MEDICAL UPDATE:

DIAGNOSIS AND MANAGEMENT OF TUBERCULOSIS IN THE PREGNANT PATIENT

WEBINAR: December 15, 2010

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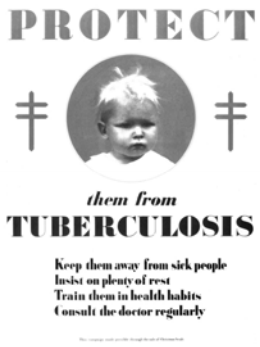

American Lung Association, www.nlm.nih.gov

Tuberculosis in Pregnancy

- Tuberculosis in Reproductive Aged Women
- Prenatal care in the United States
- Screening guidelines
- Signs and symptoms of TB in pregnancy
- Treatment guidelines
- Postpartum care and breastfeeding
- Family planning strategies
- Deficits in research

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Tuberculosis: Global

- Over 900 million women worldwide have TB
- Men more likely to become infected, but women much more likely to progress to active disease
- In reproductive age women (15-44yo), TB contributes to 9% of all deaths
  - HIV/AIDS 3%
  - Heart disease 3%

Tuberculosis: Global

- The majority of those infected with *M. tuberculosis* do not have active disease
- Untreated, approximately 10% of infected patients will develop active TB
  - First 1 to 2 years after the primary infection
- Worldwide, TB kills more women each year than any other infection
- Avoidance or lack of access to medical care may contribute to the underreporting of TB in women

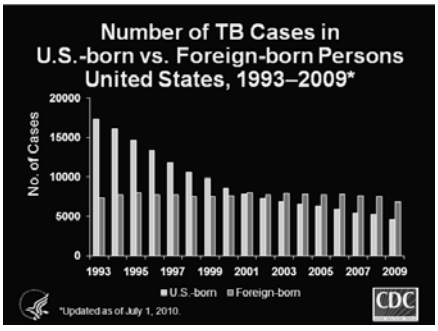
Tuberculosis: US cases

Tuberculosis cases and deaths per 100,000 population

	Tuberculosis Cases				Tuberculosis Deaths			
			Percent Change				Percent Change	
Year	Number	Rate	Number	Rate	Number[1]	Rate[1]	Number	Rate
1990	25,701	10.3	9.4	8.2	1,810	0.7	-8.1	-12.5
1991	26,283	10.4	2.3	0.9	1,713	0.7	-5.4	0.0
1992	26,673	10.4	1.5	0.1	1,705	0.7	-0.5	0.0
1993	25,107	9.7	-5.9	-7.1	1,631	0.6	-4.3	-14.3
1994	24,205	9.2	-3.6	-4.8	1,478	0.6	-9.4	0.0
1995	22,728	8.5	-6.1	-7.2	1,336	0.5	-9.6	-16.7
1996	21,210	7.9	-6.7	-7.8	1,202	0.5	-10.0	0.0
1997	19,751	7.2	-6.9	-8.0	1,166	0.4	-3.0	-20.0
1998	18,287	6.6	-7.4	-8.5	1,112	0.4	-4.6	0.0
1999	17,501	6.3	-4.3	-5.4	930	0.3	-16.4	-25.0
2000	16,309	5.8	-6.8	-7.8	776	0.3	-16.6	0.0
2001	15,945	5.6	-2.2	-3.2	764	0.3	-1.6	0.0
2002	15,056	5.2	-5.6	-6.5	784	0.3	2.6	0.0
2003	14,836	5.1	-1.5	-2.3	711	0.2	-10.2	-33.3
2004	14,499	4.9	-2.3	-3.2	662	0.2	-6.9	0.0
2005	14,064	4.8	-3.0	-3.9	648	0.2	-2.1	0.0
2006	13,734	4.6	-2.3	-3.3	644	0.2	-0.6	0.0
2007	13,280	4.4	-3.3	-4.3	554	0.2	-14.0	0.0
2008	12906	4.2	-2.8	-3.7	…	…	…	…
2009	11545	3.8	-10.5	-11.3	…	…	…	…

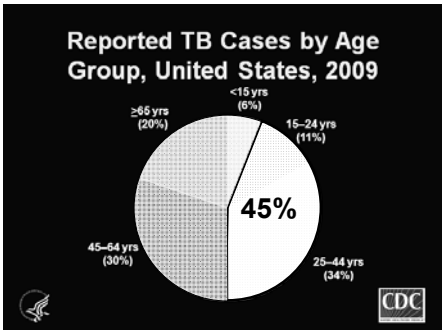
Adapted from www.cdc.gov/tb/statistics/reports/2009/pdf/Table1.pdf

US-born vs Foreign-born



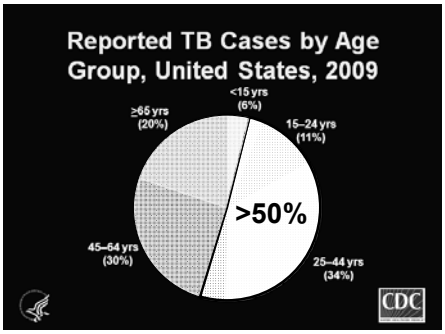
www.cdc.gov/tb/statistics/reports/2009

Tuberculosis: US cases



www.cdc.gov/tb/statistics/reports/2009

Tuberculosis: Reproductive Age



www.cdc.gov/tb/statistics/reports/2009

Tuberculosis in Pregnancy

- Historically, women with tuberculosis were offered termination of pregnancy
- Contemporary studies show that women with pulmonary TB who are <u>treated appropriately</u> do <u>not</u> have:
  - Increased rates of maternal complications
  - Neonatal complications

Schaefer G et al. Obstet Gynecol. 1975;46:706–715
Jana N et al. N Engl J Med. 1999;341:645–649
http://memory.loc.gov/ammem/wpaposters/wpahome.html

Vertical Transmission

- *M. tuberculosis* identified in:
  - Amniotic fluid
  - Placenta (granulomas)
  - Autopsy in neonates
- Identification of TB granulomas in the placenta may reflect only maternal disease and not congenital tuberculosis

