

REVIEW

Acupuncture in IVF: A review of current literature

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Women's choice to delay fertility due to various reasons is making subfertility a growing problem and increased use of IVF as a last resort. Despite advances in the technology, IVF success remains low, especially in older women. Hence, many of these women need to undergo several cycles of IVF and are faced with unprecedented anxiety and frustration. In desperation, they resort to anything that might increase the success of their IVF treatment. Acupuncture has gained popularity among the various complementary medicines available and many go privately to have acupuncture while undergoing IVF. Since 1999, in spite of multiple trials and systematic reviews, the beneficial effect of acupuncture in improving the success of IVF remains unproven and debatable. As clinicians, we face the dilemma of what to suggest to our patients when asked about having acupuncture during IVF, given that different meta-analyses have come to different conclusions. Hence, this review is conducted with the aim to summarise the available literature and provide a better insight into this complex and controversial topic.

Keywords: Acupuncture, anxiety, embryo transfer, infertility, IVF, oocyte aspiration

Introduction

IVF is associated with significant stress, which can affect the outcome of the treatment and can also affect the general wellbeing of the couple undergoing the procedure. There is a growing body of evidence that acupuncture reduces the stress of IVF and also improves its success rate (de Lacey et al. 2009; Kovářová et al. 2010). The first clinical trial was published in 1999, which suggested that acupuncture was effective in improving the clinical pregnancy rate in IVF (Stener-Victorin et al. 1999). Since then, more than 40 clinical trials and nine systematic reviews have emerged assessing the benefits of acupuncture in various aspects of IVF. However, all these trials differ significantly in their study design, acupuncture timing, protocol and final outcome measures. Due to this extreme heterogeneity, it is still not clear whether acupuncture is beneficial and should be offered to women undergoing IVF, as routine. As the popularity of acupuncture is growing, many women having IVF treatment ask their clinician about using acupuncture. Some of them do have acupuncture privately while undergoing IVF treatment and in many cases, this is not even reported to their clinicians (MacPherson et al. 2006). This shows the psychological desperation these women feel, which encourages them to accept any options that might improve the success of their treatment.

As clinicians, we become duty bound to provide evidence-based advice to these couples regarding the safety and efficacy of this adjuvant treatment. This review aims to summarise the available literature in this field, which will help clinicians and patients understand the existing evidence and make informed choices and will also help researchers to design further trials that might give concrete guidance.

What is acupuncture?

Acupuncture is a form of Traditional Chinese Medicine (TCM), which is more than 3,000 years old. Recently, it has gained significant popularity in the Western world, mainly because of its perceived lack of side-effects, convenience and unique effect on general wellbeing.

Acupuncture is based on the principles of TCM, which suggests that there are main and collateral channels of meridians along the whole body, through which the vital energy travels. There are fourteen main meridians, along which 300 acupoints are distributed. Acupoints are special points on the surface of the body where the vital energy of particular viscera infuses. Hence, there is an inherent connection of the acupoints with those particular viscera and stimulating those acupoints with acupuncture can affect the corresponding organs through the meridians. Traditional acupuncture involves inserting disposable sterilised acupuncture needles along the acupoints and then stimulating them manually.

Recently, new techniques of acupuncture have emerged, such as electro-acupuncture, where a small electric current is used to stimulate the acupuncture needle. In laser acupuncture, a low energy laser beam is used to directly irradiate the acupoints. All methods of acupuncture have been shown to be safe (Omodei et al. 2010; Dalton-Brewer et al. 2009; Anderson et al. 2007; Smith et al. 2006; Ida et al. 2010).

Mechanism of action of acupuncture

The mechanism of action of acupuncture is based on the ancient Chinese medical theory. Various studies have suggested the following methods of action for acupuncture.

Through endogenous opioids. It has been suggested that acupuncture alters the secretion of endogenous opioids, especially beta-endorphin in the central nervous system and thus influences the secretion of GnRH, which in turn influences the secretion of gonadotrophins. (Huang et al. 2011; Anderson et al. 2007)

This makes it logical to hypothesise that acupuncture improves ovulation, alters the menstrual cycle and also reduces stress and depression.

