

Infertility IVF (2019)

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Overview

Key Points

A 2018 systematic review and meta-analysis found acupuncture to have a significant treatment effect in improving the birth rates of sub-fertile women undergoing IVF or ICSI.

A summary of previous reviews from 2009 to 2017 found acupuncture had a beneficial treatment effect on clinical pregnancy rate. However, according to GRADE assessment guidelines, the scientific methods of the studies included in this review need to be improved.

Acupuncture may be a suitable treatment option to help reduce stress and anxiety levels for women suffering with subfertility.

Research indicates that the effectiveness of acupuncture may be dose-dependent, that is a sufficient number of acupuncture treatments are required over an adequate period of time.

Future research should explore the impact of acupuncture administration during ovarian stimulation. The aim should be to improve embryo and blastocyst quality, rather than focus on acupuncture post fertilisation.

Live Birth Rates

Live birth rate can be considered the most important measure of success for sub-fertile people undergoing assisted reproductive treatment. In the UK, the overall birth rate following assisted reproduction is 21% to 22% (fresh and frozen transfer). The birth rate varies and decreases with age and the type of transfer [2].

Acupuncture has been shown to have a significant treatment effect on live birth rates, indicating that acupuncture may complement an IVF or ICSI cycle. A 2018 comprehensive systematic review and meta-analysis investigated the effects of acupuncture on sub-fertile women during in vitro fertilisation (IVF) or intra-cytoplasmic sperm injection (ICSI).[1] A total of 3,188 sub-fertile women from 12 randomised controlled trials were included in this study. Acupuncture significantly improved the live birth rate of sub-fertile patients undergoing IVF or ICSI (birth rate: RR = 1.36, 95% CI 1.09–1.69, P=0.006).

One of the central problems of acupuncture research is that the acupuncture given is not the same as acupuncture in practice: a lack of external validity. Trials conducted into the

benefits of acupuncture in supporting people going through IVF have too often limited the number of treatments to the time of egg collection only or embryo transfer only.[3] This systematic review included studies where women had additional acupuncture treatments, which is a strength of the review.

Pregnancy rates

An overview of systematic reviews from 2009 up to 2017 found that acupuncture given at the time of egg collection and embryo transfer improved clinical pregnancy rates.[5] The authors did not find a treatment effect for live birth rates when acupuncture was administered around egg collection only or embryo transfer only. This evidence was graded as low quality, which means that the true effect of acupuncture administration could be substantially different from this overview's findings.

The inconclusiveness of the evidence base in this overview reflects the inadequacy of the scientific methods applied so far to evaluate IVF or ICSI and acupuncture. Recommendations for the future included a focus on acupuncture during the ovarian stimulation phase to influence follicular development and egg maturity, rather than treating women post fertilisation.

Clinical pregnancy rate: acupuncture around embryo transfer

The primary outcomes of some systematic reviews and meta-analyses indicate that there are no significant treatment effects of acupuncture on clinical pregnancy rate.[3,4,9*] However, the primary outcomes of other systematic reviews do show a benefit.[1,10,11,12*] These reviews demonstrate either a possible significant treatment effect [11] or a treatment effect of statistical significance for improved rates of clinical pregnancy.[1,10,12*]. One interesting characteristic of the studies included in the systematic reviews where an effect was found is that acupuncture was not just focused around the time of embryo transfer only. The samples of sub-fertile women undergoing an IVF or ICSI cycle also received acupuncture treatment at various time points during the treatment cycle. This indicates that acupuncture may be more effective with additional treatment prior to the day of embryo transfer and after embryo transfer. More research is required.

A recently published trial from Australia, not included in the reviews discussed above [6], It is the largest randomised controlled trial so far of IVF or ICSI with acupuncture. Technical issues, for example regarding the undertreatment of women with acupuncture and its sham control group make the conclusions difficult to relate to routine clinical practice. [7,8] (See Commentary)

Acupuncture during ovarian stimulation

A 2018 RCT in China involving 169 sub-fertile women looked specifically at the impact of having acupuncture during the ovarian stimulation phase of an IVF or ICSI cycle. This experimental study found acupuncture improved ovarian blood supply and, in turn, both biochemical and clinical pregnancy rates. Live birth rate was not an outcome measurement in this trial. The clinical pregnancy rate was 52.6% (acupuncture group) v 33.3% (sham acupuncture group) and 32.8% (observational group). The researchers

recommended that future experimental research should incorporate a larger sample of women.[17]

The conclusions of several systematic reviews indicate that the effectiveness of acupuncture may be dose dependent. In other words, a sufficient number of acupuncture sessions over an adequate period of time may be required.[9*,12*,13].

