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Helmerhorst FM, Van Vliet HAAM, Gornas T, Finken MJ, Grimes DA

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Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples

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ABSTRACT

Background

The postcoital test has poor diagnostic and prognostic characteristics. Nevertheless, some physicians believe it can identify scanty or abnormal mucus that might impair fertility. One way to avoid 'hostile' cervical mucus is intrauterine insemination. With this technique, the physician injects sperm directly into the uterine cavity through a small catheter passed through the cervix; the theory is to bypass the "hostile" cervical mucus. Although most gynaecological societies do not endorse use of intrauterine insemination for hostile cervical mucus, some physicians consider it an effective treatment for women with infertility thought due to cervical mucus problems.

Objectives

The aim of this review was to determine the effectiveness of intrauterine insemination with or without ovarian stimulation in women with cervical hostility who failed to conceive.

Search methods

We searched Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* Issue 3, 2008, MEDLINE (1966 to August 2008), EMBASE (1980 to August 2008), POPLINE (to August 2008) and LILACS (to August 2008). In addition, we contacted experts and searched the reference list of relevant articles and book chapters.

Selection criteria

We included randomised and quasi-randomized controlled trials comparing intrauterine insemination with intercourse timed at the presumed fertile period or expectant management. Participants were women with cervical hostility who failed to conceive for at least one year.

Data collection and analysis

We assessed the titles and abstracts of 396 publications and two reviewers independently abstracted data on methods and results from five studies identified for inclusion. The main outcome is pregnancy rate per couple.

Main results

We did not pool the outcomes of the included six studies in a meta-analysis due to the methodological quality of the trials and variations in the patient characteristics and interventions. Narrative summaries of the outcomes are provided. Each study was too small for a clinically relevant conclusion. Only one of the studies provided information on important outcomes such as spontaneous abortion, multiple pregnancies, but none of studies reported on the occurrence of e.g. ovarian hyperstimulation syndrome.

Authors' conclusions

There is no evidence from the published studies that intrauterine insemination is an effective treatment for cervical hostility. Given the poor diagnostic and prognostic properties of the postcoital test and the observation that the test has no benefit on pregnancy rates, intrauterine insemination (with or without ovarian stimulation) is unlikely to be a useful treatment for putative problems identified by postcoital testing.

PLAIN LANGUAGE SUMMARY

Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples

Three elements are required for human fertilization to occur: an egg, a sperm, and the ability of the egg and sperm to meet. One possible cause of egg and sperm not meeting could be a lack of cervical mucus or mucus that is of poor quality. Mucus in the cervix is thought to help a sperm reach the egg. In 1866, the American gynaecologist James Marion Sims first described the postcoital test with which sperm motility can be observed in mucus of the cervical canal: "If we take a drop of semen from the vagina immediately after intercourse, and place it under the microscope, we shall see the hurried movements of seemingly thousands of spermatozoa." By the 1990's, however, the postcoital test appeared to have poor diagnostic and prognostic characteristics. Nevertheless, some doctors believe that intrauterine insemination is an effective treatment for cervical 'hostility' (poor-quality or insufficient mucus). With this technique, doctors insert a tiny tube with selected sperm into the woman's vagina, through the cervix, ready to meet the egg (in the tube). The idea is to bypass the mucus thought to be causing the infertility problem. To evaluate the usefulness of this technique, we looked for all the controlled trials that have studied it. Intrauterine insemination was compared with timed intercourse: intercourse was advised by pinpointing the most fertile time of the cycle. Five studies were found and are included in this systematic review. The outcomes of the six studies were impossible to combine due to the poor quality of the trials and variations in the participant characteristics and approaches to insemination. There is no evidence that intrauterine insemination is an effective treatment for cervical hostility. Intrauterine insemination is unlikely to be helpful in this setting.

BACKGROUND

The cervix generally functions as an effective barrier against sperm. Under good conditions only 200 spermatozoa of approximately 280 million spermatozoa deposited in the upper vagina after an average ejaculation may successfully pass the cervical canal ([Harper 1982](#)). Given this high attrition, even slight changes in cervical mucus quality may rapidly transform the cervix into a 'hostile' environment which may prevent conception. One of the original objectives of the famous American gynaecologist James Marion Sims in developing the postcoital test (PCT) was to "determine whether the secretions of this canal are favourable or not to the vitality of the spermatozoa" ([Sims 1868](#)).

Since its introduction in 1866, postcoital testing of cervical mucus

for the presence of progressively motile sperm has become a common tool in the investigation of subfertile couples, especially for diagnosing a 'cervical factor' in subfertility ([Barnea 1982](#)). Observational studies ([Griffith 1990](#); [Oei 1995a](#)) showed that the diagnostic and prognostic characteristics of the test are limited. More importantly, a randomised controlled trial ([Oei 1998](#)) found that routine use of the postcoital test did not improve the pregnancy rate. Although several organisations adopted the new evidence by stating that routine postcoital testing is unnecessary or not recommended ([ACOG 2002](#); [ASRM 2000](#); [RCOG 2004](#); [Speroff 2005](#)), the postcoital test is still popular ([Oei 1995b](#)). Equally popular is the treatment for an abnormal postcoital test. Intrauterine insemination (IUI) seems to be a logical treatment for cervical factor hostility; IUI bypasses the hostile cervical mucus by

directly depositing sperm into the uterine cavity, so that women with no other fertility related problems would be likely to conceive with this method.(Allen 1985; Balasch 2000; Check 1995; Cohlen 2004; Ombet 1997; Van den Eede 1995).

Since the first publication of this review in the Cochrane Library in 2005 and in Obstetrical & Gynecological Survey (Helmerhorst 2006) a Dutch group (Steures 2004; Van der Steeg 2004) published a RCT on couples with an isolated cervical factor. After informed consent, couples were randomly allocated to IUI or to expectant management for 6 months (Steures 2007). Although this type of intervention has not been secured in the original protocol, we decided to include the type and study in this adapted and updated review.

OBJECTIVES

The aim of this review was to determine the effectiveness of IUI using partner's sperm, with and without ovarian stimulation, in women with cervical hostility (abnormal PCT as defined by (Oei 1995a) or as defined by the trialists). Our a priori hypothesis was: IUI with or without ovarian stimulation will increase the pregnancy rate per couple compared to timed intercourse (TI; during the presumed fertile days) or to expectant management in women with cervical mucus hostility.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials are included in this review. We included both parallel and cross-over trials.

Types of participants

Couples with cervical hostility (abnormal PCT as defined by (Oei 1995a) or as defined by the trialists), who failed to conceive for at least one year and who underwent IUI or timed intercourse.

Types of interventions

We examined the following treatment comparisons:

- IUI in natural cycles versus TI in natural cycles.
- IUI in cycles with ovarian stimulation versus TI in cycles with ovarian stimulation.
- IUI in cycles with ovarian stimulation versus TI in natural cycles.

