Pregnancy Maintenance Trial (PMTrial)

1.TITLE

Formal - In pregnant women with previous subfertility, does progesterone supplementation decrease the likelihood of miscarriage?

Lay Title – Does using progesterone reduce the miscarriage rate for subfertile women?

Short Title – Pregnancy Maintenance Trial – PMTrial

2. ABSTRACT

This research will involve a population of pregnant women with a history of subfertility.

This trial will investigate progesterone as a therapy to decrease the likelihood of miscarriage. Participants will be randomly allocated to nightly progesterone or placebo pessaries during the first trimester of pregnancy.

3. SUMMARY

Public title
Does using progesterone reduce the miscarriage rate in high risk pregnancies?

Study title
In pregnant women with previous subfertility and recurrent unexplained miscarriages, does progesterone support/supplementation decrease the likelihood of miscarriage?

Title acronym
PMTrial

Health condition to be studied
Miscarriage, in previously subfertile women (including those with recurrent unexplained miscarriage).

Description of intervention and control treatment

Interventions – 400 mg progesterone as vaginal pessaries, until 12 weeks and 0 days
Control – placebo vaginal pessaries, until 12 weeks and 0 days

Primary outcome
Miscarriage

Key secondary outcomes
Live birth, Gestation at birth, Birth weight, Congenital anomaly, Threatened miscarriage

Key inclusion criteria
Pregnant women under 7 weeks and 0 days gestation, conceiving on PATrial 2 (luteal phase defects) ***or*** PATrial 3 (anovulation) ***or*** with a history of 3 or more previous miscarriages

Key exclusion criteria
Women who are pregnant as a result of assisted reproductive technologies (ART), women conceiving on PATrial 1 (no luteal phase defect), women with threatened miscarriage

Study type
Randomised, placebo-controlled trial

Purpose of study
To determine if the likelihood of miscarriage is decreased by the use of progesterone supplementation in early pregnancy, in a population of woman at higher risk of miscarriage.

Allocation to intervention
A computer-generated variable block randomisation, allocated sequentially by a blinded third party.

Blinding status
Participants, Investigators and Pharmacists will be blinded to both 'therapy' arms

Control group (placebo or active treatment)
Control group – placebo pessaries

Assignment
Once pregnancy established by a positive urine (>25 nmol/l) or serum bHCG, and expected gestational age calculated by LNMP (if regular cycles) or ultrasound if irregular cycles, participant is randomly assigned to study arm

Anticipated start date
Aug 2011

Target sample size
344 women

Funding sources
Principal Investigator – current Mothers' and Babies Golden Casket Clinical Fellowship.

Primary sponsor
Mater Mothers' Hospital

Secondary sponsor
Nil presently

Ethics approval Mater Health Service Human Research Ethics Committee (pending)

4. INTRODUCTION

Background, health impact and justification

Pregnant women who have previously experienced subfertility are more likely to experience both early and late pregnancy complications. They are more likely to experience a miscarriage in this pregnancy(1) and to have experienced a previous miscarriage(2). They are more likely to be diagnosed with adverse obstetric outcomes including hypertensive disorders of pregnancy, preterm birth and perinatal death(3). Similarly, those who experience recurrent unexplained miscarriage seem to be part of a clinical spectrum encompassing subfertility and late pregnancy complications (3, 4). Miscarriage rates in the previously subfertile population are reported to be approximately 18% for women with unexplained subfertility who spontaneously conceive(5), 27% for subfertile women with endometriosis(6), 42-58% for subfertile women with PCOS(1), and 65% (7) to 76% (8) for women with recurrent unexplained miscarriage of unknown aetiology. The pathophysiology of miscarriage in subfertile women is complex and includes anatomic, genetic and molecular abnormalities, endocrine disorders, thrombophilias and anti-phospholipid syndrome. The literature describes that subfertile women have an increased time to pregnancy (TTP), experiencing increased rates of miscarriage, extra-uterine pregnancy and preterm birth rates (9-11).

