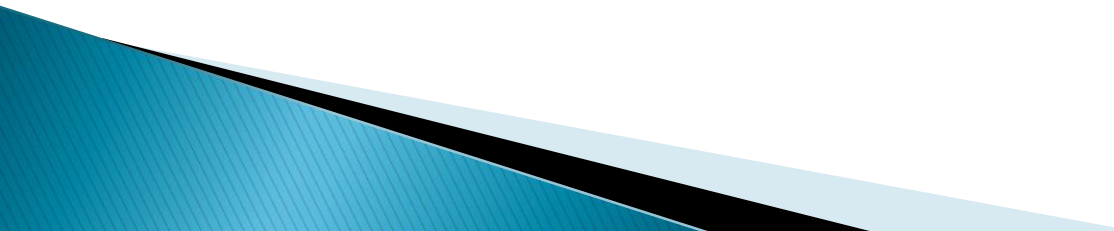
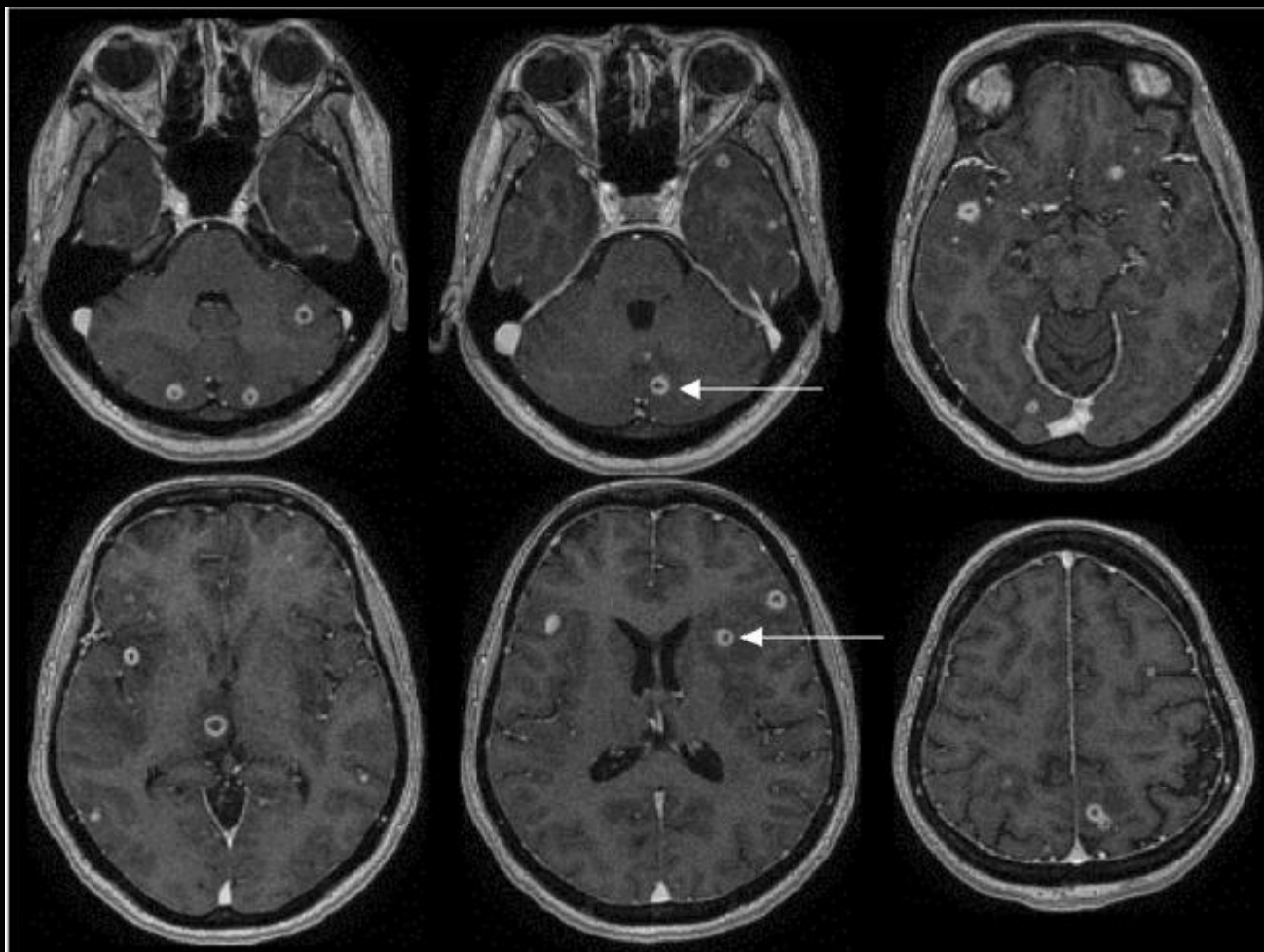
