

Together. All the way™

EmbryoGlue

- Summaries of selected studies

Studies summarised by Vitrolife

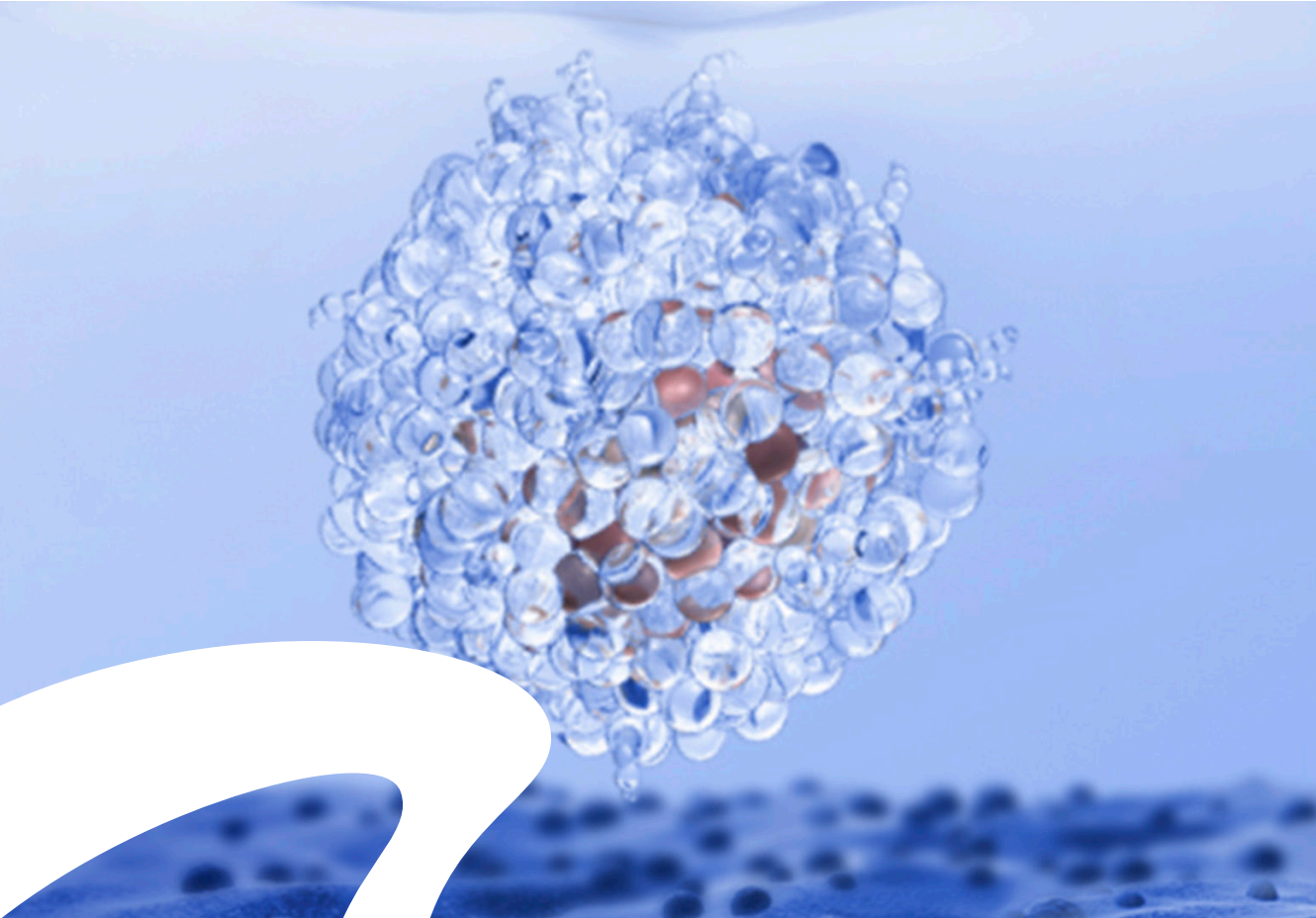


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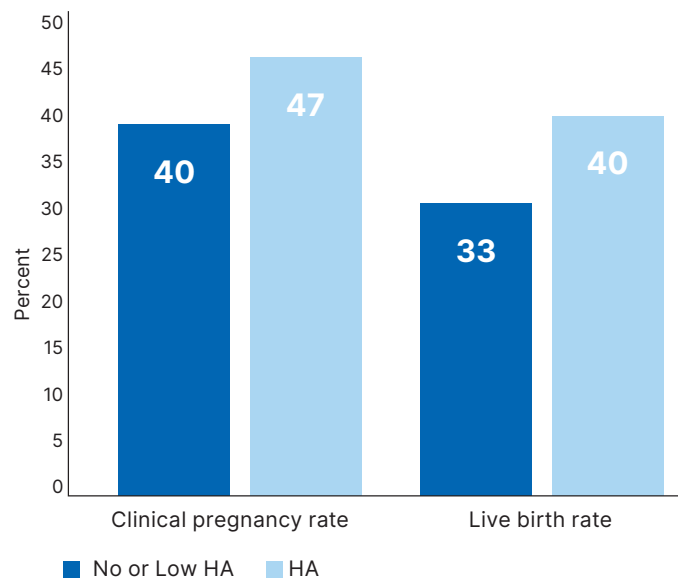
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Improved live birth and clinical pregnancy rates with the use of high hyaluronic acid (HA) in embryo transfer media, with one additional live birth achieved for every 14 embryos transferred

Heymann et al. 2020

Three reviews on the effect of hyaluronan in transfer media have been published by the Cochrane Library in 2010, 2014, and 2020 showing improved live birth and clinical pregnancy rates with the use of high HA in embryo transfer media.

Embryo transfers were performed either with a high level of HA or in culture medium with low or no HA. HA groups were labelled as high (0.5 mg/mL), low (0.125 mg/mL), or no HA (0.0 mg/mL). In 26 studies analysed, a total of 6,704 patients undergoing IVF/ICSI treatments were included. Primary outcomes were live birth rate and miscarriage rate.



Methods

Electronic databases, trial registers, and websites were searched until 7 January 2020 for all randomised controlled trials (RCTs) comparing embryo transfer media with high concentrations of adherence compounds versus embryo transfer media with no/low concentrations of adherence compounds.

Results

The reviews included 26 studies including 6704 women aged 27 to 35 years who underwent IVF/ICSI comparing embryo transfer using media containing high concentrations of HA versus solutions containing no or low concentrations of HA.

Ten of these studies showed that HA during embryo transfer increases the number of live births compared with using solutions with low concentrations or no HA. The live birth rate was increased with the use of HA regardless of embryo transfer day. Seventeen of these studies showed that high concentrations of HA in the embryo transfer solution also increase the number of clinical pregnancies.

Seven studies showed that high concentrations of HA during transfer also may result in slightly fewer miscarriages. But if one of these studies was excluded, this effect was no longer seen.