By altering blood flow. Acupuncture is also said to exhibit a sympathetic-inhibitory effect and thereby improves the uterine blood flow, reduces the uterine motility and also improves the ovarian blood flow (Huang et al. 2011; Chang et al. 2002; Anderson et al. 2007; Ho et al. 2009). Improved uterine blood flow may improve the embryo implantation.

By modulating immune function. Studies have also shown that acupuncture alters the immune function by modulating cytokine production, which improves the outcome of IVF (Huang et al. 2011; Anderson et al. 2007).

Holistic approach. Traditional Chinese Medicine does not follow the strict principle of a specific diagnosis and targeted treatment. It rather takes into consideration the various aspects of lifestyle, effect of disease on body and mind and provides a holistic treatment, which not only treats the underlying disease but also improves self-confidence, self-help and empowerment (Paterson and Britten 2004).

Prevalence of use of acupuncture in IVF

As complementary and alternative medicine (CAM) is being proven to be relatively safe, more and more women having subfertility and seeking assisted conception are having treatment with various forms of CAM (Galst 1999; Coulson and Jenkins 2005; Schaffir et al. 2009). CAM makes them feel that they have done everything possible to enhance the success of their treatment and perhaps helps them to relax psychologically (Coulson and Jenkins 2005). Out of the various forms of CAM, the most commonly used are acupuncture, reflexology and nutritional advice (Coulson and Jenkins 2005). The highest use of CAM is among private patients (Coulson and Jenkins 2005). As the funding for acupuncture is difficult in the NHS (Lim 2010), many patients seek help from independent private acupuncturists (MacPherson et al. 2006). A national cross-sectional survey of 800 acupuncture practitioners in UK showed that an estimated 4 million acupuncture sessions were provided in the UK in 2009 and two-thirds of them were provided outside the NHS (Hopton et al. 2012). Though the majority of these acupuncture sessions were provided for back, shoulder and neck pain, a substantial number of sessions were given to infertile women. Acupuncture for infertility has increased five-fold over the past decade (Macpherson et al. 2006). In a questionnaire survey of 861 acupuncture practitioners, 15% reported that fertility patients have become a substantial proportion of their practice, and the majority were related to assisted conception (Bovey et al. 2010). The majority of the acupuncturists offering mainly private treatment were physiotherapists, nurses or doctors. They mainly practised Western medical acupuncture, which involves acupuncture using trigger points, segmental points and formula points (Smith et al. 2012), rather than traditional Chinese medicine, where acupuncture needles are inserted at specific acupoints located along the meridians (Hopton et al. 2012).

However, not all practitioners offering acupuncture to these vulnerable infertile women have the appropriate qualification in acupuncture and fertility (Bovey et al. 2010). This raises the question – should someone offer such treatment without specialist training? Having said that, there is no formal structure for higher training in this field in the UK. Fortunately, an

increasing number of new courses are becoming available for the future acupuncturists. The British Medical Acupuncture Society offers training courses and certifications in this field (www.medical-acupuncture.co.uk/Default.aspx?tabid=63).

Acupuncture to reduce stress in IVF

Failing to conceive naturally poses significant stress on the infertile couple. It creates a feeling of failure, frustration and humiliation (Robinson and Steward 1996). They find it emotionally challenging to discuss their fertility issues with family and friends, who might not have faced this problem (Rayner et al. 2009). The social stigma, pressure and the desperation to achieve motherhood forces these women to seek help from fertility specialists. However, their experience is not always positive: lack of communication with their clinician and the feeling of being reduced to a series of body parts, subjected to various technical procedures, leaves them feeling isolated (Rayner et al. 2009).

The use of complementary therapies makes women feel empowered, with a sense of regaining control of the body and being supported (Rayner et al. 2009). When used before and after IVF, it improves the woman's psychological state and overall experience (de Lacey et al. 2009; Kovářová et al. 2010).

