Female Infertility

The evidence for the effectiveness of ACUPUNCTURE

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INFERTILITY AND ACUPUNCTURE: evidence for effectiveness

A. Anovulation/amenorrhoea/oligomenorrhoea

1. Controlled trials

<table>
<thead>
<tr>
<th>Author / conditions</th>
<th>Type of control</th>
<th>Number</th>
<th>Outcomes (acupuncture group value given first)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerhard &amp; Postneek 1992 /various hormonal disorders; all amenorrhoea or oligomenorrhoea</td>
<td>Retrospective matched pairs: vs best medical treatment</td>
<td>90</td>
<td>PR: similar in each group (ns). Fewer miscarriages, no side effects</td>
</tr>
<tr>
<td>Ji et al 1999 /ovulation induction for infertility/amen/oligomenorrhoea</td>
<td>Unknown: vs clomiphene, HCG, stilboestral, progesterone</td>
<td>98</td>
<td>OR: 79 v 83% (ns) PR: 69 v 40% (*)</td>
</tr>
<tr>
<td>Zhao &amp; Jin 2001 /ovulation induction for pubertal oligomenorrhoea.</td>
<td>RCT: vs oestrogen vs acup + oestrogen (3 groups)</td>
<td>60</td>
<td>OR: 60 v 25 v 70%</td>
</tr>
<tr>
<td>Jin 2002 /ovulation induction for pubertal dysfunctional uterine bleeding</td>
<td>Unknown: vs clomiphene</td>
<td>22</td>
<td>OR: 87 v 70%</td>
</tr>
<tr>
<td>Yang et al 2005 /ovulation induction for hormonal infertility</td>
<td>RCT: vs clomiphene</td>
<td>240</td>
<td>PR: 65 v 45% (*)</td>
</tr>
</tbody>
</table>

**OR = ovulation rate  **   **PR = pregnancy rate**

(*) indicates statistical significance (where given)

(ns) not significant
2. Uncontrolled trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Condition</th>
<th>No.</th>
<th>Acupuncture treatment</th>
<th>OR %</th>
<th>PR %</th>
<th>Outcome – more details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerhard &amp; Postnek</td>
<td>oligomenorrhoea &amp; luteal body insufficiency</td>
<td>27</td>
<td>Auricular points, semi-formulaic</td>
<td>Similar to medication</td>
<td>Fewer side effects and abortions; best results if +ve gestagen test/normal hormones/hyper-androgen</td>
<td></td>
</tr>
<tr>
<td>Yu et al 1989</td>
<td>anovulation, mostly PCOS</td>
<td>11</td>
<td>TCM formula, electroacup, 3 days in 1 cycle</td>
<td>46</td>
<td>33</td>
<td>Increases in LH and FSH in those ovulating</td>
</tr>
<tr>
<td>Mo et al 1993</td>
<td>diverse causes of anovulation, most with amenorrhoea</td>
<td>34</td>
<td>TCM formula, 3 per week for 3 months</td>
<td>18% no improvement at all, 47% some, 35% cycling or pregnant [after 3 cycles]</td>
<td>Hormone levels and follicular development better</td>
<td></td>
</tr>
<tr>
<td>Li 1995</td>
<td>diverse infertility</td>
<td>100</td>
<td>TCM formula, 10 per cycle up to 5 cycles</td>
<td>79 [1-2 cycles]</td>
<td>97% pregnant after 5 cycles</td>
<td></td>
</tr>
<tr>
<td>Cai 1997</td>
<td>ovulation induction for ovarian hyper-stimulation syndrome</td>
<td>10</td>
<td>TCM semi-formula, 1-3 per day for 1 cycle</td>
<td>90</td>
<td>Ovarian hyper-stimulation better</td>
<td></td>
</tr>
<tr>
<td>Stener-Victorin 2000</td>
<td>PCOS &amp; amen/oligomen</td>
<td>24</td>
<td>TCM/medical formula, 14 in 3 months</td>
<td>37.5 [after 3 cycles]</td>
<td>Can predict best responders from hormones &amp; body mass index</td>
<td></td>
</tr>
<tr>
<td>Luo &amp; Sa 2001</td>
<td>anovulatory infertility</td>
<td>11</td>
<td>TCM formula, 1-3 per day for 10-12 days</td>
<td>82</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Zhang et al 2004</td>
<td>ovulation induction, most amen/oligomen</td>
<td>35</td>
<td>TCM semi-formula, 6 per course for up to 4 courses</td>
<td>89 [after 4 courses]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peng &amp; Zhao 2004</td>
<td>PCOS, bleeding, amen, anovulation</td>
<td>106</td>
<td>TCM semi-formula, one cycle</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xu 2004</td>
<td>ovulation induction for PCOS</td>
<td>15</td>
<td>Electro-acup, 6 sessions</td>
<td>41 (0% pre-treatment)</td>
<td>Increases in progesterone and endometrial thickness</td>
<td></td>
</tr>
</tbody>
</table>
Summary of anovulation/amenorrhoea/oligomenorrhoea papers