Kaplan C. et al. Am J Obstet Gynecol. 1980;137:858–860
Henderson CE et al. J Natl Med Assoc. 1993;85:685–687
Machin GA et al. Pediatr Pathol. 1992 Sep-Oct;12(5):707-16

Vertical Transmission

- Tuberculosis could be transmitted antepartum:
  - Fetal aspiration of infected amniotic fluid
  - Direct hematogenous spread though the placenta
- Intrapartum
  - Aspiration/ingestion of infected amniotic fluid or genital secretions
- Postpartum
  - Inhalation/ingestion of respiratory droplets

Kaplan C. et al. Am J Obstet Gynecol. 1980;137:858–860
Henderson CEet al. J Natl Med Assoc. 1993;85:685–687
Machin GA et al. Pediatr Pathol. 1992 Sep-Oct;12(5):707-16

Vertical Transmission

- There is a higher incidence of congenital TB in women who have extrapulmonary TB
- 15% of neonates sampled in first 3 weeks of life had TB bacilli
  - ? Either vertical or horizontal transmission

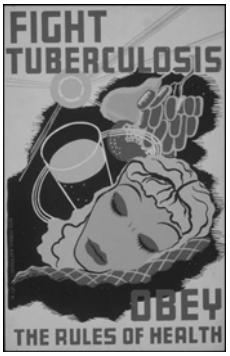
Pillay T et al. Clin Infect Dis. 1999;29(2):467-8
Pillay T et al. Lancet Infect Dis. 2004;4(3):155-65
Jones JL et al. Int J Tuberc Lung Dis. 2000 Nov;4(11):1026-31

Vertical Transmission

- TB in HIV+ pregnant women may increase risk of HIV in-utero transmission
  - 19% in-utero infection rate among 42 HIV/TB pregnant women compared to 5-10% in HIV
    - Patients who have access to HAART have perinatal transmission of <1%

Pillay T et al. Lancet Infect Dis. 2004;4(3):155-65
Jones JL et al. Int J Tuberc Lung Dis. 2000 Nov;4(11):1026-31
De Cock et al. JAMA 2000;283:1175-82
European Collaborative Study. Clin Infect Dis. 2005;40(3):458-65

What are the risks?



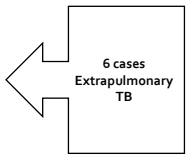
http://memory.loc.gov/ammem/wpaposters/wpahome.html

Tuberculosis in Pregnancy

- **Latent TB:**
  - **No increased risk to fetus in utero**
  - **Postpartum risk of developing active TB**
- **Active TB:**
  - **Complications are controversial**

Active TB in pregnancy

- **Higher prevalence than expected in epidemic communities**
  - **New York City 1985-1992**
    - **Kings County Hospital and Saint Vincent's Hospital**
    - **16 cases of active TB**
      - **10 pulmonary TB**
      - **2 meningeal TB**
      - **1 mediastinal**
      - **1 renal**
      - **1 gastrointestinal**
      - **1 pleural**



Margono F et al. Obstet Gynecol 1994;83:911-4

Pulmonary Tuberculosis in

Study	Figueroa-Damian et al	Jana N et al	Schaefer G et al	Bejerkedal T et al	Ratner B et al
Number	35	79	68	542	55
Year of study	2001	1994	1975	1975	1951
Origin	Mexico	India	New York	Norway	New York
Prematurity	↑	↑	↔	↔	↑
Low birth weight	↑	↑	↔	↔	N/A
IUGR	↔	↑	N/A	N/A	N/A
Perinatal death	↑	↑	N/A*	↔	N/A*
Fetal distress	N/A	↑	N/A	N/A	N/A
Medical complications	↔	N/A	N/A	↑	N/A

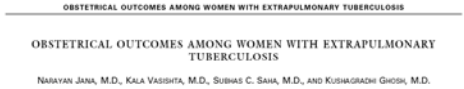
*Cases to be related to prematurity

<10th %ile

Figueroa-Damian R et al. Archives of Med Research 2001;32:66-69
Jana N et al. Int J Gynaecol Obstet 1994 Feb;44(2):119-24
Ratner B et al. Am J Dis Child 1951;81:471
Schaefer G et al. Obstet Gynecol 1975;46:706
Bjerkedal T et al. Scand J Respir Dis 1975;56:245

Extrapulmonary TB

- **Extrapulmonary TB are associated with adverse maternal and neonatal outcomes**


OBSTETRICAL OUTCOMES AMONG WOMEN WITH EXTRAPULMONARY TUBERCULOSIS

OBSTETRICAL OUTCOMES AMONG WOMEN WITH EXTRAPULMONARY TUBERCULOSIS

NARAYAN JANA, M.D., KALA VASISHTA, M.D., SUBHAS C. SAHA, M.D., AND KUSHAGRADHI GHOSH, M.D.

- **In a report on the outcomes of 33 women with extrapulmonary TB:**
  - **1983-1993**
  - **29/33 were treated**
    - **Majority isoniazid, rifampin, and ethambutol for nine months**
  - **Compared with 132 healthy pregnant women**

Jana N et al. N Engl J Med. 1999;341:645–649

Extrapulmonary TB:
Complications

Extrapulmonary Site	Number of patients (%)	Clinical Presentation	Method of Diagnosis
Lymph nodes	12 (36)	Cervical lymphadenopathy, cold abcess and sinus discharge	Fine-needle or surgical biopsy
Intestines	9(27)	Subacute intestinal	Laparatomy or fine-
Sk			
Kidney	2(6)	perinephric abscess	intravenous pyelography
Meninges	2(6)	Fever and altered sensorium	Cerebrospinal fluid analysis
Endometrium	1(3)	Primary infertility	Endometrial biopsy

Extrapulmonary tuberculosis that is confined to the lymph nodes has no effect on obstetrical outcomes.

