CASE REPORT

Infertility and abnormal cervical mucus in two sisters who are compound heterozygotes for the cystic fibrosis (CF) ΔF508 and R117H/7T mutations

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Objective: To describe two cases of infertile sisters who are compound heterozygote carriers of the cystic fibrosis (CF) ΔF508 and R117H/7T mutations and who were found to have significantly abnormal cervical mucus.
Design: Case reports and review of literature.
Setting: Infertility practice based in an academic medical center.
Patient(s): Two sisters (ages 34 and 42), compound heterozygote carriers of CF mutations, who presented with involuntary infertility.
Intervention(s): The partners of both patients tested negative for CF. The evaluation of both sisters did not indicate other causes of infertility aside from advanced maternal age in the 42-year-old patient. Both sisters underwent natural-cycle intrauterine insemination.
Main Outcome Measure(s): Pregnancy conception.
Result(s): The 34-year-old patient has subsequently conceived twice through natural-cycle inseminations.
Conclusion(s): This is the first reported case of infertility due to a cervical mucus factor in a patient who is a compound heterozygote of the ΔF508 and R117H/7T mutations. This case is important not only because of the distinct phenotypic abnormality seen with specific CF mutations but also because of the associated genotype. (Fertil Steril® 2008;90:1201.e19–e22. ©2008 by American Society for Reproductive Medicine.)

Key Words: CF, R117H, ΔF508, 7T allele, cervical mucus

As recommended by the American College of Obstetrics and Gynecology, testing for Cystic fibrosis (CF) mutations should be offered to patients desiring pregnancy (1). Patients with CF have abnormal chloride conduction across the apical membrane of epithelial cells, resulting in thickened, abnormal secretions that affect sinus, pulmonary, pancreatic, and intestinal function (2).

We describe two cases of abnormal cervical mucus in sisters who presented for infertility evaluation. These cases are demonstrative not only of the pathophysiology of abnormal cervical mucus in CF but also of the significance of the CF genotype–phenotype correlation.

CASE REPORTS

A 34-year-old nulligravida woman of Norwegian ancestry presented with 1 year of involuntary infertility. The patient reported having regular intercourse with her husband at least four times weekly during this period. She had documented luteinizing hormone (LH) surges with a urinary ovulation predictor kit and had had timed intercourse before and after the LH kit demonstrated a surge. Her gynecologic history was unremarkable, with regular menses every 30 days, lasting 4 days with moderate flow and minimal dysmenorrhea. She had previously used oral contraceptive pills for 9 years and had no history of pelvic infections. Five years before, she had had an abnormal Papanicolaou smear, but colposcopy, cervical biopsy, and repeat Papanicolaou smears were all normal. She had had no other evaluations or treatment for infertility. Otherwise, her history was notable for mitral valve prolapse and an uncomplicated appendectomy. She denied any history of sinus, pulmonary, or gastrointestinal problems. Her family history was noncontributory and was negative for CF. The patient's physical examination and pelvic ultrasound were within normal limits. Her husband was 58 years old with a history of a myocardial infarction, and he had fathered four children with a previous partner. His semen analysis parameters were as follows: volume 1 mL, concentration 75.0 × 10^6/mL, motility 65%, and morphology 5% (strict criteria).

The patient underwent routine testing for CF and was found to be a compound heterozygote for the ΔF508 and

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the R117H/7T mutations, but she tested negative for the 5T allele. Her husband's CF carrier screen was negative.

