

Trends in embryo disposition decisions: patients' responses to a 15-year mailing program

V. Provoost^{1,*}, G. Pennings¹, P. De Sutter², A. Van de Velde, and M. Dhont²

¹Bioethics Institute Ghent, Ghent University, Blandijnberg 2, B-9000 Ghent, Belgium ²Department of Reproductive Medicine, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium

*Correspondence address. Tel: +32-50315973; Fax: +32-9-264-41-87; E-mail: veerle.provoost@ugent.be

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BACKGROUND: This study examined the responses of patients of a Belgian fertility center to mailed requests to make or renew an embryo disposition decision (EDD), over a period of 15 years, to investigate trends in the decisions.

METHODS: A retrospective analysis was performed on a mailing program from 1992 to 2006, for patients, of the Department of Reproductive Medicine, Ghent University Hospital (Belgium), from whom embryos had been cryopreserved at least 2 years.

RESULTS: In 15 years, 3840 EDD forms were prepared for 2334 couples or female patients. The number of forms increased from 21 in 1992 to 558 in 2006. Each year, around a third of the forms were not returned. In general, a quarter of patients who received more than one form never answered. Donation to others for reproduction was overall the least popular option and decreased over the years. The rising trend in decisions to discard reversed into a negative trend from the introduction of donation for science (1997). Since then, donation for science has been the most popular option and its popularity increased with time. In 15 years, 2504 embryos were donated for science. More than a quarter of the patients who chose more than one final EDD in different years did not select the same EDD the second time.

CONCLUSIONS: This study showed a positive trend in donation for science and a negative trend in donation to others and discarding. A substantial number of individual patients chose different types of EDDs in consecutive mailings, which shows that advance EDD directives should be used with caution.

Key words: embryo disposition / cryopreserved embryos / ethics / stem cell research / informed consent

Introduction

The cryopreservation (and later transfer) of supernumerary embryos is now offered as a standard practice in most clinics. For the patients, it has brought opportunities along with ethical and emotional challenges related to the need to make a decision about (i) whether or not to have the embryos transferred in a subsequent cycle (and therefore continue the storage temporarily), and (ii) a final embryo disposition. For this final embryo disposition decision (EDD), the patients typically have the following options: donation to others for reproduction; donation for science and discarding.

The increase in the use of cryopreservation of supernumerary embryos after an IVF or ICSI cycle has led to stockpiles of stored embryos worldwide, causing logistic as well as ethical concerns (Edwards and Beard, 1997; Hoffman *et al.*, 2003; Bankowski *et al.*, 2005; Walsh *et al.*, 2010). The ethical difficulties are especially hard to

address in the absence of national legislation on what should be done with the embryos and who is allowed to make the decision (Pennings, 2000). Many centers have attempted to address this situation by sending their patients letters to ask them to make or renew an EDD in the hope of reducing the number of 'abandoned' embryos (Brzyski, 1998). However, substantial numbers of patients have been reported to leave such requests unanswered (Brzyski, 1998; Newton *et al.*, 2007).

To date, no reports have been published covering patients' responses to these requests in general and its' evolution over the years, apart from a French study in 1995 covering 6 years (1987–1992) based on six successive yearly questionnaires for 145 couples who had cryopreserved embryos (Lornage *et al.*, 1995). This study suggested a shift in EDD preference from donation to others to discarding. A few studies have described patients' decisions after a period of embryo storage (Klock, 2001; Cattoli *et al.*, 2004; Newton *et al.*, 2007). However, most quantitative studies on patients' EDDs have had small sample sizes (Van

Voorhis et al., 1999; Klock, 2001; Svanberg et al., 2001; Hammarberg and Tinney, 2006) and/or low response rates (McMahon et al., 2003; Hammarberg and Tinney, 2006) or they have measured intentions, preferences or attitudes instead of actual decisions (Bangsbøll et al., 2004; Burton and Sanders, 2004; Lysterly and Faden, 2007; Newton et al., 2007; Nachtigall et al., 2009; Lysterly et al., 2010). One study including data over a long period of time only used this data for comparisons of categories of patients and did not report on any trends within the data (Hill and Freeman, 2011).

In 1992, the Department of Reproductive Medicine, Ghent University Hospital (Belgium) set up a mailing program to contact patients and ask them to make or renew an EDD. The program continued until 2007, when a Belgian law on assisted reproductive medicine and the destination of supernumerary embryos and gametes was put into practice. This law set a maximum duration of storage of 5 years (with possible exceptions) and obliged patients to make a decision prior to their first treatment (Pennings, 2007). This study describes patients' responses to the mailing program since the start of the program in 1992–2006.

