QJM Advance Access published January 31, 2015

TITLE: Untreated Chronic Tuberculous Salpingitis followed by successful IVF Conception and Congenital Tuberculosis.

AUTHORS: Laura E. Gleeson[1, 2], Chithra Varghese[1], Emer Ryan[3], Maria Kane[1], Colm McDonald[1], Noreen Gleeson[4], Anne-Marie McLaughlin[1], Karina Butler[3], Patrick Gavin[3], Joseph Keane[1, 2].

[1] Department of Respiratory Medicine, St James's Hospital, James's Street, Dublin 8

[2] Department of Clinical Medicine, Trinity College Dublin, St James's Hospital, James's Street, Dublin 8

[3] Department of Infectious Diseases, Our Lady Children's Hospital, Crumlin, Dublin 12

[4] Department of Gynaecology, St James's Hospital, James's Street, Dublin 8

CORRESPONDANCE:

CORRESPONDING AUTHOR:

Dr Laura E Gleeson, MB; **Email:** gleesole@tcd.ie

ALTERNATE CORRESPONDING AUTHOR:

Prof Joseph Keane, MD; **Email:** jkeane@stjames.ie

WORD COUNT:

Abstract: 77 words

Learning Point for Clinicians: 47 words

Case Report and Discussion: 654 words

Figure Legend: 28 words

ABSTRACT:

We report a remarkable case of missed tuberculous salpingitis in a healthcare worker in a low-incidence country, followed by successful *in vitro* Fertilisation conception with persistent endometrial tuberculosis, presenting as congenital tuberculosis in the infant. Though female reproductive tract tuberculosis is rare in the developed world, this case highlights the serious sequelae and diagnostic challenges associated with vertical transmission, rendering it an important differential to include in the work-up of any gynaecological presentation in a healthcare worker.

LEARNING POINT FOR CLINICIANS:

Female reproductive tract tuberculosis (TB) is rare in the developed world and its diagnosis is challenging. However, this case illustrates the importance of including female reproductive tract TB in the differential for any gynaecological complaint in healthcare workers, due to the high mortality associated with vertical transmission.

CASE:

A 4-month-old Caucasian girl presented with a cyanotic episode requiring immediate intubation, following two weeks history of cough and fever, and failure-to-thrive since birth. She was born 2.9kg at full term via uncomplicated vaginal delivery. She was up-to-date with the UK vaccination schedule. On physical examination, there were delayed developmental milestones, muscle wasting, generalised lymphadenopathy and hepatosplenomegaly. Peripheral chorioretinitis was evident on fundoscopy.

Chest radiograph showed widespread bilateral nodular infiltrates. Centrally-necrotic cervical lymph nodes and massive hepatosplenomegaly were seen on ultrasound. Routine blood tests demonstrated elevated liver transaminases (AST 118IU/L, ALT 341IU/L) and acute phase reactants (CRP 55mg/L, ESR 28mm/hr), but serological tests for HIV, CMV and toxoplasmosis were negative. CSF analysis was also normal. Initial QuantiFERON®-TB test was negative. Repeat sampling yielded an equivocal result.

Despite standard antibiotic therapy, she failed to improve clinically. Cervical lymph node scrapings were then obtained, showing caseating granulomas. Pansensitive *Mycobacterium tuberculosis* (Mtb) was confirmed by microscopy and culture of both lymph node biopsy specimens and bronchial washings obtained at bronchoscopy. She was commenced on isoniazid, rifampicin, pyrazinamide and ethambutol and, after four days therapy, successfully extubated.

Her mother, a 32-year-old healthcare worker, described a three-year history of intermittent vaginal discharge. Past medical history was notable for bilateral salpingectomy for cyclical pain and a self-limited episode of optic neuritis 6 weeks prior to her daughter's

presentation. She had known exposure to two patients with TB through her work and her maternal grandmother had been treated for TB previously, however she reported having a negative Tuberculin PPD (Purified Protein Derivative) skin test 4 years ago. Physical examination including pelvic examination was normal, chest radiograph clear and trans-vaginal ultrasound unremarkable.

A repeat Tuberculin PPD skin test was strongly positive at 25mm. She proceeded to endometrial biopsy, which revealed non-caseating granulomas (Figure A). ZN (Ziehl-Neelson) stain was negative, as was GeneXpert-MTB/RIF® PCR-based assay. However, pansensitive Mtb was cultured from biopsy specimens at 14 days and GenoType®-MTBDR assay was positive. She was commenced on isoniazid, rifampicin and pyrazinamide. (Ethambutol was omitted due to her history of optic neuritis.)

At this stage, clinical notes from her investigations for cyclical pain three years previously were reviewed. Hysterosalpinography and laparoscopy had demonstrated “badly scarred” fallopian tubes and she had undergone bilateral salpingectomy. Both salpingectomy and endometrial biopsy specimens had contained non-caseating granulomas and Langerhan’s giant cells, felt possibly to be consistent with resolved tubercular infection (Figure B). ZN stain was negative, however, and as symptoms had resolved following surgery, no further investigations were pursued. TB culture and PCR-based assays were not performed.

