About Implantation support medium transfer

Implantation support medium transfer (ISME-T) is referred as cultivation and transfer of embryos using advanced enriched medium that all nutrients and energy sources needed for an optimal embryo development. They may serve as cultivation as well as transferring medium. Enriched cultivation medium reduces the embryo stress through in vitro fertilization (IVF) process by providing a more physiological and natural in vitro environment therefore enhances embryo transfers especially in those patients with recurrent embryo transfer failures.

Optimal management of infertility patients with previous unsuccessful implantations in spite of transferring good quality embryos remains undetermined, suggesting that implantation remains a major limiting step in the success of human assisted reproductive technology. Several approaches have been attempted, including changing the ovarian stimulation protocol, performing vitrified-warmed embryotransfer (ET) as opposed to fresh ET, or increasing the number of embryos transferred. However, because impaired interaction between the embryo and endometrium might be an underlying problem, these methods are prone to fail in patients with multiple ET failures. Thus, it is necessary to search for alternative approaches to improve implantation of human embryos in the IVF-ET procedure (embryotransfer following in vitro fertilization). In an attempt to optimize human in vitro embryo culture systems, supplementation of proteins which provide a source of energy for embryo development and act as reservoirs for vitamins and minerals has traditionally been performed.

There are three types of enriched medium differing in its properties and use:
**EmbryoGen**

EmbryoGen is cultivation medium used for cleavage-stage embryos (day 2-3) cultivation that contains recombinant human GM-CSF cytokine (granulocyte macrophage colony stimulating factor) a protein expressed in the female reproductive tract and upregulated throughout embryo development which is produced during the early stages of embryo development. GM-CSF protects the embryo from stress and therefore embryo becomes stronger and more robust in the days following conception.

EmbryoGen can also be used as an embryo transfer medium for cleavage-stage embryo transfer. If cultivation up to blastocyst stage is used, cultivation media called BlastGen is used after day 3 of cultivation.

**BlastGen**

BlastGen is the world’s first culture medium for blastocyst-stage embryos containing the recombinant human GM-CSF cytokine. After cultivation, blastocysts may be also transferred using this medium.

**EmbryoGlue**

Since the very early stage of pregnancy is called implantation, it is referred as adhesion of embryo to the wall of uterus. This is very critical period after embryo transfer that could be facilitated by EmbryoGlue, the specialized medium for embryo transfer that acts as “glue that sticks” embryo to endometrium. This hyaluronan-enriched medium is able to mimic natural conditions in female uterus and thus helps the embryo to implant. Hyaluronan is the major follicular, oviductal and uterine fluid sacharid whose synthesis naturally increases on the day of implantation and decreases a day after and also appears to be important for placentation in human reproduction. Hyaluronan as a part of EmbryoGlue also creates a highly viscous environment enabling human embryos to be easily included in uterine secretions.

### Success or failure factors

Enriched cultivation media is suitable for all patients and can be applied to all treatment. Still, it is especially recommended for those patients with recurrent clinical and biochemical pregnancy loss, recurrent implantation failure and unexplained fertility.

Additionally, there are several factors related to the efficacy of embryo attachment or implantation into the uterine endometrium, including patient age, embryo quality, and endometrial thickness, as well as several uterine factors, such as uterine fibrioids (smooth muscle tumor), polyps (mass in the inner lining of the
uterus), and other uterine abnormalities.

Complications

It remains controversial whether the use of EmbryoGlue improves pregnancy and implantation rates among embryo transfer patients. Several randomized trials demonstrated the beneficial effect of hyaluronan-rich transfer medium on implantation and pregnancy. On the contrary, there are also studies that report no significant benefit of hyaluronan-rich transfer medium on pregnancy and implantation rates, especially in poor prognosis group (those with embryo transfer failure history).

In subgroup analysis (a tool for exploring differences in how people respond to a health intervention), however, embryo transfers on day 5 show no evidence of a treatment effect, and there is no evidence of a treatment effect in the participants exposed their embryos to hyaluronan for more than 10 minutes.

Prognosis

The beneficial nature of EmbryoGen/BlastGen in terms of clinical pregnancy rates has yet to be resolved, although there is good evidence for women with more than one miscarriage in their personal history.

The use of hyaluronan-enriched transfer medium increased implantation and clinical pregnancy rates using hyaluronan-enriched commercial ET medium compared to routine ET medium without hyaluronan. It demonstrates that the use of hyaluronan in the transfer media significantly increased the positive human chorionic gonadotropin (hCG) and implantation rate without increasing the delivery rate. Routine use of EmbryoGlue does not significantly improve pregnancy or implantation rates in non-selected patients receiving either a day 3 or day 5 embryo transfer compared with standard culture media. However, significant difference in clinical pregnancy rate is observed with the EmbryoGlue in patients with previous IVF failure.

Sources
“Effect of hyaluronan-enriched transfer medium on implantation and pregnancy rates after day 3 and day 5 embryo transfers: a prospective randomized study (http://www.epistemonikos.org/documents/ac0656155bca0b2a70320b7a7de686133aa4d107/)” —by Urman et al. licensed under CC BY 3.0

“Efficacy of hyaluronan-rich transfer medium on implantation and pregnancy rates in fresh and frozen-thawed blastocyst transfers in Korean women with previous implantation failure (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4871936/)” —by Chun et al. licensed under CC BY-NC 3.0


“Role of Embryo Glue as a transfer medium in the outcome of fresh non-donor in-vitro fertilization cycles (http://elibrary.pks.mpg.de/Record/DOAJ041975456/Description#tabnav)” —by Singh et al. licensed under CC BY-SA 1.0

“Impact of EmbryoGlue as the embryo transfer medium (http://www.epistemonikos.org/documents/ba9c86754d3dd060a5392f8eb0d38ee06979cb54/)” —by Hazlett et al. licensed under CC BY 3.0