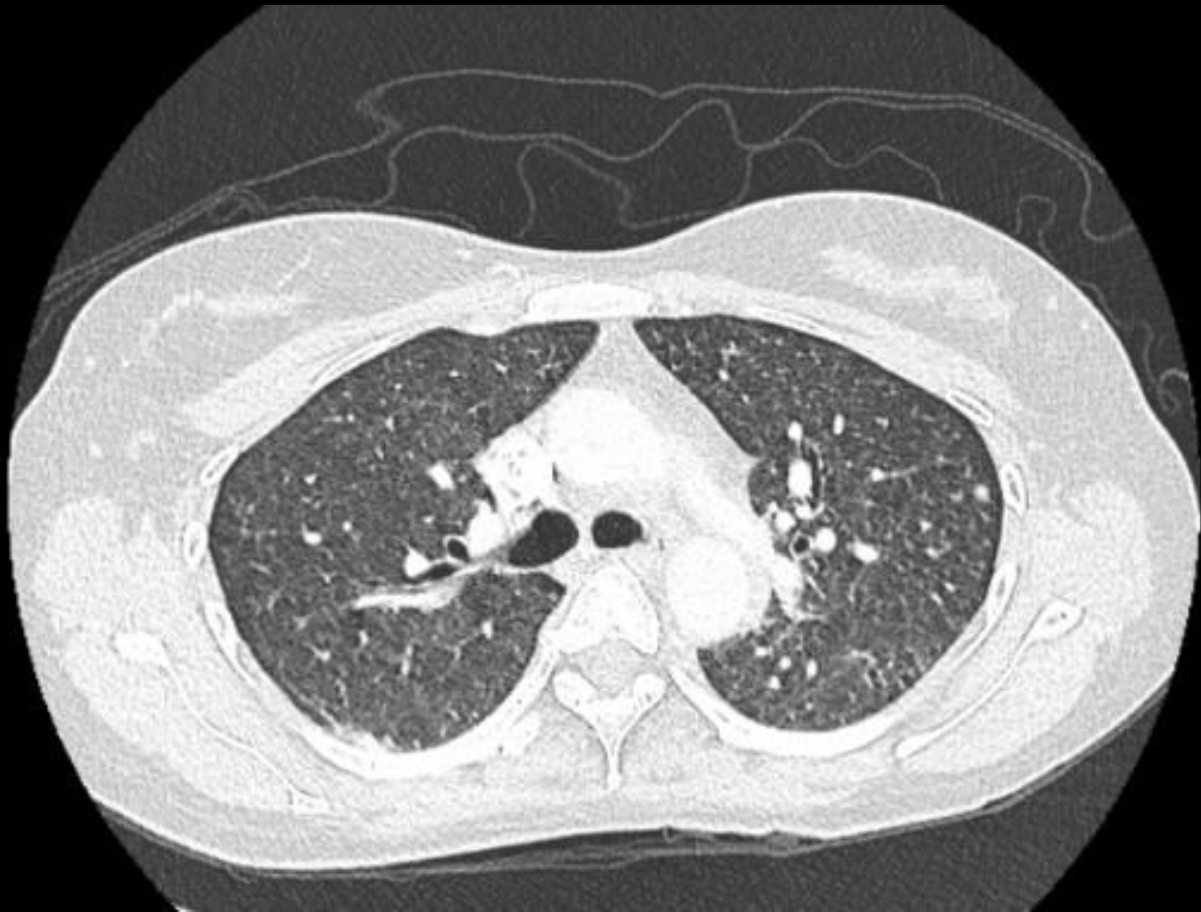


