

Patients' attitudes towards donation of surplus cryopreserved embryos for treatment or research

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BACKGROUND: The aim of the study was 2-fold: first, to investigate couples' reasons for not using cryopreserved embryos within the maximum storage period; second, to study their attitudes towards potential embryo donation for specific purposes. **METHODS:** A questionnaire was sent to 284 IVF/ICSI couples who experienced destruction of their cryopreserved embryos ($n = 1180$) because the cryopreservation period exceeded the Danish legislative limit of 24 months. **RESULTS:** Seventy-four per cent of the couples responded. The main reasons for not utilizing surplus embryos was 'successful delivery' (85%), 'consider family completed' (61%) and 'too short legislative limit for cryopreservation' (59%). Sixty per cent of the couples agreed to the concept of donation of cryopreserved embryos for infertility research, 57% responded affirmatively to donation for stem cell research and 49% for stem cell treatment, but only 29% agreed to the concept of donation to infertile couples. Multiple logistic regression analysis showed that delivery of a child after IVF treatment (OR 3.8, 95% CI 1.4–10.2) and female age <35 years (OR 2.2, 95% CI 1.3–6.0) were predictive of agreement to the idea of donation for stem cell research and stem cell treatment respectively; however, male age, duration of infertility, mode of conception (IVF or ICSI) and having IVF children were not significant predictors. The following predictive variables were entered into the analysis: female and male age, duration of infertility, IVF versus ICSI, donor semen and +/- IVF children. **CONCLUSIONS:** This study shows that 23% of all couples having cryopreserved embryos do not utilize them for further treatment within the legislative storage period of 2 years. A major reason is successful delivery. More than half of these patients agreed to the concept of donation of surplus outdated embryos for research, whereas less than one-third agreed to donation to other infertile couples. Based on these figures, an alternative utilization of surplus embryos for stem cell research would require a 100-fold larger pool of available embryos to provide a realistic basis for this purpose.

Key words: cryopreserved embryos/embryo donation/infertility treatment/research/stem cell

Introduction

Approximately one-third of all assisted reproductive technology-treated couples have surplus embryos of good quality following embryo transfer. These surplus embryos are usually cryopreserved for subsequent treatment cycles and are normally utilized by the couples. However, a fraction of the embryos are either left unattended, or reach a legislative maximum storage period without being used for treatment.

The fate of this spare group of embryos creates major clinical and legislative concern in many countries and has led to regulatory initiatives (Brinsden *et al.*, 1995; Saunders *et al.*, 1995; Andersen *et al.*, 1996; Edwards and Beard, 1997). Currently, legislation lays down a maximum storage period in most European countries (Jones and Cohen, 1999). Thus, embryos are disposed of, if there are no other options for their use.

In Denmark, cryopreservation was first allowed in 1992 with an initial maximum storage period of 12 months. In

1997 the storage period was prolonged to 24 months. Until June 2003, the exclusive use of surplus embryos was for infertility treatment in the couple, infertility research or disposal. Due to a recent change in legislation, however, utilization of surplus embryos for stem cell research and treatment was also allowed. Embryo donation to another infertile couple remains illegal.

As a consequence of the legislative limit of the storage period, ~2500 embryos are disposed of annually in Denmark. Considering alternative utilization of these embryos for treatment or research, one has to keep in mind that embryo donation for infertility treatment or for stem cell research raises ethical, moral and legal considerations regarding the status of the preimplantation embryo as a potential child (Söderström-Anttila *et al.*, 2001; McMahon *et al.*, 2003). Not surprisingly, a considerable number of potential donors abstain from donation of surplus embryos or wish to participate in decision-making processes regarding the donor

conditions or the research they may approve (Newton *et al.*, 2003).

A recent study investigated attitudes to embryo donation for research among 500 Australian respondents, who had embryos cryopreserved with a mean storage period of 2.3 years (range 3 months to 12 years) (McMahon *et al.*, 2003). Less than one-third responded to their questionnaire and, out of these, only one-third seriously considered donation for research. Similar figures were found in a Belgian study investigating the fate of unused frozen embryos from 196 couples at the end of the storage period of maximum 5 years (Laruelle and Englert, 1995).

Other studies have shown that factors affecting decision-making were found to be 'long time storage' and 'religious commitment'. Couples in favour of donation seemed more altruistically motivated and expressed a desire of helping another infertile couple or not to waste the embryos. Neither success in IVF treatment nor number of children at home seemed to predict willingness to donate (Lornage *et al.*, 1995; Newton *et al.*, 2003).