A pilot RCT randomised 32 women aged 20 to 45 years (trying to conceive for twelve months or waiting to start IVF in one month) into acupuncture (six sessions of acupuncture over eight weeks) and a waiting-list control group. They concluded that women having acupuncture experienced a physical and psychological sense of relaxation and calmness compared with the waiting-list group. The sample size was small and it is questionable whether the women's pre-judgement about the likely effects of acupuncture had an impact on the results (Smith et al. 2011).

Various other RCTs were conducted to assess the effect of acupuncture on stress reduction in women undergoing IVF. Almost all of them showed a positive outcome (Isoyama et al. 2012; Domar et al. 2009), apart from one where the real acupuncture group found their acupuncture sessions more 'tiring', 'fearful' and with increased 'achiness', compared with the sham control (Moy et al. 2011).

Acupuncture to improve live birth in IVF

Although acupuncture has been studied extensively to examine its effect on live birth, the debate still continues, as different studies have used different protocols and controls and their outcomes are contradictory. Clinicians and patients find it difficult to come to a definitive conclusion as to the effect of acupuncture on the live birth rate. Analysing all studies conducted so far with live birth as the primary outcome, different timings of acupuncture could be identified:

Around the time of embryo transfer. Since the first RCT by Paulus et al. (2002), in which 25 min of acupuncture was performed before and after embryo transfer and showed improved pregnancy rate in the acupuncture group (Paulus et al. 2002), several RCTs (Omodei et al. 2010; Dalton-Brewer et al. 2009; Moy et al. 2011; Andersen et al. 2010; Domar et al. 2009; Westergaard et al. 2006) and observational studies (Elisabetta et al. 2012; Madaschi et al. 2010) have been conducted to assess the effect of acupuncture on live birth when applied around the time of embryo transfer. The results have been highly contradictory. While some RCTs show improved pregnancy rate (Omodei et al. 2010; Dalton-Brewer et al. 2009; Westergaard et al. 2006), others show no difference between the acupuncture and control groups (Moy et al. 2011; Andersen et al. 2010; Domar et al. 2009).

Around the time of oocyte aspiration. The RCTs conducted around the time of oocyte aspiration were mainly designed to assess its role in pain relief during the procedure. However, they also mentioned the effect of acupuncture on the live birth rate (Stener-Victorin et al. 1999, 2003; Humaidan and Stener-Victorin 2004; Sator-Katzenschlager et al. 2006). Although the first RCT showed a significantly higher pregnancy rate with acupuncture at the time of oocyte aspiration (Stener-Victorin et al. 1999), various other subsequent trials have shown different results. The most recent systematic review confirmed no evidence of benefit on the pregnancy outcome when acupuncture was administered around the time of oocyte retrieval (Cheong et al. 2013).

Spread through the whole cycle as a few sessions during ovulation induction and around the time of embryo transfer. An RCT divided women < 40 years undergoing IVF/ICSI into two groups and performed acupuncture in one group in three sessions (each lasting for 25 min), with the first and second sessions five to seven days and two to three days before oocyte aspiration respectively, and the third session shortly after the embryo transfer. The control group had no intervention. The number of women recruited in this preliminary study was limited; however they concluded that their results did not support the hypothesis of a positive effect of acupuncture on IVF (Feliciani et al. 2011). Another trial randomised 228 women into an acupuncture group, where they received acupuncture on day nine of stimulation, before and after embryo transfer and a placebo group with non-invasive sham acupuncture. They could not show any significant difference in the pregnancy rates between the two groups. However, we must remember the 'inert' placebos might not be inert and hence, the validity of such trials is questionable (Smith et al. 2006).

Luteal phase. Again controversial evidence is available for the use of acupuncture in the luteal phase of IVF. While one RCT with 225 women supported the use of acupuncture in the luteal phase to improve the pregnancy rate (Dieterle et al. 2006), another systematic review showed no benefits and suggested that luteal phase acupuncture should not be offered until further evidence is obtained (Cheong et al. 2013).

So does acupuncture improve live birth in IVF?