Conclusion

Moderate-quality evidence shows improved live birth and clinical pregnancy rates with the use of HA in embryo transfer media. Transfer media with low concentrations or no HA have a 33% chance of resulting in a live birth, while solutions with high concentrations increase the chance of a live birth to between 37% and 44%. According to a number needed to treat calculation, one additional live birth was achieved for every 14 embryos transferred.

REFERENCE

Devorah Heymann, Liat Vidal, Yuval Or, Zeev Shoham, Hyaluronic acid in embryo transfer media for assisted reproductive technologies, Cochrane Database of systematic Reviews 2020

Hyaluronic acid at the time of transfer increases the chances of pregnancy

Tyler et al. 2022

Numerous interventions or 'add-on' therapies have been introduced over the last years to optimise the outcome of ART treatments. Add-ons at the time of embryo transfer (ET) are proposed to increase the chances of conception. The ET is also operator dependent, and suboptimal practice is often linked to cycle failure. This systematic review and meta-analysis of randomised trials evaluated interventions introduced at the time of transfer.

Methods

Electronic databases were searched (MEDLINE, EMBASE and Cochrane CENTRAL) from inception until March 2021 for all randomised controlled trials (RCTs) that evaluated an intervention introduced in the 24 h period before/after embryo transfer in women undergoing IVF treatment. The primary outcome was clinical pregnancy rate post-ET confirmed as a viable pregnancy on ultrasound scan.

The electronic search identified 3685 titles and abstracts of which 228 articles met the inclusion criteria.

In total, 188 RCTs was included, reporting on 59 530 participants and 38 interventions. Forty percent of the studies performed an ET at day 2–3, 9% at day 5–6, and 37% did not specify the day of transfer. Thirty-eight interventions introduced at the time of ET (in the 24 h period before/after embryo transfer) were analysed.

Several pharmacological interventions were analysed, including hyaluronic acid (HA). How different ET techniques can affect the results were also analysed.

Results

For most of the interventions the evidence was low. Using ultrasound guidance, HA and soft catheters at the time of transfer appear to increase the pregnancy rate. Bed rest post-ET was associated with a reduction in clinical pregnancy rate. The use of G-CSF, Atsobian and hCG showed a trend towards increased pregnancy rate, but larger trials are required. The quality of the included RCTs was moderate with most showing a low risk of bias for randomization and attrition, but there was a significant risk of publication bias.

Intervention	Date	Total participants	Study Event Rate		Certainty assessment
			Control	With intervention	
HA vs. NO HA	9 RCTs	2453	286/1305 (21.9)	3871/1148 (33.7)	HIGH
Ultrasound guided ET vs. Clinical touch	24 RCTs	7256	986/3587 (27.5)	1245/3669 (33.9)	MODERATE
Softer vs. harder catheters	27 RCTs	10688	1704/5248 (32.5)	1969/5440 (36.2)	MODERATE

Table 1. Differences in clinical pregnancy rate between treatment groups according to duration of culture

Conclusion

There are many interventions proposed to increase the chances of pregnancy at ET. The only add-ons at the time of ET that increase the chances of pregnancy are using ultrasound guidance, HA, or soft catheters.

REFERENCE

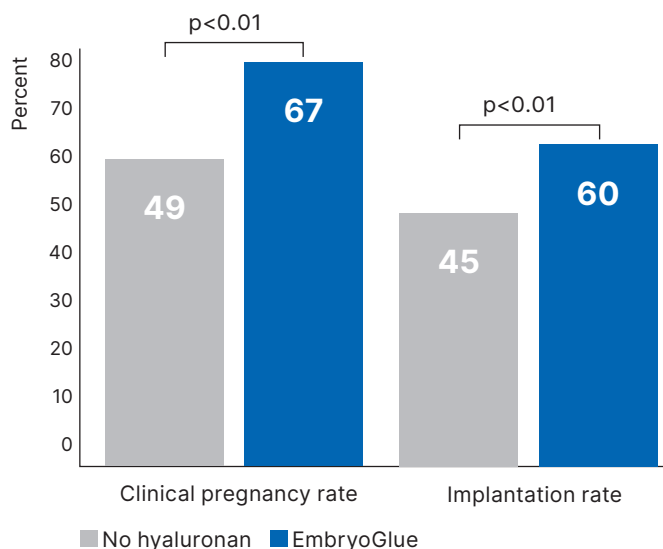
Tyler B, Walford H, Tamblin J, Keay s, Mavrellos D, Yasmin E, Al Wattar B, Interventions to optimize embryo transfer in women undergoing assisted conception: a comprehensive systematic review and meta-analyses. Human Reproduction Update, Volume 28, Issue 4, July-August 2022, Pages 480–500

Improved FET PGT outcomes for biopsied blastocyst transfer using EmbryoGlue even after short exposures

Reed et al. 2022

Poster presented orally at PCRS 2022.

Due to the time taken to perform preimplantation genetic testing (PGT) on human blastocysts, in most cases cryopreservation is required to permit timely embryo transfer. Since PGT is the dominant practice pattern in the Fertility Center of New Mexico, Albuquerque, New Mexico USA, most of the embryos are transferred in a FET cycle. Late in 2018 the transfer medium was changed to EmbryoGlue for all embryo transfers.



Methods

Embryos were cultured until day 3 when assisted hatching was performed. If blastocyst development progressed to an appropriate stage on day 5, 6 or 7, biopsy and vitrification was performed. After warming, the blastocysts were cultured for 3-4 hours before transfer. Immediately before transfer the blastocysts were washed in 1.5 mL of buffered media or EmbryoGlue and loaded in the transfer catheter with approximately 30 μ L of transfer medium. Exposure to buffered medium or EmbryoGlue was approximately 2-5 minutes.

Results

Warmed biopsied blastocyst often present with embryonic cells that can be partially or completely outside of the zona pellucida. Using EmbryoGlue instead of buffered medium as the transfer medium statistically increased the implantation rate and pregnancy rate for FET cycles with biopsied embryos, even after short exposures to Embryoglue.

Conclusion

Blastocysts with exposure to EmbryoGlue before embryo transfer showed an improved pregnancy rate in frozen blastocyst transfers with biopsied embryos, even after short exposures.