The present study had a dual purpose. First, to investigate the reasons why surplus cryopreserved embryos were not used by the couples. Second, to study the willingness to donate for specific purposes, and to identify characteristics of the patients, who would accept donation.

Materials and methods

A questionnaire with a postage-paid return envelope and a short information sheet was sent to IVF/ICSI couples, who according to the Danish law (which prohibits storage beyond 2 years), had cryopreserved embryos destroyed during a 5 year period from March 1997 to March 2002. In total, 1180 embryos were destroyed during this period (mean 4.2 per couple, range 1–13). The present cohort included all couples ($n = 284$), who had embryos destroyed.

Of the 284 couples, four had emigrated and were excluded, and one couple was excluded for other reasons. Two hundred and seven couples responded and returned a completed questionnaire (74.2%), whereas the remaining 72 (25.8%) did not respond despite a reminder 3 weeks after the initial contact.

During the 5 year period, our clinic performed 3569 embryo transfers after IVF and ICSI. In 1458 patients (40.8%), surplus embryos were cryopreserved. A total of 936 patients (64.3%) requested treatment within 2 years. In March 2002, 238 patients had embryos cryopreserved that had been frozen for <2 years. The remaining 284 couples (23%) had frozen embryos disposed due to Danish legislation.

Questionnaire

The items addressed included female and male age, type and duration of infertility, treatment method (IVF or ICSI) and delivery, reasons for not using the embryos, as well as attitudes towards embryo donation for infertility treatment or research, as well as stem cell treatment or research.

The survey comprised several types of questions. The first section ascertained demographic information and infertility history. In addition to age, the couples were asked about their history of infertility and former infertility treatment. The second section of the survey covered possible pregnancy history and outcome and children's morbidity. The third section aimed at clarifying reasons for omitting utilization of the cryopreserved embryos within the legislative limit

and consisted of 23 listed statements. The couple was asked to tick that particular statement best fitting the reason why they left the embryos unattended. For example, two of the reasons why the cryopreserved embryos were not used were: 'We have got one child and do not want more children' and 'We got twins and do not want more children'. The couple was able to choose more than one statement. This section also included space for additional comments.

In the last section of the survey, patient's attitudes towards donation of surplus embryos for infertility treatment or research or for stem cell treatment or research were explored. The response categories were 'yes', 'no' and 'do not know'. Prior to these questions, participants were given a short written explanation to embryo donation for the objects: infertility treatment or research and stem cell treatment or research. For example, the information given to the question concerning stem cell research was: 'The Danish Parliament is supposed to discuss an amendment to the present IVF legislation permitting research in so called stem cells. Stem cells can for example be immature unspecialized cells from the fertilized egg (embryo) having the ability to develop into all kinds of different tissue in the human organism. Recently it has become possible to isolate and grow these cells from fertilized eggs for a long time. It has been shown that cultured stem cells have the capacity to develop into different types of cells, for example nerve cells or cells secreting insulin, and hopefully such stem cells might be tools for treatment of a number of serious diseases in the future. A stem cell line is established by culturing some of these cells found in the 6–8 day old embryo. After having isolated the stem cells, the embryo as such no longer exists. Stem cells alone will never have the ability to develop into a new individual.'; 'If you had been asked, would you then have given your permission to utilization of your surplus embryos for stem cell research, provided that these embryos were exclusively used for research in the laboratory and never were used in other human beings?'

Statistics

The results were analysed using SPSS (Statistical Package for Social Sciences) version 10.0. Statistical significance was defined as $P < 0.05$. Frequencies were calculated for responses to questions on attitudes. Means and SD were calculated for continuous data (female/male age, gestational age and birthweight).

Separate multivariate logistic regression analysis was performed to examine predictors of the willingness to donate embryos for the four different outcomes: infertility treatment, infertility research, stem cell treatment and stem cell research. Outcome measures were dichotomously recorded as either 'yes' or 'no'. Responses in the category 'do not know' were not included in the analysis. The following five predictive variables were entered into the models: (i) female age, (ii) male age, (iii) duration of infertility, (iv) IVF or ICSI treatment, (v) +/– children after IVF treatment.

We used backwards elimination and excluded predictive variables not significantly associated with the outcome measure. Duration of infertility was separated into two groups: <5 years and ≥ 5 years of infertility, and IVF children was entered as a binary variable, either ≥ 1 child versus no children. Female and male age were entered as <35 years or ≥ 35 years.