- IUI in natural cycles versus TI in cycles with ovarian stimulation.
- IUI (with or without ovarian stimulation) versus expectant management .

Types of outcome measures

The main outcome of interest was live birth or ongoing pregnancy. A secondary outcome was pregnancy per couple determined with a hCG test in urine or blood or ultrasound examination for early pregnancy. Other secondary outcome measures included number of spontaneous abortions, multiple pregnancies and ovarian hyperstimulation syndrome (OHSS).

Search methods for identification of studies

We conducted computerized searches of Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, MEDLINE (1966 to June 2005/August 2008), EMBASE (1980 to June 2005/August 2008), POPLINE (2004/2008) and LILACS (2004/2008) using the following search strategies:

- CENTRAL

intrauterine insemination

- PUBMED

((intrauterine insemination OR insemination, artificial OR reproductive techniques, assisted) AND intrauterine)

AND

((coitus OR intercourse) AND (time* OR time factors)) OR timed intercourse)

AND

(randomised controlled trials OR randomised controlled trial(pt))

- POPLINE

infertility

AND

intercourse

AND

treatment

- EMBASE

intrauterine insemination

AND

timed(w)intercourse

- LILACS

((intrauterine insemination OR insemination, artificial OR inseminacion artificial OR inseminacao artificial OR reproductive techniques, assisted OR tecnicas reproductivas asistidas OR tecnicas reproductivas asistidas)

AND

((intrauterine OR intrauterina)) (Words)

We searched the reference lists of all identified studies for additional, previously unidentified trials. Relevant book chapters, review articles and reports of symposia were searched for all relevant trials. We attempted to find unpublished studies through personal communication with authorities.

Data collection and analysis

Study identification

Two reviewers evaluated the titles and abstracts identified from the literature search and assessed copies of all possibly relevant articles for eligibility. Discrepancies were resolved by discussion.

Methodological Quality

We critically appraised the validity of trials by assessing potential biases. The appraisal of potential biases focused on study design; the method of generating the allocation sequence; the use and method of allocation concealment; the use and method of blinding; exclusion of participants after randomisation; early discontinuation; loss to follow-up and funding. We did not calculate summary scores from quality scales as it is problematic (Juni 2001).

Data extraction

We developed and field tested a data collection form, as described in the Cochrane Reviewers' Handbook (Alderson 2004; <http://www.cochrane.org/resources/handbook/>). Two reviewers independently collected the data on extraction forms. We extracted the data under unblinded conditions (Berlin 1997). In addition to the outcome measures, we systematically extracted data on the following variables: couple characteristics; assessment of ovulatory status; assessment of tubal patency; semen quality; PCT; screening for antisperm antibodies; method of ovarian hyperstimulation; sperm preparation; timing method; insemination procedure; mean number of sperm inseminated; number of inseminations per cycle; and method of pregnancy diagnosis. When necessary we contacted the authors of the trials to seek additional information. Discrepancies were resolved by discussion. We did not assess inter-observer reliability.

Data analysis

The following data have been tried to extract from the trials.

- (1) The method of generating the allocation sequence
- (2) The use and method of blinding
- (3) The use and method of allocation concealment
- (4) Number of patients randomised, excluded or lost to follow up
- (5) Whether an intention to treat analysis was done
- (6) Whether a power calculation was done
- (7) Duration, timing and location of the study
- (8) Participant characteristics
- (9) Interventions.

The abstracted data were entered into RevMan 4.2. Correct entry of the data was verified by one other reviewer. The data in the present review are based on the analytic method (e.g. intention-to-treat, per-protocol) used in the study report. We could not combine the clinical outcomes of any of the studies in meta-analysis;

the studies varied with respect to the participant characteristics and interventions. In addition, the trials were generally of poor methodological quality. Consequently, we provide narrative summaries alone.

If new eligible trials are identified in the future we will calculate odds ratios with a 95% confidence intervals for the binary outcome pregnancy using the random effects model. We will test for heterogeneity between the pooled results using the I^2 statistic. A sensitivity analysis based on the methodological quality of the trials will be conducted to test the robustness of the outcomes. We will follow the format as displayed in the section Tables 'Comparisons and data'.

RESULTS

Description of studies

In 1 June 2005 were recruited: in POPLINE 46 items, from which 45 were not related to the subject, and one was related but was not a controlled study. In EMBASE 28 items were recruited, and all were related to the general subject but not to cervical hostility. In PUBMED we found 21 hits; three of them were useful. In LILACS 20 items were identified, but none of them were useful. CENTRAL rendered 230 titles; six of them were useful. The search strategy yielded a total of 386 publications. The remaining were identified in reference lists. In the 5 August 2008 search we found 9 additional hits in EMBASE and 1 in PUBMED. We photocopied 15 potentially relevant studies, of which six met the inclusion criteria for the review. The six trials (Check 1995; Glazener 1987; Kirby 1991; Martinez 1990; Steures 2007; te Velde 1989) included 384 couples (range 2 to 184).

(1) Trial

Two trials were quasi randomised, Check (Check 1995) used last digit of the year of birth and the last digit of the social security number, Glazener (Glazener 1987) took the date of birth to generate the allocation sequence. In contrast to one trial (Check 1995), four trials had a cross-over design (Glazener 1987; Kirby 1991; Martinez 1990; te Velde 1989). These trials presented pregnancy rates per treatment branch, and not per initially allocated group. Three trials offered patients six cycles with IUI alternated with intercourse cycles (Glazener 1987; Kirby 1991; te Velde 1989); another trial (Martinez 1990) randomised 40 couples to four treatment modalities during four different consecutive treatment cycles: IUI with clomiphene citrate, IUI without clomiphene citrate, timed intercourse with clomiphene citrate, and timed intercourse without clomiphene citrate. In this trial only two patients were diagnosed with cervical factor infertility. Check (Check 1995) evaluated only the first treatment. The Steures trial (Steures 2007) uses a safe allocation concealment for randomisation of subfertile cou-

ples with an isolated cervical factor to intrauterine insemination for 6 months or expectant management for 6 months.

(2) Patient baseline characteristics

Age of the included population was reported by two trials (Glazener 1987; Martinez 1990), and it ranged from 18 to 42 years. The mean maternal age in the Steures trial (Steures 2007) was in each group 30 years. Duration of infertility was reported by five trials (Glazener 1987; Kirby 1991; Martinez 1990; Steures 2007; te Velde 1989) and ranged from one year to 15 years. Trials differed with regard to inclusion and exclusion criteria. Although all trials only included women with normal ovulatory cycles, considerable differences emerged between trials regarding the definition and performance of an abnormal postcoital test and other sperm-mucus interaction tests.