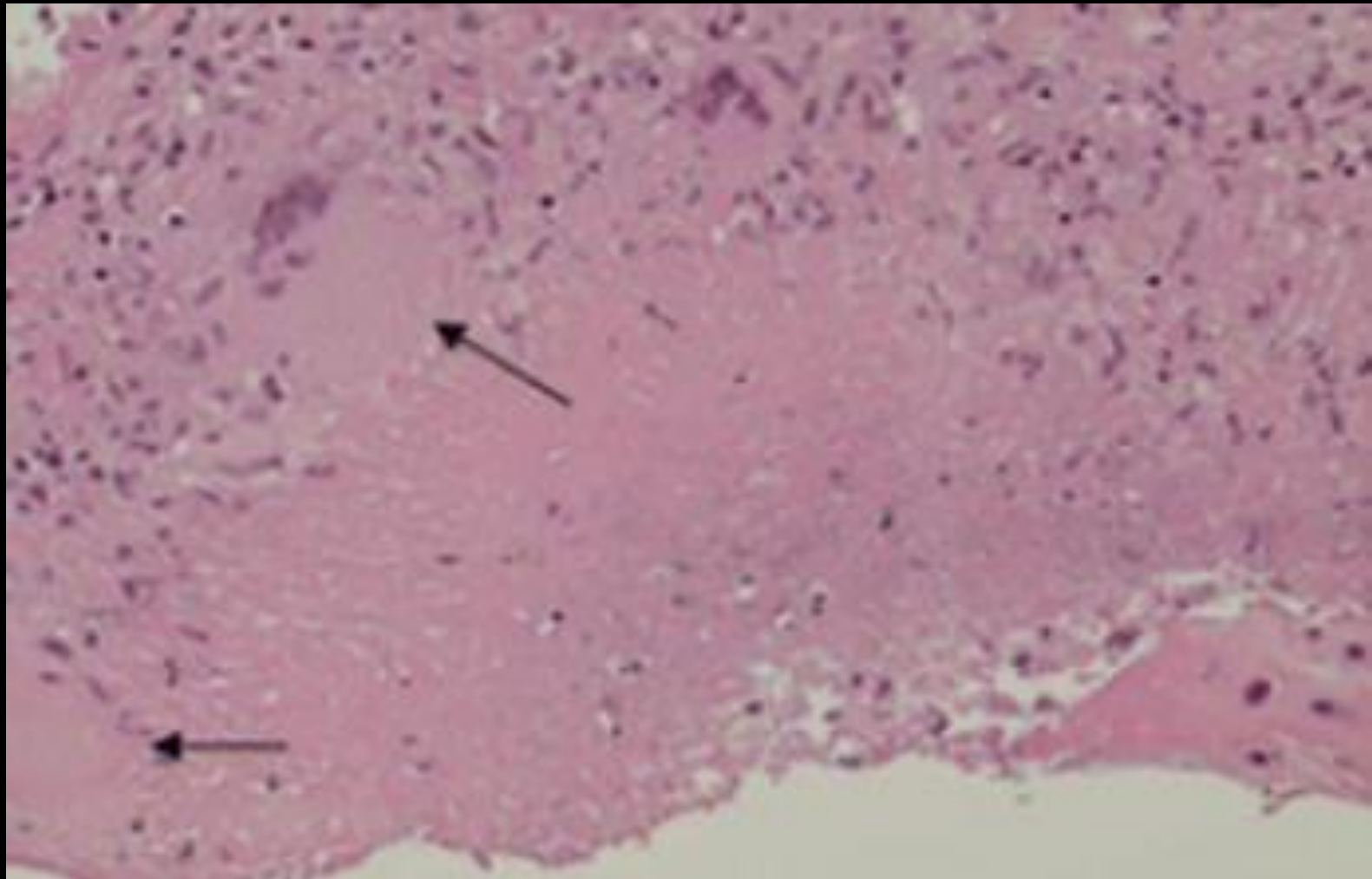
# TB, infertility, and congenital TB

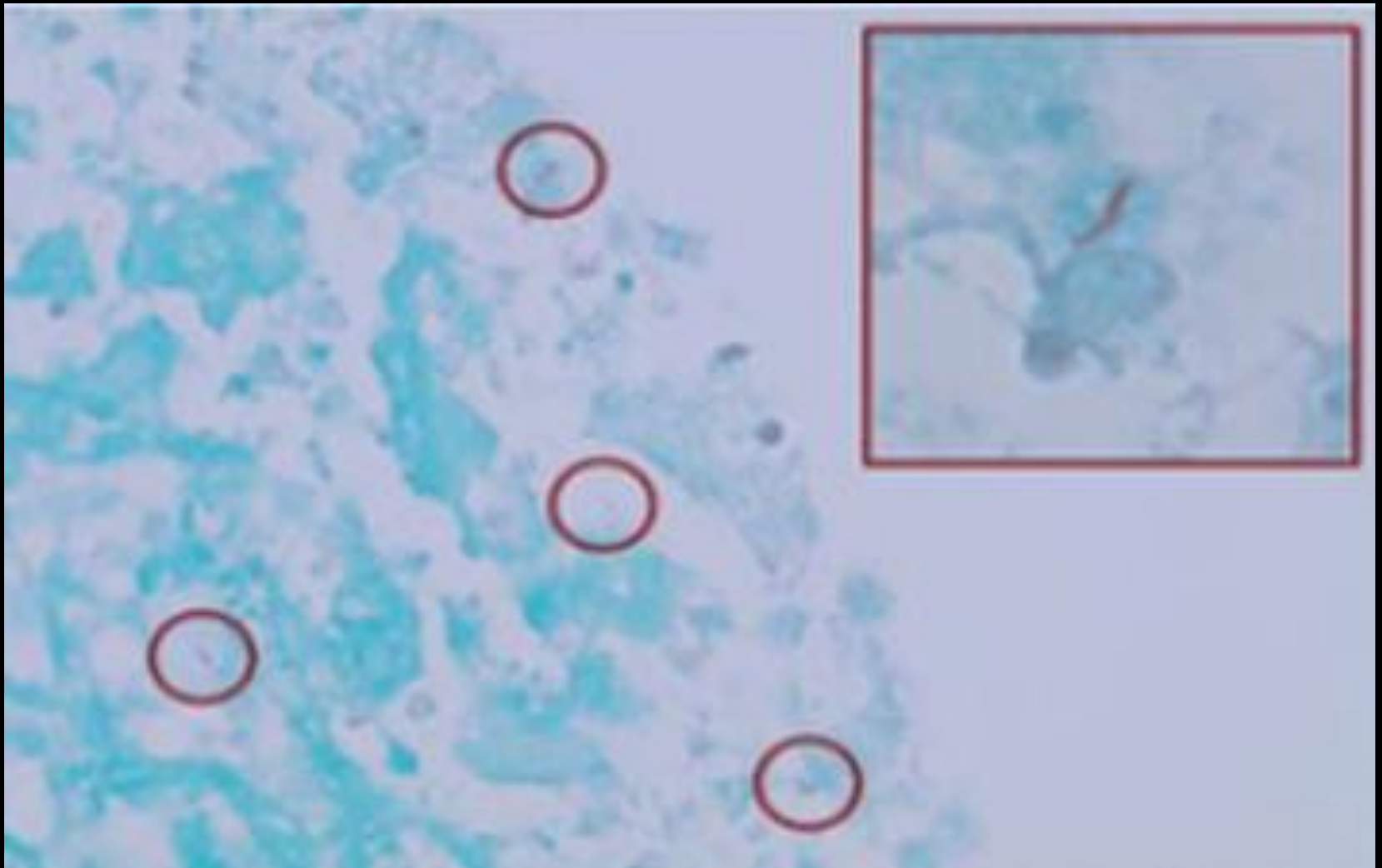
Dr Dina Fisher MD, MSC, FRCPC  
NAR IUATLD Chicago March 2018

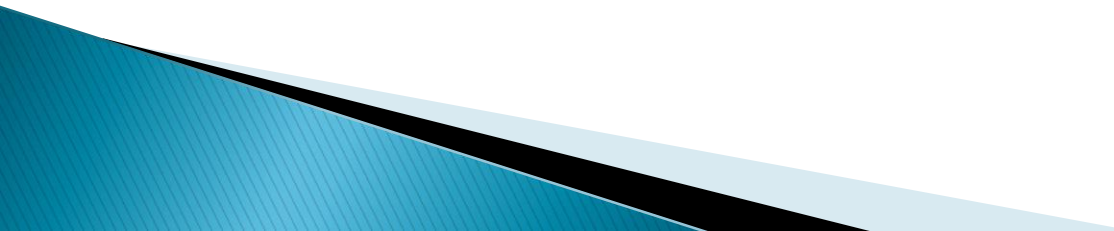
- ▶ **38 year old female from SouthEast Asia underwent IVF/ET after standard infertility diagnostic assessment**
  - ▶ **Pregnancy was complicated by**
    - Premature rupture of membranes
    - Oligohydraminos
  - ▶ **Presented to hospital with new onset seizures**
- 