Progesterone is important for the establishment and maintenance of pregnancy. Its presence creates a mature endometrium and a favourable immune environment for early embryonic development. Low serum progesterone has been shown to be an independent risk factor for miscarriage in women with no obvious risk factors for pregnancy loss (12). Those who experience recurrent unexplained miscarriage have been shown to have particularly low endometrial progesterone levels(13). Progesterone fosters a favourable imunomodulatory environment through the action of Progesterone Induced Blocking Factor (PIBF). This PIBF acts on lymphocytes in the pregnant woman to induce a favourable cytokine shift from pro to anti-inflammatory(14). The literature supports progesterone as a potent inducer of these anti-inflammatory Th2-type cytokines(15, 16). These cytokines are known to be involved in the interstitial and endothelial trophoblast invasion made by the placenta, and may account for an association of low progesterone or luteal phase defects with late pregnancy complications(17). The utilisation of mifepristone (RU486), an anti-progesterone used for the medical termination of pregnancy, highlights the importance of adequate progesterone for the successful carriage of pregnancy. Human experience and animal models show significant to universal miscarriage rates when the corpus luteum is surgically excised in early pregnancy giving suboptimal progesterone levels(18, 19).

Clinically, this inadequate progesterone level at the time of expected corpus luteum production is known as luteal phase defect. Of subfertile women with a luteal phase defect, previous non-randomised studies have reported pregnancy rates of 30-81% with appropriate progesterone supplementation(20-26). This supplementation has been given by various routes, doses and durations. There is only one RCT to date that has reported(27) on progesterone treatment for the support of the luteal phase in natural conception cycles.

The existence of a luteal phase defect is reported extensively in the ART literature where the preceding cycle has been downregulated. A crucial aspect in the provision of therapy for an ART treatment cycle is the use of progesterone or hCG for support of the luteal phase and the early pregnancy(28) and typically progesterone support is used in ART treatment cycles until 10-12 weeks gestation. Presently vaginal progesterone is considered the therapy of choice for women undergoing ART treatment, (29)

where it has been shown to increase the initial and ongoing pregnancy rate. A small, poorly powered study (30) showed no difference in the miscarriage rate with only 14 days of luteal phase support versus a control group. A meta-analysis of five trials showed a non-significant trend (RR 0.52 CI 0.23 – 1.18) away from miscarriage with luteal phase support in non-stimulated ART embryo transfer cycles, however, again the numbers of participants (125 total) in the review were small (27).

In the naturally cycling woman the presence of a luteal phase defect has been reported(31), however the clinical application of this diagnosis is contentious(32). In those who have experienced subfertility and recurrent unexplained miscarriages, up to 40% have been shown to have menstrual cycles with a deficient luteal phase(33). Very little formal research has been undertaken in this area. Observational studies have reported good pregnancy outcomes after supportive progesterone treatment in women with recurrent unexplained miscarriage(34, 35).

There is some evidence supporting the use of progesterone supplementation in women with recurrent unexplained miscarriage. The Cochrane review reported a benefit for the subgroup of women who had experienced recurrent unexplained miscarriages(36). Of note, the four randomised controlled trials in the sub-group analysis used different types and dosages of progestins. Only one of the four included trials was conducted since the advent of clinical ultrasound(37). This trial used a progesterone analogue, dydrogesterone. This drug has been shown not to be as favourable on the uteroplacental circulation in the early pregnancy(38) and less anti-androgenic(39) when compared with progesterone. This review called for more trials in this particular area of miscarriage prevention. This call has been echoed by others in the field(40, 41). Recently a RANZCOG College statement(42) called for, and encouraged more research in this area of progesterone support of the luteal phase and early pregnancy.

Caution needs to be exercised in using hormones in the early embryological and organogenesis stage of development. There has been concern regarding the use of progestins in pregnancy, particularly with respect to the potential for genital (hypospadias/female virilisation) and non-genital anomalies. The progestins, norethindrone and ethisterone are the two most frequently implicated in the literature, and these were used extensively in the past for the diagnosis of early pregnancy. Progestins (all forms) have been shown to approximately double the background risk (approx 0.5%) of hypospadias in a recent population based study(43). This is equivalent to the hypospadias risk to infants of mothers over 40 years or with pre-existing diabetes(44). This is in contrast to the specific analysis of progesterone and 17-hydroxy progesterone which has not been shown to have any significant teratogenic effects in large cohort and case-control studies, involving 17,695 women(35, 45-48). A meta-analysis(49) of 14 studies, involving 65,567 women, concluded there was no association between first-trimester sex hormone exposure and external genital malformations.

