Santa Clara County
PUBLIC HEALTH

Latent TB Infection Screening and Treatment During Pregnancy

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OCTOBER, 2023

TB in pregnancy - objectives

- To illustrate the impacts of TB disease on the pregnant woman and her fetus
- Describe the known epidemiology of TB in pregnancy
- Examine the risk / benefit of screening for and treating latent TB infection before and during pregnancy

Disclosures

I have no disclosures or conflicts of interest

For simplicity - I will refer to a pregnant parent as a woman

TB and health equity

Who is at increased risk of TB?

- Among others:
  - People born outside the US / Canada / Australia / Western Europe
  - People with diabetes, renal failure
  - People living with HIV or who have other immunocompromising conditions

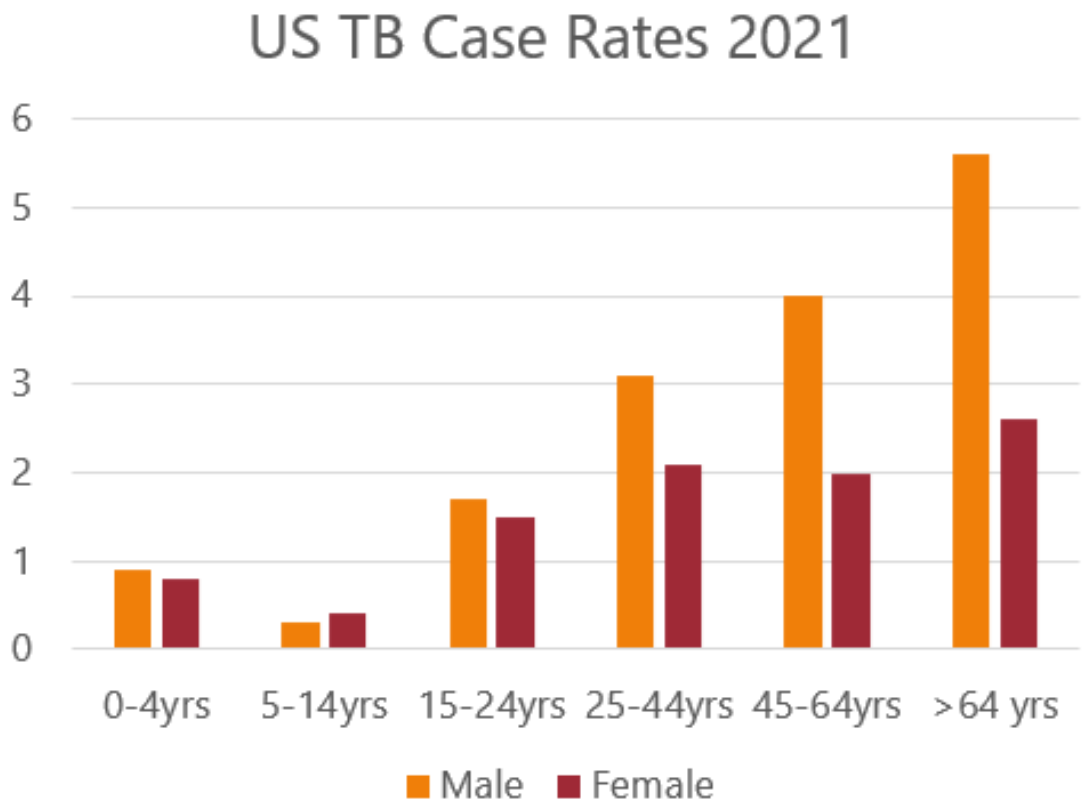
TB and health equity

Who is at increased risk of TB (infection or disease) ?

- People born outside the US / Canada / Australia / Western Europe
- People with diabetes, renal failure
- People living with HIV or who have other immunocompromising conditions

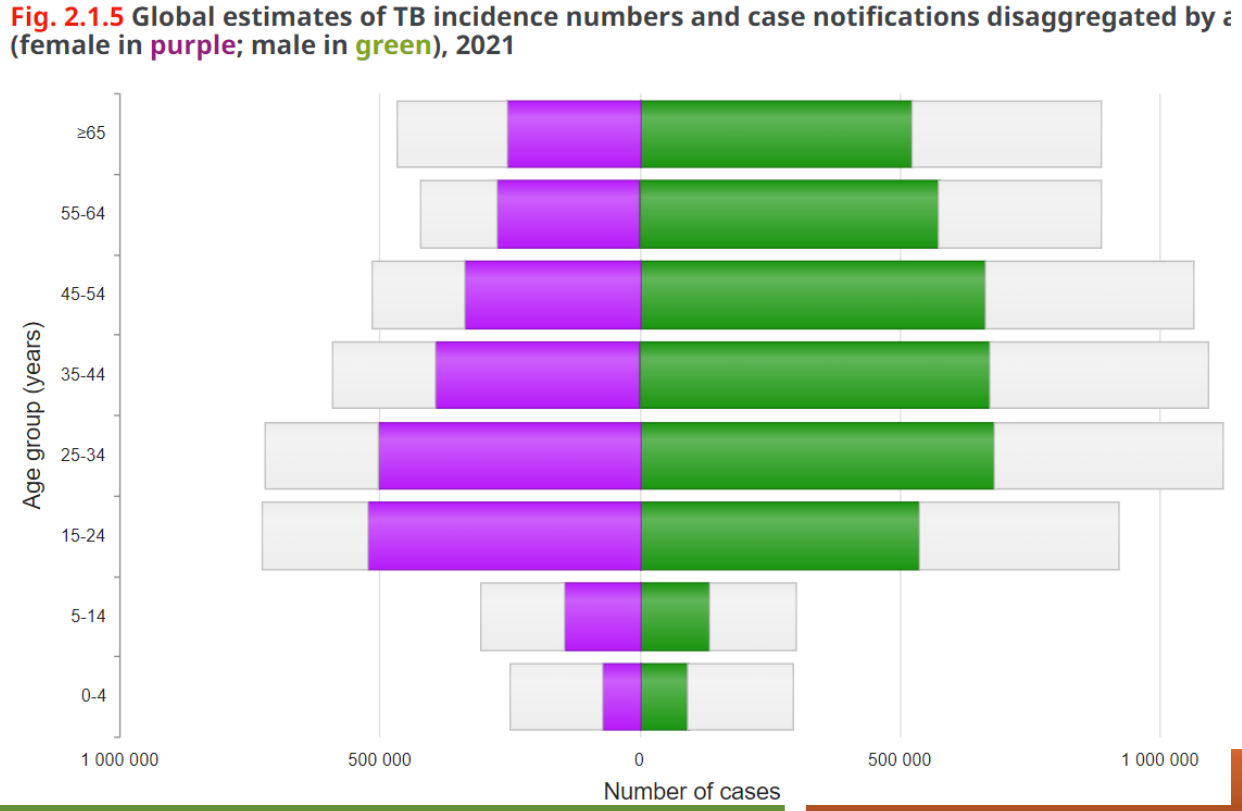
- **Postpartum women and likely pregnant women**