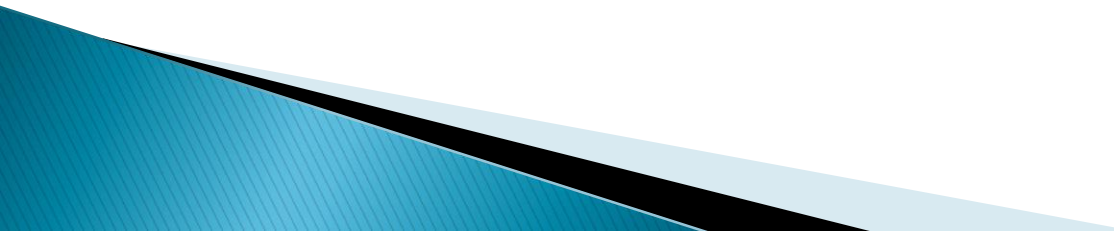
- ▶ Urine smear positive and culture positive for fully-susceptible *mycobacterium tuberculosis*
  - ▶ Sputum smear negative, culture positive for fully susceptible *mycobacterium tuberculosis*
  - ▶ Started on standard TB treatment/steroids with good clinical outcome
- 

EC





# IVF-related Congenital TB

- ▶ Infant born at 24 weeks gestation
  - ▶ Treated for congenital TB without culture confirmation
  - ▶ Multiple complications with 14 month hospitalization
- 

# Female Genital Tuberculosis (FGTB)

- ▶ **15-20 % of cases of EPTB are GU TB**
  - Fallopian tube involvement (90%)
  - Endometrial dysfunction (50-70%)
  - Ovarian dysfunction (20-30%)
- ▶ **10-85 % are infertile (40-60%)**

# Female Genital Tuberculosis (FGTB)

## ▶ Attending Infertility Clinics

- 1 % in United states
- 3 – 26 % High incidence TB countries
- 48.5 % tubal factor infertility in high incidence countries

## How to investigate :

- ▶ Several studies have failed to identify history/physical exam findings that differentiate between TB and non-TB causes of infertility

# How to investigate :

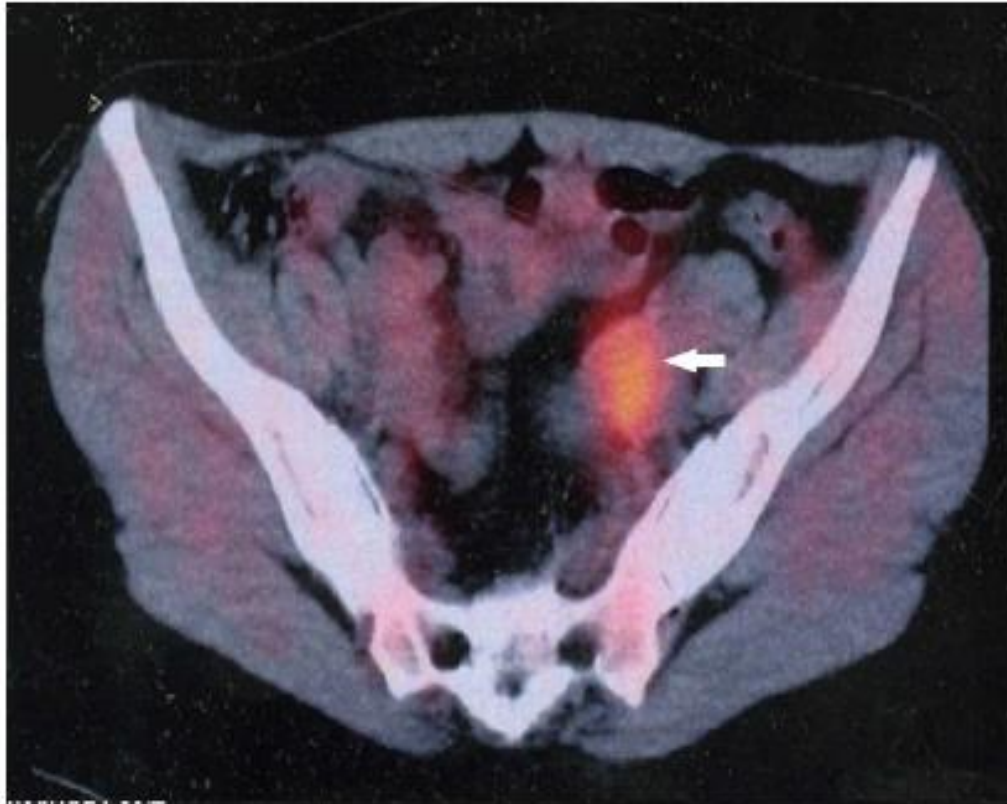
- ▶ Older, small studies in TB endemic countries have demonstrate high yield of menstrual fluid sampling for mycobacterial culture