REFERENCE

Michael Leroy Reed, Al-Hasen Said, Douglas James Thompson, Improved FET PGT outcomes for biopsied blastocyst transfer using EmbryoGlue instead of buffered transfer media: could direct, immediate contact of embryonic cells to hyaluronan be beneficial? The Fertility Center of New Mexico, Albuquerque, New Mexico, USA, Poster presented at PCRS 2022

The use of EmbryoGlue during transfer shows an increase in clinical pregnancy rate and live birth rate

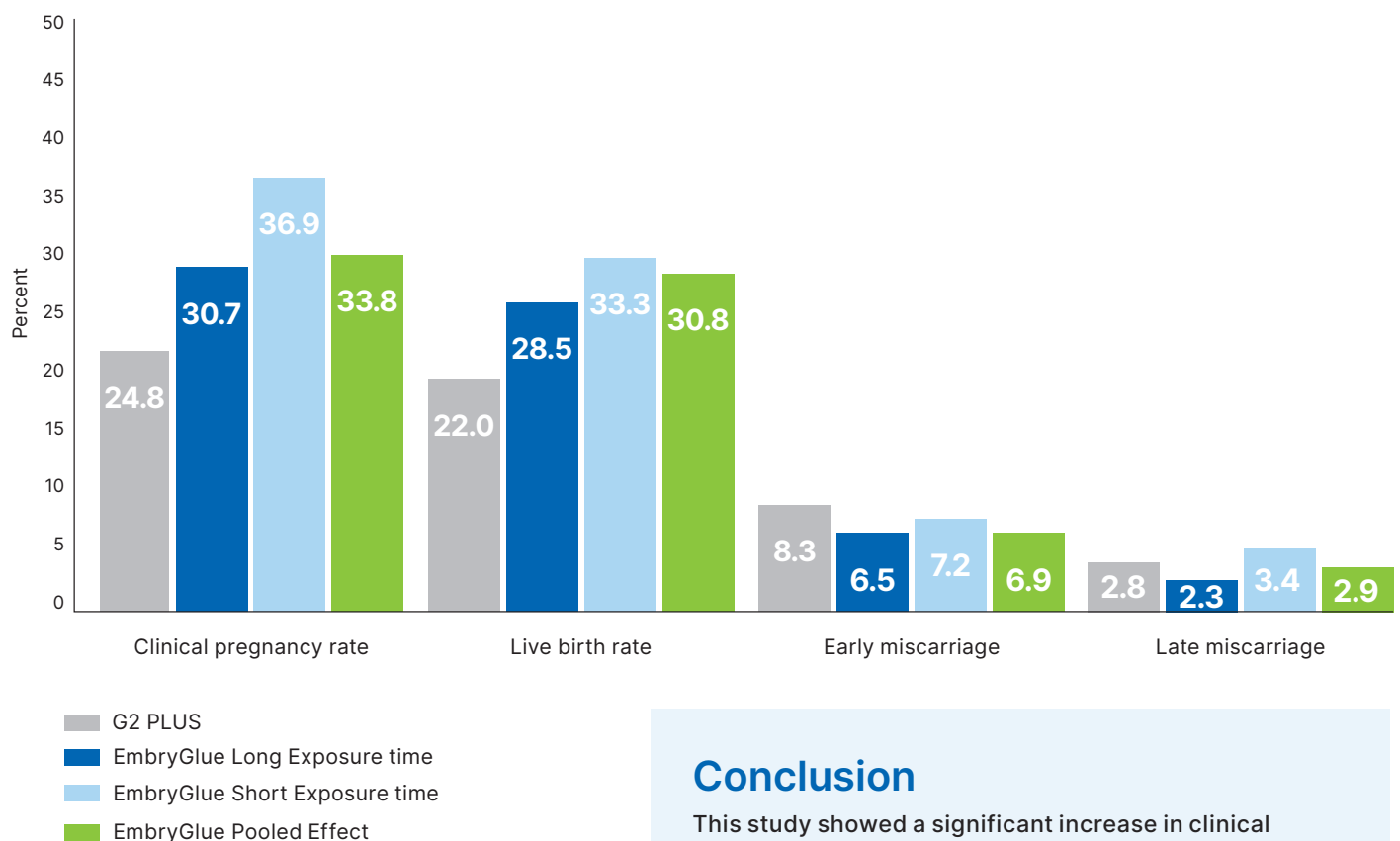
Adeniyi et al. 2021

In recent years modifications to ART culture techniques and culture media compositions have contributed to advances in the field. The use of hyaluronic acid (HA) in transfer media is one of them. Over the years the potentially beneficial effects of HA on embryo implantation have been investigated.

The use of HA-rich culture medium and other 'add-ons' for IVF are discussed. This study was carried out to evaluate the use of HA-rich culture medium in clinical practice.

Results

The use of EmbryoGlue for embryo transfer significantly increased the pregnancy rate and live birth rate compared to using low HA for transfer. Both long and short exposures were associated with improved pregnancy rate and live birth rate. The risk of early pregnancy loss tended to be reduced with the use of EmbryoGlue medium relative to the use of low HA.



Methods

To evaluate the use of HA-rich culture medium in clinical practice, clinical treatment outcomes in a cohort study were evaluated before and after EmbryoGlue was introduced in routine clinical practice. A total of 3391 patients undergoing IVF treatments between 2011 to 2015 were evaluated in three different groups. A total of 1018 ETs were performed with the use of G2 PLUS, and 2373 ET were performed with EmbryoGlue. In 1198 of them the embryo was pre-equilibrated for 2-4 h, and in 1175 for 10-30 minutes. The embryos were transferred at day 2, 3 or 5. Frozen embryo transfer, donor cycles and surgically obtained sperm were excluded.

Conclusion

This study showed a significant increase in clinical pregnancy rate and live birth rate when using EmbryoGlue during transfer compared to the use of low HA. The risk of early pregnancy loss tended to be reduced with the use of EmbryoGlue relative to the use of low HA.

REFERENCE

Tope Adeniyi, Gregory Horn, Peter T Raunde, Daniel R Brison and Stephen A Roberts, Clinical efficacy of hyaluronate-containing embryo transfer medium in IVF/ICSI treatment cycles; a cohort study, Hum Reprod Open. 2021; 2021(1)

EmbryoGlue

– a possible alternative to freeze-all cycles in PCOS

Kandari et al. 2019

Polycystic ovary syndrome (PCOS) is known to affect implantation rates, miscarriage rates and live birth rates in fresh embryo transfers. The freeze-all strategy has been developed to avoid ovarian hyperstimulation syndrome and reduced endometrial receptivity in these patients, but the added vitrification and preparation in subsequent cycles significantly increases the costs and time associated with treatment. The Cochrane review (2014) on the use of adherence compounds shows evidence that EmbryoGlue increases implantation and pregnancy rates. The objective of this study by Kandari (2019) was to evaluate whether the use of embryo transfer medium enriched with hyaluronan (EmbryoGlue) improves outcomes like implantation rates, live birth rate and miscarriage rates in time-lapse selected fresh SET in women with PCOS. This was a prospective randomised study. Sample size was calculated for statistical power of 80% with alpha = 0.05 and beta = 0.2. The study was presented orally at ASRM 2019.

