1. **Project Title**

The TUI study. The intrauterine insemination with stimulation in women with unexplained infertility: a randomised controlled trial.

1. **Chief Investigator**

 Chief Investigator: Prof Cynthia Farquhar, Fertility PLUS, Greenlane Clinical Centre, Auckland District Health Board and University of Auckland, New Zealand.

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1. **Background**

 Up to 20% of couples will experience infertility at some point in their lives. The TUI study aims to evaluate the effectiveness of a fertility treatment called intrauterine insemination (IUI) with stimulation. IUI with ovarian stimulation involves the women taking medication to ensure ovulation before introducing sperm directly into the uterus.. Currently knowledge around the effectiveness of this treatment in women with unexplained infertility and low chance of pregnancy (less than 30% chance) is unknown. In 2013 NICE guidelines released in the United Kingdom did not recommended stimulated IUI as the quality of evidence was low and there was no improvement in pregnancy outcomes

1. **Hypotheses to be tested**

 **Aim:**

 To evaluate whether intrauterine insemination with ovarian stimulation with clomiphene citrate results in improved pregnancy and live birth rates compared with expectant management for couples with unexplained infertility and a prediction score for spontaneous fertility of less than 30%.

 **Hypothesis:**

 That the use of intrauterine insemination (IUI) with ovarian stimulation with clomiphene citrate results in improved pregnancy and live birth rates compared with expectant management for couples with unexplained infertility and a prediction score for spontaneous fertility of less than 30%.

1. **Review of existing research**

 Assisted reproductive techniques (ART) offered by New Zealand and Australian fertility clinics includes intrauterine insemination in combination with ovarian stimulation with either clomiphene citrate or follicle stimulating hormone. This strategy is offered to couples with unexplained infertility factors.

 Intrauterine insemination is a simple, non-invasive and cost-effective technique where there is an intrauterine injection of 0.5ml of sperm suspension. Sperm are then able to swim up to meet with the egg in the fallopian tube. In natural conception, fertilisation occurs within the fallopian tubes. The addition of stimulation to IUI is important as a RCT of IUI without stimulation had the same outcomes as expectant management. ([Bhattacharya, Harrild et al. 2008](#_ENREF_1))

 However, the evidence base for offering IUI with stimulation is poor. A recent Cochrane review identified only one RCT of stimulated IUI compared with expectant management. ([Steures, van der Steeg et al. 2006](#_ENREF_4)) The ongoing pregnancy rate was 23% after 6 cycles of stimulated IUI and 27% in the expectant management group. However, the inclusion criteria for this study was a prediction score for spontaneous fertility of >30%. This excluded the majority of women who would undergo IUI with stimulation in New Zealand. The Cochrane review also identified multiple evidence gaps including several important outcomes that were not reported consistently across many studies including live birth rate, ovarian hyperstimulation syndrome and miscarriage.([Veltman-Verhulst, Cohlen et al. 2012](#_ENREF_6))

 The National Institute for Health and Clinical Excellence has recently released updated draft guidelines on fertility.([NICE 2012](#_ENREF_3)) The recommendations concluded “that IUI with stimulation should not be recommended in any situation.” The reasoning behind the recommendation was the low quality of evidence from two trials ([Tummon, Asher et al. 1997](#_ENREF_5); [Steures, van der Steeg et al. 2006](#_ENREF_4)) that showed no difference between IUI with stimulation and the concern that multiple pregnancies may be increased. However, a RCT of unstimulated IUI compared with expectant management also did not report an improved pregnancy rate. ([Bhattacharya, Harrild et al. 2008](#_ENREF_1)) This leaves women and clinicians in a difficult position as there is little evidence to support any strategy for recommending to women IUI with or without stimulation. Yet the study by Steures was in couples who had 30-40% prediction for spontaneous pregnancy in the next 12 months. These women are not necessarily the same couples who we offer IUI to in New Zealand. Our clinic (Fertility PLUS) in Auckland has previously considered the prediction scores in women with unexplained infertility and found that 40% had scores <30%.([Farquhar, van den Boogaard et al. 2011](#_ENREF_2))

 Our response to this gap in evidence is to undertake a further randomised controlled trial of IUI with ovarian stimulation in couples with spontaneous pregnancy prediction score of <30%. This is more likely to reflect the New Zealand population of women with unexplained infertility who are currently recommended stimulated IUI as they wait for public funding of IVF to become available to them. This study will provide evidence as to whether IUI with stimulation is an effective,. less invasive and cost effective alternative to IVF.

 This study aims to conduct a randomised controlled trial to compare stimulated IUI with expectant management in women with unexplained infertility who have a prediction score for spontaneous pregnancy in the next 12 months of less than 30%.

1. **Experimental Design**

#####  Methodology:

 A randomised controlled trial of women with unexplained infertility will be undertaken.

 Women will be randomised to either 3 cycles of IUI with either clomiphene citrate or expectant management for 3 months. The trial will be coordinated by Professor Cindy Farquhar at the University of Auckland.

**Recruitment:**

 Following approval by the Ministry of Health Ethics Committee, women with unexplained infertility attending Fertility PLUS, Repromed and Fertility Associates who wish to have intrauterine insemination will be advised of the study and encouraged to take part. The patients will be given written information about IUI and the study and will be given an opportunity to consider taking part. A consent form will then be signed by the participant.

 Approximately 200 women are seen at Fertility PLUS each year for at least one cycle of IUI. This number is increasing as the waiting time for publicly funded IVF cycles has increased from two months to nine months, and patients with unexplained infertility are looking for other options during the waiting time. The other two Auckland clinics will also be asked to take part in the study.