Given the pharmacological heterogeneity of the progestins, the FDA in 1999 revoked its single class labeling of them(50) and similarly the Australian Drug Evaluation Committee has classified progesterone as a Category A drug(51), being without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus. Progesterone has been used in several studies for the prevention of preterm birth (52-54), and recently approved in February 2011 for this indication by the FDA.

We have included a depression anxiety stress scale (DASS 21) as a tool to determine whether this therapy is of benefit, or atleast no harm psychologically to the previously subfertile population. Subfertility and previous miscarriage have been shown to be associated with higher levels of

depression and anxiety (55, 56) and the DASS 21 tool correlates well with other psychometric property tests designed to elucidate depression and anxiety in these populations (57). There is also some evidence that progesterone may possess some anxiolytic properties through it's effect on the cerebral GABA receptor (58).

Miscarriage rates are higher for all causes of previous subfertility. It is plausible progesterone is effective in decreasing the miscarriage rate by a combination of hormonal, endometrial and imunomodulatory means enhancing appropriate placentation. Progesterone has been shown to be effective in spontaneous conceptions in non-controlled trials, and a possible effective trend shown in small randomised controlled trials. Progesterone as luteal phase support is beneficial where there has been a history of recurrent unexplained miscarriages, but the need for larger trials has been identified. In ART, progesterone is the preferred luteal phase support required to enhance ongoing pregnancy rates. Our area of interest in this study looks at the use of progesterone to support previously subfertile women, presenting in early pregnancy.

5. SPECIFIC OBJECTIVES AND HYPOTHESES

Aim
This project will assess the effect of progesterone therapy on pregnancy outcomes in women previously diagnosed with subfertility.

Hypothesis
Vaginal progesterone supplementation in early pregnancy decreases the likelihood of miscarriage and possibly later pregnancy complications, in women with previous subfertility due to anovulation, luteal phase defect or recurrent unexplained miscarriage.

6. DESIGN

A randomised placebo-controlled trial involving pregnant, previously subfertile women.

7. PARTICIPANTS

Source of participants
Couples will be recruited to this fertility research trial from the following locations:

a) Fertility Assessment and Research Clinic;
b) Early Pregnancy Assessment unit of the MMH;
c) Natural Fertility Services unit of the MMH;
d) Gynaecology outpatients;
e) General Practitioners; or
f) self-referral

The trial will be co-ordinated by staff of the Fertility Assessment and Research Clinic.

Number of centres involved
Single centre – Mater Mothers' Hospital, South Brisbane

Inclusion criteria

- Women who have conceived whilst on PATrial 2 (having pre-existing luteal phase defect) ***or***
- Women who have conceived whilst on PATrial 3 (previous anovulation) ***or***
- Pregnant women with a history of 3 or more miscarriages, ***and***

- Pregnancy duration of less than 7 weeks + 0 days determined by
  - (in women with regular menstrual cycles): last normal menstrual period commenced less than 49 days ago
  - (in women whose menstrual cycles which vary in length by more than 4 days): an ultrasound scan to confirm the gestation of the pregnancy, as per normal dating scan.

Exclusion criteria

- Women who are pregnant as a result of assisted reproductive technologies (ART)
- Women with threatened miscarriage
- Women who have conceived whilst on PATrial 1 (having had a normal luteal phase and not expected to benefit from hormonal support in early pregnancy)

Neither minority groups nor NESB/LOTE persons will be excluded provided they possess the capacity (ie ability to understand, retain, comprehend and dutifully consider a response) to consent.

8. INTERVENTION AND COMPARATOR

Intervention and Comparator

Intervention – Progesterone pessaries (400 mg PV nocte) until 12 weeks + 0 days.
Comparator – Placebo pessaries until 12 weeks + 0 days.

