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A multicenter study on rates and reasons for discontinuation of treatment in subfertile patients with remaining cryopreserved embryos

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Key Message

Discontinuation from fertility treatment, even in case of remaining frozen embryos, is more common than anticipated. Patients discontinuing FET treatment highly recommend enhanced psychological support throughout the entire ART treatment.

Abstract

Research question: What is the discontinuation rate among patients with remaining cryopreserved embryos in Belgium and what are the reasons for discontinuation?

Design: Multicenter, cross-sectional study performed in 11 Belgian fertility clinics (covering 80% of ART population). Patients were eligible (n=1917) in case they underwent an unsuccessful fresh embryo transfer (fresh group) or FET (in between group) and did not start a subsequent FET cycle within one year despite the presence of remaining cryopreserved embryos. Denominator were all patients with embryos cryopreserved during the same period (2012-2017) (n=21329). Data were collected through an online anonymous questionnaire.

Results: The discontinuation rate for patients with remaining cryopreserved embryos is 9% (1917/21329). For the final analysis, 304 completed questionnaires were included. The most important checked reasons for discontinuation of FET cycles were psychological (50%) and physical (43%) burden, impact on work (29%), woman's age (25%) and impact on relationship (25%). In 69% of the cases the patient her/himself made the decision to delay FET treatment. In 16% of the respondents, the decision to delay FET was determined by external factors: treating physician (9%), social environment (4%), close family (3%) and society (3%). Suggested improvements by the respondents were psychological support before (41%), during (51%) and after (51%) treatment, as well as lifestyle counseling (44%) and receiving digital information (43%).

Conclusions: The discontinuation rate is remarkably high in patients with remaining cryopreserved embryos, who are considered to have a good prognosis. Respondents stressed the need to better integrate psychological and patient tailored care in our daily ART practice.

Key Words

Cryopreserved embryos; Discontinuation; FET cycles; Questionnaire; Reasons for discontinuation.

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Introduction

Fertility patients are considered to be highly motivated during the course of their assisted reproductive technology (ART) treatment. Nevertheless, several reports have shown that a significant number of patients terminate their treatment prematurely, even in the absence of financial burden. In the United States, Bedrick et al. found an estimate of 40% discontinuation rate among women with ART insurance coverage (Bedrick et al. 2019). A recent analysis of the German IVF registry showed that the discontinuation rates among patients without life birth were 16%, 21%, 24% and 25% at the first, second, third, and fourth ART cycle, respectively (Kreuzer et al. 2018). In Portugal, where the public health-care system is tax-financed and provides partial reimbursement for infertility medication and well as three ART cycles, the discontinuation rate was 29.5% (Pedro et al. 2017). In Belgium, where six ART cycles are reimbursed, De Neubourg et al. calculated discontinuation rates of complete cycles between 2014 and 2017: respectively 27%, 29%, 33%, 39%, and 47% of patients discontinued ART treatment after the first to the fifth completed cycle (De Neubourg et al. 2021). According to a recent meta-analysis of the 13 worldwide cohort studies from August 2000 to 2019, the total incidence rate for discontinuation of infertility treatments was as high as 36.2% (95% CI:29.02–43.47) (Gorbani et al., 2022). In addition, discontinuation of ART treatment may contribute to compromised cumulative pregnancy rates in ART (De Neubourg et al., 2016; De Neubourg et al., 2021).

In fresh ART cycles, the physical and psychological burden associated with an ART treatment is the major reason for insured patients to delay or even discontinue their treatment (Lande et al., 2015; Van den Broeck et al., 2009). It has been shown many times that subfertility leads to psychological burden. Chen et al. (2004) submitted 122 women visiting a fertility center for the first time consecutively to a structured diagnostic interview by a psychiatrist (Chen et al., 2004). Forty percent were diagnosed with a psychiatric disorder, the most common being anxiety (23.2%), closely followed by depression (17%). These women did not differ in age, education, income, or years of infertility with those who were not diagnosed with a psychiatric disorder. In another study of 1090 consecutive IVF patients, 31% had a psychiatric diagnosis (self-report psychiatric questionnaire), the most common of which was major depression (Volgsten et al., 2008). More recently, it was shown that the criteria

for major depressive disorder were met in a high amount of fertility treatment patients as well as their partners during an 18-month unsuccessful fertility course (Holley et al., 2015).

Potential other sources of stress eventually leading to patient treatment discontinuation might include the impact on the couple's relationship, logistics and transportation issues, psychological consequences of the infertility itself, an inability to withstand more invasive procedures, or fear about the potential side effects of medications or treatment (Domar et al., 2010; Rajkhowa et al., 2006; Verberg et al., 2008).

