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Knowledge and attitudes of subfertile couples towards disposition of supernumerary cryopreserved embryos: an Indian perspective

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Abstract In many cases, supernumerary embryos are cryopreserved for future use following assisted reproductive technology (ART) treatment. Once a couple has completed their family following treatment, the fate of these excess cryopreserved embryos becomes uncertain. The options available for the disposition of cryopreserved embryos are donation to other infertile couples, donation to research and discontinuation of cryostorage. In order to evaluate the knowledge and attitudes of subfertile couples from the Indian subcontinent regarding the fate of their excess cryopreserved embryos, a cross-sectional study was planned at a university-level infertility unit. A two-stage structured interview was conducted with the couples. Some questions in the interview were hypothetical in nature. In total, 87 couples were interviewed, of which 33 (37.9%) were unaware of the options for disposition of supernumerary embryos. Forty (46%) couples indicated a preference to donate their embryos to other subfertile couples, while 10 (11.5%) couples preferred donation to research. Twenty-four (27.6%) couples opted for donation to both other couples and research, while three (3.4%) couples indicated a preference to discontinue storage. Penalized bivariable logistic regression showed that none of the factors examined (i.e. age, education, income or presence of a living child) influenced the couple's decision regarding

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embryo donation. The majority of subfertile couples preferred to donate the embryos rather than discontinue storage. The donation of embryos to other subfertile couples was the most preferred option for disposition of embryos.

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Introduction

Assisted reproductive technology (ART) is an important therapeutic option for subfertile couples. An increasing number of ART cycles are being performed across the world, and in certain countries, 1-6% of all babies are born following ART treatment (De Geyter et al., 2018). In many of these cases, excess viable embryos of good quality remain after fresh embryo transfer, and clinics cryopreserve these supernumerary embryos for future use. There has been a consistent effort to reduce the number of embryos transferred to one or two in order to reduce the risk of multiple pregnancies (Bhattacharya and Kamath, 2014; De Geyter et al., 2018). These restrictive embryo number policies and improvements in cryopreservation techniques have contributed to an increase in the number of cryopreserved supernumerary embryos. Introduction gonadotrophin-releasing hormone antagonist protocol and a 'freeze all' policy for embryos to prevent ovarian hyperstimulation syndrome have also contributed to an upsurge in treatment cycles with cryopreserved embryos (De Geyter et al., 2018; Devroey et al., 2011).

Once a couple has completed their family after a successful pregnancy or pregnancies, the fate of these excess cryopreserved embryos becomes uncertain. In many instances, couples with cryopreserved supernumerary embryos discontinue treatment even when they have not been able to achieve a successful live birth for reasons such as marital disharmony, stress or increasing cost (Goldfarb et al., 1997). There is uncertainty regarding the maximum time period for storage of embryos in many countries, with no definite laws that explicitly state the conditions for storing cryopreserved embryos. In European countries, the regulatory bodies decide the storage period for cryopreserved embryos, and storage is allowed for up to 5 years in most countries (Wånggren et al., 2013). After this time, the options available for the disposition of these excess embryos are donation to other infertile couples, donation to research and discontinuation of cryopreservation (Bangsbøll et al., 2004; Wånggren et al., 2013).

This decision is made mostly in accordance with existing national legislation or guidelines. Among the existing options, the final decision of the couple is influenced by many factors such as female age, duration of infertility and successful delivery (Bangsbøll et al., 2004). An earlier study from Denmark explored the attitudes of couples with excess cryopreserved embryos, and reported that donation to research was the most preferred option, whereas a study from Sweden reported that the most preferred option was donation to other couples (Bangsbøll et al., 2004; Wånggren et al., 2013). A study from Australia investigated the decisions of couples who were contacted in relation to

their embryos in long-term storage, and found that donation to research was the preferred choice for most couples (Hammarberg and Tinney, 2006). As well as clinical factors, these decisions are also influenced by sociocultural factors. In India, there has been an exponential increase in the number of ART cycles being performed. The most recent published data from the national registry reported 21,500 ART cycles in 2006, and this was projected to increase beyond 110,000 cycles by 2011 (Malhotra et al., 2013). The current guidelines in India propose a maximum storage period for cryopreserved embryos of 5 years (Assisted Reproductive Technology bill draft, 2010, 2017). The guidelines give couples who have undergone ART and have excess cryopreserved embryos two options for the disposition of embryos: donation to research under strict regulatory conditions or discontinuation of storage (Assisted Reproductive Technology bill draft, 2010, 2017).