Woman disproportionately develop TB disease during the childbearing years



Online Tuberculosis Information System (OTIS) Data (c

Who Global Report 2022



Magnitude

Sugarman Lancet Glob Health 2014; 2: e710–16

	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**

Magnitude

Globally, more than 200,0000 women have TB in pregnancy each year

We have just started collecting RVCT "pregnancy" status in the US

They are excluded from clinical trials despite FDA rules requiring inclusion

There is conflicting data around risk of progression to TB during pregnancy – but

- Clear evidence of immune changes during pregnancy which increase risk of certain infections
  - Th1 proinflammatory response is suppressed in pregnancy which may mask symptoms and increase susceptibility
  - Reversal after pregnancy may promote exacerbation of symptoms
- Clear evidence of marked increased risk of TB disease in the postpartum period (likely started during pregnancy!)

Are pregnant women a vulnerable population ?

Maternal outcomes with TB	Increased risk (Odds ratio)	Baby outcomes (mom with TB)	Increased risk (Odds ratio)
Maternal death	5.25	Perinatal death	9.75
Morbidity	7.48	Low birthweight	1.36
Antenatal admission	9.56	Pre-term birth	2.44
Miscarriage	9.05	Asphyxia	3.24

Sohby Metanalysis BJOG 2017;124:727-733; (Dennis inpatient data PLoS ONE 2018 13(3)z;r0194836)

Preventing TB in pregnancy

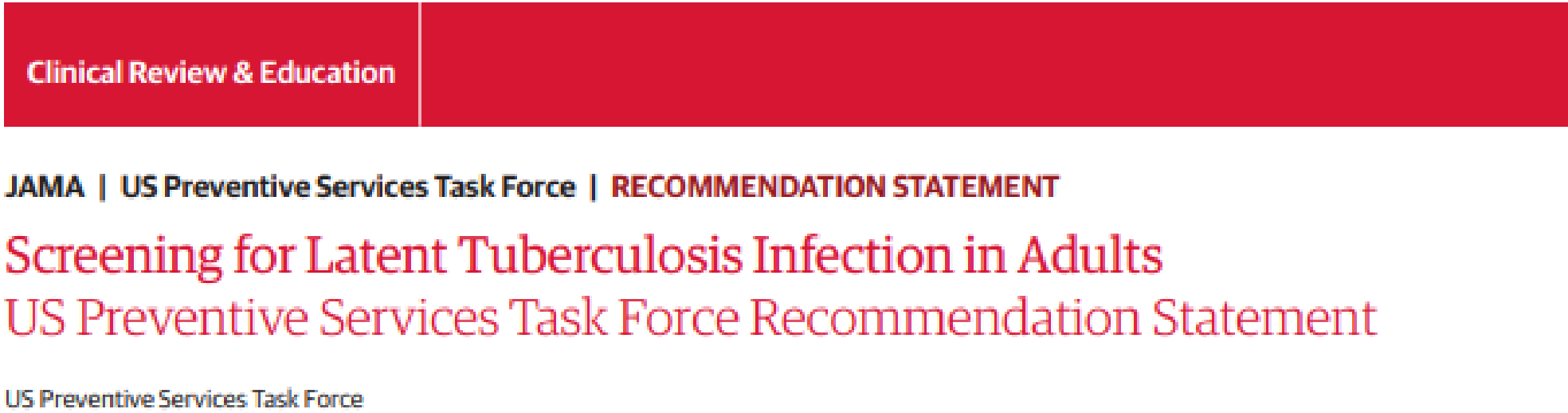
I hope that I have convinced you that preventing (or at least early treatment) of TB in pregnancy is hugely valuable!

AND – OB care may be the only time a young healthy woman accesses health care

Strategies:

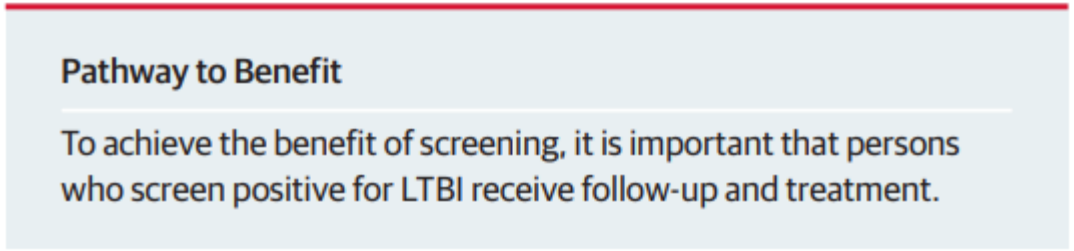
- **Universal** TB screening of high-risk categories across the population
- Screening for TB **symptoms** - VERY difficult given the many non-specific symptoms that overlap with pregnancy and suppression of immune response
- Screening of women of childbearing years / **planning pregnancy**
- Screening **during obstetric care**
- Screening at the **time of delivery** (Spoiler alert - lower yield)