Materials and Methods

Patients

From 1992 until 2007, all patients of the Department of Reproductive Medicine, Ghent University Hospital (Belgium) who had embryos in storage at the department were sent an EDD form by standard mail every 2 years following the year in which their embryos were cryopreserved. The first 2 years of embryo storage are included in the price of the retrieval cycle. After 2 years of storage, patients who decided to continue storage were asked to pay 125 euros for two more years of storage. Patients were asked to complete and send back the form by means of which they could make or renew an EDD. Inclusion criteria for the mailing program were (i) having embryos stored at the center for at least 2 years, (ii) without having contacted the center to renew their decision on their own initiative. This EDD mailing program was changed in 2007 with the introduction of the law on medically assisted reproduction and the disposition of supernumerary embryos and gametes.

Procedure

Each year from 1992, all patients whose embryos were cryopreserved (or who asked to continue storage) 2 years before were mailed. No reminders were sent. For patients whose form was returned as undeliverable because they moved, the general practitioner was contacted to obtain the current address, and (when successful) the form was sent out again. The mailing procedure included the use of a personalized cover letter signed by the head of the department and the EDD form that consisted of basic information on the patient and the embryos (patient name and date of birth; cycle number, date of embryo freezing and number of embryos). The quality of the cryopreserved embryos was not reported on the form. At the time of cryopreservation, the patients were informed about the quality of the cryopreserved embryos and about the policy of the clinic not to freeze embryos with $\geq 25\%$ fragmentation. Patients were instructed to tick the box next to their preferred option and to have the document signed by both partners except when the patient was a single woman. At the start in 1992, the EDD form provided three options: continued storage for two more years and two options for a final EDD: anonymous and unconditional donation to other(s) for reproduction or discarding. From 1997 onwards, patients were offered the option of donation for science as a generic option (with no possibilities

to choose or exclude types of research). Initially, data were stored in written format and were digitalized between 2007 and 2009. Over the 15-year period, three staff members worked on the EDD mailings. One of them (A.V.) worked on the program for the entire period, always assisted by one colleague.

Embryos were stored in one or more straws per batch resulting from one retrieval cycle and patients received a form for each batch of embryos stored at the center. When embryos were stored resulting from two cycles in 1 year, the patient received two forms. When patients decided to continue storage for two more years or when they did not reply the EDD form, they received a new EDD form 2 years later unless they made another decision about the disposition of their embryos in the mean time (for instance, to use them in a subsequent treatment cycle). The embryos of the patients who did not respond or reach a final EDD remained in storage until the end of 2007, when all embryos that were stored for >5 years were discarded, in accordance with the law. Patients who decided to use their stored embryos for their own treatment but were unsuccessful or who wanted more children frequently had a new retrieval cycle and hence sometimes new embryos in cryopreservation for which they received an EDD form 2 years later. The data were stored in records per form for a particular batch of embryos. Summarizing variables were computed per patient: number of forms received and response series over time. Data were stored on whether patients' had answered, whether they had moved without notifying the clinic and, when they answered, what EDD they chose for this batch of embryos: continue storage, donation to others, donation for science or discarding. Information about the marital status (separation of the couple or the death of one of the partners) was not solicited in the form but was sometimes specified. When offered, this information was also included in the file. When patients asked for another disposition for their embryos (for instance, to transfer them to another hospital) or provided extra information (for instance, on how they felt about the mailing program or the decision-making), this was also categorized. Linking with patient files was not done for privacy reasons. This study was approved by the Ethics Committee of the Ghent University Hospital.

Analyses

Bivariate analyses were performed using Fisher's exact or Kruskal–Wallis, Monte Carlo version (StatXact) for ordered variables. $P < 0.05$ was considered statistically significant. We compared the outcome of the EDD mailing (response or decisions) with the number of stored embryos in the batch, the duration of embryo storage, the age of the female patient at the time of the form and the patients' marital status at the time of the form. The categories 'no reply' and 'undeliverable' were combined for most of the analyses.

Logistic regression analyses (forward stepwise Wald, PASW) were used with outcome of the EDD mailing as the dependent variable (response versus non-response; continued storage versus final EDD; or type of final EDD versus other EDDs). The year in which the form was sent, number of embryos in the batch, duration of embryo storage in years and the age of the female patient at the time of the form were used as a continuous variables. Variables with a $P < 0.05$ in the bivariate analyses were entered as covariates. Regressions for the type of EDD were calculated for all forms, with a final EDD over the last 10 years (since the introduction of the option 'donation for science').

