Trial Protocol

Acupuncture to improve live birth rates for women undergoing IVF: a randomised controlled trial

1. INTRODUCTION

1.1 BACKGROUND

Over the last 30 years the clinical treatment of infertility has changed dramatically. Three major developments have occurred: firstly, the introduction of IVF and other assisted reproductive technologies (ART); secondly, there is a greater number of women attempting pregnancy at an older age when they are less fertile; and thirdly there is greater awareness of fertility treatment with Medicare funding. During 2007, there were 56,817 ART cycles, however only 22.6% resulted in a clinical pregnancy and 17.4% (10,994) resulted in live deliveries[1].

Despite the significant personal costs of ART, over the last five years, the number of ART procedures has increased on average by 10% per year in Australia[1]. In fact, Australia has one of the highest levels of utilization at 1,574 cycles per million population, and with the average cost of a standard IVF cycle at $5,549[2].

The increasing demand for ART services has led to substantial costs to the Government. Expenditure on ART services doubled from $66.3 million to $156.1m between 2000-2005[3]. Federal funding is provided for an unlimited number of ART cycles deemed "clinically relevant" and in line with State and Territory legislation. Co-payments are required but insurance through third parties players is available. The total direct costs of ART treatment undertaken in 2002 were estimated to be $130.9 million for fresh cycles[4].

IVF is a resource intensive and costly treatment option for both women and their families and for public health care expenditure. Therefore new therapies that improve reproductive outcomes are highly desirable.

The use of acupuncture by women undergoing IVF

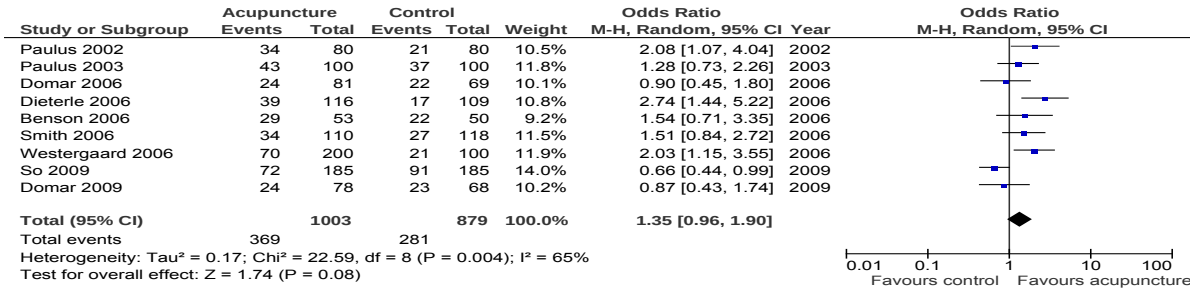
Complementary medicines and therapies (CM) are concerned with both the maintenance of wellness and the treatment of illness. CM is widely used in the community, during 2007 over 60% of Australians reported using CM, and 44% had visited a CM practitioner[5]. Studies indicate that CM are widely used by women to enhance their fertility. In one survey of CM use by patients attending an IVF unit in Adelaide, 45% of men and women continued to use CM during their ART treatment. The study found use of many CM modalities declined during ART, however the use of acupuncture increased[6]. This may be explained by women's awareness of research evaluating the effect of acupuncture as an adjunct to IVF.

There is a growing body of research evaluating the effect of acupuncture administered during IVF, and specifically on the day of embryo transfer (ET). One of these trials was undertaken by *CI Smith*[7] addressed a significant methodological flaw in previous studies by using an appropriate control (the placebo needle). Our trial randomised 228 women to acupuncture or a control group using the placebo needle. The first treatment was administered on day 9 of the stimulated cycle, and two treatments administered before and after ET. The clinical pregnancy rate was 31% in the acupuncture group vs 23% in the control group ($p<0.18$), (OR 1.51, 95% CI 0.84 to 2.72), and the ongoing pregnancy rate at 18 weeks was 28% in the acupuncture group compared to 18% in the control group (OR 1.71, 95% CI 0.92 to 3.19, $p<0.08$). The trial may have been under-powered but a treatment effect can not be excluded.

A review of the evidence of acupuncture RCTs undertaken on the day of ET:
We present an updated review and meta-analysis of RCTs undertaken on the day of ET to examine the effect on reproductive outcomes. We have included published trials (up to February 2010) comparing acupuncture to a control group, and reported on a clinical pregnancy, or live birth. Trials of manual and electro-acupuncture were included. Exclusion criteria included laser acupuncture, cross over trials, and the trial intervention administered a significant distance off site from the IVF unit. The meta-analysis pooled data from all trials and uses a random effects model. Two trials were excluded from this review[14,15]; one trial performed acupuncture at a distance offsite, and one trial reported inadequate randomisation.