Jana N, et al. N Engl J Med 1999;341:645-9

Extrapulmonary TB:
Methods of Diagnosis

<2,500gm

Outcome	Lymph-Node TB	Other extra-pulmonary sites	Control	P-value
Mean duration of gestation (weeks)	38.9±1.5	38.6±2.1	38.8±1.7	NS
Mean birth weight (g)	2894±430	2617±540	2868±498	0.04
Prematurity	1 (8%)	2 (10%)	10 (8%)	NS
Low birth weight	1 (8%)	7 (33%)	14 (11%)	0.01
Apgar score ≤6 at 1 minute	1 (8%)	4 (19%)	4 (3%)	0.01
Congenital anomaly	0	2 (10%)	2 (2%)	NS
Perinatal death	0	2 (10%)	2 (2%)	NS

Jana N, et al. N Engl J Med 1999;341:645-9

Low Birth Weight

- Neonatal Complications:
  - Respiratory distress syndrome
  - Intraventricular hemorrhage (IVH)
  - Patent ductus arteriosus
  - Necrotizing enterocolitis
  - Retinopathy of prematurity
- Adult Complications:
  - Hypertension
  - Type 2 (adult-onset) diabetes
  - Heart disease
  - Birth were 10 times more likely to have metabolic syndrome

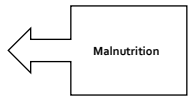
March of Dimes

Impact of Concurrent HIV and TB

National Library of Medicine

Impact of Concurrent HIV and TB

- Maternal outcomes
  - Increased maternal deaths (Zambia, Durban, Malawi)
    - Secondary to TB, penumonia, meningitis
  - Lower CD_4 counts (compared with TB or HIV alone)
  - Higher antenatal admissions for complications
- Fetal outcomes
  - Increased perinatal death
  - Increased prematurity
  - Increased low birthweight
  - Increased SGA
  - Increased TB and HIV transmission to infant



Ahmed Y et al. Int J Tuberc Lung Dis 1999;3:675-80
Khan M et al. AIDS 2001;15:1857-63
Adhikari M et al. Pediatr Infect Dis J 1997;16:1108-12
Wiebanga JE et al. Malawi Med J 1992;8:19-23
Pillay T et al. Lancet Infect Dis. 2004;4(3):155-65

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Pregnancy in the US

- 6.4+ million pregnancies in 2005
  - 49-65% are unintended
  - 4.14 million live births
  - 1.21 million induced abortions
  - 1.06 million fetal losses
- Approximately 13% of all pregnant women are uninsured

http://www.cdc.gov/nchs/data/nvsr/nvsr58/nvsr58_04.pdf

Pregnancy in the US

- Uninsured pregnant women:
  - Less likely to seek prenatal care in the first trimester
  - Less likely to receive the optimal number of visits during their pregnancy
- 31% higher likelihood of experiencing an adverse health outcome after giving birth
- Universal Prenatal Care Assistance Program (PCAP) is underutilized
  - Patient awareness
  - Undocumented immigrants afraid of deportation

www.acog.org

Prenatal Visits

- Visits
  - <28 weeks: q 4 weeks
  - 28 –36 weeks: q 2 weeks
  - >36 weeks: q week

5-14 prenatal visits

- Ultrasound
  - First trimester (genetic screen 11-13weeks)
  - Second trimester anatomy scan (17-23 weeks)
  - Third trimester scans only if chronic disease or Size ≠ Date

www.acog.org

Prenatal Visits

- Blood pressure
- Weight
- Urine dip
  - Protein
  - Glucose
  - Ketones
- Fundal height
- Fetal heart rate
- Edema

http://memory.loc.gov/ammem/wpaposters/wpahome.html

Weight Gain in Pregnancy

TABLE S-1 New Recommendations for Total and Rate of Weight Gain During Pregnancy, by Prepregnancy BMI

	Total Weight Gain		Rates of Weight Gain* 2nd and 3rd Trimester	
Prepregnancy BMI	Range in kg	Range in lbs	Mean (range) in kg/week	Mean (range) in lbs/week
Underweight (< 18.5 kg/m²)	12.5-18	28-40	0.51 (0.44-0.58)	1 (1-1.3)
Normal weight (18.5-24.9 kg/m²)	11.5-16	25-35	0.42 (0.35-0.50)	1 (0.8-1)
Overweight (25.0-29.9 kg/m²)	7-11.5	15-25	0.28 (0.23-0.33)	0.6 (0.5-0.7)
Obese (≥ 30.0 kg/m²)	5-9	11-20	0.22 (0.17-0.27)	0.5 (0.4-0.6)

* Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997).

KM Rasmussen and AL Yaktine, Editors; Institute of Medicine, 2009

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Screening Strategy

- Unique time period in non US-born women
- Many non US-born women first access health care during pregnancy
  - Ideal time period to reach out to the family and community and provide screening and care to immigrant population

Medchill MT. Am J Obstet Gynecol. 1999;180(6 Pt 1):1579–1583

Screening Strategy: CDC and ACOG

- Women with HIV infection
- Close contact with individuals known or suspected to have tuberculosis
- Medical risk factors known to increase risk of disease if infected
  - Lymphoma, diabetes mellitus, chronic renal failure
  - Immunosuppression/chronic steroid use
  - Low BMI
- Born in country with high tuberculosis prevalence (HBC's)
- Medically underserved, low socioeconomic status
- Alcoholism
- Intravenous drug use
- Residents of long-term care facility
  - Correctional institutions
  - Mental institutions
  - Nursing homes and facilities
- Health care professional working in high risk health care facilities

CDC

ACOG Committee Health Opinion ,Number 452, December 2009

Screening Strategy

- Universal screening programs:
  - Programs in the setting of prenatal care clinics may be more effective than risk based programs
- In a New York City clinic setting with a large immigrant population, universal screening was to be highly effective
  - Resulted in high PPD read and treatment compliance
    - Hispanic and US-born women were less likely to be compliant
    - Asian women more likely to be compliant
  - Universal screening strategy also identified LTBI in 11.1% of US-born women
    - Compliance PP and chest X-ray was lower when compared with non US-born women

Medchill MT. Et al. Am J Obstet Gynecol. 1999;180(6 Pt 1): 1579–1583
Schwartz N et al. Am J Perinatol. 2009;26: 447–451

