Title: A Randomized Controlled Trial Assessing Whether Listening To Music At Time Of Embryo Transfer Effects Anxiety Levels

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Abstract

Background:

Fertility treatment may have a negative emotional impact on women. Lower levels of anxiety have been associated with improved treatment success but there is no standardised method for addressing these needs. Music is a safe and beneficial non-pharmacological intervention in a number of medical fields. It may alter subjective and objective psychological anxiety as well as physiological functioning. However, little data exists surrounding the therapeutic use of music in fertility treatment but it may attenuate anxiety.

Methods:

An assessor-blinded parallel case control study in an IVF center, England UK. 42 women undergoing assisted reproductive treatment were recruited between February and December 2013. Women were randomised by random envelopes containing equal sized 'music' (listened to self-selected music during embryo transfer) or 'control' (no music) groups. Participants completed the Spielberger State-Trait Anxiety Inventory prior to, and immediately following a post-treatment observation period. Primary outcome was change in anxiety level.

Results:

32 of 42 women (76.2%) were less anxious following treatment (mean change in anxiety score 6.9 95%CI 4.2-9.6, P<0.01) without difference between the study group (7.1 95%

CI 3.5-10.7) (P=0.46) and controls (6.7 95%CI 2.3-11.1). Clinical pregnancy rates (55.0%) did not differ between music and control groups (P=0.95).

Conclusion:

Listening to self-selected music 15 minutes before and after embryo transfer does not significantly impact on anxiety levels of women undergoing assisted conception treatment nor clinical pregnancy rates. Music therapy has not been shown to reduce anxiety at time of ET and the effects of interventions such as hypnosis, acupuncture, aromatherapy and other forms of relaxation therapy remain to be explored.

Trial registration number (ClinicalTrials.gov): NCT02223845 (August 21, 2014)

Regional Ethical Committee reference number: 12/SC/0689

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Keywords: Music, Anxiety, IVF

Background

Assisted Reproductive Treatment (ART) is shown to have a negative emotional impact, with a significant number of women undergoing *In vitro* fertilisation (IVF) reporting treatment as moderate to extremely stressful (1). Whilst preconception stress has been recently shown to increase the risk of subfertility (2), ART is associated with fertility-specific distress beyond the effect of infertility alone with up to 23% of women experiencing clinical anxiety and 20% depression (3). Optimal IVF should reduce treatment burden and enhance care delivery for patients (4). Lower levels of anxiety (5, 6) and interventions directed to reduce these effects have been suggested to improve treatment outcomes (7, 8) but there is little evidence for this providing clinical benefit. Music may be a simple therapeutic adjunct to IVF treatment, it has been shown to decrease anxiety and improve quality of life in other medical settings, and is easy to apply and of low cost (9).

Music is shown to be a beneficial non-pharmacological intervention in pain management, palliative and cancer care and may improve birth satisfaction in women undergoing caesarean section (10-12). It reduces subjective and objective psychological anxiety and improves mood and when used in a colposcopy setting, music appears to have an anti-anxiolytic effect (13). These effects are mediated in part by physiological changes in plasma cortisol levels, heart rate, respiratory rate and blood pressure (10). Little data exists surrounding the therapeutic use of music in fertility treatment and as such, the use of music as a therapeutic adjunct is not routine practice.

The limited evidence available suggests that music therapy may be of benefit in reducing anxiety and clinical fertility outcomes (14). Reported here is whether listening to music at time of embryo transfer effects state anxiety; the objective being to determine whether listening to music at time of embryo transfer effects state anxiety as measured by the primary outcome of state anxiety scores before and after embryo transfer within an assisted conception cycle.

Methods

A single-blind parallel randomized control trial with balanced randomization conducted in an IVF center in the United Kingdom according to a predetermined protocol and reported in accordance with the CONSORT Statement (15). The trial had Regional Ethical Committee approval from the National Research and Ethics Service Committee South Central (Southampton A), reference number: 12/SC/0689.

Participants

Eligibility criteria:

Women aged between 25-40 years, undergoing IVF or ICSI (intra cytoplasmic sperm injection) with fresh or frozen embryos to completion from February 2013 to December 2013.

Exclusion criteria:

Women unable to consent or with hearing impairment.

Baseline demographics (age, body mass index, smoking status) and fertility characteristics (cause of infertility, cycle number and type, number and quality of embryos transferred) were collected for all patients who consented to the study.