Nine RCTs with a total of 1,882 women met our inclusion criteria[7-12,14,16-17]. Internal validity was high for all trials with adequate allocation sequence generation, and randomisation concealment was judged as adequate in eight trials. There was no imbalance at randomization for all trials. Blinding was successfully maintained in groups using the placebo needle or sham control. There were losses to follow up in two trials[11-12]. However, not all trials report on the key outcome of live birth, sample sizes were small and trials were underpowered to detect statistical differences between groups, and inadequate controls have been used to examine the efficacy of acupuncture. These study design limitations impacted on the findings from a meta-analysis of data.

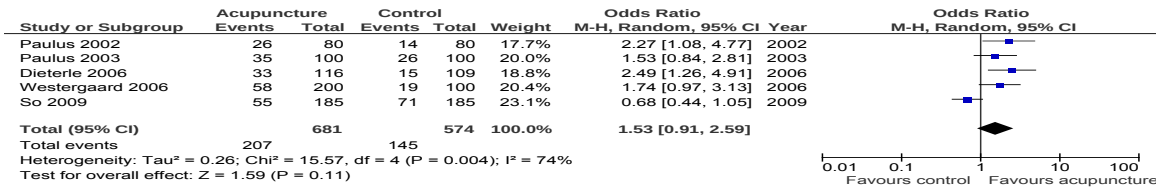
Figure 1 Outcome clinical pregnancy (all trials)



Nine trials [7-12, 14, 16-17] (1,882 women) reported on clinical pregnancies. Data were pooled due to the heterogeneity by control group design. The meta-analysis found insufficient evidence of a benefit from acupuncture with improving clinical pregnancy rates (OR 1.35, 95% CI 0.96 to 1.90 P=0.08), however there was significant heterogeneity (Figure 1). Significant heterogeneity was explained by one trial undertaken by So[17],where the design of the control group stimulated active points and was not inert. Excluding this trial from the meta-analysis reduced the heterogeneity (I^2=30%), and *a benefit was found from acupuncture (OR 1.53, 95%1.17 to 2.01, p<0.002).*

Only five trials[7,9,10,11,17] (1255 women) reported on live births. The forest plot shows a trend towards an increase in live births for the acupuncture group, although it did not reach significance (OR 1.53, 95% CI 0.91 to 2.59 P=0.11) (I^2=74%) (Figure 2). Excluding the So trial reduced heterogeneity (I^2=0%), and a benefit from acupuncture on live births was found OR 1.91, 95%CI 1.39 to 2.64, P=0.001).

Figure 2 Outcome Live Births (all trials)



The findings from our meta-analysis and published systematic reviews[18,20] indicate acupuncture may have a beneficial effect on reproductive outcomes, however results are influenced by small

samples and in adequate controls. Implications for practice cannot be made until acupuncture has proven efficacy and shown to be more effective than a placebo.

Can the effect of acupuncture on reproductive outcomes be explained biologically?
Mechanisms underlying acupuncture have been widely researched in relation to pain. Acupuncture analgesia research suggests acupuncture triggers a sequence of events involving the release of endogenous opioid like substances, for example β-endorphin, and enkephalin that modulate pain signals[21]. Further, imaging technology studies show the hypothalamus-limbic system plays a role with acupuncture analgesia by modulating sensory and emotional aspects of pain processing. Mechanisms underlying other health conditions may involve modulation of the autonomic nervous system, as seen in patients with irritable bowel syndrome and major depression[22].
Electro acupuncture has been shown to release ß-endorphin a neurotransmitter and neuro hormone via two systems[23]. One system involves the hypothalamus and neuronal network which results in an inhibitory effect on the vasomotor centre resulting in decreased sympathetic tone. Secondly, ß-endorphin released into the blood may exert an effect on both the hypothalamic-pituitary axis and hypothalamic-pituitary-gonadal axis and may have an effect on gonadotropin-releasing hormone (GnRH) and pituitary gonadotrophin secretion[24,25]. Acupuncture may exert a sympatho-inhibitory effect reducing uterine artery impedance and increase uterine and ovarian blood flow. Improved blood flow in women undergoing the down regulation phase of IVF from acupuncture has been reported[26]. This improved blood flow could hypothetically improve the growth and thickness of the endometrium and endometrial receptivity. To date these findings have not been confirmed in controlled studies[27].

