

## Point of Influence: What is the Role of Acupuncture in *In Vitro* Fertilization Outcomes?

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### ABSTRACT

Augmenting *in vitro* fertilization (IVF) with acupuncture is a popular adjuvant therapy in the United States, but its influence on IVF birth outcomes remains controversial. Recent meta-analyses found acupuncture is effective to increase the risk of live births by 30% when acupuncture was compared with no treatment in nine trials of 1,980 women. The efficacy of acupuncture is unclear, however, and confounded by the need for an adequate, inert control. Acupuncture does not increase the risk of miscarriage. Additionally, acupuncture was 42% more effective to increase live births when women had previously failed a cycle, and baseline pregnancy rate continues to mediate acupuncture's effects. The characteristics of treatment more favorable to improving birth outcomes included more treatments, timing treatments in the period before and on the day of embryo transfer (ET), and using a modified Paulus protocol on the day of ET. These findings should inform the dosage, timing, and components of acupuncture therapy and type of comparator in future trials investigating the effects of acupuncture on IVF outcomes.

### INTRODUCTION

**I**NFERTILITY IS A PUBLIC HEALTH ISSUE, affecting 1 in 8 people in the United States—a substantial proportion of Americans hoping to build their families.<sup>1,2</sup> In women ages 35–44, 7.3 million will pursue some type of fertility treatment<sup>1</sup> in which *in vitro* fertilization (IVF) is one option. There are several IVF cycle types, including fresh or frozen cycles with nondonor or donor eggs. In general, IVF procedures require a woman or a person whose gender was assigned female at birth, to take medications to stimulate her ovaries and induce multiple follicular development. When the follicles are mature, they are retrieved and fertilized in a laboratory. Usually no more than 1 viable fresh embryo can be transferred to the womb of the intended mother in a fresh, nondonor cycle; or, they can be tested for genetic abnormalities and then frozen. After genetic testing identifies euploid embryos, the frozen embryo is thawed and transferred as part of a frozen embryo transfer (FET)

cycle. It is important to note that embryos can be autologous or donated, and oocytes can be fertilized in a petri dish or via intracytoplasmic sperm injection. Alternatively, any mature eggs retrieved can also be cryopreserved unfertilized until needed, a procedure also known as egg banking. In 2016, there were 65,840 egg banking cycles reported in the United States.<sup>3</sup>

All cycle outcomes are reported to the Centers for Disease Control and Prevention (CDC).<sup>3</sup> According to the pooled data from the CDC, pregnancy rates vary widely among clinics and regions within the United States, and the prevalence of frozen cycles and egg-freezing cycles is growing.<sup>3</sup> Multiple variables modulate an outcome, including age of the mother, her infertility diagnosis, and the type of cycle performed.<sup>3</sup> In 2016, there were 52,686 embryo transfers (ETs) with fresh, autologous embryos in the United States that resulted in 19,137 live births—a 36.3% success rate across all ages of women.<sup>3</sup> There is no guarantee of success, and patients endure invasive physical

interventions, psychosocial burdens, and risks of financial strain while completing these treatments.<sup>4</sup>

To help improve their odds of delivering a child, couples may turn to complementary and integrative health approaches to supplement their fertility treatments.<sup>5–7</sup> Surveys have estimates that 8%–47% of couples add acupuncture to their IVF cycles.<sup>5,8,9</sup> However, the evidence on acupuncture's effects on IVF birth outcomes remains unclear.<sup>10,11</sup> Despite the publication of multiple trials and, subsequently, multiple meta-analyses, the effect of acupuncture on IVF outcomes is promising but not definitive. Cheong et al.<sup>11</sup> and Manheimer et al.<sup>10</sup> both found acupuncture on or around ET was not superior to any control condition for improving clinical pregnancy rates (CPRs) or live births. More trials have been completed since those previous meta-analyses were published.