Screening/Testing Methods

http://memory.loc.gov/ammem/wpaposters/wpahome.html

Screening: Tuberculin Skin Test

- **The tuberculin skin test (TST) with Mantoux technique is the preferred tool to identify patients with LTBI**
  - **It has been validated for use in pregnant women**
- **Stimulate a T lymphocyte-mediated delayed type hypersensitivity response**
  - **Sensitization to mycobacterial antigens**
  - **Measurable cutaneous irritation 2 to 12 weeks after exposure**

CDC, ACOG

Screening: Tuberculin Skin Test

Induration (mm)	Risk factor
≥5	•HIV infection •Close contact of active contagious case •Abnormal chest x-ray with radiographic changes consistent with old TB •Immunosuppressed patients: TNF-alpha inhibitors, chemotherapy, organ transplantation, glucocorticoid treatment
≥10	•Persons with clinical conditions that increase the risk of reactivation: Silicosis, chronic renal failure requiring dialysis, diabetes mellitus, Some malignancies (leukemias,lymphomas, carcinoma of the head, neck, or lung) •Underweight (10% ideal body weight), malnutrioned (jejunoileal bypass) •Injection drug users •Children less than 4 y of age •Foreign born from countries with high incidence of TB (HBC's) •Residents and employees in high risk settings, such as prisons, jails, healthcare facilities, mycobacteriology labs, and homeless shelters
≥15	•Healthy US born persons with low likelihood of true TB infection

CDC, ACOG

Interferon-Gamma Release Assays

- **Interferon-gamma release assays (IGRAs)**
  - **Detection of cell-mediated immune response**
  - **A single specimen of whole blood is stimulated in vitro to antigens that are unique to M. tuberculosis**
- **Provides diagnostic accuracy:**
  - **In large multi-ethnic populations**
  - **Not affected by:**
    - **A history of BCG vaccine**
    - **Prior infection with nontuberculous mycobacteria**
- **Theoretical compliance is 100% of patients,**
  - **True screening rate may be as low as 84% owing to phlebotomy failure or clotted specimens**

Interferon-Gamma Release Assays

- **The US Food and Drug Administration has approved the use of the QuantiFERON®-TB Gold (QFT-GIT) assay**
  - **Particularly in patients exposed to BCG vaccine**
- **Supported by the CDC as the primary screening tool for LTBI**
  - **May be used in all circumstances for which the Mantoux TST is indicated**

CDC, FDA
www.cellestis.com

Interferon-Gamma Release Assays:
In Pregancy

Use of the QuantiFERON®-TB Gold Assay in Pregnant Patients

Bassem M.Chehab, M.D.[1], K. James Kallail, Ph.D.[2], Riad O. El Fakih, M.D.[3], Rosalee E. Zackula, M.A.[4], Garold O. Minns, M.D.[2]
[1]University of Kansas School of Medicine-Kansas City
Department of Internal Medicine, Division of Cardiovascular Diseases
[2]University of Kansas School of Medicine-Wichita
Department of Internal Medicine
[3]University of Oklahoma College of Medicine
Department of Internal Medicine
[4]University of Kansas School of Medicine-Wichita
Office of Research

Chehab BM. Et al. KJM 2010; 3(2):24-30

Interferon-Gamma Release Assays

- **152 women between ages 18 and 45**
  - **HIV negative**
  - **Concordant results between the tests were shown in 131 subjects (86.2%)**
    - **Pregnant women, 91.2% had concordant results**
    - **Non-pregnant women, 76% had concordant results**
      - **Significantly more discordant results occurred in non-pregnant women (p<.022).**
- **Conclusion:**
  - **QuantiFERON®-TB Gold assay is accurate to use in pregnant women**
  - **"The decision to use either test in pregnant women should be based mainly on the compliance of the patient to return to have the TST read"**

Chehab BM. Et al. KJM 2010; 3(2):24-30

Interferon-Gamma Release Assays

MAJOR ARTICLE

Latent Tuberculosis Detection by Interferon γ Release Assay during Pregnancy Predicts Active Tuberculosis and Mortality in Human Immunodeficiency Virus Type 1–Infected Women and Their Children

Sasi Jonnalagadda,[1] Barbara Lohman Payne,[1a] Elizabeth Brown,[1] Dalton Wamalwa,[2] Elizabeth Maleche Obimbo,[2] Maxwel Mujwa,[2] Carey Farquhar,[1,3] Phelgona Otieno,[2] Dorothy Mbori-Ngacha,[2] and Grace John-Stewart[1,4]
Departments of [1]Epidemiology, [2]Biostatistics, [3]Medicine, [4]Global Health, and [5]Pathobiology, University of Washington, Seattle; [6]Department of Paediatrics, University of Nairobi, and [7]Kenya Medical Research Institute, Nairobi, Kenya

- **333 women tested (cryopreserved blood)**
  - **52 (15.6%) had indeterminate IGRA results**
  - **281 women with interpretable results**

Jonnalagadda S et al. J Infect Dis. 2010 Dec 15;202(12):1826-35.

Interferon-Gamma Release Assays

- **120 (42.7%) Positive**
  - **Associated with a 4.5-fold increased risk of active tuberculosis (aHR 4.5; 95% CI, 1.1-18.0)**
  - **In with with CD4 cell count, <250 cells/µL, positive IGRA results were associated with increased:**
    - **Maternal mortality (aHR 3.5; 95% CI, 1.02-12.1)**
    - **Maternal active TB or mortality (aHR 5.2; 95% CI, 1.7-15.6)**
    - **Infant active TB or mortality (aHR 3.0; 95% CI, 1.0-8.9)**
- **CONCLUSION:**
  - **"Positive IGRA results for HIV-1-infected pregnant women were associated with postpartum active tuberculosis and mortality among mothers and their infants."**

Jonnalagadda S et al. J Infect Dis. 2010 Dec 15;202(12):1826-35.