Universal screening



May 2023 – Screen for LTBI in high-risk populations

Note: does not apply to symptomatic folks



jama_mangione_2023_us_230005_1682611571.73428 (2).pdf

Universal screening

Clinical Review & Education

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Latent Tuberculosis Infection in Adults
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

May 2023 – Screen for LTBI in high-risk populatio

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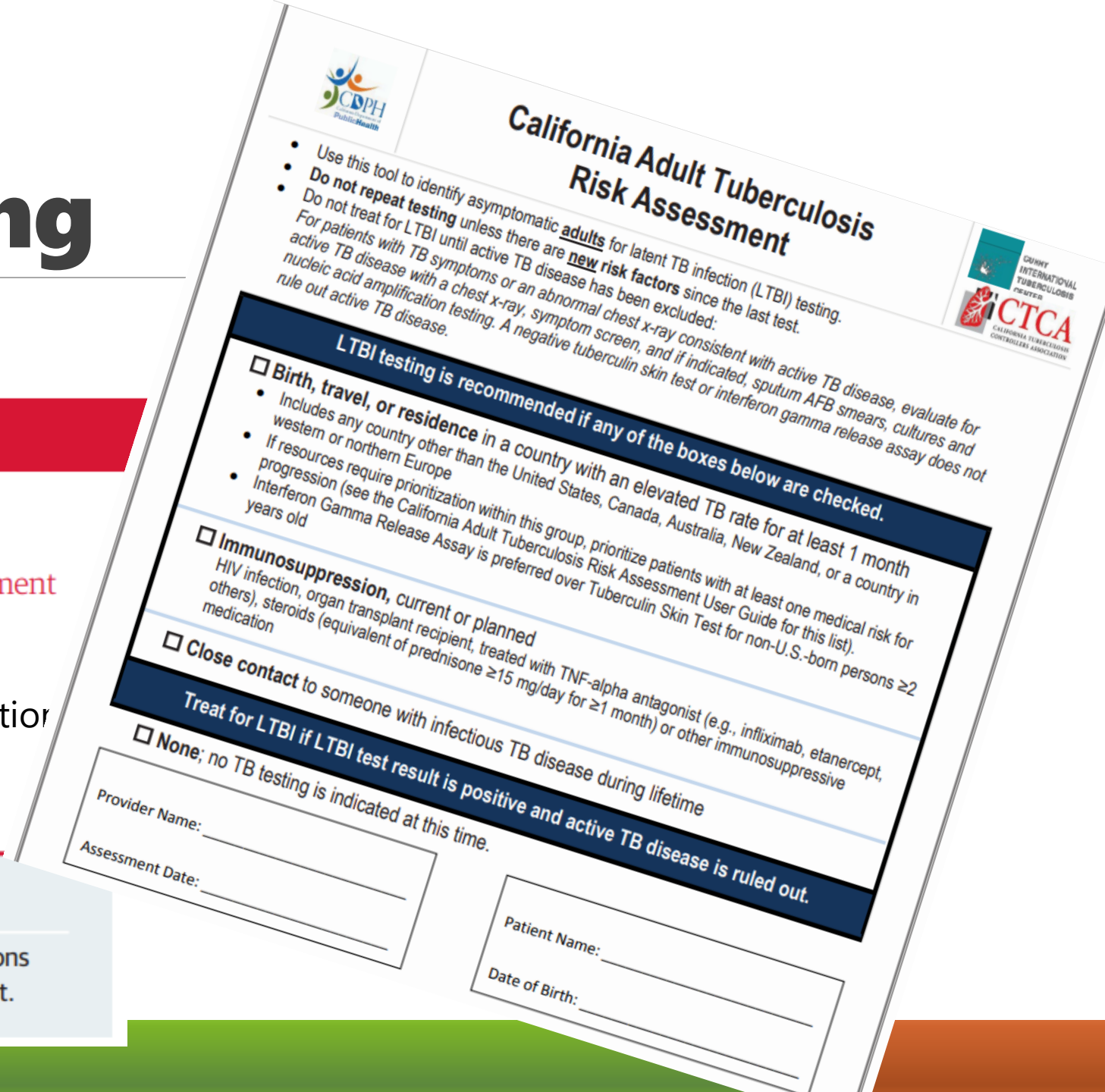
Pathway to Benefit

To achieve the benefit of screening, it is important that persons who screen positive for LTBI receive follow-up and treatment.



No national guidance for pre-natal TB screening

One academic infertility center has screened its patients for TB risk factors

- 25 women out of 323 with risk factors had + QFT (92% born outside US)
- Woman with + QFT had much rates of recurrent Pg loss and Asherman syndrome (buildup of uterine scar tissue)
- 2 had subnormal chest radiograph
- 1 woman had TB smear / culture / PCR + endometrial biopsy

Female genitourinary TB (FGTB) is a significant cause of infertility in TB endemic countries

In vitro fertilization in the context of untreated FGTB has resulted in many cases of congenital tuberculosis

Yale ref

PREGNANT, BREASTFEEDING, AND POSTPARTUM WOMEN

National Tuberculosis Controllers Association

Screen pregnant women for risk factors and test them only if they have a risk factor for infection or for progression to active TB disease.

If an asymptomatic, pregnant woman has a positive TB test result, either IGRA or TST, she should receive a medical evaluation, including a CXR with a lead shield.

The CXR may be deferred until after the first trimester unless she has one or more of the following:

- HIV or other immunosuppression
- History of recent contact with a person with infectious TB disease
- Documented TB infection test conversion in the past 2 years

The CXR should not be deferred until peri- or post-partum.