The mechanisms for acupuncture's effect on reproduction are not yet clear, but research suggests multiple potential pathways. First, acupuncture inhibits central sympathetic nerve tone, which can induce vasodilation and blood flow to the uterus and ovaries, both of which are vital to reproduction. It is theorized this might be initiated through the A- $\delta$  and C fibers of the skeletal tissue.<sup>12</sup> Acupuncture also floods the body with endorphins,<sup>13</sup> ultimately mitigating the stress response associated with infertility and infertility-related treatment. The release of neurotransmitters—such as dopamine, serotonin, neuropeptides, and oxytocin—might be initiated by acupuncture, which, in turn, could influence the hypothalamus–pituitary–ovarian axis to promote ovulation, regulate menses, and increase overall fertility.<sup>12,14</sup> In polycystic ovary syndrome, acupuncture could affect glucose uptake in the skeletal tissue,<sup>15,16</sup> might decrease hyperinsulinemia, and might increase insulin clearance.<sup>17</sup>

The aim of this article is to provide an overview of the current literature evaluating acupuncture's effects on IVF outcomes.

## OVERVIEW OF RECENT IVF META-ANALYSES

As of this writing, 2 rigorous systematic reviews and meta-analyses were published in 2019 that looked specifically at acupuncture as an adjuvant to IVF.<sup>18,19</sup> See Table 1. In these meta-analyses, acupuncture was compared with sham, no treatment, and all comparators.

CPR is an intrauterine gestational sac and/or fetal heart motion confirmed by ultrasound (US). Overall, there was no difference when acupuncture was compared in a systematic review to a sham controls to improve CPR, but verum acupuncture increased CPR by 28%<sup>19</sup>–32%,<sup>18</sup> compared to no treatment. When acupuncture was compared to all control groups in another systematic review by Xie et al.,<sup>19</sup> acupuncture increased pregnancy rates by 21%.<sup>19</sup>

Ongoing pregnancy rate (OPR) is an intrauterine pregnancy beyond 12 weeks and confirmed by US. Acupuncture increased OPR by 42% in Smith et al.'s analysis,<sup>18</sup> and Xie et al.<sup>19</sup> did not assess OPR.

The live birth of an infant resulting from conception after IVF is measured as a live birth rate (LBR). When acupuncture was compared with a sham control, the impact of acupuncture was equivocal on this outcome. When acupuncture was compared with no treatment, Smith et al.<sup>18</sup> found that acupuncture increased LBR by 30%, and Xie et al.'s<sup>19</sup> analysis found no significant difference among groups, but the LBR was trending toward significance.

Miscarriage rates are of particular interest in IVF<sup>20</sup> and are an adverse outcome. Smith et al.<sup>18</sup> found that

TABLE 1. OUTCOMES COMPARISON OF META-ANALYSES OF ACUPUNCTURE'S INFLUENCE ON *IN VITRO* FERTILIZATION PREGNANCY OUTCOMES BY SMITH ET AL.<sup>18</sup> AND XIE ET AL.<sup>19</sup>