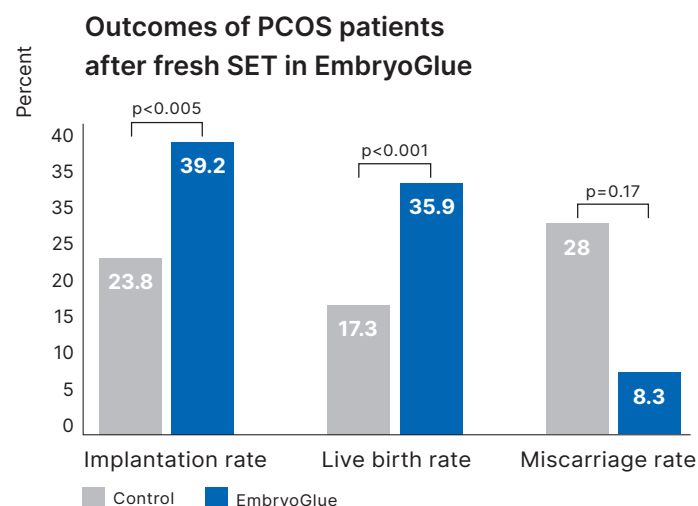
Methods

Patients were allocated on the day of transfer into two groups, transfer in EmbryoGlue or in a culture medium. For the patients in the study group (n = 153) the embryos (day 3 or blastocysts) were placed in EmbryoGlue before transfer and transferred in the same medium. The embryo transfers of the control group (n = 168) were performed in a culture medium without hyaluronan, CSCM (Irvine Sci).

Fertilisation and culture conditions (time-lapse) were the same for all patients regardless of group. Age, infertility duration, previous IVF cycles, oocyte number and stage of transferred embryo were similar in both groups as well. SET was employed for all patients.

Results

Statistical differences: Implantation rate $p < 0.005$, live birth rate $p < 0.001$, miscarriage rate $p < 0.17$.



Conclusion

The use of EmbryoGlue for time-lapse SET in PCOS shows a significant increase in implantation rate and live birth rate with lower miscarriage rates compared with conventional embryo transfer medium. This strategy should also be explored to improve outcomes as an effective alternative to freeze-all cycles for PCOS patients.

REFERENCE

Kandari, S. (2019). Time lapse selected elective single embryo transfer in hyaluronan enriched transfer medium in PCOS improves live birth rates compared to use of conventional embryo transfer media. A possible alternative to freeze-all cycles in PCOS. *Fert & Steril* (112): 3. e47-e48.

Pregnancy rates and implantation rates increased after prolonged exposure of frozen blastocysts to EmbryoGlue

Perez et al. 2019

EmbryoGlue is a hyaluronan-enriched medium specifically developed for embryo transfer. It can be used for all stages of embryo development including cryopreserved embryos. Before transfer, the manufacturer recommends that embryos are placed in the medium for a minimum of 10 minutes. In the study abbreviated below the effect of different exposure times was investigated. The objective of the study was to examine if pregnancy rates and implantation rates could be increased by using a longer exposure time. The study was presented orally at ASRM 2019.

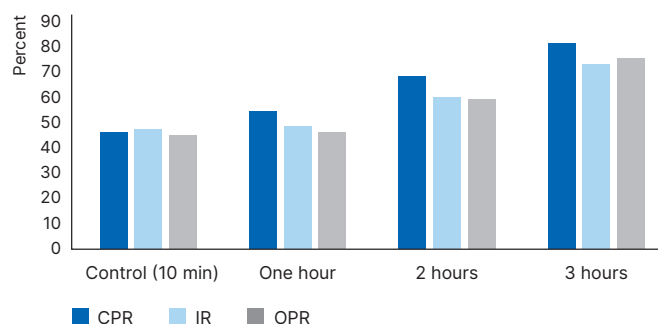
Methods

Frozen blastocysts from 119 patients were included in the study and randomly allocated to four groups according to exposure time to EmbryoGlue. The first group served as the control, and the blastocysts in that group were exposed to EmbryoGlue according to the minimum recommended exposure time, 10 min, before transfer. The average exposure times to EmbryoGlue in the other groups were 1.3 hours, 2.2 hours and 3.3 hours, respectively. The study was prospective and randomised. The endpoints were clinical pregnancy rate (CPR), ongoing pregnancy rate (OPR) and implantation rate (IR). The number of transferred blastocysts were 1.2 or 1.3 in the respective groups, and the patients' ages were 33 or 34 years.

Results

Statistical differences: Implantation rate $p < 0.005$, live birth rate $p < 0.001$, miscarriage rate $p < 0.17$)

Outcomes after different exposure times to EmbryoGlue



Conclusion

Blastocysts with extended exposure to hyaluronan enriched medium before embryo transfer showed an improved implantation rate in frozen embryo transfers. This procedure before embryo transfer provides better clinical outcomes when thawed blastocysts were exposed to EmbryoGlue for more than 2 hours.

REFERENCE

Perez, O. Adriaanse, H. Tilley, B. Navarette, G. Kay, L. Little, L. Gada, R. Lawrence, L. Lee, K. Thomas, M. and Chantilis, S. (2019). The effect of extended blastocyst exposure of hyaluronan-enriched transfer medium on implantation rate in frozen embryo transfers. *Fertility & Sterility*, Vol 112, No 3, Supplement. ASRM abstract.

The use of EmbryoGlue increases the chance of conception by approximately 9%

Zbořilová et al. 2018

EmbryoGlue contains a high level of hyaluronan and recombinant human albumin. Hyaluronan is known to be involved in physiological processes such as embryo development, migration and adhesion. Hyaluronan increases cell-cell and cell-extracellular matrix adhesion, which significantly supports the apposition process and adhesion of blastocysts.

The aim of this prospective study was verification of the effect of EmbryoGlue transfer medium enriched with hyaluronan on the embryo transfer process.

Methods

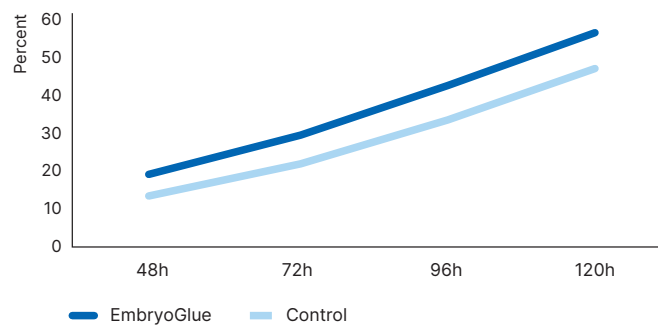
A total of 484 patients were included in the study and divided according to the media used for transfer, Sage 1-Step (control, n = 135) or EmbryoGlue (n = 349). Embryos were cultured either in Sage 1-step medium or in G-TL (Vitrolife) and transferred after 48 hours (21%), 72 hours (32%), 96 hours (20%) or 120 hours (27%). In the EmbryoGlue group the embryos were equilibrated in this medium for 20 minutes up to 1 hour before transfer. Embryos in the control group were cultured and transferred in the same culture medium. The mean number of transferred embryos was the same in both groups, 1.2. The endpoint of the study was clinical pregnancy rate, CPR.

Results

Duration of culture	CPR EmbryoGlue (%)	CPR Control (%)	Difference between treatment groups (%)
48 hours	19	13.6	5.4
72 hours	29.2	21.8	7.4
96 hours	42.3	33.1	9.2
120 hours	56.6	46.8	9.8

Table 1. Differences in CPR between treatment groups according to duration of culture

Clinical pregnancy rates with or without EmbryoGlue



Conclusion

Using the transfer medium EmbryoGlue before embryo transfer affects the pregnancy rate in a positive manner. The effect was seen for all culture periods and was highest for transfer at the blastocyst stage.

