NEW DEBATE

How can the genetic risks of embryo donation be minimized?

Proposed guidelines of the French Federation of CECOS (Centre d’Etude et de Conservation des Oeufs et du Sperme)

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Embryo donation is now an acceptable practice which offers new possibilities to many infertile couples wishing to procreate. In France, embryo donation, like gamete donation, is controlled by law, but its application has been poorly developed because too many questions remained unsolved and because of the lack of practical guidelines. Here we report the results of the debate which took place within the Genetics Commission of the French Federation of CECOS and the proposed recommendations which followed, emphasizing the genetic background to be considered for embryo donation.

Key words: embryo donation/genetic risks/infertility/genetic guidelines/CECOS

Introduction

Assisted reproductive technology (ART) is offered as a widespread medical service for treating infertile couples who have a parental project. In the case of IVF with or without ICSI, supernumerary embryos may be cryopreserved for future transfer in the couple. French law prohibits creating human embryos using both female and male donor gametes. However, couples without a personal parental project may consent to transfer their own cryopreserved embryos to another couple to help them achieve their parental project.

The number of cryopreserved embryos is increasing regularly in all countries because fewer embryos are now being transferred after IVF attempts. In the USA, nearly 400 000 embryos were stored in 2003 (Hoffman et al., 2003). In France, the number of stored embryos was ~118 000 in January 2001, most of them being collected and conserved, in public hospitals, by the CECOS (Centre d’Etude et de Conservation des Oeufs et du Sperme). This number is estimated to increase by ~20 000 every year. We estimate that 5–10% of cryopreserved embryos could be available for donation because of couples giving up on their initial parental project. For instance, among 29 882 embryos cryopreserved in 11 out of 23 CECOS on December 31, 2002, a total of 2826, resulting from IVF in 756 couples, were clearly available for transfer to other couples.

Philosophical, ethical, religious and technical considerations have already been widely debated (Robertson, 1995; Van Voorhis et al., 1999; Söderström-Anttila et al., 2001; American Society for Reproductive Medicine, 2002a; Appleton, 2002; ESHRE Task Force on Ethics and Law, 2002; Newton et al., 2003), but medical guidelines for embryo donation are still to be clarified (Kingsberg et al., 2000). Guidelines for genetic screening of gamete donors have been proposed (Jalbert et al., 1989; American Society for Reproductive Medicine, 2002a), but genetic aspects of embryo donation are not well defined. They were debated and reviewed by the Genetics Commission of the French Federation of CECOS and are presented here.

Clinical and genetic background of embryo donation

Embryo donation may be offered to a couple in cases of double lack of gametes or gametic failure, or after several unsuccessful attempts at ART. Embryo donation may also be considered when there is a high risk of transmission of a severe genetic disease to the child or in the case of uncertainty of the mode of inheritance of a genetic disease in the family. Lastly, embryo donation could be proposed because gamete donation may be inadvisable, e.g. when azoospermia co-exists with an autosomal dominant or X-linked disease in the woman’s family.

Embryo donation is different from gamete donation since the recipient couple makes no contribution to the genetic background of the future child, whereas half of the genes are provided by one parent in the case of gamete donation. Furthermore, most gamete donors are healthy and, in some countries, such as France, having at least one child is a requirement before being accepted as a donor. Consequently,
the gamete donors are less likely to generate genetic anomalies. In contrast, most embryos available for donation have been conceived by couples who may carry known or unknown genetic alterations related to their infertility.

Embryo donation is also different from adoption because medical assessment of the child before adoption may result in the diagnosis of a genetic disease, allowing an informed decision by the couple. In the case of embryo donation, the only available procedure for genetic testing of the embryo prior to transfer would be preimplantation genetic diagnosis (PGD), but this procedure is labour intensive and its widespread use is still much debated.

Although infertility in one or both biological parents may be due to non-genetic causes, such as tubal obstruction or male reproductive tract infection, it may also be genetic in origin. Sometimes, a genetic abnormality, such as a chromosome rearrangement, a deletion of the Y chromosome or a CFTR (cystic fibrosis transmembrane conductance regulator) mutation, has been diagnosed in one or both biological parents and the probability of transmission to the embryo may then be evaluated. In other cases, the origin of gametic failure is unknown and a genetic cause cannot be ruled out. Therefore, it cannot be excluded that supernumerary embryos available for donation are at increased risk of carrying a known or unknown genetic defect related to parental infertility.

Guidelines for embryo donation

Embryo donation therefore raises several questions concerning this risk, such as (i) should the genetic background of the biological parents and their age be considered in order to exclude the donation supernumerary of embryos?; (ii) what kind of information should be looked for to exclude, or include, the donation of an embryo?; (iii) what is the level of genetic risk acceptable in embryo donation?; (iv) should other genetic factors be considered in matching embryos to recipients?; and (v) what information should be given to the recipients and to the donors?

In order to issue guidelines for embryo donation in the Federation of CECOS, two general principles were used: (i) embryos with a well identified genetic risk warranting a prenatal diagnosis, or at high risk of infertility for the resulting child, should not be made available for donation; and (ii) the recipient couples should be clearly informed of the genetic risk in any pregnancy following ART, but also of a potential genetic risk related to infertility in the biological parents, which cannot be ruled out by medical investigations.

Collection of information and genetic testing prior to embryo donation

Before IVF, genetic testing of the biological parents is usually restricted to investigations done in the context of their infertility, as karyotype or detection of CFTR mutations or Y chromosome microdeletions.

Prior to embryo freezing, the consultation could also take into account the possibility of future embryo donation. Therefore, a pedigree should be established in all cases in order to identify the possibility of a genetic disease in the family and, if found, referral to a geneticist should be considered.