Cervical hostility was defined in terms of an abnormal or negative postcoital test by Check, Glazener and Steures (Check 1995; Glazener 1987; Steures 2007) as absence of forward progressing spermatozoa. The time period between intercourse and performance of the postcoital test was explicitly mentioned in the Check study (8 to 12 h) and in the Glazener study (6 to 18 h) (Check 1995; Glazener 1987). Check used ultrasonic measurements of the follicle as well as estradiol and progesterone concentrations for timing of the test (Check 1995). Timing of the test in the Steures trial (Steures 2007) was based on basal body temperature chart or with ultrasonography. Except for the Steures trial (Steures 2007) the other studies excluded or explicitly mentioned cases with an impaired sperm-mucus interaction due to an immunological reason.

Kirby defined nonimmunological cervical mucus hostility when a low pH of the mucus (<6) and/or a lack or absence of adequate amounts of cervical mucus in the peri-ovulatory phase was found (Kirby 1991). Te Velde described 27 couples with an impaired sperm-mucus interaction; eight of them were categorized in an immunological subgroup, fifteen of them in a so called explained cervical hostility group (3 with a low pH of the mucus, twelve with a moderate or poor mucus according to the Insler score) and four couples resided in the unexplained cervical hostility subgroup due to a poor postcoital test ("immotile spermatozoa in good mucus") (te Velde 1989). In the Martinez study the definition of a negative postcoital was not stated; the test was performed at the time of "adequate midcycle mucus" (Martinez 1990) For more details we refer to the table of characteristics of included studies.

(3) Timing of insemination

Trials differed in timing of an intervention during the cycle. In one trial cervical mucus as a measure for the timing of the cycle was applied (Glazener 1987), whereas the other trials measured LH in urine (Martinez 1990), in serum (Check 1995; Kirby 1991) or in plasma (te Velde 1989); Kirby measured also sex steroids in serum. Martinez performed vaginal ultrasound for follicular development; Check 1995 reported that follicular maturation was always confirmed, but not how it was done. Only Check 1995 and te Velde 1989 described the start of the measurements: at the

tenth day of the cycle and beginning 16 days before the presumed menses, respectively.

All trials reported when IUI was performed: on alternate days during the pre-ovulatory phase of cervical mucus secretion (Glazener 1987), the day after the LH rise (te Velde 1989), 16-28 hours after detection of the first positive LH peak (Martinez 1990), 40 hours after the start of the LH rise (Kirby 1991), or 36 hours after the beginning of the LH surge or 12 hours after the peak (Check 1995). Kirby 1991, Martinez 1990 and te Velde 1989 requested patients to abstain from intercourse until three days after insemination. Glazener 1987 reported that IUI was usually performed twice each cycle.

Four trials stated when intercourse was advised: on the evening of the day of the LH rise and on the following day (te Velde 1989), 16 to 28 hours after detection of the first positive LH peak (Martinez 1990), approximately 40 hours after the start of the LH rise (Kirby 1991), or for the next two consecutive nights after the LH surge/peak (Check 1995). Coitus was probably not timed in the trial of Glazener (Glazener 1987), which might not meet the entry criterion of timed intercourse. Later in the process of developing the review, when we decided not to lump data of the studies and to mention all the studies on a narrative way, we included this study for completeness. Martinez 1990 asked all patients to avoid intercourse from the beginning of the LH testings until either timed coitus was indicated or until three days after insemination. In the Steures trial (Steures 2007) cycle monitoring, detection and/or induction of ovulation were performed according to hospital-specific protocols.

(4) Sperm preparation

Trials differed with regard to the preparation of sperm. In one trial the method of sperm preparation was not stated (Glazener 1987). In one trial centrifuged semen on 70% Percoll was used (te Velde 1989), whereas in three trials discontinuous gradients of either Percoll (Kirby 1991; Martinez 1990) or Percoll/Hanks' solution (Check 1995) were used. Further, Kirby also stated that a modified swim-up procedure occurred during the early part of the study. In the Steures trial (Steures 2007) gradient semen preparation was performed according to hospital-specific protocols.

(5) Insemination procedure

Trials differed with regard to insemination procedures. Sperm were inseminated either into the cervical canal (Glazener 1987) or into the uterine cavity (Check 1995; Kirby 1991; Martinez 1990; te Velde 1989). Different volumes of (diluted) samples were used, ranging from 0.2 (Check 1995; Martinez 1990) to 1 ml (Glazener 1987). In the Steures trial (Steures 2007) insemination regimens were performed according to hospital-specific protocols.

(6) Outcome measures

Only two trials reported how pregnancy was confirmed. Martinez 1990 applied an immuno-enzymatic assay for qualitative determination of hCG in urine 14 days after IUI; if positive, a quantitative assay for serum hCG was used one week later. Kirby 1991 reported that pregnancies were confirmed by elevated serum lev-

els of hCG, clinical examination, and ultrasound. In the Steures trial (Steures 2007) the primary endpoint was ongoing pregnancy within 6 months. Ongoing pregnancy was defined as the presence of fetal cardiac activity at transvaginal sonography, at a gestational age of 12 weeks.

Risk of bias in included studies

Description of study methods

Overall, the description of 5 of the 6 study methods was poor, except in the Steures trial (Steures 2007). Two quasi randomised studies reported the method of generating the allocation sequence (Check 1995; Glazener 1987). In 5 of the included trials (Glazener 1987; Kirby 1991; Martinez 1990; Steures 2007; te Velde 1989) the use or method of concealing the allocation sequence was not reported. Due to the nature of the interventions, blinding of the investigators and participants was not feasible. None of the trials reported whether the outcome assessors were blinded. Most trials did not report details concerning the number and reasons for early discontinuation, exclusions after randomisation and loss to follow-up for each group. None of the studies, except the Steures trial (Steures 2007) stated an a priori hypothesis or sample size calculation. None presented a valid analysis of their data and none followed pregnancies to assess outcome, except the Steures trial (Steures 2007).

Methodological quality

Two studies did not use random sequence generation (Check 1995; Glazener 1987) and three did not describe the random method (Kirby 1991; Martinez 1990; te Velde 1989). None of the studies described allocation concealment, except the Steures trial (Steures 2007). Four studies excluded participants after randomisation (Check 1995; Glazener 1987; Martinez 1990; Steures 2007). Non-random methods of generating the allocation sequence, inadequate concealment of the allocation sequence, and exclusion of participants after randomisation all may result in bias (Schulz 1995; Schulz 2002b; Schulz 2002c; Schulz 2002d). A cross-over design was used in four trials (Glazener 1987; Kirby 1991; Martinez 1990; te Velde 1989). The use of a cross-over design in infertility trials leads to exaggerated treatment effects (Khan 1996). None of the trials were conducted by pharmaceutical companies.

