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Timed intercourse for couples trying to conceive (Review)

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[Intervention Review]

Timed intercourse for couples trying to conceive

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ABSTRACT

Background

Fertility problems are very common, as subfertility affects about 10% to 15% of couples trying to conceive. There are many factors that may impact a couple's ability to conceive and one of these may be incorrect timing of intercourse. Conception is only possible from approximately five days before up to several hours after ovulation. Therefore, to be effective, intercourse must take place during this fertile period. 'Timed intercourse' is the practice of prospectively identifying ovulation and, thus, the fertile period to increase the likelihood of conception. Whilst timed intercourse may increase conception rates and reduce unnecessary intervention and costs, there may be associated adverse aspects including time consumption and stress. Ovulation prediction methods used for timing intercourse include urinary hormone measurement (luteinizing hormone (LH), estrogen), tracking basal body temperatures, cervical mucus investigation, calendar charting and ultrasonography. This review considered the evidence from randomised controlled trials for the use of timed intercourse on positive pregnancy outcomes.

Objectives

To assess the benefits and risks of ovulation prediction methods for timing intercourse on conception in couples trying to conceive.

Search methods

We searched the following sources to identify relevant randomised controlled trials, the Menstrual Disorders and Subfertility Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, PubMed, LILACS, Web of Knowledge, the World Health Organization (WHO) Clinical Trials Register Platform and ClinicalTrials.gov. Furthermore, we manually searched the references of relevant articles. The search was not restricted by language or publication status. The last search was on 5 August 2014.

Selection criteria

We included randomised controlled trials (RCTs) comparing timed intercourse versus intercourse without ovulation prediction or comparing different methods of ovulation prediction for timing intercourse against each other in couples trying to conceive.

Data collection and analysis

Two review authors independently assessed trial eligibility and risk of bias and extracted the data. The primary review outcomes were cumulative live birth and adverse events (such as quality of life, depression and stress). Secondary outcomes were clinical pregnancy, pregnancy (clinical or self-reported pregnancy, not yet confirmed by ultrasound) and time to conception. We combined data to calculate pooled risk ratios (RRs) and 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the I^2 statistic. We assessed the overall quality of the evidence for the main comparisons using GRADE methods.

Main results

We included five RCTs (2840 women or couples) comparing timed intercourse versus intercourse without ovulation prediction. Unfortunately one large study (n = 1453) reporting live birth and pregnancy had not published outcome data by randomised group and therefore could not be analysed. Consequently, four RCTs (n = 1387) were included in the meta-analysis. The evidence was of low to very low quality. Main limitations for downgrading the evidence included imprecision, lack of reporting clinically relevant outcomes and the high risk of publication bias.

One study reported live birth, but the sample size was too small to draw any relevant conclusions on the effect of timed intercourse (RR 0.75, 95% CI 0.16 to 3.41, 1 RCT, n = 17, very low quality).

One study reported stress as an adverse event. There was no evidence of a difference in levels of stress (mean difference 1.98, 95 CI% -0.87 to 4.83, 1 RCT, n = 77, low level evidence). No other studies reported adverse events.

Two studies reported clinical pregnancy. There was no evidence of a difference in clinical pregnancy rates (RR 1.10, 95% CI 0.57 to 2.12, 2 RCTs, n = 177, I^2 = 0%, low level evidence). This suggested that if the chance of a clinical pregnancy following intercourse without ovulation prediction is assumed to be 16%, the chance of success following timed intercourse would be between 9% and 33%.Four studies reported pregnancy rate (clinical or self-reported pregnancy). Timed intercourse was associated with higher pregnancy rates compared to intercourse without ovulation prediction in couples trying to conceive (RR 1.35, 95% CI 1.06 to 1.71, 4 RCTs, n = 1387, I^2 = 0%, very low level evidence). This suggests that if the chance of a pregnancy following intercourse without ovulation prediction is assumed to be 13%, the chance following timed intercourse would be between 14% and 23%. Subgroup analysis by duration of subfertility showed no difference in effect between couples trying to conceive for < 12 months versus couples trying for ≥ 12 months. One trial reported time to conception data and showed no evidence of a difference in time to conception.

Authors' conclusions

There are insufficient data available to draw conclusions on the effectiveness of timed intercourse for the outcomes of live birth, adverse events and clinical pregnancy. Timed intercourse may improve pregnancy rates (clinical or self-reported pregnancy, not yet confirmed by ultrasound) compared to intercourse without ovulation prediction. The quality of this evidence is low to very low and therefore findings should be regarded with caution. There is a high risk of publication bias, as one large study remains unpublished 8 years after recruitment finished. Further research is required, reporting clinically relevant outcomes (live birth, clinical pregnancy rates and adverse effects), to determine if timed intercourse is safe and effective in couples trying to conceive.

PLAIN LANGUAGE SUMMARY

Timed intercourse for couples with subfertility

Review question

Researchers in The Cochrane Collaboration reviewed the evidence about the effect of timed intercourse versus spontaneous intercourse in couples trying to conceive.

Background

Many couples find it difficult to achieve a pregnancy and have concerns about their fertility. Each cycle, a woman is fertile from approximately five days before ovulation until several hours after ovulation, due to limited survival times of the sperm and egg. Therefore, prospectively identifying this fertile period of a woman's menstrual cycle, to guide timing of intercourse, may improve conception rates. This may reduce unnecessary medical treatment and costs of advanced infertility treatment, but could also cause adverse events such as stress. The fertile period can be identified by different methods including urinary fertility monitoring, calendar charting, observing

changes in cervical mucous and basal body temperatures or follicular maturation on ultrasound. The aim of this review was to assess the benefits and risks of timed intercourse on pregnancy outcomes in couples trying to conceive.

Study characteristics

We found five randomised controlled trials comparing timed intercourse versus intercourse without ovulation prediction, in a total of 2840 women or couples trying to conceive. The evidence was current to August 2014.

Key results

One large included study (1453 women) has not published usable results and could therefore not be analysed. One study reported live birth rates and found no evidence of a difference; however, the study was too small to have any clinical value. Only one study reported levels of stress and showed no evidence of a difference between timed intercourse with urinary fertility monitoring and intercourse without urinary fertility monitoring. No other adverse events were reported. Only two studies reported clinical pregnancy rates, and showed no evidence of a difference in pregnancy rates in couples with subfertility. The evidence suggested that if the chance of a clinical pregnancy following intercourse without ovulation prediction was assumed to be 16%, the chance of a clinical pregnancy following timed intercourse would be between 9% and 33%. However, if including self-reported pregnancies (not confirmed by ultrasound), pregnancy rates were higher after timed intercourse. The evidence suggested that if the chance of a pregnancy following intercourse without ovulation prediction was 13%, the chance following timed intercourse would be between 14% and 23%.

No difference in effect was found between couples trying to conceive for less than 12 months versus 12 months or more. One trial reported time to conception data and showed no evidence of a difference in time to conception.

Quality of the evidence

The overall quality of the evidence ranged from low to very low for all outcomes. The main limitations of the evidence were imprecision, poor reporting of clinically relevant outcomes and a high risk of publication bias, as one large study remains unpublished. Therefore, the findings should be regarded with caution.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Timed intercourse compared to intercourse without ovulation prediction for couples trying to conceive

Patient or population: couples trying to conceive
Settings: home-based and fertility clinics
Intervention: timed intercourse
Comparison: intercourse without ovulation prediction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Intercourse without ovulation prediction	Timed intercourse				
Live birth rate	**333 per 1000**	**250 per 1000** (53 to 1000)	**RR 0.75** (0.16 to 3.41)	17 (1 study)	⊕◯◯◯ **very low**[1,2,3]	
Adverse event: total stress Perceived Stress Scale (PSS). Scale from: 0 to 40.	The mean adverse event: total stress in the control groups was **15.78**	The mean adverse event: total stress in the intervention groups was **1.98 higher** (0.87 lower to 4.83 higher)		77 (1 study)	⊕⊕◯◯ **low**[4,5]	
Clinical pregnancy rate	**157 per 1000**	**173 per 1000** (90 to 333)	**RR 1.1** (0.57 to 2.12)	177 (2 studies)	⊕⊕◯◯ **low**[3,4]	
Pregnancy rate (clinical pregnancy and self-reported pregnancy)	**135 per 1000**	**182 per 1000** (143 to 230)	**RR 1.35** (1.06 to 1.71)	1387 (4 studies)	⊕◯◯◯ **very low**[3,4,6,7]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Early stopping of trial
[2] Serious imprecision, results are based on the results of a single, unpublished, very small trial
[3] High risk of publication bias
[4] High risk of performance bias
[5] Study funded by manufacturer of the intervention method
[6] Low clinical relevancy of self-reported pregnancy (based on a pregnancy test only)
[7] Two studies funded by manufacturer of the intervention method

BACKGROUND

Description of the condition

Fertility problems are currently very topical and healthcare providers are frequently consulted by couples with concerns (NICE 2013). Subfertility is the inability to conceive after 12 months of regular unprotected sexual intercourse (ASRM Practice Committee 2013). It is a common condition, affecting up to between 10% and 15% of couples trying to conceive, with important psychological, economic, demographic and medical implications (Evers 2002; Gnoth 2005;). Despite advances in the diagnostic assessment of subfertility at least 15% of these couples have no identifiable cause for their subfertility and are considered to have unexplained subfertility (Quaas 2008; ASRM Practice Committee 2013). Assisted Reproductive Technology (ART) such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are increasingly used to assist couples in becoming pregnant. However, these techniques are expensive, invasive and not guaranteed to be successful (de Mouzon 2010; CDC 2014). Moreover, many studies have shown that women with unexplained subfertility will still conceive spontaneously with no specific treatment (Snick 1997; Farquhar 2010). Due to the limited life span of the sperm and egg, conception is generally only possible from about five days before ovulation and ending on the day of ovulation (Dunson 1999; Wilcox 2000). The highest probability of conception appears to be with intercourse one or two days prior to ovulation (Stanford 2002). Therefore, prospectively identifying this fertile time of the menstrual cycle is important for both couples with unexplained subfertility and couples beginning to attempt conception.

Description of the intervention

Most cycles in fertile women show a typical pattern of increasing preovulatory estrogen levels that is associated with a luteinizing hormone (LH) surge and a subsequent progesterone rise (Alliende 2005). The changing patterns of hormones give rise to specific signs and symptoms that couples can use to identify their fertile phase of the menstrual cycle. Timing intercourse consists of observing the key signs that mark the fertile phase and having intercourse during that period to achieve pregnancy. Several methods are available to predict ovulation and estimate peak fertility, including urinary hormone measurement, Fertility Awareness Based Methods (FABM) and pelvic ultrasonography.

- Urinary hormone measurement involves the serial monitoring of urinary LH levels in order to detect the LH surge that occurs 24 to 36 hours prior to ovulation (Miller 1996). Urinary hormone kits are now commercially available for home use. Urinary monitors have also been developed that monitor both the estrogen metabolites and LH rise in urine based on an enzyme immunoassay to predict ovulation more precisely (Behre 2000).
- FABM estimate the fertile time by the consistent monitoring of a combination of cycle length and the woman's observation of fertility signs, such as changes in cervical secretions and basal body temperature, including:
    - cervical secretions; changes in cervical secretions, suggestive of a preovulatory estrogen effect, are proven to be highly predictive of ovulation (Bigelow 2004; Scarpa 2006). Cervical mucus changes, increasingly becoming more slippery, clear and stretchy, predict the time of ovulation and consequently the peak of fertility. These changes can be observed and utilised in any length of menstrual cycle (Alliende 2005). Studies conducted by the World Health Organization (WHO) indicate that 93% of women, regardless of their education level, are capable of identifying and interpreting the cervical mucus changes in their vaginal discharge to identify the days of peak fertility (WHO 1981);
    - basal body temperature, which rises shortly after ovulation, approximately 0.5 °F, as a result of progesterone release from the corpus luteum. However, the temperature rise can be unreliable and is usually identified retrospectively (Luciano 1990). Several computerised devices based on basal body temperature have been developed in order to estimate the time of ovulation in subsequent cycles (Fehring 1991);
    - calendar calculation; women with a maximum cycle length variation of two days can accurately predict ovulation because ovulation occurs approximately 14 days before the onset of menstruation. However, many women do not have such regular cycles and therefore their luteal phase may vary individually from 10 to 16 days, making it harder to predict ovulation by calendar calculations alone (Wilcox 2000).
- Pelvic ultrasonography is used to identify a preovulatory follicle, which is on average between 20 and 25 mm in diameter before rupture. By serial examination, the development of the follicle can be tracked and rupture can usually be identified confirming ovulation.

How the intervention might work

Several studies have established the accuracy of ovulation prediction methods as markers of high fertility (Stanford 2003; Scarpa 2006; ASRM Practice Committee 2013a). By prospectively identifying ovulation, the women's fertile intervals can be determined. It is important that intercourse should occur during this fertile interval in order for pregnancy to occur. Therefore, timed intercourse according to the detection of ovulation may reduce time to conception and improve pregnancy rates.

Why it is important to do this review

While ovulation prediction methods are gaining in popularity, couples trying to conceive are given varied advice on the usefulness of timing intercourse in achieving a pregnancy (ASRM Practice Committee 2013a). Existing reviews on timed intercourse according to ovulation detection are based on observational studies without a comparison group (Gnoth 2002; Stanford 2002; ASRM Practice Committee 2013a). An existing Cochrane Review compares the effectiveness of timed intercourse versus intra-uterine insemination (Veltman-Verhulst 2012) but does not cover our specific interest in the comparison of timed intercourse with spontaneous intercourse.

There is an increasing acceptance, availability and therefore demand for infertility services and clinicians are in an ideal position to give advice regarding strategies such as optimal timing of intercourse. Accurate information and formal instruction in the recording of peak fertility, given early, have the potential to improve pregnancy rates for many couples, and subsequently reduce unnecessary medical intervention and costs (Stanford 2002). On the other hand, these prediction methods can be time consuming, costly and may cause additional stress (NICE 2013). Recommending and documenting ovulation prediction by any method may be useful for couples trying to achieve pregnancy once the therapeutic effectiveness of timing intercourse is known. This review considered the evidence from randomised controlled trials for the use of timed intercourse on pregnancy outcomes.