Various systematic reviews have been conducted over the years to assess the effect of acupuncture on the live birth rates in IVF (El-Toukhy et al. 2008; Ng et al. 2008; Manheimer et al. 2008; Sunkara et al. 2009; Cheong et al. 2010; Cheong et al. 2013). However, their conclusions have been inconsistent and contradictory (see Table I).

The largest systematic review and meta-analysis so far, in March 2012, included 24 trials with 5,807 participants and has shown that although the pooled clinical pregnancy rates were higher in the acupuncture group, the live birth rates were not significantly different than in the control group. However, the live birth rates were found to be higher with acupuncture when the studies using the Streitberger control were excluded, suggesting that the Streitberger needle might not be inactive. Further differences were seen when different timings of acupuncture were analysed. They concluded that acupuncture around the time of oocyte aspiration or controlled ovarian hyperstimulation might be more effective in improving the pregnancy outcome in IVF (Zheng et al. 2012). This meta-analysis was re-evaluated recently in view of the marked heterogeneity and after removing some trials; no significant benefit of acupuncture could be shown (Meldrum et al. 2013). Another systematic review around the same time as Zheng et al. (2012), analysed 17 trials and showed no significant difference in the clinical pregnancy/biochemical

pregnancy/ongoing pregnancy or live birth rate between the acupuncture and the control groups (Qu et al. 2012).

Basically, the evidence regarding the efficacy of acupuncture to improve clinical pregnancy rate is controversial. In spite of 40 clinical trials and nine systematic reviews, the debate still continues.

Acupuncture in women with previous failed cycles

Not many studies have been conducted to assess the effect of acupuncture in women with previous failed cycles. One observational study looked at the role of acupuncture in these women who had previous failed IVF treatment in spite of transferring good quality embryos. They showed a significant increase in the pregnancy rate in these women when acupuncture was given before the oocyte aspiration and after the embryo transfer (Chiara et al. 2012).

Acupuncture to improve success in older women

As fertility declines with age, frequently women are faced with the challenges of conception and are forced to try various assisted conception treatments. Knowing their reduced fertility makes them feel desperate and they are ready to try anything to improve their chance of success (Rayner et al. 2009).

Various observational studies have shown that acupuncture during IVF in older women 35 to > 40 years has benefit in terms of the pregnancy rate (Elisabetta et al. 2012; Rubin et al. 2012). An RCT compared the effect of acupuncture on the pregnancy rate when it is administered before and after embryo transfer and found that the results were better for women aged 35–39 years and > 40 years, than their controls. They concluded that acupuncture is safe and particularly beneficial to older women (Dalton-Brewer et al. 2009). However, the study was seriously limited by its sample size.

The great majority of the studies in women with previous failed cycles and in older women are observational and no firm conclusion can be drawn.

Acupuncture for pain relief during oocyte aspiration in IVF

Various methods have been used for pain relief during transvaginal oocyte aspiration. These are paracervical block (Ng et al. 2003), conscious sedation (Bhattacharya et al. 1997), epidural (Martin et al. 1999) and general anaesthesia (Gonen et al. 1995). Since the first RCT on the anaesthetic effect of acupuncture in IVF (Stener-Victorin et al. 1999), further studies have shown that acupuncture can be used safely as an adjunct for pain relief during ultrasound-guided oocyte aspiration. However, pain, being a subjective experience, varies from individual to individual and depends largely on the woman's motivation and ability to cope. It is also influenced by the woman's BMI, duration of the procedure of oocyte retrieval, number of oocytes retrieved and the size of the needle used (Ng et al. 1999). Hence, trials aiming to assess the efficacy of acupuncture in pain relief during egg collection have obvious methodological limitations and these results need to be considered cautiously. In spite of various RCTs, a subsequent systematic review analysing the existing RCTs has failed to consider any method of analgesia as superior to another for pain relief during oocyte retrieval (Stener-Victorin 2005).

Problems with the available literature

Protocol used in different studies

As the effect of acupuncture changes with the menstrual cycle, if acupuncture is applied at different time points, it will produce different results (Anderson and Rosenthal 2013). Hence, different studies using acupuncture at different time points are likely

Table I. A comparison of various systematic reviews and results.