	+	-
Sample examination in infertility patients		
Menstrual fluid culture ( <i>N</i> = 40)	40 (100%)	0
Curettage sample culture ( <i>N</i> = 11)	0	11
Curettage sample histology ( <i>N</i> = 17)	0	17
Histological examination of entire upper genital tract ( <i>N</i> = 4)		
Fallopian tubes	4	0
Ovaries	2	2
Endometrium	2	2
Cervix	0	4
Myometrium	0	4
Ziehl-Neelsen staining on more than one specimen from same patient ( <i>N</i> = 17)		
All positive	8	
All negative	4	
Some positive and some negative	5	

# How to investigate :

- ▶ Consider diagnosis based on diagnostic imaging abnormalities, specifically tubal involvement
- ▶ Consider diagnosis based on hysteroscopy/laparoscopy appearance

# How to investigate :



**Fig. 1** PET scan showing *left* tubo-ovarian mass (*arrow*) with increase FDG uptake in FGTB case

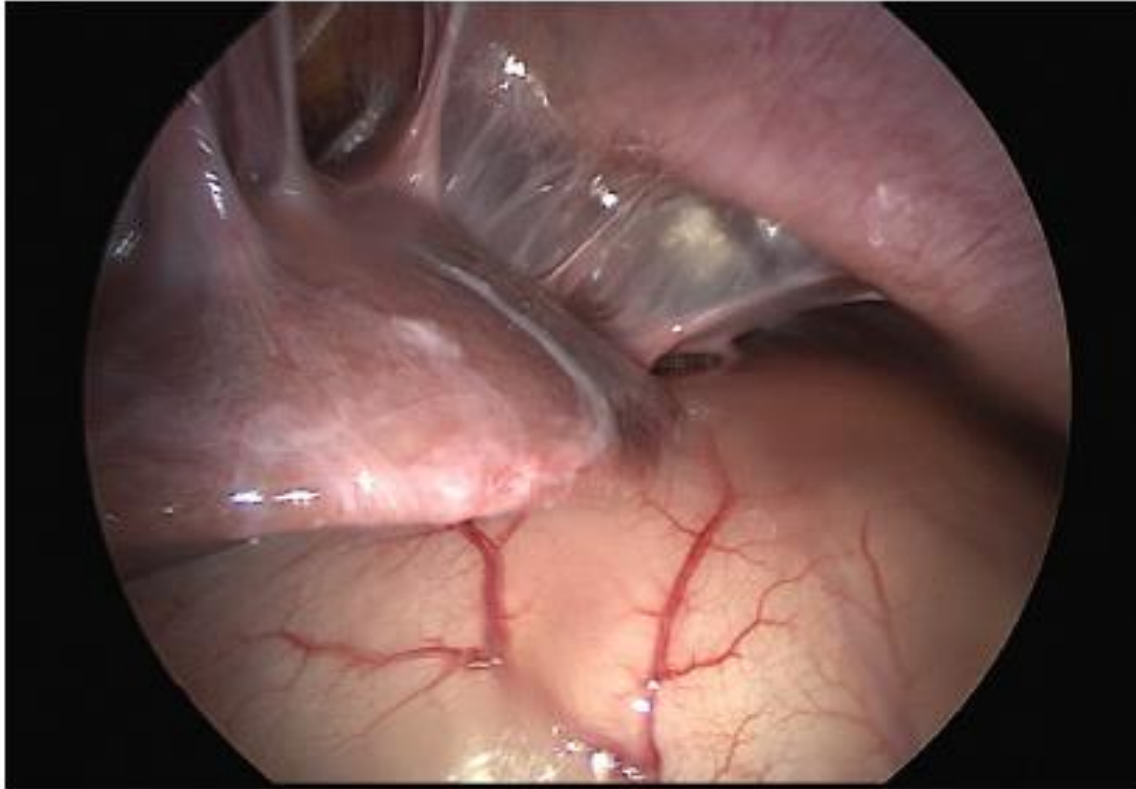
# How to investigate :



