

Chronic cough and infertility: a report of two cases

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Objective: To report two cases of infertility caused by primary ciliary dyskinesia in patients who presented with an associated complaint of a chronic cough.

Design: Case report.

Setting: University teaching hospital.

Patient(s): Two patients presenting with unexplained infertility and an associated history of long-term chronic cough.

Intervention(s): Patients underwent a nasal mucosal biopsy by an otolaryngologist. Electron microscopy (EM) examination of biopsy specimens was performed.

Main Outcome Measure(s): Diagnosis and appropriate treatment for functional tubal factor infertility.

Result(s): Both patients were diagnosed with primary ciliary dyskinesia based on EM of the nasal biopsy specimens. Given this diagnosis, they immediately underwent IVF-ET. Both patients became pregnant with their first IVF-ET cycle.

Conclusion(s): Other investigators have shown that almost 20% of patients with a chronic cough will have EM evidence of ciliary dyskinesia. Patients presenting with idiopathic infertility and an associated unexplained chronic cough should be referred for nasal biopsy with EM evaluation to rule out primary ciliary dyskinesia. Infertility in these cases, which is due to a functional tubal factor, is best treated with IVF-ET rather than superovulation and intrauterine insemination treatments. (*Fertil Steril*® 2000;74:1251–3. ©2000 by American Society for Reproductive Medicine.)

Key Words: Ciliary dyskinesia, ciliary dysfunction, immotile cilia syndrome, Kartagener's syndrome, dynein arms, infertility

The importance of cilia for the normal function of the fallopian tube is well established. Early research hypothesized that by combining ciliary beat frequency and myosalpingeal contraction, the fallopian tube retrieves the ovulated ovum, moves the sperm from uterus to distal oviduct, and subsequently transports the resultant embryo from distal oviduct into the uterine cavity.

The ultrastructure of the cilium consists of nine pairs of microtubular doublets surrounding two tubules that are enclosed in a central sheath. Both inner and outer dynein arms (DAs) contain ATPase activity that provides the energy for the doublets to slide over one another—this mechanochemical coupling is believed to be the source of the ciliary beat. Perhaps the best described condition in which the cilia do not function properly is Kartagener's syndrome (KS), characterized by bronchi-

ectasis, chronic sinusitis, dextrocardia, and male factor infertility. The ultrastructure of the cilia in KS has been shown to consist of abnormalities of the DAs. Initially it was felt that the structural abnormalities of the cilia rendered the cell totally immotile. However, subsequent work has determined that cilia with ultrastructural abnormalities may be dyskinetic rather than totally immotile. Primary ciliary dyskinesia (PCD) is the term now used for a group of syndromes associated with immotile or dyskinetic cilia, of which KS represents a subset.

To date, the bulk of research pertaining to cilia and infertility has focused on women with KS, but there is little reported about infertile women with possible PCD. We present two cases of women presenting with infertility who have significant histories of chronic sinusitis and chronic lung disease.

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CASE 1

A 28-year-old woman was referred to the Fertility Centre at the Ottawa Hospital in 1996 with a 5-year history of primary infertility. Ovulatory function was normal. Her partner's semen analysis was normal (according to WHO criteria). Laparoscopy and hysterosalpingography were normal. Her medical history was significant for recurrent sinusitis, recurrent pneumonia, chronic bronchitis, and bronchiectasis. She underwent several cycles of clomiphene citrate treatment followed by six cycles of rFSH superovulation and intrauterine insemination cycles without a pregnancy occurring. Because of the history of chronic sinusitis and chronic upper respiratory tract infections, the patient was referred to an otolaryngologist for evaluation and nasal biopsy. With the use of electron microscopy (EM), the cilia of the nasal mucosa were examined and found to have an absence of inner DA and inconsistent outer DA. These findings were consistent with PCD. The patient has an ongoing singleton intrauterine pregnancy after her first IVF-ET treatment cycle.

CASE 2

A 33-year-old woman presented with a 4-year history of infertility. Her only pregnancy that occurred independent of therapy ended in a left salpingectomy for ectopic pregnancy. The patient's partner had a normal semen analysis (WHO). Ovulatory function was normal.