These studies are largely of stand-alone acupuncture used for ovulation induction. Most patients were either not cycling at all or erratically so. Polycystic ovaries or dysfunctional uterine bleeding featured in a substantial number of the trials but others covered a range of different causes of infertility.

The five controlled trials included only two randomised ones (RCTs). Four of the controlled trials were Chinese and for three of them only very brief details are available. All the controlled studies compared acupuncture with standard Western drug treatment. Only one was large, a recent Chinese RCT showing a 20% advantage in pregnancy rate for acupuncture over clomiphene. The other Chinese studies also found similar significant advantages in either pregnancy or ovulation rates. By contrast the one Western trial showed no overall difference in pregnancy rates (though those with irregular menstruation did better with acupuncture) but there was a distinct advantage in reduced miscarriages and no side-effects.

The ten uncontrolled trials were again largely Chinese (7/10) and mostly rather small (only two had more than 100 subjects; the rest fewer than 40). None used entirely individualised treatment protocols even though they were mostly TCM-based. The outcomes covered a wide range of values for ovulation rate (35-90%) and pregnancy rate (35-80%). Also noted were fewer complications and normalised hormonal profiles.
### B. Acupuncture adjunctive to Assisted Reproductive Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type /nature of control</th>
<th>No.</th>
<th>Pregnancy Rate %</th>
<th>Ongoing PR or live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stener-Victorin et al 1996 /IVF</td>
<td>Uncontrolled</td>
<td>10</td>
<td>Normal uterine blood flow restored in 75% of women</td>
<td></td>
</tr>
<tr>
<td>Balk et al 2003 /IVF</td>
<td>Uncontrolled</td>
<td>10</td>
<td>PR not increased by acupuncture [No change in uterine blood flow]</td>
<td></td>
</tr>
<tr>
<td>Emmons &amp; Patton 2000 /ICSI</td>
<td>N=1 /patients are own controls</td>
<td>6</td>
<td>Follicles recruited for IVF: 8 v 4: 3 pregnancies, only 1 maintained</td>
<td></td>
</tr>
<tr>
<td>Paulus et al 2002 /ICSI, IVF</td>
<td>RCT; vs no acupuncture</td>
<td>80+80</td>
<td>42.5 v 26.3 (*)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[No differences in oestradiol, endometrial thickness, uterine blood flow]</td>
<td></td>
</tr>
<tr>
<td>Zhang et al 2003 /ICSI, IVF</td>
<td>RCT; vs sham acup vs no acupuncture</td>
<td>70+70+70</td>
<td>44 v 27 v 24. Acu. v sham or v no acu. (*)</td>
<td></td>
</tr>
<tr>
<td>Magarelli et al 2004 /good prognosis IVF patients</td>
<td>Retrospective case control; vs no acupuncture</td>
<td>53+61</td>
<td>51 v 36 (<em>) 23 % higher (</em>)</td>
<td></td>
</tr>
<tr>
<td>Magarelli &amp; Cridennda 2004 / IVF poor responders</td>
<td>Retrospective case control; vs no acupuncture</td>
<td>53+94</td>
<td>53 v 38 (*) [after statistical adjustment]</td>
<td></td>
</tr>
<tr>
<td>Quintero et al 2004 /IVF</td>
<td>RCT crossover (in 2nd cycle if 1st not successful); vs Sham acup</td>
<td>17</td>
<td>70 v 30 (*)</td>
<td></td>
</tr>
<tr>
<td>Dieterle et al 2006 /ICSI, IVF</td>
<td>RCT; vs sham acup</td>
<td>119+109</td>
<td>34 v 16 (<em>) 28 v 14 (</em>)</td>
<td></td>
</tr>
<tr>
<td>Smith et al 2006 /IVF</td>
<td>RCT; vs sham acup</td>
<td>228 (2 groups)</td>
<td>31 v 23 (ns) 28 v 18 (ns)</td>
<td></td>
</tr>
<tr>
<td>Westergaard et al 2006 / ICSI, IVF</td>
<td>RCT; 2 acup arms - either 2 or 3 treatments vs no acup</td>
<td>95+91+87</td>
<td>39 v 36 v 26 Acup 1 (*) Acup 2 (ns)</td>
<td></td>
</tr>
<tr>
<td>Johnson 2006 /IVF</td>
<td>Case control; vs no acupuncture</td>
<td>22 + ?</td>
<td>58 v 45 (ns)</td>
<td></td>
</tr>
</tbody>
</table>

