

Does Psychotherapy Improve Success Rates of *In Vitro* Fertilisation? Systematic Review

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Abstract

Background: Despite increasing in vitro fertilisation (IVF) success rates there is a continual drive to improve this. Whilst improvements in embryology laboratory techniques and ovarian stimulation regimes have been major contributors, researchers have explored adjuvant medical treatments and acupuncture as means to increase the success rates. Could psychotherapy be beneficial in improving the IVF success rates?

Methods: 8 databases including Medline, Cochrane and PsychINFO, were searched systematically for papers in English between 1978 and September 2018. The participants were women undergoing IVF who received psychotherapeutic intervention of any sort. The outcome measure was the success rate of IVF treatment. With cross-referencing literature total of 2070 studies were identified and 7 constituted the material for the review.

Results: 5 randomised control trials showed that cognitive behavioural therapy (CBT) significantly improves the success rate, hypnotherapy has a positive but statistically insignificant effect, hypnosis has comparable effect with diazepam, counselling and provision of information significantly increases pregnancy rates and emotional and fact-writing does not have any effect. One controlled study showed that hypnosis significantly improves the success rate and 1 cohort study showed that psychotherapy does not influence pregnancy rate.

Conclusion: The findings from this review do not offer any robust evidence on psychotherapy increasing IVF success rates although some positive effect was noted. This should be addressed in the future research.

Keywords: Psychotherapy; Psychotherapeutic Interventions; Embryo Transfer; Success of *In Vitro* Fertilisation; Hypnosis

Introduction

The World Health Organisation defined infertility as absence of pregnancy after 12 months of regular unprotected intercourse [1]. In the United Kingdom up to one in six couples may be subfertile [2], out of which only small portion will require assisted reproduction technique called *in vitro* fertilisation (IVF). This treatment is used for a wide range of infertility causes including damaged or absent tubes, ovulation disorders or impaired sperm production. In 2011 there were 17,041 babies born in the UK from IVF treatment, which represents 2% of live born babies. Overall in the same year 48,147 women underwent IVF [3].

IVF procedure consists of downregulation of egg production by gonadotrophin-releasing hormone agonists or antagonists, which prevents ovulation prior to the egg collection. Human chorio-gonadotrophin (HCG) is then given to trigger ovulation and follicles are

aspirated transvaginally under sedation approximately 36 hours later. They are incubated with the sperm leading to embryo transfer 2 - 5 days later. Surplus good quality embryos may be frozen.

One IVF cycle can cost up to £5,000. Funding for infertility treatment reflects the understanding of involuntary childlessness being a major stress for individuals.

It is a well-known fact that infertile patients are more depressed than fertile controls [4,5]. Among infertile patients, those in the IVF program seem to be best adjusted to the situation and display better coping mechanisms. Previous studies, which focused on depression in patients undergoing IVF, surprisingly did not identify this group as any more depressed or stressed than normal population [6,7]. This may be explained by their active participation in IVF helping them adjust emotionally. Other explanation offered by Freeman, *et al.* [6] is that couples might have developed good coping strategies over the years of infertility when they are about to receive their IVF treatment.

One meta-analysis on 3583 infertile women undergoing assisted reproduction looked into the effect of stress on fertility outcome [9]. Their findings reassured doctors that stress does not compromise women's chances of getting pregnant. When the research question was however broadened also to indicators of psychological distress the conclusion was that there is a significant effect of anxiety and stress on the assisted reproduction outcome [10].

European Society of Human Reproduction and Embryology [11] stated that in most clinics patients are offered counselling with no obligation to attend. Presumably this applies for European countries. For example in Austria since the propagation bill from July 1992 the Austrian fertility specialists are obliged to offer counselling as part of the fertility treatment [12]. The availability of Independent Counsellors for support is also mandatory for all centres in the United Kingdom licensed by Human Fertilisation and Embryology Authority (HFEA) [13].

