

## Review Article

# Comparison of Human Trophoblast Cells function after In vitro Fertilization and Embryo Transfer and Natural Conceived Pregnancy

Rui Yang<sup>1,3</sup> and Ying Wang<sup>1,3\*</sup><sup>1</sup>Department of Obstetrics and Gynecology, Peking University Third Hospital, China<sup>2</sup>Key Laboratory of Assisted Reproduction, China<sup>3</sup>Beijing Key Laboratory of Reproductive Endocrinology and Assisted Reproduction, China**\*Corresponding author**

Ying Wang, Reproductive Medical Center, Peking University Third Hospital, No. 49 North Garden Road, Haidian District, Beijing, China, 100191, Tel: 86-010-82266836; Fax: 86-010-82266849; Email: wangying02114@bjmu.edu.cn

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**OPEN ACCESS****Abstract**

Assisted reproductive technologies (ART) have helped solving infertility problem and improved greatly in recent years. The key to normal embryo implantation and pregnancy lies in the preferential invasion of early pregnancy trophoblastic cells into the uterine wall. The trophoblast cell function of in vitro fertilization and embryo transfer (IVF-ET) group in first trimester is different from natural conceived ones in proliferation, invasion, apoptosis and vascular development.

**INTRODUCTION**

Successful embryonic implantation is dependent on a complex interplay between the invading trophoblast and the maternal tissue. Trophoblast cells are derived from cells in the outer layer of early embryos or blastocysts. On the seventh day after fertilization, trophoblasts proliferate and then differentiate into interstitial trophoblast cells and vascular endothelial trophoblast cells. Vascular endothelial trophoblast cells infiltrate the spiral arteries, replacing part of the vascular endothelium [1], and then substitute the medial smooth muscle or elastic tissue in vessels with a fiber-like substance. This results in the disappearance of elastic tissues in vessels and the dilatation of spiral arteries, which decreases the peripheral vascular resistance of the placental bed. Thus, normal growth of the placenta and fetus can be ensured by smooth influx of more blood into the placental intervillous space. These changes are normally completed in the first 6–7 weeks of pregnancy [2].

Previous research [3] suggests that Inadequate invasion, specifically restricted endovascular invasion, has been implicated in the pathophysiology of such conditions as pre-eclampsia (gestational proteinuric hypertension), preterm premature rupture of membranes, preterm labour, and intrauterine growth restriction, while excessive trophoblast invasion is likely to cause abnormally firm attachment of the placenta to the myometrium (placenta accreta) with increased maternal and perinatal morbidity.

Assisted reproductive technologies (ART) have helped

solving infertility problem and improved greatly in recent years. *In vitro* fertilization and embryo transfer (IVF-ET) have resulted in a revolution in infertility treatment. However, many clinical literatures [4–7] has reported that IVF-ET technology may be closely related to many adverse outcomes during the perinatal period, including miscarriage, premature birth, low birth weight, and gestational hypertension.

The key to normal embryo implantation and pregnancy lies in the preferential invasion of early pregnancy trophoblastic cells into the uterine wall. Zhang et al.[8], reported that IVF manipulation may affect fetal development by changing maternal-fetal immunoreactions and nourishing cell proliferation and differentiation, or by impairing transmembrane transport. In first trimester, the trophoblast cell function in IVF-ET group is different from natural conceived ones [4–7, 9].

Epidermal growth factor (EGF) is an important growth factor that binds to EGFR on trophoblast cells, stimulates the receptor tyrosine kinases, and triggers their own and substrate phosphorylation reactions, thereby increasing the nutritional intake by villi, promoting proliferation and differentiation of the placenta, promoting trophoblastic cell survival, and increasing the secretion of placenta [10]. Fu et al., study showed [11] that EGF promotes trophoblast cell growth in a dose-dependent manner, and EGFR deficiency results in reduced trophoblast proliferation. Fu et al.[11], also found EGFR with enzyme activity increased significantly during the period of placenta formation, but with the progress of pregnancy, the expression of EGFR decreased, although in IVF-ET cases the expression of EGFR

increased significantly in the late pregnancy. Yang et al., study [9] showed that the expression of EGFR in the villous tissue in IVF-ET group was significantly lower than in natural conceived group.