After a Positive Screening Test

- **Chest X-Ray**
- **Reassess for evidence of active TB**
- **Encourage family to be screened**

Diagnostic Imaging in Pregnancy

- **American College of radiology and American Congress of Obstetricians and Gynecologists**
  - **"No single diagnostic x-ray results in radiation exposure to a degree that threatens the developing preembryo, embryo, or fetus."**

ACOG Committee Opinion. Number 299, September 2004
Brent RL. Semin Oncol. 1989;16:347-68

Diagnostic Imaging in Pregnancy

Procedure	Fetal exposure
Chest X-ray (2 views)	0.02-0.02 mrad
Abdominal film (single view)	100 mrad
Hip film (single view)	200 mrad
Mammography	7-20 mrad
Intravenous pyelography	≥ 1 rad
Barium enema or small bowel series	2-4 rad
CT scan of head or chest	<1 rad
CT scan of abdomen and lumbar spine	3.5 rad
CT pelvimetry (low exposure technique)	250 mrad

Cunningham FG et al. Williams Obstetrics 21st ed. NY; McGraw-Hill; 2001.

Diagnostic Imaging in Pregnancy

- **1-2 rad = 1.5-2.0 fold increase the risk of leukemia**
  - **1 in 2,000 of leukemia exposed to ionizing radiation**
  - **1 in 3,000 background rate**
- **100 rad = 40% risk of mental retardation**
- **150 rad = 60% risk of mental retardation**

20-40 rad

Brent RL. Semin Oncol 1989;16:347–68.
Hall EJ. Radiographics 1991;11:509–18.

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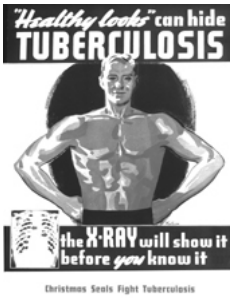
Barium enema or small bowel series	2-4 rad
CT scan of head or chest	<1 rad
CT scan of abdomen and lumbar spine	3.5 rad
CT pelvimetry (low exposure technique)	250 mrad

Cunningham FG et al. Williams Obstetrics 21st ed. NY; McGraw-Hill; 2001.

X-Ray in Pregnancy

- Informed consent
- Double lead shielding of abdomen
- After 15 weeks



http://www.nlm.nih.gov/exhibition/visualculture/tuberculosis.html

Testing in Pregnancy:
Cultures

- Culture
  - The gold standard for the diagnosis of pulmonary TB
  - Take 2 to 10 weeks
- Method:
  - Three sputum specimens
  - Sputum induction with inhalation of hypertonic saline or bronchoscopy (those who are unable to provide sputum)
  - An acid-fast bacillus stain (AFB) on a smear immediately.
    - Approximately 50%to80% of patients with pulmonary tuberculosis will have positive sputum smears.
  - Susceptibility testing should be conducted on the first positive culture

Diagnostic Standards and Classification of Tuberculosis in Adults and Children. Am J Respir Crit Care Med. 2000;161(4 Pt 1): 1376–1395.

Testing in Pregnancy:
Cultures

- Other sources for culture:
  - Early morning gastric aspirate
  - Pleural fluid
  - Blood or the body fluid
  - Tissue biopsy from the organ of clinical suspicion

Diagnostic Standards and Classification of Tuberculosis in Adults and Children. Am J Respir Crit Care Med. 2000;161(4 Pt 1): 1376–1395.

Testing in Pregnancy:
Cultures

Extrapulmonary Site	Method of Diagnosis
Lymph nodes	Fine-needle or surgical biopsy
Intestines	Laparatomy or fine-needle or endoscopic biopsy
Skeleton	Radiography of bones and joints
Kidney	Urinalysis and intravenous pyelography
Meninges	Cerebrospinal fluid analysis
Endometrium	Endometrial biopsy

Jana N, et al. N Engl J Med 1999;341:645-9

Testing in Pregnancy

- Rapid Assay
  - 2 to 7 hour turnaround time
  - Nucleic acid amplification technology (NAAT)
  - RNAbased
    - Gen-Probe MTD: Gen-Probe Incorporated, San Diego, CA
  - DNA PCR based
    - Amplicor Mycobacterium tuberculosis test: Roche Diagnostic Systems, Inc., Branchburg, NJ
    - Anyplex MDR TB test: detect the mutations of drug- resistant genes to rifampicin, (INH), and inhA promoter: (Seegene, Korea)
  - The sensitivity and specificity of the rapid assays have mixed reviews; therefore, these tests support but do not replace the standard culture
  - NAAT results may remain positive for months after treatment due to to the presence of dead mycobacterium

Diagnostic Standards and Classification of Tuberculosis in Adults and Children. Am J Respir Crit Care Med. 2000;161(4 Pt 1): 1376–1395.

Tuberculosis in Pregnancy

- Tuberculosis in Reproductive Aged Women
- Prenatal care in the United States
- Screening guidelines
- Signs and symptoms of TB in pregnancy
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- Family planning strategies
- Deficits in research

Signs & Symptoms

"Great Masquerader"

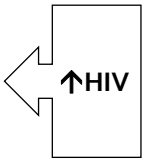
http://danceofthemasks.blogspot.com/2010/10/la-traviata-by-giuseppe-verdi.html

Signs

- The clinical presentation of TB in pregnancy is similar to that of nonpregnant women
  - Fever
  - Cough
  - Night sweats
  - Anorexia
  - Weight loss
  - General malaise
  - Weakness
- May have fewer of the typical TB symptoms
- 20-67% of pregnant patients with pulmonary TB unaware of their disease and without significant symptoms
- Pulmonary signs and symptoms are present in only one-third of the patients

Extrapulmonary TB:
Common Sites

- Lymph glands
- Pleura
- Genito-urinary tract:
  - Women: uterus and fallopean tubes
  - Men: Epididymis
  - Both sexes: renal and bladder
- Skeletal (both bones and joints)
- Meninges
- Bowel and/or peritoneum
- Pericardium
- Skin