Negative expectations are detrimental in IVF treatment [14]. Pessimism predicts higher IVF failure rate in women undergoing their first cycle independent of other risk factors. One possible explanation can be a relation of pessimism to low mood, which fails to buffer psychological stress and leads to an enhanced neuroendocrine stress response.

If the stress and pessimism have a negative effect on IVF outcome, would psychotherapy improve the IVF outcome? There were three meta-analysis conducted in 2005, 2009 and 2015 investigating the benefits of psychotherapy on various types of fertility treatment and mental well-being of the participants. The most recent one by Frederiksen, *et al.* [15] focused on the effect of psychosocial interventions on reducing distress and improving success rate in assisted reproduction (ART). They included 39 papers, out of which 10 reported on pregnancy rates. The inclusion criteria for ART were rather wide, including artificial insemination, intracytoplasmic sperm injection and IVF. Their conclusion was that psychosocial interventions, cognitive behavioural therapy (CBT) in particular, seem to be efficacious in increasing pregnancy success rate.

Hammerli Znoj and Barth [16] found significant positive effect of psychotherapies on pregnancy rate in infertile couples, however this was applicable only in patients not undergoing IVF or ICSI. This would suggest that fertility treatment more dependent on natural mechanisms is easier to influence by psychotherapy. Authors however did not expand on theories how the effect occurs.

The second meta-analysis [17] was by de Liz and Strauss who tried to establish the efficacy of group, couples or individual therapy in infertile couples. The authors concluded that both group and individual, or couples, counselling provide similarly increased pregnancy rates in infertile participants. The interesting finding was identical pregnancy rate in psychotherapy supported by *in vitro* fertilisation and psychotherapy alone. This would suggest that IVF does not contribute to the pregnancy rate in any way, which even the authors discarded as heavily biased.

Aim of the Study

This review aims to explore the evidence on the effectiveness of psychotherapy in the IVF treatment. As this assisted reproduction technique is widely used and represents considerable portion of money spent on infertility treatment, the aim is to identify the potential for improvement of the success rate by low cost means.

Methods

This paper aims to answer research question ‘what is the evidence of effectiveness of psychotherapy in increasing IVF success rate?’ The researchers conducted systematic review on various psychotherapies and their effect on IVF pregnancy success rate.

Inclusion criteria

Inclusion criteria were: (I) participants were infertile women in IVF treatment, (II) prospective or retrospective design of the study, (III) participants received a psychological intervention of any kind (IV) psychotherapeutic intervention was done during any stage of the IVF treatment starting from pharmacological preparation for egg collection to embryo transfer, (V) the study reported on success rate of clinical pregnancy at any stage of gestation.

The included studies were published in English language between years 1978 and September 2018 in the peer-review journals. The year 1978 was selected as a milestone of the first child born from *in vitro* fertilisation. All levels of evidence from peer-review journals were included for comprehensive cover of the topic.

Participants

Search included women undergoing either IVF with no limitation to the race, ethnicity, age or sociodemographic status.

Intervention

Review focused on any psychotherapeutic intervention used before or during embryo transfer (full list is provided in the Literature search and data sources section).

Outcome measures

The outcome measure was set as a success rate of clinical pregnancy, measured at any point during the pregnancy. The ideal outcome would be live birth but many early studies in IVF used clinical pregnancy as the primary outcome measure.

Literature search and data sources

A systematic approach was used to identify relevant studies. The following databases were searched: AMED, CINAHL, PsychINFO, Cochrane, Medline via Pubmed, NHS Evidence, NICE, UpToDate.

When searching keywords two main concepts were used: (I) fertility, infertility, IVF, *in vitro* fertilisation, fertility treatment, infertility treatment AND (II) psychotherapy, CBT/cognitive behavioral therapy, hypnosis/hypnotherapy, narrative psychotherapy, group therapy, individual psychotherapy, psychological intervention, psychotherapy, counseling, self-help intervention, interpersonal psychotherapy, psychoanalytical therapy, psychodynamic therapy, humanistic therapies, arts therapy, mindfulness therapy, psychosexual therapy, family therapy, couples counseling.

