Implantation and Immune System

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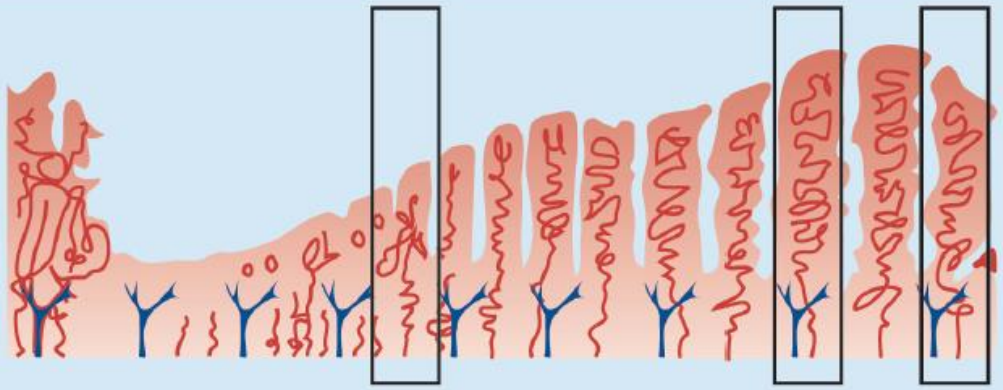
- A challenging question is whether the maternal immune system is a friend or a foe of pregnancy.

- During normal pregnancy, the human decidua contains a high number of immune cells.

- Depletion of immune cells have deleterious effects on placental development, implantation, or decidual formation.

Immune cells in the receptive endometrium



Day of cycle	Prolif. 10–12	Mid-sec. 22–23	Pre-men. 26–28
Macrophages ($CD68^+$)	+	++	+++
Uterine NK cells ($CD56^+$)	-	+/++	+++
Eosinophils (ECP^+)	-	-	++
Neutrophils (HNE^+)	-	-	+++
Mast cells ($tryptase^+$)	++	++	++
T lymphocytes ($CD3^+$)	+	+	+
B lymphocytes ($CD45RA^+$)	-/+	-/+	+

uNK

- production of:

  IL-8

  interferon-inducible protein-10 chemokines

- trophoblast invasion in the uterus
- angiogenic factors

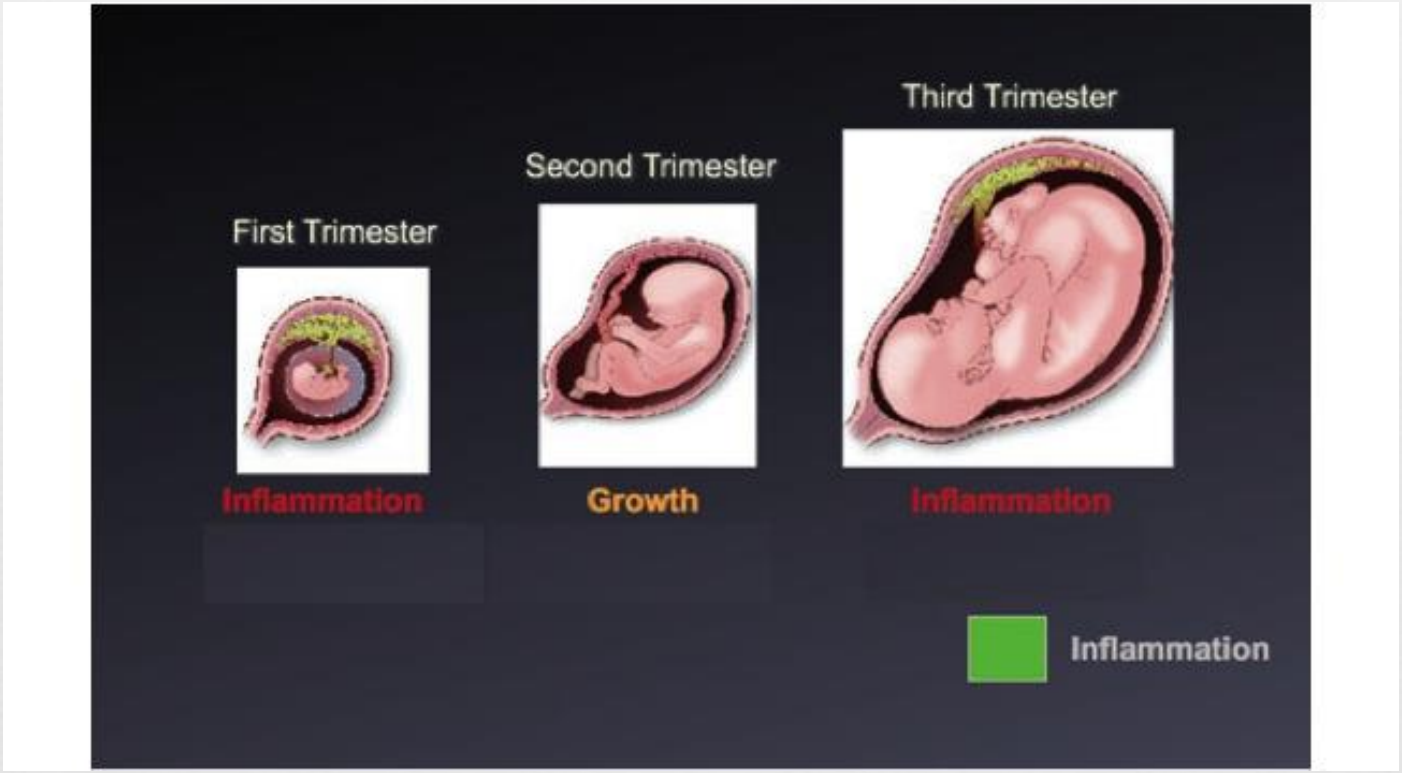
- Depletion ofDCs prevented blastocyst implantation and decidual formation.
- uDC may affect the angiogenic response.

