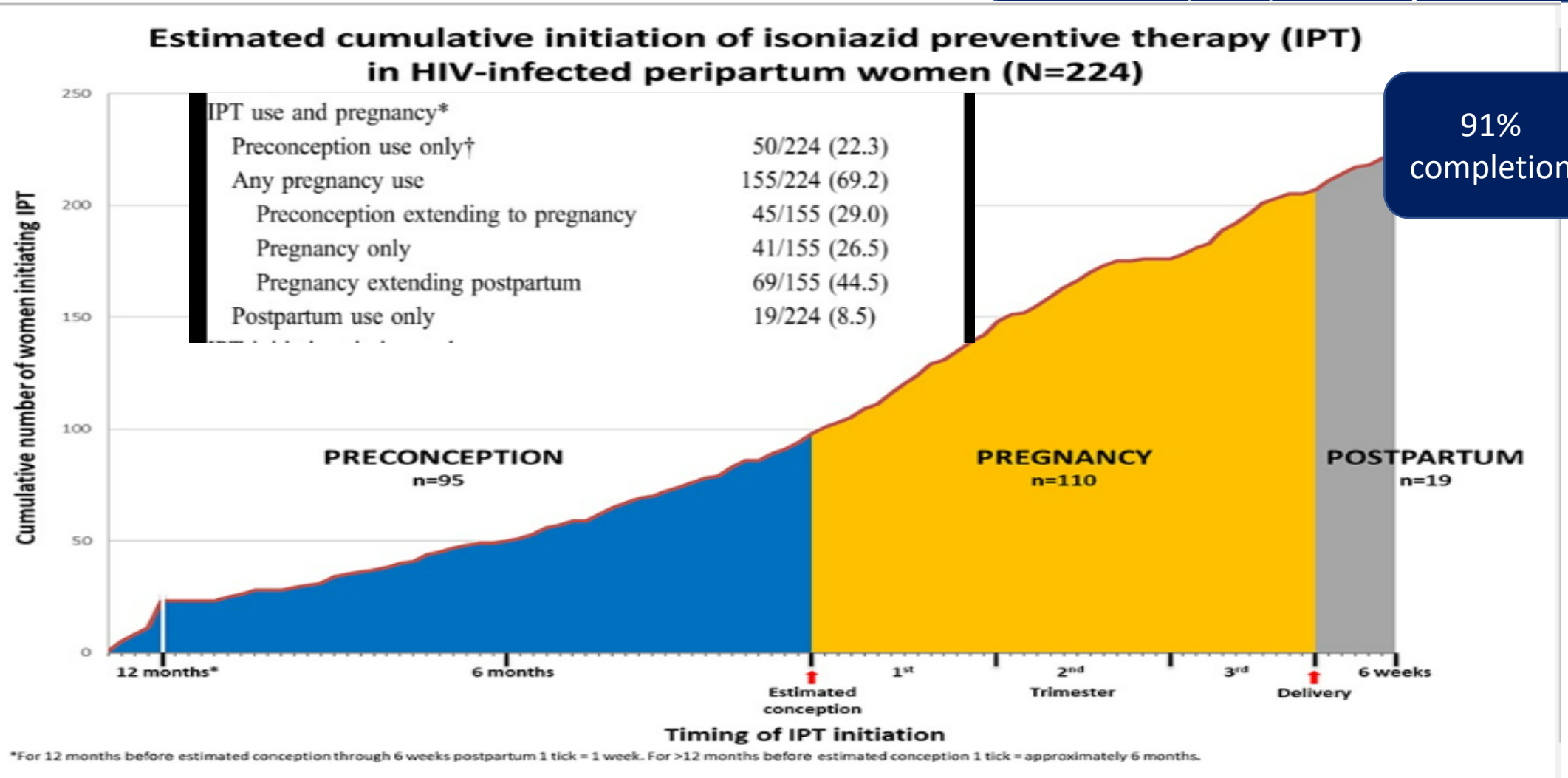
- **IMPAACT P2001: PK and safety of 3 months of weekly INH and rifapentine (3HP)**

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

- **Next step – Global Registry**

Brief Report: High Programmatic INH Preventive Therapy (IPT) Use in Pregnancy Among HIV-Infected Women.

LaCourse, et al; JAIDS Sept 2019



91% completion

Safety of INH TB preventive treatment in pregnant and postpartum women: systematic review and meta-analysis. Hamada et al, *Eur Respir J* 2020

- 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"

