First trimester progesterone therapy to reduce miscarriages in women with a history of unexplained recurrent miscarriages: A randomised, double blind, placebo-controlled, multi-centre trial.

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To test the hypothesis that in women with unexplained recurrent miscarriages, progesterone started as soon as possible after a positive pregnancy test) and continued to 12 weeks of gestation, compared to placebo, increases live births beyond 24...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Abortions and stillbirth
Study type	Interventional

Summary

ID

NL-OMON33690

Source
ToetsingOnline

Brief title
Progesterone in unexplained recurrent miscarriage (Promise)

Condition

- Abortions and stillbirth

Synonym
recurrent miscarriage (unexplained)

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Engelse subsidie (HTA/NHS)

Intervention

Keyword: livebirth, Progesterone, prognosis, recurrent miscarriage

Outcome measures

Primary outcome

live birth beyond 24 weeks;

Secondary outcome

ongoing pregnancy at 12 weeks (range 11 * 13 weeks), miscarriage rate,

gestation at delivery, survival at 28 days of neonatal life, adverse events,

subgroup effects of progesterone (see 2. secondary objectives)

Study description

Background summary

Recurrent miscarriage, the loss of three or more first trimester pregnancies (miscarriages), is a distinct clinical entity. Even after comprehensive investigations, a cause for RM is identified in less than 50% of couples. The majority of couples are therefore labelled as having unexplained RM and have been subjected over the decades to treatments based on anecdotal evidence, historical beliefs and the results of small uncontrolled studies. RM can have devastating emotional effects on a woman and her partner, and causes immeasurable human costs as well as being costly to the health care system.

Progesterone, produced by the corpus luteum, is essential for the maintenance of early pregnancy. This is supported by the finding that mifepristone, an anti-progesterone, is effective in terminating pregnancies at less than 8 weeks gestation. The primary mechanism of the effects of progesterone is believed to be through immune modulation at the feto-maternal interface. A systematic review of trials of progestagens in RM was conducted by the Promise team, and

identified four studies. Although these studies were small and of poor quality, they all reported a trend towards benefit. A meta-analysis of these four studies showed a large and statistically significant reduction in miscarriage rate with progestagen use (RR 0.49, 95% CI: 0.31 to 0.76). However, a survey of clinicians (n=84) has shown that this finding has not resulted in the use of progestagen in the treatment of RM due to the small size of individual studies (largest of the studies randomising only 130 women) and their poor quality (unpublished data).
Thus, a randomized, controlled, multi-center study comparing two different strategies including progesterone therapy and placebo in women with a history of unexplained RM is highly warranted.

Study objective

To test the hypothesis that in women with unexplained recurrent miscarriages, progesterone started as soon as possible after a positive pregnancy test) and continued to 12 weeks of gestation, compared to placebo, increases live births beyond 24 completed weeks by at least 10%.

Study design

Randomized double-blind placebo-controlled trial.

Intervention

All women will be randomly allocated to receive either Progesterone (Utrogestan®) pessaries 2 x 200 mg twice daily, total dose 800 mg per day (intervention group) or placebo pessaries, two twice daily (control group) soon after diagnosis of pregnancy (less than 6 weeks gestation) to 12 weeks gestation.

Study burden and risks

Women with RM receive standard diagnostic care. The risks and burden of participating in the trial are little. The women will use vaginal progesterone pessaries or placebo pessaries in a subsequent pregnancy, commencing on observing a positive pregnancy test and continuing until 12 weeks of pregnancy. The outcome of that pregnancy will be followed. The (minimal) risk of participation is the risk of progesterone use. Substantial evidence exists that progestagen supplementation is safe to the mother and fetus.
In a subgroup of the patient population participating in the two Dutch centres, additional studies will be carried out aimed at elucidating the endocrine and endometrial function in the luteal phase in study participants in their spontaneous untreated cycle (pre-randomization). In this subgroup, a temperature curve, urinary LH test, serial serum samples of progesterone (4x) and a mid-luteal biopsy endometrial tissue sampling will be taken in a cycle

preceding randomization.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Women with unexplained RM (3 or more consecutive first trimester miscarriages)
2. Age 18 - 39 years at randomisation (likelihood of miscarriages due to chromosomal aberrations is higher in older women; such miscarriages are unlikely to be prevented by progesterone therapy)
3. Spontaneous conception (as confirmed by urinary pregnancy tests)
4. Willing and able to give informed consent.

Exclusion criteria

1. Inability to conceive spontaneously within 1 year of recruitment
2. Antiphospholipid syndrome (lupus anticoagulant and/ or anticardiolipin antibodies [IgG or IgM])
3. other recognised thrombophilic conditions (testing according to usual clinic practice)
4. Intrauterine abnormalities (as assessed by ultrasound, hysterosonography, hysterosalpingogram or hysteroscopy)
5. Submucous fibroids
6. Abnormal parental karyotype
7. Other identifiable causes of RM (tests initiated only if clinically indicated): e.g. diabetes, thyroid disease and SLE.
8. previous enrolment in the Promise trial

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-08-2010
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Utrogestan®

Generic name:	progesterone

Ethics review

Approved WMO Date:	18-02-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-011208-42-NL
ISRCTN	ISRCTN92644181
CCMO	NL24797.018.09