- The presence of immune cells at the implantation site is not associated with a response to the “foreign” fetus but is attracted to facilitate and protect the pregnancy.

- Therefore, the immune system at the implantation site is not suppressed—on the contrary, it is active, functional, and is carefully controlled.

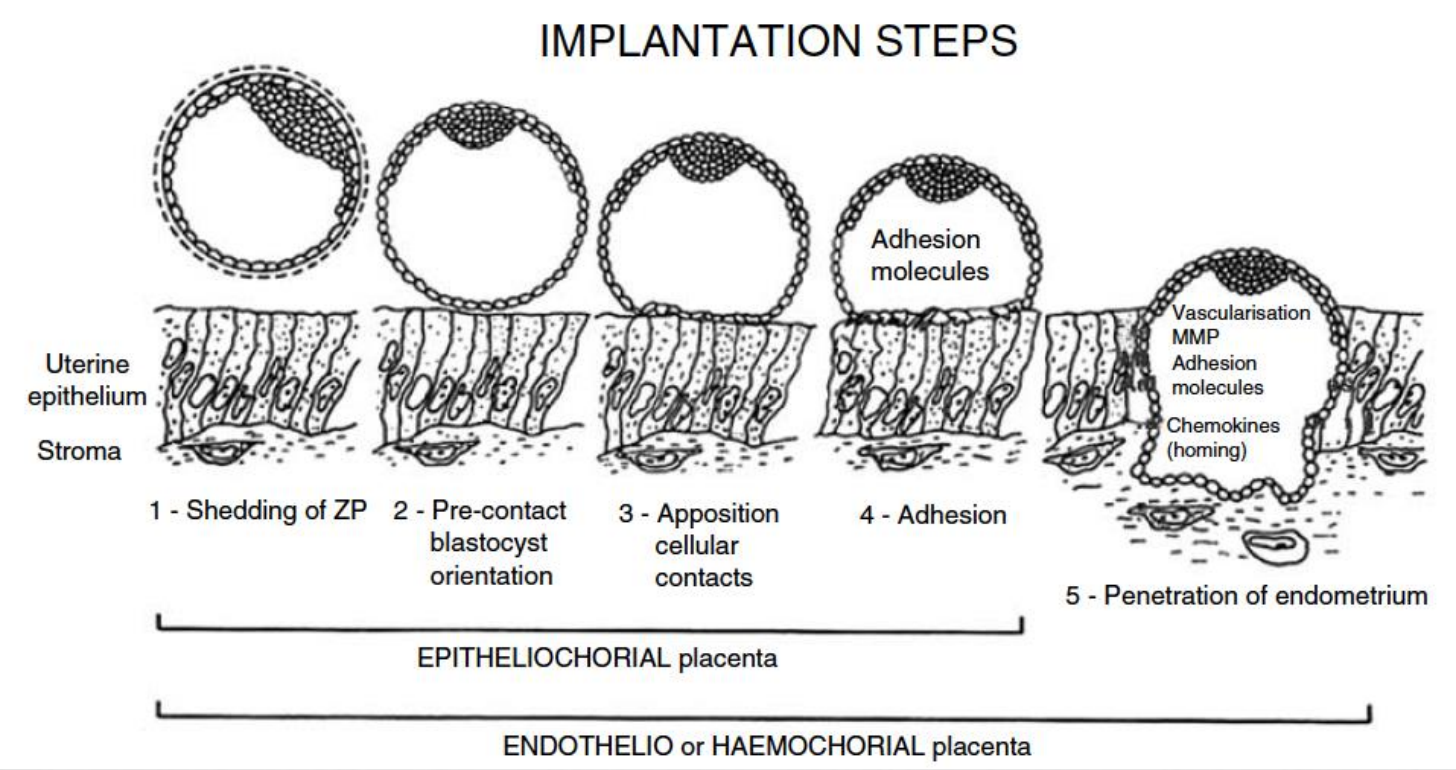
- It is appropriate to refer to pregnancy as a unique immune condition that is modulated but not suppressed.