The views of important stakeholders, such as couples, should be considered when drafting legislation and guidelines on complex issues such as the fate of supernumerary cryopreserved embryos. Presently, data are lacking regarding the views of Indian couples on the disposition of cryopreserved embryos. As such, the authors decided to conduct a prospective study to assess the knowledge, attitudes and beliefs of Indian couples undergoing ART about supernumerary cryopreserved embryos.

Materials and methods

A cross-sectional study was performed in the Department of Reproductive Medicine, Christian Medical College, Vellore, India (tertiary level referral hospital) between April and November 2016. Ethical approval was granted by the institutional review board before the study commenced.

Subfertile couples who had undergone ART treatment (fresh or frozen) at the centre and had supernumerary cryopreserved embryos were invited to participate in the study. Couples who were willing to participate were included in the study after giving written informed consent. Couples who underwent ART for fertility preservation were excluded. Interviews were conducted by the gynaecologist (infertility specialist) who was handling the ART treatment, and were conducted in English as well as local languages (Tamil and Bengali) for those couples who were not familiar with English.

Structured two-stage interviews were conducted with the couples. The first stage assessed the couple's knowledge regarding various options for disposition of stored supernumerary embryos, although some of these options were not available (embryo donation to other couples) due to existing regulatory restrictions. The questions were hypothetical in nature (assuming that desired family size had been

achieved). They covered non-identifying demographic information and the couple's view on ideal family size. The first stage of the interview was more open ended, and couples were encouraged to speak of their knowledge about excess stored embryos.

After the first stage of the interview, the available options for disposition of supernumerary cryopreserved embryos were explained to the couple in detail if they were unaware, and a detailed information sheet was provided. They were given time to go through the information sheet and understand the content. Couples were encouraged to seek clarification for any queries regarding the information provided. The second stage of the interview was held on the same day, after allowing some time for couples to reflect on the information given about supernumerary embryos. In the second stage, structured interviews were conducted to assess attitudes and beliefs. The broad reasons were listed for each of the choices (discontinuation. donation to couple, donation to research and unable to make a decision), and couples were asked to choose whichever reason reflected their thought process.

Additional analysis was undertaken to determine demographic factors (e.g. age, education, income or presence of a living child) which could have influenced the couple's decision to donate embryos to research or another couple.

The responses of all couples were noted in a pre-designed questionnaire, written in English, and entered using Epi data software. For those couples who could not comprehend English, the questionnaire was translated into the local language by the interviewers, and their responses were recorded. The required sample size to show at least 65% of responses (Hammarberg and Tinney, 2006) stating that the couple preferred to donate their embryos to research was found to be 87 couples with 10% precision and 95% confidence limits.

Statistical analysis

All categorical variables were summarized using frequencies and percentages, and continuous variables were measured using mean and standard deviation. Associations between risk variables and outcome (decision to donate embryos) were tested separately using Fisher's exact test. As the numbers were small, penalized bivariable logistic regression analysis was performed. The results are presented as odds ratios and 95% confidence intervals. SPSS 25.0 (IBM Corp., Armonk, NY, USA) was used for data analysis.

