Fertility in men with Down syndrome: a case report

Mandakini Pradhan, D.M., Ashwin Dalal, M.D., Faisal Khan, M.Sc., and Suraksha Agrawal, Ph.D.

Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Objective: To inform clinicians about fertility in males with Down syndrome.

Design: Case report.

Setting: Medical Genetics Department of a tertiary-care hospital.

Patient(s): A 26-year-old man with confirmed nonmosaic trisomy 21.

Intervention(s): Karyotype, amniocentesis, paternity testing using microsatellite markers.

Main Outcome Measure(s): Confirmed paternity in the son of a male with nonmosaic trisomy 21.

Result(s): A male with nonmosaic Down syndrome fathered a normal son, and the paternity was proven by microsatellite marker analysis.

Conclusion(s): Although Down syndrome males have been reported to be infertile, it may not always be true. Infertility in males has been attributed to defective spermatogenesis, but ignorance of the sexual act may be one of the contributing factors. It is important to advise postpubertal Down syndrome males on contraceptive measures. (Fertil Steril 2006;86:1765.e1–3. ©2006 by American Society for Reproductive Medicine.)

Key Words: Down syndrome, fertility, sterility, trisomy 21

Chromosomal trisomy has been reported to occur in at least 4% of all pregnancies (1). It is the most common chromosomal abnormality found in humans. The presence of an additional sex chromosome is often found to be associated with physical, behavioral, and intellectual impairment. The presence of an additional autosome (trisomy) is even more serious since it is associated with multiple malformations and results in either early pregnancy loss or death in infancy.

The incidence of trisomies varies widely among different chromosomes. Trisomy 21 (Down syndrome) is one of the most common chromosomal abnormalities, occurring in about 1 in 700 live births (1). As it is the only autosomal trisomy compatible with postpubertal survival, the question of fertility in these patients often arises. While females with Down syndrome are reported to be fertile or subfertile, males are reported to be infertile.

To date, there are reports of three pregnancies that were fathered by two male Down syndrome patients (1, 2). We report a case of a nonmosaic Down syndrome male who fathered a normal child. This is third such report in the literature to date.

CASE REPORT

A 26-year-old man presented with characteristic features of Down syndrome. His mother was 28 years old at the time of his birth, and he had three normal siblings. His karyotype revealed nonmosaic trisomy 21 on two occasions. He was married to a 22-year-old normal female. On examination, he had no signs of hypogonadism and his semen analysis, serum LH, FSH, and T were within normal range.

On interviewing his wife on the first visit to our center, it was ascertained that they never had intercourse, although her husband had normal erection and ejaculation. The risk of chromosomal abnormality in the baby if pregnancy occurs was explained to the parents of the patient and to his wife. The wife conceived within 3 months and opted for prenatal chromosomal analysis. Amniocentesis was done at 15 weeks of gestation, and it showed a normal chromosomal complement in the fetus. Antenatal ultrasound and fetal echocardiography were normal. She delivered a healthy male child weighing 3 kg at term.

To prove paternity, DNA was extracted from the venous blood of the patient, his wife, and the putative son. Microsatellite analysis was carried out for a panel of 10 autosomal short tandem repeat (STR) loci, namely, vWA, vWF-1, Tho-1, TPO, D16, DHFRP2, F13, and Apo B3’HVR. Polymerase chain reaction amplification was carried out for individual loci, amplicons were size fractionated on 10% polyacrylamide gel, and alleles were genotyped using silver staining.

Along with the autosomal STR markers, four additional Y chromosomal STR loci were also genotyped in the patient and putative son. It was found that the putative son carried one allele each from the mother and the patient on all 10 autosomal STR loci, and the alleles were common between son and father on all four Y-STRs genotyped. The paternity index was calculated based on the allele frequency data of all the analyzed markers among North Indians. The paternity index was found to be 99.9996 for autosomal STR loci and 99.9998 for Y-STR loci.
To rule out the possibility of false paternity, DNA of the father of the Down syndrome patient was also genotyped for the same panel of 14 STRs. As expected, the same allele was found in both the grandfather and the putative son on all the Y-STRs but no common allele was found on four out of 10 autosomal STRs genotyped.

