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ORIGINAL ARTICLE ***Psychology and counselling***

Patients' attitudes and preferences towards a freeze-all strategy in ART treatment

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STUDY QUESTION: What are the attitudes towards different aspects of a freeze-all strategy and elective frozen embryo transfer (eFET) in comparison with fresh embryo transfer in assisted reproductive technology treatment among female and male patients before and after their first ART treatment cycle in a public health care setting?

SUMMARY ANSWER: Despite concerns about the delay in embryo transfer associated with eFET, nearly 60% of the participants were in favor of eFET compared with fresh embryo transfer assuming that the clinical pregnancy rate was equivalent.

WHAT IS KNOWN ALREADY: Vitrification and blastocyst transfer have considerably improved success rates after FET with ongoing pregnancy rates in frozen cycles approaching those seen in fresh treatment cycles. Furthermore, the risk of ovarian hyperstimulation syndrome (OHSS) is essentially eliminated in FET cycles, and FET may be beneficial to the endometrial and fetal development because a hormonal environment mirroring the natural cycle is enabled. However, the freeze-all strategy is not yet implemented as standard care. One reason is the presumption of negative patient attitudes towards a freeze-all embryo strategy. So far, no data regarding patients' attitudes on a freeze-all strategy have been published.

STUDY DESIGN, SIZE, DURATION: This study was designed as a descriptive cross-sectional study including 165 fertility patients referred for their first ART treatment from December 2014 to June 2016.

PARTICIPANTS/MATERIALS, SETTING, METHODS: All newly referred patients participating in a mandatory meeting before initiating ART treatment at the Fertility Clinic, Hvidovre Hospital, Copenhagen, Denmark were requested to fill in an online web-based questionnaire separately for men and women covering attitudes towards a freeze-all strategy, socio-demographic data and reproductive history. The patients were informed about both conventional fresh embryo transfer strategy and the freeze-all strategy prior to answering the questionnaire.

MAIN RESULTS AND THE ROLE OF CHANCE: The total response rate was 77.1% ($n = 165$), and for women and men respectively 85.8 versus 66.0%. The female respondents were significantly more likely to consider the postponement of embryo transfer difficult compared to the male population (78.6 versus 35.5%; $P < 0.001$) and they were significantly more willing to accept a risk in treatment on own health to achieve a pregnancy than were the male respondents on their partners health (82.5 versus 96.8%; $P = 0.025$). However, 59.2% of the women and 59.7% of the men agreed that they would choose eFET over fresh embryo transfer if the chance of pregnancy were the same. Most of the patients furthermore agreed that the health of the mother and their baby was of highest importance. In the adjusted analyses we found no significant predictive factors for preferences towards a freeze-all strategy apart from a negative attitude towards delay of transfer in case of previous unsuccessful ART attempts.

LIMITATIONS, REASONS FOR CAUTION: Selection bias cannot be excluded, as the total response rate was 77.1%. The hypothetical nature of the items may furthermore limit the validity of the results. In addition, the participants were from a single Fertility Clinic in the Capital Region of Denmark and may therefore not be representative for all fertility patients.

WIDER IMPLICATIONS OF THE FINDINGS: In a clinical setting with similar pregnancy rates for eFET and fresh embryo transfer, these results indicate that patients, when given access to information on advantages and disadvantages of both fresh embryo transfer and eFET, are less prone to opt for fresh embryo transfer. This may be ground breaking for a patient-centered paradigm shift in routine ART treatment with a wider implementation of a freeze-all and eFET-strategy eliminating the risk of OHSS.

STUDY FUNDING/COMPETING INTEREST(S): The Danish Council for Independent Research and Merck Serono supported the study. The study is part of the Reprounion Collaborative study, co-financed by the European Union, Interreg V ÖKS. No competing interests exist.

Key words: attitudes / ART / eFET / freeze-all / questionnaire-based study

Introduction

In recent years frozen embryo transfer (FET) has become a viable and promising alternative to fresh embryo transfer in ART treatment. Blastocyst-stage embryos and optimizations in the cryopreservation techniques from slow freezing to vitrification are increasingly encouraging the use of FET with post-thawing survival rates at up to 95% (Loutradi *et al.*, 2008; Cobo *et al.*, 2012). Following these refinements in laboratory techniques, pregnancy and live birth rates are correspondingly improving in frozen cycles and are now approaching those associated with fresh embryo transfer (Zhu *et al.*, 2011; Shapiro *et al.*, 2013). A freeze-all strategy has frequently been suggested as a way of further improving pregnancy rates in ART, arguing that the use of the best embryos in FET cycles instead of in fresh cycles could potentially increase pregnancy rates (Roque *et al.*, 2013, Chen *et al.*, 2016). The transfer of an embryo in a subsequent natural cycle further has the advantage of avoiding the supraphysiological levels of estradiol and progesterone present during controlled ovarian stimulation (COS) in fresh cycles as these negatively affect endometrial receptivity causing impaired implantation and fetal development (Kansal Kalra *et al.*, 2011; Shapiro *et al.*, 2011). In addition, a freeze-all strategy minimizes the risk of ovarian hyperstimulation syndrome (OHSS) (Devroey *et al.*, 2011; Pereira *et al.*, 2017; Shi *et al.*, 2018).