Results

Demographic characteristics of the respondents included age, mode of treatment, duration of infertility, number of treatments and infertility diagnosis. Mean female age was 33.0 years. Mean male age was 35.2 years. IVF was performed in 73.8% of the patients, ICSI in the remainder.

Mean duration of infertility was 5.7 years (range 0–20), mean number of treatments 2.6 (range 1–9).

One hundred and seventy-five (84.5%) of the respondents conceived and delivered at least one child. About one-third of the patients had experienced a biochemical pregnancy or spontaneous abortion and ~10% an ectopic pregnancy during former treatment.

According to the routine clinical files, 43 (59.7%) of the 72 non-respondents had given birth to at least one child, whereas 20.8% did not conceive at all; 19.5% had experienced either a biochemical or ectopic pregnancy or a spontaneous abortion.

Table I presents reasons for abandoning cryopreserved embryos after expiration of the maximal embryo storage period. In the present study the 1180 disposed cryopreserved embryos originated from 3569 embryo transfers.

Apart from delivery (84.5%), the two main reasons for not using the embryos were that the couple considered their family completed after delivery of one, two or three children (31.9%), and that the couples found the maximum storage period of 2 years too short for family planning after a delivery following the IVF/ICSI treatment (58.5%). Other reasons were that the couple felt that they themselves were too old to

Table I. Reasons for abandoning cryopreserved embryos > 24 months in 207 couples (more than one answer possible)

	<i>n (%)</i>
I. Conceived and delivered	
Considered family completed:	
singleton delivery	15 (7.2)
twin delivery	48 (23.2)
triplet delivery	3 (1.4)
conceived spontaneously after treatment with fresh embryos	10 (4.8)
adopted a child	5 (2.4)
too old to raise children	34 (16.4)
unable to face further treatment	12 (5.8)
total	127 (61.4)
No wish for further treatment because:	
complicated pregnancy/delivery	27 (13.4)
pre-term delivery	4 (1.9)
morbidity in existing child	3 (1.4)
morbidity in existing twins/triplets	2 (1.0)
morbidity in parents	7 (3.4)
worried whether treatment would result in healthy children	13 (6.3)
total	56 (27.1)
No wish for further treatment because:	
the legislative limit for cryopreservation is too short	121 (58.5)
Unaware of treatment with thawed embryos:	
forgot the existence of the embryos	11 (5.3)
believed the legislation limit to 1 and not 2 years ^a	5 (2.4)
believed further treatment impossible after one delivery	11 (5.3)
total	27 (13.0)
Miscellaneous:	
pecuniary reasons	5 (2.4)
are divorced	10 (4.8)
no specific reason	6 (2.9)
preferred treatment at another clinic	0
moved to another part of the country	3 (1.4)
total	24 (11.6)
II. No conception	
No wish for further treatment	14 (6.8)

^a The storage time for cryopreserved embryos was extended from 1 to 2 years in 1997.

Table II. Attitudes towards donation of cryopreserved embryos for treatment and research (*n* = 207)

Donation to:	Yes	No	Uncertain
Another infertile couple	59 (28.5)	96 (46.4)	52 (25.1)
Infertility research	125 (60.4)	39 (18.8)	43 (20.8)
Stem cell research	117 (56.5)	36 (17.4)	54 (26.1)
Stem cell treatment	101 (48.8)	40 (19.3)	66 (31.9)

Values in parentheses are percentages.

raise more children (16.4%), complicated pregnancy and delivery (15.0%), adoption of a child or spontaneous conception after IVF treatment (7.2%), misunderstanding of the legislative limits for frozen embryos (7.7%) or no wish for further treatment (12.6%).

Table II shows the distribution of answers to the items concerning donation of the surplus embryos for research or treatment purposes. All couples answered these questions.

Of the couples, 28.5% responded affirmatively to embryo donation to other couples, 60.4% towards embryo donation for infertility research and 56.5 and 48.8% agreed to embryo donation for stem cell research and stem cell treatment respectively.

Four separate regression analyses were computed to examine predictors of agreement to embryo donation for the four different outcomes: (i) infertility treatment or (ii) infertility research and (iii) stem cell treatment or (iv) stem cell research. The following predictive variables were entered into the model: female and male age, duration of infertility, IVF versus ICSI treatment, and ≥ 1 child versus no children. The results of the regression analysis are presented in Table III. Excluding treatment with donor semen as a predictive variable in the analysis, none of the entered variables was independently predictive of agreement to embryo donation for infertility treatment or infertility research in the final models. In terms of embryo donation for stem cell research and treatment, ' ≥ 1 child' was independently predictive of agreement to both purposes, whereas female age < 35 years was independently predictive of agreement to stem cell treatment OR 2.2 (95% CI 1.3–6.0), although not independently predictive of agreement to embryo donation for stem cell research OR 2.3 (95% CI 1.0–5.2).

