Tuberculosis of the female genital tract in patients attending an infertility clinic

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Summary

*Mycobacterium tuberculosis* plays a major role in infertility, which is the commonest symptom of genital tuberculosis in women. From August 1987 to July 1988, 109 women presenting with infertility were investigated for tuberculosis. None had any other symptoms or signs of the disease. In all cases it was diagnosed by culture of *M. tuberculosis* in one or more of the 5 specimens (3 menstrual fluid specimens, endometrial tissue and peritoneal fluid) obtained from each woman. In addition Ziehl-Neelsen staining and histological examination were performed on all the specimens. Twenty-three patients (21%) had positive cultures for *M. tuberculosis*. Of the 26 positive specimens, 16 (69.6%) were menstrual fluid, 4 (17%) endometrial tissue and 6 (26%) peritoneal fluid (3 patients had more than one positive culture). Chest radiographs were normal in all cases.

*M. tuberculosis* cultured in human tissue must be recognised as a pathogen and necessitates treatment. Selective screening procedures should be done to exclude genital tuberculosis as a cause of infertility.

Despite many new developments in medical science, tuberculosis remains a significant problem in South Africa as the 20th century draws to a close. Infertility is the commonest symptom associated with genital tuberculosis, the presence of which must therefore be excluded before steps are taken to treat infertility. If specific investigations for genital tuberculosis are not conducted, the disease may remain undiagnosed because it often causes no physical symptoms.

The fallopian tubes are most commonly affected; according to Sutherland, they are always involved in genital tuberculosis in women. In these cases a primary focus is rarely found outside the genital tract. Routine screening tests for pulmonary tuberculosis, including chest radiographs, tuberculin skin tests and sputum cultures, are totally unreliable for diagnosing genital tuberculosis. Positive tuberculin tests and sputum cultures are only indicative of previous contact with *Mycobacterium tuberculosis* and do not indicate any specific infection.

With the above in mind, a study was conducted into the prevalence of genital tuberculosis at the Infertility Clinic at Universitas Hospital in Bloemfontein.

Patients and methods

A protocol was established to determine the prevalence of genital tuberculosis in infertile women. During a 1-year period 109 patients were subjected to intensive investigations for genital tuberculosis. Three menstrual fluid specimens, an endometrial biopsy specimen and fluid from the pouch of Douglas were obtained from each patient. A total of 5 specimens for culturing and microscopy was therefore obtained in each case.

The 3 menstrual fluid specimens were obtained at half-hour intervals on the day of maximal flow, using a 250 mm 22G needle coupled to a 10 ml sterile syringe. The syringe and needle were sterilised in the prescribed manner in Cidek before being rinsed in a 0.09% saline solution to remove any residual chemicals. Each specimen was transported in a 50 ml Falcon tube to the Department of Medical Microbiology of the University of the Orange Free State for evaluation and culture.

During hysteroscopy the uterus was flushed with a 0.9% saline solution. If the fallopian tubes are patent the solution flows freely to the pouch of Douglas. After the hysteroscopy fluid was aspirated from the pouch of Douglas. On completion of the laparoscopy, a diagnostic dilatation and curettage was performed. The endometrial tissue obtained in this manner was subjected to histological, cytological and microbiological examination.

The culture technique was as follows: Each specimen was decontaminated by means of *N*-acetyl-L-cystine-sodium-hydroxide. The Kubica digestion method was used. Two thin sections were stained using the Ziehl-Neelsen and auramine-O techniques and then examined for the presence of acid-resistant organisms. The remaining sediment was cultured for 6 weeks.
on two Löwenstein-Jensen mediums at 37°C. These cultures were examined for growth every week and aerated at the same time to create an aerobic environment. Positive cultures were examined further to confirm the presence of M. tuberculosis.

Histological tests were conducted on a routine basis on preparations stained with haematoxylin and eosin. Ziehl-Neelsen staining was performed only in the case of granulomatous lesions.

Results

Of a total of 109 women, 23 were positive for M. tuberculosis. Two cultures were positive for M. phlei and 1 each for M. chelone and M. avium-intracellulare (the latter 3 organisms were not taken into account in statistical analyses because of the controversy surrounding their pathogenicity). No positive histological proof of tuberculosis was found on examination of the specimens.