9. RCT METHODS

Randomisation will be according to computer-generated variable block randomization, stratified by women with subfertility (including anovulation or luteal phase defect) OR recurrent unexplained miscarriage. A printed allocation list prepared by MMRI will be stored in the hospital pharmacy. After written consent is obtained a 'script' will be written for the participant (by study number) by the research team. The pharmacist after obtaining the written prescription will dispense the next allocated therapy according to the allocation list.

Participants, investigators and pharmacists will be blinded to treatment allocation.

Participants will be able to request information about the clinical findings upon the trial's completion.

10. OUTCOMES

PRIMARY OUTCOME

The primary outcome of this trial is miscarriage.

Miscarriage is defined as one or more of the following:

- A crown-lump length or embryonic pole of 6 mm or more without evidence of cardiac activity;
- A gestation sac with a mean diameter of at least 20 mm (on transvaginal ultrasound) or 25 mm (on transabdominal ultrasound) without a fetal pole present;
- A gestational sac with a mean diameter of at least 10 mm (on transvaginal ultrasound) without a yolk sac present;
- Growth of a gestational sac by less than 2 mm over a five day period or less than 3 mm over a seven day period with no fetal pole identified;
- The complete passing of a pregnancy (up to 22 weeks + 6 days of pregnancy) by natural means. Medical and surgical means of passage, if any one of the above criteria have been met prior to intervention.

SECONDARY OUTCOMES (see criteria for outcomes at Section 23)

Live birth
Gestation at birth
Preterm birth
Preterm premature rupture of membranes
Threatened preterm labour
Antepartum haemorrhage
Birth weight
Small for gestational age
Congenital anomaly
Nursery admission
Neonatal mortality
Mode of delivery
Threatened miscarriage
Ectopic pregnancy
DASS 21 questionnaire scores
Postnatal depression
Gestational diabetes
Venous thromboembolism
Pre-eclampsia
Gestational hypertension

Descriptive comparisons

Baseline characteristics will be recorded based on the following pieces of data collected.

Medical History form (Attachment 1)
Enrolment form (Attachment 2)
Depression Anxiety Stress Scale (DASS)-21 questionnaire (Attachment 3, pre/post)

Therapy and pregnancy outcome information will be collected from the following pieces of data.

Pregnancy outcome form (Attachment 4)

Additional data collected

Serum progesterone levels will be performed at/on initial antenatal bloods.

11. SAMPLE SIZE CALCULATION

Participants will be stratified according to subfertility (pre-existing luteal phase defect, anovulation) OR recurrent unexplained miscarriage history.

Confidence levels, p-value and power

Type 1 (p-value) of <0.05 and Power 80%.

Assumptions

PMT – subfertility. Subfertility (including due to anovulation and luteal phase defect) have an expected miscarriage rate of 32%, which if treated with progesterone would be expected to fall to 16%(1, 6, 59, 60). This requires 111 women per arm.

PMT – recurrent unexplained. Idiopathic recurrent unexplained miscarriage population have an average subsequent miscarriage rate of 52%, which if treated with progesterone is expected to fall to 23%(5, 7, 8, 37, 61, 62). This requires 44 women per arm.

Recruitment

We hypothesise that 100% of pregnant women seen through the Fertility Assessment and Research Clinic (FAR Clinic) will be eligible for recruitment and that 95% of these will consent to participate (given the Natural Fertility Services previous clinical experience).