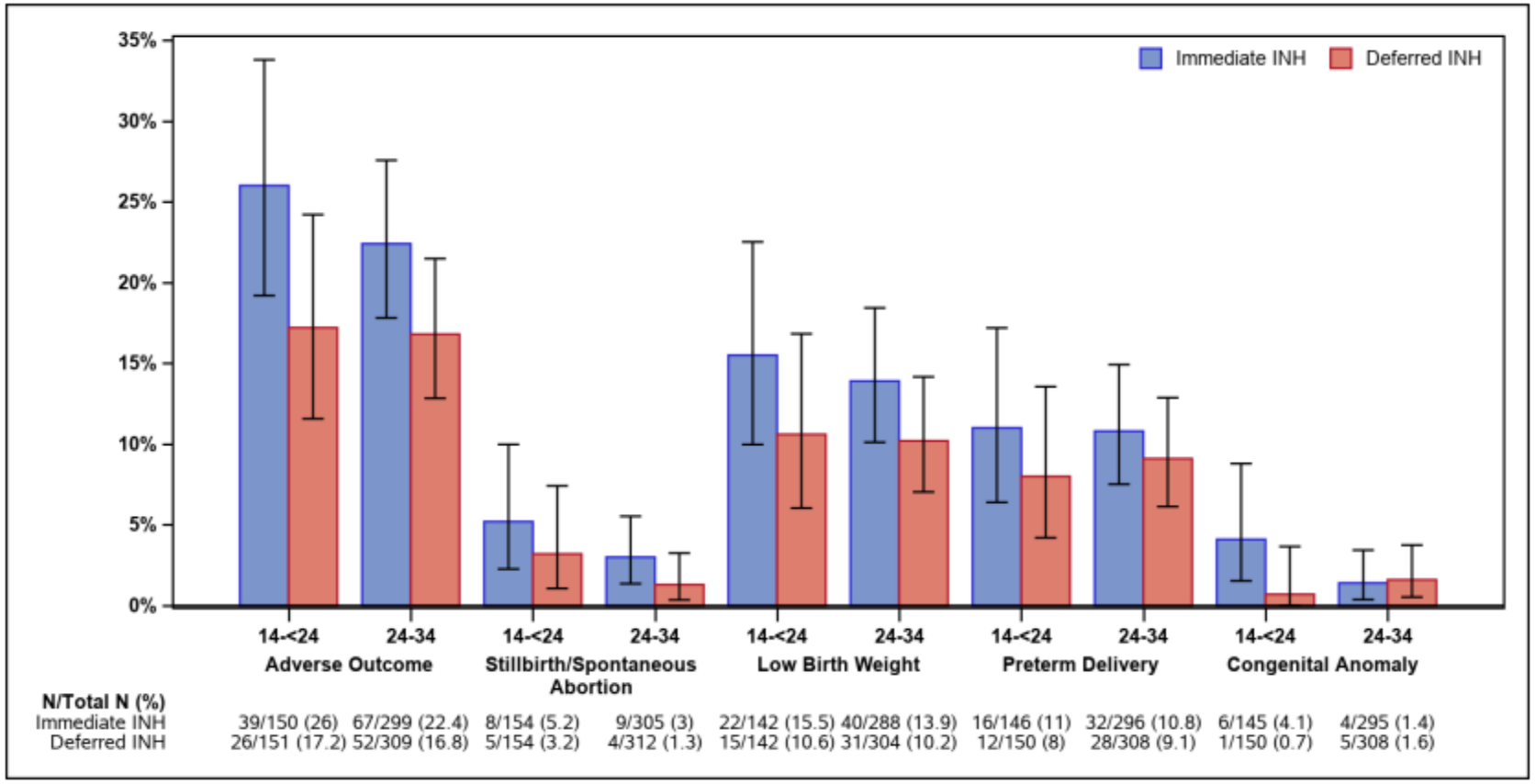
Gupta et al, NEJM 2109

- 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 (%)	14-<24 Adverse Outcome	24-34 Adverse Outcome	14-<24 Stillbirth/Spontaneous Abortion	24-34 Stillbirth/Spontaneous Abortion	14-<24 Low Birth Weight	24-34 Low Birth Weight	14-<24 Preterm Delivery	24-34 Preterm Delivery	14-<24 Congenital Anomaly	24-34 Congenital Anomaly
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

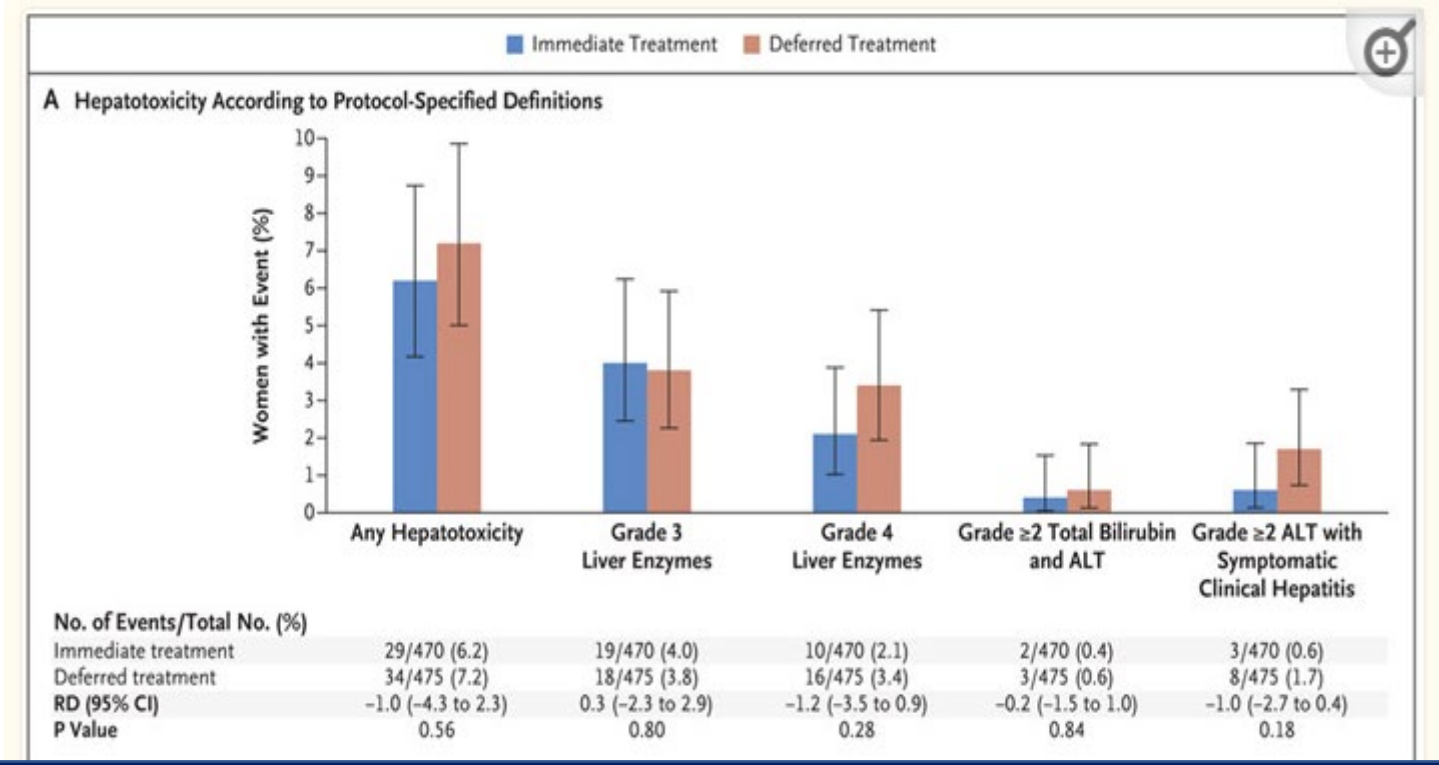
INH preventive therapy in HIV-infected pregnant and postpartum women

Gupta et al, NEJM 2109

Liver Toxicity:

Not all associated with INH

All on efavirenz



No. of Events/Total No. (%)	Any Hepatotoxicity	Grade 3 Liver Enzymes	Grade 4 Liver Enzymes	Grade ≥2 Total Bilirubin and ALT	Grade ≥2 ALT with Symptomatic Clinical Hepatitis
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)