Knowledge of patient's attitudes, perceptions and concerns is imperative, when informing and counseling fertility patients in their preference in ART treatment. Hesitance towards a further adaptation to freeze-all may be due to a false impression by doctors that their patients prefer fresh embryo transfer. A qualitative study of 16 couples who had undergone IVF treatment found that nuanced and complex considerations take part in the decision-making of whether to freeze embryos, and the study also revealed study participants´ being confused about the term 'freezing' and the practical aspects of the procedure (Goswami *et al.*, 2015). Despite the debate and hesitance due to caution of patients, no studies have investigated fertility patients' attitudes towards a freeze-all strategy when given access to written and oral information about the procedure, clinical facts and pregnancy rates following both fresh and frozen embryo transfer. The aim of this study was to elucidate patient attitudes towards freeze-all on an informed basis as well as the possible underlying concerns. The results of the study will aid the decision making regarding future ART treatment strategies including elective FET (eFET) as a standard care option in a clinical setting taking patients attitudes and preferences into account and individualize treatment strategies.

Materials and Methods

Setting

The study was performed in the setting of the Danish public health care system at a university hospital based fertility clinic. In Denmark, ART treatment is offered to couples and to single women. In the public health care system ART treatment is offered to women under 40 years of age and only to couples having no joint children or no child in the case of single women.

At the public fertility clinics, patients are reimbursed for a maximum of three complete ART cycles including fresh and/or frozen–thawed embryo transfer(s) and commonly all spare frozen embryos from a given treatment cycle are used before a new ovarian stimulation. If a child is born, no further fresh treatments are reimbursed.

In Denmark, the standard treatment strategy in the public fertility clinics is fresh embryo transfer in the stimulated cycle and the patients are usually not able to decide for themselves which treatment strategy is used. Elective FETs are usually performed if any specific issues may need to be taken into consideration or if the woman has previously experienced severe discomfort or symptoms of overstimulation and the decision to freeze all embryos and postpone the embryo transfer to a subsequent cycle is most oftenly made during the course of treatment and not planned in advance.

Study population and design

This is a descriptive cross-sectional study comprising two separate data collections in the same study population, one initial and a follow-up after ~2 months. The study sample consisted of 165 fertility patients who were referred to the Fertility Clinic, Copenhagen University Hospital, Hvidovre for their first ART treatment during the period December 2014 to June 2016. At the Fertility Clinic all newly referred patients attend an introductory meeting held by the clinical staff prior to initiating ART treatment in the public health care system. At the meeting all participants were informed about this questionnaire study and invited to fill in the online web-based questionnaire. Written consent and contact information was obtained from all female and male patients attending the meeting including single women and women in a same-sex relationship, who were interested in participating in the study. Female partners were not invited to participate due to the relatively low prevalence of this specific group in the patient population and the sample size therefore not being able to reach an adequate number of responses within the setting of this study. An online link to the questionnaire was sent by email the following day and an email reminder was sent 2 weeks after the initial contact. When filling-in the questionnaire the respondents were asked to provide their email addresses in order for them to receive a follow-up questionnaire after completing the first ART treatment cycle.

At the 2-h introductory meeting all couples and single women were given full information on the clinical and laboratory part of the ART

treatment including information on psychological aspects of the treatment. Information regarding research and ongoing studies at the clinic were also included.

Participation in the meeting is mandatory before initiating ART treatment at the clinic unless couples are not able to understand Danish language, in which case they will obtain the information in the outpatient clinic.

Pilot testing

The questionnaire was pilot-tested in November 2014 on five men and five women in ART treatment. The participants were invited to comment on the comprehensibility of the informational part as well as the design of the questions and the response categories and on any important theme that had not been addressed. The statements concerning attitudes and perceptions were modified according to the written comments from the participants.

Baseline questionnaire

The questionnaire was designed in two similar versions with differences in gender-related issues, one for the female and one for the male partner. Included was written information describing the two different strategies in ART treatment in regards to treatment procedure (ovarian stimulation, egg retrieval, fertilization methods and embryo transfer strategies (fresh and frozen–thawed embryo transfer)) as well as the clinics own pregnancy rates following the two treatment strategies. In addition, OHSS was described in terms of frequency, symptomatology and means of preventing this (e.g. eFET). Lastly, the risk of large-for-gestational age babies with the use of frozen–thawed embryos was mentioned and the postponement of embryo transfer in the eFET cycles was emphasized.

Medical and socio-demographic variables

The questionnaire included items on the participant's age, previous conceptions/pregnancies, infertility history as well as infertility diagnosis, and socio-demographic information. Sexual orientation was furthermore documented. Socio-economic status (SES) was measured using standardized questions including seven parameters concerning education, vocational training and job position according to the Danish Occupational Social Class Measurement (Christensen *et al.*, 2014) and categorized into six groups of occupational social classes I (high)–VI (low). A minor group was outside classification due to leave, sickness, on-going studies, unemployment or indeterminable occupation (VII and VIII).