The personal and social context of acupuncture
Studies suggest psychological factors may influence successful outcomes from IVF[28,29]. Ebbsesen et al found a large number of life events perceived as having a negative impact on quality of life may indicate chronic stress, and this may reduce the chances of a successful outcome from IVF[29]. In addition, the stress associated with IVF treatment may invoke anxiety, and affect feelings of self worth, loss and potentially depression. Research shows that distress among women undergoing IVF increases over time[30], and peaks between the second and third year[31]. Longitudinal studies show that unsuccessful IVF has substantial psychosocial consequences, with anxiety and depression found to increase in women following unsuccessful treatment[32].

Acupuncture may have a calming effect at the time of ET and so elicit beneficial effects. The mechanism for this may be through reducing synthesis of stress hormones, now recognised to impact on pregnancy success. This suggestion is supported by data from our RCT showing a relaxation effect following acupuncture on the day of ET[8]. CIs Smith and de Lacey recently reported on an exploratory qualitative research examining women's experiences following a course of acupuncture as an adjunct to ART[4][33]. Our findings suggest acupuncture may provide properties of self enhancement such as increased confidence, clarity and wellbeing, enhanced coping and adaptation and encouraged positive emotion and provided social support[33]. Women reported feeling relaxed, less stressed and an increased capacity to cope for about a week after treatment. If the effects of acupuncture are sustained over a week as indicated by our research, our treatment hypothetically could reduce women's distress in the period leading up to the pregnancy test, and more immediately around the time of implantation thus minimizing the impact of stress on implantation. A recent study in Melbourne in which focus groups were conducted with women having CMs reported similar experiences of psychosocial support for women[34]. We also have data from uncontrolled and controlled studies showing a short course of acupuncture for women undergoing ART demonstrated improved self efficacy and coping skills[35,36]

1.2 RATIONALE FOR STUDY

There is a need for further appropriately powered, well designed RCTs evaluating the role of acupuncture on live birth. Whilst international clinical trial registries indicate four RCTs are in progress, the effect of acupuncture on live births will remain unanswered.

- The primary endpoint of these trials is clinical pregnancy, with sample sizes ranging from 60-635, trials will not be powered to detect a statistical effect on live birth.

- The two largest RCTs compare acupuncture with either the placebo needle, or sham needle or standard care alone, therefore determining the efficacy of acupuncture compared with an optimal placebo control, and standard care with improving live births will remain unanswered.

There are clearly methodological concerns with the experimental design of ongoing trials, none of which will adequately address the methodological limitations of previous acupuncture research. There is a need for a further appropriately powered well designed RCT using of the placebo needle to enhance the quality of the studies, and standard care group to allow for a comparison with the baseline pregnancy rate.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 To determine the clinical effectiveness of acupuncture in improving the proportion of women undergoing in vitro fertilization (IVF) having live births

2.1.2 To determine the improved cost effectiveness of IVF with acupuncture.

2.1.3 To determine the personal and social context of acupuncture in IVF patients, explain the reasons why the acupuncture may or may not have worked, and identify other effects of acupuncture.

2.2 ENDPOINTS

2.2.1 Primary study endpoints: Proportion of women reporting a live birth defined as the delivery of one or more living infants, greater than 20 weeks gestation or 400grams or more birth weight.

2.2.2 Secondary study endpoints Proportion of women reporting a clinical pregnancy defined as demonstration of fetal heart activity on ultrasound scan, measured at 7-8 weeks, miscarriage defined as a non viable pregnancy prior to 12 weeks, quality of life and fertility related stress, and anxiety measured at trial entry, two and 14 weeks from trial entry. Acceptability of acupuncture and therapeutic alliance measured at the end of the intervention.

3. STUDY DESIGN

1. A single blind randomised controlled trial of acupuncture during IVF treatment.
2. Qualitative interviews with women selected from the sampling frame of the RCT.
3. An economic analysis to determine the cost effectiveness of acupuncture as an adjunct to IVF.
4. An integrated analysis of the findings from all studies.

4. STUDY POPULATIION

4.1 NUMBER OF PARTICIPANTS

1. The proportion of women with a live birth for women with multiple cycle failures in the placebo control group in our previous study was 12.1%[8]. To detect a 7% increase in the proportion of women that report a live birth between the treatment and placebo control, with 80% power at the 5% significance level will require *449* women per group. We have allowed for *a loss of 30%* due to cancelled cycles, or no ET. A sample size of 1168 women is required.

2. We expect a larger treatment effect (10%) when comparing acupuncture and standard care. Allowing for a 30% loss, 231 women in the non randomised group will have 80% power to detect a difference in the proportion of women that report a live birth rate compared to the acupuncture group.

4.2 INCLUSION CRITERIA

Entry criteria:

Women aged less than 43 years, undergoing a fresh IVF or ICSI cycle.