ADVERSE PREGNANCY OUTCOMES AMONG HIV-INFECTED WOMEN EXPOSED TO ISONIAZID IN BRIEF-TB

BRIEF-TB Trial 2020

Table. Adverse pregnancy outcomes among HIV-infected pregnant women exposed versus not exposed to isoniazid (INH) preventive therapy in the BRIEF-TB ACTG 5279 trial

	INH-exposed during pregnancy N=39	INH-unexposed during pregnancy N=89	Unadjusted OR (95% CI)	OR adjusted for covariates at study entry[1] (95% CI)	OR adjusted for covariates proximal to pregnancy outcome[2] (95% CI)
Live Birth					
Yes	23 (59%)	70 (79%)			
No	16 (41%)	19 (21%)	2.56 (1.13, 5.79)	2.97 (1.26, 7.02)	1.87 (0.75, 4.69)
Spontaneous abortion <20 wks	12 (31%)	13 (15%)			
Elective abortion	3 (8%)	3 (3%)			
Ectopic pregnancy	0 (0%)	2 (2%)			
Still birth >=20 wks	1 (3%)	1 (1%)			
Composite Adverse Pregnancy Event					
Yes	13 (33%)	16 (18%)	2.28 (0.97, 5.38)	2.63 (1.06, 6.53)	1.73 (0.67, 4.50)
No	26 (67%)	73 (82%)			
Low Birthweight <2.5kg in live births					
Yes	3 (14%)	7 (13%)	1.02 (0.24, 4.35)	Not obtained[3]	Not obtained[3]
No	19 (86%)	45 (87%)			
Missing	1	18			
Preterm Birth <37 weeks in live births					
Yes	4 (20%)	11 (23%)	0.84 (0.23, 3.04)	Not obtained[3]	Not obtained[3]
No	16 (80%)	37 (77%)			
Missing	3	22			

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

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

3HP, 3HR (twice weekly), 6 H, INH continuously (during study 9/2002 – 6/2005)

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

Pregnancy in Women with HIV in a TB Preventive Therapy Trial

Singh et al J AIDS Dec 2022

- Pregnancy outcomes in 34 who became pregnant while taking TPT
  - 50% mom/baby healthy
  - **3 (9%) spontaneous abortion (1- 3HR, 2-INHc)**
  - **2 (6%) neonatal deaths (1-3HR, 1-INH)**

6 (18%) elective abortion

1 (3%) premature birth

TABLE 4. - Delivery Outcomes for Pregnancies Occurring During Study Treatment by Arm

Count of Delivery	Delivery Results						
Arm	Healthy	Spontaneous Abortion	Elective Abortion	Premature Birth	Infant Death	Unknown	Grand Total
3HP	1 (2.9%)		2 (5.9%)			1 (2.9%)	4 (11.8%)
3HR	2 (5.9%)	1 (2.9%)			1 (2.9%)		4 (11.8%)
6H	1 (2.9%)		1 (2.9%)	1 (2.9%)			3 (8.8%)
H-cont	13 (38.2%)	2 (5.9%)	3 (8.8%)		1 (2.9%)	4 (11.8%)	23 (67.6%)
Grand total	17 (50.0%)	3 (8.8%)	6 (17.6%)	1 (2.9%)	2 (5.9%)	5 (14.7%)	34 (100%)

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 %

Nguyen et al. BMC Infectious Diseases 2014, 14:617
http://www.biomedcentral.com/1471-2334/14/617

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Tuberculosis care for pregnant women: a systematic review

Hang Thanh Nguyen[1*], Chiara Pandolfini[1], Peter Chiodini[2] and Maurizio Bonati[1]

2014

•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

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.

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

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.

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*

	Baseline Symptoms		
	Group 1 N = 15 (%) Pulmonary TB group	Group 2 (Low risk Pregnant patients) N = 191 (%)	P value and significance
Symptoms:			
Cough	15 (100%)	4 (2.09%)	p = 0.001 HS
Chest pain	12 (80%)	2 (1.04%)	p = 0.01 SIG
Expectoration	15 (100%)	3 (1.57%)	p = 0.001 HS
Hemoptysis	5 (33.3%)	0	p = 0.02 SIG
Fever	14 (93.3%)	6 (3.14%)	p = 0.03 SIG
Anorexia	13 (86.6%)	3 (1.57%)	p = 0.01 SIG
Loss of weight	12 (80%)	4 (2.09%)	p = 0.02 SIG

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

Symptom	ALL n (%)	NO TB n (%)	TB 10 (%)
Cough-YES	143 (7.22%)	139 (7.06)	4 (40)
Fever -Yes	2 (0.2)	2 (0.2)	1 (10)
Weight Loss	54 (2.73)	52 (2.64)	2 (20)
Night sweats	30 (1.52)	28 (1.42)	2 (20)
Loss of appetite	67 (3.38)	63 (3.2)	4 (40)