Results

During the 15-year period, 3840 EDD forms were sent out to 2334 couples or female patients asking them to make or renew a decision about the disposition of their cryopreserved embryos. The number of

forms in the mailing program increased from 21 in 1992 to 558 in 2006, also demonstrating the rise in the number of embryos stored for at least 2 years (Supplementary data, Fig. S1). The batches of embryos referred to in the forms were cryopreserved between 1989 and 2004, and the number of embryos in these batches ranged from 1 (in 15.9% of forms) to 28 (in 0.1% of forms). The mean number of embryos per batch was 4.53 (median 4). At the time of the mailing procedure, the embryo storage time ranged from 2 years for 2594 forms (67.6%) to 14 years for 4 forms (0.1%). The embryos were stored for 3.03 years on average (median 2 years).

The women to whom the forms were addressed during the 15-year period were born between 1951 and 1984. At the time of the mailings, they were between 20 and 52 years old (average 34.96 years, median 35). In Table I, the age of the female patient and the number of embryos referred to in the forms are presented in categories, along with the marital status of the patients at the time of the mailing. Of all received forms ($n = 2412$), 96.8% were heterosexual couples who mentioned no changes in their marital status since the start of treatment. In 0.8% of the forms ($n = 20$), the patients disclosed their separation (all heterosexual couples). In 1.4% of the forms the patients were single women ($n = 27$; 1.1%), lesbian

couples ($n = 2$; 0.1%) or one of the partners died during the time when the embryos were stored ($n = 6$; 0.2%).

Response over the years

Overall, for the 15-year period, the response rate for the forms was 62.3%. In addition to the 2391/3840 fully completed forms, 21 forms (0.5%) were returned partly completed, mostly with one of the partners' signature missing (Table II). In 34.0% ($n = 1306$) of cases, the forms were sent without reply while for 3.2% ($n = 122$), the forms could not be delivered because the patients had moved and had not updated their addresses. The latter category consisted of patients whose general practitioner had not been able to provide information about their current addresses.

Over the 15-year period, there was a statistically significant increase in non-response ($P < 0.001$), mainly due to a cumulative effect of patients who did not respond or were not reachable and stayed in the database for subsequent mailings, frequently resulting in another non-response. Looking at the patients' response to their first EDD form over the 15-year period ($n = 2323$), thus ruling out this cumulative effect, there was no significant trend. Three quarters of all patients (75.0%) replied to their first EDD form (second half of Table II). For 22.5% of first forms, the patient did not respond and in 2.4% the first form was undeliverable. In the bivariate analyses, there was no significant association with the number of embryos or duration of

Table I Number of embryos referred to in the form and age and marital status of the female patient at the time of the mailing procedure.

	<i>n</i>	%
No. of stored embryos per form ($n = 3837$) ^a		
<5	2693	70.2
6–10	907	23.6
11–15	186	4.8
16–20	25	0.7
21–25	23	0.6
>25	3	0.1
The female patient		
Age at the time of the mailing ($n = 3840$ forms)		
<25	50	1.3
26–30	535	13.9
31–35	1613	42.0
36–40	1202	31.3
41–45	392	10.2
46–50	47	1.2
>50	1	0.0
Marital status ($n = 2412$) ^b		
Heterosexual couple: no new info	2357	97.7
Separation of heterosexual couple	20	0.8
Death of a partner	6	0.2
Single woman	27	1.1
Lesbian couple	2	0.1

^aData missing for three cases for 'nr of embryos in storage'.

^bUnsolicited information. $n =$ all fully and partly completed forms.

Table II Outcome of the EDD mailing.

	<i>n</i>	%
Outcome of all forms over 15 years ($n = 3840$)		
Undeliverable	122	3.2
No reply	1306	34.0
Reply of partly completed form	21	0.5
Reply of fully completed form	2391	62.3
Continue storage	874	22.8
Donation to others	323	8.4
Donation for science	613	16.0
Discarding	568	14.8
Two final EDDs	8	0.2
Transport of the embryos ^a	5	0.1
Outcome of all patients' first form over 15 years ($n = 2334$)		
Undeliverable	56	2.4
No reply	525	22.5
Reply of only partly completed form	11	0.5
Reply of fully completed form	1742	74.7
Continue storage	673	28.8
Donation to others	245	10.5
Donation for science	405	17.4
Discarding	410	17.6
Other decision ^a	9	0.4

^aThese patients wanted to transport the embryos to another center (4) or their home to be discarded (1).

storage. The age of the female patient at the time of the letter was significantly associated with the patients' response to the first form in a bivariate analyses ($P < 0.001$), suggesting that women who did not respond were slightly older (mean 34.09; median 34) compared with those who did (median 33.94; median 34), but this variable was not upheld as a predictor in the regression model.