Results

In total, 87 subfertile couples participated in this study. The mean ages of female and male partners were 30.43 ± 3.58 and 35.83 ± 4.11 years, respectively. Thirteen couples (14.9%) had at least one living child. The majority of couples (62/87, 71.3%) felt that having two children would complete their family, while only three couples (3.4%) felt that one child was sufficient to complete their family (Table 1). The majority of couples had either completed graduate or postgraduate education (female partner - 64/87, 73.6%; male partner - 70/87, 80.4%). Most female partners were unemployed (64/87, 73.6%), while the majority of male partners had a professional job (60/87, 68.9%) (Table 2).

Of 87 couples interviewed, 33 (37.9%) couples were unaware of the options for disposition of supernumerary embryos. Among the remaining 54 couples who were aware of the options, the majority knew about the option to donate their embryos to other subfertile couples (Table 3).

After the second stage of the interview, the majority of couples (40/87, 46%) indicated a preference to donate their embryos to other subfertile couples, if legally allowed. Some

Table 1 Characteristics of the study participants (n=87).

Female partner's age (mean ± SD), years	30.43 ± 3.58
Male partner's age (mean ± SD), years	35.83 ± 4.11
Couples with primary infertility	62 (71.3)
Couples with secondary infertility	25 (28.7)
Family income per month (INR)	
<20,000	28 (32.2)
20,000–50,000	35 (40.2)
>50,000	24 (27.6)
Ideal number of children in the family	
One	3 (3.4)
Two	62 (71.3)
Three	7 (8)
Four	15 (17.2)
Couples with living children	13 (14.9)
Couples with one living child	12 (92.3)
Couples with two living children	1 (7.7)
Previous children born through natural conception	4 (30.8)
Previous children born through ART	8 (61.5)
Previous children born through non-ART	1 (7.7)

INR, Indian National Rupee; SD, standard deviation; ART, assisted reproductive technology. Data in parentheses are percentages unless otherwise indicated.

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Table 2 Education and occupation details of the participants (n=87).

Female partner's education	
Illiterate	2 (2.3)
Primary school	-
High school	4 (4.6)
Secondary school	17 (19.5)
Graduate	32 (36.8)
Postgraduate	32 (36.8)
Male partner's education	
Illiterate	1 (1.1)
Primary school	-
High school	3 (3.4)
Secondary school	13 (15)
Graduate	35 (40.2)
Postgraduate	35 (40.2)
Female partner's occupation	
Unemployed (homemaker)	64 (73.6)
Unskilled (e.g. manual labour)	-
Semi-skilled (e.g. mechanic)	-
Skilled (e.g. tailor)	1 (1.1)
Clerical work, shop owner, farmer	2 (2.3)
Semi-professional	15 (17.2)
Professional	5 (5.7)
Male partner's occupation	
Unemployed	-
Unskilled (e.g. manual labour)	3 (3.4)
Semi-skilled (e.g. mechanic)	3 (3.4)
Skilled (e.g. tailor)	6 (6.9)
Clerical work, shop owner, farmer	15 (17.2)
Semi-professional	37 (42.5)
Professional	23 (26.4)

Data in parentheses are percentages.

couples opted to donate their embryos to other couples and to research (24/87, 27.6%), while 10 couples were unable to make a decision (Table 4). The reasons for choosing a particular preference are shown in Table 5.

Penalized bivariable logistic regression analysis showed that none of the demographic factors examined influenced the decision for donation of embryos to other subfertile couples or research (Table 6): female age (P=0.95), male age (P=0.61), female partner's education (P=0.68), male partner's education (P=0.62), income (P=0.37) or presence of a living child (P=0.09).

Discussion

This study suggests that almost half of the interviewed subfertile couples who underwent ART and had supernumerary cryopreserved embryos would prefer to donate their excess embryos to other subfertile couples after completion of their family. Approximately one-quarter of the couples indicate a preference for combined donation of their excess embryos to subfertile couples and to research. The main reason for choosing to donate their excess embryos to other couples was an overwhelming desire to help couples suffering from subfertility. None of the demographic factors such as age, family income, education or presence of living

Table 3 Knowledge of couples regarding options for disposition of stored excess embryos (n=87). ^a

Discontinuation of storage	17 (19.5)
Donation to other infertile couples	41 (47.1)
Donation to research	41 (47.1) 15 (17.2) 33 (37.9)
Do not know about the available options	33 (37.9)

^a Answers were not mutually exclusive.

children influenced the decision to donate embryos to infertile couples and research.