OBJECTIVES

To assess the benefits and risks of ovulation prediction methods for timing intercourse on conception in couples trying to conceive.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) were eligible for inclusion. We excluded non-randomised and quasi-randomised studies (for example studies with evidence of inadequate sequence generation, such as alternate days, patient numbers) as they are associated with a high risk of bias.

We included crossover trials but only the data from the first phase were included in meta-analyses, as crossover is not a valid design in this context.

Types of participants

Inclusion criteria

- Couples with unexplained subfertility, defined as no ongoing pregnancy after 12 months of usual sexual intercourse, or after 6 months in women 35 years and older. Women with only minimal endometriosis (American Fertility Society criteria grade I) and men with mild male factor (when two or more semen analyses have no more than two variables below the fifth centile, as defined by WHO in 2010) were included within the categorisation of 'unexplained'.
- Couples trying to conceive and not yet diagnosed as subfertile (no ongoing pregnancy for less than 12 months of usual sexual intercourse).

Exclusion criteria

- Couples with other causes of subfertility.

Types of interventions

Trials comparing timed intercourse according to ovulation prediction versus spontaneous intercourse (without ovulation prediction) were eligible for inclusion.

Trials comparing one ovulation prediction method versus any other ovulation prediction method were eligible for inclusion.

Trials comparing ovulation prediction methods for intra-uterine insemination (IUI), as well as trials comparing timed intercourse versus IUI, were excluded.

Ovulation prediction methods included:

- urinary hormone measurement with home ovulation monitors;
- Fertility Awareness Based Methods (FABM) with an educational component (standard days method, cervical mucus method (Billings Ovulation Method, Creighton Model System, FertilityCare, TwoDay Method), symptothermal method, basal body temperature measurement, calendar calculations);
- pelvic ultrasonography.

Types of outcome measures

Primary outcomes

1. Live birth, defined as delivery of a live fetus after 20 completed weeks of gestation. Multiple live births (for example twins or triplets) were counted as one live birth event.

2. Adverse events (including acceptability of the method, quality of life, mood levels, depression, anxiety and stress caused by the intervention, as measured by validated scales). If studies reported more than one scale for quality of life, preference was given to

the Short Form (SF)-36, then other validated generic scales and finally condition-specific scales. If studies reported more than one time point when adverse event data were measured, preference was given to data from the last time point.

Secondary outcomes

3. Clinical pregnancy, defined as the presence of a gestational sac confirmed by ultrasound.
4. Pregnancy, which included a clinical pregnancy as well as a self-reported pregnancy (defined as a pregnancy not yet confirmed by ultrasound and reported by the participants of the study).
5. Time to conception, as defined by authors of individual trials.

Search methods for identification of studies

We searched for all published and unpublished RCTs of timed intercourse, without language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator.

Electronic searches

We searched the following electronic databases, trial registers and websites:

- Ovid Cochrane Central Register of Controlled Trials (CENTRAL) (from inception to present) (Appendix 1);
- Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of controlled trials (from inception to present) (Appendix 2);
- Ovid MEDLINE (from inception to present) (Appendix 3);
- Ovid EMBASE (from inception to present) (Appendix 4);
- Ovid PsycINFO (from inception to present) (Appendix 5);
- EBSCO CINAHL (from inception to present) (Appendix 6).

We combined the MEDLINE search with the Cochrane highly sensitive search strategies for identifying randomised trials in MEDLINE as illustrated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We combined the EMBASE, PsycINFO and CINAHL searches with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/methodology/filters.html#random).

We also searched the following electronic sources of trials:
• trial registers for ongoing and registered trials including ClinicalTrials.gov (http://www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch) (Appendix 7);
• Database of Abstracts of Reviews of Effects (DARE) in the Cochrane Library (Appendix 8);
• Web of Knowledge (Appendix 9);
• Virtual Health Library (VHL), which includes the LILACS database (Appendix 10);
• PubMed and Google (Appendix 11);
• OpenSIGLE for grey literature (Appendix 12).

Searching other resources

We handsearched reference lists of articles retrieved by the search and contacted experts in the field to obtain additional data. We also handsearched relevant journals and conference abstracts that are not covered in the Cochrane Menstrual Disorders and Subfertility Group Specialised Register in liaison with the Group's Trials Search Co-ordinator.

Data collection and analysis

Selection of studies

After an initial screening of titles and abstracts retrieved by the search, the full texts of all potentially eligible studies were retrieved. Two review authors (MM and BS) independently examined these full text articles for compliance with the inclusion criteria and selected studies eligible for inclusion in the review. We corresponded with study investigators, as required, to clarify study eligibility. We resolved disagreements as to study eligibility by discussion and by consulting a third review author (CF). We documented the study selection process using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Data extraction and management

Two review authors (MM and BS) independently extracted data from eligible studies using a data extraction form designed and pilot-tested by the authors. We resolved any disagreements by discussion and by involving a third review author (CF). Data extracted included study characteristics and outcome data (see data extraction table for details, Appendix 13). Where studies had multiple publications, we collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review, and such studies had a single study ID with multiple references. We corresponded with study investigators for further data on methods or results, as required.

Assessment of risk of bias in included studies

Two review authors (MM and BS) independently assessed the included studies for risk of bias using the Cochrane risk of bias assessment tool (www.cochrane-handbook.org) to assess the following domains:

- selection bias (random sequence generation and allocation concealment);
- performance bias (blinding of participants and personnel);

- detection bias (blinding of outcome assessors);
- attrition bias (incomplete outcome data);
- reporting bias (selective reporting).

These domains were characterized as 'high risk of bias', 'low risk of bias' or 'unclear risk of bias'. Disagreements were resolved by discussion and by a third review author (CF). We described all judgements fully and presented the conclusions in the 'Risk of bias' table, which we planned to incorporate into the interpretation of review findings by means of sensitivity analyses. However, we did not perform sensitivity analyses due to the small number of studies included (Sensitivity analysis, see below).

We took care to search for within-trial selective reporting, such as trials failing to report obvious outcomes, or reporting them in insufficient detail to allow inclusion. We sought published protocols and compared the outcomes between the protocol and the final published study.

Measures of treatment effect

For dichotomous data (live birth, pregnancy) we used the numbers of events in the control and intervention groups of each study to calculate risk ratios (RRs) with 95% confidence intervals (CIs).

For continuous data (for example levels of stress), if all studies reported exactly the same outcomes we planned to calculate mean differences (MDs) between treatment groups. If similar outcomes were reported on different scales we planned to calculate the standardized mean difference (SMD). We reversed the direction of effect of individual studies, if required, to ensure consistency across trials. We intended to treat long ordinal data (for example quality of life scores) as continuous data. We planned to use hazard ratios (HRs) for the outcome time to conception.

We presented 95% CIs for all outcomes. Where data to calculate RRs or MDs were not available, we planned to utilize the most detailed numerical data available that may facilitate similar analyses of included studies (for example test statistics, P values), but all studies reported RRs or MDs. We compared the magnitude and direction of effect reported by studies with how they are presented in the review, and took account of legitimate differences.

Unit of analysis issues

The primary analysis was per woman randomised. All included studies reported data per woman. Multiple live births (for example twins or triplets) were counted as one live birth event. We planned to include only first-phase data from crossover trials due to improper study design for this topic, but no crossover trials were found.

Dealing with missing data

We analysed the data on an intention-to-treat basis as far as possible, and we attempted to obtain missing data from the original trialists. Where these were unobtainable, we planned to undertake imputation of individual values for the outcomes live birth rates and clinical pregnancy rates only. We assumed live births and pregnancies did not occur in participants without a reported outcome. For other outcomes, we analysed only the available data. We intended to subject any imputation undertaken to sensitivity analysis. If studies reported sufficient detail to calculate MDs but no information on associated standard deviations (SDs), the outcome was assumed to have a standard deviation (SD) equal to the SD from studies of similar size within the same analysis.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity by the I^2 statistic. An I^2 value greater than 50% was taken to indicate substantial heterogeneity (Higgins 2011). We intended to explore moderate heterogeneity using subgroup analysis and carrying out a sensitivity analysis, but we did not find any heterogeneity.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimize their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If there were 10 or more studies in an analysis, we intended to use a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies). We did not construct a funnel plot since there were only five included studies.

Data synthesis

We carried out statistical analyses using the Cochrane Collaboration statistical software, Review Manager 2014. If the studies were sufficiently similar, we combined the data using a fixed-effect model (because we assumed that the underlying effect size was the same for all the trials in the analysis) in the following comparisons.

1. All available methods for timing intercourse versus spontaneous intercourse or no intervention.
2. Urinary fertility monitoring versus intercourse without ovulation prediction.
3. FABM versus intercourse without ovulation prediction:
    - calendar calculations (Standard days method);
    - cervical mucus investigation (the Billings Ovulation Method™, the Creighton Model FertilityCare™ System,TwoDay Method®);
    - basal body temperature measurement;
    - symptothermal method (calendar calculations, cervical mucus investigation and basal body temperature measurement combined).

4. Pelvic ultrasonography versus intercourse without ovulation prediction.
5. Any method for timing intercourse versus another method.
We displayed an increase in the risk of a particular outcome, which may be beneficial (for example live birth) or detrimental (for example adverse effects), graphically in the meta-analyses to the right of the centre-line and a decrease in the risk of an outcome to the left of the centre-line. We intended to use generic inverse variance for the meta-analysis of HRs. In the case of substantial heterogeneity between studies (> 50%) sufficient to suggest that treatment effects may differ between trials, we intended to explore this heterogeneity by sensitivity analysis followed by random-effects meta-analysis if required, but this was not necessary.

Subgroup analysis and investigation of heterogeneity

Where data were available, we conducted a subgroup analysis to determine the separate evidence within the following subgroups:

- couples taking part in a fertility programme or with diagnosed unexplained subfertility (≥ 12 months trying to conceive),
- compared with couples not yet diagnosed as subfertile (< 12 months trying to conceive).

If we detected substantial heterogeneity, we intended to explore possible explanations in sensitivity analyses and to employ a random-effects model. We took any statistical heterogeneity into account when interpreting the results, especially if there was any variation in the direction of effect.

Sensitivity analysis

We intended to conduct sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding eligibility and analysis. These analyses included consideration of whether the review conclusions would have differed if:

1. eligibility was restricted to studies without high risk of bias;
2. a random-effects model had been adopted;
3. alternative imputation strategies had been implemented;
4. the summary effect measure was odds ratio rather than relative risk (RR).

Because there were too few studies and no substantial heterogeneity (> 50%), we did not carry out the planned sensitivity analyses.

Summary of findings table

We prepared a summary of findings table using the GRADEpro software (GRADEpro version 3.6.1). This table evaluates the overall quality of the body of evidence for the main review outcomes (live birth, adverse effects, clinical pregnancy, pregnancy rate) using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria (study limitations (that is risk of bias), consistency of effect, imprecision, indirectness and publication bias). We justified, documented and incorporated our judgements about evidence quality (high, moderate or low) into the reporting of results for each outcome.

RESULTS

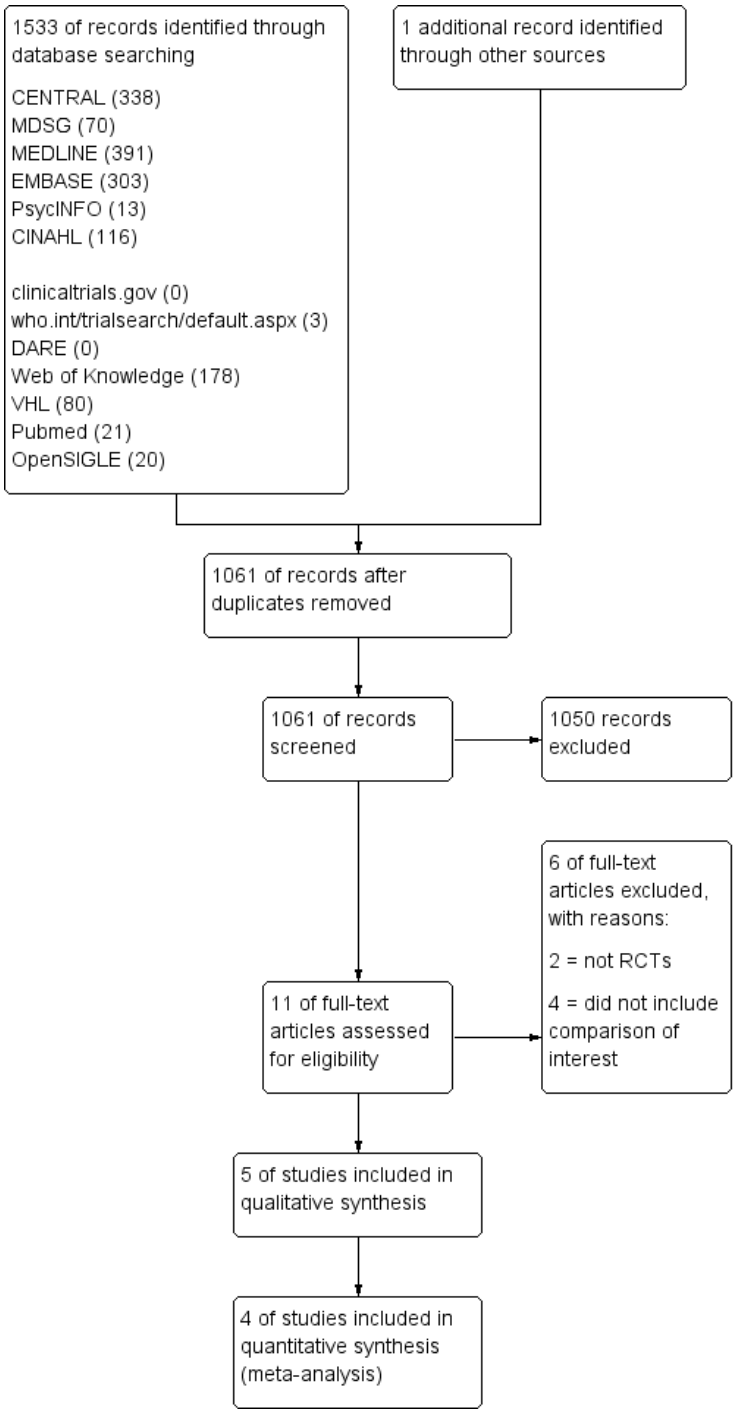
Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

See study flow diagram Figure 1.