Though being obvious as a predictive variable, 'treatment with donor semen' was excluded from the regression analysis, as only nine couples had utilized donor semen. With respect to stem cell treatment, the couples treated with donor semen responded less positively than to infertility treatment and research though they were more agreeable than couples treated with husband sperm (unadjusted OR 1.4, 95% CI 1.3–1.6). Regarding embryo donation for stem cell research, no difference in attitudes was seen between couples treated with donor and husband semen (unadjusted OR 0.8, 95% CI 0.1–7.8).

Discussion

This study demonstrates that the main reason for not using the cryopreserved embryos was delivery of a child (children),

Table III. Multiple logistic regression analyses with odds ratios (95% confidence intervals) on agreement to embryo donation for different purposes

	Infertility treatment	Infertility research	Stem cell research	Stem cell treatment
Female age <35 years	1.8 (0.8–4.0)	0.9 (0.4–2.2)	2.3 (1.0–5.2)	2.2 (1.3–6.0) ^a
Male age <35 years	0.7 (0.3–1.5)	1.3 (0.6–3.1)	1.8 (0.7–4.9)	1.3 (0.5–3.2)
+IVF child	0.7 (0.3–1.9)	1.6 (0.6–4.4)	3.8 (1.4–10.2) ^a	2.1 (0.8–5.8)
IVF versus ICSI	1.4 (0.6–3.0)	1.6 (0.6–3.6)	1.4 (0.5–3.9)	1.5 (0.6–3.9)
Duration of infertility >5 years	1.3 (0.6–2.5)	1.3 (0.6–2.1)	1.3 (0.6–3.0)	1.3 (0.6–2.9)
+donor semen (unadjusted)	2.8 (2.3–3.5) ^a	1.3 (1.2–1.5) ^a	0.8 (0.1–7.8)	1.4 (1.3–1.6) ^a

^a*P* < 0.05.

as 85% of the couples having frozen embryos destroyed had already conceived. The validity of the conclusions obtained in the present study is reinforced by the inclusion of all couples, who had embryos destroyed during the given period.

Sixty-one per cent of the patients considered their family completed after delivery or adoption, and ~16% of this subgroup considered age as a limiting factor, finding themselves too old to raise children. Among patients who had delivered, 58.5% found the cryopreservation period too short. This suggests that a 2 year cryopreservation limit does not meet the needs of a large group of patients. It should be emphasized that all treated couples at our clinic have no common children, as this is a criterion for treatment free of charge within the Danish National Health System. Furthermore, this group has a favourable fertility potential, and utilization of the cryopreserved embryos for fertility purposes would only put minimal strain on the woman to be treated. A Swedish study by Svanberg *et al.* (2001) supported this view by concluding that a positive outcome of the original IVF treatment and a short maximum legal storage time were the most common reasons for discarding embryos. Considering that the maximal time span from delivery to the expiry date of frozen embryos is limited to 15 months during which the couple has to plan and be prepared for another pregnancy, the magnitude of these figures may not be surprising and calls for an amendment to the legislation. According to the figures obtained from the Danish Birth Registry (Danmarks Statistik, 1995–2003), the average time interval between delivery of the first and second child in Denmark is currently 3.0 years (National Board of Health, personal communication). In 2002, the mean number of children born in a Danish family was 1.83 (Danmarks Statistik, 2003).

Legislation permitting utilization of cryopreserved embryos should include an optimal time span for family planning giving this permission, and a prolongation of the legislative limit to 4 or 5 years would meet these demands and put Denmark in line with a number of other European countries, as no limits exist in Germany and The Netherlands and most other countries have a 5–10 year limit (Jones and Cohen, 1999).

More than half of the couples in the present investigation were open to the idea of embryo donation for infertility (60.4%) and stem cell research (56.5%), whereas less than one-third of the couples responded affirmatively to the concept of embryo donation to other infertile couples (28.5%). The couples responded a little less affirmatively to stem cell treatment (48.8%).