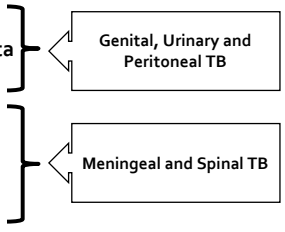


Extrapulmonary TB:
Presenting symptoms

- Numerous case reports of extrapulmonary presentations in pregnancy have been described in literature:
  - Symptoms of TB have significant overlap with symptoms of pregnancy
    - Fatigue, malaise, anorexia, nausea/ vomiting, weight loss and generalized abdominal or back discomfort
    - A dull pain in the retrosternal intrascapular area has been noted to be associated with worsening with swallowing
  - TB is misdiagnosed frequently, leading to a delay of treatment
    - Particularly in developed countries
  - Differential diagnosis of women with both common and rare symptoms should include TB

Extrapulmonary TB:
Presenting symptoms

- Of note, extrapulmonary TB has presented during pregnancy as:
  - Perineal abscesses
  - Degenerating leiomyomata
  - Ascites
  - Nausea and vomiting
  - Back pain
  - Neurologic deficits
  - Paraplegia



Tuberculosis in Pregnancy

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Latent TB in Pregnancy

- Post-partum treatment
- Exceptions:
  - Women with HIV
  - Women with close recent contact with a patient with active TB
  - Women who have had a skin test conversion within the last 2 years

Latent TB in Pregnancy: Why wait?

- Fear of tetatogenicity and toxicity to the fetus
- Low risk of latent TB to mother and fetus during the pregnancy
- The postponement of treatment to the postpartum period may result in delay and loss of follow-up for a large number of patients

Boggess KA et al. Obstet Gynecol. 2000;96(5 Pt 1):757–762
Cruz CA et al. Am J Obstet Gynecol.2005;192:1455–1457

Post-partum compliance

- Compliance with post-partum treatment:
  - In a San Francisco clinic population
    - 42% compliance with a follow-up visit in their TB clinic
    - 18% overall treatment completion rate among
  - Reasons for non-compliance:
    - Lack of treatment referral (31%)
    - Failure to keep referral appointment (18%)
    - Nonadherence with prescribed treatment (35%)

Cruz CA et al. Am J Obstet Gynecol.2005;192:1455–1457

Important Strategy:

- **Current approach strategy for LTBI:**
  - **Referral for treatment**
  - **Aggressive follow-up on the part of the prenatal care provider**
  - **Involvement of cultural case managers**
  - **Directly observed preventive therapy programs**

Boggess KA et al. Obstet Gynecol. 2000;96(5 Pt 1):757–762
Cruz CA et al. Am J Obstet Gynecol.2005;192:1455–1457

Why wait? "It's too expensive"

- **Cost-Effectiveness:**
  - **Markov decision-analysis model comparing antenatal to postpartum INH treatment strategies**
    - **Assumptions:**
      - **INH started at 20 weeks gestation for 6 months**
      - **67% completion rate**
      - **0.1% serious hepatitis**
      - **0 fetal deaths from hepatitis**
  - **Showed an overall marginal <u>increase in life expectancy</u> despite an increased risk of side effects in the antenatal treatment group**

Boggess KA et al. Obstet Gynecol. 2000;96(5 Pt 1):757–762

Cost-Analysis

Table 2. Predicted Cases of Tuberculosis Within the Cohort, Cases Secondary to Horizontal Transmission, Cases of Fatal and Nonfatal Hepatitis, and Discounted and Undiscounted Total Costs and Life Expectancy

Assumptions and Strategy	Cases of TB per 100,000 within the cohort	Additional cases secondary to horizontal transmission	Total TB cases prevented vs. no treatment	TB deaths	Cases of INH-related hepatitis	Hepatitis deaths	Undiscounted total costs ($)	Undiscounted life expectancy (y)	Total costs discounted at 3% annually ($)	Life expectancy discounted at 3% annually (y)	Incremental cost/life-year saved (discounted) ($)
Case-fatality rate 1%, ages 20–34											
Antepartum	1453	1744	4098	9	200	2	35.9 million	57.1	22.4 million	26.7	…
Postpartum	1789	2147	3359	12	90	0.9	50.1 million	57.1	34.4 million	26.7	Dominated
No treatment	3316	3979	…	21	0	0	75.1 million	57.1	44.2 million	26.7	Dominated
Case-fatality rate 0.1%, ages 20–34											
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Postpartum	1789	2147	3359	1.2	90	0.9	40.3 million	57.2	30.4 million	26.7	479,198
No treatment	3316	3979	…	2.1	0	0	57.2 million	57.2	57.3 million	26.7	1,324 million

TB = tuberculosis, INH = isoniazid.

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Postpartum	1789	2147	3359	1.2	90	0.9	40.3 million	57.2	30.4 million	26.7	479,198
No treatment	3316	3979	. . .	2.1	0	0	57.2 million	57.2	37.3 million	26.7	1,324 million

TB = tuberculosis, INH = isoniazid.

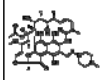
- Antepartum treatment was the least expensive.
- At 1% rate of case-fatality:
  - Antepartum treatment resulted in a marginal increase in life expectancy
- At 0.1% rate of case-fatality:
  - Antepartum treatment become the least advantageous strategy

Boggess KA et al. Obstet Gynecol. 2000;96(5 Pt 1):757–762

Active TB in Pregnancy

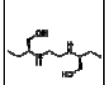
- **Treat! Treat! Treat!**
- **Maternal and fetal benefits outweigh any potential harm to fetus**
  - **Beware of organogenesis in early first trimester**

