

# Hyaluronic acid in embryo transfer media for assisted reproductive technologies

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## Abstract

**Background:** This is an update of a Cochrane Review first published in the Cochrane Library (2010, Issue 7). To increase the success rate of assisted reproductive technologies (ARTs), adherence compounds such as hyaluronic acid (HA) have been introduced into subfertility management. Adherence compounds are added to the embryo transfer medium to increase the likelihood of embryo implantation, with the potential for higher clinical pregnancy and live birth rates.

**Objectives:** To determine whether adding adherence compounds to embryo transfer media could improve pregnancy outcomes, including improving live birth and decreasing miscarriage, in women undergoing assisted reproduction.

**Search methods:** We searched the Cochrane Gynaecology and Fertility Group Trials Register, CENTRAL, MEDLINE, Embase, and PsycINFO electronic databases on 7 January 2020 for randomised

controlled trials that examined the effects of adherence compounds in embryo transfer media on pregnancy outcomes. Furthermore, we communicated with experts in the field, searched trials registries, checked reference lists of relevant studies, and conference abstracts were handsearched.

**Selection criteria:** Only truly randomised controlled trials comparing embryo transfer media containing functional concentrations of adherence compounds to media with no or low adherence compound concentrations were included.

**Data collection and analysis:** Two review authors selected trials for inclusion according to the above criteria, after which the same two review authors independently extracted data for subsequent analysis. Statistical analysis was performed according to the guidelines developed by Cochrane. We combined data to calculate pooled risk ratios (RRs) and 95% confidence intervals (CIs). We assessed statistical heterogeneity using the  $I^2$  statistic. We used GRADE methods to assess the overall quality of evidence for the main comparisons.

**Main results:** We analysed 26 studies with a total of 6704 participants. Overall, the certainty of evidence was low to moderate: the main limitations were imprecision and/or heterogeneity. Compared to embryos transferred in media containing no or low (0.125 mg/mL) HA, the addition of functional (0.5 mg/mL) HA concentrations to the transfer media probably increases the live birth rate (RR 1.21, 95% CI 1.1 to 1.31; 10 RCTs, N = 4066;  $I^2 = 33%$ ; moderate-quality evidence). This suggests that if the chance of live birth following no HA addition in media is assumed to be 33%, the chance following HA addition would be between 37% and 44%. The addition of HA may slightly decrease miscarriage rates (RR 0.82, 95% CI 0.67 to 1.00; 7 RCTs, N = 3091;  $I^2 = 66%$ ; low-quality evidence). Nevertheless, when only studies with low risk of bias were included in the analysis, there was no conclusive evidence of a difference in miscarriage rates (RR 0.96, 95% CI 0.75 to 1.23; N = 2219;  $I^2 = 36%$ ). Adding HA to transfer media probably results in an increase in both clinical pregnancy (RR 1.16, 95% CI 1.09 to 1.23; 17 studies, N = 5247;  $I^2 = 40%$ ; moderate-quality evidence) and multiple pregnancy rates (RR 1.45, 95% CI 1.24 to 1.70; 7 studies, N = 3337;  $I^2 = 36%$ ; moderate-quality evidence). We are uncertain of the effect of HA added to transfer media on the rate of total adverse events (RR 0.86, 95% CI 0.40 to 1.84; 3 studies, N = 1487;  $I^2 = 0%$ ; low-quality evidence).

**Authors' conclusions:** Moderate-quality evidence shows improved clinical pregnancy and live birth rates with the addition of HA as an adherence compound in embryo transfer media in ART. Low-quality evidence suggests that adding HA may slightly decrease miscarriage rates, but when only studies at low risk of bias were included in the analysis, the results were inconclusive. HA had no clear effect on the rate of total adverse events. The increase in multiple pregnancy rates may be due to combining an adherence compound and transferring more than one embryo. Further studies of adherence compounds with single embryo transfer need to be undertaken.

# Update of

Adherence compounds in embryo transfer media for assisted reproductive technologies.

Bontekoe S, Heineman MJ, Johnson N, Blake D.

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