**Fig. 2** Hysteroscopy showing grade 2 adhesions and pale endometrium in a FGTB case



# How to investigate :



**Fig. 3** Laparoscopic findings showing Fitz-Hugh–Curtis syndrome in FGTB case

# How to investigate :



**Fig. 4** Laparoscopic findings showing tubercles and caseous nodules (*arrows*) in FG TB case

# How to investigate :

**Table 1. Laparoscopy findings.**

<b>Findings</b>	<b>Previous laparoscopy (n=23)</b>	<b>Laparoscopy during study (n=25)</b>
Tubal block	12	21
Adhesions	8	13
Frozen pelvis	5	5
Hydrosalpinx	5	9
Tubercular salpingitis	10	12

Some patients had more than one abnormal finding

# How to investigate - Biopsy :

- ▶ Infertility Clinic India (endometrial and laparoscopic)
  - 40% diagnosed on histopathology
  - 16% diagnosed on AFB smear
  - 40% on mycobacterial culture result
  - 50 % on PCR result

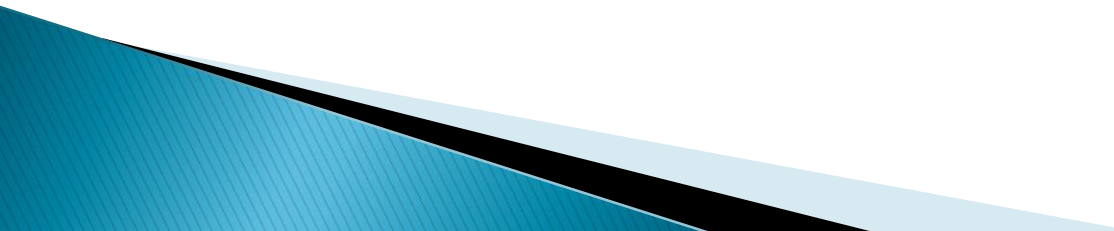
# How to investigate :

**Table 1** The results of investigations.

Test	No. of cases	+ ve results	-ve results	<i>P</i> value
HPE	61	34 (55.7)	27 (44.3)	.104
PCR	34	15 (44.1)	19 (55.9)	.136
Laparoscopy	33	19 (57.6)	14 (42.4)	.1084
HSG	61	8 (5.4)	140 (94.6)	.0001
Tuberculin test	61	26 (42.6)	35 (57.3)	.052
ESR	61	21 (34.4)	40 (65.6)	.000
Culture	19	5 (26.3)	14 (73.7)	.0017
GTB	61	47 (77.0)	14 (22.9)	.0001

HPE: histopathological examination; PCR: polymerase chain reaction; HSG: hysterosalpingography; ESR: erythrocyte sedimentation rate; GTB: genital tuberculosis.

# Guideline Development :

- ▶ Variability in incidence of FGTB
  - ▶ Lack of data in best testing/screening strategy for FGTB
  - ▶ Invasive diagnostics to obtain confirmed diagnosis
  - ▶ Treatment of FGTB does not lead to improved fertility and may delay IVF-ET treatment
- 

## 2015 NATIONAL SUMMARY

Technical terms are defined in the Glossary of Terms (Appendix A, pages 63–66). For more information on how to interpret the statistics in this table, see pages 11–20 in the *2015 Assisted Reproductive Technology Fertility Clinic Success Rates Report*.