Check 1995 was a quasi-randomised controlled trial; it generated the allocation sequence by date of birth and social security number. Systematic methods such as assignment based on date of birth or social security number preclude adequate allocation concealment (Schulz 2002b). Blinding of outcome assessors was not described. Fifteen couples in the IUI group and 11 couples in the timed intercourse group were excluded after randomisation because the test cycle revealed sperm with progressive forward motion or the couples refused the method. Loss to follow up was not reported. Number of allocated couples was 184, 156 of them were analysed. Glazener 1987 was a quasi-randomised controlled trial using allo-

cation by date of birth. The trialists reported that ensuring strict alternation of cycles with and without "artificial insemination with husband's semen" proved impossible. Systematic methods such as allocation based on date of birth prevents adequate allocation concealment (Schulz 2002b). Blinding of the outcome assessors was not reported (Schulz 2002a). An unspecified number of couples were excluded after randomisation because they did not complete six cycles with one form of treatment and at least three cycles with the other. The paper reported a relatively high drop-out rate, but the numbers are not specified. Included and analysed were 46 couples.

Kirby 1991 was reported as a randomised controlled trial but did not describe the method of randomisation. Allocation concealment, blinding, exclusions after randomisation, loss to follow-up were not described. Twenty four couples were included, 58 cycles of IUI and 52 cycles were analysed.

Martinez 1990 was described as a randomised controlled trial but did not report the method of randomisation. Allocation concealment and blinding were not mentioned. Three of the forty entered couples were lost to follow-up. Their diagnosis was not stated. Only two of the 40 entered couples were diagnosed as having a cervical factor. Their cycles were analysed.

te Velde 1989 was reported as a randomised controlled trial but did not describe the method of randomisation. The paper did not report allocation concealment, blinding, exclusions after randomisation or loss to follow-up. Nineteen couples with (explained and unexplained) cervical hostility were included and analysed per cycle (from a group of 27 couples with sperm-mucus interaction, of whom 8 were diagnosed as 'immunologic').

The Steures trial (Steures 2007) has been performed according to the CONSORT guidelines (CONSORT 2001). In total, 3,894 consecutive couples with a regular cycle underwent a basic fertility workup in one of the participating centres. In 264 couples, an isolated cervical factor was found, and among these, 163 couples were either not invited for participation or declined to participate. Of the other 101 couples, 52 were allocated to IUI, and 49 were allocated to expectant management. In each group, one woman appeared to have polycystic ovary syndrome, and therefore these women were excluded from the analyses.

Effects of interventions

We did not pool the outcomes of the five studies with timed intercourse in the control group in a meta-analysis due to the methodological quality of the trials and variations in the patient characteristics and interventions. In the Check 1995 trial 17 women conceived out of 80 women allocated to one cycle IUI compared to three women out of 76 women allocated to one cycle timed intercourse ($p < 0.009$ from report). See also Table 1. After four cycles of treatment Martinez 1990 observed one pregnancy out of three cycles IUI and none out of four cycles timed intercourse. In the twelve-treatment-cycle study by Glazener 1987 two con-

ceptions occurred in 223 cycles with IUI versus three conceptions in 252 cycles of timed intercourse. Following twelve treatment cycles Kirby 1991 reported seven pregnancies in 58 cycles IUI in comparison with four pregnancies in 52 cycles timed intercourse ($p > 0.05$ from report). The studies by Glazener 1987; Kirby 1991 and Martinez 1990 did not mention the number of pregnancies after the first treatment cycle. In the te Velde 1989 study ten conceptions occurred during IUI and none during timed intercourse in the nineteen women with explained and unexplained cervical hostility after 12 treatment cycles. None of the studies mentioned data on the outcomes spontaneous abortions, multiple pregnancies and OHSS.

In the Steures trial (Steures 2007) 26 women (51%) in the intrauterine insemination group and 16 women (33%) expectant management group conceived. Of these pregnancies, 22 (43%) vs. 13 (27%) were ongoing (relative risk, 1.6; 95% confidence interval, 0.91 to 2.8). There was one multiple pregnancy in the group that was allocated to intrauterine insemination. Sixteen of the 22 of the ongoing pregnancies in the intrauterine insemination group were directly related to the intrauterine insemination.

DISCUSSION

Although the American Fertility Society (AFS 1991) once considered cervical factors “the most obvious indications for IUI,” the same organization (now called American Society for Reproductive Medicine) does not mention the indication anymore (ASRM 2004). This policy also seems to apply to the European Society of Human Reproduction and Embryology (ESHRE 2000; Van den Eede 1995). The guidelines of the Royal College of Obstetricians and Gynaecologists do not bring up the indication cervical hostility for IUI (RCOG 2004). Nevertheless, some authors (in one country) still believe that IUI is an effective treatment for cervical factor subfertility (Van der Steeg 2004; Steures 2007). We found

six trials that examined IUI with partner's sperm in women with cervical hostility. Five of these studies revealed important flaws in design, conduct, and reporting (Glazener 1987; Kirby 1991; Martinez 1990; te Velde 1989). These included improper methods of randomisation, failure to conceal the upcoming assignment from those involved, and losses after randomisation. Only one trial (Steures 2007) was adequately conducted according the CONSORT guidelines (CONSORT 2001), but the results were not statistically significant. Because of poor research methods, differences in participant characteristics and inconsistent clinical approaches to IUI, we were unable to pool trial results. Nevertheless, these reports overall provide no evidence that IUI is an effective treatment for cervical hostility.

AUTHORS' CONCLUSIONS

Implications for practice

The existing literature does not indicate that IUI is an effective treatment for cervical hostility. Hence, any use of IUI for this indication is justified on the basis of a properly designed and conducted randomised controlled trial, with appropriate informed consent.

Implications for research

If further trials of IUI are to be done, they should adhere to internationally accepted standards for the design, conduct, and reporting of such research. Importantly, cross-over designs must not be used, since they introduce substantial bias (Khan 1996).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Check 1995

