Embryo-endometrium crosstalk: a new understanding from in vitro model

Embryo-endometrium crosstalk has a pivotal role during implantation. However, it is difficult to reveal the actual events and mechanisms involved in the crosstalk because of ethical and technical limitations. On the one hand, it is almost impossible to conduct such experiments on human beings. On the other hand, it is challenging to establish an embryo-endometrium crosstalk model to mimic the in vivo process in vitro.

Endometrial glandular organoid culture has been developed recently (1). The organoids are 3D spherical structures formed from self-organizing endometrial epithelial cells and can be expanded for a long time. The current organoid model can recapitulate most of the molecular and functional characteristics of the human endometrial epithelium.

With a modification of the original glandular organoid protocol, Dr. Piomboni and coworkers (2) previously established the endometrial organoid culture from the human eutopic endometrium. In their study, they showed that endometrial organoids exhibited features mimicking the cells/tissue of their origin. First, the organoids displayed the glandular organization and cellular ultrastructural characteristics as they do in vivo. Second, they responded to treatment with steroids which simulate the hormonal milieu of the menstrual cycle and formed proliferative phase-induced and secretory phase-induced organoids with morphology and gene expressions similar to those found in primary tissue. Third, the organoids exhibited markers of endometrial receptivity, including the development of pinopodes and the expression of glycodelin-A, in an environment simulating the mid-secretory phase.

In this issue of *Fertility and Sterility*, the same group took advantage of the established organoid model and continued their work investigating embryo-endometrium interactions (3). The group cultured endometrial organoids with the spent medium from a culture of human embryos up to Day 3. The conditioned medium was expected to contain secretory products of embryonic origin. The results showed that the conditioned medium induced the endometrial organoids to change their glycodelin-A expression in terms of an increase in abundance as well as a change in the glycoform pattern. The group also compared the in vitro fertilization (IVF) outcome in patients that received Day 3 embryo transfer in the presence of the embryo spent culture medium or the fresh culture medium. They found a significant increase in the biochemical and clinical pregnancy rate when the spent medium was also loaded during the transfer (17.5% vs. 36.6% and 16.5% vs. 35.1%, respectively; $P<.05$).

We thank the authors for their contribution to the literature. The study provides evidence that the embryo secretory molecule(s) could facilitate implantation via modulating endometrial receptivity. The results echo a previous study, showing the association of certain cell-free microRNAs in embryo conditioned medium from implanted euploid blastocysts (4). The role of embryo-derived cell-free microRNAs and their potential use as a biomarker of the implantation potential of embryos are hot research topics. An exciting novel observation of the study is the improved IVF outcome with the inclusion of the embryo conditioned medium during embryo transfer. It represents a simple and practical method for enhancing IVF performance.

Although of great interest, several questions remain unanswered. First, it is unclear which of the active components in the embryo conditioned medium affect endometrial receptivity. Nowadays, these components can be identified using omics technologies. The identification of these components is not only of academic interest but can potentially be used for the treatment of infertility due to endometrial factors.

Second, the factors affecting the expression of these components are not known. It will be interesting to know if their production is associated with embryo development (cleavage-stage vs. blastocyst), developmental competence, and karyotype. More importantly, their potential use as non-invasive markers of embryo implantation potential should be investigated.

Third, the proof of concept that the inclusion of embryo spent medium increases the IVF outcome is meaningful. But the sample size in the study is insufficient. The observation needs to be substantiated with properly powered and designed randomized controlled trials. From a physiological perspective, the use of blastocyst instead of cleavage-stage embryo conditioned medium for transfer should be considered.

Fourth, the regulation of the formation of pinopodes in the organoid system is not known. The organoid culture is established for the culture of endometrial glands. The formation of pinopodes, a luminal epithelial feature, in the organoids is interesting and may enable us to use the model for investigating the differentiation of glandular epithelium to the luminal epithelium.

This study opens the door to investigate cellular and molecular aspects of the embryo-endometrial crosstalk in vitro. At the same time, it also calls for more work to be done. Nevertheless, our field is on the right track in building knowledge toward optimizing IVF treatment.

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https://doi.org/10.1016/j.fertnstert.2021.01.034

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