Cryopreservation of embryos is a standard practice in most ART-centers around the world. Moreover, current pregnancy rates after vitrification and warming of embryos are almost as high as following fresh embryo transfer (Rienzi et al., 2017). The presence of frozen embryos increases optimism and reduces pessimistic feelings about pregnancy among women undergoing ART treatment (Svanberg et al., 2001). Therefore, discontinuation of the treatment is probably less frequent in case of the presence of cryopreserved embryos, given the lower burden of a natural or artificially prepared frozen embryo transfer cycle combined with the high success rates (Shi et al., 2018; Stormlund et al., 2020). Nevertheless, scarce data are available regarding discontinuation rates and reasons for discontinuation in case of remaining cryopreserved embryos (Troude et al., 2014).

The objectives of the current study were to investigate the discontinuation rate in a large Belgian ART population, covering 80% of ART activity, in case of remaining cryopreserved embryos (cryo dropout for more than one year). Additionally, we explored the reasons and rationale of patients to not come back for embryo transfer within one year in case cryopreserved embryos were still available. Finally, we aimed to provide recommendations on how to guide and follow-up patients with cryopreserved embryos and to ensure better compliance to care of this patient population.

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Materials and methods

Participants

Patients with remaining cryopreserved embryos were categorized in three specific groups: 1) patients who underwent an unsuccessful fresh embryo transfer between 1/1/2012 and 31/12/2017, and who did not start a FET cycle within 1 year after freezing, despite the presence of remaining cryopreserved embryos (fresh group); 2) patients with embryos cryopreserved after 1/1/2012, and who underwent an unsuccessful frozen-thawed embryo transfer between 1/1/2012 and 31/12/2017, and who did not start a FET cycle within 1 year, despite the presence of remaining cryopreserved embryos (in between group); 3) patients who underwent a fresh ART cycle in which embryos were cryopreserved between 1/1/2012 and 31/12/2017, and who did not get a fresh embryo transfer, and who did not start a cycle for transfer of frozen-thawed embryos within 1 year after freezing (freeze-all group). The second and third group could contain patients who did not get any fresh embryo transfer. An unsuccessful embryo transfer cycle refers to: no pregnancy, biochemical pregnancy, ectopic pregnancy or miscarriage <12 weeks of gestational age. To calculate the discontinuation rate all patients with embryos cryopreserved between 2012 and 2017 were used as denominator. The following patients were excluded from the analysis: cryopreservation in case of preimplantation genetic testing (PGT), fertility preservation cycles, and oocyte donation cycles.

Questionnaire

A cross-sectional questionnaire was developed and internally validated by the members of the Belgian fertility consortium in cooperation with a psychologist specialized in patient centered care. The questionnaire explored respondents' reasons for delaying their FET cycle for at least 1 year and contained the following sections: 1) questions regarding the specific reasons for discontinuation and who influenced the decision to discontinue; 2) questions regarding the satisfaction of the past fertility treatment(s) and the care in the fertility center; 3) demographic variables and 4) questions regarding fertility history (at the moment of filling out the questionnaire). The questionnaire consisted of the following answering options: open questions; scoring questions: Likert scale from 1 ("This does not apply to me at all" / "Very bad care" / "Not at all") to 10 ("This applies entirely to me" / "Excellent care" /

"Certainly"); discrete quantitative variables, e.g. number of completed IVF treatment cycles (1 to 6, >6); nominal categorical variables e.g. educational level, obstetrical history.

Patient selection and data flow

Patients were recruited from 11 tertiary ART referral centers around Belgium (the "Belgian fertility consortium", covering 80% of ART activity in Belgium). Eligible patients were identified by the principal investigator of each participating center and contacted by email via Mailchimp®. When no email address was available, eligible patients were contacted by telephone first to retrieve their email address. Via this email address an invitation letter was sent, which contained a unique link per patient. This link led to an electronic information and informed consent form (ICF). Once consent was given, the questionnaire could be opened and filled out. At the beginning of the questionnaire two screening questions had to be filled out: 1) "I started treatment in another fertility center" and 2) "I became pregnant spontaneously". The respondents answering affirmative on these questions were not considered eligible, not allowed to further complete the questionnaire and thus not incorporated in the final analysis. Two reminders were sent in case the questionnaire was not filled out yet: a first reminder after two weeks, a second reminder after four weeks. Logistics regarding the online questionnaire were provided by Listen® Research and Intelligence (Rue Chaussée 67, B-4342 Hognoul, Belgium). Listen® was designated and funded by Merck nv/sa for this project. Listen® only provided the unique ICF and questionnaire link per center, therefore patient identification data were not available for Listen® nor Merck nv/sa. After filling out the consent box and questionnaire, Listen® closed the link, to make sure that each participant only filled out the questionnaire once. The main investigators of each center were provided with the list of links of complete questionnaires, as a proof of informed consent. The answers to the questionnaire were gathered by Listen® and provided to the main investigators apart from the used web links. As a consequence, the investigators were blinded to individual answers.