Many experts recommend treating these pregnant women for LTBI after the first trimester (others wait till post-partum).

Many women access medical care only when they are pregnant. Women may lose their maternal health care benefits after one postpartum visit. **If treatment is deferred, a referral should be made to a facility that offers treatment of LTBI**.

PREGNANT, BREASTFEEDING, AND POSTPARTUM WOMEN

Monitor symptoms and consider TB disease

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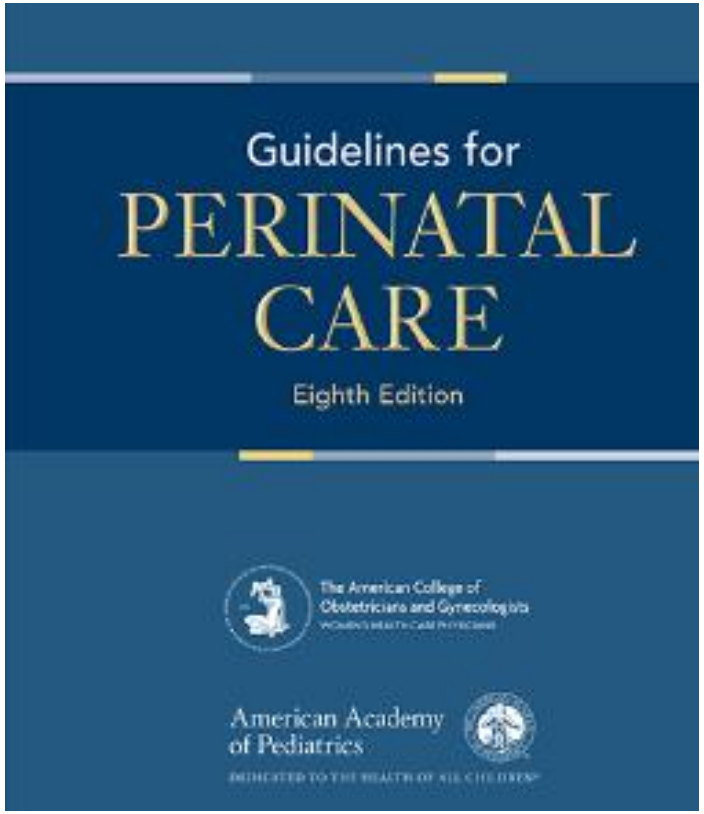
Screening for TB in pregnancy

SCREEN FOR HIGH RISK IN EARLY VISIT

- Foreign born patients
- Exposure history
- Medical risk factors (including Immunocompromising conditions, HIV, Pregestational diabetes mellitus, dialysis-dependent renal failure, being medically underserved)
- Living or working in LTCF, corrections, etc
- Experiencing homelessness

