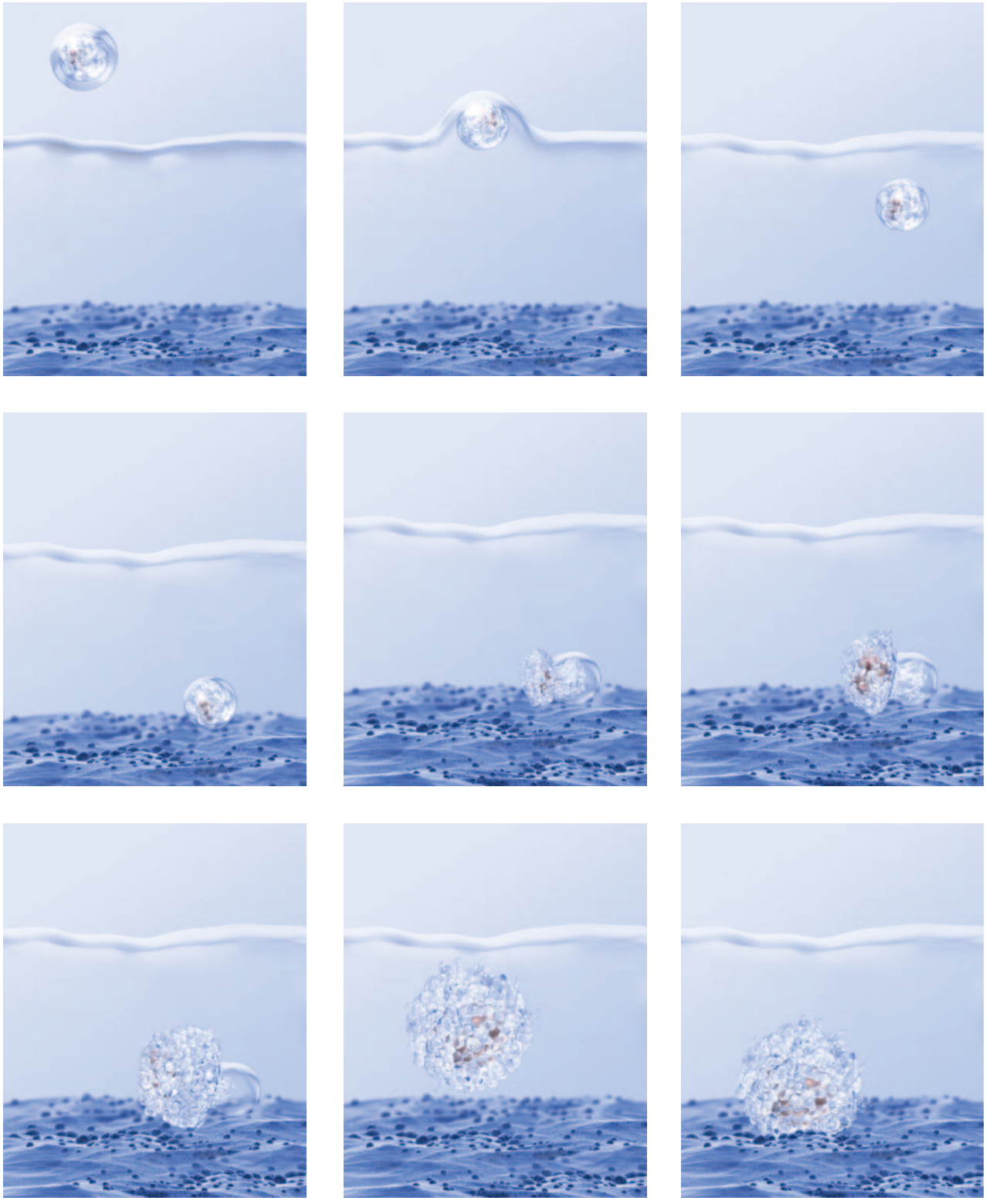
EMBRYOGLUE
– FOR SUCCESSFUL IMPLANTATION



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EMBRYOGLUE

Implantation promoting medium for
increased take-home baby rate.

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Embryo transfer is one of the most sensitive and critical procedures in IVF treatment. From retrieval to transfer, you can help the egg and embryo develop by providing optimal culture conditions. After transfer, the embryo has to rely on its own ability to implant. Using a hyaluronan-rich medium will promote a successful implantation.