Statistical analysis

Scores on the Likert scales asking about possible reasons for dropout, satisfaction with the fertility center, and desired improvements of care were not normally distributed. Therefore, patients were categorized into three groups according to their score on the respective Likert

scale (1-3, 4-7, and 8-10).

Simple generalized linear mixed models were fitted. A random intercept for centers was used to take into account the clustering of patients within centers. The models for the categorized Likert scores had a multinomial distribution with a logit link function. The odds for having a score between 8 and 10 instead of between 1 and 3 was compared between groups.

The models for binary endpoints (related to advising the fertility center and to persons with influence in the decision to delay the treatment) had a binomial distribution with a logit link function. The odds for the treated woman / partner / doctor or nurse having an influence in the decision to delay the treatment was also compared between groups.

The fixed effects part of the simple generalized linear mixed models included one of the following explanatory factors: age (< 37y versus ≥ 37 y), education (higher non-university, lower education versus university), number of pregnancies (0, 1 versus ≥ 2), number of births (0, 1 versus ≥ 2), cycles with transfer of fresh embryo(s) (0, 1 versus ≥ 2), cycles with transfer of frozen embryo(s) (0, 1 versus ≥ 2), and treatment group ("fresh" versus "in between"). All analyses were performed at the two-sided 5% significance level, no corrections for multiple testing were made. Analyses were performed in IBM® SPSS® Statistics version 27.

Ethical approval

All aspects of the study were given approval by the 11 local medical research ethics committees. The Ethical Committee of the Antwerp University Hospital, Belgium, served as central committee (B300201838440). Informed consent was given electronically before proceeding to the actual questionnaire. The IC form was downloadable for the participant (PDF-format).

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Results

Respondents

The number of eligible discontinuation patients was 1917, whereas the number of invited patients was 1851, due to the lack of email addresses and bounced emails. Of the contacted patients, 44% (819/1851) connected to the questionnaire and 30.1% (557/1851) answered two screening questions at the beginning of the questionnaire. Of the patients answering the screening questions, 5.7% (32/557) started treatment in another center and 18.1% (101/557) became pregnant spontaneously. The remaining 424 patients were admitted to fill out the questionnaire. Upon closing of the questionnaire, it was decided not to include the freeze-all patients in the analysis, since almost all of the freeze-all respondents were treated in a single center and results would therefore not be generalizable for other centers or settings. For the final analysis, 304 completely filled out questionnaires were included, exclusively consisting of patients from the fresh and in between groups.

Dropout rates

The overall discontinuation rate after one year for patients with remaining cryopreserved embryos was 9.0% (1917/21329). The dropout rate in the fresh group was significantly higher compared to the in between group: 9.7% (1216/12545) and 8.0% (701/8784), respectively ($p<0.001$).

Baseline characteristics

Baseline characteristics of the respondents are presented in Table 1. Mean age (±Standard Deviation (SD)) of the women in treatment at the moment of discontinuing FET cycles was 35.3±5.4 years, and was significantly higher in the fresh group compared to the in between group (35.6±5.7 y versus 34.8±4.7 y respectively, $p<0.018$). The majority of questionnaires were filled out by the women in treatment (84.5%), and a minority by the partner (5%) or both (10.5%). This was not different between the fresh and the in between group. Most of the women followed higher education (32.6% non-university and 29.6% university), which was also not different for both groups, neither was a past history of having at least one pregnancy (89.1%) or one birth (70.4%). Most of the respondents had a history of at least one fresh or frozen-thawed embryo transfer (94.7% and 78.3%, respectively). The number of respondents with 2 or more fresh transfers was significantly higher in the fresh group

(p<0.001); whereas the number of respondents with 2 or more frozen-thawed transfers was significantly higher in the in between group (p<0.001).

Reasons to stop or postpone FET cycles

Both groups, fresh and in between, brought up very similar reasons for discontinuation of their FET cycles (open question): 23% of the respondents from the fresh group and 25% of the respondents from the in between group mentioned that they were feeling mentally and/or physically too tired to continue treatment. In both groups, 8% of the respondents mentioned a health problem as being the main reason to discontinue treatment with frozen embryos, and 6% quoted relational problems. Of the respondents in the fresh group and in the between group 10% and 5%, respectively, said they were not aware of the presence of any remaining frozen embryos. Also, 9% of the respondents in the fresh group and 10% of the respondents in the in between group wrote they could not remember why they discontinued their treatment in the past.

Among a list of reasons for not contacting the fertility center for a while, presented to the participants and scored on a Likert scale from 1 (this does not apply to me at all) to 10 (this applies entirely to me), we found, taking into consideration Likert scores 6 or higher, that the most important checked reasons for discontinuing treatment were psychological (50%) and physical (43%) burden, the impact on work (29%), age of the woman in treatment (25%) and impact on relationship (25%) (Figure 1). Significantly more respondents in the fresh group (29%) scored 6 or higher on the reason “age of the woman in treatment” compared to the respondents in the in between group (18%) ($p < 0.05$). The other Likert scores were not different between both groups.