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

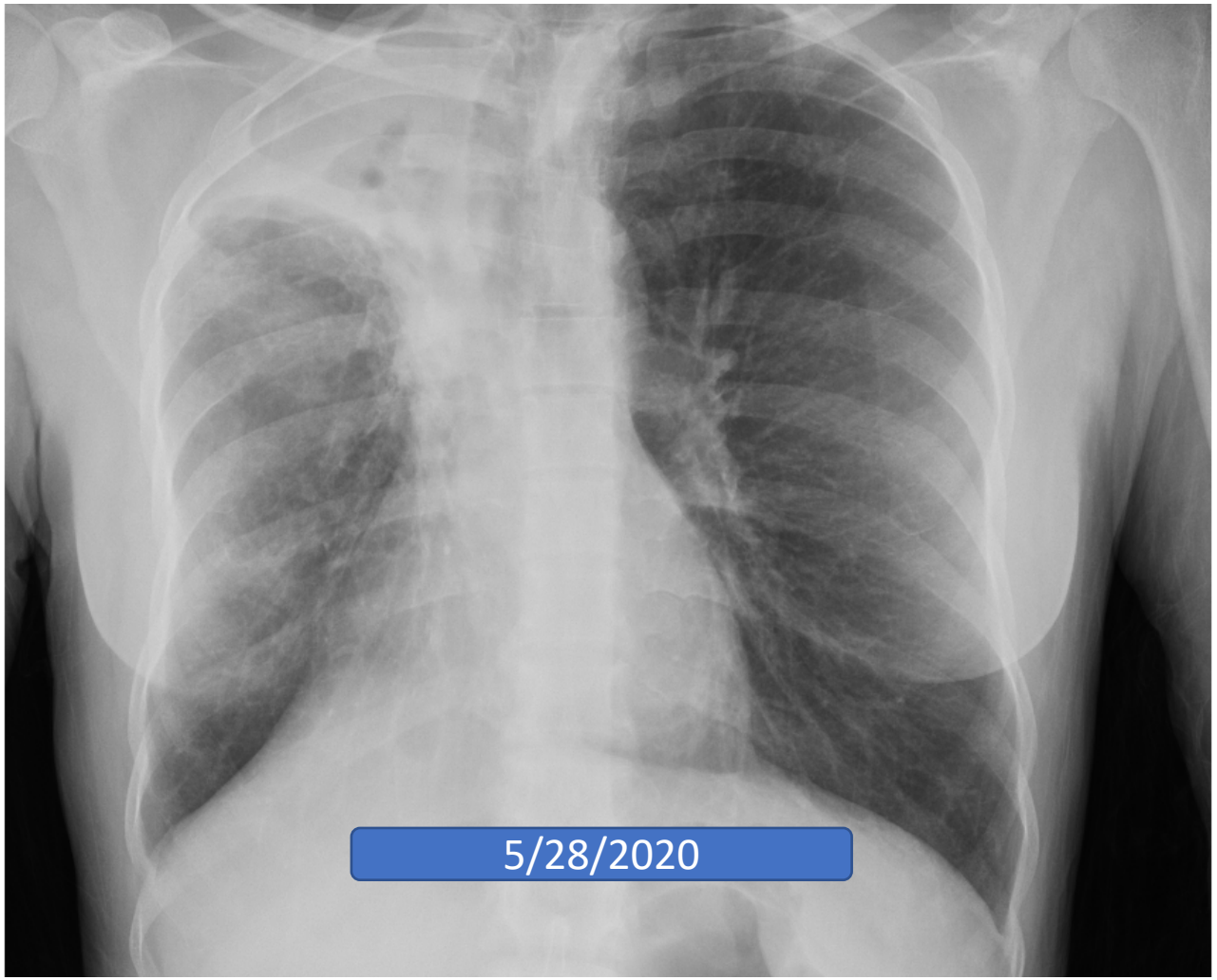
Culture no growth

Marked clinical improvement:

Decreased cough/shoulder pain

Resolution of anemia and low albumin

Delivered healthy infant 11/25/2020



Nguyen et al. BMC Infectious Diseases 2014, 14:617
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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Tuberculosis care for pregnant women: a systematic review

Hang Thanh Nguyen[1*], Chiara Pandolfini[1], Peter Chiodini[2] and Maurizio Bonati[1]

2014

•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

Nguyen et al. BMC Infectious Diseases 2014, 14:617
http://www.biomedcentral.com/1471-2334/14/617

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Tuberculosis care for pregnant women: a systematic review

Hang Thanh Nguyen[1*], Chiara Pandolfini[1], Peter Chiodini[2] and Maurizio Bonati[1]

2014

•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

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

- **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%
  - 1st trimester - 11%
  - 2nd trimester - 12%
  - 3rd trimester or postpartum - 4%

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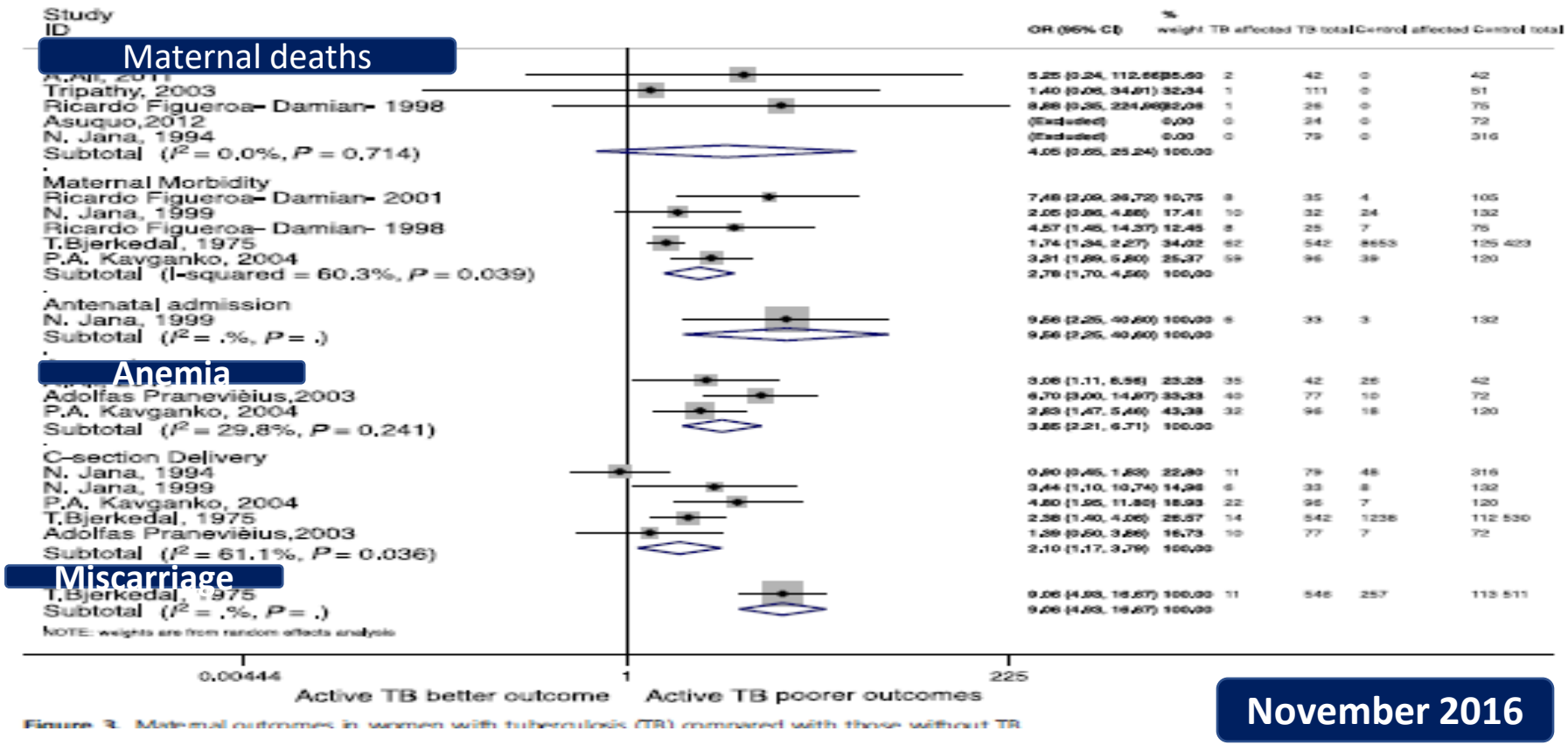