A cohort study from Australia used a questionnaire-based survey (n=123) to investigate factors affecting decisionmaking regarding the disposition of supernumerary embryos (Hammarberg and Tinney, 2006). The most preferred option was donation to research (42%), followed by disposal of embryos (30%), while donation to other subfertile couples was the least preferred response (16%). Another questionnaire-based survey from Denmark among subfertile couples (n=207) found that more than half of the couples (56.5%) preferred to donate their excess embryos to stem cell research, and less than one-third of the couples indicated a preference to donate to other subfertile couples (Bangsbøll et al., 2004). These findings are not in agreement with the results of the present study, which found that the donation of embryos to other subfertile couples was the most preferred option. The lower preference for donating to other couples found in earlier studies could be due to the influence of existing legislation, awareness regarding newer stem cell technologies, and attitude and belief systems of the interviewed couples. Many couples may not accept the thought of other subfertile couples bringing up their biological child (Bangsbøll et al., 2004). In contrast, a cross-sectional study from Sweden involving 471 subfertile couples found that the majority (76%) supported donation of excess embryos to other subfertile couples, while close to 60% indicated support for embryo donation to research (Wånggren et al., 2013). One-third of couples stated that embryo donation should remain anonymous. The current study found that fewer couples preferred to donate their excess embryos to research compared with previous studies, possibly due to lack of awareness about stem cell technologies and its benefits among the general population. Further, due to the deep psychosocial impact of subfertility in Indian society, the subfertile couples may have felt a stronger desire to help other subfertile couples who were in a similar situation as themselves (Patel et al., 2018).

In the current study, approximately one-third of the interviewed couples were unaware of the options for

 Table 4
 Preferred options for disposition of supernumerary embryos.

Most preferred option (n=87)	
Discontinuation of storage	3 (3.4)
Donation to other infertile couples if legally allowed	40 (46.0)
Donation to research	10 (11.5)
Donation to research and infertile couples	24 (27.6)
Unable to make a decision	10 (11.5)

Table 5 Reasons given for choosing a particular option for disposition of supernumerary embryos.

	1
Discontinuation of storage $(n=3)$	
Do not want more siblings created after donating to other couples	1 (33.3)
Do not want manipulations of embryos	-
The child from donated embryos would trace back genetic parents creating legal/social issues in future	-
Religious or cultural reasons	2 (66.7)
Donation to other infertile couples $(n=64)^a$	
Did not want the embryos to be discarded	5 (7.8)
Did not want the embryos to be discarded and felt that donating to other couples was better than research/manipulation of embryos	8 (12.5)
Wanted to help other infertile couples achieve parenthood	51
	(79.7)
Donation to research (n=34) a	
Did not want the embryos to be discarded	7 (20.6)
Did not want the embryos to be discarded and felt that the research option was better than donating to other couples	4 (11.8)
Wanted to help other patients with diseases for which cure can be found through stem cell technology	23
	(67.7)
Unable to make a decision (n=10)	
Difficult to decide due to ethical and moral dilemma	1 (10)
Difficult to decide and deferring the decision indefinitely and continuing storage	1 (10)
Difficult to decide due to lack of understanding of the full implications and may make a decision in future	8 (80)

Data in parentheses are percentages.

disposition of excess cryopreserved embryos. While couples attend extensive counselling sessions in groups and individually before embarking on ART in the study unit, the complexities of ART may be overwhelming for some couples. An earlier study from Belgium found that couples had

minimal knowledge about cryopreservation technologies, and two-thirds of couples did not feel the need to know more about cryopreservation (Provoost et al., 2010). Their confidence in the medical team compensated for their lack of knowledge about cryopreservation methods. There may

Table 6 Penalized logistic regression analysis for possible predictive variables for decision to donate embryos to other subfertile couples or/and research.