Associations were evaluated between the Likert score on the 5 most checked reasons for discontinuation and a number of explanatory variables. The estimated odds of scoring 8 to 10 compared to 1 to 3 are shown in Table 2. Summarized, nulliparous respondents as well as respondents with higher treatment ranks (fresh as well as FET) checked more often psychological and physical burden as an important reason for discontinuation of FET cycles. Nulliparous respondents scored impact on work significantly higher. Older women and respondents from the fresh group checked more often age of the women in treatment as an important consideration to discontinue FET cycles.

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Who influenced the decision to discontinue FET cycles for at least one year?

The decision of the patient to discontinue treatment was mainly taken by the patient or partner. Sixty-nine percent of the respondents pointed out the woman in treatment and/or the partner as most important influencer to discontinue treatment. Only in 16% of the respondents the decision to discontinue treatment was determined by external factors. The physician was the major external influencer, mainly in women above 43 years of age (25% versus 8% in women below 40 years of age, $p < 0.01$). Other external factors were social (4%), close family (3%) and society (3%). The estimated odds of pointing out a certain influencer to discontinue treatment were calculated and are shown in Table 3. For the respondents who checked the women in treatment being a major influencer in the decision to discontinue FET cycles, parity and FET cycle rank played a significant role. Taking into account the respondents who checked the partner as being an important influencer in the decision to discontinue FET cycles, women's age as well as the patient group played a significant role.

Satisfaction with the care given by the fertility center and respondent's views on improvements of care

We asked the respondents if they were satisfied with the care delivered by their fertility center during different treatment stages (during diagnosis, between diagnosis and treatment, during fresh ART treatment, during ART treatment with FET cycles, in between ART treatments). The level of satisfaction of the treatment stage itself scored highest with 79% of the respondents scoring 8 or higher on a score level from 1 (very bad care) to 10 (excellent care). This was 74% for the pre-treatment stage and 65% in between ART treatments. However, 19% of the respondents scored between 1 to 5 for satisfaction of care in between treatments. Respondents of fresh or in between groups did not score significantly different on these questions regarding satisfaction. Of the fresh group, 93.8% of the respondents would recommend the fertility center to others, and this was not significantly different for the in between group (90.9%).

A significant association was observed between gravidity and satisfaction with the fertility center. The estimated odds of scoring 8 to 10 compared to 1 to 3 on a Likert scale for satisfaction with the fertility center (1 = worst care ever, 10 = best care ever) are 42% lower

in nulligravida compared to women with a history of pregnancy (95% CI 71.2% to 98.8% lower, p = 0.001). This association could not be shown for other explanatory variables.

With regards to improvements our respondents would like to be seen at their fertility clinic, 51% percent of the respondents checked improvement of psychological support during and after treatment (Likert scale 6 to 10), whereas 44% wanted better advice on lifestyle factors, 43% improved digital info regarding treatment relevant topics, 41% improved psychological support before treatment and 39% more contacts with the own physician (Figure 2). There was no significant association between the respondent group (fresh or in between) and the answers on this question.

Associations were evaluated between the Likert score on suggestions for improvement of care and the same explanatory variables. The estimated odds of scoring 8 to 10 compared to 1 to 3 are shown in Table 4. We found a significant association between lower gravidity and parity and the scoring on the suggestion to improve psychological care before, during and after ART treatment as well as on receiving life style advice and having consultation with their own physician. Patients with 2 or more FET cycles valued more often lifestyle advice and consultation with their own physician.

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Discussion

Although FET cycles are associated with low physical burden and high success rates, our multicenter data show that a non-negligible part of ART patients do not return to proceed FET cycles within one year after a previous unsuccessful fresh transfer or FET cycle. Eventually, this will have a negative effect on cumulative live birth rates.

The discontinuation rate in patients following an unsuccessful fresh embryo transfer appeared significantly higher compared to the discontinuation rate in between FET cycles. Possibly, the first group of patients is not sufficiently aware of the good prognosis of a transfer of frozen-thawed embryos. Also, the respondents of the fresh group were significantly older compared to the in between group. Overall, age is an important predictor in our group to delay next FET cycles. Patients above 37 years of age are at higher risk for FET treatment discontinuation. For respondents discontinuing FET cycles after a fresh unsuccessful transfer, the age of the woman in treatment is estimated of higher importance to delay FET cycles compared to respondents discontinuing transfer in between FET cycles. This is in line with earlier data stating that older patients more often do not embark on a next treatment cycle and are thus more prone to treatment discontinuation (De Neubourg et al., 2021; Mumusoglu et al., 2017; Troude et al., 2014;).