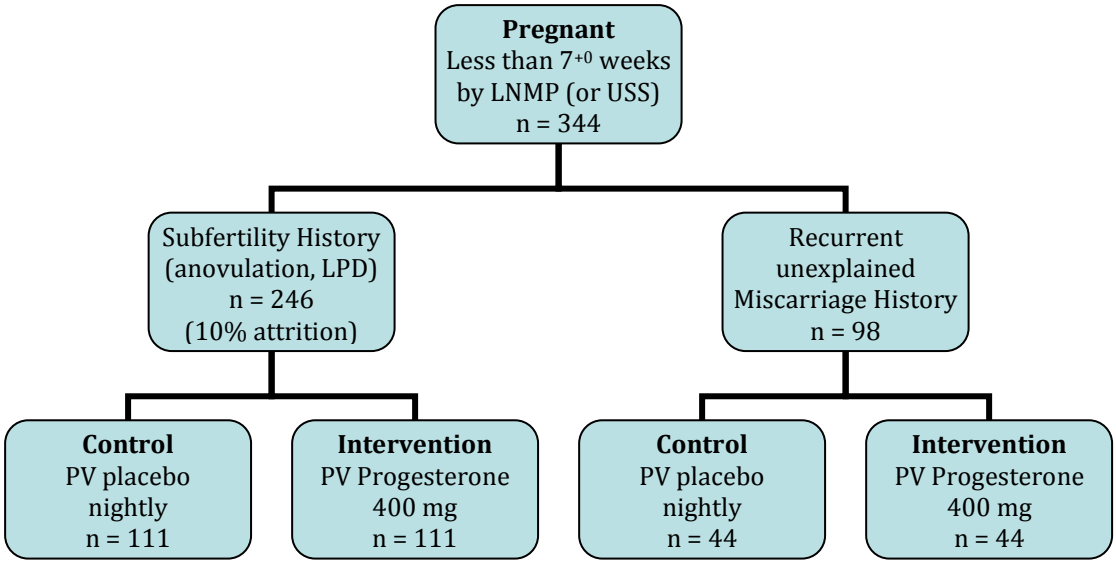
In addition, we anticipate that 85% of those who present via other referral sources will be eligible for recruitment, of whom 90% will consent to participate.

Attrition

We hypothesise that 10% of women will be non-compliant or lost to follow-up at 12 weeks.

Overall sample size

Based on sample size calculation, and recruitment and attrition estimates, the overall sample size of this trial is 344 women. (This will require at least 363 pregnant women to present to the Fertility Assessment and Research Clinic for consideration of PMTrial participation).



12. RECRUITMENT

Participant recruitment

Recruitment will be conducted over 18 months from mid 2011. Clinical staff will be made aware of the trial through education sessions and staff in-service.

The research midwife will keep a Research Log of all potentially eligible participants and the reasons for participation or not as per CONSORT guidelines.

Detail of the recruitment and participation process follows:

a. **Phone call (or attendance)** explaining and welcoming to FAR Clinic and highlighting the research nature of the service. Appointments will be made as soon as possible, and potential trial recruits will be emailed, faxed or posted a Participant Information Sheet (Attachment 5), and Standardised history (Attachment 1). A research log entry will be initiated.

For the majority of women who were receiving care under the FAR Clinic prior to conception, they will have been introduced to the PMTrial and will have completed the Standardised history (Attachment 1) and already have received the Participant Information Sheet (Attachment 5) during their previous care program.

b. **Doctor or Research Midwife Consultation**

Standardised history (Attachment 1) receipt, and review of recent results
Routine antenatal bloods requested if not performed, copy to primary care physician
Confirm gestational age, arrange ultrasound if previous irregular cycles/unknown dates
Offer and discussion of PMTrial, clarification of maternal wishes
Enrolment form completed, if appropriate
Consent form (Attachment 6) for study participation signed, and copy given to participant
Randomisation occurs as per Section 9 above. (RCT Methods)
Study number allocated, with appropriate suffix (if not already in PATrial)
'Prescription' written including study number, and sent with patient to hospital pharmacy

c. Women who decline participation

If a woman declines participation in the trial, she will receive usual antenatal care with her primary healthcare provider and referral to a health facility as per usual referral guidelines.

Women will be informed that non-participation will mean that early pregnancy progesterone supplementation is not able to be offered.

Conversely, women who are on trial are not automatically provided antenatal care at the Mater Mothers' Hospital. Their usual primary care provider will be responsible for coordinating her antenatal care referral.

13. STUDY PROCEDURE

Once a woman has been recruited, she will fill her prescriptions on a 20 day basis.
Pack size is 20 pessaries.

Both intervention and control groups will be able to make contact with the research midwives at any time, and will be given a card detailing relevant contact details and their study number.