Embryo disposition decisions

On 36.5% of all received forms (874/2391), the patients opted for continued storage while on 63.4% (1512/2391) of the forms they chose a final EDD or two final EDDs. There was no significant trend over the years in the proportion of decisions to continue versus discontinue embryo storage. This analysis was based on all patients' first forms to avoid cumulative effects. The decision to continue storage was to a small effect related to the age of the women at the time of the letter ($P < 0.001$) and the number of embryos referred to in the letter ($P = 0.014$). On average, the women deciding to continue storage were somewhat younger (33.23 years; median 33) compared with those who chose a final EDD (34.39; median 34; $P = 0.004$). Decisions to continue storage were also made slightly more often about batches with a higher number of embryos (4.92; median 4) compared with final EDDs (4.30; median 3; $P = 0.034$). Both the number of embryos in the batch as well as the age of the woman were identified as predictors in the logistic regression model although the effect of these two variables is small [odds ratios (ORs) close to 1; Table III].

Of all forms in which the patients opted for one final EDD ($n = 1504$), donation for science was the most popular disposition option over the years (40.8%), followed by discarding (37.8%). On 21.5% of forms with a final EDD, patients chose to donate to others. On eight other forms, the patients chose two dispositions: donation to others or donation for science (five) and donation for science or discarding (three). All except one of these patients left the final choice to the center. In the latter case, the patients wanted to donate the six embryos with the highest quality to others and the six lower quality embryos for science. Overall, over the 15 years, a final EDD was chosen for 6687 embryos: 1611 embryos became available for donation to others, while 2504 embryos were donated for science and 2572 embryos were discarded.

A significant time trend was found in the final EDDs chosen (Fig. 1). Over the 15 years, there was a proportional decrease in decisions to donate to others ($P < 0.001$). From 1997, donation for science was increasingly popular ($P < 0.001$), while there was a decrease in decisions to discard ($P < 0.001$). Table IV shows the proportion of final EDDs over the last 10 years of the mailing program, as of 1997, when the option 'donation for science' was introduced (Table IV; $n = 1399$).

Further analyses were performed for the last 10 years only. Apart from an association with the year in which the form was sent, bivariate analyses suggested that patients donated more often for science when the number of embryos was lower (mean 4.08; median 3) compared with the patients who opted for another final EDD (mean 4.51; median 4; $P = 0.020$) and that the duration of storage was associated with the choice to discard ($P = 0.032$). Batches of embryos that were discarded had been stored slightly longer (mean 2.60; median 2 years) than batches that were donated to others or

Table III Logistic regression of the decision to continue storage versus a final EDD and of each of the final EDDs.

Remaining predictors	OR	95% confidence interval	P-value
Continue storage versus final EDD ^a			
Number of embryos	1.04	(1.01–1.07)	0.009
Age of the female patient	0.93	(0.91–0.96)	0.000
Final EDDs			
Donation to others			
Year in which the form was sent	0.89	(0.85–0.93)	0.000
Donation for science			
Year in which the form was sent	1.16	(1.12–1.21)	0.000
Discarding ^b			
Year in which the form was sent	0.93	(0.89–0.96)	0.000
Separated (versus still together) ^c	0.13	(0.03–0.63)	0.011

^aRegression for all patients ($n = 1733$), including all received forms where the patients chose either to continue storage or one of the three final EDDs. Continuing storage was coded as 1, and final EDD as 0.

^bRegression for each of the final EDDs in the last 10 years, as of 1997 ($n = 1399$). In a regression of discarding of the years prior to the introduction of donation for science, the year in which the form was sent remained in the model (OR: 1.53; confidence interval: 1.15–2.04; $P = 0.004$).