Methods	Non-randomized controlled trial using last digit of the year of birth and the last digit of the social security number to generate the allocation sequence; hence allocation concealment was inadequate. The use of blinding was not reported. Four couples in the IUI group versus 2 couples in the TI were excluded after randomisation because the test-cycle PCT revealed progressive sperm and 11 couples in the IUI group versus 9 couples in the TI group were excluded after randomisation due to refusal of the assigned treatment. Numbers lost to follow up were not described. The report does not describe an a priori hypothesis or sample size calculation. Analysis not according to intention-to-treat principle
Participants	184 couples with cervical factor infertility in the United States. Age of the couples: not stated. Duration of infertility: not stated. Primary infertility: not stated. Previous treatment: not stated. Ovulatory status: progesterone level > 12 ng/ml in mid-luteal phase and in-phase endometrial biopsy in the late luteal phase. Tubal patency assessment: the methods are not described. No endometriosis. PCT: negative PCT defined as no spermatozoa with progressive forward motion in the cervical mucus 8-12 hr after intercourse at the time a follicle was demonstrated to have an average diameter of at least 18 mm associated with a minimum serum estradiol level of 200 pg/ml and a serum progesterone level of no more than 1.8 ng/ml in two cycles. Moghissi score < 10. Screening for antisperm antibodies: direct immunobead and indirect immunobead test. Only couples negative for anti-sperm antibodies were included. Semen quality: volume >1.5 ml, >20 million with >50 % progressive motility and >50 % normal morphology
Interventions	IUI in natural cycles and cycles with ovarian hyperstimulation versus TI in natural cycles and cycles with ovarian hyperstimulation. Ovarian hyperstimulation method: clomiphene citrate, human menopausal gonadotropin and bromocriptine. Duration of treatment: 1 cycle Sperm preparation: Medium: Hepes buffered Hanks solution supplemented with bovine serum albumin. Technique: Percoll gradient method and wash. Timing method: morning and when possible evening LH levels in blood and ultrasound for follicular development. Timing: IUI 36 h after the beginning of the LH surge or 12 h after the LH peak. intercourse on following 2 nights after LH surge. Insemination procedure: 0.5 ml in a KDF-2.3 catheter. Patient remained on the exam table for 20 minutes after the insemination. Mean number of sperm inseminated: not stated. Number of inseminations per cycle: not stated. Cancellation criteria: not stated. Note: LH surge was defined as a doubling of the level from the preceding day provided that the rise continued on the next day and the peak LH surge generally attained at least a five-fold rise

Check 1995 (Continued)

Outcomes	Number of pregnancies per total number of cycles. Diagnosis of pregnancy: not stated. Number of miscarriages: not stated. Multiple pregnancies: not stated. OHSS: not stated.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Glazener 1987

Methods	Non-randomized controlled, cross-over trial using date of birth to generate the allocation sequence; hence allocation concealment was inadequate. Outcome assessors were not blinded. Couples not completing 6 cycles with one form of treatment and at least three cycles with the other treatment were excluded unless they conceived. The report does not specify the number of couples excluded. The paper mentions that a relatively high number of women discontinued, yet the numbers were not specified. The study stated that ensuring strict alternation of treatment was impossible. The report does not describe an a priori hypothesis or sample size calculation. Analysis not according to intention-to-treat principle	
Participants	46 couples in the United Kingdom. Age of the couples: women 19-37 years (mean 28.5 years). men 18-42 years (mean 31 years). Duration of infertility: 12-146 months (mean 29.5 months). Primary infertility: 62 % of the women. Previous treatment: not stated. Ovulatory status: cycle 21-42 days, progesterone level ≥ 30 nmol/l in mid-luteal phase, normal FSH, prolactin and thyroid hormone levels. Tubal patency: laparoscopy. PCT: negative PCT defined as an absence of forward-progressing spermatozoa in fully developed pre-ovulatory endocervical mucus 6-18 hours after coitus in two cycles. Screening for antisperm antibodies: mixed agglutination reaction, tray agglutination test or a modified Kurzrock-Miller slide test. Antisperm antibodies subgroup: positive screening. No antisperm antibodies subgroup: negative screening. Semen quality: motile normal sperm density > 1 million spermatozoa/ml (mean of 2-3 samples). Normal semen quality subgroup: mean mnsd > 4 million spermatozoa/ml. Abnormal semen quality subgroup: motile normal sperm density < 4 million spermatozoa/ml. Coital frequency: $\geq$ two times a week.	
Interventions	Artificial insemination with husband's sperm versus coitus. Duration of treatment: 12 cycles. Sperm preparation: not stated. Timing method: not stated. Timing: pre-ovulatory phase of cervical mucus secretion. Insemination procedure: 1 ml in a disposable	

Glazener 1987 (Continued)

	insulin syringe into the cervical canal. Mean number of sperm inseminated: not stated. Number of inseminations per cycle: two times. Cancellation criteria: not stated.	
Outcomes	Number of pregnancies per total number of cycles. Diagnosis pregnancy: not stated. Number of miscarriages: not stated. Multiple pregnancies: not stated. OHSS: not stated.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Kirby 1991

Methods	Randomized controlled, cross-over trial. The method of randomisation, the use of allocation concealment and the use blinding were not reported. Numbers lost to follow up and exclusions after randomisation were not mentioned. The report does not describe an a priori hypothesis or sample size calculation. Analysis not according to intention-to-treat principle	
Participants	285 couples in Australia of whom 24 couples had cervical mucus hostility. Age of the couples: not stated. Duration of infertility: > 2 years. Primary infertility: not stated. Previous treatment: not stated. Ovulatory status: assessment ovulation and cycle endocrinology. the methods were not reported. Tubal patency: laparoscopic tubal dye insufflation. Cervical mucus hostility: investigation of sperm-mucus interaction in conjunction with accurate determination of ovulation. pH mucus <6 or inadequate amounts of mucus in the peri-ovulatory phase. Screening for antisperm antibodies: exclusion of couples with antisperm antibodies. Semen quality: >40 million spermatozoa/ml, >45% progressive motility and >40% normal morphology on two occasions	
Interventions	IUI in natural cycles versus TI in natural cycles. Duration of treatment: 12 cycles. Sperm preparation: Medium: Hepes-buffered T6 and Hepes-buffered human tubal fluid supplemented with human serum albumin. Technique: begin of the study centrifugation and swim-up method, no wash; later on Percoll gradient method and wash. Timing method: LH, estradiol and progesterone levels in blood. Timing: 40 h after start of LH rise intercourse or IUI. Insemination procedure: 0.5 ml in 11.5 cm Tomcat catheter. Mean number of sperm inseminated: not stated. Number of inseminations per cycle: 1	

Kirby 1991 (Continued)

	Cancellation criteria: not stated. Note: patients were requested not to have intercourse for 3 days before the day of semen collection and insemination	
Outcomes	Number of pregnancies per total number of cycles. Diagnosis pregnancy: human chorionic gonadotrophin in blood, clinical examination and ultrasound examination. Number of miscarriages: not stated. Multiple pregnancies: not stated. OHSS: not stated.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Martinez 1990