November 2016

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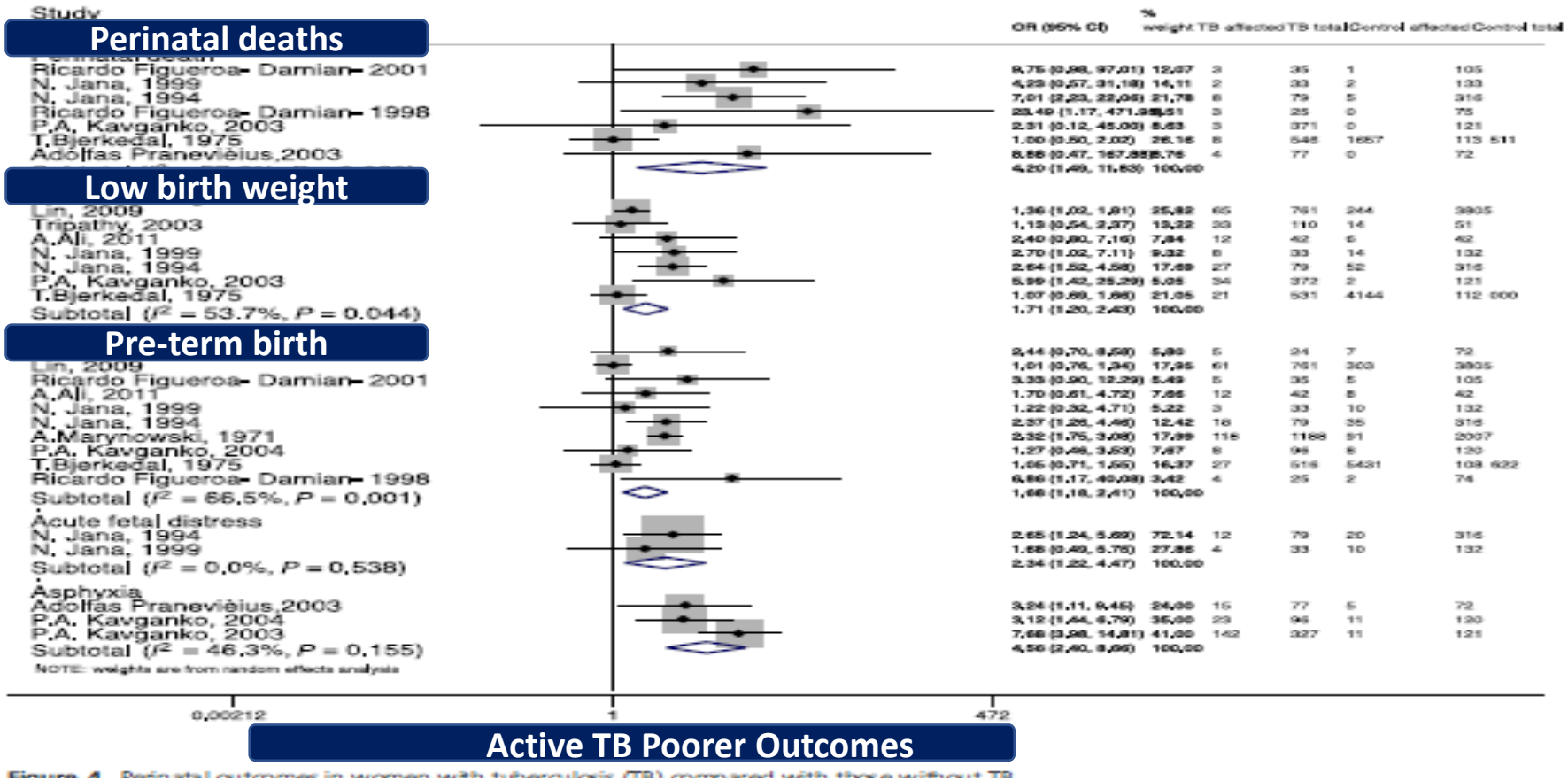

Figure 4 Perinatal outcomes in women with tuberculosis (TB) compared with those without TB

BJOG An International Journal of Obstetrics and Gynaecology
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Systematic Review

Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis

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- 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.

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.

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

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

January 2021

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 2nd 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

Increased risk of hepatotoxicity and temporary drug withdrawal during treatment for active TB in pregnancy. Beck-Friis et al. *Int J Inf Dis. 2020*