^cIn a variant of the model excluding single women; lesbian couples and couples where one of the partners had died ($n = 1378$).

for science (mean 2.57; median 2 years). The number of embryos in the batch was not associated with the decisions to donate to others or to discard, and the age of the women was not associated with any of the three final EDDs. The patients' marital status was the only statistically significant association: patients who wrote on the form that they were separated more often had their embryos discarded compared with the other patients (7/9 versus 486/1369; $P = 0.013$). In the logistic regression analyses, all variables that were significant in the bivariate analyses were included. As shown in Table III, the year in which the form was sent was significant for all three dispositions. As time increased, donation for science increased, while donation to others and decisions to discard decreased. In fact, time was the only remaining predictor in all three regressions except for the effect of the marital status on the discarding decision. The latter finding was based on a variant of this regression for discarding, excluding lesbian couples, couples where one partner had died and single women ($P = 0.011$). The effect of the separation of the couple on the choice to discard the embryos could be underestimated because information about a separation was not solicited on the form itself and only occasionally volunteered by patients. Moreover, it is possible that separated couples are represented to a greater proportion in the group of patients who do not reply their forms. Interestingly, Fig. 1 shows a rise in discarding decisions up to 1997 when the trend changes and the proportion of discarding decisions decreases over time. A regression analysis of decisions to discard in the years prior to 1997 (and the introduction of donation for science) also identifies the year in which the form was sent as a significant predictor of the discarding

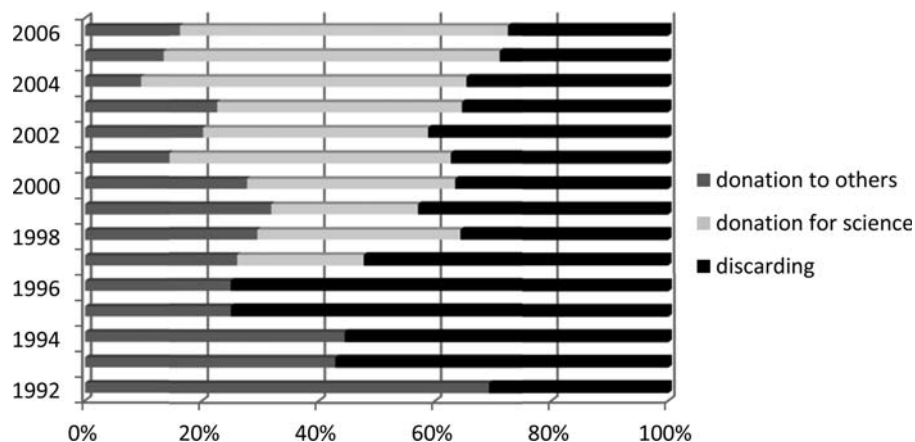


Figure 1 Proportion of final EDDs chosen over the years (1992–2006; N=1504).

Table IV Final EDDs over the last 10 years of the mailing program (n = 1399).

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Total
Donation to others	18 (26.1)	39 (29.5)	38 (31.9)	35 (27.8)	21 (14.5)	32 (20.3)	34 (22.7)	13 (9.6)	20 (13.4)	35 (16.3)	285 (20.4)
Donation for science	15 (21.7)	46 (34.8)	30 (25.2)	45 (35.7)	70 (48.3)	61 (38.6)	63 (42.0)	76 (55.9)	86 (57.7)	121 (56.3)	613 (43.8)
Discarding	36 (52.2)	47 (35.6)	51 (42.9)	46 (36.5)	54 (37.2)	65 (41.1)	53 (35.3)	47 (34.6)	43 (28.9)	59 (27.4)	501 (35.8)
Total	69	132	119	126	145	158	150	136	149	215	1399

Column percentages between parentheses.

decision (OR: 1.53; confidence interval: 1.15–2.04; $P = 0.004$). The proportion of the decisions to discard increased from 30.8% of all final EDDs in 1992 to 75% in 1995 and 1996.

Individual patients' decisions over the years

Since the law of 2007 on assisted reproductive medicine and the destination of supernumerary embryos and gametes in Belgium, cryopreserved embryos must be used (transferred into the womb) before initiating a new retrieval cycle as a general rule (exceptions are possible). Beforehand, patients could have two or three retrieval cycles following each other in which one or more supernumerary embryos were cryopreserved without transfer of these embryos in-between the retrieval cycles. Therefore, during the 15-year period of this mailing program, several forms could be set up for one patient in 1 year, relating to the several batches of embryos resulting from different retrieval cycles. Patients could also receive a sequence of forms over the years, each referring to new batches of embryos resulting from retrieval cycles that had taken place after sending former EDD forms back to the clinic (and after using their former stored embryos or choosing a final EDD). Furthermore, in-between the forms they received every 2 years, some patients returned for a transfer with a part, but not all, of their embryos.

