Dear Editor,

Regarding the questions raised and comments made on the paper authored by me *"Secretion of Vascular Endothelial Growth Factor in a Three-Dimensional Culture of Human Endometrium; an In-Vitro Model for Endometriosis"* I have provided the following response for more clarification. I bid my appreciations in advance for the trouble you take for publishing this response.

- Regarding the microenvironment surrounding the cells and the tissue in the [human] body, one cannot definitively state that the tissue in the fibrin matrix model has gene expression and growth factor secretion equal to what happens in natural conditions (1,2).

- If the respected viewer, had carefully studied the paper, he would have noticed the sentence *"the cultures were studied by an inverted microscope (Olympus, USA) every three days and the supernatant (a total of 100 wells) was removed and replaced for VEGF evaluations"* that clearly indicates replacement of the media and subsequent evaluation of VEGF with significant statistical results. The article previously contained a graph depicting VEGF changes and its unit of measurement but one of the respected referees asked for its removal.

- Stromal cell do secrete VEGF too (3, 4).

- The authors have not claimed that the method used is based on model proposed by Fujii's et al. and it has not been mentioned there either but it has been elaborated upon in the “discussion”.

- Malignant Ovarian Cysts can secrete VEGF but Benign Ovarian Cysts cannot (5) and the authors have mentioned the cases were not suffering from ovarian cancer.

- The compared figures have the same magnification.

- The definition provided for endometriosis is a correct one and blood vessels can ectopically grow outside the endometrium in this disease too (6).

- The *Conclusion* has been fairly expressed and this study has the capacity to be introduced as a model for endometriosis. If this is not agreed upon, one may seek Mr. Fasciani's consultation as he first suggested a basically similar model for endometriosis. Moreover, his study has been cited in the article (7).

- References 10, 11 and 23 accurately refer to their respective articles.

- The point on "Thrombin concentration" is due to a missed typo.

- Furthermore, references 11 and 12 which have been provided by the respected viewer in the letter are in the form of "abstracts" and not "full text papers". Moreover, the first and second referenced papers on three-dimensional culture of endometrial tissue by Iranian researchers has been published in 2007 (8, 9) and the present author's name has been included there. For further clarification I have provided a list of 11 papers by me on endometrium published since 2007:

1. Ai J, Mehrabani D. Are endometrial stem cells novel tools against ischemic heart failure in women? A hypothesis. IRCMJ. 2010;12(1):73-5.
2. Ai J, Esfandiari N, Casper RF. Expression of prolactin (PRL) following 3-D culture of human endometrial tissue. Shiraz E-Med J. 2009;10(1).
3. Ai J, Esfandiari N, Casper RF. Detection of aromatase in human endometrial tissue cultured in three-dimensional fibrin matrix in vitro. Iran J Reprod Med. 2009;7(3):105-9.
4. Ai J, Tabatabaei FS, Larijani BA. Possible cell therapy for critical limb ischemia in women by using endometrial adult stem cells. Med Hypotheses Res. 2009;5(2):93-97.
5. Ai J, Tabatabaei FS, Jafarzadeh Kashi TS. Human endometrial adult stem cells may differentiate into odontoblast cells. Hypothesis. 2009;7(1).
6. Ai J, Tabatabaei FS, Kajbafzadeh AM. Myogenic potential of human endometrial adult stem cells papers presented. Iran J Med Hypotheses Ideas. 2009;3:25.
7. Ai J, Esfandiari N, Casper RF. [Secretion of VEGF following three dimensional culture of human endometrial tissue: an in vitro endometriosis model]. J Reprod Infertil. 2009;10(2):95-100. Persian.
8. Esfandiari N, Ai J, Khazaei M, Nazemian AJ, Casper RF. Angiogenesis following three-dimensional culture of isolated human endometrial stromal cells. Int J Fertil Steril. 2008;2(1):19-22.
9. Esfandiari N, Ai J, Bielecki R, Gotlieb L, Casper RF. Expression of glycodelin and cyclooxygenase-2 in human endometrial tissue following three-dimensional culture. Am J Reprod Immunol. 2007;57(1): 49-54.
10. Esfandiari N, Ai J, Khazaei M, Bielecki R, Gotlieb L, Ryan E, et al. Effect of a statin on an in vitro model of endometriosis in three-dimensional culture. Fertil Steril. 2007;87(2):257-62.
11. Ai J, A Noroozi Javidan A, Mehrabani D. The possibility of differentiation of human endometrial stem cells into neural cells. Iran Red Crescent Med J. 2010;12(3):328-31.

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2. Meyer U, Meyer T, Handschel J, Wiesmann HP. Fundamentals of tissue engineering and regenerative medicine. 1st ed. Berlin Heidelberg: Springer-Verlag; 2009. Chapter 7, Cytokine Signaling in Tissue Engineering; p. 71.83.
3. Torry DS, Holt VJ, Keenan JA, Harris G, Caudle MR, Torry RJ. Vascular endothelial growth factor expression in cycling human endometrium. Fertil Steril. 1996;66(1):72-80.
4. Moller B, Rasmussen C, Lindblom B, Olovsson M. Expression of the angiogenic growth factors VEGF, FGF-2, EGF and their receptors in normal human endometrium during the menstrual cycle. Mol Hum Reprod. 2001;7(1):65-72.
5. Hazelton D, Nicosia RF, Nicosia SV. Vascular endothelial growth factor levels in ovarian cyst fluid correlate with malignancy. Clin Cancer Res. 1999;5 (4):823-9.
6. Liu Y, Lu L, Zhu G. Anginogenesis of eutopic and ectopic endometria in endometriosis. J Huazhong Univ Sci Technolog Med Sci. 2003;23(2):190-1.
7. Fasciani A, Bocci G, Xu J, Bielecki R, Greenblatt E, Leyland N, et al. Three-dimensional in vitro culture of endometrial explants mimics the early stages of endometriosis. Fertil Steril. 2003;80(5):1137-43.
8. Esfandiari N, Khazaei M, Ai J, Bielecki R, Gotlieb L, Ryan E, et al. Effect of a statin on an in vitro model of endometriosis. Fertil Steril. 2007;87(2): 257-62.
9. Esfandiari N, Ai J, Bielecki R, Gotlieb L, Casper RF. Expression of glycodelin and cyclooxygenase-2 in human endometrial tissue following three-dimensional culture. Am J Reprod Immunol. 2007; 57(1):49-54.

Faithfully yours,

Jafar Ai, Ph.D.
Department of Tissue Engineering, School of Advanced Technologies, Tehran University of Medical Sciences, Tehran, Iran
Address: Jafar Ai, Department of Tissue Engineering, School of Advanced Technologies, Tehran University of Medical Sciences, Tehran, Iran
Email: jafar_ay2000@yahoo.com

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