Figure 1. Study flow diagram.



The search retrieved 1533 studies (for our search strategies and search dates see Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12). One additional study was found by searching other sources. After removal of duplicates 1061 studies were screened, of which 11 were potentially eligible and retrieved in full text. Five trials met our inclusion criteria. We excluded six studies. Attempts were made to contact the authors of all included studies for further information. Two included studies remain unpublished (Pyper 2006; McLindon 2011). One study (Pyper 2006) only published the protocol with interim results, and not arranged by intervention group. We unsuccessfully tried to contact the authors for final outcome data. The study data of the other unpublished study (McLindon 2011) were received in correspondence with the authors.

Included studies

Study design and setting

Five parallel-design randomised controlled trials (RCTs) were included. One study was three-armed (Pyper 2006) and four studies were two-armed (Leader 1992; Robinson 2007; McLindon 2011; Tiplady 2013). Two studies were set in a fertility clinic (Leader 1992; McLindon 2011) while the other studies had a home based setting. Two studies were conducted in Australia (Leader 1992; McLindon 2011), one study in the United States (Robinson 2007) and two studies in the United Kingdom (Pyper 2006; Tiplady 2013).

Participants

A total of 1387 women, or couples, trying to conceive were randomised in the included studies, 703 women in the intervention groups and 684 women in the control groups. In Pyper 2006, 1453 women were recruited but the numbers randomised to the intervention and control groups have not been published. All participants were recruited after an expression of interest following targeted advertisements. The age of the included participants ranged from 18 to 43 years. Two studies (Leader 1992; McLindon 2011) included subfertile participants only (trying for $\geq$ 12 months). In Leader 1992 the subfertility was either diagnosed as unexplained (group 1) or thought to be due to a male factor with a reduced motility index (group 2). In McLindon 2011 all women had unexplained subfertility. The three other studies included populations without a diagnosis of subfertility. In Pyper 2006 only women trying to conceive for < 3 months were included. In two other studies (Robinson 2007; Tiplady 2013) the majority of participants (78% and 86%, respectively) had been trying to conceive for < 12 months before the start of the study. Both Tiplady 2013 and Pyper 2006 excluded women currently undergoing fertility treatment or investigation, whereas Robinson 2007 excluded women who had been trying for > two years. Women who had previously been pregnant were not excluded in any of the included studies.

Interventions and comparisons

Intervention

One study (McLindon 2011) compared timed intercourse through Fertility Awareness Based Methods (FABM) versus intercourse without FABM. Women in the intervention group received instructions on the symptothermal method (the use of calendar calculations, cervical mucus investigation and basal body temperature measurement combined) in order to predict fertility. The other included studies compared timed intercourse with and without urinary fertility monitoring. All of these studies used the same commercially available urinary fertility monitor, monitoring levels of estrone-3-glucuronide (E3G) and LH to estimate fertility status. Women in the intervention groups were provided with the fertility monitor kits and given instructions on usage. In one study (Pyper 2006) there were two intervention groups. Women in the first intervention group received information from the fertility monitor about the early fertile time only, whereas women in the second group received information about the late fertile time only.
None of the studies compared any ovulation prediction method with any other method.

Control

In Pyper 2006, women in the control group were provided with a urinary fertility monitor. However, the monitor did not reveal information about the fertility status. In the other included studies women in the control group were not given specific methods for timing intercourse. Instead, they were given general information about fertility and how to spontaneously improve chances of conception (Leader 1992; McLindon 2011; Tiplady 2013) or were free to use aids to conception other than the intervention, including other home ovulation tests (Robinson 2007).

Treatment length

Treatment length varied between two cycles (Tiplady 2013), three cycles (Leader 1992; Robinson 2007), six cycles (Pyper 2006) and eight cycles (McLindon 2011). Due to insufficient evaluable data provided for the third cycle, Robinson 2007 analysed data for the

first two complete cycles only. In the four studies with reported results (Leader 1992; Robinson 2007; McLindon 2011; Tiplady 2013), final outcome data were retrieved within the first week after the last treatment cycle.

Outcomes

Two studies reported live birth rate (Pyper 2006; McLindon 2011). Two studies reported clinical pregnancy rate, confirmed by ultrasound (Leader 1992; McLindon 2011). Three studies (Pyper 2006; Robinson 2007; Tiplady 2013) reported self-reported pregnancy rate, based on a positive pregnancy test. One study (Tiplady 2013) reported levels of stress. It used the Perceived Stress Scale (PSS), which ranges from 0 to 40, for measuring levels of stress. A higher PSS-score suggests a higher level of stress. Tiplady 2013 provided data on time to conception. No further time to conception data were suitable for analysis. No other included studies reported any other adverse events (levels of depression, anxiety etc.). None of these studies followed up participants after final outcome data were retrieved. One study (Pyper 2006) reported interim outcome data only, not arranged by intervention group. E-mails were sent to the author to request the final outcome data but we were unable to obtain these data.

Funding sources

In three studies (Pyper 2006; Robinson 2007; Tiplady 2013) the intervention manufacturer provided funding. Furthermore, authors of Tiplady 2013 were employees of the company of the intervention method. In another study (Leader 1992), the urinary fertility monitors were provided by the manufacturer.
See Characteristics of included studies for more details.

Excluded studies

We excluded six studies from the review, for the following reasons:

- 2/6 appeared not to be RCTs (Fehring 1994; Mu 2014);
- 2/6 compared timed intercourse for pregnancy avoidance (Medina 1980; Fehring 2013);
- 1/6 compared ovulation prediction for timing of the postcoital test (Corsan 1993);
- 1/6 excluded participants trying to achieve a pregnancy (Leiva 2014).

See Characteristics of excluded studies for more details.

Risk of bias in included studies

The risk of bias was assessed for each included trial in the 'Risk of bias' table, see Characteristics of included studies. We summarised our findings in the 'Risk of bias' summary (see Figure 2) and in the 'Risk of bias' graph (see Figure 3). Authors of all studies were contacted for supplementary information.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

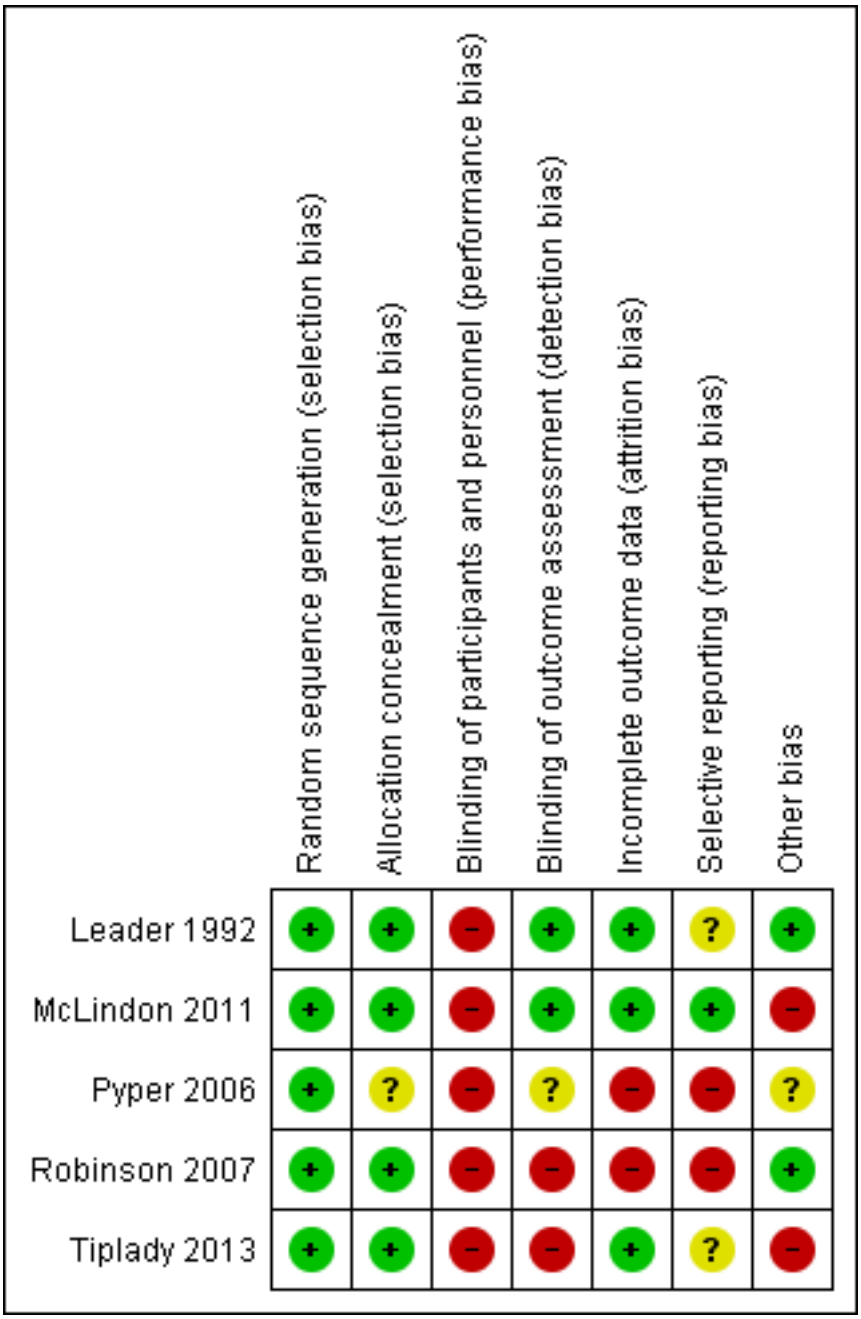
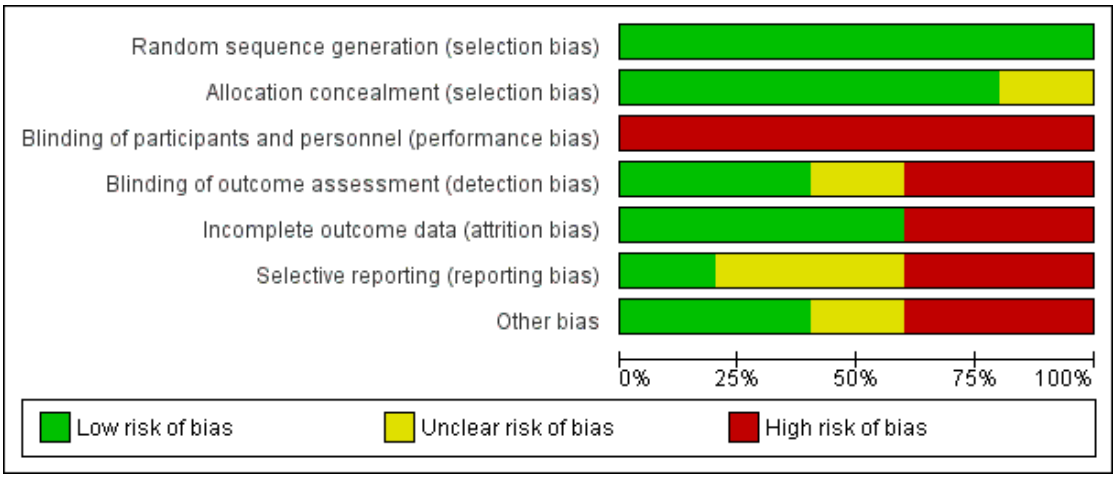


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence allocation

All studies were at low risk of selection bias related to sequence generation as they used shuffling of envelopes (Leader 1992), 'stratified randomisation' (Robinson 2007) and computer generated randomisation schedules (Pyper 2006; McLindon 2011; Tiplady 2013).

Allocation sequence concealment

Four studies were at low risk of selection bias related to allocation concealment as two studies (Leader 1992; McLindon 2011) used sealed envelopes and in two studies (Robinson 2007; Tiplady 2013) the randomisation schedules were accessible to the randomisation co-ordinator only. One study (Pyper 2006) failed to specifically describe methods of allocation concealment and was therefore judged to be at unclear risk of bias for this domain.

Blinding

Blinding of participants and personnel (performance bias)

Participants in all five included studies were aware of randomisation allocation, as the intervention did not allow for blinding. In the three-armed study (Pyper 2006), women in the first two intervention groups were blinded to which arm of the intervention they had been assigned. Pyper 2006 reported that personnel were not blinded. No other studies reported their method of blinding of personnel. Blinding of participants was considered to be important as knowledge of allocation may lead to changes in behaviour, such as intercourse patterns, and therefore introduce performance bias. For this reason, all studies were judged to be at high risk of performance bias.

Blinding of outcome assessors (detection bias)

We did not consider that blinding was likely to influence findings for the main review outcomes (live birth, clinical pregnancy). Therefore, we judged studies reporting these outcomes (Leader 1992; Pyper 2006; McLindon 2011) to be at low risk of detection bias. However, in two studies (Robinson 2007; Tiplady 2013) pregnancies were self-reported and confirmed by a pregnancy test only. We considered this more likely to be influenced by blinding, as pregnancies can be missed more easily in early pregnancy. The lack of blinding may influence the awareness of having a pregnancy and consequently the frequency of conducting a pregnancy test. Therefore, both studies were found to be at high risk of detection bias. In one study (Pyper 2006) it was unclear if pregnancies were confirmed by a biochemical pregnancy test or by an ultrasound, and therefore this study was at unclear risk of detection

bias for this outcome. Blinding might influence outcomes for adverse events (depression, levels of stress, etc.) but only one study (Tiplady 2013) reported levels of stress. Unblinding did not take place until statistical analysis of the data was complete, therefore this study was judged to be at low risk of detection bias for this outcome. However, due to the lack of blinding of participants, the overall risk of detection bias was judged to be high for this study.