Nearly two-thirds of patients (64.2%, $n = 1499$) received only one EDD form during the 15-year period, whereas 835 patients (35.8%) received several mailings (Supplementary data, Table S1). Of all patients, 98.5% received up to a maximum of five forms, while 1.5% received more than five forms. The four patients with the most forms received 12, 13, 15 and 16 forms, respectively. The variety in patients' reply scenarios over time was enormous. After several years of not replying, some couples returned for a transfer of their cryopreserved embryos while others moved without communicating their new addresses, thereby blocking all further contact with the center. Other patients did not respond to the first form(s) (or were not reachable) before making a final EDD or deciding to continue storage. For some of these patients, the decision came after six or more years of no contact with the center. Others chose to continue storage at first and never replied to any of the following forms. Furthermore, patients who received several forms and chose a final EDD once, not always did so at the end of the sequence of forms: they sometimes chose a final EDD in the first form and later never answered any other form about other batches of embryos resulting from new retrieval cycles. To give one individual example, one couple did not reply to the first two forms they received but chose to discard on the third. A year later, they returned to the clinic for a new retrieval cycle resulting in more cryopreserved embryos.

Table V Response on the EDD forms per patient ($n = 2334$).

Summary of patients' response series	<i>n</i>	% of all patients ($n = 2334$)	% of patients with >1 form ($n = 835$)
Never answered	408	17.5	25.1
Answered at least once	1926	82.5	74.9
Only or always chose to continue storage	518	22.2	22.3
Only once chose a final EDD	1276	54.7	38.4
Chose another final disposition than one of the presented options ^a	24	1.0	1.2
Chose a final EDD in several forms	108	4.6	12.9
Always the same final EDD	92	3.9	11.0
Different final EDDs ^b	16	0.7	1.9
First discarding, then donation for science	4		
First donation to others, then discarding	3		
First discarding, then donation to others	2		
First donation to others, then donation for science	2		
First donation for science, then discarding	2		
First donation for science, then donation to others	1		
First other choice (staff may decide between donation for science and donation to others), then donation for science	1		
Donation for science and donation to others in two forms in 1 year	1		

^aThese patients wanted: a transfer of their embryos to another center (3); open donation that the center did not permit (1); their best quality embryos to be donated to others and the others to science (1); the staff to choose between two selected options [donation for science and discarding (2); donation for science and donation to others (2)]. In three cases, the husband passed away (one woman wanted a transfer) and in one case the woman died (this man wanted to donate to others)]. In 11 cases, the forms were not signed by both partners: 9 men's signatures were missing, versus 2 women's. In six of these latter cases, the replying patient made a note of the couples' separation (and their lack of current address of their ex-partner).

^bAt the time of the first EDD, the option donation for science was presented on the form for all of this patients, except for one patient who chose first to discard, and later to donate to others. All but one of these patients chose different types of final EDD in different years.

However, by the time the next form arrived, the couple had separated and could not reach a joint decision. On the two last forms, they each indicated other options.

The individual response sequences over time of all patients ($n = 2334$) and of patients who received more than one form ($n = 835$) have been summarized in Table V. A quarter of the patients for whom more than one form was prepared, never responded. These include the patients who could not be reached because they did not inform the center of their new addresses. The others (74.9%) replied to at least one form. Nearly a quarter of all patients with more than one form never chose a final EDD: when replying to a form, they always selected continuation of storage. Over a third (38.4%) opted for a final EDD on one occasion while 12.9% of patients with more than one form selected two final EDDs in at least two forms ($n = 108$; of which 53 selected final EDDs for different forms in the same year). Sixteen patients chose two different types of final EDD. Fifteen of them selected these different final EDDs in different years, pointing to a change in disposition preference over time. These patients account for 27.3% (15/55) of all patients who chose more than one final EDDs in different years. All combinations of first and second choices were found although donation for science was the option least often turned away from and most often turned to.

Fourteen patients wrote comments on their forms. One patient complained about the mailing procedure being too impersonal. Two patients expressed their delight about the news that they still had embryos left and promptly planned a transfer treatment. Two patients

wanted to continue the storage of their embryos only provisionally (until they respectively received the results of an amniocentesis or made a decision about adoption). Other comments were related to the EDD options: two requests for information on the types of scientific research, an expression of preference for donation for a specific type of scientific research (on their child's disease), and an expression of preference for non-anonymous directed donation to others. There were five comments or requests about discarding: two patients asked for a notification letter after the discarding took place, one asked to send the microscope pictures of the embryos, another asked to collect her embryos to discard them at her home, and one patient wrote a goodbye note to her embryos ('It's very hard for me to say goodbye: bye bye kids!').

