Use of oocytes from anonymous, matched, fertile donors for prevention of heritable genetic diseases

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Abstract

Heritable genetic diseases can be prevented with the use of donor oocytes. We report our experience in using donor oocytes from anonymous, matched, fertile donors in four women with heritable genetic disorders. Our results show that use of donor oocytes is a practical, successful, and currently available technique for the prevention of genetic disorders.

Donor oocytes can be used to overcome female infertility owing to ovarian causes and to decrease the burden of certain genetic diseases. We have established an anonymous, matched, fertile donor oocyte programme under the University of Iowa internal review board's approval and oversight. Donors are screened for sexually transmitted and genetic diseases, and phenotypic characteristics of the donors and recipients are then matched as much as possible according to a priority list made by the recipient. So far, four women have entered our programme for the purpose of preventing transmission of genetic disease and their cases are detailed.

Heritable genetic diseases have been listed as an indication for the use of donor oocytes for several years.¹ Despite the increasingly large number of recognised heritable genetic disorders, there are no reports detailing experience with these patients in donor oocyte programmes. Therefore, we report our experience with the use of donated oocytes from anonymous, matched, fertile, and genetically screened donors for the prevention of genetic disease. These preliminary results suggest that use of donor oocytes can be a successful technique for the prevention of genetic disorders.

Case reports

CASE 1

This patient was a 33 year old white female who had had a 19 week spontaneous abortion (sex unknown) followed by a term, live born, karyotypically normal male with multiple congenital anomalies including microcephaly, tetralogy of Fallot, hypospadias, and dysmorphic features. The patient was then discovered to have a large uterine septum which was resected hysteroscopically by her referring physician. Her third pregnancy resulted in a live born male at 34 weeks, again with a normal

karyotype but with multiple congenital anomalies including genitourinary tract anomalies. These anomalies resulted in neonatal death. Pedigree analysis showed a maternal nephew born with genitourinary tract anomalies. Although the precise aetiology of these malformations was unknown, the findings of genitourinary tract anomalies in the mother, her two children, and her nephew suggested the possibility she was a carrier for an X linked recessive mutation.

After extensive counselling, she entered our donor oocyte programme. An anonymous donor with no history of genetic diseases was matched phenotypically with recipient characteristics. The donor underwent a programmed combined clomiphene citrate/human menopausal gonadotrophin stimulation regimen. Thirty-six hours after an ovulatory dose of human chorionic gonadotrophin (hCG), a total of 12 mature oocytes was retrieved. Nine out of the 12 oocytes were fertilised and, 24 hours later, three pronuclear stage embryos were transferred into the recipient's fallopian tube under laparoscopic guidance. The recipient's endometrium was synchronised to the donor's cycle by GnRH-agonist suppression followed by oestrogen and progesterone replacement therapy as described by Meldrum *et al.*² A single intrauterine pregnancy was established and she subsequently delivered a normal female infant at term by caesarean section.

CASE 2

The patient was a 25 year old white female who desired oocyte donation because she was a known carrier for mitochondrial myopathy with cytochrome C oxidase deficiency, an X linked recessive lethal disease. Her past history was remarkable for a pregnancy which resulted in a term live born male seemingly without complications. This child was subsequently diagnosed as having mitochondrial myopathy and he died at 20 months from complications of the disease.

After extensive genetic counselling, she began oral contraceptive therapy and enrolled in our donor oocyte programme. A phenotypically matched, anonymous donor underwent ovarian stimulation, as described in case 1, with 19 mature oocytes retrieved under ultrasound guidance. Sixteen of the 19 oocytes were fertilised and four pronuclear stage embryos were placed into the fallopian tube by laparoscopy. One embryo implanted and she delivered a healthy male infant at term.

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CASE 3

This patient was a 28 year old female who had Gardner syndrome, an autosomal dominant disorder characterised by multiple colonic adenomatous polyps with a high malignant potential. She underwent a colectomy at the age of 15 and had a tubal ligation at the age of 22 to prevent transmission of the disease. Owing to her desire to have children, she enrolled in our donor oocyte programme. She has undergone a total of three transcervical fresh embryo transfers (four embryos each time) and one frozen embryo transfer (five embryos transferred) with no pregnancies resulting. Two different, matched, fertile donors were used for these cycles. She is planning further attempts with remaining frozen embryos.

CASE 4

This patient was a 31 year old female who is an obligate carrier for the fragile X syndrome. This diagnosis was determined by extensive cytogenetic and DNA linkage studies which showed that the patient's father had the fragile X syndrome. To avoid the possibility of transmitting this condition to her offspring, this patient entered our donor oocyte programme. Fourteen oocytes were retrieved from an anonymous donor and nine of these fertilised normally. Four pronuclear stage embryos were transferred to the fallopian tube by laparoscopy. A heterotopic pregnancy resulted with the tubal pregnancy removed by laparotomy at 10 weeks gestational age. The intrauterine pregnancy is in the third trimester at present.

Discussion

Heritable genetic disorders are a great dilemma for afflicted couples. Given the risk for each offspring to develop serious disease, many couples will not attempt conception. Although specific prenatal diagnosis is possible for many conditions, this was not the case for the couples described here. With the advent of donor oocyte programmes, new reproductive options now exist for couples at risk of transmitting genetic disorders.

Careful genetic screening of donors is important in all cases, particularly when oocytes are being used to prevent heritable genetic disease. This is accomplished in our programme by three generation pedigree analysis and by the inclusion of only fertile women with offspring free of genetic disease. The three

generation pedigree analysis questionnaire is completed by the potential donor and verified during an interview with a physician, as described for screening potential semen donors.³ Medical geneticists are consulted when family history concerns require their expertise and advice. As is the case with many donor semen programmes,⁴ we do not consider chromosomal analysis of donors to be necessary. The risk of a given subject having a balanced translocation is small, particularly in women with a normal reproductive history. If the family history is suggestive of a heritable balanced translocation (for example, a member having multiple miscarriages or unkaryotyped, malformed offspring or both), a donor karyotype would be performed. All donors are required to be under the age of 35 by the time a recipient's children would be delivered in an effort to decrease the chance of chromosomal abnormalities in these offspring.

Our initial results suggest that the transfer of embryos resulting from donor oocytes via the fallopian tubes is efficacious in these women, the majority of whom have no known infertility factors. Until a randomised clinical trial establishes that transcervical transfer of embryos is equal to transfallopian tube transfer in efficacy, we suggest that alternatives to tubal ligation as a means of birth control be considered in women who may desire to use donor oocytes sometime in the future.

Our experience with these patients indicates that donor oocytes are a practical, successful, and currently available means for achieving pregnancy and preventing genetic diseases. Women with these conditions should be made aware of this child bearing option and donors should be screened appropriately for genetic diseases before use of their oocytes. With increasing awareness by physicians and patients of this option for couples with heritable disorders, prevention of genetic disease may become a more frequent indication for the use of donor oocytes.

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