<table>
<thead>
<tr>
<th>Examination</th>
<th>Positive</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial tissue</td>
<td>4</td>
<td>17.4</td>
</tr>
<tr>
<td>Peritoneal fluid</td>
<td>6</td>
<td>25.1</td>
</tr>
<tr>
<td>Menstrual fluid</td>
<td>16</td>
<td>69.6</td>
</tr>
<tr>
<td>More than 1 specimen positive</td>
<td>3</td>
<td>13.0</td>
</tr>
<tr>
<td>Cytology (Z-N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology (H &amp; E)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Z-N = Ziehl-Neelsen; H & E = haematoxylin and eosin.

Three patients (13%) had positive cultures for more than one specimen. Furthermore, 4 atypical mycobacteria were cultured (Table II) but were not included in the calculations (if they are included, 24.8% of cultures were positive.)

<table>
<thead>
<tr>
<th>Organism</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. phlei</td>
<td>2</td>
</tr>
<tr>
<td>M. chelone</td>
<td>1</td>
</tr>
<tr>
<td>M. avium-intracellulare</td>
<td>1</td>
</tr>
</tbody>
</table>

Discussion

The above results indicate that Ziehl-Neelsen staining and histological examination are not effective diagnostic techniques for tuberculosis of the female genital tract, a ‘silent’ or subclinical infection. Both these techniques are labour-intensive and time-consuming. Culturing of infected tissue is far more effective. Approximately 70% of infected patients in this study were diagnosed by culture of menstrual fluid, a relatively simple technique. If it had been repeated in patients with negative findings the diagnostic rate might have been even higher.

The reported prevalence of genital tuberculosis varies widely. Schaefer states that the prevalence world-wide is between 5% and 10%, while in India it is 19%. The prevalence at Natal-spruit Hospital during 1983 was 4.85%. We found the prevalence to be 21%. There are many possible reasons for these differences, including unsatisfactory screening tests. The standard of laboratory practice and the sensitivity and specificity of screening tests are important factors. Unfortunately no other figures exist for subclinical genital tuberculosis.

The infertility clinic at Universitas Hospital mainly serves white patients from Bloemfontein, surrounding country districts and the northern Cape. On average, 270 new couples are admitted annually. The majority come from the higher socio-economic bracket, which generally has a low rate of tuberculosis.

In this study, all patients reported with a primary complaint of infertility. Genital tuberculosis can, however, also be associated with menstrual abnormalities (amenorrhoea, menorrhagia, metrorrhagia), pelvic pain, dysmenorrhoea, ascites, dyspareunia, vaginal discharge and general malaise. The typical symptomatology of tuberculosis, viz. fever, perspiration and weight loss, was not encountered in our patients.

It is currently believed that genital tuberculosis results from haematogenous transmission from the primary focus, which is usually located in the lungs. Three fallopian tubes are affected in more than 90% of cases, the endometrium in 60%, the ovary in 25% and the uterine cervix in approximately 10%. The fallopian tubes therefore display a high affinity for this infection, which can cause pyosalpinx, hydrosalpinx or a low degree of interstitial salpingitis. The latter results in infertility and/or ectopic pregnancy as a result of interference with ciliary activity and muscle peristalsis. Pyosalpinx, hydrosalpinx and tubercular pelvic abscesses are among the clinical features of fulminating genital tuberculosis. A hysterosalpingogram displays a characteristic appearance in these cases. In contrast, no visible radiological abnormalities have been described in subclinical interstitial salpingitis. Hysterosalpingography is therefore not recommended in the investigation of subclinical genital tuberculosis.

Affected endometrial tissue is expelled during menstruation. On histological examination of this tissue small tubercles, which are similar to the tubercles in affected lung tissue, may be noticed. In patients with amenorrhoea further development of tubercles may follow. The classic tubercle with Langhans cells and the potential to develop into fulminating tuberculosis is then encountered.

Most cervical lesions are ulcerative. They can also form a brittle mass, clinically almost indistinguishable from a cervical carcinoma. Although infection of the vagina and vulva is rare, it is typified by ulcer and sinus formation.