Discussion

This study describes patients' EDDs over a 15-year period of postal requests to make or renew an EDD. Over the years, there was a considerable increase in the number of EDD forms in the program, reflecting the increase in the number of embryos stored at the center. Each year, approximately a third of the forms were not returned. A quarter of the patients who received more than one form never answered, leaving the center with a substantial number of embryos in prolonged storage and difficult ethical questions to address. Other studies on postal communication of fertility centers have reported non-response percentages around 25% (with the use of a reply-paid letter, Cattoli et al., 2004) and 62% (Brzyski, 1998).

Non-repliers more often had a negative outcome in previous treatment cycles (Cattoli *et al.*, 2004; Provoost *et al.*, 2011). They also valued their embryo more often on the basis of probability of use, experienced anticipated regret and especially seemed to have difficulties making a joint decision among partners (Provoost *et al.*, 2011).

An answer to the problem of the so-called abandoned embryos has been formulated by the Belgian law in 2007, obliging patients to make an EDD before the start of the treatment and setting storage limits at 5 years (allowing exceptions). Two studies measuring patients' initial choices at the beginning of treatment and their preferences after a 3 and 5 year storage period, respectively, found that substantial numbers of patients change their minds about their EDD (Klock, 2001; Newton *et al.*, 2007). For that reason, concerns have been raised about the use of advance directives at a time when most patients are capable of making and communicating a decision and some authors have pleaded for a two-stage process to obtain full informed consent (Newton *et al.*, 2007; Pennings, 2007). Our study findings, based on actual EDDs, contribute to this appeal by showing that over a quarter of patients who made final EDDs in separate years chose different types of EDDs.

In over a third of all forms, patients chose to continue storage. The proportion of decisions to continue storage did not change significantly over the years.

During the 10 years period in which it was offered, the option to donate for science was the most popular option. This is in accordance with figures from other studies from 2004 (Bangsbøll *et al.*, 2004; Burton and Sanders, 2004; Choudhary *et al.*, 2004; Hammarberg and Tinney, 2006; Newton *et al.*, 2007; Lanzendorf *et al.*, 2010; Lyerly *et al.*, 2010) but in contrast with (on average older) studies reporting considerably lower proportions of donation for science (Laruelle and Englert, 1995; Van Voorhis *et al.*, 1999; Klock, 2001; Cattoli *et al.*, 2004; Hill and Freeman, 2011).

Donation to others was the least popular final EDD. The low number of patients willing to donate to others is in accordance with other reports (Saunders *et al.*, 1995; Hounshell and Chetkowski, 1996; Darlington and Matson, 1999; Van Voorhis *et al.*, 1999; Burton and Sanders, 2004; Newton *et al.*, 2007; Nachtigall *et al.*, 2009; Lanzendorf *et al.*, 2010) and the percentage of donation to others (39%) found in the only other Belgian study (reported in 1995) is in accordance with the percentages found between 1993 and 1995 in our study (Laruelle and Englert, 1995). Only one French study (of 71 couples over 6 years, starting in 1987) reported a possible negative time trend for donation to others (Lornage *et al.*, 1995).

The year in which the form was sent was an independent predictor of the type of EDD chosen. Donation for science increased with an increase in time, and donation to others decreased in time. This study clearly shows a positive time trend for donation for science which opens more optimistic prospects for the availability of embryos for (stem cell) research than have been formulated by Hoffman *et al.* (2003) for the USA. As remarked by Nachtigall *et al.* (2009), and described earlier, on the whole, studies performed in the 1990s (among which also a Belgian study) reported little willingness to donate for science (Laruelle and Englert, 1995; Van Voorhis *et al.*, 1999), whereas later studies report a more substantial willingness to do so (Bangsbøll *et al.*, 2004; Burton and Sanders, 2004; Hammarberg and Tinney, 2006; Lyerly and Faden, 2007; Nachtigall *et al.*,

2009; Lanzendorf *et al.*, 2010). Our study confirms this rising pattern within one single data collection on EDDs of a large number of patients over a considerable period of time.