Three years later her daughter, conceived following one cycle of *in vitro* Fertilisation (IVF), presented with potentially-fatal congenital tuberculosis as described. Fortunately, though the pre-conception diagnostic opportunity had been missed in this case, both mother and child responded well to antimicrobial therapy and the child has experienced no long-term sequelae to date.

DISCUSSION:

Congenital TB presents a diagnostic challenge. Symptoms are generalised and non-specific, immune-based diagnostics (such as QuantiFERON®-TB) are frequently negative in the early weeks of life, and though by definition requiring vertical transmission (either by haematogenous spread or by inhalation of infected amniotic fluid in utero), Cantwell's detailed review of published cases found over half of mothers to be undiagnosed until after the diagnosis was made in their infant[1]. However, delayed diagnosis is associated with a five-fold higher mortality compared to cases where prompt and appropriate antimicrobial therapy is initiated[1, 2].

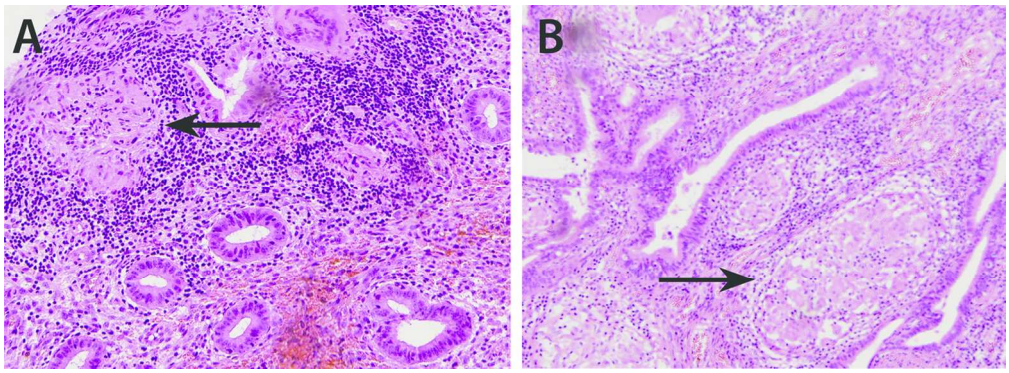
Pre-conception identification and treatment of female genital tract TB could prevent congenital TB. However, wide variety in nature and severity of clinical presentation[3] and lack of a gold standard diagnostic test (as well as the inconsistency of different diagnostic modalities, demonstrated in this case)[4, 5] render this challenging. Though extremely rare in developed countries[3], this case demonstrates that female genital tract TB must be included as a differential for healthcare workers presenting with any gynaecological complaint[4]. Furthermore, combined diagnostic modalities must be employed to enhance identification of cases and prevent vertical transmission[4, 6].

REFERENCES

1. Cantwell MF, Shehab ZM, Costello AM, Sands L, Green WF, Ewing EP et al. Brief Report: Congenital Tuberculosis. *N Engl J Med* 1994; 330(15):1051-4.
2. Flibotte JJ, Lee GE, Buser GL, Feja KN, Kreiswirth BN, McSherry GD et al. Infertility, *in vitro* fertilisation and congenital tuberculosis. *Journal of Perinatology* 2013; 33:565-8.
3. Schaefer G. Female genital tuberculosis. *Clin Obstet Gynaecol* 1976; 36(3):223-39.
4. Kulshrestha V, Kriplani A, Agarwal N, Singh UB, Rana T. Genital tuberculosis among infertile women and fertility outcome after antitubercular therapy. *Int J Gynecol Obstet* 2011; 113(3):229-34.
5. Kumar P, Shah NP, Singhal A, Chauhan DS, Katoch VM, Mittal S et al. Association of tuberculous endometritis with infertility and other gynaecological complaints of women in India. *J Clin Microbiol* 2008; 46(12):4068-70.
6. Bhanu NV, Singh UB, Chakraborty M, Suresh N, Arora J, Rana T et al. Improved diagnostic value of PCR in the diagnosis of female genital tuberculosis leading to infertility. *J Med Microbiol* 2005; 54(Pt 10):927–31.

FIGURE LEGEND:

Histopathological sections from endometrial biopsy (A) taken from mother after infant's diagnosis and of fallopian tubes (B) resected from mother three years previously, both demonstrating non-caseating granulomas (arrows).



123x45mm (300 x 300 DPI)

Acronyms not explained in the text:

kg – kilograms

UK – United Kingdom

AST – aspartate aminotransferase

ALT – alanine aminotransferase

CRP – C reactive protein

ESR – erythrocyte sedimentation rate

HIV – human immunodeficiency virus

CMV – cytomegalovirus

CSF – cerebrospinal fluid

PCR – polymerase chain reaction

Acronyms explained in the text:

TB – tuberculosis

Mtb – *Mycobacterium tuberculosis*

PPD – purified protein derivative

ZN – Ziehl-Neelson

IVF – *in vitro* fertilisation

Registered trademarks mentioned in the text:

QuantiFERON®-TB (immune-based diagnostic test)

GeneXpert-MTB/RIF® (PCR-based diagnostic test)

GenoType®-MTBDR (PCR-based diagnostic test)