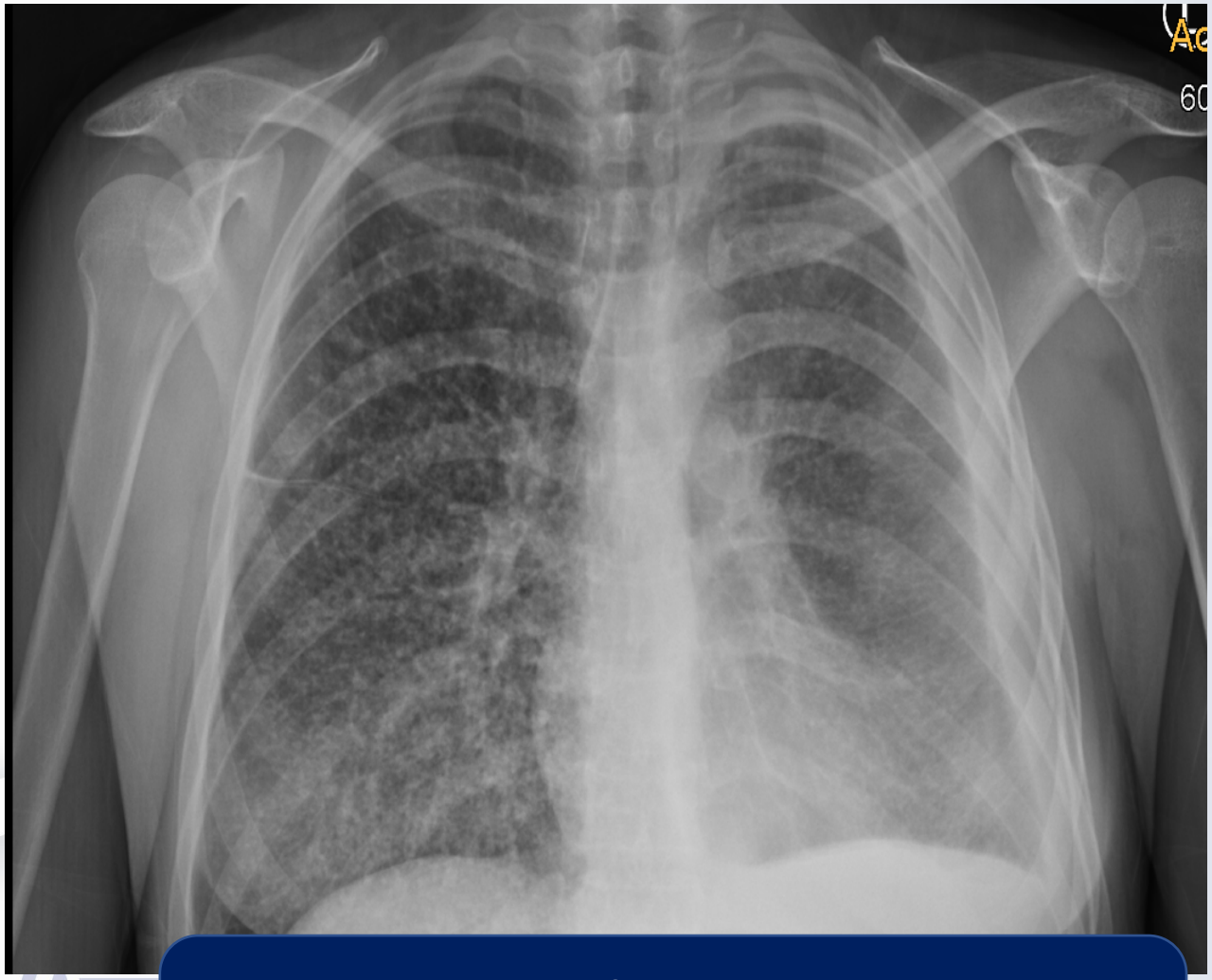
- **Retrospective study** on
  - pregnant and age matched non-pregnant women receiving treatment for active TB at 4 hospitals in Western Sweden between 1992-2017
    - 40 pregnant women/95 non-pregnant
- Frequency of severe liver toxicity (LFTs > 5 x upper normal)
  - 40% pregnant vs 6 % non-pregnant
- 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