4.3 EXCLUSION CRITERIA

Women undergoing a frozen ET, previous randomisation to the trial, planning pre-implantation genetic diagnosis, or receiving donor eggs, or having current acupuncture use.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

The recruitment strategy will include self referral or referral from clinicians. The recruitment strategy will include for example networking with medical specialists and clinicians at the IVF units, and placement of information on internet web sites of the research institutions.

5.2 SCREENING FOR ELIGIBILITY

Recruitment will be undertaken by research nurses or a trial co-ordinator employed at the IVF Unit. Research nurses or the trial co-ordinator will disseminate information to clinical staff, and seek referrals from clinicians. Potential women will also be screened from appropriate clinic listings

Eligible women will be screened by the research nurses/ trial co-ordinator. Women meeting the criteria will be invited to consent to the trial on day 6-8 of the stimulated cycle. Women refusing randomisation will be invited to join the standard care group.

If women are eligible and interested in joining the study, an appointment will be made. The research nurse/co-ordinator will confirm this in writing with an email, phone or by post. A map will be provided and details of the acupuncture location will be confirmed.

5.3 CONSENTING PARTICIPANTS

Following consent, a trial entry form will record information on reproductive, clinical, demographic and socio-economic characteristics.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

A log will be made of women who do not meet the eligibility criteria. The reason must be recorded on the log sheet.

If women are not interested in joining the trial, the reason for declining should be logged.

5.5 RANDOMISATION

5.5.1 Randomisation

Randomisation will be in balanced, variable blocks. Women will be allocated to a study group by an internet randomisation service, prepared and based at the NHMRC Clinical Trials Centre. There will be stratification by number of ET cycles (0-1, 2-6 and 6+), woman's age (<38, and 38-42 years), and collaborating centre. Randomisation will be into two study groups, acupuncture and a sham control. If a woman declines randomisation and she wishes to contribute data to the trial she will be allocated to the non randomised cohort arm of the study.

5.5.2 Treatment Allocation

Randomisation will be into two study groups, acupuncture, and sham acupuncture.

5.5.3 Emergency Unblinding Procedures

CI Smith is responsible for requesting emergency unblinding. The study randomisation code will only be unblinded if there is a serious medical or safety reason. For example, a serious adverse

event. In an emergency Ros Priest on 0449258902 should be contacted for unblinding. CI Smith will document the unblinding in a case report file.

5.5.4 Withdrawal procedures

If a participant expresses a desire to withdraw from the trial they can withdraw immediately. Treatment will cease in the two acupuncture groups.

Women will be requested to complete the measurement at the nearest time point following the last treatment.

If a subject withdraws during the intervention they will not be replaced. If they withdraw immediately following randomisation they will be replaced.

6. INVESTIGATIONAL THERAPY AND CONTROLS

Following randomisation women will see the acupuncturist based at the IVF centres, or at close proximity to the centres. Women will undergo a traditional Chinese medicine (TCM) diagnosis. The diagnosis and treatment will follow an agreed algorithm and will take 60-90 minutes[38]. This treatment will be administered day 6-8 of the stimulated cycle. Two subsequent treatments will be administered for 25 minutes on the day of ET, before and after ET.

6.1 ACUPUNCTURE

The initial treatment will be given according to a TCM diagnosis and will be based on an individualized treatment protocol**.** On the day of ET the acupuncture treatment based on the Paulus protocol[7] will be used. The first ET treatment will use: Pericardium 6, Spleen 8, Liver 3, Stomach 29, Conception Vessel 6 and Governing Vessel 20, and four auricular (ear) points. The second ET treatment will use acupuncture points Stomach 36, Spleen 6, and Spleen 10, and the same auricular points. The rationale for points used on the day of ET include points which regulate immune system responses in general, these include Stomach 36 and Colon 4, and reduce uterine contractility Spleen 6 and Spleen 10. The acupuncture points on the ears relate to the uterus and endocrine system and stimulate specific parts of the hippocampus. Other points relax the woman. Acupuncture will be applied bilaterally, with the exception of the ear points, where two points will be needled in the right ear, and the other two points needled in the left ear before treatment. Acupuncture needles will be inserted to tissue level and stimulated manually. The needles will be stimulated once more during this treatment session. There is little divergence in the published literature with respect to the frequency and stimulation of points for this treatment on the day of ET. Single-use disposable stainless steel needles (0.25 x 40mm for body acupuncture) will be used. All points will be located according to standard texts.