Written information concerning a standard ART-protocol and a freeze-all strategy

Following the items concerning medical and socio-demographic information, the participants were introduced to fresh embryo transfer as well as eFET and a freeze-all strategy in a written section. The written section included a description of how the two different strategies are implemented in our clinical setting, also providing information about the postponed embryo transfer and the possible delay in time-to-pregnancy associated with a freeze-all strategy. Furthermore, OHSS was explained as well as the association with fresh and frozen embryo transfer. Lastly, advantages (decreased risk of OHSS) and disadvantages (delayed time-to-embryo transfer, loss of embryos due to the freezing–thawing process, large for gestational age) of eFET and a freeze-all strategy were addressed as well as the current pregnancy rates with fresh embryo transfer and FET in our clinic.

Knowledge of and attitudes to eFET and a freeze-all strategy

The written information was followed by five items investigating patients knowledge of eFET and their initial preference of treatment, also taking into consideration the risk of OHSS. These items were followed by an item regarding concerns about the postponement of embryo transfer related to eFET as well as an item exploring the patient's attitudes towards the possible risks of the two treatments. Both questions were designed as statements with response categories on a 5-point Likert scale going from very important to not important as well as comprising the possible response 'Do not know'. The concluding part of the section was constructed by way of seven listed statements about eFET and fresh embryo transfer aiming to explore patient's attitudes and perceptions towards the two treatment methods. The response categories in the statement items were a 5-point Likert scale from 1 (completely agree) to (5) completely disagree (Norman, 2010).

Follow-up questionnaire

The follow-up questionnaire comprised the exact same items as the initial questionnaire supplemented by items on age and socio-demographic data. Furthermore, information on the fertility treatment in the follow-up period and the results hereof were addressed.

Statistical analysis

The results were analyzed by SPSS (Statistical Package for Social Sciences) version 22.0. Statistical significance was defined as a probability value of $P < 0.05$. Frequencies were calculated for responses to questions regarding attitudes and preferences. Means and SD were calculated for continuous data (female/male age and duration of infertility). In the analyses SES measured by occupational social class was categorized into three groups: High occupational social class (I + II; professionals, executives, medium level white collar employees), medium (III + IV; low-level white collar employees, skilled workers) and low (V + VI; unskilled and semi-skilled workers, participants receiving social transfer income). Patients in the social class group VII and VIII (e.g. students, unemployed) were not included in the analyses as they were outside the occupational social classification in relation to the labor market at the time of filling in the questionnaire. The outcome measures in the responses to the statements on attitudes towards treatment were response variables with five ordered categories (completely agree, partly agree, neither agree nor disagree, partly disagree and completely disagree). In Tables III and IV these were joined into three categories: (i) agree category comprised the ('completely agree' and 'partly agree') answers; (ii) neither agree nor disagree; and (iii) disagree category comprised the ('partly disagree' and 'completely disagree') answers.

Multiple logistic regression analyses were performed to examine predictors of the likelihood of the participants to agree to three different statements regarding a freeze-all strategy (i) the chance of conceiving, (ii) the safety aspect and (iii) the difficulty of having to postpone time to embryo transfer. The response variables to the statements were dichotomously recorded in the adjusted analyses as either 'agree' or 'disagree' with the 'disagree' category comprising all other answers than completely agree and partly agree. The response distribution for the three abovementioned selected items exploring agreement to three different aspects of the freeze-all strategy were analyzed in a multiple logistic regression analysis with adjustments for six predictive factors: (i) gender (male versus female), (ii) age (<35 or ≥35 years), (iii) previous delivery/children from previous relationships (yes or no), (iv) male factor infertility (yes or no), (v) previous fertility treatment (yes or no) and (vi) occupational social class (high or low).

Ethical approval

The study followed the Helsinki II Declaration for medical studies. According to the Danish National Authorities ethical approval from the Scientific Ethical Committee is not required for anonymous questionnaire

based studies. The study was approved by the Danish Data Protection Agency journal nr. I-Suite-nr. 03368 and ID-nr. AHH-2014-032.

Results

Study population

In total, 214 patients filled in the informed consent form and were invited to answer the online web-based questionnaire by email invitation. We received 165 individual responses representing an overall response rate of 77.1%. A total of 103 women (85.8%) and 62 men (66.0%) responded. Of the 165 participants filling-in the initial questionnaire, four of the woman, and two men did not provide email-addresses for the follow-up. Furthermore, one couple never started treatment, and one couple conceived naturally before treatment initiation. Of the remaining 157 patients, 91 patients (66 women and 25 men) completed the follow-up questionnaire representing a response rate of 58.0% in the follow-up questionnaire. Participants received two email reminders.

Participant characteristics

Socio-demographic characteristics of the respondents included age, marital status, duration of infertility, previous conceptions/children from previous relationships, main infertility diagnosis, previous modes of infertility treatment and social status (Table I). The mean female and male age among respondents was 33.3 and 35.3 years, respectively. Mean duration of infertility was 2.3 years in the female population and 2.5 years in the male population (range 0–8). Of the women, 29 (28.2%) had previously conceived, but only 3 (2.9%) had given birth. Male factor infertility was the main diagnosis of infertility in both the female and male respondent group, accounting for 38.8% of the main diagnoses in the female group and 59.7% in the male group. Most of the study population was cohabiting, 88 (85.4%) of the women and 62 (100%) of the men, whereas 12.6% of the women were single and

Table I Clinical characteristics and socio-demographic data of the study population comprising 103 women and 62 men initiating ART treatment.