| Rates              | Acupuncture vs. no treatment                                       |                                                                    | Verum vs. sham acupuncture                                        |                                                                    | Acupuncture vs. all controls                                       |
|--------------------|--------------------------------------------------------------------|--------------------------------------------------------------------|-------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------|
|                    | Smith et al.                                                       | Xie et al.                                                         | Smith et al.                                                      | Xie et al.                                                         | Xie et al.                                                         |
| Clinical pregnancy | <i>N</i> = 12, <i>n</i> = 2230<br>RR: 1.32<br>(95% CI: 1.07, 1.62) | <i>N</i> = 17, <i>n</i> = 3084<br>RR: 1.28<br>(95% CI: 1.08, 1.52) | <i>N</i> = 9, <i>n</i> = 2901<br>RR: 1.07<br>(95% CI: 0.88, 1.30) | <i>N</i> = 11, <i>n</i> = 3060<br>RR: 1.14<br>(95% CI: 0.94, 1.39) | <i>N</i> = 27, <i>n</i> = 6116<br>RR: 1.21<br>(95% CI: 1.07, 1.38) |
| Ongoing pregnancy  | <i>N</i> = 6, <i>n</i> = 1144<br>RR: 1.42<br>(95% CI: 1.17, 1.73)  | —                                                                  | <i>N</i> = 6, <i>n</i> = 1884<br>RR: 0.98<br>(95% CI: 0.86, 1.13) | —                                                                  | —                                                                  |
| Live birth         | <i>N</i> = 9, <i>n</i> = 1980<br>RR: 1.30<br>(95% CI: 1.00, 1.68)  | <i>N</i> = 9, <i>n</i> = 1992<br>RR: 1.26<br>(95% CI: 0.99, 1.60)  | <i>N</i> = 6, <i>n</i> = 2465<br>RR: 1.01<br>(95% CI: 0.80, 1.28) | <i>N</i> = 6, <i>n</i> = 2480<br>RR: 1.01<br>(95% CI: 0.80, 1.27)  | <i>N</i> = 15, <i>n</i> = 4472<br>RR: 1.14<br>(95% CI: 0.96, 1.35) |
| Miscarriage        | <i>N</i> = 10, <i>n</i> = 2042<br>RR: 1.43<br>(95% CI: 1.03, 1.98) | —                                                                  | <i>N</i> = 7, <i>n</i> = 2698<br>RR: 1.15<br>(95% CI: 0.79, 1.67) | —                                                                  | <i>N</i> = 15, <i>n</i> = 1504<br>RR: 1.14<br>(95% CI: 0.93, 1.41) |

Data are presented as *N* = number of trials, *n* = number of participants, relative risk (RR), and 95% confidence interval (CI).

—, represents no data reported.

acupuncture reduced the miscarriage rate by 43%, compared with no treatment; however no difference emerged between verum and sham acupuncture and. In a pooled analysis of studies with any comparators, Xie et al.<sup>19</sup> found that there was also no difference between acupuncture and control groups on miscarriage rates.

The discordance among analyses is likely due to each review's inclusion criteria. In their analysis, Smith et al.<sup>18</sup> only included studies in which the primary endpoint was a birth outcome and excluded studies that evaluated acupuncture's impact on pain during oocyte retrieval. The researchers cited the mechanisms of action as being different for analgesia versus reproductive support as a rationale for their exclusion.<sup>18</sup> Those pain trials were included in Xie et al.'s<sup>19</sup> analysis. The variability of included trials analyzed underscores the differences in results between the 2 meta-analyses as outcomes will change when different studies are pooled together.

Both meta-analyses found several variables that were significant sources of heterogeneity. Variables that mediated outcomes included the number of acupuncture treatments during the IVF cycles,<sup>18,19</sup> baseline pregnancy rates,<sup>18</sup> timing of acupuncture treatment,<sup>18</sup> acupuncture protocols used,<sup>18,19</sup> and previously failed cycles.<sup>19</sup>

When there were more than 3 acupuncture treatments during a cycle, acupuncture improved CPR by 50%–60%.<sup>18,19</sup> The effects of more sessions have also been observed in women who choose acupuncture to supplement their IVF treatments. Nine<sup>21</sup> to 12<sup>22</sup> sessions were associated with significant increases in the odds of live births in observational studies. These sessions were administered prior to ET and included day of ET acupuncture.<sup>21,22</sup>

A significant modifier of effect is the baseline pregnancy rate.<sup>18</sup> Among 11 trials in which CPR outcomes averaged <32%, women who were randomized to day of ET acupuncture had an increased likelihood of pregnancy of 60%.<sup>18</sup> Manheimer et al.<sup>10</sup> also found that the effects of acupuncture were incrementally diminished as baseline pregnancy rates improved. Currently, the U.S. national average already exceeds the 32% threshold.<sup>3</sup>

The effect of acupuncture therapy during IVF cycles is also relative to the timing of sessions and protocols used. There was a 17% increase in CPR when acupuncture was provided solely or before ET.<sup>18</sup> Modifications of the Paulus<sup>23</sup> protocol were also more effective for increase CPR by 34% than strict reproduction of the Paulus protocol.<sup>18</sup> In addition, of particular interest, when women had cycles that had previously failed, acupuncture, when added to IVF, increased the likelihood of CPR by 60% and of live births by 42%.<sup>19</sup>

## DISCUSSION

Previous analyses<sup>10,11</sup> found similar IVF outcomes when verum acupuncture was compared with sham acupuncture.