Systematic reviews	Year	Number of studies included	Total number of participants	Intervention	Time of acupuncture	Result
El-Toukhy et al.	2008	13 RCT	2,500	Acupuncture vs Control	5 RCT – at the time of egg collection 8 RCTs – at the time of embryo transfer	No significant association of acupuncture with clinical pregnancy rates
Ng et al.	2008	10 RCT	2,003	Acupuncture vs Control	5 RCT – at the time of egg collection 5 RCTs – at the time of embryo transfer	Significant increase in the pregnancy rates when acupuncture is done on the day of embryo transfer
Manheimer et al.	2008	7 RCT	1,366	Acupuncture vs no treatment or sham acupuncture	All RCTs – acupuncture done around the time of embryo transfer	Improved pregnancy rates when acupuncture is given with embryo transfer
Sunkara et al.	2009	14 RCT	3,000	Acupuncture vs no treatment or sham acupuncture	All RCTs – acupuncture done around the time of embryo transfer	No improvement in clinical pregnancy rates when acupuncture is done around the time of embryo transfer
Cheong et al.	2010	14 RCT	2,670	Acupuncture and/or Chinese herbal medicine in IVF	5 RCT – at the time of egg collection 7 RCT – on the day of embryo transfer only 2 RCT – on the day of embryo transfer and 2–3 days later	No benefit of acupuncture during assisted conception
Zheng et al.	2012	24 RCT	5,807	Acupuncture vs no treatment, placebo or sham acupuncture	5 RCT – during ovarian stimulation 5 RCT – at the time of egg collection 14 RCT – around the time of embryo transfer	Improved live birth rate when acupuncture is performed with ovarian stimulation and during egg collection
Qu et al.	2012	17 RCT	3,713	Acupuncture vs no treatment, placebo or sham acupuncture	1 RCT – during ovulation induction 5 RCT – during egg collection 11 RCT – around the time of embryo transfer	No benefit of acupuncture was found in improving outcome of IVF
Cheong et al.	2013	20 RCT	4,544	Acupuncture vs no treatment, placebo or sham acupuncture	6 RCT – at the time of egg collection 14 RCT – at the time of embryo transfer	No effect of acupuncture on increasing the live birth rate in IVF

to produce different effects and are not comparable. Even a slight alteration in the regimens might produce a significant change in the result. While some trials have used acupuncture only around oocyte aspiration (Stener-Victorin et al. 1999) or around embryo transfer (Omodei et al. 2010; Dalton-Brewer et al. 2009; Rubin et al. 2012; Moy et al. 2011; Andersen et al. 2010; Domar et al. 2009; Westergaard et al. 2006), some have used it at different time points throughout the IVF treatment, including ovarian stimulation, oocyte aspiration and around embryo transfer (Feliciani et al. 2011; Smith et al. 2006). Significant differences are noted not only in the timing but also in the acupoints used in different studies.

Many of these trials have used two or a maximum of three sessions of acupuncture. This is considered to be low dosage, especially in chronic conditions, where optimal treatment involves four to ten acupuncture points given in more than six sessions (Anderson and Rosenthal 2013).

Also, most of the trials have used quite fixed protocols for everyone in the trial, without taking into consideration that many of these women do have underlying gynaecological factors that contribute to their infertility. Ideally, the treatment should be tailored according to individual characteristics to get the optimal outcome.

To address this problem with the acupuncture protocol, fifteen international acupuncturists with extensive experience in treating women with acupuncture during IVF participated in three rounds of Delphi questionnaires and reached a consensus for the use of Traditional Chinese medicine acupuncture, manual acupuncture. They had 86% agreement among themselves. They suggested three rounds of acupuncture during IVF: the first treatment of acupuncture to be administered on day six to eight of the controlled ovarian hyperstimulation and to include core points ST29, CV4, CV6, SP6, SP10, + 5 additional points to be individualised to each patient. The second treatment to be administered on the day of the embryo transfer (ET) using points SP8, SP10, LR3, ST29, CV4 and one selected from HT7/PC6/YinTang (depending on the individual patient). The third treatment to be used post-embryo transfer (any time following ET but before the pregnancy test) using points GV20, KD3, ST36, SP6, PC6. Auricular acupuncture using points Shenmen and Zigong only to be used on the day of embryo transfer. De qi (needling sensation) to be maintained with additional stimulation during initial treatment on day six to eight and pre-embryo transfer (Smith et al. 2012).