	Women (n = 103) % (n)	Men (n = 62) % (n)
Age (years) (mean ± SD)	33.3 ± 4.4	35.3 ± 5.0
Duration of infertility (years) (mean ± SD)	2.3 ± 1.6	2.5 ± 1.4
Previously conceived	*28.2 (29)*	–
Previous delivery (women)/Children from previous relationship (men)	2.9 (3)	11.3 (7)
Main diagnosis		
Male factor infertility	38.8 (40)	*59.7 (37)*
Unexplained infertility	25.2 (26)	24.2 (15)
Tubal factor infertility	6.8 (7)	3.2 (2)
Anovulation (including PCOS)	11.7 (12)	6.5 (4)
Endometriosis	2.9 (3)	3.2(2)
Other	14.6 (15)	3.2 (2)
Previous fertility treatment	56.3 (58)	50.0 (31)
IUI	54.9 (56)	46.8 (29)
IVF	4.9 (5)	6.5 (4)
ICSI	1.9 (2)	3.2 (2)
Donor semen	7.8 (8)	1.6 (1)
Egg donation	0 (0)	0 (0)
Marital status		
Single	12.6 (13)	0 (0)
Lives alone, steady partner	1.9 (2)	0 (0)
Lives with wife/husband/partner	85.4 (88)	100 (62)
Occupational social class		
High	37.9 (39)	43.5 (27)
Medium	40.8 (42)	40.3 (25)
Low	11.7 (12)	4.8 (3)
Outside classification	9.7 (10)	8.9 (7)

The figures are given in frequency % (n) of the total number of respondents to each question.
The mean age and mean duration of infertility is presented with SDs.
PCOS = polycystic ovarian syndrome.

Table II Preferred treatment strategy in relation to risk-assessment for OHSS before initiating IVF treatment.

Statement	Response	Women ($n = 103$) % (n)	Men ($n = 62$) % (n)	*P*-value
'Did you know that it is possible to transfer frozen, thawed embryos?'	Yes	91.2 (94)	80.6 (50)	0.128
	No	8.7 (9)	16.1 (10)	
	Do not know	0 (0)	3.2 (2)	
'If you could choose freely, which method would you then prefer?'	Fresh embryo transfer	22.3 (23)	32.3 (20)	0.591
	FET	20.4 (21)	37.1 (23)	
	Do not know	57.3 (59)	30.6 (19)	
'Would you prefer eFET if you/your partner had a *low risk* of OHSS?'	Yes	20.4 (21)	33.9 (21)	0.130
	No	37.9 (39)	33.9 (21)	
	Do not know	41.7 (43)	32.3 (20)	
'Would you prefer eFET if you/your partner had a *moderate risk* of OHSS?'	Yes	52.4 (54)	66.1 (41)	0.980
	No	11.7 (12)	14.5 (9)	
	Do not know	35.9 (37)	19.4 (12)	
'Would you prefer eFET if you/your partner had a *high risk* of OHSS?'	Yes	71.8 (74)	72.6 (45)	0.852
	No	11.7 (12)	12.9 (8)	
	Do not know	16.5 (17)	14.5 (9)	

FET = frozen embryo transfer; OHSS = ovarian hyperstimulation syndrome.

1.9% lived alone, but had a steady partner. In the female population, most of the respondents were in a heterosexual relationship with exception of five women (4.9%), who were in a same sex relationship. The female population had a distribution amongst the three major social class groups of 37.9, 40.8 and 11.7% for high, medium and low social class, respectively, and the distribution was similar in the male population, where 43.5 and 40.3% were of high and medium social class, respectively, with only 4.8% being in the low occupational social class.

In terms of sexual orientation, all of the male and 93.2% of the female participants were attracted to the opposite sex, whereas the remaining 5.8% of the female population were attracted to either both men and women or same-sex partners. One patient did not respond to this question.

In the follow-up questionnaire, 16 of the women and 4 of the men stated that they had a positive hCG following their first treatment.

Knowledge of FET and freeze-all and initial preference of treatment

Responses to the questions regarding knowledge of FET and freeze-all and initial preferred treatment are shown in Table II. As seen, 91.2% of the women and 80.6% of the men recognize the possibility of transferring frozen, thawed embryos. When asked about initial preference in treatment strategy, 22.3% of the women and 32.3% of the men state that they would choose fresh embryo transfer, while 57.3% of the women and 30.6% of the men are undecided in this item. The responses in relation to preference of treatment strategy and the risk of OHSS show that the preference towards eFET increases with an increased risk of OHSS with 71.8% of the women and 72.6% of the men preferring eFET in the situation of being at high risk of OHSS compared to 20.4 and 33.9% for women and men respectively for low risk of OHSS. In these items, however, 16.5 and 14.5% of women and men, respectively, answered 'do not know' in relation to treatment strategy in a hypothetical situation of high risk of OHSS but as many as 41.7 and 32.3% of women and men, respectively, answered 'do not know' in the scenario of low risk of OHSS. No significant differences between responses in these items between the male and female population were found.