The database search resulted in 2068 publications, 5 were used in the review. Further 2 were identified by cross-referencing literature.

Study selection and data extraction

The primary search identified 2070 studies. 2051 studies were excluded based on their title or abstract. In the secondary reading 12 of studies were excluded after more detailed review of the content, as they did not comply with the inclusion criteria. Four studies reported on pregnancy rate without IVF, 8 focused on decreasing psychological distress and did not report clearly on pregnancy success rate.

From the 7 selected papers, 5 were randomized control trials (level 2 evidence), 1 was a controlled study (level 3 evidence) and 1 was a cohort study (level 4 evidence).

Results

A total of seven papers met the inclusion criteria. Gorayeb, *et al.* [18] conducted a randomised controlled study on the effect of group cognitive behavioural therapy (CBT) on the pregnancy rate after IVF. The authors randomised participants who expressed interest in psychotherapeutic intervention into intervention (CBT) and control (no CBT) group. Despite the initial interest 30% of participants were excluded due to low attendance. The intervention group and control group were however equal in size at the end (93 therapy participants and 95 controls). All participants had two-hour sessions weekly for five weeks. The interventions were focused on cognitive restructuring (use of CBT techniques) and teaching relaxation techniques, such as progressive muscle relaxation (also used in induction to hypnosis). After the psychotherapy they underwent an embryo transfer.

According to their results couples who received 3 - 5 sessions of group CBT had 2.2-fold higher chances of conceiving through IVF than couples that received only IVF treatment ($p = 0.01$).

Panagopoulou, *et al.* [19] investigated the effect of emotional and fact writing on pregnancy success rate in IVF patients. Hundred and forty eight participants were divided into 3 groups: emotional writing, fact writing and control. Fourth group constituted of people who did not want to participate directly but agreed to fill out all questionnaires. Emotional writing consisted of keeping a diary and writing down the deepest thoughts and emotions on daily basis. Fact writing group was also asked to keep a diary but to write about facts on infertility and its treatment. Control group and non-participating group were given information about the procedure and went home without further intervention. Among the 3 experiment groups there was no significant difference in pregnancy outcome (p value not stated). On inclusion of the non-participating group there was a significant increase in pregnancy rate in the 4th group compared to the other groups ($p < 0.05$).

There was no apparent difference between control group and non-participating group while the pregnancy results were striking (13% vs. 38%). Authors also did not provide exact numbers of participants in experimental groups and information on demographics in the groups was limited.

Terzioglu [20] reported on increased pregnancy rate after 5 counselling/interview sessions. 30 couples constituted the experimental group who were given 5 sessions throughout the whole IVF treatment. Those sessions lasted 15 - 30 minutes and were focused on information relating to the procedures. Control group of 30 patients did not receive any psychosocial intervention. Pregnancy success rate was 43.3% in the experimental and 16.7% in the control group ($p < 0.05$). The report on statistical output was very poor and detailed information regarding the content of the session was missing.

Murphy, *et al.* [21] investigated the effect of music therapy on patients undergoing *in vitro* fertilisation. The hypothesis was that as shown in previous research the harp therapy will decrease sympathetic reaction of the body before, during and after embryo transfer (measured on blood pressure, heart rate and respiratory rate) and will indirectly increase success rate of the embryo transfer. 202 patients were randomised into two groups with symmetrical dropout rate 10%. Treatment group received 20-minute harp therapy during embryo transfer while the control group did not receive any complementary therapy.

There was a small increase in pregnancy success rate in the treatment group (48 pregnancies compared to 44 pregnancies in the control group) but this was not statistically significant ($p = 0.5$). The power analysis of the study showed that much bigger samples would be required in order to detect statistically significant differences. The study failed to prove decrease in the heart or respiratory rate at any of the 3 measurements during embryo transfer. The only difference in sympathetic reaction of the control group was significantly higher blood pressure before and after embryo transfer. The design of the study was however good.