With EmbryoGlue®, you can help Mother Nature and go the extra mile for your patients, helping them to bring a child home.

EMBRYOGLUE - WHAT IS IT?

EmbryoGlue is a medium developed exclusively for embryo transfer and the only existing product with a proven implantation-enhancing effect[1]. EmbryoGlue has the basic composition of a rich blastocyst culture medium and contains a high concentration of hyaluronan and recombinant human albumin. It can be used for transfer of all embryo developmental stages, including blastocysts after assisted hatching, biopsy and cryopreservation.

The use of EmbryoGlue for embryo transfer will increase the clinical pregnancy rate and delivery rate.

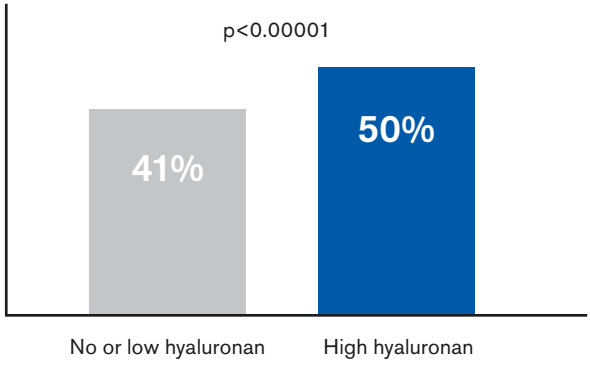
The positive effect of EmbryoGlue is proven

Since the market introduction of EmbryoGlue in 2003, several studies have been published regarding its effect. In 2010, the independent Cochrane Collaboration published a meta-analysis on all prospective, controlled, randomized studies on "Adherence compounds in embryo transfer media". The only molecule found to give a positive effect on implantation rates was hyaluronan. To give the desired effect the concentration of hyaluronan in the medium should be high. Low concentrations conferred no positive effect[1].

EmbryoGlue is the only available transfer medium containing a high concentration of hyaluronan.

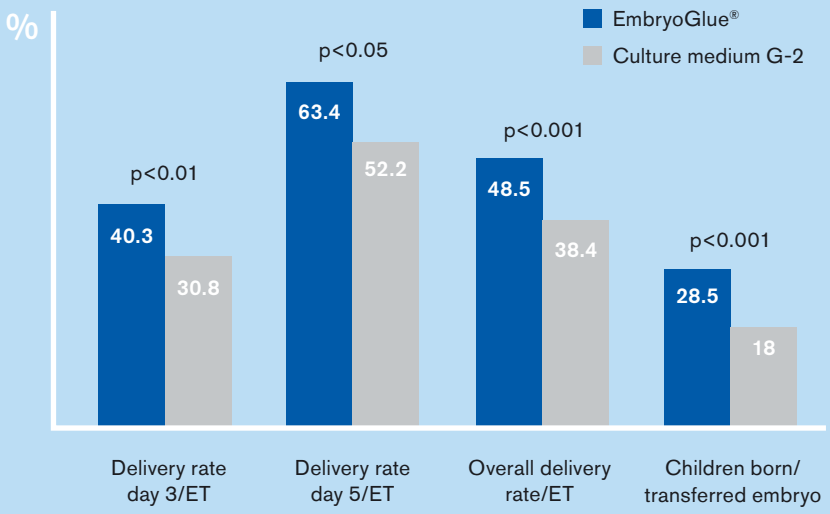
When EmbryoGlue was used for embryo transfer the clinical pregnancy rate was significantly increased from 41% to 50% compared to when a conventional culture medium with low or no hyaluronan was used. The meta-analysis of the 13 publications included in the Cochrane review article included more than 3200 patients. Importantly, the analysis did not show any increase in miscarriages or other adverse events. The conclusion by the Cochrane authors was that "a clear positive effect *(of having high concentrations of hyaluronan in the transfer medium)* was identified".

Clinical pregnancy rate



The Cochrane Collaboration,
established in 1993, is an independent international network of people helping healthcare providers, policy makers, patients, their advocates and carers, make well-informed decisions about human health care by preparing, updating and promoting the accessibility of Cochrane Reviews – over 4,000 so far, published online in The Cochrane Library.