Emotional wellbeing during an IVF or ICSI cycle

Assisted reproduction treatment can be stressful and anxiety provoking. Interventions to support the psychological impact of subfertility and fertility treatment should be offered, so that a patient can make an informed decision and a choice regarding an appropriate stress and anxiety management strategy that may help them.

A study indicated that acupuncture treatment can reduce stress and/or anxiety and increase women's ability to cope with the IVF process.[18] A systematic review that also included this study found that traditional acupuncture could be an effective strategy to alleviate stress and anxiety experienced by sub-fertile women.[19]

*denotes high risk of bias – See Commentary

Commentary

Quality of acupuncture: external validity

In terms of intervention, some researchers impose questionable, ambiguous treatment restrictions, for example no moxibustion for patients with polycystic ovarian syndrome [11] (which possibly limited data for analysis). In other cases, a systematic review may have a well-designed search strategy, but be poor in terms of the inclusion criteria for an acupuncture intervention. For example, the inclusion of randomised controlled trials to assess the impact of acupuncture on clinical pregnancy rate using acupuncture designed for pain relief around the time of egg collection.[3] This is technically inappropriate.

A comprehensive acupuncture treatment management approach may be required prior to an IVF or ICSI cycle, for example lasting three to six months pre-treatment, to influence folliculogenesis.[25] Acupuncture should be administered at the start of an assisted reproduction cycle, and frequently during the beginning of ovarian stimulation up to egg maturation. The aim should be to influence the response and development of ovarian follicles via improved blood flow, and embryo or blastocyst quality. Male factor subfertility could also be addressed.

A recent RCT study is limited by the fact that one acupuncture session, adopted on day 6 to 8 of ovarian stimulation and before and after embryo transfer, did not reflect the recommendation of their consulted experts on the required amount and frequency of acupuncture to produce an intended result. The acupuncture intervention used in this study was below a minimal threshold.[6] As with the same author's 2006 trial,[26] which followed a similar three-session treatment model, there was a tendency favouring acupuncture when compared to sham acupuncture for clinical pregnancy rate, but this

did not reach statistical significance. Researchers should not undertreat subfertility patients by delivering a deficient number of treatments.

The acupuncture intervention should be well considered, and future randomised controlled trials should be designed to be appropriate in terms of an adequate amount of treatment, frequency and timing.

Control groups: placebo/sham acupuncture

The control group in efficacy trials should now be considered very carefully with a relevant, properly validated control. To date, controls to determine the efficacy of acupuncture in two-armed randomised controlled trials compare for example, acupuncture penetration by needling away from specific acupuncture points, 'mild needling' (pricking) [21] or 'pressure' (apparently telescoping the skin).[22] The Streitberger placebo needle was developed to explore the effects of needle insertion in pain [21] rather than for the sub-fertile population or wider aspects of acupuncture theory. Further, a limitation of the Park sham validation study was the likelihood of abnormal sensation in study participants due to a recent stroke and disorientation. [22]

Sham acupuncture needling controls have been found to be physiologically active, with varied effect sizes relative to the type of sham. Therefore, the effect size of the sham control (if applied) should now be considered in future sample size calculations. [23] Sham needling controls may underestimate the effect of acupuncture, leading to the unnecessary withdrawal of a potentially effective intervention that supports sub-fertile patients' reproductive treatment. Cheong et al. (2013) advocated that randomised controlled trials should therefore consist of three study arms for comparative purposes.[3] These arms could be (a) an adequate acupuncture intervention, (b) a validated control method, and (c) usual care. It is recommended that a pragmatic trial design [24] with comparisons to usual care that include other therapies should be used to investigate the effectiveness of acupuncture on live birth rates.

Registration of a systematic review protocol

Only two systematic reviews were registered. [3,4] It is preferable for authors of systematic reviews to register their research protocol with PROSPERO, the international prospective register of systematic reviews. This permits transparency and helps assessment of the outcomes based on systematic review processes.