Incomplete outcome data

In two studies (Leader 1992; Tiplady 2013), numbers of and reasons for missing outcome data were reported. Reasons were considered to be unrelated to the intervention and, therefore, both studies were found to be at low risk of attrition bias. McLindon 2011 reported no missing outcome data and was also judged to be at low risk of attrition bias. Two studies were judged to be at high risk of attrition bias (Pyper 2006; Robinson 2007). There was a high unexplained dropout rate (33.5%) at the beginning of the study in Robinson 2007. In addition, pregnancy data were not reported for the pre-specified three cycles. Instead, only data for two cycles were reported, due to an undefined but 'substantial' number of participants lost to follow-up for the third cycle. One study (Pyper 2006) has only published interim pregnancy and live birth data, which are not arranged by intervention group. Furthermore, final outcome data have not been published eight years after recruitment was completed, and therefore this study was rated as at high risk of attrition bias.

Selective reporting

One study (Pyper 2006) has reported interim results only, not arranged by intervention group, and was therefore rated to be at high risk of reporting bias. One study (McLindon 2011) reported all pre-specified outcomes, including live birth, and was therefore at low risk of reporting bias. The other included studies did not report the most clinically relevant outcome, live birth, and protocols with the pre-specified outcomes of the studies could not be obtained. For this reason, all studies were found to be at unclear risk of reporting bias.

Other potential sources of bias

Three studies were rated to be at high risk of other bias (Robinson 2007; McLindon 2011; Tiplady 2013). In Robinson 2007 other bias was rated as at high risk due to early stopping of data analysis in the study. In Tiplady 2013, an additional biased recruitment was implemented after the trial commenced to counteract higher pregnancy rates found in the test group compared to the control group. This was to ensure sufficient data could be obtained regarding levels of stress for women who failed to become pregnant in the test group. McLindon 2011 was judged to be at high risk of other bias due to discontinuing the trial early because of the recruitment difficulties encountered. We found no potential sources of within-study bias in Leader 1992. We had insufficient information to assess whether an important risk of bias existed in Pyper 2006.

Effects of interventions

See: **Summary of findings for the main comparison** Timed intercourse compared to intercourse without ovulation prediction for couples trying to conceive

- All studies compared timed intercourse versus intercourse without ovulation prediction methods.
- Four studies compared timed intercourse through urinary fertility monitoring versus intercourse without urinary fertility monitoring.
- One study compared Fertility Awareness Based Methods (FABM) versus spontaneous intercourse.
- No studies comparing pelvic ultrasonography versus spontaneous intercourse were found.
- No studies comparing methods for timing intercourse versus each other were found.

We compared the effectiveness of timed intercourse in couples trying to conceive for < 12 months versus couples trying for ≥ 12 months.

One included study comparing timed intercourse through urinary fertility monitoring versus intercourse without urinary fertility monitoring remains unpublished and did not provide outcome data suitable for analysis. We had insufficient data to be able to construct a funnel plot.

1. Timed intercourse versus intercourse without ovulation prediction

Primary outcomes

1.1 Live birth

See Analysis 1.1; Figure 4.

One study (McLindon 2011) reported live birth, but the sample size was too small to draw any conclusions (RR 0.75, 95% CI 0.16 to 3.41, 1 RCT, n = 17, see Analysis 1.1). No sensitivity analysis or subgroup analysis could be done.

Figure 4. Forest plot of comparison: 1 Timed intercourse versus intercourse without ovulation prediction, outcome: 1.1 Live birth rate.

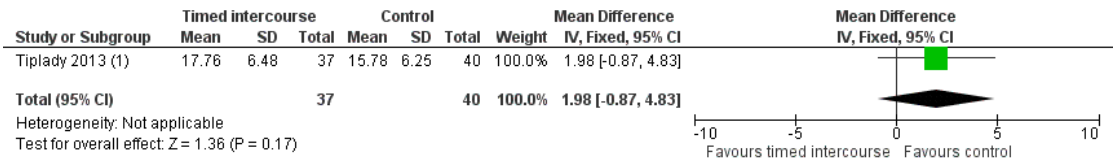
Footnotes
(1) timed intercourse through FABM, subfertile couples only (trying to conceive ≥12 months)

1.2 Adverse events

See: Analysis 1.2; Figure 5.

One study reported levels of stress per woman randomised (Tiplady 2013). Stress was measured using a number of different scales. In this analysis total stress data from the Perceived Stress Scale (PSS), measured at the final time point of the study, were used. There was no evidence of a difference in total stress between the group using a home ovulation test and the control group (MD 1.98, 95 CI% -0.87 to 4.83, 1 RCT, n = 77, see Analysis 1.2). No other adverse events were reported. There were too few studies to conduct any planned sensitivity or subgroup analyses.

Figure 5. Forest plot of comparison: 1 Timed intercourse versus intercourse without ovulation prediction, outcome: 1.2 Adverse event: total stress.



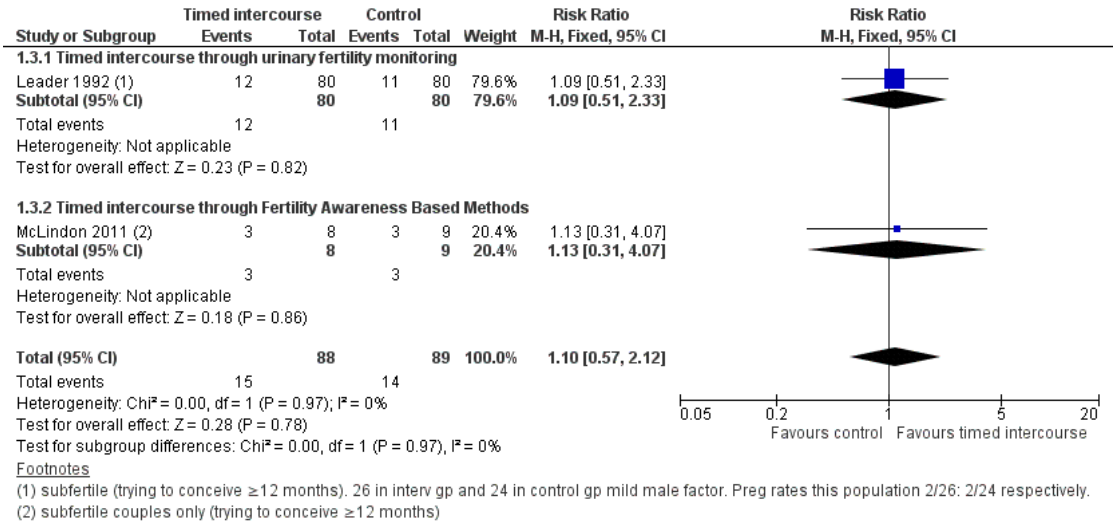
Footnotes
(1) Timed intercourse through urinary fertility monitoring, mostly non subfertile couples (trying to conceive <12 months). Higher score = higher stress

Secondary outcomes

1.3 Clinical pregnancy rate

See Analysis 1.3; Figure 6.

Figure 6. Forest plot of comparison: 1 Timed intercourse versus intercourse without ovulation prediction, outcome: 1.3 Clinical pregnancy rate.



Two studies reported the clinical pregnancy rate (Leader 1992; McLindon 2011). There was no evidence of a difference in clinical pregnancy rate between the two groups (RR 1.10, 95% CI 0.57 to 2.12, 2 RCTs, n = 177, I^2 = 0%, see Analysis 1.3). This suggested that if the chance of a clinical pregnancy following timed intercourse is assumed to be 16%, the chance following intercourse without ovulation prediction would be between 9% and 33%. It was unclear if timed intercourse was associated with higher pregnancy rates than intercourse without ovulation prediction. Because there were too few studies and no heterogeneity was found, we did not conduct any planned sensitivity or subgroup analyses.

1.3.1 Clinical pregnancy rate after timed intercourse through urinary fertility monitoring

Specifically, one study reported the clinical pregnancy rate after timed intercourse using urinary fertility monitoring (Leader 1992). There was no evidence of a difference in clinical pregnancy rate between the intervention and control group (RR 1.09, 95% CI 0.51 to 2.33, 1 RCT, n = 160, see Analysis 1.3).

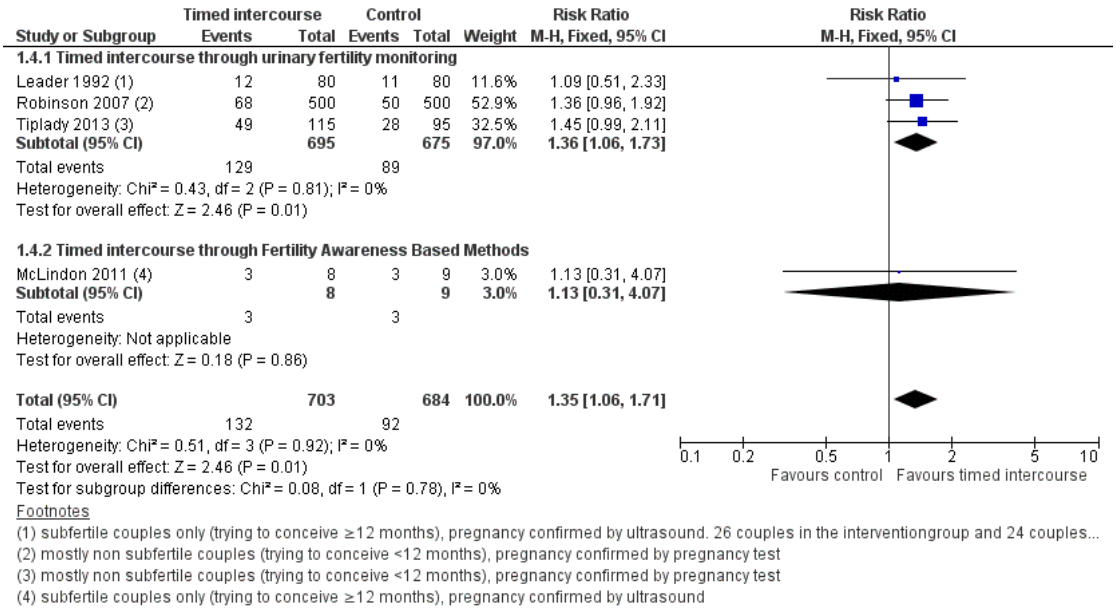
1.3.2 Clinical pregnancy rate after timed intercourse through Fertility Awareness Based Methods

Specifically, one small trial reported clinical pregnancy after timed intercourse through FABM (McLindon 2011). There was no evidence of a difference in clinical pregnancy rate between the two groups (RR 1.13, 95% CI 0.31 to 4.07, 1 RCT, n = 17, see Analysis 1.3).

1.4 Pregnancy rate

See Analysis 1.4; Figure 7.

Figure 7. Forest plot of comparison: 1 Timed intercourse versus intercourse without ovulation prediction, outcome: 1.4 Pregnancy rate (clinical and self-reported pregnancy).



All four included studies reported pregnancy rates (clinical or self-reported pregnancy). Timed intercourse was associated with higher pregnancy rates than intercourse without ovulation prediction (RR 1.35, 95% CI 1.06 to 1.71, 4 RCTs, n = 1387, I^2 = 0%, see Analysis 1.4). This suggested that if the chance of a pregnancy following timed intercourse without ovulation prediction is assumed to be 13%, the chance following timed intercourse would be between 14% and 23%. Because there were too few studies, and no heterogeneity was found, we did not conduct any planned sensitivity analyses.

1.4.1 Pregnancy rate after timed intercourse through urinary fertility monitoring

Three included studies (Leader 1992; Robinson 2007; Tiplady 2013) reported pregnancy rates after timed intercourse through urinary fertility monitoring. Timed intercourse through urinary fertility monitoring was associated with higher pregnancy rates than intercourse without urinary fertility monitoring (RR 1.36, 95% CI 1.06 to 1.73, 3 RCTs, n = 1370, I^2 = 0%, see Analysis 1.4). This suggested that if the chance of self-reported pregnancy following intercourse without urinary fertility monitoring is assumed to be 13%, the chance following timed intercourse with urinary fertility monitoring would be between 14% and 23%.

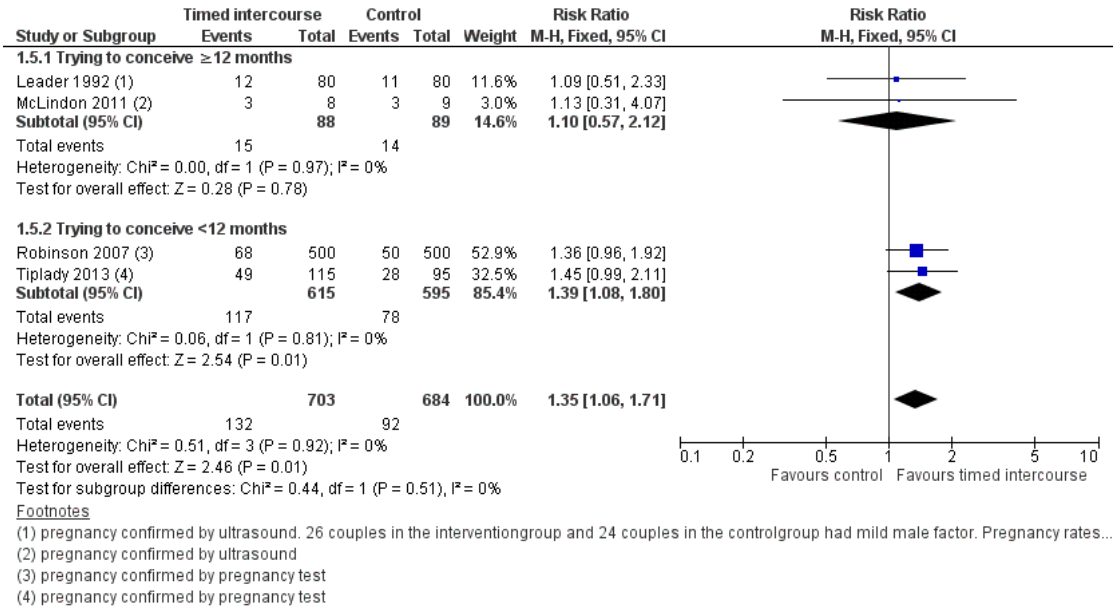
1.4.2 Pregnancy rate after timed intercourse through Fertility Awareness Based Methods

One small study (McLindon 2011) reported pregnancy rate after timed intercourse through FABM and found no evidence of a difference (RR 1.13, 95% CI 0.31 to 4.07, 1 RCT, n = 17, see Analysis 1.4).