**DISCUSSION**

A literature search for pregnancies fathered by Down syndrome patients revealed reports of three pregnancies fathered by two Down syndrome patients (1, 2). In the first report, the patient fathered twice. On both occasions the fetal chromosomal complement was normal, but one pregnancy resulted in spontaneous abortion at 16–17 weeks; the other was a normal baby born at term (2, 3). In the second report, the patient had normal external genitalia with normal semen analysis and fathered a normal female child (1). None of these reports address the issue of impotence. In the first report, pregnancy followed the wife’s first unprotected cycle, but no mention of this issue was made regarding the second pregnancy. The pregnancy in the second patient followed after two instances of sexual intercourse.

Several females with Down syndrome have been reported to have offspring. Sheridan et al. (3) reviewed the literature and found 29 pregnancies reported in 26 nonmosaic Down syndrome females (3). There were 10 offspring with Down syndrome, of which two aborted spontaneously (karyotype not available). Chromosomally normal children were born in 18 pregnancies (including one monozygotic twin pair). Of these, two were mentally retarded, four had other congenital malformations, and three were either aborted spontaneously or died prematurely. Hojager et al. (4) attributed the subfertility in Down syndrome females to the reduced number of ovarian follicles and increased rate of atresia (4).

So far, the range of sterility versus fertility in cases of male Down syndrome patients is not clear. Cryptorchidism, small penis, and decreased testicular size have been reported to be the common findings on examination (3). Facial hair is absent in a significant proportion of patients, and sparse hair is present in some.

We have reviewed the literature to look for semen analysis findings and sex hormone levels in these patients to determine the cause of infertility. A summary of selected studies is shown in Table 1. Histology performed on Down syndrome testes has shown markedly decreased spermatogenesis. The inability of Down syndrome males to reproduce may be related to their inability to produce sufficient gametes (6).

Histopathological evidence of decreased spermatogenesis with oligospermia and diminished testicular size were seen in some, while sexual impotence was observed in others. The FSH and LH levels were found to be increased in most of the reports. Hsiang et al. (13) reported on gonadal function in 53 Down syndrome males of different age groups. They suggested that a progressive gonadal failure may be seen in

<table>
<thead>
<tr>
<th>Serial no.</th>
<th>Reference</th>
<th>No. of patients</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Stearns et al. (7)</td>
<td>9</td>
<td>Azoospermia (n = 4), oligospermia (n = 5)</td>
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<tr>
<td>2</td>
<td>Salvadorini et al. (11)</td>
<td>5</td>
<td>Normal LH</td>
</tr>
<tr>
<td>3</td>
<td>Horan et al. (8), Hasen et al. (9)</td>
<td>6</td>
<td>Normal T with baseline increased LH and FSH</td>
</tr>
<tr>
<td>4</td>
<td>Jagiello et al. (12)</td>
<td>6</td>
<td>Normal testicular size (n = 3), normal T levels (n = 5), increased LH (n = 5), increased FSH (n = 2)</td>
</tr>
<tr>
<td>5</td>
<td>Campbell et al. (5)</td>
<td>17</td>
<td>Diminished testicular size at all ages and significantly increased LH and FSH compared with controls</td>
</tr>
<tr>
<td>6</td>
<td>Johannisson et al. (6)</td>
<td>1</td>
<td>Histopathological evidence of decreased spermatogenesis</td>
</tr>
<tr>
<td>7</td>
<td>Pueschel et al. (10)</td>
<td>46</td>
<td>Normal pubertal development with normal penile length and testicular volume and normal T, LH, and FSH levels compared with controls</td>
</tr>
<tr>
<td>8</td>
<td>Ying Hui et al. (13)</td>
<td>53</td>
<td>Infants: elevated FSH; prepubertal: LH and FSH normal; postpubertal: LH and FSH elevated, normal T, and mean stretched penile length and testicular volume below normal. Timing of puberty was normal.</td>
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<tr>
<td>9</td>
<td>Arnell et al. (14)</td>
<td>23</td>
<td>Early growth spurts; primary gonadal insufficiency (high FSH, negative correlation between LH levels and testicular volume)</td>
</tr>
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</table>

Down syndrome males, but it is not universal and Down syndrome males are not always sterile (13). There are also reports of normal pubertal development with normal penile length, testicular volume, T levels, serum LH, and serum FSH in many patients (Table 1).

Our patient had structurally and functionally normal genitalia, but he lacked the knowledge of sexual intercourse. This might be one of the reasons for infertility among Down syndrome patients with normal spermatogenesis and normal sexual function. With more and more Down syndrome males living beyond the pubertal period it is imperative to counsel the parents about their reproductive ability and the need for contraceptive measures. The theoretical risk of Down syndrome in the offspring is 50%, until more pregnancies fathered by Down syndrome males are reported.

REFERENCES