Endometrial TB-PCR positivity in women with unexplained infertility with no visible, microbiological or histopathological evidence of disease in a high TB burden area: whether to ignore or treat

Sir,

We read the paper entitled ‘Favourable infertility outcomes following anti-tubercular treatment prescribed on the sole basis of a positive polymerase chain reaction test for endometrial tuberculosis’ (Jindal et al., 2012) with a sense of growing alarm.

To come to a conclusion such as this, based on a study with a flawed methodology where intervention and non-intervention groups are so noticeably unequal, is not just illogical but also dangerous.

The authors’ argument that it was unethical to leave women testing positive for tuberculosis (TB)-PCR untreated and hence their inability to have TB-PCR positive individuals in the non-intervention group seems to be based on a very flawed premise.

First of all, how do the authors explain the pathogenesis of infertility in women with latent TB? Where is the evidence to support their claim that molecular mechanisms are responsible for infertility in such women who have no visible, laparoscopic, histopathological, radiologic or microbiologic evidence of the disease? The studies that the authors cite to support their claim of molecular mechanisms causing infertility in latent TB (Gurgan et al., 1996; Kumar and Rattan, 1997; Malik, 2003; Singh et al., 2011) in fact deal with mechanisms of infertility in women with active TB. On the contrary, Singh et al. (2011) found no difference in pregnancy rates or endometrial blood flow in women with or without genital TB based on TB-PCR.

Also, the prevalence of latent TB in India is estimated to be between 35 and 50% depending on the methods used for testing (Aggarwal, 2005; Pai et al., 2005). There are no published studies yet that give us the prevalence of latent genital TB in fertile versus infertile couples or suggest that latent TB is sequenced more in the infertile population. There are published studies that have found the presence of mycobacterial DNA in the endometrium of couples with unexplained infertility, who suffer recurrent implantation failures (Dam et al., 2006), but whether this is the cause for either infertility or recurrent implantation failure is arguable. Until we have studies to prove otherwise, it seems logical to conclude that mycobacterial DNA is found in equal frequency in women with and without infertility in a TB endemic zone such as India. So the question of ‘with-holding treatment in individuals confirmed to have latent genital tuberculosis because it is un-ethical’ should not arise, since the association between latent TB and infertility is still intangible. Hence we come back to our opinion that this was a study that was majorly flawed in methodology.

The other thing that shakes us up is the confidence the authors seem to place on PCR as a test for confirming or rejecting latent TB. For them, endometrial TB-PCR positivity seems to be synonymous with TB. It is true that most studies they quote including their own have found it to be a highly specific but not such a sensitive test for picking up TB (92% specificity as opposed to 59% sensitivity as per the authors’ own 2010 study) (Jindal and Bala, 2010). Fifty-nine percent sensitivity means that 41% of patients who had latent TB have been labelled by the test as not having TB. This in numbers comes to 118 individuals (169 x 0.59–169), who were pushed into the control group because of a false negative TB-PCR. This population that had TB but tested negative on PCR now forms 43% (118/274) of the control group. This group did not receive treatment and yet they fared just as well as the intervention group (pregnancy rates over 3 years 60.9 versus 59.8%, respectively).

So the pertinent question to be answered by the authors is whether the so-called study group really benefited from this really toxic, prolonged, chemotherapy that is not without serious gastro-intestinal, hepatic, ophthalmic and auditory adverse effects (Yee et al., 2003). The only apparent ‘benefit’ that the authors claim of treatment (shortening of median time to conception from 10 to 7 months) hardly seems to be any benefit at all if one has to deal with such serious aforementioned complications. The social implications of being labelled a tubercular patient in a country like India are immense. Also, indiscriminate and incorrect use of anti-tubercular treatment based on a flimsy and flawed premise, such as positive TB-PCR alone, leads to a very real and present danger of the emergence of multi-drug-resistant strains of TB, which remains the biggest challenge for Revised National Tuberculosis Control Program (RNTCP) health personnel battling active TB in India today.

References


Kumar A, Rattan A. Antigonadotrophic effect of mycobacterium tuberculosis. 

Malik S. Genital tuberculosis and implantation in assisted reproduction. 