1.4.3 Subgroup analysis by duration of subfertility

See Analysis 1.5; Figure 8.

Figure 8. Forest plot of comparison: 1 Timed intercourse versus intercourse without ovulation prediction, outcome: 1.5 Pregnancy rate subgrouped on duration of subfertility.



Subgroup analysis showed no evidence to suggest a difference by duration of subfertility (P = 0.51). However, there were only two small studies comparing the effectiveness of timed intercourse in couples trying to conceive for ≥ 12 months.

1.5 Time to conception

There was only one trial (Tiplady 2013) reporting time to conception data in a Kaplan-Meier curve suitable for analysis. There was no evidence of a difference in time to conception.

DISCUSSION

Summary of main results

This review evaluated the benefits and risks of timed intercourse versus spontaneous intercourse on pregnancy outcomes in couples trying to conceive. One included study with 1453 participants (Pyper 2006) could not be used for analysis as results arranged by intervention group have not been published. However, results of this study are likely to influence the overall findings of this review. Only one study (McLindon 2011) reported live birth but the sample size was too small to draw any conclusions, with only 17 included participants. Two studies reported clinical pregnancy rate (Leader 1992; McLindon 2011) but found no evidence of a difference in clinical pregnancy rate between the two groups. Two studies (Robinson 2007; Tiplady 2013) analysed self-reported pregnancies only (based on a positive pregnancy test without ultrasound confirmation). When analysing pregnancy rates (clinical or self-reported pregnancies), timed intercourse was associated with slightly higher pregnancy rates than intercourse without ovulation prediction methods. However, the effect size was small and these findings may be less favourable to timed intercourse if all the studies reported live births or clinical pregnancies confirmed by ultrasound.

Only one study (Tiplady 2013) reported a possible adverse effect (levels of stress). This study showed no difference in levels of stress between women using urinary fertility monitors to time intercourse versus women attempting conception without additional methods. There were insufficient data regarding other adverse effects of timed intercourse. Time to conception was only reported by one study (Tiplady 2013), showing no difference in time to conception between the two groups.

Our subgroup analysis showed no difference in effectiveness related to duration of subfertility, though only two small studies (Leader 1992; McLindon 2011) looked at participants trying to conceive for 12 months or more. The two other studies (Robinson 2007; Tiplady 2013) were considered within the category of couples trying to conceive for less than 12 months, as in both studies the majority of participants were trying to conceive for less than 12 months (more than 75%). When considering only these two studies on couples trying to conceive for less than 12 months (Robinson 2007; Tiplady 2013), the benefits of timed intercourse

seem to apply to this population. However, the lack of more studies reporting clinically relevant pregnancy outcome data makes it difficult to draw definite conclusions. Because a possible moderating effect of the duration of subfertility on the effectiveness of timed intercourse can not be excluded, further research is needed. See Summary of findings for the main comparison for a complete overview.

Overall completeness and applicability of evidence

One included study with a large sample size which reported (interim) live births and pregnancies has not arranged the results by intervention group and therefore could not be analysed. Live birth was only reported by one minor study (McLindon 2011) and findings were of no clinical value. Only two trials reported clinical pregnancy rate (Leader 1992; McLindon 2011). The other studies reported self-reported pregnancies only, based on a positive pregnancy test. Due to the high risk of miscarriage in early pregnancy (Macklon 2002), pregnancy rates reported in early pregnancy and not yet confirmed by ultrasound are clinically less relevant outcomes, which makes drawing conclusions difficult. However, self-reported pregnancies still provide support for the potential success of timed intercourse upon conception rates, and therefore these results were included in the meta-analysis.

All studies reported pregnancy outcomes per woman randomised, and participants in all studies were women or couples trying to conceive. Only one minor study (McLindon 2011) used FABM as their method for timing intercourse, and it is therefore impossible to draw conclusions on this method for timing intercourse. The other studies used urinary fertility monitoring as their method for timing intercourse, using the same commercially available urinary fertility monitor. No studies were found on the effectiveness of pelvic ultrasonography for timing intercourse.

A difference in overall pregnancy rates between studies was detected, possibly due to differences in the inclusion and exclusion criteria. Overall pregnancy rates were higher in Tiplady 2013 compared to the other included studies, possibly due to the inclusion of a more fertile population. Furthermore, the number of participants lost to follow-up was relatively low in this study. Robinson 2007, on the other hand, had a high percentage of participants lost to follow-up with no outcome data. Our intention-to-treat analysis assumed no pregnancy was achieved in these participants, which may have been the reason for lower overall pregnancy rates in this study. Leader 1992 and McLindon 2011 specifically looked at participants with subfertility, which may have influenced overall pregnancy rates.

The intervention in the control groups of all included studies differed slightly from spontaneous intercourse as participants were given general information about fertility and how to improve the chances of successful conception (Leader 1992; McLindon 2011; Tiplady 2013) or were allowed to use methods for timing intercourse other than the chosen intervention (Robinson 2007).

Treatment length and follow-up were two to three cycles in three included studies (Leader 1992; Robinson 2007; Tiplady 2013) and pregnancy data were confirmed shortly after ending of treatment cycle. The duration of treatment may not have been long enough to observe clearer differences between the intervention and comparison groups, given a usual low per cycle conception rate, especially in the subfertile couples. In addition, the follow-up length made it impossible to obtain clinically relevant outcomes such as live birth.

Only one study looked at possible adverse effects of ovulation prediction, that is levels of stress, and reported time to conception data suitable for analysis (Tiplady 2013). Further research is required to draw definite conclusions on this and other adverse events.

Economic impacts of timed intercourse were not reported in any study, which may determine the chosen method and length of time continued (or able to be continued due to monetary pressures) before success is achieved.

Quality of the evidence

The overall quality of evidence was rated using GRADE criteria and ranged from low to very low. Main limitations were imprecision, poor reporting of clinically relevant pregnancy outcomes (such as live birth or clinical pregnancy) and the high risk of publication bias, as one large study remains unpublished eight years after recruitment completion (See Summary of findings for the main comparison). This study recruited 1453 participants and these results are likely to influence the overall findings of this review.

We were unable to conduct a meta-analysis for the main outcomes, live birth and adverse events, due to the lack of studies reporting these outcomes. We included four studies with a total of 1387 participants in our meta-analysis for self-reported pregnancy rate. In all included studies, participants were aware of which group they were randomised to as the intervention does not allow for blinding. This caused a high risk of performance bias as knowledge of allocation may have led to changes in behaviour, such as intercourse patterns and the use of additional methods for fertility awareness. In addition, because pregnancies were based on positive pregnancy tests only in two studies (Robinson 2007; Tiplady 2013), the lack of blinding may have influenced the awareness of being pregnant and consequently the frequency of conducting a pregnancy tests, leading to detection bias. In two studies (Leader 1992; McLindon 2011) pregnancies were confirmed by ultrasound, and we did not consider this outcome likely to be influenced by blinding. One study (Robinson 2007) had an unexplained high dropout rate after randomisation and, furthermore, did not analyse the data for the last treatment cycle, which caused a high risk of bias. Two studies (Robinson 2007; Tiplady 2013) were funded by the manufacturer of the intervention method, and in one study (Leader 1992) the

intervention method was provided by the manufacturer. This may have introduced a bias in favour of timed intercourse. No heterogeneity was detected between studies, and therefore no sensitivity analysis was performed.

The completeness of the data is currently limited, and therefore results from this review require cautious interpretation as additional studies may alter the effect estimates. Further research is required, comparing more methods for timing intercourse and with longer treatment and follow-up times to investigate the long-term beneficial or deleterious effects of timed intercourse for conception.

Potential biases in the review process

Only four studies with data suitable for analysis were identified, with two studies reporting self-reported pregnancy rather than clinical pregnancy. Live birth was only reported by one very small study (McLindon 2011). We made a post hoc decision to include the two studies reporting self-reported pregnancy, by adding the outcome pregnancy (which includes clinical and self-reported pregnancy), as we felt that they had some clinical information. However, we acknowledge that this may have introduced bias to the review.

We conducted a comprehensive search with the help of an experienced trials search co-ordinator and, in addition, extensive manual searching in an effort to retrieve all eligible studies. However, unpublished studies may not have been identified. Furthermore, one included study (Pyper 2006) with a high number of randomised participants is still unpublished, and results are awaited. Because of the small number of studies, we did not construct a funnel plot. Therefore, we were unable to estimate the existence of publication or other reporting biases. Because of the commercial value of the testing monitor it is more likely that negative studies may not have been published.

Agreements and disagreements with other studies or reviews

It is difficult to draw conclusions on overall efficacy of timed intercourse. Our findings are in agreement with Stanford 2002, which reports that prospectively identifying the full window of fertility may lead to higher rates of conception. We also agree with ASRM Practice Committee 2013a, which stated that there is no conclusive evidence that monitoring fertility increases the chance of conception, as only two small studies reporting clinically relevant outcomes were found. Furthermore, we agree that more prospective randomised controlled trials with clinically relevant outcome data are needed.

AUTHORS' CONCLUSIONS

Implications for practice

There was insufficient evidence to draw definite conclusions on the effectiveness of timed intercourse for live birth, adverse events or clinical pregnancy in couples trying to conceive. Our findings suggest that timed intercourse is associated with higher pregnancy rates (including self-reported pregnancy) in couples trying to conceive, but the confidence interval almost included one and the size of the benefit is small. The overall quality of the evidence is low to very low and thus these conclusions should be regarded with caution.

In conclusion, while a small benefit for timed intercourse, without additional stress, cannot be excluded, the use of ovulation prediction methods to guide timed intercourse to achieve clinical pregnancy or live birth remains uncertain. These findings would be expected to impact healthcare providers' recommendations for using ovulation prediction methods for conception.

Implications for research

Large scale randomised controlled trials over a longer period of time are required to compare different methods for timing intercourse versus spontaneous intercourse or versus each other. The clinically relevant outcomes of live birth or clinical pregnancy (confirmed by ultrasound) should be reported. Intervention length should be clinically relevant and long enough for a potential difference in effect to be detected. Follow-up time needs to be long enough to be able to obtain these clinically relevant outcome data. Further research is also needed to determine whether other methods for timing intercourse, such as FABM or ultrasonography, are useful for couples trying to conceive. Duration of subfertility should be subgrouped within the same trial so a subgroup analysis can be conducted.

Finally, the economic impact of the different ovulation prediction methods should be reported as this must be considered when determining the method of ovulation prediction used.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Leader 1992

Methods	RCT, parallel two-arm trial, setting in fertility clinic Recruitment of participants following the appearance of a newspaper article Country: Australia
Participants	**Inclusion criteria:** - participant group 1: couples with unexplained infertility, with regular adequate ovulation confirmed each patient's physician, tubal patency confirmed by laparoscopy and dye insufflation and a normal semen analysis - participant group 2: couples with infertility thought to be due to a male factor, reduced motility index (≤ 150). This was calculated by multiplying by the grade (quality) of motility that may be present in a sample. Completed and normal female investigations **Exclusion criteria:** not stated **Number of participants randomised:** 160 (80 intervention, 80 control) participant group 1: 54 intervention, 56 control participant group 2: 26 intervention, 24 control **Number of exclusions, withdrawals, lost to follow up:** 12 (6 intervention, 6 control) participant group 1: 5 (cause subfertility found) in the intervention group participant group 2: 1 (severe male factor) in the intervention group, 6 (severe male factor) in the control group **Median (range) age (years):** participant group 1: 31 (24 to 39) in intervention group, 32 (23 to 41) in control group participant group 2: 31 (27 to 42) in intervention group, 30.5 (21 to 43) in control group **Duration of subfertility:** ≥ 12 months
Interventions	**Intervention**: use of Clearplan fertility monitor kits provided to use for 3 cycles + instructions on their use to time intercourse **Control**: contacted by telephone and advised about the best time of the menstrual cycle to achieve a pregnancy, i.e. how to calculate their ovulation by counting the length of their cycles **Treatment length, follow-up**: 3 cycles + follow up until clinical pregnancy
Outcomes	Clinical pregnancy, self-reported, confirmed by ultrasound Time point measured: after 3 cycles participants with missed periods had a pregnancy test. Follow up until their clinical pregnancy
Notes	Funding source: Fisons, company of Clearplan fertility kits Conflicts of interest: fertility monitors (Clearplan) were provided by the manufacturer

Risk of bias

Bias	Authors' judgement	Support for judgement

Leader 1992 (*Continued*)

Random sequence generation (selection bias)	Low risk	'shuffling envelopes'
Allocation concealment (selection bias)	Low risk	'sealed envelopes'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible because of the nature of interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome (clinical pregnancy) not likely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for missing outcome data reported; 12 of 160 not analysed (7. 5%). Reasons unrelated to intervention
Selective reporting (reporting bias)	Unclear risk	Protocol not available. Live birth data were not reported
Other bias	Low risk	No other sources of bias were found

McLindon 2011

Methods	RCT, parallel trial, setting in fertility clinic Recruitment of participants through visiting fertility clinic Country: Australia
Participants	**Inclusion criteria**: no ongoing pregnancy after 12 months of random intercourse, normal ovulatory cycle, bilateral tubal patency, normal seminal fluid analysis **Exclusion criteria**: known cause of subfertility **Number of participants randomised**: 17 **Number of participants analysed**: 17 **Number of exclusions, withdrawals, lost to follow up:** none **Mean age (range)**: intervention group 31.5 years (28 to 35) control group: 31.5 years (21 to 40) **Duration subfertility**: $\geq$ 12 months
Interventions	**Intervention**: symptothermal method charting **Control**: record of menstrual dates All couples received a standardised fertility awareness instruction (anatomy and physiology) prior to randomisation **Treatment length, follow-up**: 8 cycles
Outcomes	Live birth Clinical pregnancy

