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Klinefelter's syndrome and assisted reproduction

The type of therapy that should be given to men with Klinefelter's syndrome who are of reproductive age and who want to father a child is not clear. Conservative treatments, which were introduced before the availability of the recent highly efficient techniques of micromanipulation-assisted fertilization, relied on substitute therapies with hormonal preparations containing androgens (1). However, very limited numbers of spermatozoa may be recovered by testicular biopsy from some men with nonmosaic Klinefelter's syndrome; these spermatozoa can be used for successful conception by means of ICSI (2). Because of the well-known disruptive effects of androgen administration on spermatogenesis, patients with Klinefelter's syndrome who receive symptomatic treatments with hormonal preparations containing androgens may have an irreparable loss of reproductive potential. It is thus clear that a choice must be made between two alternative treatment strategies: one which may result in the inability to become a parent and the other taking into account an eventual assisted reproduction attempt.

The choice of the latter treatment strategy has been questioned by some investigators concerned about the risk of transmission of this pathology by assisted reproductive techniques (1). However, new clinical and laboratory data suggest that this risk is lower than previously believed. Two recent reports (3, 4) update the number of healthy neonates with normal karyotypes after ICSI using spermatozoa from patients with nonmosaic Klinefelter's syndrome to 19. Sperm chromosome analysis, performed with 112 spermatozoa from 8 patients, showed chromosomal abnormalities in 7 (6.3%) spermatozoa, and the anomalies detected were related to the sex chromosomes in only 5 of them (4). These frequencies of chromosomal abnormalities in spermatozoa are similar to those detected in other severe primary testiculopathies unrelated to Klinefelter's syndrome. Thus, they do not seem to be caused by sperm maturation from XXY-bearing precursor germ cells.

In support of these data we have achieved the birth of normal twins by ICSI using spermatozoa recovered by testicular biopsy from a patient with nonmosaic Klinefelter's syndrome. This work had been approved by the Ethics Committee of the European Hospital (equivalent to Institutional Review Board approval). The patient was 34 years old and was referred to our center after 3 years of primary infertility. Physical examination revealed normal male features and hair distribution. No signs of gynecomastia were noted. The testicular volume was bilaterally reduced (right, 6.5 mL; left, 5.8 mL). No varicocele was found. Semen analysis showed normal volume and fructose concentration. No spermatozoa were detected in the ejaculate after centrifugation. These results were confirmed by three subsequent semen examinations performed monthly. Blood analysis showed an elevated serum concentration of FSH and LH, low testosterone, and normal prolactin. Chromosomal analysis, performed on 50 peripheral blood leukocytes, showed a 47,XXY karyotype in all cells. A second peripheral blood leukocyte analysis, performed on 200 cells, confirmed the previous diagnosis of a nonmosaic form of Klinefelter's syndrome. A search for Y-chromosome microdeletions gave negative results.

The patient's wife was 28 years old, with a normal hormonal profile, a 46,XX karyotype, and no pathology detected by physical examination. After controlled ovarian stimulation, a total of 17 oocytes were recovered, of which 15 were at metaphase II and were subjected to ICSI. On the following day, signs of normal fertilization were observed in seven oocytes, three oocytes were dead, three remained at metaphase II, one showed only one (female) pronucleus, and one had three pronuclei and only one polar body indicating a triploid status. The seven normally fertilized oocytes were cultured further for an additional 2 days when three of them were transferred to the patient's uterus at the 8-cell, 7-cell and 7-cell stage, respectively. The remaining embryos resulting from normal fertilizations were cryopreserved. The couple declined embryo biopsy for preimplantation genetic diagnosis. The luteal phase was supported by daily IM injections of 50 mg of natural progesterone (Prontogest, Amsa, Barberino del Mugello, Italy), beginning on the day of oocyte retrieval. Two of the 3 embryos transferred implanted. After an uneventful pregnancy, two healthy boys with normal 46,XY chromosomal constitution were born.

As opposed to the 21 healthy babies (including our two births mentioned above), there is only one reported case in which fertilization with spermatozoa from a patient with nonmosaic Klinefelter's syndrome resulted in 47,XXY karyotype (5). These data corroborate the view that, in the testis, the nonmosaic Klinefelter constitution may be locally converted to mosaic during premeiotic multiplication of germ cells and that the resulting "corrected" germ cell lineages give rise to most, if not all, of the spermatozoa eventually produced

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Reprint requests: Jan Tesarik, M.D., Ph.D., Laboratoire d'Eylau, 55 rue Saint-Didier, 75116 Paris, France (FAX: 33-1-53-70-64-94; E-mail: tesarik@hotmail.com).

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by these patients, because of an as yet uncharacterized developmental advantage. Assisted reproduction with patient's own spermatozoa is thus a relatively safe treatment and should be proposed to all patients with nonmosaic Klinefelter's syndrome, diagnosed from peripheral blood preparations, in whom spermatozoa can be found in the ejaculate or recovered by testicular biopsy.

Ermanno Greco, M.D.
Laura Rienzi, Ph.D.
Filippo Ubaldi, M.D.
Jan Tesarik, M.D., Ph.D.
Department of Reproductive Biology and Medicine, European Hospital, Rome, Italy

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