Initial evaluation of the patient included a screen for sexually transmitted infections, which was negative. She underwent a postcoital test on day 14 of her natural cycle, following intercourse the night before. Pelvic ultrasound demonstrated an 8-mm trilaminar endometrium and an 18-mm follicle of the right ovary. Speculum examination revealed a pinpoint cervix with mucus that was thick, viscous, ropelike, and tenacious. Attempts to spread the mucus were limited by its ropelike nature; abundant epithelial cells but no spermatozoa were seen by phase contrast microscopy. On this day, her level of serum estradiol (E_2) was 234 pg/mL, LH was 31.3 mIU/mL, and progesterone was 1.25 ng/mL. The patient did not become pregnant this cycle. A repeat postcoital test was performed 2 months later on day 12 of her cycle. At this time, the patient had a 16.5-mm ovarian follicle and an 8.0-mm trilaminar endometrium as seen by ultrasound; however, she again had scant, poor, thick cervical mucus. Because of the diagnosis of cervical mucus factor, the patient was monitored in the natural cycle for a spontaneous LH surge and underwent intrauterine insemination (IUI) 24 hours after the surge. The patient became pregnant during her third cycle of natural-cycle IUI and delivered a healthy baby at term. Three years later, at the age of 37, the patient desired another child and underwent another successful natural-cycle IUI. She is currently near term.

The patient's sister, a 42-year-old nulligravid woman, presented to the same physician with 3 years of involuntary infertility. She also had an unremarkable medical and gynecologic history. Her random day-3 E_2 level was 39.7 pg/mL, and FSH level was 7.7 mIU/mL. Her husband's semen analysis was within normal limits except for 0 strict morphology.

The patient underwent CF testing, which showed that she also was a compound heterozygote for the ΔF508 and the R117H/7T mutations. Her husband's CF testing was negative. Her postcoital test findings on day 12 of her natural cycle after intercourse were similar to those of her sister, with thick, viscous, tenacious mucus (Fig. 1). Microscopic examination revealed dense, cellular material with no spermatozoa seen. The patient similarly underwent two natural IUI cycles, during which she developed ovarian follicles with serum E_2 measuring 398 and 352 pg/mL, respectively. Both times, she demonstrated thick, tenacious mucus before ovulation. She did not become pregnant, and she was advised to proceed with IVF due to maternal age.

DISCUSSION

This is the first reported case of infertility due to a cervical mucus factor in a patient who is a compound heterozygote of the ΔF508 and R117H/7T mutations. This case is important not only because of the distinct phenotypic abnormality seen in a carrier of a CF mutation but also because of the associated genotype.

FIGURE 1

Cervical mucus of cystic fibrosis compound heterozygote. The spinnbarkeit measured 5 cm. The mucus was thick, viscous, cloudy, and ropelike with little water content.

Schoyer. Cervical mucus in CF compound heterozygotes. Fertil Steril 2008.

Reproductive complications in women with CF have been well described in the literature (3, 4). In addition to infertility resulting from anovulation due to chronic illness, patients with CF may demonstrate abnormal cervical mucus (3–5). It has been demonstrated that CF is caused by mutations in the gene on chromosome 7 encoding the CF transmembrane conductance regulator (CFTR) gene (6, 7); CFTR conducts chloride across the cell membrane, regulates sodium transport and potassium channels, and may function in exocytosis (8). In neonates and adults, the uterine cervix has been shown to have high levels of expression of CFTR messenger RNA (mRNA) (9). The primary pathophysiology that leads to chronic illness in CF patients is mucosal obstruction of exocrine glands; every tissue affected by the disease is defective in the secretion of chloride and fluid (8).

The abnormal cervical mucus seen in CF patients is typically described as thick, tenacious mucus that functions as a barrier to sperm penetration and fails to demonstrate cyclic changes during the menstrual cycle (5, 10). Kopito et al. (5) studied characteristics of cervical mucus in patients with CF compared with that of controls. The mucus of patients with CF was significantly dehydrated throughout the menstrual cycle and contained on average less than 30% of the water seen in healthy patients' mucus. In healthy controls, the content of water and sodium in cervical mucus typically increases during the menstrual cycle. The water content of the cervical mucus of patients with CF was consistently found to be significantly lower than the level of 93% some investigators have suggested is necessary to be penetrable by spermatozoa (11). Additionally, as a result of the decreased water content of the mucus, electrolyte concentrations in these patients' mucus samples were found to be consistently higher.