REFERENCE

Zbořilová, B., Oborna, I., Tkadlec, E., Procházka, M., Březinová, J., Sobek, A. Jr and Sobek A. (2018). Does EmbryoGlue transfer medium affect embryo transfer success rate? Česká Gynekologie 83(3). pp-177-184.

EmbryoGlue increases the ongoing pregnancy rate and reduces the miscarriage rate after transfer of frozen/thawed blastocysts in patients with previously failed implantation

Charulata et al. 2017

Hyaluronan, a glycosaminoglycan, increases in the female reproductive tract at the time of implantation, and it is postulated that it may form a sticky matrix on the endometrial wall facilitating embryo implantation. EmbryoGlue is a hyaluronan-enriched transfer medium that can be used for all embryo development stages. In the study described here, EmbryoGlue was used for transfer of frozen blastocysts. The objective of this retrospective study was to examine the effect of hyaluronan-enriched transfer medium on reproductive outcomes in couples with failed implantations.

Methods

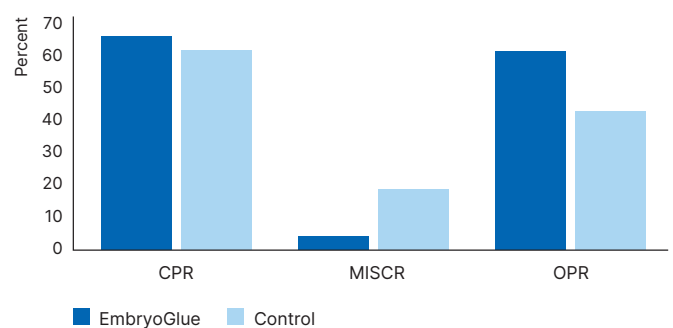
A total of 44 patients with at least two previously failed implantations after blastocyst transfer were included in the study (study group), and their embryos were placed in hyaluronan before transfer and transferred in the same medium. The results of the study group were compared against a control group of 100 patients who also had a history of failed implantations but who had blastocyst transfers without EmbryoGlue treatment.

All embryo transfers were performed with frozen/thawed blastocysts. Endpoints of the study were clinical pregnancy rate (CPR), miscarriage rate (MISCR) and ongoing pregnancy rate (OPR). Live birth rates were not included.

Results

The differences in miscarriage rates and ongoing pregnancy rates between the study group and the control group were both statistically significant ($p < 0.05$).

Clinical outcomes



Conclusion

The use of EmbryoGlue for transfer of frozen/thawed blastocysts significantly reduced the miscarriage rate in patients with previously failed implantations subsequently leading to significantly higher ongoing pregnancy rates.

REFERENCE

Charulata, C. Mantravadi, K and Rao, D.G. (2017). Hyaluronan enriched transfer medium improves reproductive outcomes in frozen thawed cycles for couples with repeated implantation failure. P-223. ESHRE Annual meeting, Geneva.

Significantly improved clinical outcomes with the use of EmbryoGlue as the embryo transfer medium

Flouri et al. 2017

EmbryoGlue is a medium specifically developed for embryo transfer, and it contains a high level of hyaluronan in combination with recombinant human albumin. The transfer medium was first introduced on the market in 2003 as an implantation-promoting medium and has been used for several million embryo transfers. The positive effect on implantation, clinical pregnancy rate and live birth rate was demonstrated in a review by the Cochrane collaboration in 2014 and in several subsequent studies, including the abstract by Flouri et al. from 2017 reproduced below. The study was retrospective.

Methods

The study included 234 IVF/ICSI cycles using EmbryoGlue for embryo transfers, matched against controls for maternal age, attempt number and day of embryo transfer. A culture medium was used as control for EmbryoGlue. Separate analyses were also performed for age <38 and >38 years and for embryo transfer day, day 2/3 or 5. Mean age was approximately 37 years. Endpoints of the study were clinical pregnancy (CPR), implantation (IR), live birth (LBR) and miscarriage (MISCR) rates.

Results

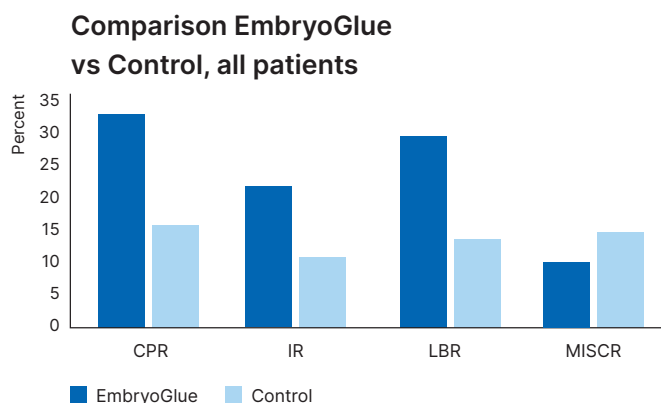


Fig 1. The differences between CPR, IR and LBR were all statistically significant ($p < 0.01$) and in favor of EmbryoGlue. The difference in MISCR was not significant.

REFERENCE

Flouri, C. Tailor, S. Vourliotis, M. Francis, G. Papoff, F Sotircho, G. and Almeida, P. (2017). The effect of EmbryoGlue on clinical outcome. P-179. Fertility 2017, Edinburgh, UK.

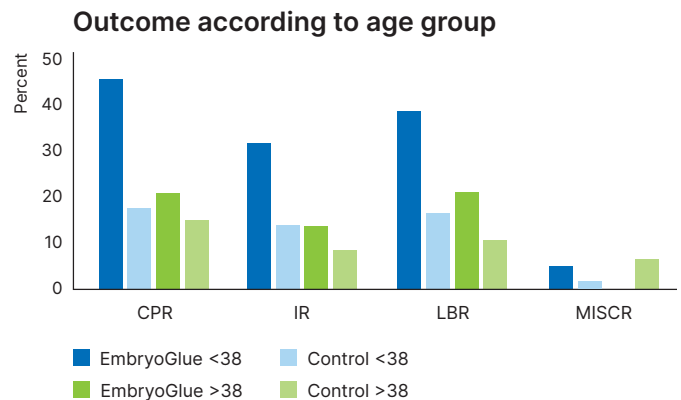


Fig 2. The group <38 years had a higher CPR ($p < 0.01$), IR ($p < 0.01$) and LBR ($p < 0.01$) when EmbryoGlue was used. MISCR was not significantly different. In the group >38 years IR was higher after the use of EmbryoGlue ($p < 0.05$) and MISCR was lower ($p < 0.01$). The differences in CPR and LBR were not significant.

The results were also analysed according to embryo transfer day, Fig 3.