Attitudes towards a freeze-all strategy

Tables III and IV show the distribution of responses to the items concerning attitudes and perceptions towards a freeze-all strategy with Table III showing the differences in the male and female population prior to the initiation of treatment, and Table IV showing the responses to the items before and after the initiation of the first ART cycle. Of all the respondents, 62.4% agreed that they would find it difficult to wait one or two months for the embryo transfer with the female respondents being significantly more likely to consider it difficult to postpone embryo transfer compared to the male population (78.6 versus 35.5%, respectively; ($P < 0.001$)). Questioned if they would choose eFET over fresh embryo transfer assuming that the chance of conceiving was the same, almost 60% of the respondents (59.2% of the female and 59.7% of the male respondents, respectively) stated that they agreed, whereas only 9.7% of the female and 6.5% of the male respondents said that they disagreed. Both men and women agreed that they would choose the treatment strategy posing the least threat to their future child regardless of this having to prompt a delay in time to embryo transfer with 100% of the men and 98.1% of the women agreeing to this item. In the item exploring the willingness to accept a treatment risk on own/partners health, there was a significant difference ($P < 0.025$) between the female and male respondents with the women being more willing to accept a risk on own health to achieve pregnancy. When looking at the responses to the same items

Table III The distribution of responses to statements regarding attitudes towards a freeze-all strategy before the first treatment cycle.

Statement	Response	Women ($n = 103$) % (n)	Men ($n = 62$) % (n)	*P*-value
'The chance of pregnancy would have to be greater using frozen, thawed embryos than fresh embryos, if I were to choose this method'	Agree	50.5 (52)	35.5 (22)	0.109
	Neither agree nor disagree	31.1 (32)	41.9 (26)	
	Disagree	18.4 (19)	22.6 (14)	
'It would be difficult for me to wait a month or two for the embryo transfer'	Agree	78.6 (81)	35.5 (22)	<0.001
	Neither agree nor disagree	7.8 (8)	22.6 (14)	
	Disagree	14.6 (14)	41.9 (2 6)	
'If the chance of pregnancy were the same for FET as for fresh embryo transfer, then I would choose this method'	Agree	59.2 (61)	59.7 (37)	0.748
	Neither agree nor disagree	31.1 (32)	33.9 (21)	
	Disagree	9.7 (10)	6.5 (4)	
'If it were safer for me/my partner, I wouldn't mind the embryo transfer being delayed for a couple of months'	Agree	82.5 (85)	96.8 (60)	0.025
	Neither agree nor disagree	6.8 (7)	1.6 (1)	
	Disagree	10.7 (11)	1.6 (1)	
'If it were safer for my future child, I wouldn't mind the embryo transfer being delayed for a couple of months'	Agree	98.1 (101)	100 (62)	0.544
	Neither agree nor disagree	1.0 (1)	0 (0)	
	Disagree	1.0 (1)	0 (0)	
'I want the treatment that gives me the greatest chance of giving birth, regardless of whether this is fresh embryo transfer or FET'	Agree	92.2 (95)	85.5 (53)	0.128
	Neither agree nor disagree	6.8 (7)	8.1 (5)	
	Disagree	1.0 (1)	6.5 (4)	
'Transfer of a frozen thawed embryo in a subsequent cycle appeals to me, as it seems more natural and hormone-free for my/our fetus'	Agree	67.0 (69)	51.6 (32)	0.040
	Neither agree nor disagree	28.2 (29)	46.8 (29)	
	Disagree	4.9 (5)	1.6 (1)	

before and after treatment, no significant differences in response patterns were found over time.

In Table V the crude and adjusted odds ratios (OR/AOR) for agreement to the three items are shown. In the adjusted analyses on the items 'agreeing to freeze-all if the pregnancy chance is similar and agreement to accept a delay in embryo transfer if safety is higher', none of the covariates showed any significant increases or decreases in the adjusted risk. In the item 'agreement to accept a delay in embryo transfer if safety is higher' the covariate previous delivery/children from previous relationships was not included due to the distribution of answers in this item being too unequal to be adjusted for.

In the item concerning 'agreement to finding it difficult to accept a delay in embryo transfer', having been through previous fertility treatment increased the adjusted risk of finding it difficult to accept a delay in embryo transfer (AOR 2.85; 95% CI: 1.21–6.70), whereas being male gender decreased the adjusted risk (AOR 0.06; 95% CI: 0.03–0.15). None of the other covariates showed significance.

Discussion

We found that two-thirds of the study population had positive perceptions towards a freeze-all strategy in a clinical setting where pregnancy rates would be equal in fresh embryo transfers compared to eFET and a freeze-all strategy. Most of the respondents were in favor of a freeze-all strategy assuming this could potentially reduce risks for mother and/or child regardless of the delayed embryo transfer. Nevertheless, the emotional aspect of waiting for embryo transfer was unquestionably considered a strain. The female respondents were significantly more likely to consider the postponement of embryo transfer difficult compared to the male population (78.6 versus 35.5%, respectively) and they were significantly more willing to accept a risk on their own health achieving pregnancy than were the male respondents on their partner's health. In the adjusted analyses we found no significant predictive factors for preferences towards a freeze-all strategy apart from a negative attitude towards delay of transfer in case of previous unsuccessful ART attempts and a more positive attitude towards a delay when being of male gender.