According to French law, a consultation must be provided at the time of donation to obtain the final consent of the biological parents. This consultation is also required to obtain medical information, laboratory data such as screening results for infectious diseases (hepatitis B and C, HIV) and family details from embryo donors. This should provide an opportunity to review the results of the tests carried out before IVF, to check the pedigree of the genitor family, looking for hereditary diseases in the family, and to decide on further testing of the biological parents, if needed. In this latter case, donors may refuse further testing of no direct interest to them, but their embryos are then not eligible for donation. No systematic genetic testing, such as karyotyping, is required from the biological parents if not otherwise indicated.

Other information, such as blood groups and morphological characteristics (body weight, height, hair, eye or skin colour) of the biological parents, is also collected, since, as in gamete donor programmes, the recipients may wish to share some of their physical traits with the future child (Le Lannou et al., 1998).

No genetic testing, other than identification of a potential incompatibility between the mother and the fetus, such as a rhesus allo-immunization, is warranted in the recipient couple.

Genetic risks excluding embryos from donation

According to the opinion of most members of the Genetics Commission of the French Federation of CECOS, a number of genetic risks appear clearly to be a valid reason for excluding an embryo from the donation process (Table I).

The existence of a balanced chromosomal structural abnormality, a low level of autosomal mosaicism in at least one biological parent, as well as a Y chromosome microdeletion should be a reason for removing an embryo from the donation process. On the other hand, mosaicism involving a gonosome or chromosomal variants could be accepted depending on the geneticist’s opinion.

Advanced donor age may also increase the occurrence of a genetic anomaly in embryos. The risk of aneuploidy significantly increases with maternal age, whereas paternal age is related to a higher risk of dominant mutations and structural chromosomal rearrangements. Following the guidelines for sperm donation, embryo donation should not be accepted if the biological father is > 40 years of age (American Society for Reproductive Medicine, 2002b). Because the increase in chromosomal risk with maternal age is related to nondisjunction during maternal meiosis, embryo donation should also be refused when the biological mother is > 38 years of age (the threshold for prenatal diagnosis of chromosomal abnormalities in France) in order to avoid the systematic prenatal diagnosis of aneuploidies after amniocentesis during the recipient’s pregnancy.

In order to avoid the uncertainties and difficulties of defining genetic acceptability in embryo donation, the recommendation should be to exclude every embryo for which a prenatal diagnosis or a PGD would have been proposed to biological
parents. In the same way, embryos from couples with a personal history of birth of a child or of pregnancy termination of a fetus carrying multiple and unexplained malformations should not be offered for donation. Nowadays, the possibilities of detecting gene modifications involved in genetic diseases are still limited. However, knowledge of and available tests for achieving the detection of such genetic defects are increasing rapidly. Should these possibilities limit the acceptability of embryos for donation in the future? Probably not, but this could support further debate and revision of guidelines according to new genes and genetic diseases identified. Whatever the situation may be, every controversial situation, such as in the case of embryos from related parents, should be discussed within an ad hoc committee. In France, the Genetics Commission of the Federation of CECOS meets twice a year to discuss questions concerning cases of patients or donors.

Matching of embryos and recipients

Transfer of embryos with a specific but relatively benign risk, such as a Y chromosome microdeletion, to recipients with the same risk has been proposed to increase the number of available embryos. However, this is not an acceptable practice since a potential genetic risk has been clearly identified in the embryo.

Maternal age is an important parameter in screening strategies for the detection of fetal chromosomal abnormalities, in association with ultrasound and serum parameters. Aneuploidies mostly result from meiotic non-disjunction, occurring before or at fertilization, and thus are related to the donor. Indeed, in one study, there was no increased rate of aneuploidy in gestations of older embryo recipients (Kornafel and Sauer, 1994). When possible, the ages of female recipients and donors should be matched because it may allow prevention of chromosomal abnormalities without disclosing information about donation. Whenever a discrepancy between the donor and recipient ages is identified, screening criteria should be based on the biological mother’s age, but, whatever this latter may be, the recipient couple should be informed of the possible risk of increased pregnancy complications such as gestational hypertension or diabetes, pre-eclampsia, preterm or Caesarean delivery and low birth weight, as revealed by obstetric outcome data after oocyte donation (Sheffer-Mimouni et al., 2002).

Matching donor and recipient couples according to blood groups and morphological characteristics is recommended, although recipient parents must be aware that the availability of embryos for donation may limit such matching possibilities. In gamete donation, this type of matching is done mainly for psychosocial reasons, allowing the future parents not to inform their child of its conception story. In embryo donation, where neither parent will be the child’s biological parent, the same policy will be very difficult to apply. The consequence is that the future parents should be prepared to inform their child of its origin.

Conclusion

Embryo donation is a complex procedure which requires a great deal of medical attention. Besides screening for infectious diseases, the guidelines suggest that the origin of available frozen embryos is taken into account and that a careful assessment is made of the genetic risk related to infertility in the potential donors.

The Genetics Commission of the French Federation of CECOS proposes to assess this risk in the consultations preceding embryo donation, using available clinical and laboratory data, and adding relevant pedigree information. No systematic genetic testing is required and only tests related to specific issues raised by the clinical assessment should be performed. Embryos with a well identified genetic risk for the future child should not be made available for donation. The age of female donors and recipients should be matched. No matching related to the infertility status of donors and recipients is recommended. Any situation that would not correspond to the previous recommendations should be discussed on a case by case basis using a multidisciplinary approach.

The recipient couples should be clearly informed of the risk related to this specific procedure, including a possible increased risk of infertility in the offspring. These
guidelines should be revised regularly, taking into account new scientific data and evolution in the practice of ART. Furthermore, one should not ignore the more general debate on ethical questions and possible psychosocial implications raised by embryo donation.

References