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[Intervention Review]

Natural cycle in vitro fertilisation (IVF) for subfertile couples

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ABSTRACT

Background

Subfertility affects 15% to 20% of couples trying to conceive. In vitro fertilisation (IVF) is one of the assisted reproduction techniques developed to improve chances of achieving pregnancy. In the standard IVF method with controlled ovarian hyperstimulation (COH), growth and development of multiple follicles are stimulated by using gonadotrophins, often combined with a gonadotrophin-releasing hormone (GnRH) agonist or antagonist. Although it is an established method of conception for subfertile couples, the treatment is expensive and has a high risk of adverse effects. Studies have shown that IVF in a natural cycle (NC) or a modified natural cycle (MNC) might be a promising low risk and low cost alternative to the standard stimulated IVF treatment since the available dominant follicle of each cycle is used. In this review, we included available randomised controlled studies comparing natural cycle IVF (NC and MNC) with standard IVF.

Objectives

To compare the efficacy and safety of natural cycle IVF (including both NC-IVF and MNC-IVF) with controlled ovarian hyperstimulation IVF (COH-IVF) in subfertile couples.

Search methods

An extended search including of the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, ClinicalTrials.gov, conference abstracts in the Web of Knowledge, the World Health Organization International Trials Registry Platform search portal, LILACS database, PubMed and the OpenSIGLE database was conducted according to Cochrane guidelines. The last search was on 31st July 2013.

Selection criteria

All randomised controlled trials (RCTs) comparing either natural cycle IVF or modified natural cycle IVF versus standard IVF in subfertile couples were included.

Data collection and analysis

Data selection and extraction and risk of bias assessment were carried out independently by two authors (TA and AC). The primary outcome measures were live birth rate and ovarian hyperstimulation syndrome (OHSS) rate per randomised woman. We calculated Mantel-Haenszel odds ratios for each dichotomous outcome and either the mean difference or the standardised mean difference (SMD) for continuous outcomes, with 95% confidence intervals (CIs). A fixed effect model was used unless there was substantial heterogeneity, in which case a random effects model was used.



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Main results

Six randomised controlled trials with a total of 788 women were included. The largest of these trials included 396 women eligible for this review.

No evidence of a statistically significant difference was found between natural cycle and standard IVF in live birth rates (OR 0.68, 95% CI 0.46 to 1.01, two studies, 425 women, I²= 0%, moderate quality evidence). The evidence suggests that for a woman with a 53% chance of live birth using standard IVF, the chance using natural cycle IVF would range from 34% to 53%. There was no evidence of a statistically significant difference between natural cycle and standard IVF in rates of OHSS (OR 0.19, 95% CI 0.01 to 4.06, one study, 60 women, very low quality evidence), clinical pregnancy (OR 0.52 95% CI 0.17 to 1.61, 4 studies, 351 women, I²=63%, low quality evidence), ongoing pregnancy (OR 0.72, 95% CI 0.50 to 1.05, three studies, 485 women, I²=0%, moderate quality evidence), multiple pregnancy (OR 0.76, 95% CI 0.25 to 2.31, 2 studies, 527 women, I²=0%, very low quality evidence), gestational abnormalities (OR 0.44 95% CI 0.03 to 5.93, 1 study, 18 women, very low quality evidence) or cycle cancellations (OR 8.98, 95% CI 0.20 to 393.66, 2 studies, 159 women, I²=83%, very low quality evidence). One trial reported that the oocyte retrieval rate was significantly lower in the natural cycle group (MD -4.40, 95% CI -7.87 to -0.93, 60 women, very low quality evidence). There were insufficient data to draw any conclusions about rates of treatment cancellation. Findings on treatment costs were inconsistent and more data are awaited. The evidence was limited by imprecision. Findings for pregnancy rate and for cycle cancellation were sensitive to the choice of statistical model: for these outcomes, use of a fixed effect model suggested a benefit for the standard IVF group. Moreover the largest trial has not yet completed follow up, though data have been reported for over 95% of women.

Authors' conclusions

Further evidence from well conducted large trials is awaited on natural cycle IVF treatment. Future trials should compare natural cycle IVF with standard IVF. Outcomes should include cumulative live birth and pregnancy rates, the number of treatment cycles necessary to reach live birth, treatment costs and adverse effects.

PLAIN LANGUAGE SUMMARY

Natural cycle in vitro fertilisation for subfertile couples

Review question: To determine whether in vitro fertilisation (IVF) in a natural cycle is a good alternative to standard IVF for subfertile couples.

Background: Assisted reproduction techniques such as IVF can help subfertile women to achieve a pregnancy. In IVF, an egg is fertilised in a laboratory and placed back in the woman's uterus. Different IVF protocols have been developed since the first IVF in 1978 including natural cycle IVF (without hyperstimulation of the ovaries), modified natural cycle IVF (with low dose ovarian hyperstimulation) and IVF with controlled ovarian hyperstimulation. The aim of this systematic review was to assess the efficacy and safety of natural cycle IVF and modified natural cycle IVF compared with controlled ovarian hyperstimulation IVF in subfertile couples.

Study characteristics: Six trials were included, with a total of 788 women undergoing an IVF treatment. The evidence is current to 31st July 2013. The largest trial in the review (with 396 women) has not yet reported full results.

Key points: The evidence suggested that for a woman with a 53% chance of live birth using standard IVF, the chance using natural cycle IVF ranges from 34% to 53%. No significant difference was found in rates of clinical pregnancy, ongoing pregnancy, multiple pregnancy, incidence of ovarian hyperstimulation syndrome, gestational abnormalities or cancellations of treatment. However findings were imprecise for all outcomes and further evidence from larger studies is awaited. There was evidence from single studies that a lower number of oocytes was retrieved in the natural cycle group. Findings on cost-effectiveness were inconsistent.

Quality of evidence: Quality ratings for the evidence ranged from very low to moderate, the main limitation being imprecision due to insufficient data. When the review authors checked the effect of using an alternative method of analysis the findings suggested higher rates of clinical pregnancy with standard IVF than with natural cycle IVF.