

WHITE PAPER

EMBRYOGLUE® - IMPLANTATION PROMOTING MEDIUM WITH PROVEN AND DOCUMENTED SUCCESS INCREASING LIVE BIRTH RATES

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Most culture media have been developed to optimise the development of the human embryo, and are not designed specifically for embryo transfer or the uterine environment. EmbryoGlue is an innovative embryo transfer medium that contains the implantation promoting factor, hyaluronan, and recombinant human albumin. EmbryoGlue is a member of the Vitrolife G-Series, which is based on the research of Prof. David Gardner and his team.

Part of the Vitrolife G-Series

The G-Series has been formulated with an optimised ionic composition to maintain osmolality and pH between the different media within the series. EmbryoGlue has been used clinically since 2003 and is the most documented embryo transfer specific medium. It has been shown to increase implantation rates and live birth rates^{1, 2, 3, 4, 5}.

Importance of hyaluronan

Back in 1999 Gardner et al.⁶ studied the effect of several macromolecules that might have a positive effect on embryo development and viability. Hyaluronan was not only found to support development on its own, but worked in synergy with albumin to support the preimplantation embryo. It was further discovered that the presence of hyaluronan in the transfer medium significantly increased the success of the outcome. Hyaluronan is a glycosaminoglycan and is a key molecule in embryo development and implantation^{7,8,9}. The level of hyaluronan in the uterus is dynamic and has been shown to increase significantly on the day of implantation^{10, 11}. While hyaluronan is present in the G-Series embryo culture media, EmbryoGlue has been formulated with an elevated concentration of hyaluronan to mirror that level present in the uterus during implantation.

There are several modes of action in which hyaluronan can improve embryo implantation. Hyaluronan has been shown to promote the diffusion of the transfer medium into the more viscous uterine secretion¹². Hyaluronan is an

important facilitator of cell-cell adhesion¹³, which suggests that it could have a more active role. In fact; hyaluronan is known to bind the CD44 receptor present on both the embryo and the endometrium. This receptor mediated binding has been documented as a key function in the process of implantation (Yaegashi et al., 1995).

Importance of recombinant human albumin

Recombinant Human Albumin offers several advantages over HSA or less defined protein supplementation. Serum derived Human Albumin is inherently heterogeneous and can contain contaminants that are known to negatively affect embryo development^{15, 16, 17}, which are not contained in the recombinant albumin preparations. Recombinant albumin is a more consistent product, minimising lot-to-lot variation^{18, 19, 15, 20, 16, 21, 17}. As it is synthetically derived, recombinant albumin is also free from contamination associated with blood derived products (e.g. hormones, prions). Furthermore, Lane et al.²² demonstrated that significantly more expanded bovine blastocysts were formed when cultured in the presence of citrate and recombinant human albumin. These blastocysts also had significantly more inner cell mass and trophectoderm cells. The addition of hyaluronan to this culture medium resulted in even higher blastocyst development rates proving that culture and transfer in recombinant macromolecules is not only a safer option, but one that is effective.

Early clinical impact of EmbryoGlue

Several clinical studies have been performed to examine the effect of a hyaluronan enriched transfer medium, (i.e., EmbryoGlue), on implantation and clinical outcomes. A study performed by Urman et al.¹ was comprised of 1282 consecutive fresh transfer cycles that were randomized into two groups. Six hundred and forty three women utilised supplemented G-2 as their transfer medium. The remaining women received the embryo transfer in EmbryoGlue. It is important to disclose that because all embryos were cultured in G-1/G-2 they were also exposed to a lower level of hyaluronan during embryo culture.

There was a significant increase in clinical pregnancy rates (54.6% vs 48.5%; OR 1.28, 95th CI 1.03- 1.59) and implantation rates (32% vs 25%; OR 1.43, 95th CI 1.23 -1.66) for those embryos transferred in EmbryoGlue (Fig. 1). While the benefit was seen in all patient populations, it was determined that the greatest effect was noticed in three specific groups:



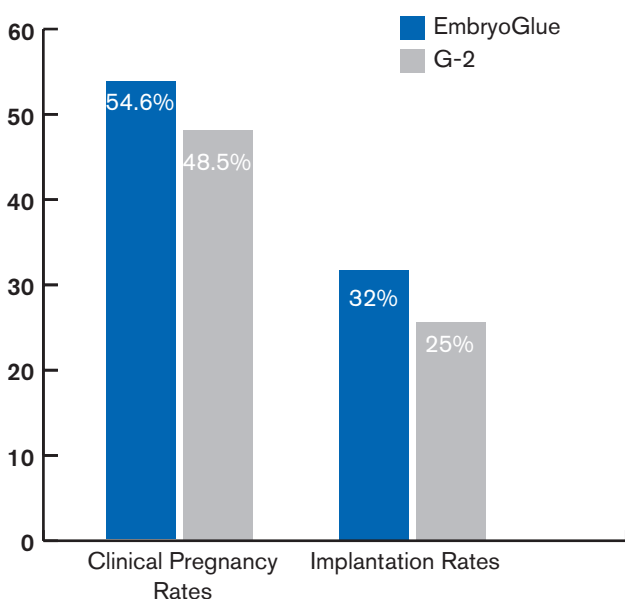
EmbryoGlue is the most documented embryo transfer medium available on the market, with a proven track record of increasing clinical outcomes.