Levitas, *et al.* [22] conducted a case-control study on 185 patients undergoing embryo transfer. Participants who volunteered for hypnosis during embryo transfer were pre-screened for susceptibility to hypnosis. 89 patients were eventually recruited as treatment group

receiving hypnosis. It was suggested to them after muscle relaxation that they are welcoming a long waited guest while they were physically undergoing the embryo transfer. The control group did not receive any psychotherapeutic intervention during their embryo transfer.

The difference in IVF outcome measured by success per one cycle was significant. In the hypnosis group the success rate was 53.1% per cycle compared to 30.2% in the control group ($p < 0.001$).

Based on the results of Levitas, *et al.* [22], Catoir, *et al.* [23] conducted a randomised control trial using combination of sedative medication and hypnosis in double blind design, using diazepam vs. placebo and hypnosis vs. muscle relaxation (placebo). The control group received diazepam with muscle relaxation only (hypnosis-placebo) and the treatment group received hypnosis and placebo (medication-placebo).

Authors recruited 124 participants out of which 93 underwent the experiment. The success rate was 34.8% pregnancies in control group (diazepam) and 36% in treatment group (hypnosis). Authors concluded that hypnosis has equal anxiolytic effect to diazepam. They saw the main benefit of the study in identifying new safer way of sedating patients for the procedure rather than increasing their chances of getting pregnant.

Poehl [12] critically investigated Austrian legal obligation for medical centres of assisted reproduction to offer a psychotherapeutic counselling (PSITCO). Women while being consented for assisted reproduction are offered psychotherapeutic counselling (tick box on the consent form). They found that 72% of 1156 women either rejected or did not comment on the offer. The more failed attempts the couples have undergone the more likely they were to engage in PSITCO.

PSITCO made no difference in success rate per embryo transfer. In the cumulative rate women who underwent PSITCO in the past had 56.4% chance to conceive, women who agreed to PSITCO during their treatment conceived in 41.9%, women who refused PSITCO conceived in 44.3% and those who made no comment got pregnant in 39% of cases. Unfortunately authors did not comment on any statistics output, including p value.

Study	Intervention	Participants	Control group	Outcome - success rate with psychotherapy/controls	Strengths (S) and weaknesses (W)
Gorayeb, <i>et al.</i> (2012)	CBT in a group setting	95/93	No psychotherapy	39.8%/23.2% Positive Significant effect	(S) randomisation, acceptable drop-out, equal group sizes (W) mix of interventions - CBT, relaxation, education
Murphy, <i>et al.</i> (2014)	Harp therapy	90/91	No psychotherapy	53%/48% Positive but not significant effect	(S) randomisation, good design, equal group sizes, correlation with sympathetic activation measured during experiment (W) small number to prove statistically significant difference, no details on definition of clinical pregnancy and if the rate is cumulative or per attempt
Catoir, <i>et al.</i> (2013)	Hypnosis	50/43	Diazepam with muscle relaxation	36%/34.8% No Effect	(S) randomisation, well described hypnotic procedure, (W) small groups, did not achieve their desired group sample, control group with relaxation technique - possible bias

<p>Levitas, <i>et al.</i> (2006)</p>	<p>Hypnosis</p>	<p>89/96</p>	<p>Nil</p>	<p>53.1/30.2% Positive Significant effect</p>	<p>(S) applying hypnosis on hypnotisable individuals - corresponds to normal psychotherapeutic practice as it should be used; equal group sizes (W) participants offered to participate and of these only those susceptible to hypnosis were recruited - possible selection bias, difference in the two groups in average length of infertility and proportion of unexplained infertility, prospective study</p>
<p>Poehl, <i>et al.</i> (1999)</p>	<p>Optional psychotherapy as prescribed by law in Austria Groups: 1. Who received therapy already 2. Who wants to received it 3. Who declines psychotherapy 4. Who made on comment on consent form about therapy</p>	<p>1. 115 2. 205 3. 488 4. 340</p>	<p>Nil</p>	<p>56.4% who received PSITCO/ 41.9% who wanted to received/44.3% who refused/39% who made no comment on participation No effect per cycle Positive not significant effect on cumulative rate</p>	<p>(S) well established psychotherapeutic intervention (W) no statistic output (p value etc), final numbers of participants in each group missing (only percentage given), retrospective study, 72% of participants declined psychotherapy, 4groups of participants - not clear who actually received the therapy by the time of conception, clients at any stage and cycle of IVF</p>