- Pregnancy has three distinct immunological phases that are characterized by distinct biological processes.


First Trimester
Second Trimester
Third Trimester
Inflammation
Growth
Inflammation
Inflammation

First immunological phase of pregnancy

- Implantation, placentation, and the first and early-second trimester of pregnancy resemble “an open wound” that requires a strong inflammatory response.


IMPLANTATION STEPS
Uterine epithelium
Stroma
Adhesion molecules
Vascularisation
MMP
Adhesion molecules
Chemokines (homing)
1 - Shedding of ZP
2 - Pre-contact blastocyst orientation
3 - Apposition cellular contacts
4 - Adhesion
5 - Penetration of endometrium
EPITHELIOCHORIAL placenta
ENDOTHELIO or HAEMOCHORIAL placenta

- Effect of endometrial injury on successful implantation

Inflammation and immune cells during implantation

- High level of the proinflammatory cytokines (IL-6, IL-8, and TNF) characterizes early implantation.
- These cytokines can be secreted by the endometrial cells as well as by cells of the immune system.

“tissue memory”

- In fact, monocyte precursors of macrophages and DCs are known to be recruited to injured sites and provide essential beneficial effects during wound healing.
- These cells are long-lived, and reside in some tissues for months, during which time they can differentiate into tissue-resident macrophages or DCs.

Endometrium

- The surface epithelium of the covered by molecules, such as Mucin 1 (MUC1) carbohydrates that prevent the attachment of the highly adhesive blastocyst to an improper site.

- Maybe cytokines/chemokines produced by DCs/Mo in the uterine stroma induce local degradation of MUC1 that enable the blastocyst to attach to a specific area of the uterus.

blastocysts binding to the epithelium may be enhanced:

- (i) stored adhesion molecules are rapidly moved to the cell surface;
- (ii) inflammation induced expression of new adhesionmolecules;
- (iii) increased affinity of specific molecules following initial cell contact;
- (iv) reorganization of adhesion molecules on the surface epithelium.

Immune mediators in endometrial–embryonic cross-talk

- Receptor expression has been demonstrated on:
- Leukocytes
- endometrial epithelium
- both the blastocyst and trophoblast