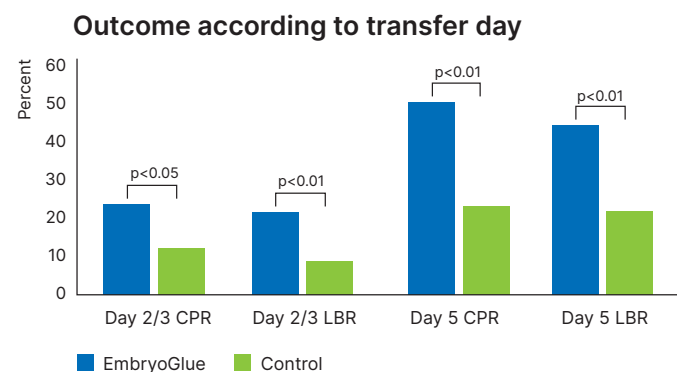


Fig 3. The differences between CPR, IR and LBR were all statistically significant ($p < 0.01$) in favor of EmbryoGlue. The difference in MISCR was not significant.

Conclusion

The authors conclude that “CPR, IR and LBR were significantly higher with the use of EmbryoGlue in all age groups and at different stages of embryo development, and miscarriage rates were significantly lower especially in patients of advanced maternal age.”

EmbryoGlue improves pregnancy and implantation rates: results from a meta-analysis of almost 10,000 embryo transfers

Hashimoto et al. 2014

The Cochrane reports published in 2010 and 2014 including almost 4000 cycles showed improved pregnancy rates as well as improved live birth rates after the use of high concentrations of hyaluronan and recombinant human albumin in an embryo transfer medium (EmbryoGlue). A number of clinics in Japan evaluated the use of EmbryoGlue and presented results at different scientific meetings between 2010 and 2013. Below is a meta-analysis of these different studies.

Methods

The use of EmbryoGlue was compared with standard transfer medium at the respective clinics. Embryos were transferred on day 3 or at the blastocyst stage either fresh or after cryopreservation. For the statistical analysis, numbers were compared using a 2x2 Chi square test with p-values <0.05 considered statistically significant. For the meta-analysis, the fixed or random effect model was applied when appropriate.

Results

The use of EmbryoGlue resulted in increased pregnancy and implantation rates according to a meta-analysis including results of 23 and 11 studies, respectively. The studies included 9 923 and 4 841 cycles, respectively. Table 1 summarises numbers and relevant statistics for pregnancy and implantation for overall results as well as for transfers using fresh or cryopreserved embryos. In all groups, pregnancy and implantation rates were significantly higher when using EmbryoGlue as the transfer medium. Analysis of miscarriage rates showed no significant difference. The overall pregnancy, implantation and miscarriage rates are presented in Figure 1. Pregnancy and implantation rates were also compared for cleavage stage and blastocyst transfers (Table 2), showing improved pregnancy and implantation rates for both developmental stages.

	Overall		Fresh cycles		Cryo cycles	
	Pregnancy	Implantation	Pregnancy	Implantation	Pregnancy	Implantation
Studies included	23	11	7	3	22	11
EmbryoGlue	39.8%	38.6%	37.1%	33.4%	40.2%	39.4%
Control	33.3%	30.3%	25.0%	20.1%	39.6%	32.2%
p-value	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	<0.001

Table 1: Numbers of abstracts and studies included for determination of pregnancy and implantation for overall results as well as for subgroups summarising transfers with fresh or cryopreserved embryos.

	Cleavage stage		Blastocysts	
	Pregnancy	Implantation	Pregnancy	Implantation
Studies included	9	4	16	8
EmbryoGlue	32.5%	26.8%	44.4%	46.1%
Control	22.3%	17.7%	39.4%	38.7%
p-value	<0.0001	<0.0001	0.0002	0.0001

Table 2. Results for the subgroups with embryo transfers at the cleavage stage and blastocyst stage.

REFERENCE

1. Bontekoe S et al. Cochrane Database Syst Rev. 2010 Jul 7;(7):CD007421. 2. Bontekoe S et al. Cochrane Database Syst Rev. 2014 Feb 25;2:CD0074213. Hashimoto, S. Joris, H. Morimoto, Y. (2014). EmbryoGlue improves pregnancy and implantation rates: results from a meta-analysis on almost 10 000 embryo transfers. Alpha biannual conference PP-009.

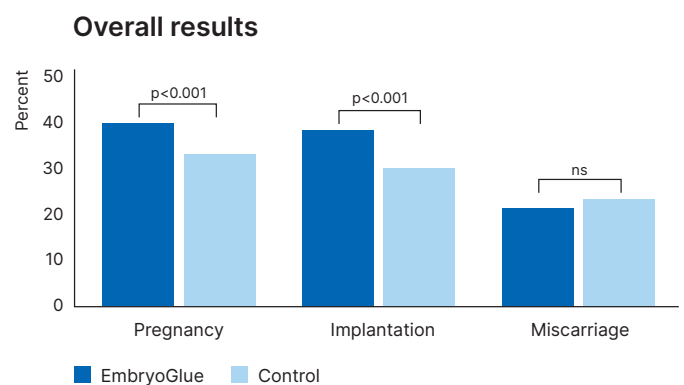


Fig 1. Overall results for pregnancy, implantation and miscarriage rates.

Conclusion

The positive effect of hyaluronan and recombinant human albumin in an embryo transfer medium (EmbryoGlue) has been shown in the two Cochrane reports as well as in numerous other publications including the meta-analysis from Japan presented here. These data of almost 10 000 embryo transfers confirm the findings from the Cochrane reports.

Improved take-home baby rate with EmbryoGlue as the embryo transfer medium

Balaban et al. 2011

In 2008 a study was published by Urman et al. (included in this folder) reporting the effects of using EmbryoGlue as the embryo transfer medium. This study was a follow-up including take-home baby rates and miscarriages, which were not reported in the initial study.

Methods

A total of 1282 fresh cycles were included, and the patients were randomised to either the EmbryoGlue group or the control group (culture medium used for embryo transfer). As shown in the previous study, the clinical pregnancy rate and implantation rate were significantly increased with the use of EmbryoGlue for unselected patients. For the subgroup of women >35 years of age with at least two previously failed implantations and with only poor-quality for transfer, the outcomes were also significantly increased.

Data on delivery results were collected from the hospital's database and analysed by Fisher's exact test for differences between groups.

Results

As reported earlier there were no significant differences between the two groups in patient characteristics. A total of 639 patients were included in the EmbryoGlue group, and 643 patients were included in the control group. As shown in Figure 1, the take-home baby rates were significantly higher after the use of EmbryoGlue regardless of embryo transfer day.

Take-home baby rates

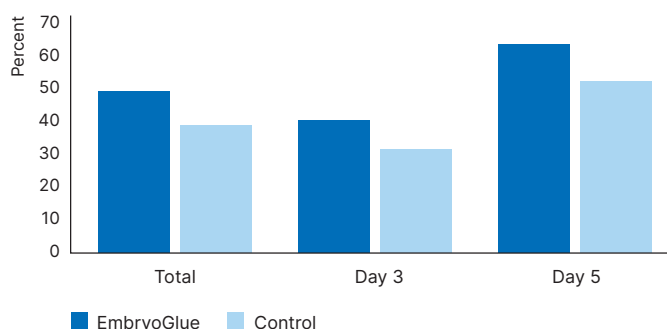


Fig 1. Take-home baby rates. P-values for the total group were $p < 0.001$ for day 3 $p < 0.01$ and for day 5 $p < 0.05$.