Pai M, Gokhale K, Joshi R, Dogra S, Kalantri S, Mendiratta DK, Narang P, 
Daley CL, Granich RM, Masurek GH et al. Mycobacterium tuberculosis 
infected in health care workers in rural India: companion of a 
Whole-blood interferon γ assay with tuberculin skin testing. 

Singh N, Bahadur A, Mittal S, Malhotra N, Bhatt A. Comparative analysis of 
edometrial blood flow on the day of hCG by 2D Doppler in two 
groups of women with or without genital tuberculosis undergoing 
IVF-ET in a developing country. 
*Arch Gynecol Obstet* 2011;283:115–120.

Yee D, Valiquette C, Pelletier M, Pansevin I, Rocher I, Menzies D. Incidence of 
serious side effects from first-line antituberculosis drugs among patients 
treated for active tuberculosis. 

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**Reply: Endometrial TB-PCR positivity in women with unexplained infertility with no visible, microbiological or histopathological evidence of disease in a high TB burden area: whether to ignore or treat**

Sir,

We appreciate the comments on our paper entitled ‘Favorable infertility outcomes following anti-tubercular treatment prescribed on the sole basis of a positive polymerase chain reaction test for endometrial tuberculosis’ in *Human Reproduction* (Jindal et al., 2012). In the absence of large, placebo-controlled and long-term studies, the authors of the letter have the right to form their own opinion and strategy for the treatment of patients of endometrial tuberculosis (TB). We would, however, like to point to the following:

(i) It is true that the pathogenesis of infertility in women with latent TB is not clearly known. We have only hinted to some of the possible mechanisms which remain to be further investigated.

(ii) Agreeably, we could not include a ‘non-treatment arm’ in the TB-PCR positive women in our study (Jindal et al., 2012). We had considered this as inappropriate.

(iii) There is an apparent misgiving with reference to latent TB based on TB-PCR positivity. Latent TB is generally defined by a positive tuberculin skin test or interferon-gamma assay (Clifton et al., 2009). On the other hand, TB-PCR tests demonstrate the presence of mycobacterial DNA, which is direct evidence of the presence of mycobacteria, justifying treatment in a symptomatic patient—‘infertile’ in this case. Even amongst otherwise asymptomatic cases with latent TB, ~5–10% are known to develop clinical TB in due course of time (American Thoracic Society (ATS) and CDC, 2000).

(iv) We agree that the indiscriminate and incorrect use of anti-tubercular treatment is fraught with the risk of drug-resistance development. The only debatable issue is related to the indication for initiation of treatment. We may also mention that the Revised National Tuberculosis Control Program (RNTCP) of India also recommends treatment of extrapulmonary TB based on clinical and other laboratory criteria even in the absence of mycobacterial demonstration (RNTCP, 2010).

(v) The risk of toxicity and other drug-related problems have to be weighed against the indication and benefits of therapy. We are quite conscious of this general dictum in medical practice.

We do look forward to more meaningful conclusions from a better conducted and placebo-controlled study from another centre.

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**References**

American Thoracic Society (ATS) and CDC, Official Statement. Diagnostic 
standards and classification of tuberculosis in adults and children. 

Central TB Division, Government of India, New Delhi. Revised National 
Tuberculosis Control Programme. 
www.tbcindia.nic.in/ Training Module for General Practitioners, 2010, p 17 (22 August 2013, date last accessed).

Clifton BE, Helena BI, Dartois V, Thomas D, Sabine E, JoAnne F, Dirk S, 
Robert JW, Douglas Y. The spectrum of latent tuberculosis: rethinking the 
biology and intervention strategies. 

Jindal UN, Verma S, Bala Y. Favorable infertility outcomes following 
anti-tubercular treatment prescribed on the sole basis of a positive polymerase chain reaction test for endometrial tuberculosis. 

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**The inflammatory regulation of tubal β-catenin expression in human ectopic pregnancy: is it too early to propose a cause-and-effect relationship?**

Sir,

Tubal ectopic pregnancy (EP) is an important and common pathology, but its development and progression are poorly understood (Shaw et al., 2012). The inflammatory regulation of tubal β-catenin expression in human ectopic pregnancy: is it too early to propose a cause-and-effect relationship?