Treatment -1st Line Agents

Medication	Dose	Maternal Effects	Pregnancy
Isoniazid 	Latent TB*: 300 mg per day for 9 months Active TB*: 5 mg/kg per day After 2 mo: 15 mg/kg, twice a week * Take with 25mg Pyridoxine per day	Hepatic dysfunction **Hepatitis** Gastrointestinal upset Peripheral neuropathy Skin reactions Anemia, thrombocytopenia CNS symptoms	**Pregnancy risk factor – C** **Breastfeeding – Probably safe** Crosses placenta Embryocidal in rat and rabbit studies No teratogenic effect in humans identified
Rifampin **2 months** 	Latent TB: 10 mg/kg (maximum 600 mg) per day in patients who are not taking Isoniazid Active TB: 10 mg/kg (maximum 600 mg) per day Or 15 mg/kg 3 times a week	Hepatic dysfunction **Hepatitis** Skin reactions Gastrointestinal upset Anemia, thrombocytopenia Fever Flu-like symptoms	**Pregnancy risk factor – C** **Breastfeeding– Compatible** Crosses placenta Teratogenic in rat and mice studies in high doses No teratogenic effect in humans identified **Associated with neonatal hemolytic anemia. Recommend vitamin K to neonate at birth**

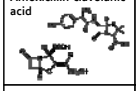
CDC, Micromedex
GG Briggs et al. Drugs in pregnancy and lactation: Eighth Ed. Lippincott Williams & Wilkins

Treatment -1st Line Agents

Medication	Dose	Maternal Effects	Pregnancy
Ethambutol 	Latent TB with HIV: 15 mg/kg per day Active TB: 15 mg/kg per day, 30 mg/kg per day for meningeal TB 30-50 mg/kg 2-3 times a week (extended for 12 months)	**Optic neuritis** Decreased color discrimination Skin reactions Gastrointestinal upset	**Pregnancy risk factor – C** **Breastfeeding–Compatible** Crosses placenta Teratogenic in animal studies in high doses No teratogenic effect in humans identified
Pyrazinamide 	Active TB: 25 mg/kg (maximum 2gm) per day Or 50 mg/kg 3 times a week	Hepatic dysfunction **Hepatitis** Gastrointestinal upset Arthalgia, Myalgia, Malaise Gout	**Pregnancy risk factor – ??C** **Breastfeeding –Probably safe** Limited data Not used in US No animal studies No teratogenic effect in humans reported

CDC, Micromedex
GG Briggs et al. Drugs in pregnancy and lactation: Eighth Ed. Lippincott Williams & Wilkins

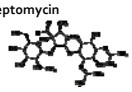
Second Line Agents (MDR-TB, XDR-TB)

Medication	Maternal Effects	Pregnancy
Fluoroquinolones Ciprofloxacin 500mg twice daily or ofloxacin 400 mg/day 	1% to 10%: dizziness, insomnia, nervousness, somnolence, fever, headache Rash , Nausea, diarrhea, elevation of liver enzymes	**Pregnancy risk factor – C** **Breastfeeding** - Manufacturer: not recommended, American Academy of Pediatrics: compatible in low doses Cipro crosses placenta **Animal studies ->damage articular cartilage and juvenile arthritis** Human exposure during the first trimester -> no musculoskeletal but a trend for higher rate of medical abortion
Amoxicillin-clavulanic acid 	>10%: Gastrointestinal effects 1% to 10%: Rash, urticaria, nausea, vomiting, vaginitis	**Pregnancy risk factor – B** **Breastfeeding** - Enters breast milk/use with caution There are no data on the use of clavulanic acid in early pregnancy In the second and third trimester, this has been used as antibacterial prophylaxis in preventing infection following premature rupture of membranes with an increased incidence of **necrotizing enterocolitis**
Paraaminosalicylic acid 	10-30% Gastrointestinal effects 5-10% hypersensitivity rash Rare: pericarditis, vasculitis, Encephalopathy, fever , goiter, agranulocytosis, anemia, leukopenia, thrombocytopenia , Hepatitis, jaundice	**Pregnancy risk factor – C** **Breastfeeding** - Enters breast milk/not recommended Collaborative Perinatal Project identified 43 women who had been exposed to the drug in the first trimester with 5 babies showing various malformations. A subsequent study identified an inconsistent association with limb and ear abnormalities

CDC, Micromedex

GG Briggs et al. Drugs in pregnancy and lactation: Eighth Ed. Lippincott Williams & Wilkins

Medications Not Used

Medication	Pregnancy
Streptomycin 	Pregnancy risk factor – D 1 in 6 risk of **hearing impairment and irreversible congenital deafness** in offspring of women who were treated with streptomycin in pregnancy (any trimester)

Robinson GC et al. N Engl J Med 1964; 271: 949-51
Varpela E, et al. Scand J Respir Dis 1969; 50: 101-9
Scheinhorn DJ et al. West J Med. 1977 Sep;127(3):195-8
Snider DE Jr et al. Rev Respir Dis 1980; 122: 65-79

Monitoring in Pregnancy

Medication	Monitoring	Special Consideration
Isoniazid	Liver function testing	Antacids reduce absorption Take with Pyridoxine
Rifampin	Liver function testing	Turns secretions orange Take on an empty stomach
Ethambutol	Check color vision and acuity	Unilateral optho exam
Pyrazinamide	Liver function testing Uric Acid	

Monitor Weight Gain

TABLE S-1 New Recommendations for Total and Rate of Weight Gain During Pregnancy, by Prepregnancy BMI

Prepregnancy BMI	Total Weight Gain: Range in kg	Total Weight Gain: Range in lbs	Rates of Weight Gain* 2nd and 3rd Trimester: Mean (range) in kg/week	Rates of Weight Gain* 2nd and 3rd Trimester: Mean (range) in lb/week
Underweight (< 18.5 kg/m²)	12.5-18	28-40	0.51 (0.44-0.58)	1 (1-1.3)
Normal weight (18.5-24.9 kg/m²)	11.5-16	25-35	0.42 (0.35-0.50)	1 (0.8-1)
Overweight (25.0-29.9 kg/m²)	7-11.5	15-25	0.28 (0.23-0.33)	0.6 (0.5-0.7)
Obese (≥ 30.0 kg/m²)	5-9	11-20	0.22 (0.17-0.27)	0.5 (0.4-0.6)

* Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997).