Interventions

At time of embryo transfer clinical procedural instructions were given to all women. Women in both the study and control groups filled out the State Trait Anxiety Inventory (STAI) prior to and the embryo transfer, which measures the state and trait anxiety. The

STAI is a psychological inventory based on a 4-point Likert scale and consists of 40 questions on a self-report basis. The STAI measures two types of anxiety - state anxiety, which is the transitory pattern of emotions elicited by environmental stressors, including physiological arousal and symptoms of apprehension, worry, and tension. The respondents are asked to qualify their current state of emotion by selecting through a list of statements, for example, 'I feel calm', or 'I am presently worrying about possible misfortunes'. Trait anxiety which refers to individual differences in the predisposition to respond to threatening situations (16). During this questionnaire, more general personality traits and feelings are elicited for example, 'I make decisions easily' or, 'I wish I could be as happy as others seem to be'. Higher scores are positively correlated with higher levels of anxiety. It is a general measure of anxiety with scores ranging from a possible 20 (minimum) to 80 (maximum) and whilst a subjective measure, it has been shown to have internal consistency and good test–retest reliability (17).

Following which the participants in the study group underwent the ET procedure whilst listening to self-selected music with no restrictions to the type of music they could select, through headphones, and listened for a further 15 minutes in the recovery room. Women in the control group completed the identical questionnaire but did not listen to music in the ET procedure or in the following 15 minutes. At the end of the 15 minutes the women in both groups completed the state portion of the anxiety questionnaire and the FertiQOL (Fertility Quality of Life), an internationally developed and validated questionnaire was used to measure quality of life of the participants (18). This score-based system assesses the emotional, social and relationship factors which influence daily living and the impact of fertility treatment. Subjective measurements are made of

physical health and quality of life. Detailed information on scoring can be accessed at: http://psych.cf.ac.uk/fertiqol/scoring/index.html

Additionally we converted the numerical scale into clinically useful measures of anxiety. These were based on previous studies integral to the design of the original scoring system and normalized values to women of reproductive age (16). Scores of <26.6 indicating a relaxed state (equivalent to relaxation training), greater than 26.6 but less than 37.2 a normal 'average' state, greater than 37.2 and less than 43.7 an 'anxious' state (equivalent to a gradual anxiety provoking stimulus, such as an exam), greater than 43.7 and less than 60.9 a hyper anxious or 'extremely anxious' state (equivalent to a sudden anxiety induction, such as an emotive audiovisual stimulus), and greater than 60.9 extreme 'heightened' anxiety (greater than the reaction one would expect from an anxiety provoking insult).

Embryo quality was assessed prior to transfer. Cleavage stage embryos were graded one to four depending on concordance of cell size and degree of fragmentation (one equating to excellent, two good and three average and four poor quality). Blastocysts were graded using a modified Gardner system (19), taking into account the degree of blastocoele expansion and hatching status (one to six); morphology of the inner cell mass (highest score A, then B, C and D); and the cohesiveness and number of trophectoderm cells (a, b, c and d). Embryos with an expansion degree greater than 2 and inner cell mass and trophectoderm grades of A or B were classed as good quality embryos (20). Early treatment success was determined by serum beta human chorionic gonadotrophin (β-hCG) levels two weeks after luteal day zero. Ongoing clinical

pregnancy was determined by demonstration of a fetal heartbeat on ultrasound scan at 6 weeks gestation.

Sample size

Power calculations were based on primary outcome. An a priori ANOVA repeated measure (within-between group interaction) calculated 34 participants were required to detect a standardized difference size of medium effect (more than a 25% change in state anxiety score with 5% significance and 95% power). Interim analyses demonstrated that pre- and post-treatment anxiety scores correlated less than initially assumed. We recruited an additional 8 participants to achieve power for medium effect size, bringing the total number of participants to 42.

Randomisation

Identical sealed opaque envelopes containing randomization group were shuffled using balanced permuted-blocks of ten and four. Random allocation sequences were generated by shuffling envelopes (by non-researchers) and sequential labeling with study numbers.

Group allocation

Participants were enrolled by members of the clinical team. Unbinding was done at time of recruitment to enable music selection. The assessor performing data extraction was blinded.

Statistical methods

Data handling was performed using PRISM Version 6.0a (2012) (GraphPad Software, Inc. USA) and SPSS Version 21 (2012) (IBM, United Kingdom). Group differences of categorical variables were evaluated using the Chi-squared test and continuous data with independent samples t-test. Paired t-tests were used to compare changes in anxiety levels. Bivariate correlations were drawn by Pearson product-moment correlation coefficient test and Analysis Of Covariance used to adjust for confounders. Statistical significance was set at $P<0.05$. Data values are represented as mean ± standard deviation (SD).

Results

55 women were assessed for eligibility, one was not suitable for in vitro fertilisation treatment, four declined to take part and seven women had their cycles deferred (Figure 1) leaving 42 for final analysis. Three women declined to participate because they perceived the study would heighten their anxiety and one declined without reason. Recruitment and follow-up was completed by January 2014 when final sample size achieved. Analysis of the outcomes included all 21 participants in the control and intervention groups.