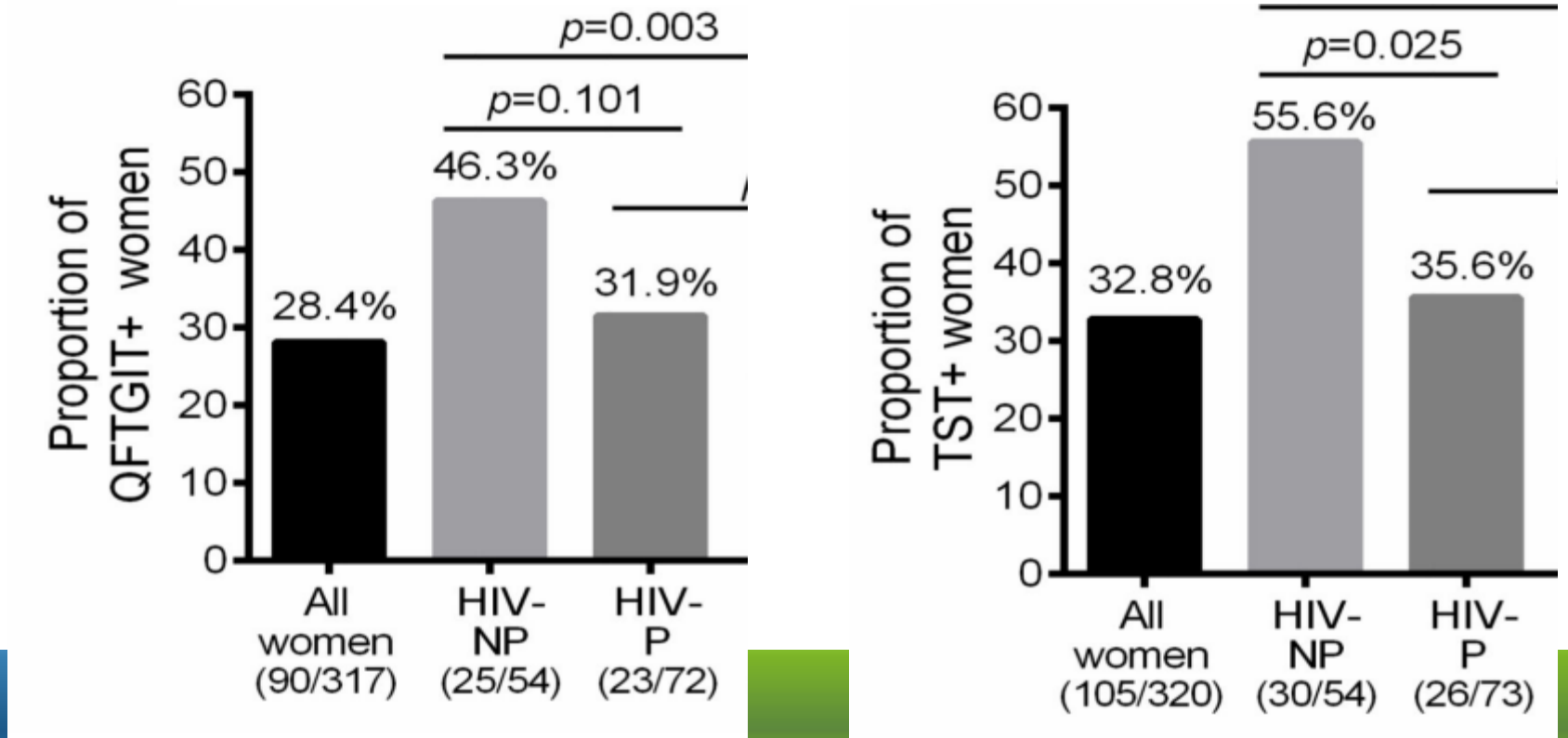


TST / IGRA in pregnancy

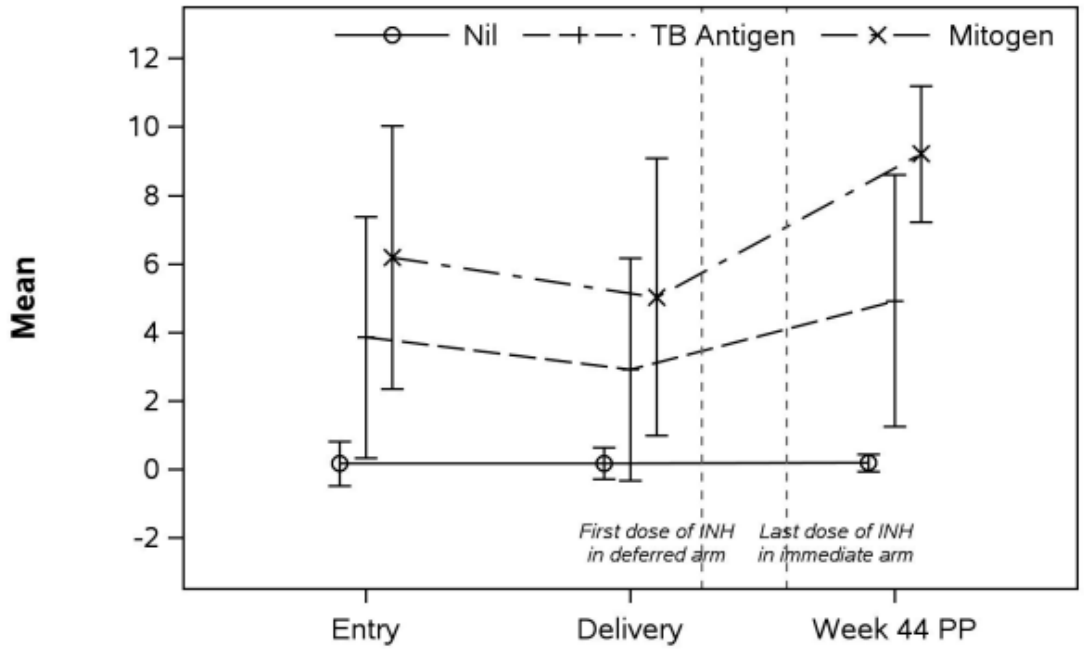
Cell mediated immunity is suppressed during pregnancy

Relative immune reconstitution immediately post-partum

Birku *Int J Infect Dis.* 2020 December ; 101: 235–242



Gamma interferon levels are lower in pregnancy



Mean (SD)	Entry	Delivery	Week 44 PP
Nil	0.16 (0.65)	0.16 (0.46)	0.18 (0.26)
TB Antigen	3.85 (3.52)	2.92 (3.25)	4.92 (3.68)
Mitogen	6.19 (3.84)	5.03 (4.05)	9.21 (1.99)

Figure 2. Changes in IFNγ production measured by QGIT in women with positive QGIT results postpartum. Data were derived

Weinberg CID 2021;73(9):e3555–62

Risk of TB in pregnancy

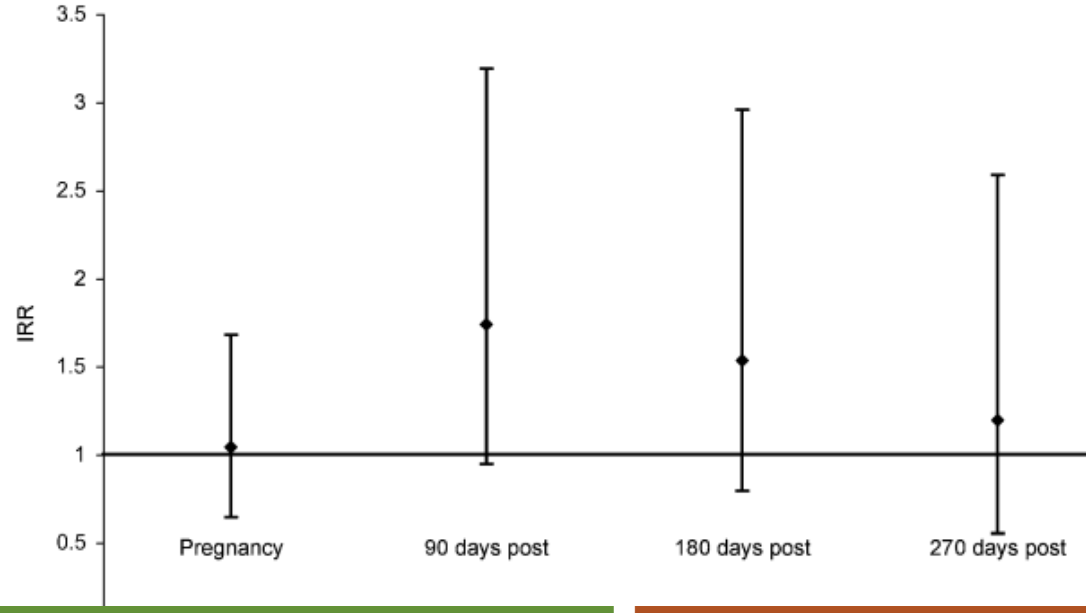
UK General Practitioner Research Database (~250,000 pregnancies)

All women aged 15 – 49 yrs and pregnancies studied 1996 – 2008

Non-pregnancy TB rates: 9.1/100,000 person years

Pregnant or post-partum TB rates: 15.4/100,000 person years

Conclusion: 90 days post partum is highest risk in a woman's life to be dx with TB.