KM Rasmussen and AL Yaktine, Editors; Institute of Medicine, 2009

Tuberculosis in Pregnancy

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Breastfeeding

- Breastfeeding is the preferred method of feeding for newborns and infants
- The ACOG recommends that exclusive breastfeeding be continued until the infant is 6 months old

ACOG Committee Opinion. Number 361 • February 2007

Breastfeeding

- Breast milk does not contain tuberculosis bacilli
- TB is a respiratory disease transmitted by aerosol droplets
  - Concern for horizontal transmission

Breastfeeding

- Latent TB:
  - No contraindication to breastfeeding
- Active TB:
  - Highest risk periods for transmission from mother to baby
  - Close respiratory proximity to the baby
  - A mother with newly diagnosed untreated active disease should be separated from her infant to prevent respiratory exposure/transmission, regardless of mode of infant feeding
  - Resume her breast-feeding after anti-TB medications have begun and negative sputum cultures are documented

Breastfeeding: Exceptions

- Exceptions are women:
  - Who take street drugs or do not control alcohol use
  - Have an infant with galactosemia
  - Infected with human immunodeficiency virus (HIV) or human T-cell lymphotropic virus type I or type II
  - Active untreated tuberculosis
  - Active varicella
  - Active herpes simplex virus with breast lesions

ACOG Committee Opinion. Number 361 • February 2007

Postpartum Period

- Family planning strategies should be initiated during prenatal care
  - Give information about methods and services that will help them meet their reproductive goals
- Options include:
  - Nonhormonal methods
  - Hormonal methods
  - Lactational amenorrhea method

ACOG Committee Opinion. Number 361 • February 2007

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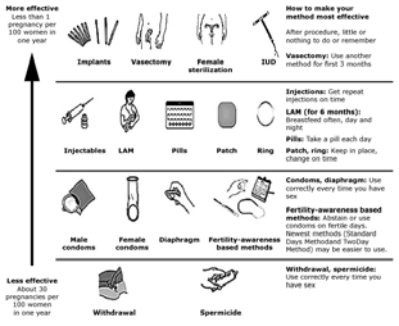
Contraception

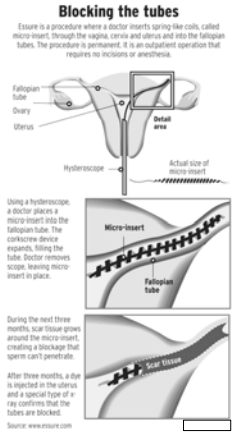


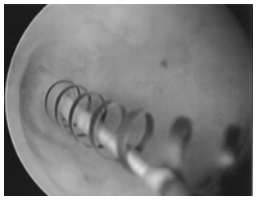
Surgical Contraception

- **Bilateral Tubal ligation**
  - **Post-partum mini-laparotomy**
  - **During cesarean delivery**
  - **Laparascopic**
- **Bilateral Tubal occlusion**
  - **Essure**

Surgical Contraception

www.essure.com





www.essure.com

Hormonal Contraception

- **Pills**
  - **Typical use: 92 %**
  - **Not contra-indicated with breast-feeding**
- **Progestin-only "mini" pill**
  - **Typical use: 92 %**
  - **Preferred method with breast-feeding**
- **Transdermal Patch**
  - **Typical use: 92 %**
- **Vaginal contraceptive ring "Nuvaring"**
  - **Typical use: 92 %**

Hormonal Contraception

- **Implants:**
  - **Implanon (subcutaneous)**
    - **Typical use: 99%**
    - **Single-rod progestin implant**
    - **Contraception is provided for 3years**
    - **Protection from pregnancy occurs within 24 hours**
    - **Fertility returns rapidly after removal of the rod**
    - **Pregnancies have been reported postmarketing**
      - **Manufacturer: 0.38 pregnancies/100 women-years of use**
  - **Mirena (intrauterine)**
    - **Typical use: 99%**
    - **Intrauterine Levonorgestrel device**
    - **Approved for 5 years of use**
    - **Benefit of decreased menstrual flow or amenorrhea**

Other forms of Contraception

- **Condoms**
  - **Male**
    - **Typical use: 85%**
  - **Female**
    - **Typical use: 79%**
- **Copper IUD**
  - **Approved for 10 years of use**
  - **Typical use: 97-99%**
- **Cervical Cap**
  - **-Typical use: 84%**
- **Spermicides**
  - **Typical use: 78-90%**
- **Withdrawal method**
  - **Not reliable: 73-80%**
- **Amenorrhea method**
  - The woman is less than six months postpartum
  - She is breastfeeding exclusively (ie, not providing food or other liquid to the infant)
  - She is amenorrheic
  - Typical use: 95%
- **Vasectomy**
  - **Typical use: 99%**

Infertility

- **1% and 10% of women with infertility have genital TB**
- **Genitourinary TB is usually caused by reactivation:**
  - **≤ 2 years following the primary infection by *M. tuberculosis***
  - **Hematogenous or gastrointestinal spread**

Nezar M et al. Arch Gynecol Obstet. 2009;280:787–791
Das P et al. Indian J Urol. 2008 Jul;24(3):356-62

Infertility

- **Women (cohort of 420 women) undergoing diagnostic laparoscopy for infertility:**
  - **PCR of peritoneal fluid and biopsy specimens identified evidence of TB in 5.7%**
- **Women with nongenital tuberculosis and genital tuberculosis frequently have menstrual disorders:**
  - **Amenorrhea**
  - **Oligomenorrhea**

Nezar M et al. Arch Gynecol Obstet. 2009;280:787–791.

Infertility

- Lead to salpingitis & impairment of cilia
  - Overcome with artificial reproductive technology (ART)
- May be of concern in the future if undiagnosed
  - -Presentation when immuno-compromised

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Research

- Evaluation of drug safety and pharmacokinetics in pregnancy
  - PZA
- Assessment of drug resistance
  - Emerging drug resistance during pregnancy or the postpartum period
- Clinical outcomes of treated extrapulmonary TB

Research

- Cost-Analysis
  - Antepartum versus postpartum treatment
    - Adherence
  - HIV-1 infected women
- Use of QuantiFERON®-TB rapid testing
  - Large scale for compliance
  - Non-cryopreserved blood
  - At delivery to late presenting women
    - Similar to Rapid HIV