Diagnostic laparoscopy performed before the ectopic pregnancy revealed normal pelvic anatomy except for minimal (rAFS-1) endometriosis without any pelvic adhesions. The fimbriated ends of both fallopian tubes were normal and patent. Hysterosalpingography before the ectopic pregnancy was normal. Subsequent to the ectopic pregnancy, a second laparoscopy with laser vaporization of minimal (rAFS-1) endometriosis was performed. Except for the absent left fallopian tube, findings were identical to the first laparoscopy. The remaining fallopian tube appeared completely normal and patent. Her medical history was significant for recurrent otitis media and chronic sinusitis requiring sinus surgery as a child. There was also a history of recurrent otitis media and bronchiectasis for which she had undergone a flexible fiberoptic bronchoscopy 10 years before. Findings on prior bronchoscopy included large thick mucous plugs in the left and right main-stem bronchi. No biopsies were taken at the time. We referred the patient for otolaryngology evaluation and nasal biopsy.

Two biopsies of the mucosa of the middle turbinate were examined using EM. The results were consistent with PCD. The patient became pregnant with her first IVF-ET treatment cycle but unfortunately underwent a right salpingectomy for another ectopic pregnancy.

DISCUSSION

In 1933, Kartagener described four patients with chronic sinusitis, bronchiectasis, situs inversus, and male factor in-

fertility; this syndrome continues to bear his name. Following the advent of the electron microscope, Afzelius and colleagues (1, 2) examined the cilia of the sperm and respiratory tract in men with clinical KS and discovered an abnormality of the cilia ultrastructure. In the respiratory mucosa, the absence of the DA leads to an absence of mucociliary clearance and subsequent chronic sinusitis, recurrent pneumonia, and bronchiectasis. Halbert et al. (3) examined the function and structure of cilia in the fallopian tube of an infertile woman with KS. Using a laser light-scattering system as well as EM, they measured the ciliary beat frequency, ciliary topography, and ciliary density of the nasal and tubal mucosa. EM demonstrated similarities among the nasal and tubal ciliated cells including abnormal structure of the DA and an absence of the central microtubules.

Although there was motility of the cilia in the fallopian tube, it was dyskinetic. They concluded that ciliary dyskinesia was the only identifiable explanation for the patient's ongoing infertility and that the structure of the cilia of the nasal mucosa mirrored that of the fallopian tube. Although the absence of DA remains the most prevalent abnormality of the cilia, at least 20 different defects have now been described affecting various components of these complex organelles. These abnormalities do not always render the cilia totally immotile, but rather often the cilia exhibit decreased motility or uncoordinated motility (4). In our two cases, the couples had no identifiable cause for infertility other than PCD in the woman. Medical history was significant for chronic sinusitis, chronic cough, and recurrent respiratory tract infections in both women. Of patients with PCD, only 50% have KS; however, 100% have cough and nearly 100% have chronic sinusitis. In the general population of infertile couples, the prevalence of PCD is approximately 1 in 40,000. Superovulation with intrauterine insemination would not facilitate pregnancy in women with PCD because the oviduct, although patent, is not functional because the abnormal cilia are unable to transport gametes and embryos. However, IVF-ET treatment for infertile women with PCD is efficacious because it bypasses the functionally abnormal oviduct. In both our cases the woman became pregnant with her first IVF-ET treatment cycle.

We propose that all women with a chronic cough or chronic sinusitis and associated infertility be investigated for PCD. Van der Baan et al. (4) compared cilia ultrastructure and activity from patients with KS to cilia from both healthy individuals and a group of patients with chronic respiratory tract infections. He found that 18% of patients with chronic upper respiratory tract infections had findings consistent with PCD. Although we would be testing five women for one true positive result, the nasal biopsy is simple, quick, and accurate and involves minimal pain and complications. Conversely, superovulation failures are time consuming, expensive, and frustrating. If one woman in five with chronic cough and infertility can be identified as

having PCD, then that woman can avoid ineffective superovulation trials and proceed directly to IVF-ET with a good prognosis for pregnancy.

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