Zenner 2012 Am J Resp CCM 185;779-784

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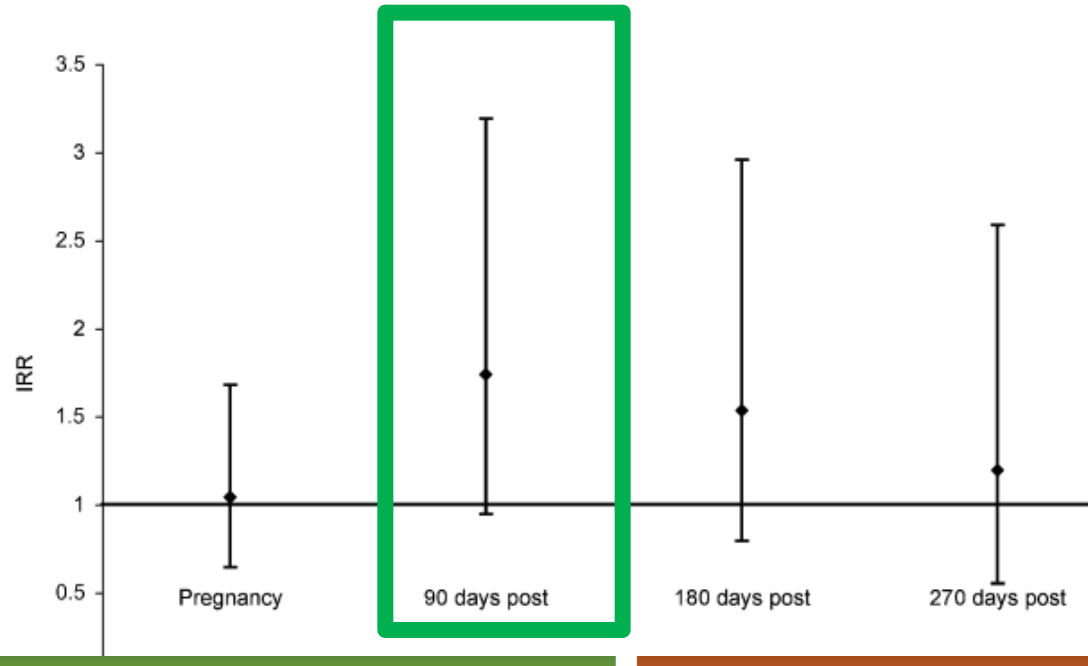


Zenner 2012 Am J Resp CCM 185;779-784

Treatment of LTBI in pregnancy

- TBTC Prevent TB trial (Study 26) - compared 3HP to 9H in non-pregnant people
- TBTC iAdhere (study33) compared SAT to DOT 3HP
- ~4400 women enrolled
- 125 women reported pregnancy: 31 exposed to 3HP and 56 exposed to 9H
- Rates of fetal loss and congenital anomalies were similar in each group and to that expected in the US
- One woman on INH developed hepatotoxicity

Moro 2018 Exp to LTBI tx in Pg Ann ATS V15(5)570-580

	Fetal loss	Congenital anomalies
INH	13%	4%
3HP	15%	3%
Baseline	17%	3%

IMPAACT 1078

956 women pregnant women living with HIV enrolled (85% on efavirenz)

Randomized to 6 mo INH treatment during pregnancy or 12 weeks after delivery

3 women in each arm developed TB disease

6 women died including one in each arm of hepatotoxicity (post partum period)

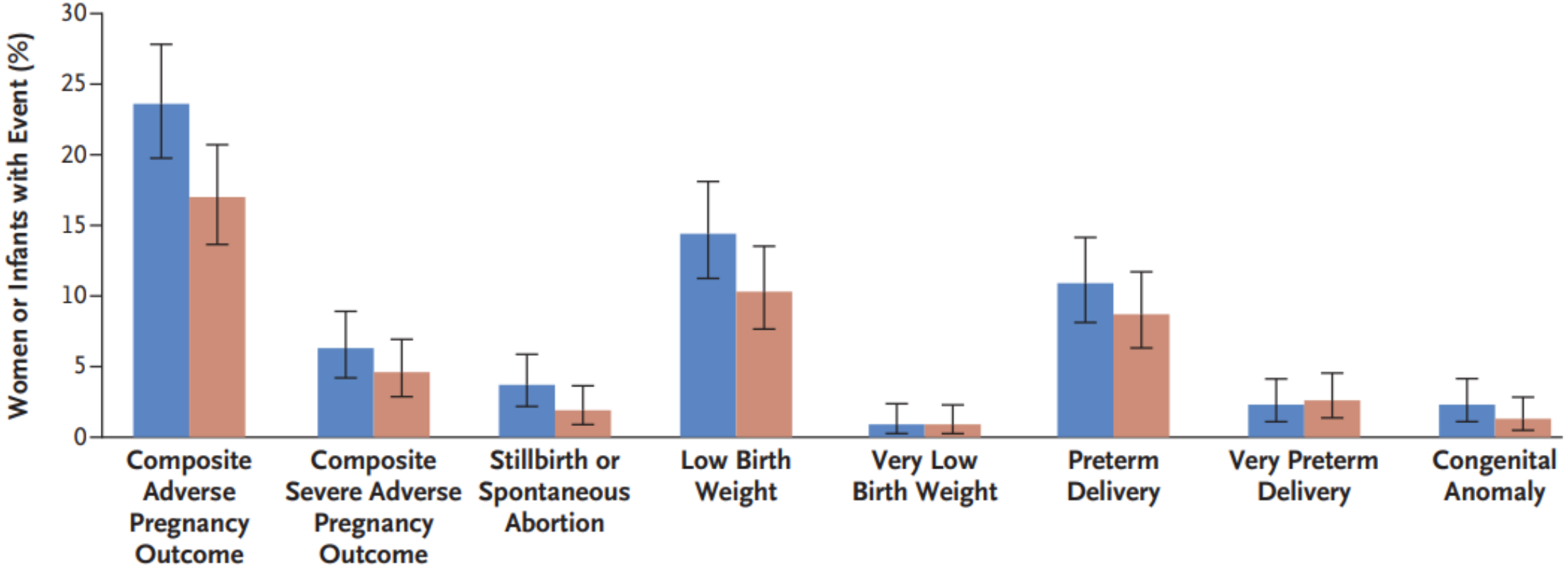
- There is a known association of hepatotoxicity and INH use in pregnancy / postpartum