Though some evidence suggests that ART outcomes may be further improved with the adaptation of a freeze-all strategy with replacement of frozen–thawed embryos in natural cycles, fresh embryo transfer is still the conventional procedure in ART as only one in five transfers in average was performed with frozen–thawed embryos in Europe in 2013 (Calhaz-Jorge *et al.*, 2017). However, the favor of FET is now reflected in some European countries including Finland, Sweden and Iceland where approximately every third child conceived after ART treatment is born after FET (Calhaz-Jorge *et al.*, 2017).

Infertile couples´ attitudes towards eFET in relation to a freeze-all strategy have not previously been studied and patients perceptions on this topic are almost unexplored. Only one qualitative study of 16 couples on how patients make the decision to freeze surplus embryos showed confusions regarding the term 'freezing' in relation to safety as well as practical aspects of the procedure (Goswami *et al.*, 2015). In

Table IV The distribution of responses to statements regarding attitudes towards a freeze-all strategy before and after the first treatment cycle.

Statement	Response	Before Treatment All (n = 165) % (n)	After first Treatment All (n = 91) % (n)	P-value
'The chance of pregnancy would have to be greater using frozen, thawed embryos than fresh embryos, if I were to choose this method'	Agree	44.8 (74)	58.2 (53)	0.051
	Neither agree nor disagree	35.2 (58)	31.9 (29)	
	Disagree	20.0 (33)	9.9 (9)	
'It would be difficult for me to wait a month or two for the embryo transfer'	Agree	62.4 (103)	64.8 (59)	0.150
	Neither agree nor disagree	13.3 (22)	19.8 (18)	
	Disagree	24.2 (40)	15.4 (14)	
'If the chance of pregnancy were the same for FET as for fresh embryo transfer, then I would choose this method'	Agree	59.4 (98)	53.8 (49)	0.448
	Neither agree nor disagree	32.1 (53)	33.0 (30)	
	Disagree	8.5 (14)	13.2 (12)	
'If it were safer for me/my partner, I wouldn't mind the embryo transfer being delayed for a couple of months'	Agree	87.9 (145)	80.2 (73)	0.102
	Neither agree nor disagree	4.8 (8)	12.1 (11)	
	Disagree	7.3 (12)	7.7 (7)	
'If it were safer for my future child, I wouldn't mind the embryo transfer being delayed for a couple of months'	Agree	98.8 (163)	96.7 (88)	0.478
	Neither agree nor disagree	0.6 (1)	2.2 (2)	
	Disagree	0.6 (1)	1.1 (1)	
'I want the treatment that gives me the greatest chance of giving birth, regardless of whether this is fresh embryo transfer or FET'	Agree	89.7 (148)	95.6 (87)	0.254
	Neither agree nor disagree	7.3 (12)	3.3 (3)	
	Disagree	3.0 (5)	1.1 (1)	
'Transfer of a frozen thawed embryo in a subsequent cycle appeals to me, as it seems more natural and hormone-free for my/our fetus'	Agree	61.2 (101)	53.8 (49)	0.474
	Neither agree nor disagree	35.2 (58)	40.7 (37)	
	Disagree	3.6 (6)	5.5 (5)	

another study, 172 fertility patients about to embark on ART treatment were presented a discrete choice experiment investigating preferences on effectiveness, safety and burden of GnRH analogs and GnRH antagonists in relation to risk of OHSS showing that the safety aspect is important to patients, but not necessarily important enough to make up for a small decrease in pregnancy rate (van den Wijngaard *et al.*, 2014).

In the present study we have demonstrated the willingness of the participating patients to accept a delay in time to embryo transfer in relation to ART treatment in a clinical setting where information is given in due time before embryo transfer and where eFET is indicated to improve the safety of mother and child. Though patients may indicate that a delay of embryo transfer is a concern, they are also very concerned on safety issues as well as outcome potential. This suggests a patient amenability to adapt to a change in treatment when this is performed on an informed basis.

The overall response rate in the study was 77.1%, which is to be considered relatively high, however, the participants in the study were mainly from the Capital city and a limited part of Denmark and may therefore not be representative for all fertility patients in other parts of the country. Hence, selection bias may be present. Furthermore, the hypothetical nature of the questionnaire items may inflict bias and limit the validity of the results.

In a recent paper by Lattes *et al.* (2017) looking at 512 freeze-all cycles in a retrospective cohort study setup, the authors found no difference in live birth rate between artificial FET performed during the first cycle following egg retrieval or during subsequent cycles. This suggests that the waiting time in such a strategy using a short GnRH antagonist protocol may be shortened to only one menstrual cycle making the time from start of ovarian stimulation to embryo transfer no longer than it would have been in the traditional long GnRH agonist protocol.

Our results show that when given access to objective and relevant information in the initial treatment process in due time before embryo transfer to adjust patients expectations, the patients in general had a positive attitude towards the possibility of eFET and a freeze-all strategy as the idea was presented early on in the course of ART treatment and not after the treatment had already been initiated. Hence, patients expectations can be adjusted to this strategy if only thorough initial information is given.