Baseline characteristics of our respondents show that they are presumably very good prognosis patients, with a mean of 35.3 years of age at the moment of treatment discontinuation, high overall gravidity and parity numbers and one fifth of the patients connecting to the questionnaire stated they became pregnant spontaneously within 12 months after treatment discontinuation. So, even good prognosis patients are at risk. Interestingly, Troude et al. (2014) showed that discontinuation of ART following a first completed ART cycle (fresh and frozen embryos) increased with the number of frozen embryos, as well as the number of frozen embryo transfers. This is in line with our cohort, being good prognosis patients. However, our cohort consisted of subjects who did not even started their FET procedure, or discontinued during FET procedure. This might, in part, be related to misconception of the patient concerning their prognosis being good to excellent or to a suboptimal center-patient communication during and/or after treatment, which is also illustrated by the fact that up to 10% of our respondents mentioned they were not

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aware of the presence of any frozen embryos. This is a surprising finding, since, all but one of the participating centers send a letter or message with the number of frozen embryos following ovum pick-up (fresh transfer) or, if no fresh transfer, shortly after embryo cryopreservation.

Questionnaires might not fully capture emotional responses or feelings. Therefore, open answer boxes were added to the 10-point Likert scale used for some of the questions. However, the strength of our study lies in the multicenter character as well as in the solid response rate compared to similar studies in the field (Lawson et al., 2021; Yee et al., 2021). A response rate is most commonly defined in two ways: the number of subjects who respond to a survey divided by (i) the number of subjects in the selected sample and/or (ii) the number of eligible subjects in the sample (Fowler FJ, 2013). In our case, if we consider that all those who took the screening questions responded, then our response rate is 30.1%. Nevertheless, in patients' surveys, the response rate varies from 10.3% to 61%, and delicate content like subfertility is known to reduce the response rate (Booker et al., 2021). Patients discontinuing their treatment are considered unsatisfied with the course of their treatment, eventually leading to treatment cessation. The fact that they were willing to participate is remarkable. About 10% of the respondents wrote they could not remember why they delayed their treatment in the past. The latter may reflect a certain degree of recall bias among our respondents.

The results of this questionnaire underline clearly the psychological and physical burden patients are facing during ART treatment, even for patients with remaining cryopreserved embryos. It was shown before that ART patients are at risk to suffer from a psychiatric diagnosis (Chen et al., 2004; Holley et al., 2015; Volgsten et al., 2008). We observed that nullipara attached more importance to psychological burden as a reason for discontinuing cryo transfers. Thus, women without children encounter more psychological burden leading to dropout. On the contrary, we found that women without previous transfer cycles (fresh and/or cryo) less often checked psychological and physical burden as an important reason for discontinuing next cryo transfers. These women have not experienced many failures yet which could explain lower psychological and physical burden. Interestingly, women with

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higher parity checked less often physical burden as an important reason for discontinuing next cryo transfers.

We should not underestimate the impact of ART treatment on professional activities and relational wellbeing of the couple, since one quarter of our respondents indicate that impact on work as well as relationship had a share in the decision to discontinue treatment with cryopreserved embryos. Impact on work as a reason for dropout was checked more frequently by women with 1 previous birth compared with women with at least 2 births. We assume that this could be explained by the fact that parents might not easily chose to work less after the birth of a first child, but rather do so when the family is extended to at least 2 children. Impact on relationship could not be linked to any explanatory variable, meaning that any couple may be faced with relational tensions due to ART treatment at some point.

Financial burden was of lesser importance in our group of respondents compared with other studies. We have to bear in mind that the majority of patients undergoing ART in Belgium is well insured, with reimbursement of up to 6 complete ART cycles. Therefore, costs are for most of our patients a minor concern throughout their ART course.

Most of our respondents decided themselves to discontinue further treatment with cryopreserved embryos. The woman in treatment herself is more prone to discontinue FET cycles in case she is nulliparous and in case she did more FET cycles. The partner influenced the decision to stop treatment prematurely significantly more often in case the woman in treatment is younger and in case of an unsuccessful fresh transfer (fresh group). The latter may be explained by the fact that partners might have been overwhelmed by the physical and or psychological burden their female partner experienced during a fresh ART cycle, and they could also argue that since their partners were considered young, discontinuing FET cycles would not hamper future success. For a minority of our respondents an external factor played a role in the decision process. Nevertheless, the physician played this role in a quarter of the women aged 43 or above. Thus, the responsibility of the physician should not be underestimated. Therefore, we also advocate shared decision making to minimize psychological burden during and after any ART treatment to prevent treatment discontinuation (Harrison et al., 2021).