Notes	Funding: Golden Casket Scholarship Fund Study not published due to difficulties with recruitment and therefore early stopping of the trial. Study data retrieved through correspondence with authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random computer generated block sequence
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes (clinical pregnancy, live birth) not likely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for all participants
Selective reporting (reporting bias)	Low risk	Reported all pre-specified outcomes
Other bias	High risk	Early stopping of the trial due to difficulties with recruitment

Pyper 2006

Methods	RCT, three-arm study Recruitment of participants through media advertisements Country: United Kingdom
Participants	**Inclusion criteria**: Women aged 18 to 40 years who are having sexual intercourse with a regular partner Trying to conceive for less than 3 months Menstrual cycle length of 21 to 39 days for the past 3 months Willing to record all medication use and sexual intercourse during the study Willing to complete recruitment session in person or by telephone Willing to be randomised into one of three groups Willing to have a baseline pregnancy test to ensure that they are not pregnant at entry **Exclusion criteria**: Either partner has a history of infertility or is currently undergoing infertility treatment Either partner is using any form of contraception Woman is breast feeding Woman has used hormonal contraception during the past three menstrual cycles

Pyper 2006 (*Continued*)

	Woman has used emergency contraception in the past two menstrual cycles Woman has used injectable contraceptive in the past year **Number of participants randomised**:1453 **Number of exclusions, withdrawals, lost to follow up:** unclear **Mean age**: unclear **Duration of subfertility**: ≤ 12 months
Interventions	All participants are given a fertility monitor that requests them to test their urine from day 6 to day 25 of the menstrual cycle. Participants are equally randomised to the two intervention arms and one control arm **Intervention group 1:** receives information from the fertility monitor about the early fertile time (from the first rise in E3G until the LH surge is detected). Monitor displays high fertility from the first appearance of urine LH and for the next 2 days. It then shows low fertility until the end of the menstrual cycle **Intervention group 2:** receives information about the late fertile time (the onset of the LH surge and the following 2 days). Monitor displays high fertility from the first appearance of E3G and low fertility from the first appearance of LH until the end of the menstrual cycle **Control group:** does not receive any information about fertility status from the monitor although participants still perform urine tests All the women were asked to record in a daily diary information about intercourse patterns and lifestyle factors. The fertility data stored in the fertility monitor are downloaded onto a card at the end of each cycle, which is sent to the research team accompanied by the diary sheet. In addition, all women are asked to complete the Hospital Anxiety and Depression questionnaires at admission and at the end of each cycle **Follow-up**: 6 cycles or until pregnancy. There is a longer (undefined) follow-up for pregnancy outcomes. Potential to follow-up baby for 5 years
Outcomes	Cumulative three-cycle pregnancy rate, based on a positive pregnancy test and followed up afterwards Time-specific conception probabilities, estimated from coitus information recorded in 12-h intervals Changes in intercourse patterns with feedback about the fertile days
Notes	Funding source: UK National Health Service Executve Primary Care Career Scientist Award supported development of the study and Dr Pyper's salary. DLM Charitable Trust supported salaries of the research staff. Childhood Cancer Research Group supported development and maintenance of the study database. Unipath provided partial support for salaries of two of the research staff. The UK National Health Service Research and Development Support Funding supported some recruitment from primary care Conflicts of interest: Unipath is manufacturer of urinary fertility monitors and involved in the funding Protocol and interim pregnancy, live birth outcomes published in 2006, but outcomes not arranged by intervention group. Author (Dr Cecilia Pyper) was contacted about the current stage of the trial, and she responded that data is being analysed over the next four months. We were unable to acquire any final outcome data
Risk of bias	

Pyper 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomised schedules
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Women in the first two intervention groups are blinded to which arm of the intervention they have been assigned. Blinding not possible in control group. Research nurses not blinded because instructions they have to give to intervention groups and control group are different
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if pregnancy was confirmed by a pregnancy test only or by ultrasound
Incomplete outcome data (attrition bias) All outcomes	High risk	Interim results published in 2006, but not arranged by intervention group. Final results remain unpublished
Selective reporting (reporting bias)	High risk	Interim results published in 2006, but not arranged by intervention group. Final results remain unpublished
Other bias	Unclear risk	Final results not published

Robinson 2007

Methods	RCT, unblinded two-arm trial, home based setting November 2001 to August 2002 Recruitment of participants after expression of interest following targeted advertisements Country: United States
Participants	**Inclusion criteria:** - Women wishing to conceive - Aged 21 to 40 years (with a maximum 15% of total participants in 35 to 40-year age group) - Partner aged between 21 and 50 years **Exclusion criteria:** - Using hormonal birth control - Using fertility drugs (containing hCG or LH) - Medical condition that presented a risk if they became pregnant - Trying for > 2 years **Number of participants randomised:** 1000 (500 intervention, 500 control) **Number of exclusions, withdrawals, lost to follow up:** 351 (198 intervention (40%)

	, 153 control (31%)) intervention: 191 non responders, 4 pregnant prior to start, 3 no cycle 1 outcome Control: 144 non-responders, 5 pregnant prior to start, 3 not meeting selection criteria **Mean age (SD):** 29 years (4.2) in both groups **Duration of subfertility:** 76% ≤ 12 months
Interventions	**Intervention**: Use of a urinary fertility monitor (Clearblue Easy Fertility Monitor) **Control**: No methods given to the participants to help them conceive **Treatment length, follow-up**: three cycles
Outcomes	Self-reported cumulative pregnancy rates over two cycles of use, based on a positive pregnancy test Time points measured: after each treatment cycle
Notes	Funding source: Unipath Ltd, company of fertility monitor (Clearblue) Conflicts of interest: study funded by the manufacturer of the intervention method

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomisation stratified by the age of participants", generated by a computer
Allocation concealment (selection bias)	Low risk	Randomisation schedules only accessible to the study coordinator
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not possible because of the nature of the interventions Fertility testing methods other than the intervention were used during a higher proportion of cycles for the control group than the intervention group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported pregnancy
Incomplete outcome data (attrition bias) All outcomes	High risk	Unexplained high dropout rate (35%), 191 non-responders in CEFM group and 144 non-responders in control group
Selective reporting (reporting bias)	High risk	Live birth data were not reported + study did only report for 2 cycles instead of the pre-specified 3 cycles ("Insufficient evaluable data were provided for the third cycle of the study, therefore data were analysed for first two complete cycle only")

Robinson 2007 (*Continued*)

Other bias	Low risk	No other sources of bias were found

Tiplady 2013

Methods	RCT, two-arm trial, home based setting February 2010 to December 2010 Recruitment of participants via an advertisement placed on the Clearblue UK website Country: United Kingdom
Participants	**Inclusion criteria:** women living in the UK who were aged between 18 and 40 years, having regular menstrual bleeds and wishing to become pregnant **Exclusion criteria:** using hormonal contraception in the last 3 months, currently undergoing fertility treatment or investigation, previously diagnosed as infertile, anyone with a history of depression, anxiety or panic attacks and anyone dependant on either drugs or alcohol. Women who had previously used ovulation tests were not excluded from participating in the study **Number of participants randomised**: 210 (115 intervention, 95 control) **Number of exclusions, withdrawals, lost to follow up (LTFU):** 46 (22 intervention, 24 control) Intervention: 6 withdrawals or LTFU before start study, 16 withdrawals or LTFU during study Control: 14 withdrawals or LTFU before start study, 10 withdrawals or LTFU during study **Mean age (range):** Intervention: 28.3 years (20 to 40) Control: 29.7 years (19 to 39) **Duration of subfertility:** 86% $\leq$ 12 months
Interventions	**Intervention**: test-group volunteers used a urinary fertility monitor (Clearblue Digital Home Ovulation Test) for the duration of the study. They were asked to begin testing on day 6 of their cycle regardless of their normal cycle length **Control**: control-group volunteers were asked not to identify their time of ovulation using methods such as ovulation testing or basal body temperature measurements and instead were advised of the NICE guidelines on how to increase the chances of conception, i.e. that sexual intercourse every 2 to 3 days for the duration of the cycle is likely to increase the chances of conception. It was the volunteers' choice as to whether or not they followed these guidelines **Treatment length:** two cycles **Follow-up length:** six days after second cycle
Outcomes	Levels of stress: · Stress measured by questionnaire - total stress (PSS and PANAS and SF-12) - total positive and negative affect (PANAS) - physical and mental attributes (SF-12) · Biochemical marker of stress - urinary cortisol - E3G

	Pregnancy rate, based on pregnancy test Time points measured: (1) Baseline data, (2) Cycle 1 day 6, (3) Day after observed or predicted ovulation, (4) Cycle 2 day 6, (5) Day after observed or predicted ovulation, (6) Cycle 3 day 6
Notes	Funding: SPD Swiss Precision Diagnostics, GmbH, manufacturer of Clearblue pregnancy and ovulation tests. SPD Development Company Limited (manufacturer Clearblue Fertility Monitor) funded the Open Access publication for the article Conflicts of interest: funded by manufacturer of intervention method (Clearblue). Two authors are employees of SPD Development Company Limited, and one author provides paid consultancy to SPD

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomised schedules using STATA software
Allocation concealment (selection bias)	Low risk	Randomisation schedules only accessible to the study co-ordinator
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants not possible because of nature of interventions
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported pregnancies Un-blinding did not take place until statistical analysis of the data was complete for the outcome 'levels of stress'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers (22%) and reasons for missing outcome data reported in a flow chart. Numbers and reasons for missing outcome data similar in both groups. "Imputation methods were used to assess the effect of missing data due to attrition"
Selective reporting (reporting bias)	Unclear risk	Live birth data were not reported
Other bias	High risk	Due to under-powered groups for the outcome levels of stress, due to higher pregnancy rates overall in the test group, an additional (biased) cohort was recruited (ratio 2:1) into test group to enrich the data in this group

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Corsan 1993	Ovulation prediction method only used for timing of postcoital test. Pregnancy rate unclear
Fehring 1994	Not a RCT
Fehring 2013	Ovulation prediction for contraceptive use
Leiva 2014	Participants trying to conceive were excluded
Medina 1980	Ovulation prediction for contraceptive use
Mu 2014	Not a RCT

DATA AND ANALYSES

Comparison 1. Timed intercourse versus intercourse without ovulation prediction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.16, 3.41]
2 Adverse event: total stress	1	77	Mean Difference (IV, Fixed, 95% CI)	1.98 [-0.87, 4.83]
3 Clinical pregnancy rate	2	177	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.57, 2.12]
3.1 Timed intercourse through urinary fertility monitoring	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.51, 2.33]
3.2 Timed intercourse through Fertility Awareness Based Methods	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.31, 4.07]
4 Pregnancy rate (clinical and self-reported pregnancy)	4	1387	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.06, 1.71]
4.1 Timed intercourse through urinary fertility monitoring	3	1370	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.06, 1.73]
4.2 Timed intercourse through Fertility Awareness Based Methods	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.31, 4.07]
5 Pregnancy rate subgrouped on duration of subfertility	4	1387	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.06, 1.71]
5.1 Trying to conceive ≥12 months	2	177	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.57, 2.12]
5.2 Trying to conceive <12 months	2	1210	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.08, 1.80]

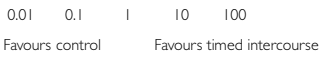
Analysis 1.1. Comparison 1 Timed intercourse versus intercourse without ovulation prediction, Outcome 1 Live birth rate.

Review: Timed intercourse for couples trying to conceive

Comparison: 1 Timed intercourse versus intercourse without ovulation prediction

Outcome: 1 Live birth rate

Study or subgroup	Timed intercourse n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McLindon 2011 (1)	2/8	3/9		100.0 %	0.75 [0.16, 3.41]
Total (95% CI)	**8**	**9**		**100.0 %**	**0.75 [0.16, 3.41]**
Total events: 2 (Timed intercourse), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					
Test for subgroup differences: Not applicable					



(1) timed intercourse through FABM, subfertile couples only (trying to conceive ≥ 12 months)

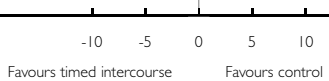
Analysis 1.2. Comparison 1 Timed intercourse versus intercourse without ovulation prediction, Outcome 2 Adverse event: total stress.

Review: Timed intercourse for couples trying to conceive

Comparison: 1 Timed intercourse versus intercourse without ovulation prediction

Outcome: 2 Adverse event: total stress

Study or subgroup	Timed intercourse N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Tiplady 2013 (1)	37	17.76 (6.48)	40	15.78 (6.25)		100.0 %	1.98 [-0.87, 4.83]
Total (95% CI)	**37**		**40**			**100.0 %**	**1.98 [-0.87, 4.83]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.36 (P = 0.17)							
Test for subgroup differences: Not applicable							



(1) Timed intercourse through urinary fertility monitoring, mostly non subfertile couples (trying to conceive <12 months). Higher score = higher stress

Analysis 1.3. Comparison 1 Timed intercourse versus intercourse without ovulation prediction, Outcome 3 Clinical pregnancy rate.