Methods	Randomized controlled, cross-over trial. The method of randomisation, the use of allocation concealment and the use of blinding were not reported. Three cycles were excluded after randomisation because they differed too much from the main body of the study. Five couples were lost to follow up. The report does not describe an a priori hypothesis and sample size calculation. Analysis not according to intention-to-treat principle	
Participants	40 couples in the Netherlands of whom 2 couples had cervical factor. Age of the couples: range 23-38 years (mean 32.1 +/- 4.1 years). Duration of infertility: range 3-15 years (mean 6.5 +/- 3.1 years). Primary infertility: not stated. Previous treatment: not stated. Ovulatory status: biphasic basal body temperature curve and in-phase endometrial biopsy in the late luteal phase. Tubal patency: hysterosalpingogram and diagnostic laparoscopy with chromopertubation. PCT: negative PCT in adequate midcycle mucus and the absence of immunological factors. Screening for antisperm antibodies: yes. Semen quality: >20 million spermatozoa/ml, 60% qualitative motility score of >3 on a scale of 1-5 on two occasions	
Interventions	IUI in natural cycles versus IUI in cycles with ovarian hyperstimulation versus TI in natural cycles versus TI in cycles with ovarian hyperstimulation. Ovarian hyperstimulation method: 100 mg of clomiphene citrate for 5 days starting on day 3. Duration of treatment: 4 cycles. Sperm preparation: Medium: HAM's F10 supplemented with either patient's serum or human serum albumen. Technique: Percoll gradient method and wash. Timing method: morning and evening LH in urine and ultrasound for follicular development and BBT. Timing: IUI or TI on 16-28 hours after positive LH test.	

Martinez 1990 (Continued)

	Insemination procedure: 0.2 ml in Mackler's device. Mean number of sperm inseminated: not stated. Number of inseminations per cycle: 1. Cancellation criteria: not stated. Note: couples were requested not to have intercourse from the beginning of the LH tests until either TI was indicated or until 3 days after insemination	
Outcomes	Number of pregnancies per total number of cycles. Diagnosis pregnancy: human chorionic gonadotropin in urine and blood. Number of miscarriages: not stated. Multiple pregnancies: not stated. OHSS: not stated.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Steures 2007

Methods	<p>The randomization sequence was computer generated in balanced-block multiples of two or four, stratified by center. Blinding is obviously impossible. Lost to follow up: zero. Intention to treat principle used</p>	
Participants	<p>In total, 3,894 consecutive couples with a regular cycle underwent a basic fertility workup. In 264 couples, an isolated cervical factor was found, and among these, 163 couples were either not invited for participation or declined to participate. After completion of the basic fertility workup, in couples with a cervical factor, diagnosed by means of a well-timed non-progressive postcoital test (PCT), the prognosis of a spontaneous ongoing pregnancy resulting in a live-born child in the next year was calculated. The prognosis was calculated according to a prediction model. A prognosis of >30% can only be reached in these couples if no other causes, apart from the abnormal PCT, exist for their declined fertility. At least one postcoital test was done for each couple during the basic fertility assessment. The test was planned according to the basal body temperature curve or findings of ultrasonography. If the timing was based on the basal body temperature curve, the postcoital test was scheduled the day before the expected ovulation. If it was based on ultrasonography, the postcoital test was done when the dominant follicle was at least 18 mm in diameter. The postcoital test result was regarded as normal if at least one progressive spermatozoon was seen in one of five high-power fields at 400 times magnification. A non-progressive PCT was defined as the absence of spermatozoa moving in a straight direction and at functional speed. Of the other 101 couples, 52 were allocated to IUI, and 49 were allocated to expectant management. In each group, one woman appeared to have polycystic ovary syndrome (PCO), and was therefore excluded. Thus these 2 women had a regular, but anovulatory cycle Maternal age: 30 yrs; duration of subfertility 1.7 yrs; 60% of couples had a primary subfertility; FSH was 6.6 IU/L; semen analysis showed a total motile sperm count of 85; and in each group, two women had one-sided tubal occlusion. The mean prognosis in both groups was 37% and 39%, respectively</p>	

Interventions	<p>Directly after randomisation, the first three IUI cycles were performed without ovarian stimulation, but with ovulation detection (urine LH test or sonography) and sometimes hCG ovulation induction. Thereafter ovarian stimulation (FSH >3 day of cycle) until a follicle of ≥ 16 mm and then hCG, all according hospital specific protocols. Semen samples were processed within 1 hour after ejaculation by using a density gradient centrifugation, followed by a washing step with culture medium. The volume of semen that was inseminated varied between 0.3 mL and 0.5 mL. Insemination took place 36 to 40 hours after hCG administration</p> <p>Cycle monitoring, detection and/or induction of ovulation, as well as semen preparation and insemination regimens were performed according to hospital-specific protocols</p> <p>Couples allocated to expectant management were followed for 6 months or until an ongoing pregnancy occurred. If no pregnancy occurred, follow-up ended after this period. If a pregnancy miscarried, follow-up continued until the next pregnancy or the end of the 6-month period</p>
Outcomes	<p>The primary endpoint was ongoing pregnancy within 6 months. Ongoing pregnancy was defined as the presence of fetal cardiac activity at transvaginal sonography, at a gestational age of 12 weeks. Secondary endpoints were clinical pregnancies (presence of a yolk sac at transvaginal sonography at a gestational age of 7 weeks), miscarriages, ectopic pregnancies, multiple pregnancies, and live birth</p>
Notes	<p>During the period June 2002 and July 2005, 17 fertility centres recruited 264 couples with a cervical factor for their trial that is on average 5 couples per centre per year</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Sequence was concealed, and sealed opaque envelopes were constructed by an independent individual. Clinicians in the participating centres enrolled the couple and subsequently unsealed the first envelope in the sequence. Thereafter, the inclusion was confirmed to the trial coordinator by fax

te Velde 1989

Methods	<p>Randomized controlled, cross-over trial. The method of randomisation, the use of allocation concealment and the use of blinding were not reported. Numbers lost to follow-up and exclusions after randomisation were not mentioned. The report does not describe an a priori hypothesis and sample size calculation. Analysis according to intention to treat principle</p>
Participants	<p>57 couples of whom "27 couples with impaired sperm mucus interaction due to cervical hostility [n=19] or immunologic male subfertility" (n=8); in the Netherlands.</p> <p>Age of the couples: not stated.</p> <p>Duration of infertility: range 3-12 years (mean 5.2 years).</p> <p>Primary infertility: 88% of the couples.</p> <p>Previous treatment: not stated.</p> <p>Ovulatory status: biphasic basal body temperature curve and normal progesterone levels during the luteal phase.</p> <p>Tubal patency: hysterosalpingogram and laparoscopy.</p>