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The reason to discontinue further treatment with cryopreserved embryos seemed not to be influenced by a sense of dissatisfaction with the fertility center. Less than 6% of patients connecting to the questionnaire stated they started treatment in another center. The vast majority of our respondents is hugely satisfied with the care they received and more than 90% would recommend their fertility center to others. However, a selection bias cannot be excluded with regard to this result. Indeed, it cannot be ruled out that the non-respondents were less satisfied with the care they got. In our respondent group, women who have been pregnant, regardless of having a live birth or not, are more satisfied with their fertility center compared to women who had never been pregnant before. Interestingly, the lowest score for satisfaction with the center was given in between treatments, underlining the importance of proper follow-up of patients, also during waiting times in between cycles. In addition, the pre-treatment stage was scored lower compared to the treatment stage. This is not surprising, as shown by Ohannessian et al. (2017), who aimed to identify prognostic factors that lead to a live birth in couples with unexplained infertility and found that one third of the included couples diagnosed with unexplained infertility dropped out from infertility treatments before even starting IVF (Ohannessian et al., 2017).

During the course of the study, it was decided not to include PGT cycles, nor to include non-PGT freeze-all cycles. Nevertheless, it would be of utmost interest to look into this specific group of patients to reveal if reasons for dropout are different compared with the general ART population.

Based on our data, patients highly expect enhanced psychological support throughout the entire ART treatment, as well as lifestyle advice and digital communication of information relevant for the treatment. Women without any pregnancy nor delivery are much more in favor of improving psychological care at the fertility center before, during as well as after ART treatment. Patients without any pregnancy or delivery in the past are more eager to receive lifestyle advice during their ART treatment, as well as women with higher cryo treatment rank. The same subgroup of patients would like to see their own treating physician more. This stresses the need to better integrate these aspects of patient centered care in our daily ART practice. These findings are in line with data stating that only 21% of

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women with a psychiatric diagnosis, who were undergoing ART treatment, were receiving some form of psychological treatment (Volgsten et al., 2008).

As shown by others, embracing the psychological needs of our patients must become high priority (Rich and Domar, 2016). Psychological care, given by trained psychologists or fertility counselors, should be available at any point throughout the treatment, as well as the possibility to get in contact with the own gynecologist. In addition, evidence based digital platforms (e.g. website, fertility apps, social media) could be rolled out and be helpful in bringing correct information “anytime anywhere” to the patient (Boedt et al., 2019). This is currently being investigated and applied also in other fields within ART, such as in fertility preservation (Benedict et al., 2021; Cheung and Zebrack, 2017; Lewin et al., 2017). Based on our data, especially, women above 37 years of age and women without any history of pregnancy or live birth, should be followed-up and supported more intensively throughout their ART journey. Psychosocial and demographic correlates of discontinuation offer opportunities to tailor interventions towards couples at risk for treatment discontinuation (Van Dongen et al., 2015). Also, we assume that social awareness and support from authorities and employers may prevent treatment dropout.

In conclusion, it is of utmost importance to further focus on FET discontinuation and to design interventions to decrease treatment distress. Eventually, this will lead to lower FET discontinuation rates and higher cumulative live birth rates, the ultimate goal in fertility care.

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Author's roles

D.D.N. proposed the research question. The consortium members designed the study and questionnaire, determined the study objectives and lead the fieldwork at their own center. F.V.M. collected and prepared the data for analysis and performed the statistical analysis. F.V.M. and D.D.N. drafted the first version of the manuscript. The consortium members contributed to the interpretation of the data analysis, revised the manuscript and approved the final version before submission.

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Conflict of interest

All authors have no conflict of interest pertaining this research.

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Figure legends

Figure 1: Reasons to delay or stop treatment with cryo embryos (n respondents = 304) on Likert scale from 1 (this doesn't apply to me at all) to 10 (this applies entirely to me).