Women will be particularly encouraged to make contact with the Research midwives should they feel they are experiencing a miscarriage.

Early endpoint

a) If a woman declines further participation, this is to be recorded and a short withdrawal questionnaire (Attachment 7) completed if the woman is agreeable. Pregnancy outcome will be sourced for Intention To Treat (ITT) data analysis.
b) Lost to follow-up, this is to be recorded and the reason for loss noted.

Endpoint achieved

a) Completion of Intervention (12 weeks + 0 days gestation)
   Phone appointment at 12/40
   DASS 21 questionnaire administered (Attachment 3)
   Completion Questionnaire (Attachment 8)
   Follow-up by phone appointment at 32/40, and 4 weeks postpartum
   Pregnancy Outcome form (Attachment 4) completion

b) Completion of Trial (miscarriage)
   Completion questionnaire (Attachment 8) and DASS 21 (Attachment 3)

Participant withdrawals

Participants can voluntarily withdraw at any point in the trial, and are requested to notify the research midwife or principal investigator. In the situation that a woman withdraws from trial, outcome measures (obtainable from routinely collected data/medical files) will be analysed in the group to which she was randomly allocated unless the woman asks for her data not to be used. If this specific request is made,

a woman's trial chart will be marked accordingly to ensure her request is followed through, and data removed prior to data analysis being undertaken.

Participants will be considered withdrawn if they undertake any specialised treatment utilising additional hormonal support.
Where the withdrawing woman is agreeable, and to assist with maintaining the quality of the clinical service, a short withdrawal questionnaire (Attachment 7), involving a DASS 21 assessment (Appendix 3), will be requested.

A Research Log recording numbers of recruits will be kept in the Fertility Assessment and Research Clinic.
This Clinic will have available a User's Guide: comprising a copy of this Protocol, Appendices and a master copy set of forms.
Participant's primary care physicians will be informed in writing about their patient's involvement in trial at the time of randomisation.

14. DATA MANAGEMENT

Data collection is as follows:

Recruitment Phase	Medical History DASS 21 questionnaire Confirm pregnancy and gestation Request additional investigations - bloods/ultrasound if required
Enrolment Phase	Enrolment checklist and recording results
Completion Phase	Pregnancy Outcome form (at 4 weeks postpartum for continuing pregnancy) Completion questionnaire (miscarriage) Withdrawal questionnaire (withdrawal) DASS 21 questionnaire, administered for all the above categories

The above required data tools will be in a trial portable organizer, the research team is responsible for the timely and accurate collection of data.

The couple will be given an individual trial folder in which to store relevant paperwork and pathology request forms.

A Staff Information Sheet (Attachment 9) will be kept in the front of the woman's medical file. This trial sheet will be identified by hospital UR/address sticker.

Any specific trial data will be stored in a locked cupboard, or password protected electronic database only accessible by staff ordinarily having access to patient's medical information.
Data collected will be progressively entered into a password protected clinical Access database and 'journey log' Excel spreadsheet, to allow subsequent statistical analysis.

Computerised data input will be identified by hospital unit record number and study number.
The principal investigator will randomly check the accuracy of the data entered during the course of the trial. Accuracy will be confirmed by the investigation team just prior to analysis.

15. DATA ANALYSIS

All analysis will be by intention to treat. Statistical analyses of the data will be performed by the investigators with support from the Clinical Research Support Unit of the MMRI.

Data will be summarized according to epidemiological and clinical risk factors and other baseline characteristics, clinical presentation, laboratory findings, and outcome appropriate summary statistics. The first step of the analysis will be to assess the adequacy of the randomisation process by comparing demographics of each of the arms of the PMTrial. If important imbalances exist, multivariate analysis may be required. Statistical analysis will be by intention to treat for all outcome measures. Categorical data will be analysed using chi-squared and presented as relative risks. Student-t test will be used for data presented on a continuous scale, including the DASS-21 scores. Subgroup analyses will be undertaken including nature of subfertility (anovulation, luteal phase defect, recurrent unexplained miscarriage), primary or secondary subfertility, maternal age, and gestation at recruitment.