 Inclusion criteria:

* Women with unexplained infertility
* Normal ovulation (or normal with the assistance of clomiphene)
* Patent fallopian tubes
* Normal semen analysis (WHO Laboratory Manual 5th edition 2009)
	+ Progressive motility ≥ 32%, conc. ≥15million/ml
* BMI < 35
* Prediction score < 30%
* Women with previous attempts at IUI or IVF will be included.

**Exclusion criteria:**

* Documented tubal occlusion (bilateral or unilateral)
* Greater than 3 follicles on USS (exclusion on the day of ultrasound)
* Azoospermia
* Women with anovulation secondary to polycystic ovarian syndrome.
* >41 years old

 **Randomisation and Blinding:**

 This is an open randomised trial. The allocation will be concealed to both the patient and the clinicians but once the treatment has been allocated then the patients and the clinicians will be aware of the treatment allocation at the time of randomisation.

 Third party randomisation will be performed using computer-generated randomisation with the assistance of the University of Auckland Clinical Trials Research Unit. Sealed, sequentially numbered and opaque envelopes were opened by a researcher at another site once the inclusion criteria and signed consent form was received.

**Treatment:**

 Women will be randomised to one of two groups:

1. Three cycles of stimulated intrauterine insemination (0.5ml of sperm suspension)

 Clomiphene citrate ovarian stimulation protocols will be used. A dose of clomiphene citrate will be started on day 2 of the menstrual cycle for 5 days. Around day 12 an estradiol level and ultrasound scan (USS) will be performed. If there are more than 3 follicles present the IUI will not proceed and the patient will be informed not to be sexually active. If this occurs, then the next cycle will be considered the 1st cycle and Clomiphene dose adjusted.

 A catheter will be used for the IUI procedure. The inseminate will be prepared using a density gradient and spermatozoa will be re-suspended in 0.5 ml of human tubal fluid. The catheter will be passed through the cervical canal high up into the uterus and the specimen slowly injected. No luteal phase support will be given.

1. Expectant management

 Couples assigned expectant management will be followed for three menstrual cycles from the time of randomisation. No additional treatment would occur during this time.

 ***Data collection and outcome measures***

 The following data will be collected:

* + Demographic data on age, ethnicity, number of previous pregnancies and number of previous treatment cycles, duration of infertility.
	+ Treatment related data including day 12 oestrogen level, number of follicles >16mm diameter on day 12 USS, dose of clomiphene, fresh or frozen sperm
	+ Quantitative β-hcg level Day 16 post procedure and Anti-Müllerian hormone
	+ USS 6 weeks (+/- fetal heart)
	+ Pregnancy details
	+ Birth details including birthweight and gestation, well being of the infant.

 Primary outcome

 Cumulative birth per couple over three completed cycles

 Secondary outcomes

* + Clinical pregnancies – gestation sac
	+ Ectopic pregnancy/Miscarriage
	+ Multiple pregnancy rates
	+ Ovarian hyperstimulation syndrome

#### Methods of Data Analysis:

For dichotomous variables such as live birth rate, the test of statistical significance will be the chi-squared test; for continuous variables such as number of follicles and birth weight, statistical analysis will be a student’s t-test for normally distributed data, or a Wilcoxon rank sum test for non-parametric data.

The primary analysis is live birth after 3 cycles of expectant management and 3 cycles of IUI. The primary analysis will be live birth by per protocol but an intention to treat analysis will also be undertaken.

Protocol addendum following DSMB report March 2014: three cycles of expectant management were timed from the current if before day 5 or next menstrual period. The women who are randomised to IUI and don’t undergo IUI in the next cycle (eg. because of scheduling difficulties, holidays) three cycles of IUI still need to be completed and any non IUI related pregnancies will be reported but not included in the analysis. Women who are subsequently found to be pregnant at the time of randomisation were not included in the analysis as technically they were in ineligible. Because of some pregnancies occurring before treatment started then from this time all women were randomised on day 1 of their 1st study cycle.

 **Power Calculations**

The primary outcome measure is an increase in the expected live birth rate per couple, from an estimated 6% for expectant management for three months to 25% in three cycles of stimulated IUI. These estimates are based on the results from the prediction model studies conducted in New Zealand and the stimulated IUI rates at Fertility PLUS.

The 6% expectant cumulative live birth rate over three months is derived from the women at the Fertility PLUS with a prediction score less than 30%, where only 22% subsequently conceived spontaneously over a 2 year period (Farquhar 2011). For the stimulated IUI rate we have based this on the 2011 from Fertility PLUS 10% live birth rate per cycle for couples (<41 years of age) undergoing stimulated IUI at Fertility PLUS and for three months estimated this to be a cumulative live birth rate of 22%. In order to have 80% power to detect a difference between the two treatment groups at the 5% level and allowing for 5% dropouts or losses to follow-up we need 80 women in each treatment group. See table below where the cumulative live birth rate with 80 women is 26% but we have taken the more cautious cumulative live birth rate of 22%. Therefore it is planned to randomise a total of 160 women.

**Table 1:** Estimated numbers of cumulative live births using a 10% live birth rate per cycle with IUI and 2% live birth rate with expectant management

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Stimulated IUI | Live births | Expectant management | Live births |
| 1st cycle | 80 women | 8 | 80 | 2 |
| 2nd cycle | 72 women | 7 | 78 | 2 |
| 3rd cycle | 65 women | 7 | 76 | 2 |
| Cumulative live birth rate | 26%  | 8% |

 **Endpoints for research**

The cumulative live birth rate for 3 months will be the major endpoint.

**8. Ethics approval**

HDEC ethical approval has been given.

1. **Reference list**

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