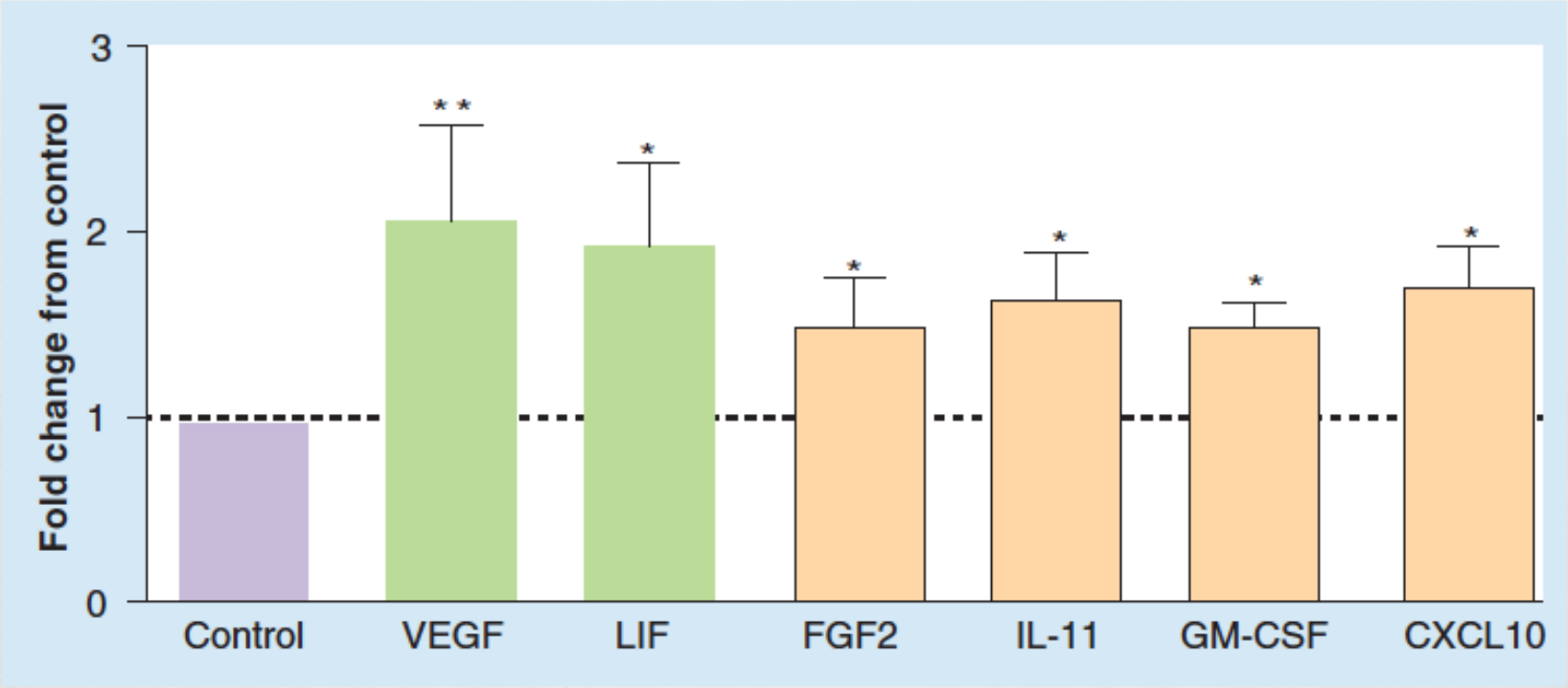
blastocyst-derived mediators

- endometrium is a biosensor for the embryo.
- endometrial stromal cells to recognize arrested embryos and reduce secretion of immune regulatory factors IL-1b, -6, -10, -17, -18, eotaxin and HB-EGF.

hCG

- Human chorionic gonadotropin (hCG) is one of the earliest blastocyst-derived signals received by the endometrium acting via its classical hCG/LH receptors.
- hCG is produced by the human endometrium itself, maximally by the endometrial epithelial cells during the period of receptivity.

hCG regulates endometrial production of



VEGFA

- VEGFA levels were significantly reduced in the uterine fluid from women with unexplained infertility compared with fertile women.
- VEGFA binds and signals via two tyrosine kinase receptors, VEGFR1 and VEGFR2, both of which are expressed by blastocysts.

Immune mediators in seminal plasma: do they play a role in implantation?

- TGF-β is abundant in seminal plasma.
- It stimulates the production of certain cytokines, including GM-CSF and G-CSF, by the endometrial epithelium.
- coitus close to the time of embryo transfer.

Trophoblast cells

- Induce the differentiation of immune cells into a trophoblast-supporting phenotype.

Uterine Selection of Human Embryos at Implantation

chromosomal abnormalities

- High prevalence of chromosomal abnormalities in human embryos.