Review: Timed intercourse for couples trying to conceive

Comparison: 1 Timed intercourse versus intercourse without ovulation prediction

Outcome: 3 Clinical pregnancy rate

Study or subgroup	Timed intercourse n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Timed intercourse through urinary fertility monitoring					
Leader 1992 (1)	12/80	11/80		79.6 %	1.09 [0.51, 2.33]
Subtotal (95% CI)	**80**	**80**		**79.6 %**	**1.09 [0.51, 2.33]**
Total events: 12 (Timed intercourse), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.23 (P = 0.82)					
2 Timed intercourse through Fertility Awareness Based Methods					
McLindon 2011 (2)	3/8	3/9		20.4 %	1.13 [0.31, 4.07]
Subtotal (95% CI)	**8**	**9**		**20.4 %**	**1.13 [0.31, 4.07]**
Total events: 3 (Timed intercourse), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.18 (P = 0.86)					
Total (95% CI)	**88**	**89**		**100.0 %**	**1.10 [0.57, 2.12]**
Total events: 15 (Timed intercourse), 14 (Control)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 0.28 (P = 0.78)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.97), I^2 =0.0%					

(1) subfertile (trying to conceive ≥12 months). 26 in interv gp and 24 in control gp mild male factor. Preg rates this population 2/26: 2/24 respectively.

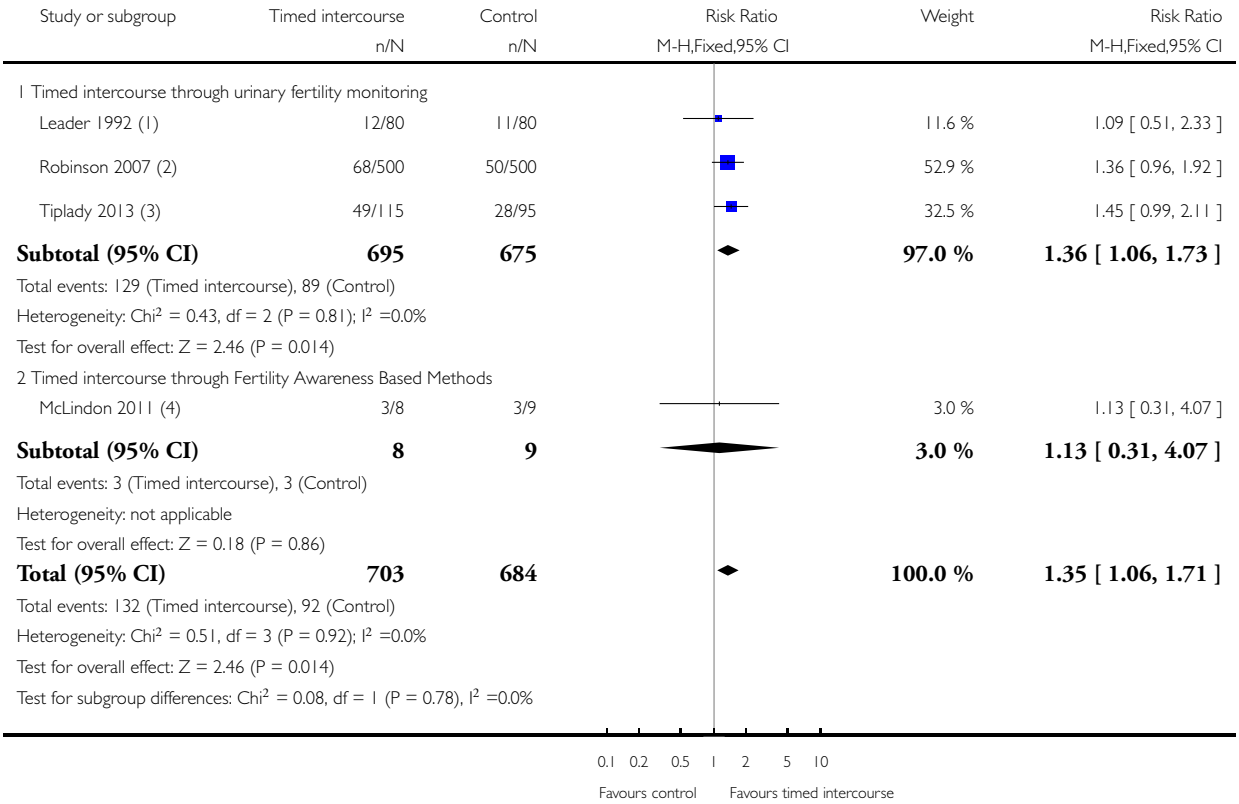
(2) subfertile couples only (trying to conceive ≥12 months)

Analysis 1.4. Comparison 1 Timed intercourse versus intercourse without ovulation prediction, Outcome 4 Pregnancy rate (clinical and self-reported pregnancy).

Review: Timed intercourse for couples trying to conceive

Comparison: 1 Timed intercourse versus intercourse without ovulation prediction

Outcome: 4 Pregnancy rate (clinical and self-reported pregnancy)



(1) subfertile couples only (trying to conceive ≥12 months), pregnancy confirmed by ultrasound. 26 couples in the interventiongroup and 24 couples in the controlgroup had mild male factor. Pregnancy rates in this population were 2/26 and 2/24 respectively.

(2) mostly non subfertile couples (trying to conceive <12 months), pregnancy confirmed by pregnancy test

(3) mostly non subfertile couples (trying to conceive <12 months), pregnancy confirmed by pregnancy test

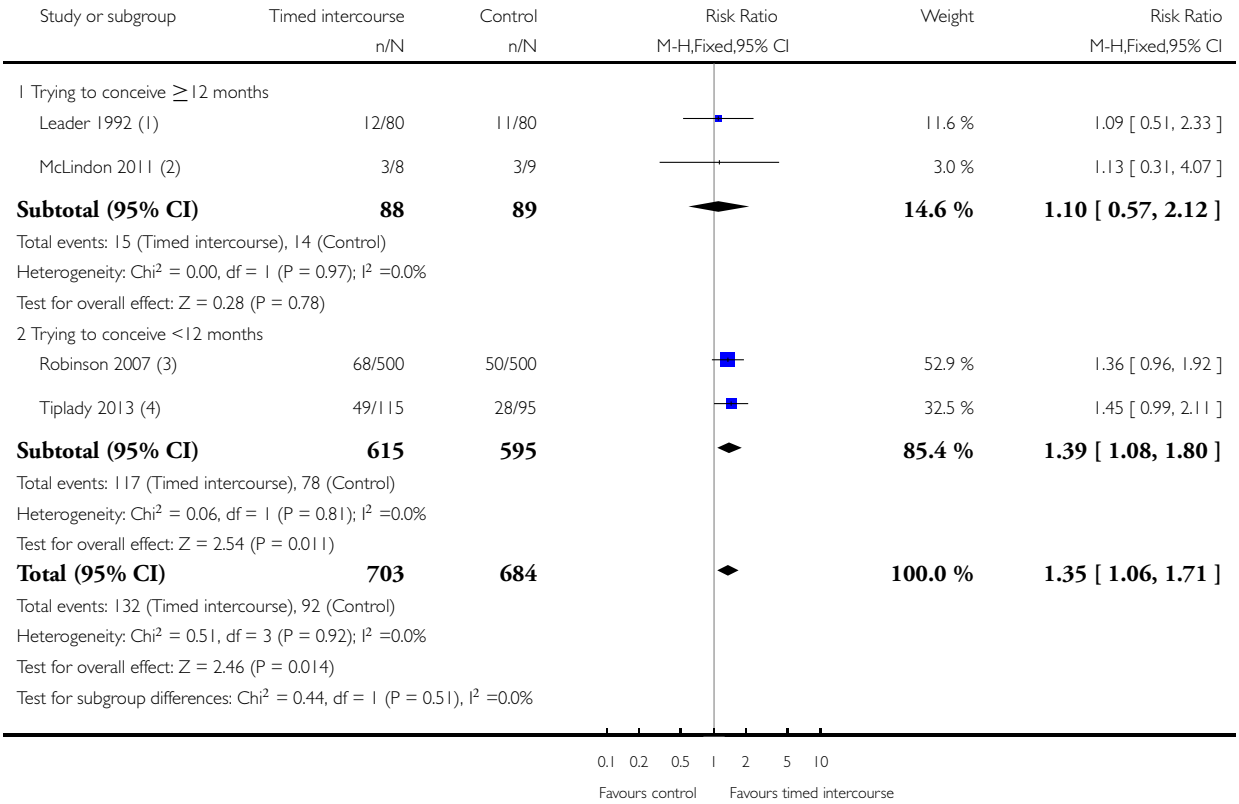
(4) subfertile couples only (trying to conceive ≥12 months), pregnancy confirmed by ultrasound

Analysis 1.5. Comparison 1 Timed intercourse versus intercourse without ovulation prediction, Outcome 5 Pregnancy rate subgrouped on duration of subfertility.

Review: Timed intercourse for couples trying to conceive

Comparison: 1 Timed intercourse versus intercourse without ovulation prediction

Outcome: 5 Pregnancy rate subgrouped on duration of subfertility



(1) pregnancy confirmed by ultrasound. 26 couples in the interventiongroup and 24 couples in the controlgroup had mild male factor. Pregnancy rates in this population were 2/26 and 2/24 respectively.

(2) pregnancy confirmed by ultrasound

(3) pregnancy confirmed by pregnancy test

(4) pregnancy confirmed by pregnancy test

APPENDICES

Appendix 1. CENTRAL search strategy

EBM Reviews - Cochrane Central Register of Controlled Trials (CENTRAL) <May 2014>
search date: 09.07.14
1 infertil$.tw. (2091)
2 subfertil$.tw. (158)
3 family plan$.tw. (302)
4 exp Fertilization/ (204)
5 fertil$.tw. (2926)
6 (conception or conceive).tw. (617)
7 exp Infertility/ (1650)
8 pregnan$.tw. (14030)
9 ovulat$.tw. (1723)
10 or/1-9 (17487)
11 (ovulat$ adj3 predict$).tw. (27)
12 (ovulat$ adj3 determin$).tw. (46)
13 (ovulat$ adj3 detect$).tw. (31)
14 (ovulat$ adj3 monitor$).tw. (32)
15 (ovulat$ adj3 measur$).tw. (82)
16 exp ovulation detection/ or exp ovulation prediction/ (14)
17 (ovulat$ adj2 method$).tw. (28)
18 timed intercourse.tw. (33)
19 (timing adj2 intercourse).tw. (5)
20 timed coitus.tw. (0)
21 (timing adj2 coitus).tw. (0)
22 Sympto-thermal.tw. (0)
23 Symptothermal.tw. (4)
24 (temperature adj2 method$).tw. (88)
25 standard days method.tw. (0)
26 two day method.tw. (0)
27 Creighton.tw. (6)
28 (calendar adj2 method$).tw. (7)
29 (rhythm adj2 method$).tw. (25)
30 FertilityCare.tw. (0)
31 Marquette.tw. (18)
32 (chart$ adj5 conceiv$).tw. (0)
33 (chart$ adj5 conception).tw. (0)
34 (chart$ adj5 fertil$).tw. (0)
35 FABM$.tw. (2)
36 (Billings adj5 method).tw. (1)
37 (Fertil$ adj2 Aware$).tw. (5)
38 home ovulation.tw. (5)
39 ((urin$ adj2 hormone$) and ovulat$).tw. (19)
40 (chart$ adj3 menstrua$).tw. (8)
41 (cervi$ mucus and ovulat$).tw. (40)
42 (basal body temperature$ and ovulat*).tw. (15)
43 ((pelvi$ adj2 ultrasound$) and ovulat$).tw. (6)
44 ((pelvi$ adj2 ultrasonography) and ovulat$).tw. (1)
45 (transvaginal ultrasound and ovulat$).tw. (35)
46 clearplan.tw. (2)
47 clearblue.tw. (3)

48 ((monitor$ adj2 urin$) and ovulat$).tw. (6)
49 (cervical secretions and ovulat$).tw. (0)
50 fertile window.tw. (2)
51 fertile period.tw. (2)
52 ((cervicovaginal adj2 change$) and ovulat$).tw. (0)
53 (chart$ adj2 cycle$).tw. (3)
54 calendar calculation$.tw. (0)
55 or/11-54 (493)
56 10 and 55 (338)

Appendix 2. MDSG search strategy

search date: 09.07.14
Keywords CONTAINS “infertility”or “subfertility”or “subfertility-Female”or“fertility”or“female factor” or Title CONTAINS “infertility”or “subfertility”or “subfertility-Female”or“fertility”or“female factor”
AND
Keywords CONTAINS “ovulation detection kit”or “Prediction” or “Clearblue Easy Fertility Monitor” or “fertile time” or “home ovulation test” or “cervical mucus” or “fertility-awareness-based methods”or Title CONTAINS “ovulation detection kit”or “Prediction” or“Clearblue Easy Fertility Monitor” or “fertile time” or “home ovulation test” or “cervical mucus” or “fertility-awareness-based methods” (70)

Appendix 3. MEDLINE search strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
search date: 09.07.14
1 infertil$.tw. (43010)
2 subfertil$.tw. (3553)
3 family plan$.tw. (17597)
4 exp Fertilization/ (19925)
5 fertil$.tw. (118701)
6 (conception or conceive).tw. (24831)
7 exp Infertility/ (53251)
8 pregnan$.tw. (371741)
9 ovulat$.tw. (32324)
10 or/1-9 (550176)
11 (ovulat$ adj3 predict$).tw. (378)
12 (ovulat$ adj3 determin$).tw. (654)
13 (ovulat$ adj3 detect$).tw. (539)
14 (ovulat$ adj3 monitor$).tw. (304)
15 (ovulat$ adj3 measur$).tw. (285)
16 exp ovulation detection/ or exp ovulation prediction/ (984)
17 (ovulat$ adj2 method$).tw. (297)
18 timed intercourse.tw. (104)
19 (timing adj2 intercourse).tw. (65)
20 timed coitus.tw. (5)
21 (timing adj2 coitus).tw. (10)
22 Sympto-thermal.tw. (42)
23 Symptothermal.tw. (72)
24 (temperature adj2 method$).tw. (1840)
25 standard days method.tw. (29)
26 two day method.tw. (3)