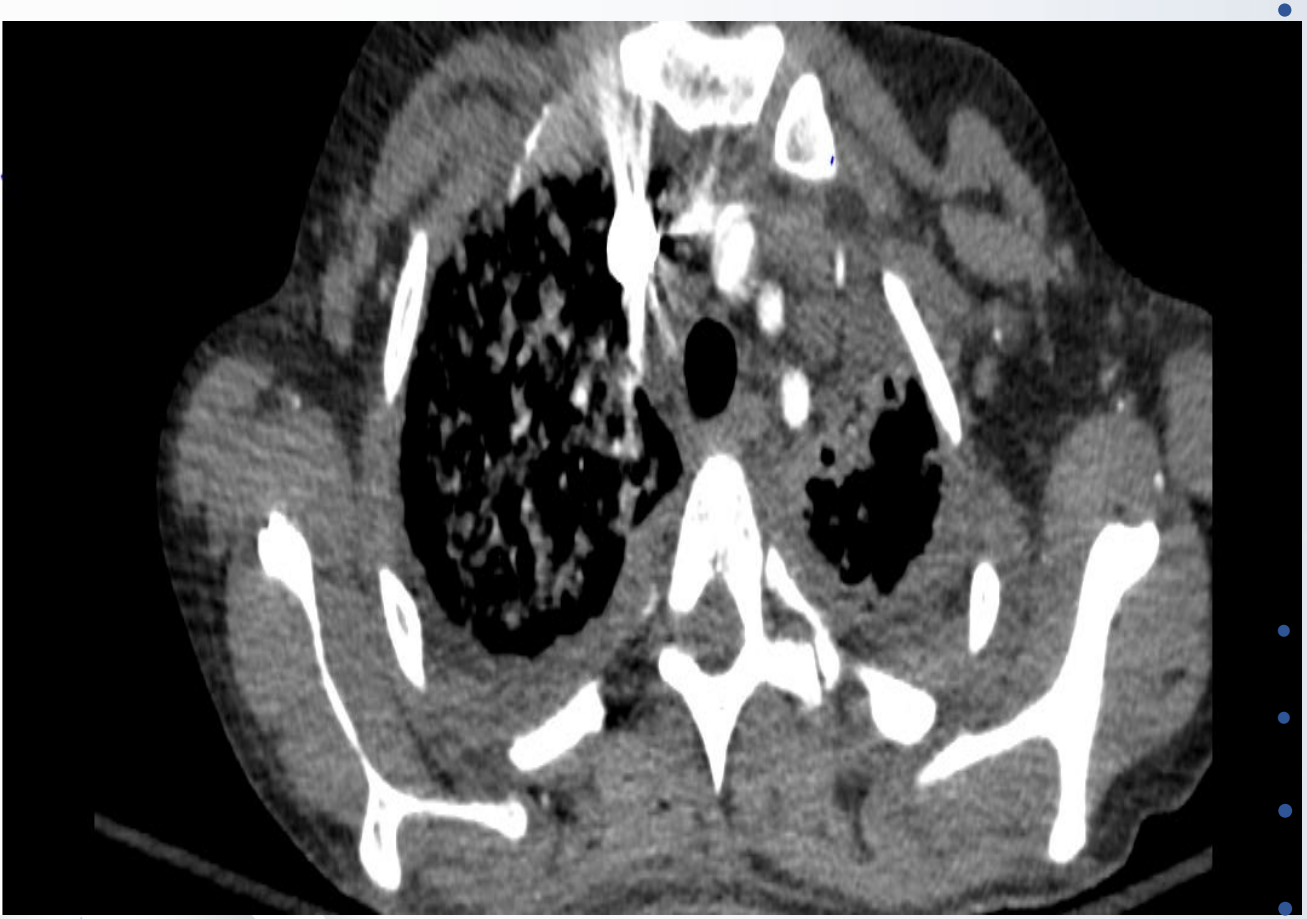
Postpartum



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

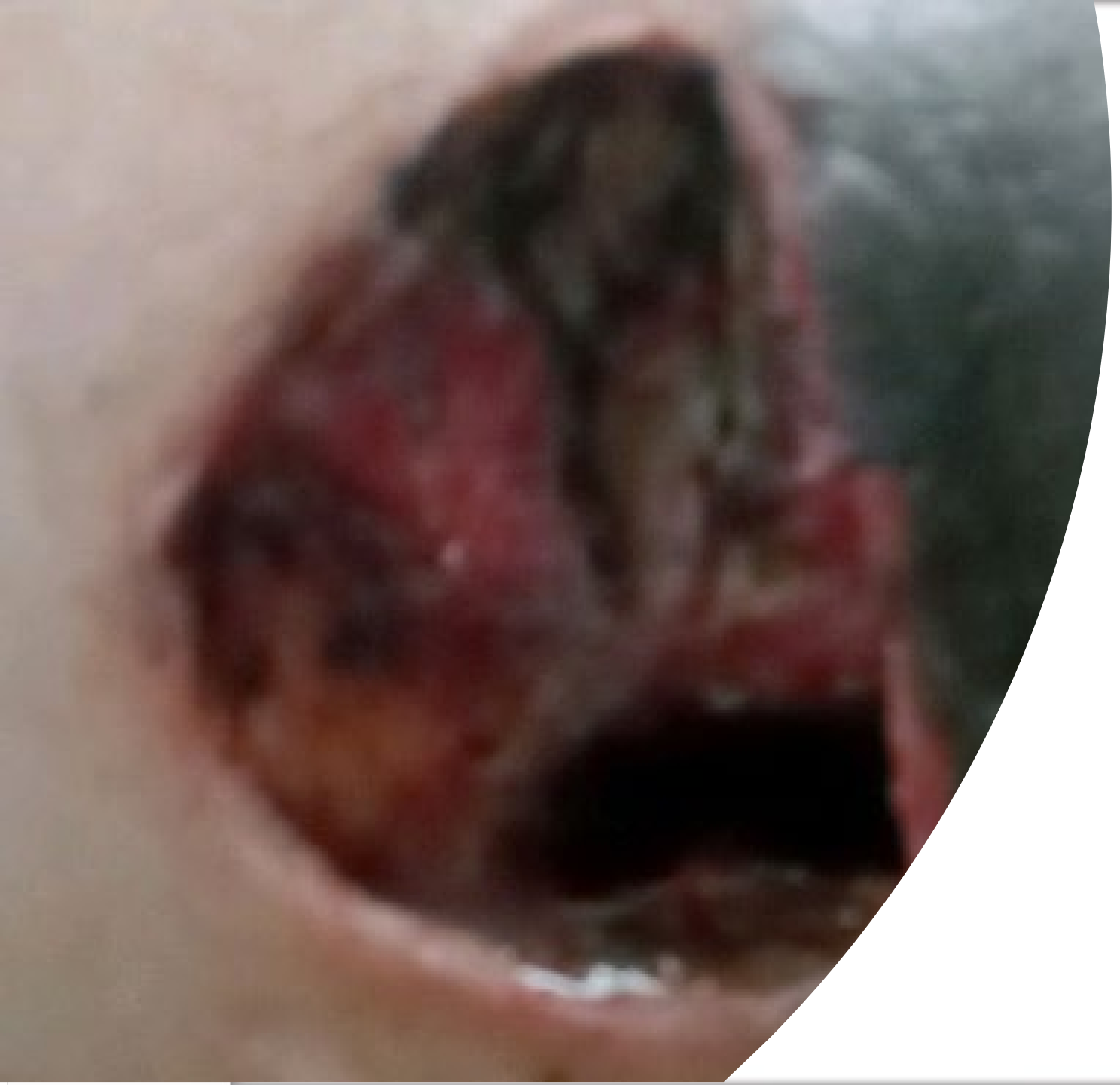
Arrested 1/26/2022; next morning blown pupils