- Evidence from several mammalian species indicates that the endometrium is intrinsically capable of mounting an implantation response that is tailored to individual embryos.

low-quality embryos

- human endometrial stromal cells (HESCs) respond selectively by inhibiting the secretion of key implantation factors, including:
  - interleukin-1 beta,
  - heparin-binding EGF-like growth factor
  - LIF

- Active embryo selection at implantation is essential for reproductive success.

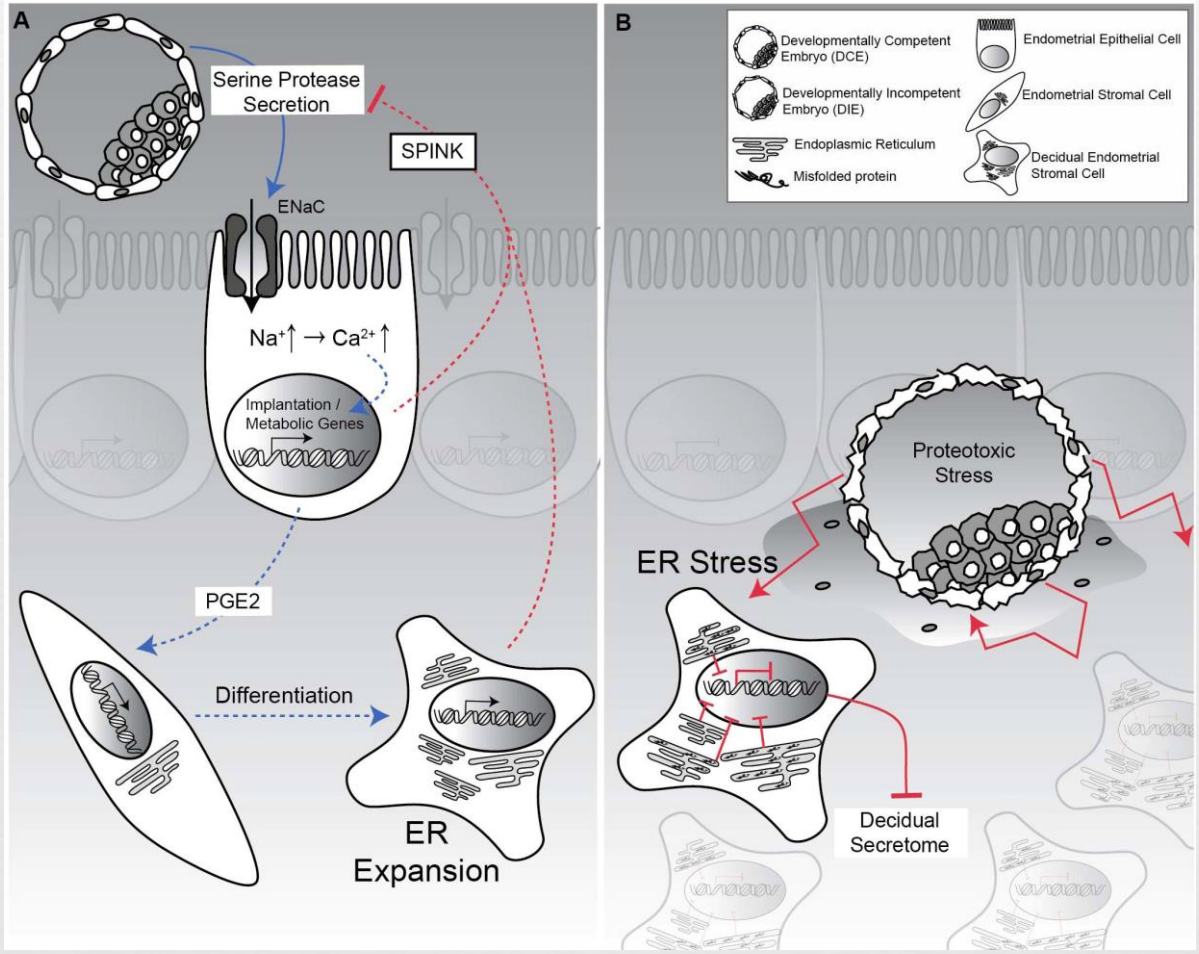
- Developmentally impaired human embryos induce ER stress response in endometrial stromal cells.
- Developmentally competent human embryos signal to promote implantation.

Developmentally Competent human Embryos signal to promote implantation.