- 1) women >35 years of age;
- 2) those with poor quality embryos and
- 3) women with previous history of implantation failure.

Based on these findings a calculation was used to further establish clinical relevance. It was determined that for every 17 patients treated with EmbryoGlue, one additional pregnancy could be obtained. In clinical terms, a clinic performing 1000 cycles could expect 58 additional pregnancies with the use of culture media containing hyaluronan and EmbryoGlue.

Fig 1. Increase in IR and CPR

Significant increase in Implantation Rates and Clinical Pregnancy Rates for those embryos transferred in EmbryoGlue¹



Confirmed clinical impact of EmbryoGlue

Urman et al.¹ demonstrated a positive effect on pregnancy rate and implantation rate when embryo transfers were performed with EmbryoGlue. Balaban et al.⁴ continued the original work, but focused on the resulting live birth rate. They concluded that there was a significant increase in the number of live births (48.5% vs 38.4%; OR 1.5; 95th CI 1.2-1.9) in the patient group that received a transfer using EmbryoGlue. The increase in live births was demonstrated in transfers performed on both day 3 and day 5. This study concluded that “a high concentration of hyaluronan [in EmbryoGlue] also has a positive effect on take home baby rate”.

In 2010 and 2014, The Cochrane Collaboration released two reports^{2,3}, both demonstrating the effectiveness of adherence compounds in embryo transfer media, specifically hyaluronan. The 2010 Report² compiled data from sixteen separate publications (>3600 transfers), of which 15 studied hyaluronan. The report indicated a treatment advantage (OR 1.41, 95% 1.22 to 1.63; $p < 0.00001$) with embryo transfer using a hyaluronan enriched medium, stating there is “evidence of an improved pregnancy rate” with use of hyaluronan. The 2014 report³ compiled data from seventeen publications (>3800 transfers), 16 of which studied hyaluronan. It was found that there was a positive treatment effect for all sixteen studies investigating the hyaluronan enriched transfer medium effect on live birth (OR 1.41, 95th CI 1.17 to 1.69). This is significant as the previous Cochrane report did not report effects on live birth rates. Furthermore the 2014 report goes on to support the finding of the 2010 report, indicating increased clinical pregnancy rates. It is also noteworthy to mention that the Cochrane reports did not indicate any negative effect of treatment with hyaluronan.

Hashimoto et al.⁵ compiled a meta-analysis of data collected from over 10,000 embryo transfers that involved the clinical intervention of EmbryoGlue. Twenty three studies were compared and concluded that the use of EmbryoGlue led to significantly increased pregnancy rates (39.8% vs 33.4%; $p < 0.0001$). A further analysis of eleven studies demonstrated a significant increase in implantation rates (38.6% vs 30.3%; $p < 0.0001$) when EmbryoGlue was used for embryo transfer. Fresh transfers using EmbryoGlue, resulted in significantly higher pregnancy rates (37.2% vs 25.0%; $p < 0.0001$). A significant increase in pregnancy rates and implantation were also obtained with embryos from cryopreserved cycles. Statistical increases for pregnancy and implantation rates ($p < 0.0001$) were also seen for the same outcomes with cleavage stage embryo transfers. This large data set from approximately 10,000 embryo transfers further supports the clinical benefit of using EmbryoGlue as the transfer medium and confirms the findings in the aforementioned Cochrane Reports.

For every 17 patients treated with EmbryoGlue, one additional pregnancy could be obtained. In clinical terms, a clinic performing 1000 cycles could expect 58 additional pregnancies with the use of culture media containing hyaluronan and EmbryoGlue.

Calculations based on Urman et al.¹

EmbryoGlue: conclusion

Culture media are not specifically designed for embryo transfer. The use of a defined embryo transfer medium can impact the success of embryo implantation. Evidence exists that undefined protein supplemented media contain potential hazards as they are human derived and should not be considered 100% safe. It is therefore strongly recommended that the transfer medium be defined and thoroughly tested to limit the effect of reprotoxicity on the developing and implanting embryo. Hyaluronan has been documented to increase not only clinical pregnancy and implantation rates, but has also been shown to significantly increase live birth rates. Finally, the use of recombinant versions of the macromolecules, hyaluronan and human albumin, creates the safest and most physiologic embryo transfer medium available.

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Our story

Vitrolife was established in Sweden in 1994 when the field of assisted reproduction was still young.

The possibility to help people become parents through assisted reproduction became a reality in the 1960s, following the development of a method for fertilising eggs outside the body. The birth of Louise Brown in 1978 – the first baby born as a result of in vitro fertilisation (IVF) – gave new hope to men and women suffering from infertility.

As IVF techniques developed, the importance of individual components on IVF success began to be understood. The founders of Vitrolife realised the value of using culture media with consistent and repeatable performance; the manufacturing and delivering of LOT-to-LOT consistency they developed is still significant for Vitrolife today.

Through well-executed product development, consistent quality controls and the acquisition of other innovative IVF companies, Vitrolife has grown with the market globally. As a result, Vitrolife provides an unbroken chain of quality products, securing results at every step of IVF treatment. Only Vitrolife can guarantee every link in this chain.

Our commitment to increase pregnancy rates has never been more dedicated. Together with equally devoted clinics, we are improving IVF success and fulfilling more couples' greatest dream. We are very proud to be a part of making this happen.

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