Variables	Decision f	Decision for donation to other subfertile couples or/and research $(n=87)$			
	Yes	No	OR (95% CI)	<i>P</i> -value	
	n (%)	n (%)			
Female partner's age (years)					
≤35	66 (89.19)	12 (92.31)	0.94 (0.14-6.46)	0.95	
>35	8 (10.81)	1 (7.69)	1.00		
Male partner's age (years)					
≤35	40 (54.05)	6 (46.15)	1.35 (0.43-4.31)	0.61	
>35	34 (45.95)	7 (53.85)	1.00		
Monthly family income (INR)					
< 50,000	52 (70.27)	11 (84.62)	0.51 (0.12-2.23)	0.37	
>50,000	22 (29.73)	2 (15.38)	1.00		
Living children					
Yes	9 (12.16)	4 (30.77)	0.31 (0.08-1.18)	0.09	
No	65 (87.84)	9 (69.23)	1.00		
Female partner's education					
Below or up to graduate	46 (62.16)	9 (69.23)	0.73 (0.23-2.65)	0.68	
Postgraduate	28 (37.84)	4 (30.77)	1.00		
Male partner's education					
Below or up to graduate	45 (60.81)	7 (53.85)	1.34 (0.42-4.27)	0.62	
Postgraduate	29 (39.19)	6 (46.15)	1.00		

INR, Indian National Rupees; OR, odds ratio; CI, confidence interval.

^a Options were not mutually exclusive; while some couples chose only donation to other couples or research as an option, a few couples opted for both options.

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be a need to review the counselling process, and additional sessions can be planned around the actual treatment when couples may be more receptive and comprehend the complex information.

The current study showed that none of the demographic factors analysed (i.e. age, education, income or presence of a living child) influenced decision-making regarding donation of excess embryos to other subfertile couples or research. An earlier study found that female age <35 years and presence of a living child were independent predictors for embryo donation to stem cell research (Bangsbøll et al., 2004). A possible reason for this conflicting finding could be the smaller sample size of the current study.

The current study is one of the first to evaluate the knowledge and views of subfertile couples from the Indian subcontinent on excess cryopreserved embryos. A study published in 2010 estimated that approximately 18 million couples were suffering from subfertility in India, and current estimates are likely to be higher (Ganguly and Unisa, 2010). There has been a steady increase in the number of ART cycles performed in India (Malhotra et al., 2013). While the ART bill for regulation of ART practices in India is under legislative consideration, the existing guidelines allow research on embryos only in an approved research laboratory after obtaining specific permission from the Department of Health Research and with consent from commissioning couples. Apart from donation to research, the only other option in the guidelines for couples with excess cryopreserved embryos is discontinuation of storage. The guidelines do not explicitly mention the option of donation of excess cryopreserved embryos to other subfertile couples. Among the strengths of this study were the adequate sample size and the use of an interview rather than a questionnaire to record the responses of the included couples. However, a fully structured interview could have restricted the ability of couples to express their thoughts and beliefs about excess stored embryos. Furthermore, language barriers were encountered when interviewing some couples due to the use of complex medical terms to describe treatment. The interviews were conducted during ART treatment and the answers were given in response to hypothetical situations. Earlier studies have indicated that couples may be less willing to donate their excess embryos to other couples when faced with a definite request instead of a hypothetical situation (Hammarberg and Tinney, 2006; Laruelle and Englert, 1995).

Conclusions

This study found that approximately three-quarters of subfertile couples indicated a preference to donate their excess cryopreserved embryos to other subfertile couples after completion of their family. An overwhelming majority preferred to donate their embryos to another couple or to research rather than letting them perish. Subfertile couples are important stakeholders and their views should be considered when regulatory bodies make appropriate regulatory legislations. Couples who find it difficult to make an appropriate decision may need detailed counselling sessions

at regular intervals by doctors, embryologists and counsellors in order to fully comprehend the complexities.

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