Table 1

Discussion and Conclusion

Hypnosis, CBT and educational counselling hold a great potential for future research. CBT is a well-established method, widely available and with a good scientific background. Hypnosis, including relaxation techniques is less researched but well known with documented effect on emotional wellbeing. Gorayeb, *et al.* [18] aimed to describe the effect of CBT but in the design they used mixed psychotherapeutic intervention formed of group therapy, CBT features and relaxation techniques, together with educational aspects (discussions about the procedures etc.). It is therefore difficult to assess if CBT alone would have such a positive effect on the IVF outcome.

Hypnosis was examined by two studies. Catoir, *et al.* [23] introduced bias by its mixed design-diazepam with muscle relaxation compared to hypnosis and placebo. Muscle relaxation constitutes one of the introduction techniques into the hypnotic state. It cannot be therefore regarded as a placebo to hypnosis. Another issue arises with the use of diazepam. It was suggested by previous research [24] that the dose of 10 mg has no anxiolytic effect in which case the conclusion would be that muscle relaxation as well as hypnosis have the same effect on pregnancy rate.

The second study on hypnosis [22] had a clearer design and statistically significant positive effect of hypnosis was shown. Authors suggested that hypnosis induces parasympathetic reaction. This was shown previously on surgical patients where hypnotic relaxation lead to decrease blood pressure and heart rate [25]. The potential effect is uterine relaxation during embryo transfer. It is known that uterine activity during the procedure affects adversely the implantation of the embryo.

The study results are however biased by selecting only participants susceptible to hypnosis, which limits its use for general population. The second bias lied in the unequal backgrounds of the two groups. Experimental group consisted of twice as much secondary infertility cases than the control group (53.1% and 27.8% respectively). The success rate in the secondary infertility is known to be higher than in the primary infertility. This 25.3% difference could account for the 22.9% difference in pregnancy rate. Authors failed to comment on that in their discussion.

Educational counselling appears to be beneficial. Gorayeb, *et al.* [18] included informative discussion in their intervention, Terzioglu [20] also showed that keeping patients informed throughout the whole process and catering to their intellectual needs increases chances of pregnancy. Moreover the same author reported on higher satisfaction and lower anxiety levels in these patients.

Experimental interventions with limited scientific background such as harp therapy or emotional writing seem to be of little use.

In regards to timing of the interventions most authors chose to offer psychotherapy before or at the time of embryo transfer, ranging from days to weeks of psychosocial intervention. Overall the sessions were designed as brief and focused, aiming for the imminent effect of boosting up mental wellbeing. It appears challenging to consider long-term psychotherapy, as the IVF cycle is a very dynamic several-week experience. If the first attempt is unsuccessful, adverse feelings and depression arises and clients are worse off than when they started. Intervention more than two months would have to account for mood swings depending on the success or failure of the treatment. Secondly the research design would be more difficult with increased cost, higher rate of drop-outs etc.

Future investigations should also focus more on male infertility. Some of the papers in this review commented on the amount of male infertility cases in their cohorts, ranging from 10 to 50%. They however did not account for male psychological wellbeing, as the investigation in question was success of embryo transfer.

Most of the psychosocial interventions were designed for couples initially but only the effect on the woman was taken in consideration, as it was her emotional comfort and bodily responses to stress, which were investigated in IVF success. The woman's role in the medical aspects of IVF is much more prominent and man's wellbeing might be of only supportive value in the whole treatment. This is yet to be addressed in the future.

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Declaration of Interest

The authors report no declarations of interest.

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