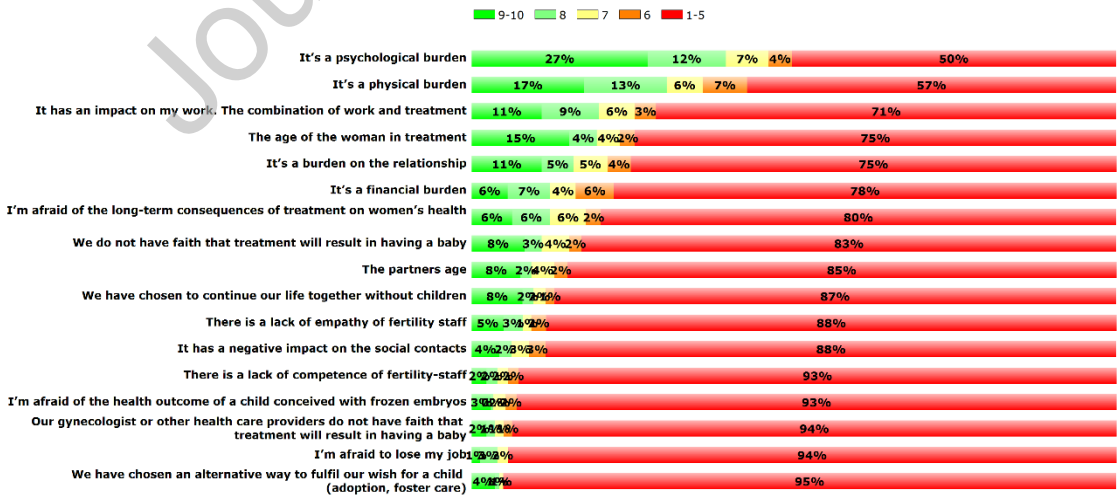
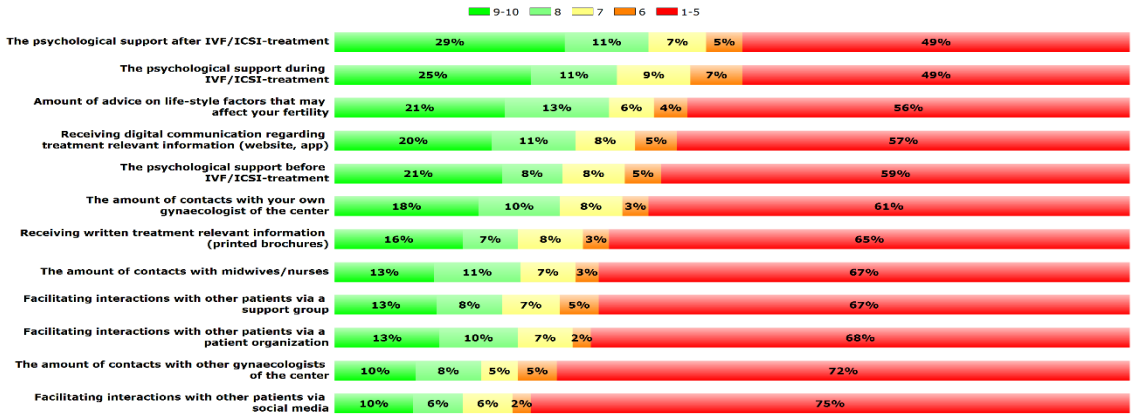


Figure 2: Whether respondents (n respondents = 304) wanted to see any of the following improved at the fertility clinic, on Likert scale from 1 (not at all) to 10 (certainly).



Tables

Table I Demographic characteristics of the respondents

	Fresh group (n = 194)	**In between group (n = 110)**	**Total sample (n = 304)**
Age (years)[$], M (SD)	35.6 (5.68)	34.8 (4.70)	35.3 (5.35)
Respondent, n (%)			
Women in treatment	163 (84.0)	94 (85.5)	257 (84.5)
Partner	10 (5.2)	5 (4.5)	15 (4.9)
Both	21 (10.8)	11 (10.0)	32 (10.5)
Education women in treatment, n (%)			
Primary	1 (0.5)	1 (0.9)	2 (0.7)
Lower secondary	18 (9.3)	6 (5.5)	24 (7.9)
Upper secondary	57 (29.4)	32 (29.1)	89 (29.3)
Higher, non-university	65 (33.5)	34 (30.9)	99 (32.6)
University	53 (27.3)	37 (33.6)	90 (29.6)
Gravidity, n (%)			
0	23 (11.9)	10 (9.1)	33 (10.9)
1	56 (28.9)	31 (28.2)	87 (28.6)
2 or more	115 (59.3)	69 (62.7)	184 (60.5)
Parity, n (%)			
0	55 (28.4)	35 (31.8)	90 (29.6)
1	81 (41.8)	53 (48.2)	134 (44.1)
2 or more	58 (29.9)	22 (20.0)	80 (26.3)
Fresh transfers[#], n (%)			
0	3 (1.5)	13 (11.8)	16 (5.3)
1	70 (36.1)	51 (46.4)	121 (39.8)
2 or more	121 (62.4)	46 (41.8)	167 (54.9)

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Cryo transfers[#], n (%)			
0	64 (33.0)	2 (1.8)	66 (21.7)
1	48 (24.7)	27 (24.5)	75 (24.7)
2 or more	82 (42.3)	81 (73.6)	163 (53.6)

M=mean, SD=standard deviation, [$]p=0.018, [#]p<0.001

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Table II. Estimated odds of scoring 8 to 10 compared to 1 to 3 on the Likert scales representing the 5 most frequently checked reasons for dropout