Some concern that the older ART regimen with efavirenz may have contributed

Gupta 2019 NEJM 381;14 IMPAACT P1078 Results | IMPAACT (impaactnetwork.org)

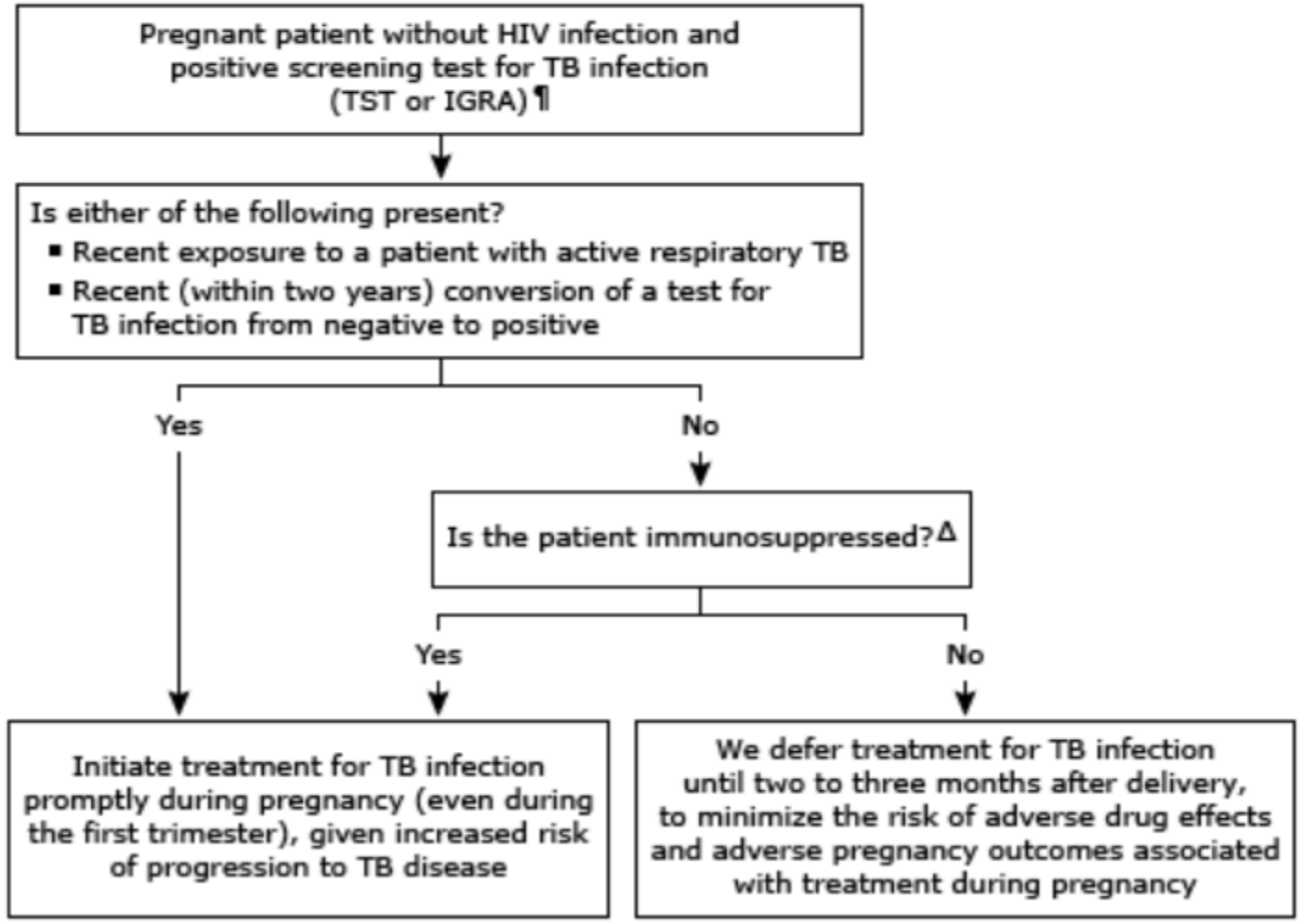
IMPAACT 1078 – surprising AE (no placebo)