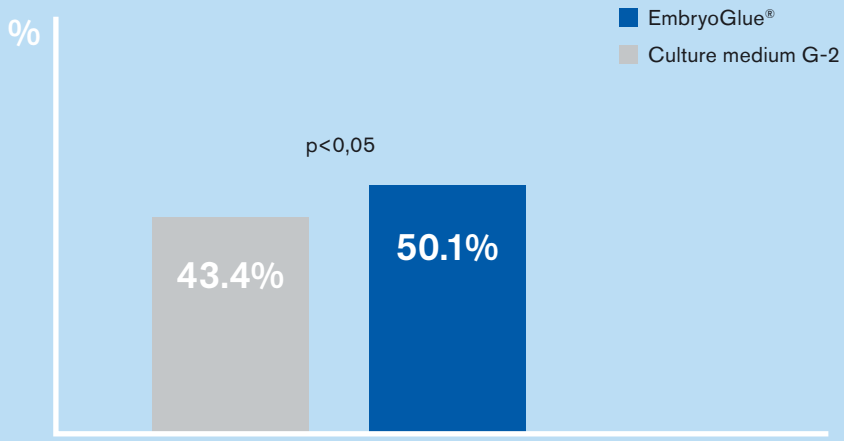
More children born with EmbryoGlue



In 2011 a follow up study of pregnancies obtained with the use of EmbryoGlue was performed. The study included almost 1300 embryo transfers[2].

The results showed a significantly increased delivery rate with the use of EmbryoGlue compared to when a culture medium was used for the embryo transfer procedure.

Delivery rate

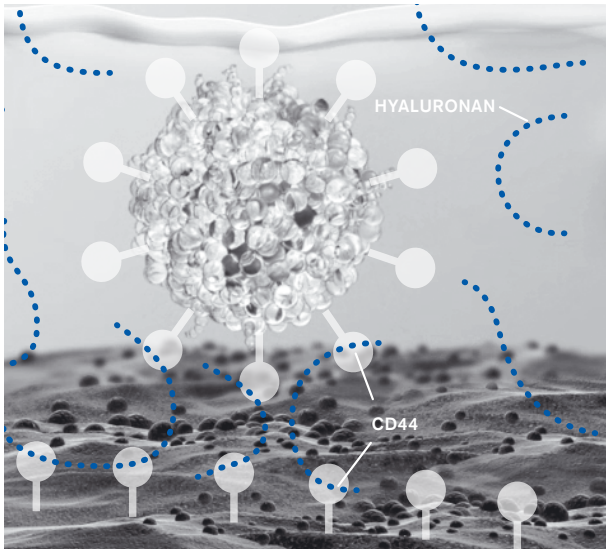


In a study by Sun et al.[3] delivery rate was again used as endpoint. Also this study included almost 1300 cleavage stage embryo transfer performed in two years. Again the study result showed a significant increase in delivery rate.

HOW DOES IT WORK?

EmbryoGlue contains all nutrients and energy sources needed for an optimal embryo development. And, most importantly, the medium contains a high concentration of implantation promoting hyaluronan. Hyaluronan is the major glycosaminoglycan present in the follicular, oviductal and uterine fluids[4,5,6]. The physiological concentrations in these fluids provide high viscosity environments in the oviduct and uterus[7].

The synthesis of hyaluronan increases dramatically on the day upon which implantation is initiated and it decreases to near basal levels by the next day, indicating its importance for the implantation event. Other types of glycosaminoglycans do not show an elevated synthesis at the time of implantation[8,9].



The implantation-promoting effect of hyaluronan is probably associated with several mechanisms:

Improved cell-cell and cell-matrix adhesion

Hyaluronan has been shown to increase cell-cell adhesion and cell—matrix adhesion[10] thereby functioning during the initial stages of apposition and attachment of the blastocyst to the endometrium.

Rapid physical diffusion with uterine secretion

Hyaluronan will facilitate rapid diffusion of the contents of the transfer medium into the viscous secretion of the uterus. An aqueous medium containing an appropriate concentration of hyaluronanrepresents far higher viscosity in comparison to a solution only containing proteins[11].

Receptor-mediated biological function

The hyaluronan surface-adhesion receptor, CD44, is present throughout development, from the oocyte to the blastocyst stage[12]. The CD44 receptor is also expressed in the human endometrium[13] and the expression is exclusively at the mid to late secretory phase, indicating the involvement of this molecule in the implantation process[14]. Another type of hyaluronan receptor, RHAMM/IHABP, is also expressed on the embryo surface at the implantation stage[15]. These data suggest that the various functions of hyaluronan including the implantation-promoting effect can be receptor mediated.