The use of sham needles in acupuncture investigations is controversial, as they are not inert<sup>24,25</sup> and obfuscate outcomes.<sup>20,24</sup> Sham-needling controls involve penetrating or nonpenetrating needles that are inserted on or off acupuncture points and/or channels. Sham/placebo needles confound results and encourage false rejection of acupuncture therapy.<sup>20</sup> Future trials should be comparative in effectiveness until a truly inert sham or placebo is developed.

Published IVF acupuncture studies have largely included fresh autologous embryos with only 1 study investigating acupuncture's effects on frozen embryo cycles. In addition, nearly all studies excluded donor embryos (fresh or frozen) as the baseline pregnancy rates with autologous embryos are generally better than with fresh or frozen cycles. Does acupuncture affect these cycles differently? It has been estimated that FETs are associated with a 49% increase in the odds of live births, compared with fresh ETs.<sup>26</sup> In a small sample of fresh, donor cycles ( $N=58$ ), ~11 sessions of acupuncture therapy were associated with a robust increase in the odds of live birth, compared with acupuncture on the day of ET alone (*odds ratio* = 4.09; 95% confidence interval: 1.02–16.38).<sup>22</sup>

Limiting the generalizability of these findings is that the current state of evidence is lagging behind usual care in the United States. All published studies occurred prior to the widespread implementation of preimplantation genetic testing (PGT) in IVF usual care in the United States. Many patients add PGT to their IVF cycles to ensure only euploid embryos are transferred, and thereby increase their chances of delivering a healthy baby and reduce the number of cycles needed.<sup>27</sup>

In the 2 systematic reviews,<sup>18,19</sup> an analysis on acupuncture's impact on relevant psychosocial outcomes was absent, yet, IVF patients are significantly burdened by infertility-related stress,<sup>28,29</sup> and insured IVF patients have cited stress as the primary reason they discontinued treatment despite not conceiving.<sup>4</sup> Because acupuncture is widely known to modulate stress, it could be an important way to support patients during their treatment. There is a gap in knowledge of the magnitude of acupuncture's effects for reducing the emotional burden of IVF treatment. Several studies have assessed patients' psychosocial outcomes as secondary endpoints; therefore, a formal systematic review and meta-analysis is needed to assess the magnitude of acupuncture's effect on this important outcome and these are currently underway.

## CONCLUSIONS

Acupuncture has been effective for increasing CPR by 28%–32%, OPR by 42%, and LBR by 30%, compared to no treatment. However, the efficacy of acupuncture was still unclear and confounded by sham controls that were not inert. Acupuncture was more effective for increasing live births when women had previous cycles that failed, compared with

BOX 1. SUMMARY OF THE CURRENT EVIDENCE  
ON ACUPUNCTURE'S INFLUENCE ON *IN VITRO*  
FERTILIZATION BIRTH OUTCOMES

1. Acupuncture, compared to no treatment, is effective for increasing:
  - Clinical pregnancy rate by 28%–32%
  - Ongoing pregnancy rate by 42%
  - Live birth rate by 30%.
2. The efficacy of acupuncture *is still unclear* and confounded by the need for an adequate, inert control.
3. Acupuncture was more effective for increasing live births:
  - In patients with previously failed cycles
  - Clinics with a baseline pregnancy rate <32%.
4. Characteristics more-favorable for improving outcomes were:
  - More acupuncture treatments,
  - Acupuncture treatment focused before and on the day of embryo transfer
  - Using a modified Paulus protocol on the day of embryo transfer.

a control condition. Baseline pregnancy rate is also a mediator of acupuncture's effects. The characteristics of treatment that were more favorable for improving outcomes were more treatments, focusing treatment before and on the day of ET, and using a modified Paulus protocol on the day of ET. See Box 1.

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