B Composite Adverse Pregnancy Outcomes and Components

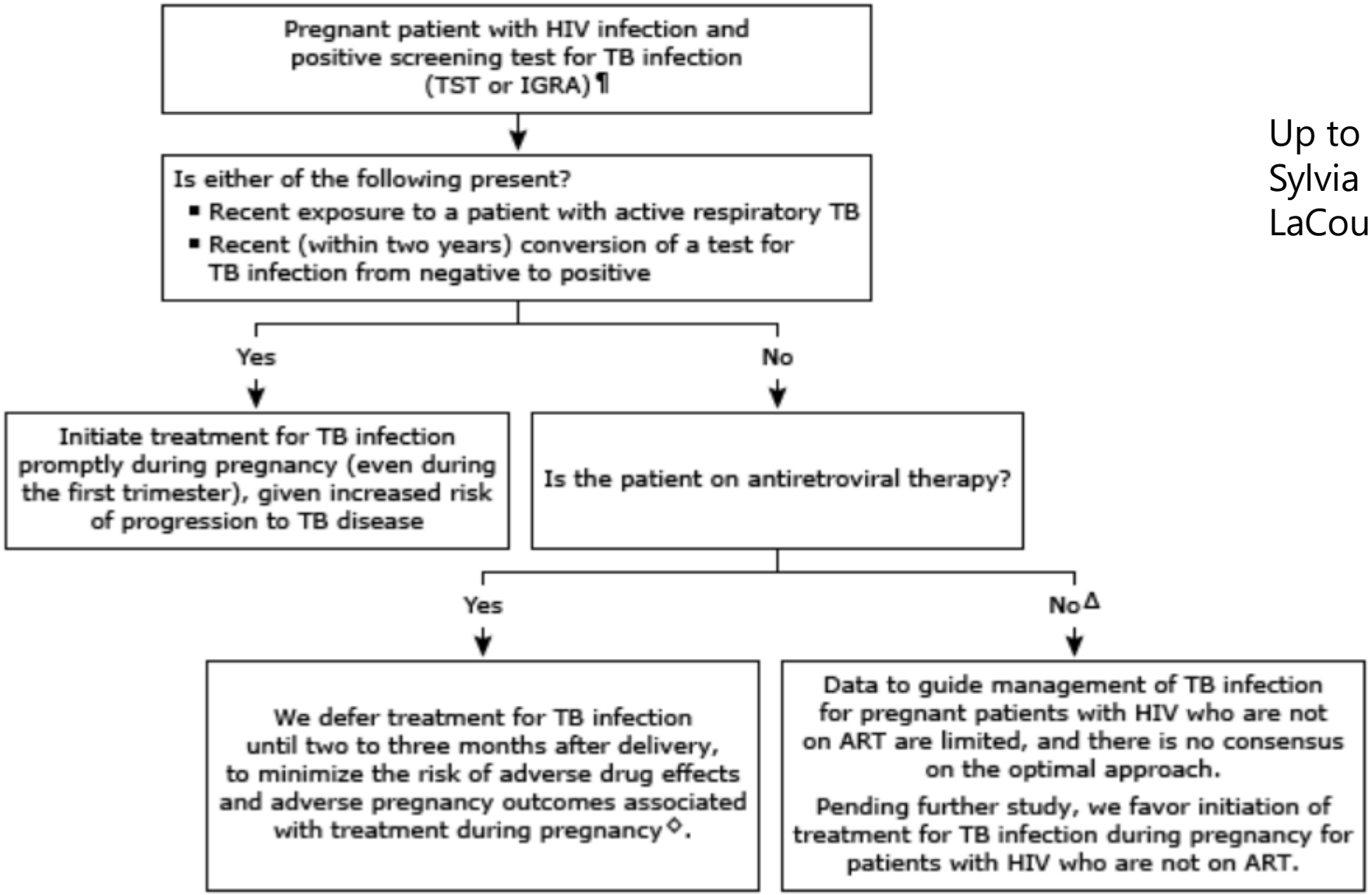


No. of Events/ Total No. (%)	Composite Adverse Pregnancy Outcome	Composite Severe Adverse Pregnancy Outcome	Stillbirth or Spontaneous Abortion	Low Birth Weight	Very Low Birth Weight	Preterm Delivery	Very Preterm Delivery	Congenital Anomaly
Immediate treatment	106/449 (23.6)	28/448 (6.3)	17/459 (3.7)	62/430 (14.4)	4/430 (0.9)	48/442 (10.9)	10/442 (2.3)	10/440 (2.3)
Deferred treatment	78/460 (17.0)	21/458 (4.6)	9/466 (1.9)	46/446 (10.3)	4/446 (0.9)	40/458 (8.7)	12/458 (2.6)	6/458 (1.3)
RD (95% CI)	6.7 (0.8 to 11.9)	1.7 (–1.3 to 4.8)	1.8 (–0.4 to 4.1)	4.1 (–0.3 to 8.6)	0.0 (–1.5 to 1.6)	2.1 (–1.8 to 6.1)	–0.4 (–2.6 to 1.8)	1.0 (–0.9 to 3.0)
P Value	0.01	0.27	0.09	0.07	0.86	0.29	0.75	0.26

Approach to timing of treatment for tuberculosis infection (laten tuberculosis) in pregnant patients without HIV infection*



Approach to timing of treatment for tuberculosis infection (latent tuberculosis) in pregnant in settings with TB transmission rates <500 per 100,000*



Up to Date
Sylvia
LaCourse, MD

Summary

- Tuberculosis is very dangerous to the pregnant and postpartum mom as well as her fetus / baby
- Treatment early in pregnancy leads to a better outcome than treatment later in pregnancy
- Diagnosis is sometimes delayed due to non-specific symptoms and denial
- The postpartum period is the time in a woman's life when she is most likely to develop TB disease
- It is not entirely clear what risk factors predispose to progression from LTBI to TB disease during pregnancy / postpartum
- In one study 2/3 of women became pregnancy AFTER their TB diagnosis

Summary

- While treatment of LTBI during pregnancy seems obvious – however:
  - Many woman decline treatment
  - There seems to be risk of adverse events / toxicity on LTBI treatment (at least INH in context of WLHIV / on older ART regimen)

- Research is needed:
  - Safe LTBI regimen
  - Pregnancy prevention while on TB treatment
  - Early diagnosis of TB disease during pregnancy
  - Features that predict risk of progression / severe TB disease