The number of children born per embryo transferred was also calculated (Fig 2), and these differences were significantly higher after use of EmbryoGlue.

REFERENCE

Balaban, B. Yakin, Ata, B. K. Isiklar, A. and Urman, B. (2011). Effect of hyaluronan take homebaby rate after day 3 and day 5 embryo transfers; a prospective randomised study. O-060, ESHRE 2011. Human Reproduction 26, Suppl 1, p-i24.

Percentage of transferred embryos resulting in live births

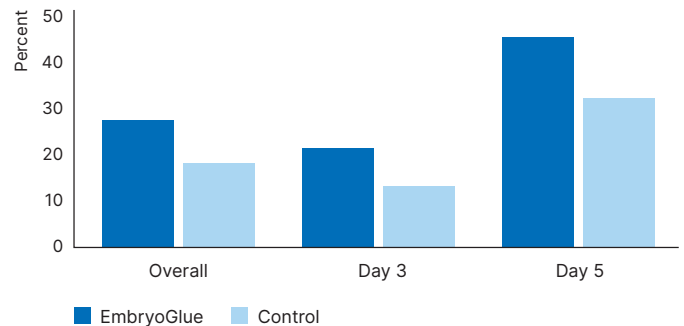


Fig 2. Percentage of children born per embryo transferred. The differences for the total number of patients as well as for day 3 and day 5 transfers were statistically significant with $p < 0.001$ for the total group (p-values not available for day 3 and day 5).

The miscarriage rates were also reported for the EmbryoGlue group and control group for all embryo transfers. As seen below (Fig. 3), the miscarriage rate in the EmbryoGlue group was lower compared to the control group.

Miscarriage rate

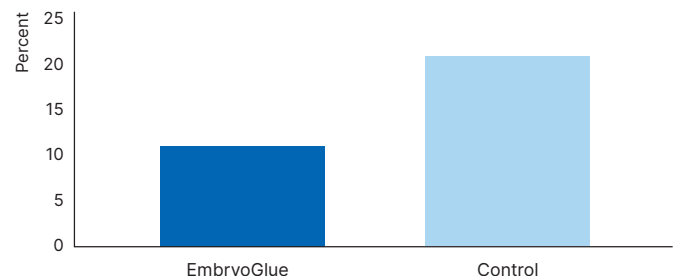


Fig 3. Miscarriage rates in the total group of patients.

Conclusion

The authors conclude that the use of EmbryoGlue had a positive effect on the take-home baby rate for both day 3 and day 5 embryo transfers.

Improved delivery rate after use of EmbryoGlue as the transfer medium for day 3 embryos

Sun et al. 2010

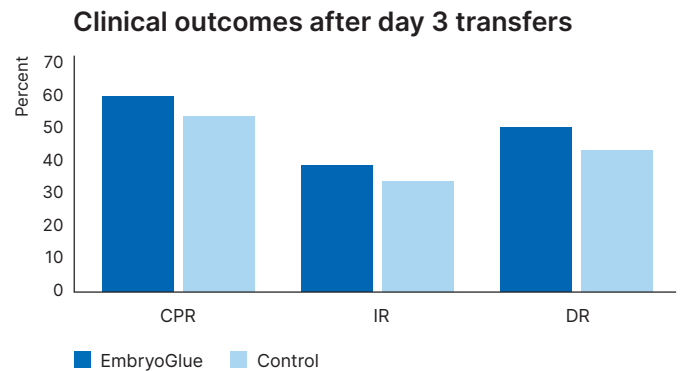
Hyaluronan is a glycosaminoglycan present in follicular, oviductal and uterine fluids. The synthesis of hyaluronan increases significantly at the time of implantation and decreases rapidly again to near basal levels already on the next day. According to a Cochrane review (2010) the implantation rate (IR) and clinical pregnancy rate (CPR) were improved with the use of hyaluronan-enriched transfer medium (EmbryoGlue) compared to when a culture medium was used for embryo transfer. However, the delivery rate was not included in the Cochrane review of 2010. The purpose of this retrospective study, also from 2010 and reproduced below, was to verify the role of hyaluronan on clinical outcomes, especially on delivery rate (primary endpoint) but also on CPR and IR (secondary endpoints).

Methods

All embryos were cultured in the same culture system using the same equipment and staff. A total of 743 embryos were incubated and transferred in EmbryoGlue containing a high level of hyaluronan and recombinant human albumin and compared to 471 control embryos that were transferred in a culture medium containing low levels of hyaluronan and human serum albumin (HSA). All transfers were performed on day 3.

Results

Both groups were similar for baseline variables.



All endpoints reached statistical significance, $p < 0.02$. The number needed to treat (NNT) to obtain one extra delivery with high concentration of hyaluronan in the transfer medium was 15.

Conclusion

EmbryoGlue containing high levels of hyaluronan and recombinant human albumin significantly increased the delivery rate. In addition, both the clinical pregnancy rate and implantation rate were improved. NNT to obtain one additional delivery was 15 in this material. In another study, by Urman et al., the NNT to obtain one additional pregnancy for unselected patients regardless of transfer day was 17.

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2. Urman, B, Yakin, K, Ata, B, Isiklar, A and Balaban, B. (2008). Effect of hyaluronan-enriched transfer medium on implantation and pregnancy rates after day 3 and day 5 embryo transfers: a prospective randomized study. *Fertil & Steril* 90(3), pp:604-612.

Significantly improved implantation and clinical pregnancy rates for day 3 and day 5 transfers with the use of EmbryoGlue

Urman et al. 2008

Traditionally embryos have been transferred in their culture medium, although a dish with fresh medium is used. To mimic the in-vivo conditions, several attempts have been made in the past to increase the viscosity of transfer media by using different macro-molecules such as human serum albumin (HSA), hyaluronan and collagen. The only molecule with positive improvements for implantation, pregnancy and live birth rates is hyaluronan. Numerous studies have shown that hyaluronan has a positive effect on IVF outcomes when added to transfer medium at high concentrations. EmbryoGlue is a medium specifically developed for embryo transfer (ET) at all developmental stages, including after cryopreservation and embryo biopsy. The product contains high levels of hyaluronan in combination with recombinant HSA. The prospective randomised study described below is the largest study performed on EmbryoGlue performed by a single clinic. The aim of the study was to analyse whether the use of a hyaluronan-enriched transfer medium (EmbryoGlue) increases rates of implantation (IR) and clinical pregnancy (CPR) after day 3 and day 5 embryo transfers compared with the use of a conventional (culture) medium.

Methods

A total of 1282 consecutive fresh embryo transfer cycles (825 day 3 and 457 day 5) were randomly allocated into two groups. In 639 women, ET was performed in EmbryoGlue, and in 643 it was performed with a conventional culture medium (G-2, containing low levels of hyaluronan and HSA).