### 2015 ART CYCLE PROFILE

Type of ART and Procedural Factors <sup>a</sup>				Patient Diagnosis <sup>b</sup>				
IVF	>99%	With ICSI	69%	Tubal factor	13%	Uterine factor	6%	<i>Multiple Factors:</i> Female factors only 12% Female & male factors 17%
Unstimulated	1%	PGD/PGS	5%	Ovulatory dysfunction	15%	Male factor	33%	
Used gestational carrier	<1%			Diminished ovarian reserve	31%	Other factor	17%	
				Endometriosis	8%	Unknown factor	13%	

### 2015 ART SUCCESS RATES<sup>c</sup>

Total number of cycles<sup>d</sup>: 231,936 (includes 4,003 cycle[s] using frozen eggs)

Type of Cycle	Age of Woman					
	<35	35–37	38–40	41–42	43–44	>44
<b>Fresh Embryos from Nondonor Eggs</b>						
Number of cycles	39,302	19,023	17,191	8,872	4,940	1,762
Percentage of cancellations before retrieval (%)	6.5	10.6	15.3	19.6	21.9	23.8
Average number of embryos transferred	1.6	1.8	2.1	2.5	2.6	2.4
Percentage of embryos transferred resulting in implantation (%)	41.3	32.1	21.0	10.7	5.2	1.9
Percentage of elective single embryo transfers (eSET) (%)	34.7	20.8	8.1	2.4	0.8	1.1
<b>Outcomes per Cycle</b>						
Percentage of cycles resulting in term, normal weight & singleton live births <sup>e</sup> (%)	21.3	17.0	11.1	5.7	2.3	0.6

**Table 2. Results of IVF- ET in patients with genital tuberculosis.**

	<b>Frydman et al <sup>6</sup></b>	<b>Parikh et al <sup>7</sup></b>	<b>Soussis et al <sup>11</sup></b>	<b>Marcus et al <sup>12</sup></b>	<b>Gurgan et al <sup>13</sup></b>	<b>Present study</b>
Number of patients	20	30	13	10	24	49
Number of transfers	32	NM	21	31	44	89
Pregnancy rate per transfer	8/32 (25%)	6/3 (16%)	6/21 (28.6%)	6/31 (19.35%)	4/44 (9.1%)	17/89 (19.1%)
Delivery/Number of patients	6/20 (30%)	5/30 (16.7%)	4/13 (30.7%)	4/10 (40%)	1/24 (4.2%)	12/49 (24.5%)
Abortion/Number of patients	1/20 (5%)	- -	2/13 (15.4%)	1/10 (10%)	3/24 (12.5%)	5/49 (10.2%)
Ectopic pregnancy/Number of patients	1/20 (5%)	1/30 (3.3%)	- -	1/30 (10%)	- -	- -

NM - Not Mentioned



# Guidelines :

- ▶ **ASRM** ( American Society for Reproductive Medicine)
  - No comment on investigations for FGFB
  - No role for routine hysteroscopy/laparoscopy/endometrial biopsy in the assessment of the infertile female
- ▶ **IFFS** (International Federation of Fertility Societies)
  - Test for infectious diseases associated with infertility
- ▶ **FIGO** (International Federation of Gynecology and Obstetrics)
  - Test for infectious diseases associated with infertility
- ▶ **ICMR** (Indian Council for Medical Research)
  - Consider hysteroscopy/laparoscopy and sampling for MTB
- ▶ **ESHRE** (European Society of Human Reproduction and Embryology)

Because GU TB causes infertility, rates of CTB have been low. However, as illustrated in this case series, CTB can occur after IVF in high-risk women in TB non-endemic regions. Currently, TB testing is not included in the standard diagnostic evaluation of infertile females,<sup>16</sup> and it is not included in the Food and Drug Administration-mandated testing for donors of human cells and tissues, which applies to reproductive tissue donation.<sup>17</sup> However, this case series highlights first that physicians in the reproductive community should perform TB testing in infertile women with risk factors. Multiple diagnostic modalities, including TST, interferon gamma release assay, imaging and endometrial biopsy with AFB smear and culture should be used. Second, neonatologists and pediatricians should maintain a high index of suspicion for CTB in infants with progressive, unexplained respiratory illness who were conceived by IVF in mothers with TB risk factors.

# Guideline Development :

- ▶ Better data to inform recommendations
- ▶ Need to consider pre-test probability of FG TB when developing guidelines
  - Difficult to develop international guidelines that are applicable to all countries

# Suggestions :

- ▶ Who to Screen
  - Individuals from high TB incidence countries
  - Tubal factor infertility
- ▶ How to Screen
  - Limit invasiveness of testing
- ▶ Number needed to screen to detect one case of FG TB
- ▶ Cost of Screening
  - In many countries cost of infertility treatment is borne by infertile couple and not included in public-payer systems