27 Creighton.tw. (207)
28 (calendar adj2 method$).tw. (115)
29 (rhythm adj2 method$).tw. (328)
30 FertilityCare.tw. (3)
31 Marquette.tw. (224)
32 (chart$ adj5 conceiv$).tw. (3)
33 (chart$ adj5 conception).tw. (9)
34 (chart$ adj5 fertil$).tw. (31)
35 FABM$.tw. (374)
36 (Billings adj5 method).tw. (92)
37 (Fertil$ adj2 Aware$).tw. (157)
38 home ovulation.tw. (9)
39 ((urin$ adj2 hormone$) and ovulat$).tw. (176)
40 (chart$ adj3 menstrua$).tw. (36)
41 (cervi$ mucus and ovulat$).tw. (674)
42 (basal body temperature$ and ovulat*).tw. (431)
43 ((pelvi$ adj2 ultrasound$) and ovulat$).tw. (70)
44 ((pelvi$ adj2 ultrasonography) and ovulat$).tw. (22)
45 (transvaginal ultrasound and ovulat$).tw. (225)
46 clearplan.tw. (16)
47 clearblue.tw. (10)
48 ((monitor$ adj2 urin$) and ovulat$).tw. (29)
49 (cervical secretions and ovulat$).tw. (25)
50 fertile window.tw. (59)
51 fertile period.tw. (370)
52 ((cervicovaginal adj2 change$) and ovulat$).tw. (1)
53 (chart$ adj2 cycle$).tw. (24)
54 calendar calculation$.tw. (24)
55 or/11-54 (7338)
56 10 and 55 (4507)
57 randomized controlled trial.pt. (378662)
58 controlled clinical trial.pt. (88836)
59 randomized.ab. (299100)
60 randomised.ab. (59989)
61 placebo.tw. (160292)
62 clinical trials as topic.sh. (171000)
63 randomly.ab. (216124)
64 trial.ti. (128718)
65 (crossover or cross-over or cross over).tw. (61341)
66 or/57-65 (956595)
67 exp animals/ not humans.sh. (3966792)
68 66 not 67 (882331)
69 56 and 68 (391)

Appendix 4. EMBASE search strategy

search date: 09.07.14
1 exp Infertility/ (88775)
2 infertil$.tw. (54051)
3 subfertil$.tw. (4324)
4 family plan$.tw. (13212)
5 fertil$.tw. (133242)
6 exp conception/ (5738)
7 (conception or conceive).tw. (28782)
8 pregnan$.tw. (426867)
9 or/1-8 (610937)
10 (Fertil$ adj2 Aware$).tw. (168)
11 Sympto-thermal.tw. (21)
12 Symptothermal.tw. (62)
13 temperature method$.tw. (537)
14 (calendar adj2 method$).tw. (144)
15 Rhythm method.tw. (122)
16 Standard days method.tw. (31)
17 Two day method.tw. (4)
18 Creighton.tw. (257)
19 FertilityCare.tw. (3)
20 Marquette.tw. (260)
21 exp ovulation detection/ (531)
22 exp ovulation prediction/ (52)
23 (ovulat$ adj2 detect$).tw. (402)
24 (ovulat$ adj2 predict$).tw. (292)
25 (chart$ adj5 conceiv$).tw. (8)
26 (chart$ adj5 conception).tw. (9)
27 (chart$ adj5 fertil$).tw. (53)
28 FABM$.tw. (496)
29 (Billings adj5 method).tw. (60)
30 (ovulat$ adj2 method$).tw. (365)
31 home ovulation.tw. (18)
32 ((urin$ adj2 hormone$) and ovulat$).tw. (169)
33 (chart$ adj3 menstrua$).tw. (39)
34 (cervi$ mucus and ovulat$).tw. (476)
35 (basal body temperature$ and ovulat$).tw. (316)
36 ((pelvi$ adj2 ultrasound$) and ovulat$).tw. (97)
37 ((pelvi$ adj2 ultrasonography) and ovulat$).tw. (31)
38 (transvaginal ultrasound and ovulat$).tw. (304)
39 clearplan.tw. (15)
40 clearblue.tw. (21)
41 ((monitor$ adj2 urin$) and ovulat$).tw. (28)
42 (cervi$ secretions and ovulat$).tw. (20)
43 (chart$ adj2 cycle$).tw. (18)
44 calendar calculation$.tw. (20)
45 or/10-44 (4640)
46 Clinical Trial/ (832239)
47 Randomized Controlled Trial/ (344969)
48 exp randomization/ (62552)
49 Single Blind Procedure/ (18468)
50 Double Blind Procedure/ (114109)

51 Crossover Procedure/ (39375)
52 Placebo/ (241950)
53 Randomi?ed controlled trial$.tw. (100004)
54 Rct.tw. (14147)
55 random allocation.tw. (1314)
56 randomly allocated.tw. (20312)
57 allocated randomly.tw. (1930)
58 (allocated adj2 random).tw. (713)
59 Single blind$.tw. (14326)
60 Double blind$.tw. (141173)
61 ((treble or triple) adj blind$).tw. (373)
62 placebo$.tw. (198462)
63 prospective study/ (254776)
64 or/46-63 (1365160)
65 case study/ (26710)
66 case report.tw. (259575)
67 abstract report/ or letter/ (894573)
68 or/65-67 (1175202)
69 64 not 68 (1327466)
70 9 and 45 and 69 (303)

Appendix 5. PsycINFO search strategy

search date: 09.07.14
1 exp Infertility/ (1688)
2 infertil$.tw. (2533)
3 subfertil$.tw. (60)
4 family plan$.tw. (2284)
5 fertil$.tw. (9333)
6 exp Fertilization/ (372)
7 (conception or conceive).tw. (19964)
8 or/1-7 (32385)
9 Sympto-thermal.tw. (3)
10 Symptothermal.tw. (1)
11 (temperature adj2 method$).tw. (43)
12 standard days method.tw. (8)
13 two day method.tw. (2)
14 Creighton.tw. (71)
15 (calendar adj2 method$).tw. (47)
16 (rhythm adj2 method$).tw. (53)
17 FertilityCare.tw. (0)
18 Marquette.tw. (31)
19 (ovulat$ adj2 detect$).tw. (11)
20 (ovulat$ adj2 predict$).tw. (11)
21 (chart$ adj5 conceiv$).tw. (0)
22 (chart$ adj5 conception).tw. (2)
23 (chart$ adj5 fertil$).tw. (2)
24 FABM$.tw. (2)
25 (Billings adj5 method).tw. (3)
26 (Fertil$ adj2 Aware$).tw. (22)
27 (ovulat$ adj2 method$).tw. (5)
28 or/9-27 (305)

29 8 and 28 (55)
30 random.tw. (40928)
31 control.tw. (317619)
32 double-blind.tw. (17938)
33 clinical trials/ (7705)
34 placebo/ (3801)
35 exp Treatment/ (583487)
36 or/30-35 (891564)
37 29 and 36 (13)

Appendix 6. CINAHL search strategy

#	Query	Results
S46	S9 AND S33 AND S45	116
S45	S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44	901,016
S44	TX allocat* random*	3994
S43	(MH "Quantitative Studies")	12,231
S42	(MH "Placebos")	8814
S41	TX placebo*	31,939
S40	TX random* allocat*	3994
S39	(MH "Random Assignment")	37,614
S38	TX randomi* control* trial*	75,203
S37	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	723,010
S36	TX clinic* n1 trial*	164,722
S35	PT Clinical trial	76,291
S34	(MH "Clinical Trials+")	177,043
S33	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32	2168

(*Continued*)

S32	TX clearblue	3
S31	TX clearplan	0
S30	TX clearplan	0
S29	TX (pelvi* N2 ultrasound*)	152
S28	TX (basal body temperature*)	37
S27	TX(cervi* mucus)	49
S26	TX(urin* N2 hormone*)	186
S25	TX home ovulation	5
S24	TX(Fertil* N2 Aware*)	59
S23	TX FABM*	14
S22	TX Marquette	1111
S21	TX FertilityCare	2
S20	TX(calendar N2 method*)	43
S19	TX standard days method	19
S18	TX(temperature N2 method*)	435
S17	TX Symptothermal	8
S16	TX timed intercourse	16
S15	(MM "Ovulation Detection") OR (MM "Ovulation Prediction")	34
S14	TX(ovulat* N3 measur*)	12
S13	TX(ovulat* N3 monitor*)	11
S12	TX(ovulat* N3 detect*)	73
S11	TX(ovulat* N3 determin*)	14
S10	TX(ovulat* N3 predict*)	23
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8	148,371

(*Continued*)

S8	TX ovulat*	1466
S7	TX pregnan*	131,384
S6	TX (conception or conceive)	19,030
S5	(MM "Fertility")	1380
S4	TX family plan*	9659
S3	TX subfertil*	405
S2	TX infertil*	6977
S1	(MM "Infertility")	3498

Appendix 7. Ongoing trials search strategy

search date: 05.08.14
http://www.clinicaltrials.gov search strategy
ovulat* AND pred* (0)
http://www.who.int/trialsearch/Default.aspx search strategy
ovulat* AND pred* (3)

Appendix 8. DARE search strategy

search date: 05.08.14
ovulat* and pred* (0)

Appendix 9. Web of Knowledge search strategy

search date: 05.08.14
(ovulat* AND predict*)
Refined by: DOCUMENT TYPES: (CLINICAL TRIAL)
Timespan: All years.
Search language=Auto (178)

Appendix 10. Virtual Health Library search strategy

search date: 05.08.14
(tw:(ovulat*)) AND (tw:(predict*)) AND (instance:“regional”) AND (db:(“LILACS” OR “BDENF” OR “CUMED” OR “DECS” OR “IBECS”) AND limit:(“humans”)) (26)
(tw:(ovulat*)) AND (tw:(detect*)) AND (instance:“regional”) AND (db:(“LILACS” OR “CUMED” OR “DECS” OR “IBECS” OR “COCHRANE-HTA”) AND limit:(“humans”)) (54)

Appendix 11. PubMed search strategy

search date: 05.08.14
“Ovulation Prediction”[Mesh] OR “Ovulation Detection”[Mesh] AND (Randomized Controlled Trial[ptyp] OR systematic[sb]) (21)

Appendix 12. OpenSIGLE search strategy

search date: 05.08.14
ovulat* AND predict* (20)

Appendix 13. Data extraction table

General information

- Study ID (created by review author)
- Report ID (created by review author)
- Review author ID (created by review author)
- Citation and contact details

Eligibility

- Type of study
- Participants
- Types of interventions
- Types of outcome measures
- Inclusion or Exclusion
- Reason for exclusion

Population and setting

- Population description
- Setting
- Inclusion criteria
- Exclusion criteria
- Method(s) of recruitment of participants
- Informed consent obtained
- Country

Methods

- Aim of study
- Study design
- Unit of allocation

- Total study duration

Risk of bias assessment (low/high/unclear)

- Selection bias

o Random sequence generation
o Allocation sequence concealment

- Performance bias

o Blinding of participants and personnel

- Detection bias

o Blinding of outcome assessment (patient-reported outcomes)

- Attrition bias

o Due to amount, nature or handling of incomplete outcome data

- Reporting bias

o Selective reporting

- Incomplete outcome data

Participants

- Total number of participants at randomisation
- Number analysed at outcome.
- Baseline imbalances
- Age
- Ethnicity
- Cause of subfertility
- Duration of subfertility
- Pregnant before
- Other treatment received

Interventions

- Total number of intervention groups.

For each intervention and comparison group of interest:

- Specific intervention (type of ovulation prediction method)
- Intervention details:

- No. randomised to group
- Description of intervention
- Duration of treatment
- Duration of follow up
- Loss to follow up
- Costs of the intervention

Outcomes

- Outcomes and time points (i) collected; (ii) reported

For each outcome of interest (live birth, adverse event, clinical pregnancy rate, time to conception):

- Outcome definition (with diagnostic criteria if relevant)
- Measurement tools or method used
- Unit of measurement (adverse events, time to conception)
- For scales: upper and lower limits, and whether high or low score is good

Results

- Number of participants allocated to each intervention group

For each outcome of interest (live birth, adverse event, clinical pregnancy rate, time to conception):

- Sample size
- Missing participants
- Summary data for each intervention group (e.g. 2 × 2 table for dichotomous data *(live birth, adverse event, clinical pregnancy rate*); means and SDs for continuous data *(adverse events, time to conception)*
- [Estimate of effect with confidence interval; P value]
- [Subgroup analyses]

Applicability

- Important populations excluded from the study?
- Intervention likely to be aimed at disadvantaged groups?
- Does study directly address the review question?

Miscellaneous

- Funding source
- Key conclusions of the study authors
- Miscellaneous comments from the study authors
- References to other relevant studies
- Correspondence required
- Miscellaneous comments by the review authors

CONTRIBUTIONS OF AUTHORS

MM wrote the protocol, selected studies, extracted data and drafted the full review.

LM acted as a clinical expert, commented on the protocol and the full review.

MB acted as a clinical expert, commented on the protocol and the full review.

BS acted as a second assessor of the literature and will comment on the systematic review.

JK acted as a clinical expert, commented on the protocol and the full review.

CF acted as a clinical expert, commented on the protocol, acted as a third author for screening and selecting studies and commented on the full review.

DECLARATIONS OF INTEREST

Review author Luke McLindon was principal investigator of the included study McLindon 2011.

SOURCES OF SUPPORT

Internal sources

- MDSG, New Zealand.

not specified

External sources

- Stichting Nijmeegs Universiteitenfonds, Netherlands.

Scholarship to support students from the Radboud University Nijmegen to study, do an internship or research abroad.

- Comissie Voorzieningen Studenten Budget (CVSB), Netherlands.

Grant to subsidise activities of (medical) student organisation and foreign internships of individual students from the medical faculty of the Radboud University Nijmegen

- UMCN St Radboud, Nijmegen, Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Because of the lack of studies reporting live births or clinical pregnancy rates, a new secondary outcome has been added as an amendment: pregnancy, including clinical pregnancy and self-reported pregnancy. This outcome was also included in the 'Summary of findings' table.

During data extraction, we realised we had not reported in the protocol which time point we would select to analyse data from, if there was more than one time point at which results were presented. For that reason, this has been added in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Coitus; *Fertilization; *Infertility; *Pregnancy Rate; Live Birth; Ovulation Detection [methods]; Ovulation Prediction [*methods; statistics & numerical data]; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Adult; Female; Humans; Pregnancy