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?**

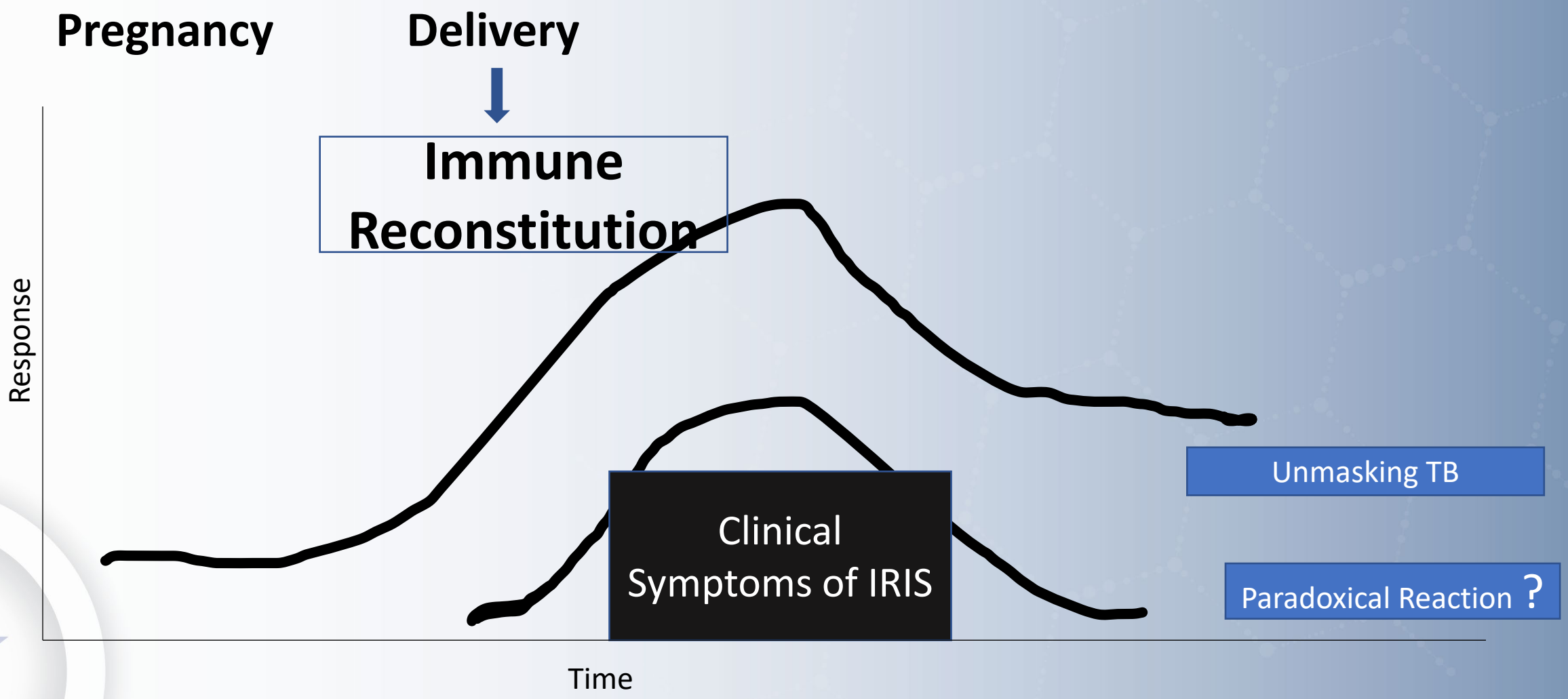


Breast Abscess

(13 weeks post op) shortly before her death…

She breastfed infant until her return to jail

Immune Events with non-HIV IRIS in Pregnancy



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"

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.

Cheng et al *Eur J Clin Microbiol Infect Dis* 2003, (Review of Liter 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**

Open Forum Infectious Diseases
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October 2022

Table 2. Cerebrospinal Fluid Results for 8 Cases of Human Immunodeficiency Virus and Pregnancy-Related Tuberculous Meningitis

CSF Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Opening pressure, mm H_2O (normal <250)	NA	400	15	200	80	280	70	170
White blood cells, cells/μL	625 (83% lymphocytes)	275 (78% lymphocytes)	165 (85% lymphocytes)	310 (85% lymphocytes)	<5	<5	<5	635 (83% lymphocytes)
Protein, mg/dL	187	147	103	184	90	79	29	138
Glucose, mmol/L	NA	<1.1	<1.1	<1.1	45	Unknown	59	Low
Lactate, mmol/L	NA	12.3	NA	NA	2.2	Unknown	2.4	5.5
AFB stain	–	–	–	–	–	–	–	–
CSF GeneXpert MTB/RIF Ultra	+	–	+	+ (trace)	–	+	–	–
Urine GeneXpert MTB/RIF Ultra	–	–	–	–	–	–	–	–
Urine LAM	–	–	–	–	+	+/–[a]	–	+
CSF culture	+	–	+	–	NA	NA	NA	NA

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

[a]Positive Fuji LAM, negative Alere LAM

Normal CSF cell count does not exclude CNS TB or TB Meningitis

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

- Female genital tract TB detected in 18-19% of women of reproductive age 2008; increased to 19-30% by 2015: Sharma et al, Indian J Med Res 2018: 148 (Suppl)

- **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

Patient Identification

Infertility with uterine and/or tubal disease
+
Endemic country
or other TB Risk Factors

Pos IGRA and/or TST (PPD) ***OR high clinical suspicion***

Chest XR ***(if positive may need treatment for pulmonary TB)***

Infectious Disease Consultation

1) Menstrual Effluent Culture and PCR
AND 2) Urine Culture and PCR

Positive PPD or IGRA AND neg CXR

Latent TB treatment

OR determination of appropriate prior TB treatment

Culture negative

Endometrial Biopsy

Sent for:
1) Pathology
2) Culture (need AST for possible MDR TB)
AND 3) PCR

Culture positive

Pathology, PCR, or cultures positive

Active TB treatment

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

McLaughlin. Delayed diagnosis of urogenital tuberculosis. Fertil Steril Rep 2022.

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

Xia et al, *Frontiers in Public Health* 2022

Association between IVF status and maternal outcomes among TB in pregnancy

	IVF-TB ($n = 28$)	Non-IVF-TB ($n = 52$)	OR*	95% CI	*P*-value (crude)	adjusted OR**	95% CI	*P*-value (adjusted)
Obstetric complications (%)								
Vaginal bleeding	13 (46.4)	1 (1.9)	44.2	5.3–366.0	<0.001	47.6	5.2–439.6	0.001
Maternal criticality	6 (21.4)	1 (2.0)	13.9	1.6–122.4	0.007	28.3	1.9–417.2	0.015
Preeclampsia	0 (0)	0 (0)	-			-		-
TB outcomes (%)								
Fever > 38.2°C	26 (92.9)	27 (51.9)	12	2.6–56.0	<0.001	16.7	3.2–87.7	0.001
Cough	21 (75.0)	30 (57.7)	2.2	0.8–6.1	0.149	2.3	0.8–6.7	0.135
Pleural effusion	1 (3.6)	19(36.5)	0.06	0.01–0.51	0.001	0.05	0.01–0.42	0.006
Miliary TB	89% vs 13.5%		53.6	12.7–225.7	<0.001	75.4	13.7–415.2	<0.001
TB Meningitis	32% vs 7.7%		6	1.6–21.9	0.008	6.2	1.5–24.8	0.01
Death	0 (0)	0 (0)	-			-		-

*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

	IVF-TB ($n = 28$)	Non-IVF-TB ($n = 52$)	OR*	95% CI	*P*-value (crude)	Adjusted OR**	95% CI	*P*-value (adjusted)
Mortality	64 vs 28%			1.7–11.8	0.004	9.8	2.6–36.8	0.001
Spontaneous abortion	46 vs 11.5%				-	-		-
					-	-		-
Preterm birth (alive) (%)	2 (7.1)	3 (5.8)	-		-	-		-
Normal birth (%)	8 (28.6)	34 (65.4)	-		-	-		-
Developed TB after birth*** (%)	0 (0)	0 (0)	-		-	-		-

*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 patients will. ***These data came from medical records or telephone review conducted at least 1 year after delivery.

Impact of Positive Interferon-Gamma Release Assay on IVF-ET Pregnancy Outcomes in Infertile Patients With Untreated Prior Tuberculosis: A Prospective Cohort Study

Gai et al Frontiers in Medicine 2021

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.

Gai et al. Untreated prior pulmonary TB adversely affects pregnancy outcomes…. *Biomed Environ Sci,* 2021

- 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