It is important to bear in mind that the Chinese medical diagnosis might be quite different from the biomedical diagnosis, so a woman with one biomedical diagnosis might have a different Chinese medical diagnosis. It is the Chinese medical diagnosis that determines the correct acupuncture doses and protocol (Anderson and Rosenthal 2013).

Controls used in different studies

Approximately five categories of controls have been used in various studies: sham acupuncture at acupoints, sham acupuncture at non-acupoints, sham laser acupuncture, adhesive tapes and no intervention (Zheng et al. 2012). Acupuncture trials have been conducted to assess various subjective and objective outcomes. While assessing subjective outcomes, such as pain, anxiety and general wellbeing, it is important to use appropriate placebo controls, as otherwise the results may be biased by the women's prejudgement about the effect of acupuncture. However, while assessing objective outcomes, such as pregnancy rates, they are unlikely to be affected by the woman's expectations and hence the use of placebo control is questioned (Manheimer 2011). Each

acupoint has its own domain and if a placebo needle is applied too close to the acupoint, then it might have the same effect as the actual acupuncture. There are so many known and unknown meridians and domains that it might not be always possible to avoid an effect on the outcome from a placebo needle. Hence, a placebo might not always be an inert control. In fact, an RCT using real and placebo acupuncture on the day of embryo transfer has shown a higher overall pregnancy rate in the placebo group (So et al. 2009).

Outcome measures

The outcome measures looked at by different studies include stress, anxiety (Smith et al. 2011; Isoyama et al. 2012; Domar et al. 2009), clinical pregnancy rate, live birth rate, ongoing pregnancy rate and biochemical pregnancy rate (Omodei et al. 2010; Dalton-Brewer et al. 2009; Moy et al. 2011; Andersen et al. 2010; Domar et al. 2009; Smith et al. 2006; Westergaard et al. 2006). The definition of these outcome measures used in various studies was not consistent, leading to inconsistent results.

Heterogeneity

Variations in the study protocol, dose and timing of the acupuncture used, use of placebo acupuncture and variations in the outcome measures make the available evidence unreliable and questions their validity in the clinical context (Meldrum et al. 2013). Due to this heterogeneity, in spite of having many trials and systematic reviews, the role of acupuncture in IVF is still questioned.

Suggestions to improve future trials

STRICTA guidelines. STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) was first published in 2001 to help researchers to conduct and report trials in a way that they are more accurately interpreted. Since then, it has been regularly updated and the most recent development involved agreement between the CONSORT (Consolidated Standards of Reporting Trials) group and the STRICTA group and led to revised STRICTA criteria, which is a formal extension of the CONSORT (MacPherson et al. 2010). The revised STRICTA provides a checklist of six items broken down into 17 sub-items, which must be adhered to while conducting and reporting trials on acupuncture.

Developing an acupuncture protocol. Acupuncture dosage and timing depends on various factors and needs to be individualised. Hence, conducting a trial on acupuncture will remain challenging. The Delphi consensus provides a reproducible protocol that can be used in future trials (Smith et al. 2012).

Use of controls. While assessing outcomes, such as pregnancy rate and live birth rate, the use of placebo for controls only adds confusion and might alter the final result and hence should be avoided (Manheimer 2011).

Conclusion

There have been significant differences in the studies so far, leading to a difficulty in coming to a conclusion regarding the possible benefits of acupuncture in IVF. Nevertheless, it is consistent in most of these studies that acupuncture is safe and it has a beneficial effect on the general wellbeing of the patients. Whether it is beneficial in terms of improving the live birth rate in IVF still remains subject to further well-constructed randomised controlled studies.

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