Risk of bias of systematic reviews primary outcomes

The risk of bias of systematic reviews evaluated in this research resource was assessed using the ROBIS tool. Two systematic reviews were found to be potentially at a high risk of bias regarding an acupuncture treatment effect. These were Qian et al [12*] which found a beneficial treatment effect, and Shen et al [9*] which reported no beneficial treatment effect (although the statistical interpretation is incorrect, and a significant treatment effect was evident).

Exploration of statistical heterogeneity

Subgroup analysis is generally recommended if variability is present resulting from the systematic review process and meta-analysis. A subgroup analysis should be considered and pre-specified at the systematic review protocol stage.

Subgroup analysis may be used to describe heterogeneity and assess any relationship between covariates (for example, ethnicity) and effect size (outcome). It is usually recommended that subgroup analysis should be relevant to the research question and limited in number. However, the authors of two systematic reviews and meta-analyses conducted up to eight or more subgroup analyses.[12*,9*] Subgroup analyses have a high risk of findings being a consequence of chance.[14] It is important to point out that meta-regression, unless there is a sufficiently large sample of studies (for example, two predictors would require 50 studies), has low power and can both produce unreliable positive results based on chance or false non-significant results. Only one systematic review contained a meta-regression on important clinical characteristics and methodological variables. A positive finding was cautioned,[4] while the non-significant findings were not cautioned.

Statistical heterogeneity appears to be a common finding in the systematic reviews outlined in this document and random effect models are used. Hierarchical subgroup analysis has been proposed to be a better application to describe heterogeneity;[16] meta-regression has been argued to have serious disadvantages.[15]

Reporting

The inclusion of graphical methods (funnel plots) in a systematic review can help the reader evaluate publication bias. Funnel plots were only evident in the publication in two [4,10] of five systematic reviews. [1,3,9*,11,12*]

Statistical tests such as Begg's and Egger's may be used to identify publication bias,[1] however, these tests can be unreliable with low study power.[20] It is recommended that a discussion of the possible impact or not of publication bias, the reliability of assessment methods applied, along with any implications, should be outlined in systematic reviews, especially as part of the conclusion.

When a systematic review uses GRADE to appraise the quality of evidence, the meaning of this could be outlined explicitly in the discussion and the conclusion section. For example, Cheong et al [3] concluded that they found no evidence of a significant effect for the primary outcomes yet did not state that 'low quality' means that they had limited confidence in this finding, and that true effect could be substantially different. The overview [5] does not have adequate reporting, particularly around the finding of the clear effect of acupuncture on the outcome measurement (clinical pregnancy rate). It is important to improve the quality of reporting in systematic reviews and meta-analyses, as well as any future overviews.

Randomised controlled trials (RCTs)

There appears to be some confusion as to whether a trial is randomised or non-randomised in design. Cheong et al [3] exclude Omodei (2010) and Feliciani (2011) for

apparently being non-randomised, while Manheimer et al [4] include these studies as randomised designs. When study eligibility has been predetermined to be a randomised controlled trial design, the inclusion of non-randomised trials is an error. For example, Qian et al's [12*] inclusion of Magarelli et al (2009), a cohort study. Non-randomised designs may overestimate an effect.

Summary

The British Acupuncture Council advocates that IVF or ICSI patients who wish to have acupuncture should receive an appropriate number of acupuncture treatments based on a thorough consultation and review.

A recent RCT with an increased number of acupuncture treatments found that daily acupuncture sessions starting on day 5 of ovarian stimulation up to egg maturation (hCG trigger) had a significant treatment effect in terms of clinical pregnancy rate (compared to sham acupuncture and an observation group). [17]

Practitioners and their patients together could consider carefully the nature of the body of research outlined in this resource when devising a treatment plan. Currently, research indicates that acupuncture at the time of embryo transfer only should be a small part of an overall treatment strategy. Acupuncture can be provided post-transfer in the early luteal phase to possibly influence implantation, and during the two-week wait prior to a pregnancy test to help manage stress and anxiety resulting from uncertainty.

The evidence base for the exact number and frequency of acupuncture sessions on birth rate has not yet been robustly determined. Nevertheless, currently, research supports the findings that acupuncture at varied time points for an IVF or ICSI cycle, with increased frequency during ovarian stimulation as well as around the time of transfer, can have a statistically positive treatment effect on clinical pregnancy and live birth rate.

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