This underlines the importance of matching expectations and preparing patients for the different possibilities and strengthening their sense of control in the treatment process. We also found that after the first treatment cycle patients tend to become slightly more impatient and willing to accept greater risks, which accentuates the importance of managing expectations at an early stage in the treatment process. Further, for individualized treatment, treatment strategies must be adjusted throughout the full treatment course.

The positive attitude towards freeze-all in our trial is possibly due to the fact that the patients were well informed about the freeze-all

Table V Multiple logistic regression analyses depicted as odds ratios (95% confidence intervals) on agreement to statements regarding a freeze-all strategy.

Question	Groups	Crude OR (95%CI)	*P*-value	AOR* OR (95%CI)	*P*-value
Agreement to freeze-all if pregnancy chance is similar					
Gender	Female	1			
	Male	1.45 (0.77–2.74)	0.25	1.67 (0.34–0.81)	0.16
Age	<35 years	1			
	≥35 years	0.86 (0.46–1.60)	0.63	0.84 (0.42–1.66)	0.61
Male factor	No	1			
	Yes	1.49 (0.81–2.79)	0.20	1.42 (0.70–2.88)	0.33
Previous delivery/children from previous relationships	No	1			
	Yes	1.92 (0.48–7.69)	0.35	1.85 (0.37–9.19)	0.45
Previous treatment	No	1			
	Yes	0.78 (0.42–1.45)	0.43	0.71 (0.36–1.42)	0.33
Occupational social class	High (I + II)	1.46 (0.47–4.49)	0.51	1.85 (0.56–6.16)	0.32
	Low (V + IV)	1			
Agreement to accept a delay in embryo transfer if safety is higher					
Gender	Female	1			
	Male	1.02 (0.45–2.33)	0.97	1.01 (0.37–2.71)	0.99
Age	<35 years	1			
	≥35 years	0.61 (0.27–1.37)	0.23	0.47 (0.18–1.21)	0.12
Male factor	No	1			
	Yes	0.91 (0.41–2.05)	0.83	0.95 (0.35–2.58)	0.91
Previous delivery/children from previous relationships	No	1			
	Yes	1.19 (0.24–5.89)	0.84	–	–
Previous treatment	No	1			
	Yes	0.44 (0.19–1.02)	0.05	0.35 (0.13–1.00)	0.05
Occupational social class	High (I + II)	2.08 (0.42–10.22)	0.36	1.92 (0.36–10.0)	0.44
	Low (V + IV)	1			
Agreement to finding it difficult to accept a delay in embryo transfer					
Gender	Female	1			
	Male	0.09 (0.04–0.18)	<0.01	0.06 (0.03–0.15)	<0.01
Age	<35 years	1			
	≥ 35 years	1.14 (0.61–2.13)	0.68	1.13 (0.48–2.62)	0.78
Male factor	No	1			
	Yes	0.68 (0.37–1.27)	0.23	0.69 (0.92–1.63)	0.39
Previous delivery/ children from previous relationships	No	1			
	Yes	0.70 (0.20–2.53)	0.59	0.46 (0.07–3.03)	0.42
Previous treatment	No	1			
	Yes	1.90 (1.02–3.56)	0.04	2.85 (1.21–6.70)	0.02
Occupational Social Class	High (I + II)	0.60 (0.18–1.95)	0.39	0.90 (0.21–3.85)	0.89
	Low (V+ IV)	1			

P-values and 95% CI correspond to tests for difference in an unadjusted and adjusted multiple logistic regression model. *N* = 165 observations. Goodness of fit *P* = 1.0. *Adjusted for the six independent covariates; Gender (male or female), age, main infertility diagnosis group (male factor or not), previous delivery/children from previous relationship, previous treatment and occupational social class. OR = odds ratio; AOR = adjusted odds ratio.

strategy before initiating their first ART treatment cycle. If patients are prepared on the possibility of freeze-all most patients will accept this strategy given a high risk of OHSS or impaired chance of pregnancy in the fresh cycle. Patient tailored strategies could, i.e. be that patients with polycystic ovarian syndrome (PCOS), severe endometriosis, more than 15 oocytes aspirated or more than 18 follicles above 11 mm of the day of hCG trigger could be tailored to a freeze-all strategy (Papanikolaou *et al.*, 2011).

Wider implications

The positive attitudes towards a freeze-all strategy in this study facilitate the possibility of implementing individualized treatment in a broad population of patients, and not only in those who are at obvious risk of developing severe OHSS.

The authors of a review and meta-analysis found that there was evidence to suggest that IVF outcomes may be improved by performing eFET compared with fresh embryo transfer, possibly explained by a better embryo-endometrium synchrony in FET cycles (Roque *et al.*, 2013).