In terms of the 2500 embryos discarded annually in Denmark as a potential source of establishing stem cell lines, approximately half of them would be available for stem cell research. If couples were to act upon their expressed openness to donation for this item, up to 1250 embryos could possibly be available for stem cell research. It can be estimated that ~60% of these embryos will survive thawing (750), and considering a success rate at ~10–15% in developing blastocysts from these cryopreserved embryos, this would account for ~100 blastocysts annually. Success rates of establishing human embryonic stem cell lines from blastocysts are currently rather poor, as only <5% can be developed into stem cell lines. Therefore, <10 stem cell lines annually is a likely estimate of the number of cell lines that would result from donated surplus cryopreserved embryos in Denmark. These figures seem negligible compared to the assumed demands as experienced from histocompatibility banks showing that the number of stem cell lines would be of the order of thousands to cover the majority of genetic variants required. Many smaller countries would probably end up in a situation similar to Denmark. This emphasizes the necessity of wider collaborations, such as the establishment of a European stem cell bank.

The option of donating surplus embryos to other couples or for research is available in many other countries (Jones and Cohen, 1999; Klock *et al.*, 2001). In a study by Van Voorhis *et al.* (1999), ~12% were willing to donate for infertility treatment when cryopreservation was <2 years, and this is consistent with other studies (Saunders *et al.*, 1995: 2.9%; Hounshell and Chetkowski, 1996: 4.1%; Lornage *et al.*, 1995: 5.2%). According to McMahon *et al.* (2003), 10% donate their embryos for research; no significant predictors of intention to donate were found by regression analysis, though there was a non-significant trend for those who were religious to be less inclined. Similar to our results, Newton *et al.* (2003) found it difficult to identify predictors of personal willingness to embryo donation.

Thus, patient willingness to donate is highly dependent on the aim of donation, and generally, patients seem more reluctant to donate for infertility treatment compared to donation for research.

The rather low acceptance of embryo donation to other couples in our study may also reflect that this is currently illegal in Denmark.

Compared to other studies, willingness to donate for infertility treatment seems more pronounced in the present material,

although fewer of our couples responded affirmatively to this option compared to donation for research. One explanation could be that in our study the answers only reflect a theoretical situation, as these couples have actually completed their involvement with assisted reproductive technology and are therefore not really potential donors, whereas one might expect less affirmation to donation facing an immediate request, as shown by Laruelle and Englert (1995).

Presumably, the more reluctant attitude towards embryo donation to other infertile couples than to areas of medical research has at least two different causes. First, couples in infertility find it difficult to donate embryos to other infertile couples while they themselves cannot be sure that they will ever have a child/children of their own. Second, infertile couples may be opposed to the thought of other people raising their biological child/children, especially when it in many cases would be a sister or a brother to the their own children. These assertions are supported by the high level of agreement towards embryo donation to other infertile couples in couples treated with donor semen (7/9, 77.8%). Couples treated with donor semen are likely to feel an obligation to help other couples in a situation similar to their own. This is in accordance with other studies showing that couples affirmative to donation for infertility treatment or research reveal an altruistic motivation (Lornage *et al.*, 1995; McMahon *et al.*, 2003).

Multivariate logistic regression analysis identified two independent predictive factors of agreement to embryo donation for stem cell research, 'having a child' and 'female age <35 years'. It is understandable that it is easier for younger women who already have a child to donate embryos for medical research.

It should be emphasized that the results obtained in the present study have not been associated with various demographic criteria such as social status or religious commitment. However, a former investigation based on national data from the Danish IVF Registry on attitudes towards twins and single embryo transfer, including all twin mothers (both IVF and non-IVF) and all IVF singleton mothers who delivered in Denmark in 1997, observed no differences in social position between IVF and non-IVF mothers when compared by a standardized method including seven items about school education, vocational training and job position (Pinborg *et al.*, 2003). Further, religious affiliation was not considered, as religious commitment generally is unlikely to be a major determinant in Danish society. Another limitation is that the items in the present study comprehend only the hypothetical idea of donation, as these patients were not in a current treatment where donation was an real possibility.

In conclusion, this study shows that about one-fourth of all patients having surplus embryos cryopreserved does not

utilize these for additional treatment, mainly due to successful treatment outcome in former treatment with fresh embryos and an insufficient storage maximum of 2 years. Patients were more open to the concept of embryo donation to infertility or stem cell research than to infertility treatment. However, the quantity of available outdated cryopreserved embryos in Denmark seems too modest to provide a realistic source for establishing of stem cell lines for research. In the light of these findings, we suggest the legislative limit be prolonged to 5 years in Denmark.

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Submitted on December 19, 2003; resubmitted on May 18, 2004; accepted on July 6, 2004