	<p>Semen quality: 10 million motile spermatozoa (volume x concentration x % motility) on two occasions.</p> <p>PCT: immotile sperm or negative on 3 occasions.</p> <p>Sperm mucus penetration test: poor or negative.</p> <p>Explained cervical hostility group: 3 couples pH cervical mucus < 6.4 and 12 couples Insler cervical mucus score < 6.</p> <p>Unexplained cervical hostility group: 4 couples with poor PCTs and SPMs results with normal sperm and good mucus qualities.</p> <p>Screening for antisperm antibodies: yes.</p> <p>Immunologic subgroup: 8 couples with antisperm antibodies measured with direct mixed agglutination reaction. the presence of antisperm antibodies in men was confirmed with the crossed sperm cervical mucus contact test</p>	
Interventions	<p>IUI in natural cycles versus TI in natural cycles.</p> <p>Duration of treatment: 12 cycles.</p> <p>Sperm preparation: best fraction of split ejaculate.</p> <p>Medium: Earl's medium supplemented with inactivated human serum.</p> <p>Technique: Percoll gradient method and wash.</p> <p>Timing method: LH level in blood. Timing: IUI on following day after LH rise. intercourse on evening and following day of LH rise.</p> <p>Insemination procedure: 0.5 ml in polyethylene catheter.</p> <p>Mean number of sperm inseminated: not stated.</p> <p>Number of inseminations per cycle: not stated.</p> <p>Cancellation criteria: not stated.</p> <p>Note: sperm was prepared as soon as possible when antisperm antibodies were present.</p> <p>Note: couples were requested not to have intercourse for 3 days after insemination.</p> <p>Note: in 11 of the 15 couples in the explained cervical hostility group the lower margin of the normality of one or two of the semen qualities were not reached</p>	
Outcomes	<p>Number of pregnancies per total number of couples.</p> <p>Diagnosis pregnancy: not stated.</p> <p>Number of miscarriages: not stated.</p> <p>Multiple pregnancies: not stated.</p> <p>OHSS: not stated.</p>	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

IUI - intrauterine insemination

TI - timed intercourse

PCT - post-coital test

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

Study	Reason for exclusion
Byrd 1987	Cited in Friedman 1989. Uncontrolled observational study.
Chaffkin 1991	Cited in Van der Steeg 2004. Retrospective study.
Friedman 1989	1. IUI with washed, concentrated husband's sperm was compared with whole-ejaculated intracervical insemination. 2. Method of randomisation was not mentioned. 3. Patient served as her own control until pregnancy. 4. Drop-out rate was not mentioned. 5. Detection of pregnancy was not described.
Hoing 1986	Cited in Friedman 1989. Uncontrolled observational study on male factor.
Kemmann 1987	Cited in Friedman 1989 . Not related to the subject.
Kerin 1984	Cited in Friedman 1989 .
Quagliarello 1986	Cited in Friedman 1989 . Uncontrolled observational study.
Sher 1984	Cited in Friedman 1989 . Uncontrolled observational study.
Steures 2004	Historical cohort study.
Toffle 1985	Cited in Friedman 1989 . Uncontrolled observational study.

DATA AND ANALYSES

Comparison 1. Intra uterine insemination without ovarian stimulation versus timed intercourse without ovarian stimulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy	5	20	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.1 All trials	5	10	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Only randomized controlled trials	3	6	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Quasi randomized controlled trials	2	4	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Multiple pregnancies	5	20	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.1 All trials	5	10	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Only randomized controlled trials	3	6	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Quasi randomized controlled trials	2	4	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Spontaneous abortions	5	20	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.1 All trials	5	10	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Only randomized controlled trials	3	6	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Quasi randomized controlled trials	2	4	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Ovarian Hyperstimulation Syndrome	5	20	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.1 All trials	5	10	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Only randomized controlled trials	3	6	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Quasi randomized controlled trials	2	4	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Intra uterine insemination with ovarian stimulation versus timed intercourse with ovarian stimulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy	5	20	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.1 All trials	5	10	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Only randomized controlled trials	3	6	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Quasi randomized controlled trials	2	4	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Multiple pregnancies	5	20	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

2.1 All trials	5	10	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Only randomized controlled trials	3	6	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Quasi randomized controlled trials	2	4	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Spontaneous abortions	5	20	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.1 All trials	5	10	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Only randomized controlled trials	3	6	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Quasi randomized controlled trials	2	4	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Ovarian Hyperstimulation Syndrome	5	20	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.1 All trials	5	10	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Only randomized controlled trials	3	6	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Quasi randomized controlled trials	2	4	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Intra uterine insemination without ovarian stimulation versus timed intercourse without ovarian stimulation, Outcome 1 Pregnancy.

Review: Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples

Comparison: 1 Intra uterine insemination without ovarian stimulation versus timed intercourse without ovarian stimulation

Outcome: 1 Pregnancy

(Continued . . .)

Analysis 1.2. Comparison 1 Intra uterine insemination without ovarian stimulation versus timed intercourse without ovarian stimulation, Outcome 2 Multiple pregnancies.

Review: Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples

Comparison: 1 Intra uterine insemination without ovarian stimulation versus timed intercourse without ovarian stimulation

Outcome: 2 Multiple pregnancies

Analysis 1.3. Comparison 1 Intra uterine insemination without ovarian stimulation versus timed intercourse without ovarian stimulation, Outcome 3 Spontaneous abortions.

Review: Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples

Comparison: 1 Intra uterine insemination without ovarian stimulation versus timed intercourse without ovarian stimulation

Outcome: 3 Spontaneous abortions

Study or subgroup	IUI n/N	TI n/N	Odds Ratio M- H,Random,95% CI	Weight	Odds Ratio M- H,Random,95% CI
I All trials					
Check 1995	0/1	0/1			Not estimable
Glazener 1987	0/1	0/1			Not estimable
Kirby 1991	0/1	0/1			Not estimable
Martinez 1990	0/1	0/1			Not estimable
te Velde 1989	0/1	0/1			Not estimable
Subtotal (95% CI)	5	5			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Only randomized controlled trials					
Kirby 1991	0/1	0/1			Not estimable
Martinez 1990	0/1	0/1			Not estimable
te Velde 1989	0/1	0/1			Not estimable
Subtotal (95% CI)	3	3			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Quasi randomized controlled trials					
Check 1995	0/1	0/1			Not estimable
Glazener 1987	0/1	0/1			Not estimable
Subtotal (95% CI)	2	2			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	10	10			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

Analysis 1.4. Comparison 1 Intra uterine insemination without ovarian stimulation versus timed intercourse without ovarian stimulation, Outcome 4 Ovarian Hyperstimulation Syndrome.

Review: Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples

Comparison: 1 Intra uterine insemination without ovarian stimulation versus timed intercourse without ovarian stimulation

Outcome: 4 Ovarian Hyperstimulation Syndrome

Study or subgroup	IUI n/N	TI n/N	Odds Ratio M- H,Random,95% CI	Weight	Odds Ratio M- H,Random,95% CI
I All trials					
Check 1995	0/1	0/1			Not estimable
Glazener 1987	0/1	0/1			Not estimable
Kirby 1991	0/1	0/1			Not estimable
Martinez 1990	0/1	0/1			Not estimable
te Velde 1989	0/1	0/1			Not estimable
Subtotal (95% CI)	5	5			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Only randomized controlled trials					
Kirby 1991	0/1	0/1			Not estimable
Martinez 1990	0/1	0/1			Not estimable
te Velde 1989	0/1	0/1			Not estimable
Subtotal (95% CI)	3	3			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Quasi randomized controlled trials					
Check 1995	0/1	0/1			Not estimable
Glazener 1987	0/1	0/1			Not estimable
Subtotal (95% CI)	2	2			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	10	10			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

Analysis 2.1. Comparison 2 Intra uterine insemination with ovarian stimulation versus timed intercourse with ovarian stimulation, Outcome 1 Pregnancy.