In a Chinese multicentre study comparing 1508 PCOS patients, overall live birth rates were superior in the freeze-all versus the fresh embryo transfer arm (49.3 versus 42.0%) for a ratio of 1.17 (95% CI: 1.05–1.31; $P = 0.004$) (Chen *et al.*, 2016). On the contrary, similar live birth rates after eFET and fresh embryo transfer were recently reported in a large RCT including ovulatory patients (48.7 versus 50.2%, respectively), as were the risks of obstetrical and neonatal complications. OHSS was significantly reduced in the eFET group (0.6 versus 2.0%; relative risk, 0,32; 95% CI: 0.14–0.74) (Shi *et al.*, 2018). Beneficial obstetric and perinatal outcomes after FET are reported by other authors (Maheshwari and Bhattacharya, 2013; Evans *et al.*, 2014; Roque, 2015).

In addition, frozen–thawed embryo transfers encourage an elective single embryo transfer policy with cumulative pregnancy rates similar to those after double embryo transfer further reducing obstetric and neonatal risks for mother and child (Thurin *et al.*, 2004).

This provides a rationale for conducting further studies. Though studies on obstetrical and perinatal outcomes of children born after ART have shown decreased risks associated with eFET compared with fresh embryo transfer, the increased risk of macrosomia and being large-for-gestational age associated with eFET is still unexplained and the significance still unclear (Wennerholm *et al.*, 2013; Pinborg *et al.*, 2014). Nevertheless existing studies on outcome on FET children show that these are in general good health with no apparent increased risk of malformation or chromosomal abnormalities (Maheshwari *et al.*, 2012).

In contrast to the growing clinical and scientific evidence supporting the potentials of a freeze-all strategy to reduce OHSS, the implementation of these strategies as standard protocol care is still far from reality in most places. Cost implications from the two different strategies need to be investigated and considered as concerns about the cost-effectiveness of elective FET compared with fresh embryo transfer with the upgrading of ART units and training personnel to accommodate the new treatments might be a concern. In a cost-effectiveness analysis by Roque *et al.* from 2015 assessing this aspect in comparison with fresh embryo transfer in a private center in Brazil, the authors found a significantly lower total treatment cost per pregnancy in the freeze-all cycles compared to the fresh cycles. This decreased cost could also be found even in a scenario where the patients in the freeze-all treatment strategy would be charged for the cryopreservation of their embryos (Roque *et al.*, 2015). No similar calculations in relation to the Danish National Health Care System exist. It is important to emphasize that cost-effectiveness analyses should be performed in own clinical settings before firm conclusions can be drawn. Studies are highly needed in different settings to elucidate the cost-effectiveness of freeze-all strategies.

In a freeze-all strategy, this risk of developing severe OHSS is minimized which might save the health care system many resources in costs in relation to treatment and hospitalization. In addition, in the patient-tailored approach it is implied that the best possible treatment option for the individual is chosen with the patient being given the best chance of obtaining a pregnancy without compromising safety related concerns as these may have severe consequences for the patients along with unnecessarily increased costs on behalf of the public health care system (Roque *et al.*, 2015). In addition, patient-centeredness is highly valued by the patients as an important part of the treatment course (van Empel *et al.*, 2011) and has also proven to increase patients well-being during the treatment process (Gameiro *et al.*, 2013). These things should be considered and balanced out in a conscious way with best possible benefits of the patient as well as the public system.

In this study, we had the advantage of a study setting where all patients received the same information on the treatments by way of the mandatory introductory meeting held by the clinical staff, which all the included patients were obliged to attend to be able to initiate treatment. At the meeting the patients were informed about the different types of treatment, advantages and disadvantages and reasons for why one treatment might be chosen over the other. The baseline knowledge of the patients prior to participating in the study can therefore be considered equal. Furthermore, the study population consisted of fertility patients who had not yet initiated ART treatment and hence were not biased by the process of having been through one or more unsuccessful ART cycles.

In Denmark, patients are reimbursed for the first three ART cycles with fresh embryo transfer including also all the surplus FET after the first oocyte retrievals performed at the public fertility clinics. It could therefore be argued that when the patients have free access to ART treatment within the public health care setting, and therefore no economic incentive exists (they are not forced to make any decisions based on financial concerns) the answers given in this type of study on attitudes and opinions will more clearly reflect the real considerations and trade-offs (advantages versus disadvantages) than would be expected if a financial aspect was also part of the consideration.

Conclusion

This study shows that almost 60% of the study population initiating ART would prefer a freeze-all strategy in a clinical setting where pregnancy outcome was equal to fresh embryo transfer. Almost 90% of the study population would prefer eFET despite the delay in embryo transfer, when implicating that risks to mother and child would be reduced. The results show patients willingness to accept eFET and a freeze-all strategy assuming that the pregnancy rate is equal, when this is preceded by substantive information about the underlying evidence on safety and risk parameters. In a clinical setting, this facilitates the implementation of eFET and a freeze-all strategy in selected populations as part of an individualized patient care strategy. A patient tailored approach is the good alternative where patients based on thorough information are included in the decision on whether to freeze or not.

Authors' roles

S.S.: Conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article. A.P.: Conception and

design of the study, analysis and interpretation of data, revising the article. L.S.: Conception and design of the study, interpretation of data, revising the article. K.L.: Conception and design of the study, interpretation of data, revising the article J.B.: Acquisition of data, revising the article. L.P.: acquisition of data, revising the article. A.Z.: acquisition of data, revising the article. All authors approved the final version of the article.

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Conflict of interest

None declared.

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