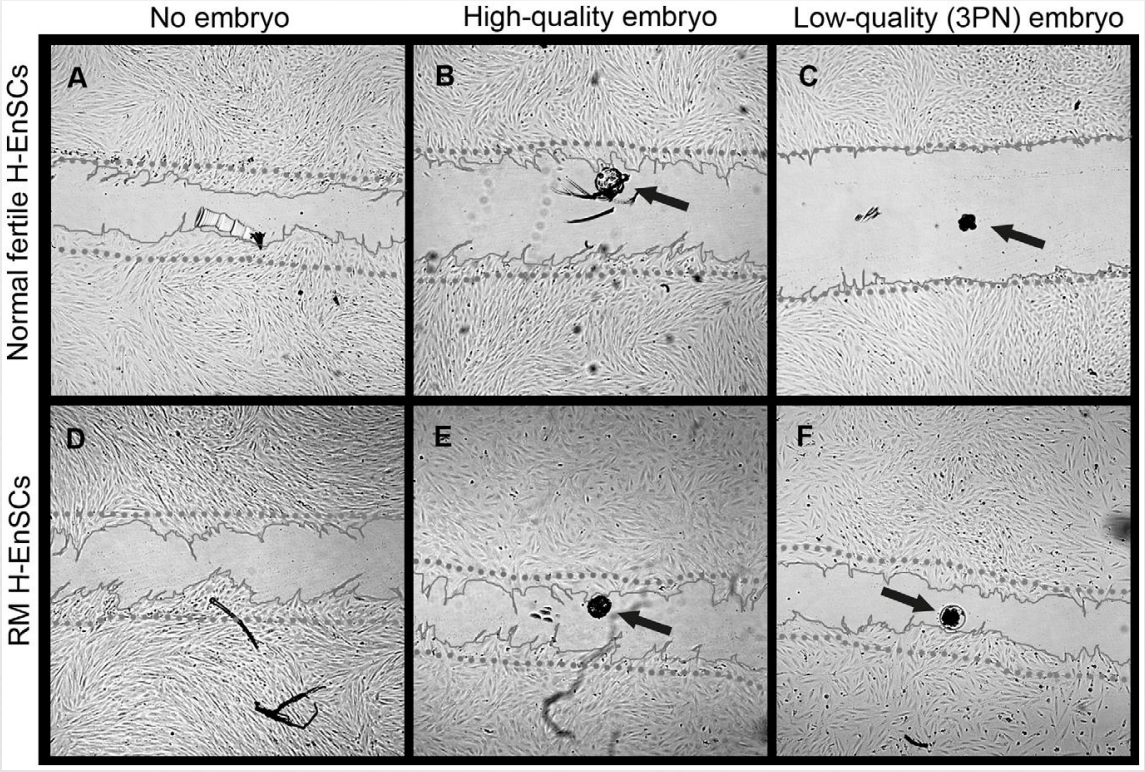
- uterine genes solely responsive to DCE signals code factors that have already been implicated in the implantation process, including COX-2 (Ptgs2), cytochrome P450 26a1 (Cyp26a1), and osteopontin (Spp1).

The role of embryo-derived trypsin in maternal embryo recognition

- Embryonic tryptases activate Ca signaling and upregulate COX-2 levels in endometrial epithelial cells (EECs), leading to prostaglandin production required for implantation.


A
Serine Protease Secretion
SPINK
ENaC
Na+↑ → Ca2+↑
Implantation / Metabolic Genes
PGE2
Differentiation
ER Expansion
B
Developmentally Competent Embryo (DCE)
Developmentally Incompetent Embryo (DIE)
Endoplasmic Reticulum
Misfolded protein
Endometrial Epithelial Cell
Endometrial Stromal Cell
Decidual Endometrial Stromal Cell
Proteotoxic Stress
ER Stress
Decidual Secretome

The migration zone after adding a high-quality, low-quality or no embryo



Control of Human Endometrial Stromal Cell Motility

- platelet-derived growth factor (PDGF)-BB
- heparin-binding epidermal growth factor-like growth factor (HB-EGF)
- VEGF (VEGF-A and its receptors)
- Trophoblast-Secreted Factors.

Finally

- Endometrial cells mount an extraordinarily polarized transcriptional response to embryonic signals, ranging from being exceptionally discrete in case of a competent embryo to extensive and complex in the presence of a low-quality embryo.