*Acupuncture group results given first*

(•) statistically significant

(ns) not significant
Summary of papers on assisted reproductive therapy

Quite unlike the stand-alone acupuncture studies these were a) nearly all controlled (10/12), and b) nearly all Western (11/12).

Of the ten controlled trials five were prospective RCTs, one a RCT crossover, one a n=1 and three case controlled. The case controls all compared acupuncture to no acupuncture. The RCTs compared acupuncture either to sham, to no acupuncture or to both. The numbers of participants were consistently higher than in the stand-alone studies: 150-270 for the RCTs; 40-150 in the case controls.

Apart from the n=1 study, which was too small to establish such statistics, there was considerable agreement in the results: the acupuncture groups show an increase in pregnancy rates of about 15% over the control. For the sham controls the difference is only about one percentage point lower than the comparison with no acupuncture. Not all of the results were statistically significant, even though apparently clinically significant.

The range of values for clinical pregnancy rate was 31-70% for acupuncture, 16-45% for the control. Some studies followed up beyond 12 weeks to measure what they call ongoing pregnancy: 26-40% with acupuncture, 14-25% in the control.

Two uncontrolled studies were both very small and both focused on uterine artery flow: one found an effect and one did not.

C. Other infertility research

PHYSIOLOGY

- Various studies have found that acupuncture can affect hormone levels: oestrogens, progesterone, LH, FSH, GnRH, cortisol, prolactin. Particular attention has been paid to its regulatory effect via \( \beta \)-endorphin on the hypothalamus-pituitary-ovarian-adrenal axis.

- Various possible routes have been suggested as to how acupuncture may help PCOS patients: corticotrophin releasing hormone, nerve growth factor, endothelin, ovarian blood flow, \( \beta \)-endorphin and the HPOA axis, ovarian \( \beta 2 \)-adrenoceptors, neurotrophin receptor, sympathetic nervous system

HEALTH STATUS OF IVF PATIENTS

A survey using the SF36 questionnaire and also diagnosis according to TCM pattern showed that women undergoing IVF had poorer health than average in several respects. Kidney Yang deficiency was the commonest TCM pattern. Qi or Blood Stasis were associated with poorer mental health.
CAM USE BY INFERTILITY PATIENTS

A survey of 400 couples showed a high use of CAM, especially amongst females and in private clinics. This was despite some scepticism about its efficacy.

D. Reviews

Chang et al (02)  [Cornell University, USA]

Describes in physiological terms how acupuncture may affect fertility
Reviews MEDLINE trials up to 2002:
- “there is sufficient evidence of acupuncture’s value to expand its use into conventional medicine and treatment of female infertility”
- further studies, especially RCTs, needed to definitely establish its clinical value

Stener-Victorin et al (02)  [Goteborg University, Sweden]

- Written to answer a sceptical paper in the same journal (Human Reproduction)
- Talks generally about the physiological mechanisms behind acupuncture’s effects
- For reproductive medicine it takes three areas as examples
  - Uterine artery flow – interesting, but needs RCT follow-up
  - Anaesthetic for oocyte aspiration – works very well, they use it routinely
  - Hormonal disturbances, e.g. PCOS, anovulation: need better studies, RCTs especially, to establish the effect, but does appear that acupuncture may have a beneficial effect – there is both clinical and experimental evidence. Hence acupuncture may be a suitable alternative or complement to drugs for inducing ovulation, and with no negative side effects

White (03)  [Peninsular Med School, UK]

- Reviews controlled trials in MEDLINE, EMBASE, COCHRANE
- Finds 3 suitable trials of acupuncture for infertility (Stener-Victorin et al, 1999; Gerhard & Postneek; Paulus): they have positive results but methodological weaknesses
- The evidence is positive but not conclusive – however, the known physiological mechanisms of acupuncture, via β-endorphin and hence gonadal hormones, would support its effectiveness. He concludes that it is promising for infertility
References


Xu J (2004) Personal communication, from PhD, Oxford Brookes University