Tubulin- $\alpha$  is a microtubule structural protein, and John stone et al.[12], research proved that its expression is significantly lower in the placenta of women with gestational hypertension, which is associated with intrauterine hypoxia and trophoblast cell apoptosis due to hypoxia. Therefore, in addition to maintaining the normal structure of trophoblast cells, the function of tubulin- $\alpha$  in these cells is mainly to act as an antioxidant in early villi. In Yang et al.[9], study the expression of tubulin- $\alpha$  in the villi tissue of women in IVF-ET group was significantly lower than that in natural conceived group, also.

The main role of Bcl-2 is to inhibit cell apoptosis. In normal tissues, the expression of the Bcl-2 protein plays a key role in balancing cell growth and apoptosis. High expression of Bcl-2 protein can inhibit apoptosis and plays an important role in the maintenance of pregnancy. Lodhi et al.[13], recently found that Bcl-2 is expressed in syncytiotrophoblasts of villus and cytoplasm and membrane of decidual cell during early pregnancy, and it is weakly expressed in syncytiotrophoblasts. In Yang et al.[9], study the expression of Bcl-2 in the IVF-ET group was significantly lower than that in the natural conceive dones.

Metallothionein is mainly located in the cytrophoblasts, decidual cells, and small vascular endothelial cells of the placenta. Metallothionein expression in the placenta is important to the structural integrity and function of the placenta. A study [14] of an *in vitro* trophoblastic cell line, JEG-3, suggested that although metallothionein does not ameliorate oxidative stress-induced perturbation of some trophoblastic functions, its expression is critical for protecting these cells against severe oxidative stress-induced apoptosis. A Chinese *in vivo* study [15] found similar results in terms of the significance of metallothionein expression in the placentas of women exposed to low levels of lead during pregnancy. In Yang et al.[9], study the expression of metallothionein in the villi tissues of women in IVF-ET group was significantly lower than that in natural conceived group. Metallothionein is found in the plasma of syncytiotrophoblast and cytrophoblast cells and is more strongly expressed in cytrophoblast cells, and its expression was significantly lower in both types of cells in the IVF-ET group.

AFP is mainly synthesized in the fetal liver, and peaks at 30 weeks of pregnancy, after which it gradually decreases, approaching the mean adult level 1 year after birth. For a long time, research on AFP has focused on cancer-related mechanisms. However, in recent years, researchers have found that trophoblast cells' invasion, infiltration, and remodeling of endometrium and spiral arteries during early development are similar to those of tumor cells. The normal physiological role of AFP is unknown but a variety of diverse functions have been postulated, including ligand binding and transport, regulation of growth and the immune system, and a role as an antioxidant, indicating its potential significance for the growth and development of a healthy fetus. Duc-Goiran et al., study indicated [16] that under normal circumstances, the expression of AFP in trophoblast cells is weak, and its expression is mainly located in discontinuous regions, at junctions between two villi and at duding sites. The

main role of AFP is to facilitate the development of the placenta and the compensatory mechanism is only expressed when the blood vessels have developed abnormally. Microscopically, pathologic changes have been observed in syncytiotrophoblast cells of anembryonic pregnancies, and AFP is strongly expressed by villous trophoblastic cells compared with in anembryonic pregnancies [17]. Yang et al study [9] showed the expression of AFP in the villous tissue in IVF-ET group was significantly higher than in the natural conceived group. It went to a hypothesis that after IVF-ET, vascular development of trophoblasts declines, and compensation is required by increase the expression of AFP, so as to ensure normal vascular development in the placenta during the second and third trimesters, as well as to maintain the normal function of the placenta and protect the exchange of substances and nutrients between the mother's womb and the fetus.

## CONCLUSION

In conclusions, the trophoblast cell function of IVF-ET group in first trimester is different from natural conceived group in proliferation, invasion, apoptosis and vascular development.

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