Primary endpoints were CPR and IR in the total material. The patients were also divided into subgroups according to age, quality of transferred embryos and previously failed implantations. The mean age of female patients was 33 years, the mean number of transferred embryos per patient was 2.8 and the mean number of previously failed cycles was 2. The numbers needed to treat (NNT) to achieve one additional pregnancy were calculated for all groups of patients, see Fig 3.

Results

Overall CPRs and IRs significantly increased with the use of EmbryoGlue. The beneficial effect was more prominent in women who were >35 years of age, in women who had previously failed cycles and in women with only poor-quality embryos for transfer. The positive effect was seen both after day 3 and day 5 transfers.

Results for all patients, and day 3 and day 5 transfers

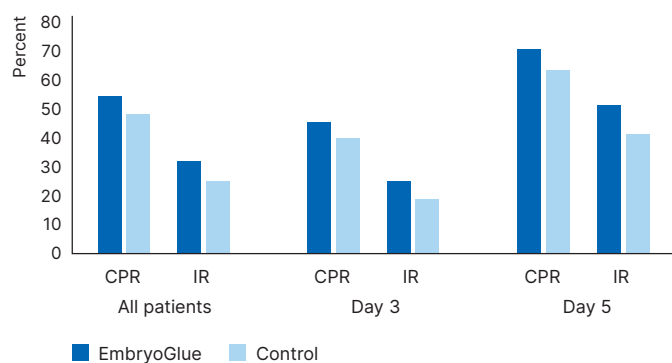


Fig 1. CPR and IR for the total patient group (left), for day 3 transfers (center) and day 5 transfers (right)

Outcomes of subgroups

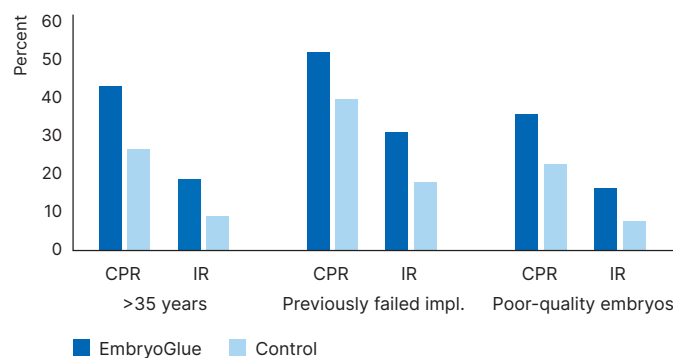


Fig 2. Outcomes of subgroups: Women >35 years (left), previously failed implantations (center) and poor-quality embryos for transfer (right).

Parameter	NNT
Overall	
For 1 additional clinical pregnancy in any women	17
For 1 additional clinical pregnancy in women >35 y of age	7
For 1 additional clinical pregnancy in women with PIF	7
For 1 additional clinical pregnancy in women who have no good-quality embryos	8
Day 3 transfers	
For 1 additional clinical pregnancy in women >35 y of age	8
For 1 additional clinical pregnancy in women with PIF	10
For 1 additional clinical pregnancy in women who have no good-quality embryos	8
Day 5 transfers	
For 1 additional clinical pregnancy in women >35 y of age	4
For 1 additional clinical pregnancy in women with PIF	7

Fig 3. Number needed to treat calculations for the total patient group and for subgroups. Copy from original article.

Conclusion

The use of hyaluronan increased both implantation and clinical pregnancy rates for all patients. Additionally, the results were improved after both day 3 and day 5 embryo transfer as well as in all subgroups.

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Increased hyaluronan concentration in the embryo transfer medium results in a significant increase in the human embryo implantation rate

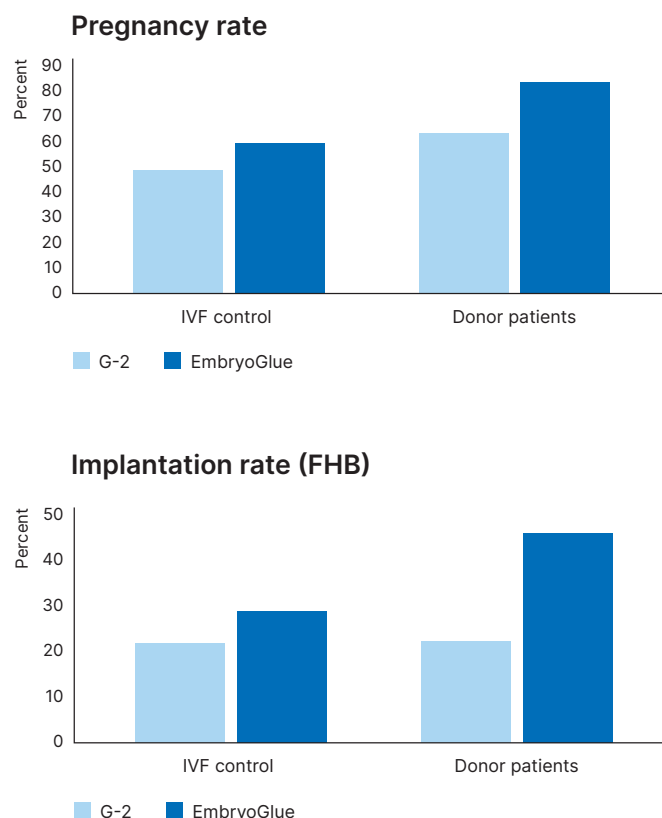
Schoolcraft et al. 2002

This is the very first EmbryoGlue study. It was presented as a talk at ASRM 2002 under the title above. This small study by W Schoolcraft et al. initiated numerous studies on transfer medium containing high levels of hyaluronan. Today (2020) there are at least 150 studies using EmbryoGlue published from all over the world. When the study was initiated it was already known that the level of hyaluronan in the female tract increases up to the time of implantation in the mouse model and that the presence of hyaluronan in the embryo transfer medium significantly increases resultant implantation rates. The objective of this study was to investigate if the same effect can be obtained in humans by introducing high levels of hyaluronan in an embryo transfer medium used at an IVF clinic. The endpoint of the prospective randomised trial was implantation rate (fetal heart beat, FHB).

Methods

After fertilisation embryos were cultured in the G-Series sequential media. Embryos were transferred either in G-2 containing a low level of hyaluronan (control) or in EmbryoGlue with a high level of hyaluronan. The study included two groups of patients, IVF patients (n = 68 in the control group and n = 73 in the study group) and patients receiving donated oocytes (n = 16 in the control group and n = 18 in the study group). Embryo transfer was performed on day 3.

Results



Statistically different rates of the primary endpoint, implantation rate, was reached ($p < 0.05$). There is also a trend towards to higher pregnancy rates in the EmbryoGlue groups, but statistical significance was not reached.

Conclusion

As concluded by the authors, this study has shown that the composition of the embryo transfer medium has a direct effect on the implantation rate in women using their own oocytes and in women using donor oocytes. The use of a medium with an increased hyaluronan concentration should lead to the transfer of fewer embryos per patient.

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