6.2 Sham control

The control group will use the Park sham needle[39] which has a retractable needle shaft, a blunt tip, skin penetration does not occur, and the needles have a supporting device. The acupuncturist will hold the “needle” in place with one hand, while moving the handle of the needle with the other hand, so the shaft disappears into the handle. The placebo needle will be placed away from acupuncture points and the protocol describing the location of these points used will be from our earlier research[8]. The Park needle is an effective device for blinding in RCTs[39]. A protocol will describe the location of non acupuncture points, these will be located away from the segmental location of the real points. Trials procedures as described for the real acupuncture group regarding duration, and interaction with the practitioner will be the same as for the placebo control group.

6.3 Standard care

Women will continue as normal. Consent will have been given to collect clinical outcome data and for women to complete the health economic diary (see below).

6.7 Prior and Concomitant Medications

6.7.1 Permitted Medications

Subjects will continue with all prescribed medication.

7. STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

Participants receiving the study intervention will be asked about how they are feeling at the start of each study intervention. Any adverse events or reactions associated with the intervention will be recorded on the patient case report file and to the principal investigator CI Smith. The investigator will exercise her scientific judgement in deciding whether an abnormal finding or other abnormal assessment is clinically significant. All adverse events (AE/SAE) reported between consent and final follow-up will be recorded in the adverse event page of case report form (CRF), regardless of relatedness to the study intervention. A safety monitoring committee will be convened to examine events.

7.2 STUDY ASSESSMENTS

Primary and secondary endpoints will be assessed at baseline, at 2 and 12 weeks. Clinical outcome data will be collected following the blood HcG test, clinical ultrasound and live birth.

Access to PBS and Medicare will be undertaken at the end of the study for all those women providing consent.

A sample of women from all sites will be invited to participate in an in-depth interview once the results of their pregnancy test are known.

8. DATA COLLECTION

The research nurse/co-ordinator employed at the IVF Unit will be responsible for data collection of the reproductive outcomes. This data is collected routinely by all IVF units. To ensure data collection on live births is timely, we will seek the women's permission to contact her following her expected date of delivery. Contact details will be collected from the woman and nominated contacts to advise on change of address, three monthly phone calls will be made to maximize retention and loss to follow up, this will be done by the trial co-ordinator.

The research nurse/co-ordinator will be responsible for administering questionnaires designed for self-completion at baseline. The trial co-ordinator will liaise with the research nurses at two and 14 weeks from trial entry to arrange posting of other repeat questionnaires. Women's quality of life will be assessed using the MOS Short Form 36 (SF36). The SF36 is the most widely used health status measure in the world and yields scores across eight health dimensions and two summary scores relating to physical and mental health[40,41]. The SF-6D scoring algorithm will be applied to generate utilities from responses to the SF-36[42]. To assess coping skills women will also be asked to complete the valid and reliable Infertility Self-Efficacy Scale[43]. It consists of 16 items that probe into the respondents perceptions about their ability to deal with various aspects of fertility treatment. The fertility problem inventory will assess fertility related stress and the STAI used to assess anxiety.

9. STATISTICS AND DATA ANALYSIS

9.1 PROPOSED ANALYSES

Data will be analysed by a statistician based at UWS. The statistician blind to study group will examine the reproductive, demographic and baseline characteristics of trial participants, and for imbalances at randomisation. Any imbalances at randomisation will be adjusted for in subsequent analysis. The analyses of the endpoints will undertake an 'intention to treat' approach and compare differences in the primary and secondary outcomes between groups. Comparisons of the primary and secondary endpoint will be made between groups by constructing odds ratios, and 95% confidence intervals based on differences in proportions between groups, and the number needed to treat. Sub group analyses will be stated *a priori*, for example influence of stimulation doses, long or short acting stimulation cycle. Levels of significance will be reported at $p<0.05$.

10. MONITORING AND QUALITY ASSURANCE

10.1 PROJECT MANAGEMENT AND TRIAL MANAGEMENT GROUP

A monthly management teleconference will be held with investigators and partners to examine trial recruitment accrual, data quality, compliance with the protocol and organization and implementation of the trial protocol. A data monitoring and safety monitoring committee will be established consisting of independent researchers/advisors to examine data for evidence of harm (e.g cancelled cycle).

11. GOOD CLINICAL PRACTICE MODULE

11.1 ETHICAL CONDUCT OF THE STUDY

The research has been approved by the UWS Human Research Ethics Committee, IVF Australia HREC, Greenslopes Private Hospital Human Research Ethics Committee, St Andrew's Hospital Ethics Committee, Southern Adelaide Flinders Clinical Human Ethics Committee, Melbourne IVF, Westmead HREC, Royal Women's Hospital, Health and Disability Ethics Committee Northern Region New Zealand, Albury Reproductive.

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