Review: Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples

Comparison: 2 Intra uterine insemination with ovarian stimulation versus timed intercourse with ovarian stimulation

Outcome: 1 Pregnancy

Study or subgroup	IUI n/N	TI n/N	Odds Ratio M- H,Random,95% CI	Weight	Odds Ratio M- H,Random,95% CI
I All trials					
Check 1995	0/1	0/1			Not estimable
Glazener 1987	0/1	0/1			Not estimable
Kirby 1991	0/1	0/1			Not estimable
Martinez 1990	0/1	0/1			Not estimable
te Velde 1989	0/1	0/1			Not estimable
Subtotal (95% CI)	5	5			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Only randomized controlled trials					
Kirby 1991	0/1	0/1			Not estimable
Martinez 1990	0/1	0/1			Not estimable
te Velde 1989	0/1	0/1			Not estimable
Subtotal (95% CI)	3	3			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Quasi randomized controlled trials					
Check 1995	0/1	0/1			Not estimable
Glazener 1987	0/1	0/1			Not estimable
Subtotal (95% CI)	2	2			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	10	10			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
0.1 0.2 0.5 1 2 5 10					
Favours treatment Favours control					

Analysis 2.2. Comparison 2 Intra uterine insemination with ovarian stimulation versus timed intercourse with ovarian stimulation, Outcome 2 Multiple pregnancies.

Review: Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples

Comparison: 2 Intra uterine insemination with ovarian stimulation versus timed intercourse with ovarian stimulation

Outcome: 2 Multiple pregnancies

Study or subgroup	IUI n/N	TI n/N	Odds Ratio M- H,Random,95% CI	Weight	Odds Ratio M- H,Random,95% CI
I All trials					
Check 1995	0/1	0/1			Not estimable
Glazener 1987	0/1	0/1			Not estimable
Kirby 1991	0/1	0/1			Not estimable
Martinez 1990	0/1	0/1			Not estimable
te Velde 1989	0/1	0/1			Not estimable
Subtotal (95% CI)	5	5			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Only randomized controlled trials					
Kirby 1991	0/1	0/1			Not estimable
Martinez 1990	0/1	0/1			Not estimable
te Velde 1989	0/1	0/1			Not estimable
Subtotal (95% CI)	3	3			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Quasi randomized controlled trials					
Check 1995	0/1	0/1			Not estimable
Glazener 1987	0/1	0/1			Not estimable
Subtotal (95% CI)	2	2			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	10	10			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

Analysis 2.3. Comparison 2 Intra uterine insemination with ovarian stimulation versus timed intercourse with ovarian stimulation, Outcome 3 Spontaneous abortions.

Review: Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples

Comparison: 2 Intra uterine insemination with ovarian stimulation versus timed intercourse with ovarian stimulation

Outcome: 3 Spontaneous abortions

Study or subgroup	IUI n/N	TI n/N	Odds Ratio M- H,Random,95% CI	Weight	Odds Ratio M- H,Random,95% CI
I All trials					
Check 1995	0/1	0/1			Not estimable
Glazener 1987	0/1	0/1			Not estimable
Kirby 1991	0/1	0/1			Not estimable
Martinez 1990	0/1	0/1			Not estimable
te Velde 1989	0/1	0/1			Not estimable
Subtotal (95% CI)	5	5			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Only randomized controlled trials					
Kirby 1991	0/1	0/1			Not estimable
Martinez 1990	0/1	0/1			Not estimable
te Velde 1989	0/1	0/1			Not estimable
Subtotal (95% CI)	3	3			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Quasi randomized controlled trials					
Check 1995	0/1	0/1			Not estimable
Glazener 1987	0/1	0/1			Not estimable
Subtotal (95% CI)	2	2			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	10	10			Not estimable
Total events: 0 (IUI), 0 (TI)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
0.1 0.2 0.5 1 2 5 10 Favours treatment Favours control					

Analysis 2.4. Comparison 2 Intra uterine insemination with ovarian stimulation versus timed intercourse with ovarian stimulation, Outcome 4 Ovarian Hyperstimulation Syndrome.

Review: Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples

Comparison: 2 Intra uterine insemination with ovarian stimulation versus timed intercourse with ovarian stimulation

Outcome: 4 Ovarian Hyperstimulation Syndrome

ADDITIONAL TABLES

Table 1. Number of pregnancies per total number of cycles.

Study	Intrauterine Insemin	Timed Intercourse
Check 1995	17/80	3/76
Glazener 1987	2/223	3/252
Kirby 1991	7/58	4/52
Martinez 1990	1/3	0/4

WHAT'S NEW

Date	Event	Description
20 September 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 4, 2005

Date	Event	Description
22 August 2008	New search has been performed	Converted to new review format.
22 August 2008	New search has been performed	A new RCt has been included. No change in conclusion.
24 August 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Frans Helmerhorst developed the idea and developed the updated version. Frans Helmerhorst, Martijn Finken, Twina Gornas and David Grimes wrote the protocol. Huib van Vliet, Twina Gornas and Martijn Finken performed the literature search and abstracted the data. Huib van Vliet and Frans Helmerhorst drafted the review. All edited and advised on the review drafts.

DECLARATIONS OF INTEREST

Frans Helmerhorst - none

Huib van Vliet - none

Twina Gornas - none

Martijn Finken - none

David Grimes - none

SOURCES OF SUPPORT

Internal sources

- Leiden University Medical Center, Netherlands.

External sources

- Dutch Ministry of Developing Affairs, Netherlands.
- World Health Organization (WHO), Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Since the first publication of this review in the Cochrane Library in 2005 and in Obstetrical & Gynecological Survey (Helmerhorst 2006) a randomised controlled trial in which couples with an isolated cervical factor were treated with intrauterine insemination or expectant management during 6 cycles (Steures 2004). In this updated review expectant management as a control was added to the original control groups.

NOTES

Helmerhorst 2006

INDEX TERMS

Medical Subject Headings (MeSH)

Biomarkers [blood]; Cervix Mucus [*physiology]; Coitus [*physiology]; Infertility [*therapy]; Insemination, Artificial, Homologous [*methods]; Luteinizing Hormone [blood]; Time Factors

MeSH check words

Female; Humans