The pathogenicity of genital tuberculosis is very controversial. Haematogenous and lymphatic transmission as well as sexual transmission are possibilities, although sexual transmission of tuberculosis is difficult to prove. In our study there was one case in which a married couple both had subclinical genital tuberculosis. M. tuberculosis was cultured from a semen specimen from the male. Although sexual transmission cannot be proved, it is certainly a possibility.

Culturing in special culture media provides good results. It takes approximately 6 weeks before the result is known, however, owing to the slow growth rate of the organism. The inoculation of guinea-pigs is a very sensitive and specific method for diagnosing tuberculosis, but the costs are high and this method should be reserved for specimens on which routine culturing cannot be performed owing to contamination by organisms that are difficult to inhibit. Culturing in a laboratory has the advantage that non-tuberculous acid-resistant organisms can be eliminated through definitive identification. A further advantage of culturing is that it is possible to assay the sensitivity of organisms to certain drugs. Modern examination methods include techniques at the molecular level that enable sensitive tests to be performed in order to distinguish M. tuberculosis from other acid-resistant organisms.
Patients who are positive for *M. tuberculosis* require chemotherapy for at least 6 months. The role of surgery in the treatment of tuberculosis has changed dramatically since the development of *in vitro* fertilisation. Previously surgical repair of the damage done by the tuberculosis was attempted. However, reconstruction of the fallopian tube is often unsuccessful, because the mucosa is usually damaged or destroyed, and the incidence of ectopic pregnancy is high. Surgery may also reactivate the original infection. The advent of transvaginal follicle aspiration with the aid of ultrasonic scanning followed by *in vitro* fertilisation and embryo transfer has virtually superseded surgery, which is now not required in the patient with subclinical genital tuberculosis and infertility as the only symptom.

Despite intensive advice regarding contraception during antituberculosis treatment, 2 patients to date have fallen pregnant shortly after starting antituberculosis treatment. Both these pregnancies ended in normal deliveries with healthy babies.

**Conclusion**

The alarmingly high incidence (21%) of subclinical genital tuberculosis among infertile women in high socio-economic groups underlines the importance of investigating for and treating this condition in all infertile couples. Intensive evaluation of infertile women is advisable. The single most important symptom of genital tuberculosis, namely infertility, cannot be overemphasised. At present idiopathic infertility is diagnosed in 10-15% of infertile couples. More intensive searching for the cause of such infertility increases the chances that it will be found. Tuberculosis seems to be an important underdiagnosed factor in infertility. The possibility therefore exists that patients with genital tuberculosis can be classified as idio pathically infertile.

Tuberculosis affects the peritoneal surface of organs is regarded as entirely reversible and causing no lasting damage. This is not the case when the mucosa is infected; here damage can result in infertility. Some patients fall pregnant after chemotherapy alone, presumably when their genital tuberculosis has been diagnosed early, before severe and permanent damage has occurred. The high incidence of ectopic pregnancy in previous series is probably the result of lesions caused by fulminating genital tuberculosis. Opinions differ regarding evaluation of patients after chemotherapy by laparoscopy, hysteroscopy and culturing for *M. tuberculosis*. Chattopadhyay et al. did endometrial biopsies after 6 months of therapy in a series of 21 patients, while Malkani and Rajani repeated endometrial biopsies weekly. Both report negative cultures for *M. tuberculosis* after treatment. Chemotherapy is therefore regarded as sufficient treatment, and follow-up examinations are not indicated.

Genital tuberculosis, which is regarded as a relatively rare disease in developing countries, was found to affect 21% of white patients in a local infertility clinic. This high prevalence is attributable to an intensive search for the disease. An effective diagnostic programme is therefore essential to eradicate it. The success of such a programme is largely dependent on standards in the microbiology laboratory. These should be maintained by performing tests on a regular basis.

*M. tuberculosis* is a pathogenic organism, and patients found to be infected must be treated. Asymptomatic infertile women should be investigated for silent or subclinical genital tuberculosis. Notwithstanding the fact that it has long been accepted that genital tuberculosis causes infertility, a further study among a control group of fertile women is planned with the aim of proving that genital tuberculosis is a cause of infertility and obtaining some idea of the prevalence of this condition in the population as a whole.

**REFERENCES**