Baseline demographics were not significantly different between groups and the clinical fertility characteristics were equivalent between groups (mean age, number of smokers, BMI, mean baseline [trait] anxiety, cause of infertility, cycle number, number of embryos transferred, day of embryo transfer, quality of embryo, type of cycle). All women had

undergone fewer than four previous IVF or ICSI cycles, and four women had suffered three or more implantation failures (9.5%).

Prior to embryo transfer, as measured by state anxiety two women (4.8%) were relaxed, 14 (33.3%) women felt neither anxious or not, 11 (26.2%) felt anxious, 13 (31.0%) hyper anxious, and two (4.8%) had heightened anxiety. There was no difference in the mean (mean ± SD) pre treatment anxiety state scores between the study group (41.1±8.7) and control group (42.1±11.0) (*P*=0.77).

Following embryo transfer, as measured by state anxiety 16 women (38.0%) were relaxed, nine (21.4%) women felt neither anxious or not, eight (19.0%) felt anxious, nine (21.4%) hyper anxious, and none (0.0%) had heightened anxiety. There was no difference in the mean post state anxiety scores between the study group (34.1 $\pm$ 10.2) and the control group (35.3 $\pm$ 9.1) (*P*=0.67).

32 (76.2%) women were less anxious following treatment as measured by absolute change in state anxiety score (mean state anxiety score before treatment 41.6±9.8 compared with 34.7±9.6 after treatment, *P*<0.001). One woman's anxiety was not changed (2.4%) and nine women were more anxious following treatment (21.4%), with no difference between the study group (n= 5) and controls (n= 4) (*P*<0.8). The mean change in anxiety score was 6.9±8.7 (*P*<0.01) with no difference between the study group (7.1±7.8) and controls (6.7±9.7) (*P*=0.46) (Figure 2). The mean percentage change in anxiety was 22.0%±12.3, with 16 women having a change of 25% or greater (mean change 35.1%±5.2) with no difference between the study group (n=7, 37.1%±5.6) and control group (n=9, 33.6%±4.6) (p=0.4).

The mean trait anxiety level was 39.6±9.2 (range 24-62). There was no difference between the mean score of the study group (39.0±8.1) and the control group (40.4±10.3) (*P*=0.6) (Figure 3). The trait anxiety was not correlated with the degree of change in state anxiety before and after treatment (r=-0.2, *P*=0.3), with no difference in the music and control groups (r=-0.4, *P*=0.1 and r=-0.03, *P*=0.9 respectively).

Both the study and control group had an equal distribution of a small number of women with multiple failed cycles, with the majority of participants in this study in their first cycle of IVF treatment. None of the participants who had a diagnosis of RIF (the failure of four good quality embryos to implant over at least three IVF cycles (21)) had hyper anxious and heightened anxiety scores in either pre treatment or trait anxiety scores, and there was no correlation between the number of previous ARTs and either pre treatment anxiety level nor trait anxiety (*P*=0.5).

Quality of life measures were high, with 37 (88.1%) women reporting to be very satisfied or satisfied with their quality of life, and five (11.9%) women being neither satisfied or dissatisfied. No women claimed to be dissatisfied with her quality of life. The Core FertiQOL scores (measuring general quality of life markers of the impact of fertility problems on emotional wellbeing, mind-body synchrony, relationship satisfaction, and social interaction domains) ranged from 40.0-93.0 (mean 71.5±14.1) with no difference between the mean score of the study group (72.5±13.6) and controls (73.5±14.0)

(*P*=0.45). Treatment FertiQOL scores (evaluating fertility treatment environment and tolerability) ranged from 38-100 (mean 76.6±15.5) with no difference between the study group (78.8±14.9) and controls (74.3±16.1) (*P*=0.12). For the breakdown of scores see Table 1. Removing all women who were undergoing repeated treatment cycles did not change the total Core and Treatment FertiQOL scores significantly.

Comparison of threshold scores for clinical anxiety and depression using the generic Hospital Anxiety and Depression Scale (22, 23) suggests that up to six participants in total may have had sufficiently low FertiQOL scores to implicate clinical depression or anxiety (three in each of the control and study group , 14.3%). Of these women, three women were undergoing their third ART cycle (two of these women were in the study group) and the remainder were undergoing their first ART cycle.

Clinical pregnancy rates (n=23, 55.0%) did not differ between music (n=11, 52.4%) and control groups (n=12, 57.4%) (*P*=0.95), nor did biochemical pregnancy rates (control group n=1, 4.8%, music group n=1, 4.8%).