To explain the positive trend in donation for science, other authors have referred to the increased public awareness of stem cell research, making patients more aware of the potential benefits of supernumerary embryos to others and possibly more comfortable with donating for science (Baylis *et al.*, 2003; Steinbrook, 2006; Nachtigall *et al.*, 2009; Lanzendorf *et al.*, 2010). However, the idea that an increase in public knowledge would be directly related to an increase in public support has been contested (Ho *et al.*, 2008). A qualitative study pointed to the media and internet as primary sources for information about embryonic stem cell research for the public, although infertility patients seemed to learn about this topic primarily from healthcare professionals who informed them about embryo donation (Peddie *et al.*, 2009). Also the university hospital setting may have positively influenced patients to donate for science as well as positive personal experiences with clinic staff, which has been suggested to be linked with patients' willingness to donate for science (Nachtigall *et al.*, 2009; Provoost *et al.*, 2010a,b).

Discarding was chosen somewhat less often than donation for science overall during the last 10 years of the program, comparable with other studies on intentions or preferences (Van Voorhis *et al.*, 1999; Cattoli *et al.*, 2004; Lyerly and Faden, 2007; Newton *et al.*, 2007; Lanzendorf *et al.*, 2010). However, the relatively high proportion of decisions to discard contrasts with the fact that it is often pictured as an unpopular or a negative option (McMahon *et al.*, 2003; de Lacey, 2007; Nachtigall *et al.*, 2009; Provoost *et al.*, 2009; Lyerly *et al.*, 2010). Our observation that this EDD is more popular in separated couples compared with those who were still together may add to the hypotheses that discarding is often a negative choice for patients (Provoost *et al.*, 2009). The time trend of the decisions to discard showed an interesting turn at the point when the option of donation for science was introduced (1997). The shift, from positive to negative, suggests that donation for science is a welcomed alternative for patients who do not want to donate to others and in the absence of the possibility to donate for science probably would have discarded their embryos.

Some studies pointed to relations between the number of embryos or the duration of storage and patients' non-response to surveys (Brzyski, 1998; Burton and Sanders, 2004). These variables were not identified as predictors of response or type of EDD in this study. Our findings that the woman's age at the time of disposition and the duration of storage time were not predictors of the type of EDD are in line with the findings of Burton and Sanders (2004), Hammarberg and Tinney (2006) and Lanzendorf *et al.* (2010), but are in contrast with other studies: Lyerly *et al.* (2010) suggested an association between the duration of storage and the choice to discard or store indefinitely; Choudhary *et al.* (2004) showed a higher number of embryos in couples donating for research; and Nachtigall *et al.* (2009) reported a positive correlation between the number of embryos and the decision to donate to others, based on a qualitative interview study.

A limitation of this study is that we could not collect data on other patient or treatment characteristics. Therefore, we do not know the influence of characteristics such as the number of (failed) treatments, the age of the patients at their first attempt or having children on the

type of final EDD they choose. Also, information on the patients' marital status was not asked on the forms, which is probably the reason for the small number of couples for which we knew they were separated. Another limitation is that this study is based on the experiences of a single center and therefore cannot be used for extrapolation to other IVF patients, or patients in other countries. However, the merits of this study lie in three main characteristics: (i) the large number of patients included and (ii) the fact that patients' actual choices (and not hypothetical choices or attitudes) have been registered (iii) over a prolonged period of time. The data collected in this 15-year mailing program provided new insights into how the patients' respond to postal EDD requests and how their actual decisions evolve over time.

In conclusion, this study shows a positive trend in donation for science, in line with the trend that has been suggested by results of separate cross-sectional studies over the last decades. It shows also that donation to others is the overall least popular EDD and is decreasing over time. An interesting time trend has been found for decisions to discard: they were rising until the year in which 'donation for science' was introduced, but decreasing from that point onwards. These results are promising for embryonic (stem cell) research in terms of the number of embryos we may expect to become available. This study also shows that over a quarter of patients who made final EDDs in separate years chose different types of EDDs. With regard to the regulation of patients' EDDs, this study contributes to the appeal for a two-stage process of obtaining full informed consent rather than using only advanced directives made before the onset of treatment.

Supplementary data

Supplementary data are available at <http://humrep.oxfordjournals.org/>.

Authors' roles

All authors take full responsibility for the reported research. We warrant that all authors have participated in the concept and design, analysis and interpretation of data and drafting or revising of the manuscript and that they have approved of the manuscript as submitted.

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Conflict of interest

None declared.

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