16. DATA MONITORING AND INTERIM ANALYSIS

Interim analysis

It is planned to perform a third-party blinded interim analysis after enrolment has reached 200 participants, this will assess efficacy and ensure sample size calculations are appropriate. The data safety monitoring committee will be informed of any changes after this analysis.

Data monitoring and quality control measures

A Data Safety Monitoring Committee (DSMC) will meet on a three monthly basis, or urgently as required. The committee will be made up of two speciality-related clinicians and an allied health representative (preferably pharmacist). A biostatistician will be recruited to assist with interim analysis to be forwarded to the DSMC.

The DSMC will be given clear directives and expectations from the research team, these will include but not be limited by:

a) stopping and discontinuation rules where;

Risks have been demonstrated to outweigh benefit, or
No clear benefit has been demonstrated, and
Recruitment/funding is not sustained.

b) handling of adverse events process where; and

Any trial associated team member becomes aware of any real or perceived harm or adverse event, the DSMC and Principal Investigator should be informed in a timely manner.

c) an adverse event being notified to the Data safety monitoring committee and/or the Principal Investigator, whereupon:

The nature of the adverse event will be appraised;
The patient/s involved will be removed from further harm;
A thorough investigation will be performed;
Specific expert opinion may be drawn upon;
The DSMC may convene an early meeting; and
The Principal Investigator will be informed of findings in a timely manner.

The expectations of the Mater Health Services HREC will be met with the appropriate and timely completion and forwarding of SAE (severe adverse event) templates. A TGA product is being used in trial, the company of production will be notified and an ADRAC report will be completed and forwarded.

17. ETHICAL CONSIDERATIONS

Patients will be informed clearly of the existence of such a trial upon engaging with the service, prior to their first visit. They are informed as far in advance as possible. Ideally for those participating in the PATrial, they will be informed at a number of points in their care pathway prior to being required to make an enrolment decision. The trial follow-up plan and formal commitment is made clear prior to consent.

Patients are offered voluntary participation in the trial. There will be no out-of-pocket expense for trial participants. Participants are informed of the random allocation to intervention or placebo arms. They are also made aware that their non-participation will not impact on their ongoing care received within Mater Health Services, or any other health facility that their primary healthcare provider may refer them to for ongoing antenatal care.

The trial participants will be informed prior to consent, that withdrawal can be requested at any point in time throughout the trial noting that their outcomes will be analysed as per randomisation. Unless there is a specific request from the participant to withdraw all data collected in trial.

Informed consent is gained after a woman's perusal of the Participant Information sheet (Attachment 5) and Consent form (Attachment 6).

18. RESOURCES AND STAFFING REQUIREMENTS

The budget presented below was submitted at the time of the Pregnancy Achieving Trial protocol submission. This was set out inclusive of the Pregnancy Maintenance Trial workload and expenses.

Budget

Salaries and wages	FTE plus Relief	**Cost for 20 months**
Nursing Research Assistant	0.32	$49,756
Clerical A03-4	0.47	$53,572
Principal Investigator	0.50	In Kind
Co-Investigator	0.20	In Kind
Total S&W costs		**$103,328**
Non Salary & Wages		
Pathology costs	2 samples for 306 ie 712 @ $15	$11,308
Drug costs	Paid as per Pharmacy agreement dated 18 April 2011	$100,000
Printing and Stationary		$10,000
Telephone/Computer expenses		$2,000
Thermometers	500 @ $7.30	$3,648
Other non S&W expenses		$5,000
Total Non S&W costs		**$131,956**

Grand Total Expenses		**$235,284**
Income		
Bishop's Funding	456 couples @ $146	$88,879
CRAQ external funding		$8,700
Thermometer (purchased by couples)		$6,080
Initial consultation with woman and partner	456 couples @ $191.94	$87,528
Review consultation	456 consultations @ $108.25	$49,360
		$240,547

Justification of budget

The cost of trial will be funded through income generated from the work-up and investigation of a larger cohort of subfertile women through the Mater's Fertility Assessment and Research clinic. This budget has the support of the medical and midwifery Directors of the Mater Mothers' Hospitals.