Explanatory variable / Reason for dropout	Age female at the moment of FET delay/stop	Education of the woman in treatment	Gravidity	Parity	Number of cycles with fresh embryo transfer	Number of FET cycles	Dropout group (fresh or in between)
Psychological burden	NS	NS	NS	2.1 (95% CI 0.91 to 4.84, p = 0.005) in P0 compared to P2 or higher 2.6 (95% CI 1.34 to 5.21, p = 0.005) in P1 compared to P2 or higher	86.7% lower (95% CI 35.8% to 97.3%, p = 0.012) in no versus ≥2 fresh ETs	60.0% lower (95% CI 20.3% to 79.9%, p = 0.009) in no versus ≥2 FET cycles	NS
Physical burden	NS	NS	NS	2.6 (95% CI 1.29 to 5.41, p = 0.008) in para 1 compared to para 2 or higher	90.7% lower (95% CI 23.3% to 98.9%, p = 0.012) in no versus ≥2 fresh ETs	52.0% lower (95% CI 0.0% to 77.0%, p = 0.009) in no versus ≥2 FET cycles	NS
Impact on work	NS	NS	NS	2.7 (95% CI 1.19 to 6.23, p = 0.017) in para 1 compared to para 2 or higher	NS	NS	NS
Impact of age of the woman in treatment	92.1% lower (95% CI 83.5% to 96.2%, p < 0.001) in ≤ 36y compared to ≥ 37y	NS	NS	NS	NS	NS	2.1 (95% CI 1.01 to 4.01, p = 0.032) for the fresh group compared to the in between group
Impact on	NS	NS	NS	NS	NS	NS	NS

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relationship							

NS = no significant association found between explanatory and outcome variable. y = years of age. P = para. FET = frozen embryo transfer.

Table III. Estimated odds of pointing out a certain influencer to delay or stop treatment with frozen embryos

Explanatory variable / Influencer to delay	Age female at the moment of FET delay/stop	Education of the woman in treatment	Gravidity	Parity	Number of cycles with fresh embryo transfer	Number of FET cycles	Dropout group (fresh or in between)
Woman	NS	NS	NS	3.7 (95% CI 1.94 to 7.07, p < 0.0001) in P0 compared to P2 or higher	NS	46.1% lower (95% CI 3.5% to 69.9%, p = 0.038) in no versus ≥2 FET cycles	NS
Partner	2.0 (95% CI 1.34 to 3.20 lower, p = 0.005) in ≤ 36y compared to ≥ 37y	NS	NS	NS	NS	NS	1.8 (95% CI 1.12 to 2.95, p = 0.016) for the fresh group compared to the in between group
Doctor/nurse	NS	NS	NS	NS	NS	NS	NS

NS = no significant association found between explanatory and outcome variable. y = years of age. P = para. FET = frozen embryo transfer.

Table IV. Estimated odds of scoring 8 to 10 compared to 1 to 3 on the Likert scale representing suggestions for improvement of care

Explanatory variable	Age female at the moment	Education of the woman	Gravidity	Parity	Number of cycles with	Number of FET cycles	Dropout group

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Desired improvement	of FET delay/stop	in treatment			fresh embryo transfer		(fresh or in between)
Psychological care before ART treatment	NS	NS	3.8 (95% CI 1.43 to 10.04, p = 0.007) in G0 compared to G2 or more	2.6 (95% CI 1.20 to 5.62, p = 0.015) in P0 compared to P2 or higher	NS	NS	NS
Psychological care during ART treatment	NS	NS	4.0 (95% CI 1.49 to 10.61, p = 0.006) in G0 compared to G2 or more	2.2 (95% CI 1.04 to 4.67, p = 0.04) in P0 compared to P2 or higher	NS	NS	NS
Psychological care after ART treatment	NS	NS	4.2 (95% CI 1.47 to 11.74, p = 0.007) in G0 compared to G2 or more	3.1 (95% CI 1.47 to 6.54, p = 0.003) in P0 compared to P2 or higher	NS	NS	NS
Lifestyle advice	NS	NS	4.5 (95% CI 1.57 to 13.21, p = 0.006) in G0 compared to G2 or more	3.1 (95% CI 1.49 to 6.63, p = 0.003) in P0 compared to P2 or higher	NS	58.9% lower (95% CI 13.5% to 80.5% lower, p = 0.019) in no versus ≥2 FET cycles	NS
Consultation with own physician	NS	NS	3.2 (95% CI 1.33 to 7.67, p = 0.01) in G0 compared to G2 or more	3.5 (95% CI 1.60 to 7.61, p = 0.002) in P0 compared to P2 or higher	NS	66.4% lower (95% CI 22.1% to 85.5% lower, p = 0.019) in no versus ≥2 FET cycles	NS
Digital communication	NS	NS	NS	NS	NS	NS	NS

NS = no significant association found between explanatory and outcome variable. G = gravida. P = para. FET = frozen embryo transfer.

Author Biography

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Frauke Vanden Meerschaut, MD, PhD, has worked in reproductive medicine since 2009. In 2013, she obtained her doctorate at Ghent University, Belgium, for research on oocyte activation and fertilization failure following ICSI. Nowadays, she is a staff member at the Department for Reproductive Medicine at Ghent University Hospital, Belgium.



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