Worrilow et al, 2013 Hum Reprod, Vol.28, No.2 pp. 306–314, 2013

Use of hyaluronan in the selection of sperm for intracytoplasmic sperm Injection (ICSI): significant improvement in clinical outcomes —multicenter, doubleblinded and randomized controlled trial.

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Abstract

STUDY QUESTION:

Does the selection of sperm for ICSI based on their ability to bind to hyaluronan improve the clinical pregnancy rates (CPR) (primary end-point), implantation (IR) and pregnancy loss rates (PLR)?

SUMMARY ANSWER:

In couples where ≤ 65% of sperm bound hyaluronan, the selection of hyaluronan-bound (HB) sperm for ICSI led to a statistically significant reduction in PLR.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS:

HB sperm demonstrate enhanced developmental parameters which have been associated with successful fertilization and embryogenesis. Sperm selected for ICSI using a liquid source of hyaluronan achieved an improvement in IR. A pilot study by the primary author demonstrated that the use of HB sperm in ICSI was associated with improved CPR. The current study represents the single largest prospective, multicenter, double-blinded and randomized controlled trial to evaluate the use of hyaluronan in the selection of sperm for ICSI.

DESIGN:

Using the hyaluronan binding assay, an HB score was determined for the fresh or initial (I-HB) and processed or final semen specimen (F-HB). Patients were classified as >65% or ≤ 65% I-HB and stratified accordingly. Patients with I-HB scores ≤ 65% were randomized into control and HB selection (HYAL) groups whereas patients with I-HB >65% were randomized to non-participatory (NP), control or HYAL groups, in a ratio of 2:1:1. The NP group was included in the >65% study arm to balance the higher prevalence of patients with I-HB scores >65%. In the control group, oocytes received sperm selected via the conventional assessment of motility and morphology. In the HYAL group, HB sperm meeting the same visual criteria were selected for injection. Patient participants and clinical care providers were blinded to group assignment.

PARTICIPANTS AND SETTING:

Eight hundred two couples treated with ICSI in 10 private and hospital-based IVF programs were enrolled in this study. Of the 484 patients stratified to the I-HB > 65% arm, 115 participants were randomized to the control group, 122 participants were randomized to the HYAL group and 247 participants were randomized to the NP group. Of the 318 patients stratified to the I-HB ≤ 65% arm, 164 participants were randomized to the control group and 154 participants were randomized to the HYAL group.

MAIN RESULTS AND THE ROLE OF CHANCE:

HYAL patients with an F-HB score ≤ 65% demonstrated an IR of 37.4% compared with 30.7% for control [n = 63, 58, P > 0.05, (95% CI of the difference -7.7 to 21.3)]. In addition, the CPR associated with patients randomized to the HYAL group was 50.8% when compared with 37.9% for those randomized to the control group (n = 63, 58, P > 0.05). The 12.9% difference was associated with a risk ratio (RR) of 1.340 (RR 95% CI 0.89-2.0). HYAL patients with I-HB and F-HB scores ≤ 65% revealed a statistically significant reduction in their PLR (I-HB: 3.3 versus 15.1%, n = 73, 60, P = 0.021, RR of 0.22 (RR 95% CI 0.05-0.96) (F-HB: 0.0%, 18.5%, n = 27, 32, P = 0.016, RR not applicable due to 0.0% value) over control patients. The study was originally planned to have 200 participants per arm providing 86.1% power to detect an increase in CPR from 35 to 50% at α = 0.05 but was stopped early for financial reasons. As a pilot study had demonstrated that sperm preparation protocols may increase the HB score, the design of the current study incorporated a priori collection and analysis of the data by both the I-HB and the F-HB scores. Analysis by both the I-HB and F-HB score acknowledged the potential impact of sperm preparation protocols.

BIAS, CONFOUNDING AND OTHER REASONS FOR CAUTION:

Selection bias was controlled by randomization. Geographic and seasonal bias was controlled by recruiting from 10 geographically unique sites and by sampling over a 2-year period. The potential for population effect was controlled by adjusting for higher prevalence rates of >65% I-HB that naturally occur by adding the NP arm and to concurrently recruit >65% and ≤ 65% I-HB subjects. Monitoring and site audits occurred regularly to ensure standardization of data collection, adherence to the study protocol and subject recruitment. Subgroup analysis based on the F-HB score was envisaged in the study design.

GENERALIZABILITY TO OTHER POPULATIONS:

The study included clinics using different sperm preparation methods, located in different regions of the USA and proceeded in every month of the year. Therefore, the results are widely applicable.

TRIAL REGISTRATION:

ClinicalTri gov NCT00741494.