19. IMPLEMENTATION PLAN

Timetable

Project Start Date	6/08/2011 - Anticipated
Project Completion Date	6/01/2013 - Anticipated
Data Collection / Recruitment Date	6/08/2011 - Anticipated
Data Analysis Date	6/08/2013 - Anticipated
Publication Date	6/06/2014 - Anticipated

Pilot studies required

The provision and process of this trial aligns closely with that previously offered by the Natural Fertility Services. As such a pilot trial is not considered necessary.

Funding requested

The Principal Investigator is the recipient of a Mater Mothers and Babies Golden Casket Fellowship which will assist in the undertaking of this trial.

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21. Glossary for PMTrial Protocol

ADRAC – Adverse Drug Reaction And Complication
ART – Assisted Reproductive Technologies
CONSORT - Consolidated Standards of Reporting Trials
FAR Clinic – Fertility Assessment and Research Clinic
FDA – Food and Drug Administration
HCG – Human Chorionic Gonadotrophin
HREC – Human Research and Ethics Committee
IVF – In Vitro Fertilisation
LOTE – Language other than English
MMH – Mater Mothers' Hospital
MMRI – Mater Medical Research Institute
NESB – Non English speaking background
PATrial – Pregnancy Achieving Trial
PIBF – Progesterone Induced Blocking Factor
RANZCOG – Royal Australian and New Zealand College of Obstetricians and Gynaecologists

TGA – Therapeutic Goods Administration
TTP- Time to pregnancy
WHO – World Health Organisation

22. APPENDICES

1. Medical History form
2. Enrolment form
3. DASS 21 Questionnaire
4. Pregnancy Outcome form
5. Participant Information sheet
6. Consent form
7. Withdrawal questionnaire
8. Completion questionnaire
9. Staff Information Sheet

23. SECONDARY OUTCOME DEFINITIONS

Live birth - as the birth of a neonate of more than 23 weeks + 0 days, showing signs of life
Gestation at birth – will be recorded in completed weeks and days from the most accurate antenatal dating method available
Preterm birth – birth recorded at gestation below 37 completed weeks, sub-analysis of gestations under 28 weeks, 28 – 33 weeks, above 33 weeks.
Preterm premature rupture of membranes – clinically confirmed rupture of membranes at less than 37 completed weeks of pregnancy
Threatened preterm labour - requiring presentation to hospital *AND* positive fetal fibronectin, *OR* steroids and tocolysis *OR* MgSO4 given for neuroprotection
Antepartum haemorrhage – any significant per vaginum (PV) loss requiring hospital presentation
Birth weight – recorded in grams
Small for gestational age – considered less than 10th centile for gestation based on standard population curves
Congenital anomaly – any anomaly recorded prior to discharge from hospital
Nursery admission – sub-analysis for Intensive Care Nursery and Special Care Nursery, consideration given to diagnoses recorded as per Perinatal Society of Australia & NZ (PSANZ) Classification, with particular analysis of intraventricular haemorrhage, necrotising enterocolitis, retinopathy of prematurity, respiratory distress syndrome
Neonatal mortality – death recorded up until 28 days after live birth
Mode of delivery – recorded as vaginal, assisted vaginal, elective Caesarean, emergency Caesarean

Complete miscarriage – as complete loss of pregnancy sub-analysed by gestation < 12 weeks, 12- 23 weeks (as per Cochrane review)

DASS-21 questionnaire scores – scores doubled to reflect the DASS-42, and recorded under Depression, Anxiety and Stress categories.

Postnatal depression - diagnosed by medical doctor or psychologist, whether medicated or not

Gestational diabetes –the antenatal Oral Glucose Tolerance Test meeting diagnostic criteria, fasting blood glucose > 5.5, and 2 hr level > 8.0

Venous thromboembolism - deep venous thrombosis or pulmonary embolus, requiring anti-coagulant therapy

Pre-eclampsia – as per SOMANZ 2008 guidelines

Gestational hypertension – as per SOMANZ 2008 guidelines