Discussion

Assisted conception is known to have a high treatment burden (1, 3, 24). The diagnosis of infertility, the medicalisation of conception including undertaking multiple medical procedures and awaiting unguaranteed pregnancy outcomes are all potent and social stressors. Heightened anxiety may negatively impact on the patient's fertility treatment journey (5, 6) although the clinical benefits of psychosocial interventions in reducing emotional distress and in improving fertility treatment outcomes is still controversial (7, 8, 25). Our study showed that self-selected music used for a short duration (15 minutes) before and after embryo transfer did not reduce anxiety but that women undergoing IVF expressed high levels of pre embryo transfer anxiety that is ameliorated following completion of the treatment procedure. This highlights the emotional 'rollercoaster' women experience during ART. We have also identified a subgroup of (n=10, 23.8%) as yet uncharacterised women who paradoxically experienced heightened anxiety after the embryo transfer procedure.

An expected proportion of patients in our study may have been clinically anxious and depressed (22, 23). It has been hypothesized that women who suffer repeated embryo transfer failures (recurrent implantation failure, RIF) experience increased stress levels, above those of women who have had no failed ET (26). The latter findings are not reflected in our study although the majority of women in our study were undergoing their first treatment cycle (n=32, 76.2%).

Certain psychosocial factors such as neuroticism and the use of escapist coping strategies, were identified in a recent systematic review as predisposing factors for increased risks of psychological distress, whilst an increased level of social support is protective (27). The individual difference in sensitivity to stressors can account for the various aspects of stress and emotional adjustment in women undergoing assisted conception. Whilst our study did not show a beneficial clinical impact of music treatment, it was apparent that whilst most women experienced a decrease in anxiety after embryo transfer on completion of treatment but for unknown reasons, a subgroup of yet uncharacterised women did not. Pre treatment identification of these women will require more detailed investigation of their psychosocial risk factors, evidence of positive and negative emotional adjustments, and detailing factors associated with the presence and absence of maladaptive and adaptive coping strategies. Further studies are required to show that effective treatment strategies exist and can be successfully integrated with psychological profiling of patients undertaking assisted conception to have a positive effect on clinical outcome.

A recent study showed that live harp music being played for 20 minutes during ET is potentially anxiety reducing (28). This type of 'music therapy' was obviously administered in a different way from in our study and music was used only within the specific context of our study design. Greater length of exposure to, or different types of music, may have effects. Music was self-selected and therefore dependent on individual preference, experience and knowledge of music. Music preference and

familiarity play an important part in the effectiveness of music relaxation and are positively correlated with the degree of relaxation obtained from listening to music (29).

Limitations/bias

The assessment of anxiety was a validated and reliable method. However as a measure of general anxiety it is subject to the bias of any written, self-completed questionnaire. The STAI is a generalised measure of anxiety and women have specific anxieties about embryo transfer so it may be a blunt instrument. The resultant underestimation of any effect could be circumvented by designing a fertility specific version, equivalent to the FertiQOL.

Due to logistical complexities, double blinding was not performed for this study although the assessor was blinded. This may mean that the women not exposed to music experienced detrimental effects on anxiety, if they perceived that they were being deprived of the benefit expected from music. The risk of clinician-mediated effects during embryo transfer was counteracted by subjects listening to music via headphones (30).

Three women declined to take part in study because they felt particularly stressed and thought that the study may induce further stress. If the study selected out the most anxious women for this reason, observed effects may be underestimated.

The completion of treatment is itself anxiety reducing, and small interventional effects may be concealed. Further studies based on a larger sample size would help ameliorate this and add enough power to assess pregnancy outcomes. Anxiety reducing interventions may be more effective if commenced prior to treatment rather than at the time of treatment, as it is potentially easier to prevent anxiety rising than to relieve a hyper anxious state. The use of music some time prior to the time of treatment, rather than purely contemporaneously may mediate measurable effects.

Conclusion

Self-selected music at the time of embryo transfer does not improve anxiety levels or clinical pregnancy rate. The majority of women experienced a significant decrease in anxiety at the completion of embryo transfer procedure compared with before although this was not observed in about 25% of yet uncharacterised subgroup. In our study, music therapy has not been shown to reduce anxiety at time of ET and the effects of other forms of relaxation therapy remain to be explored. The use of music at the time of embryo transfer in a clinical setting does not appear to adversely affect outcomes (anxiety level or pregnancy outcome). If it is requested by women undergoing ART as a useful distractor or because she feels it would help her anxiety level, this should be supported.

Abbreviations:

ART Assisted reproductive treatment

ESHRE European Society of Human Reproduction and Embryology

FertiQOL Fertility Quality of Life questionnaire

ICSI Intra cytoplasmic sperm injection

IVF *In vitro* fertilisation

STAI State-Trait Anxiety Inventory

β-hCG Beta human chorionic gonadotrophin

Competing interests:

None of the authors have any conflicts of interest to declare.

The authors' contributions to this work are as follows:

LJS wrote the manuscript contributed to recruitment and the conduct of the study and performed data collection and data analysis. KLH conceived the idea, assisted in the design of the study, contributed to recruitment and data collection and the writing of the draft manuscript. YCC designed the project, was the chief investigator of the study and was responsible for manuscript editing.

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