
بسم الله الرحمن الرحیم

Physiology of Embryo Implantation

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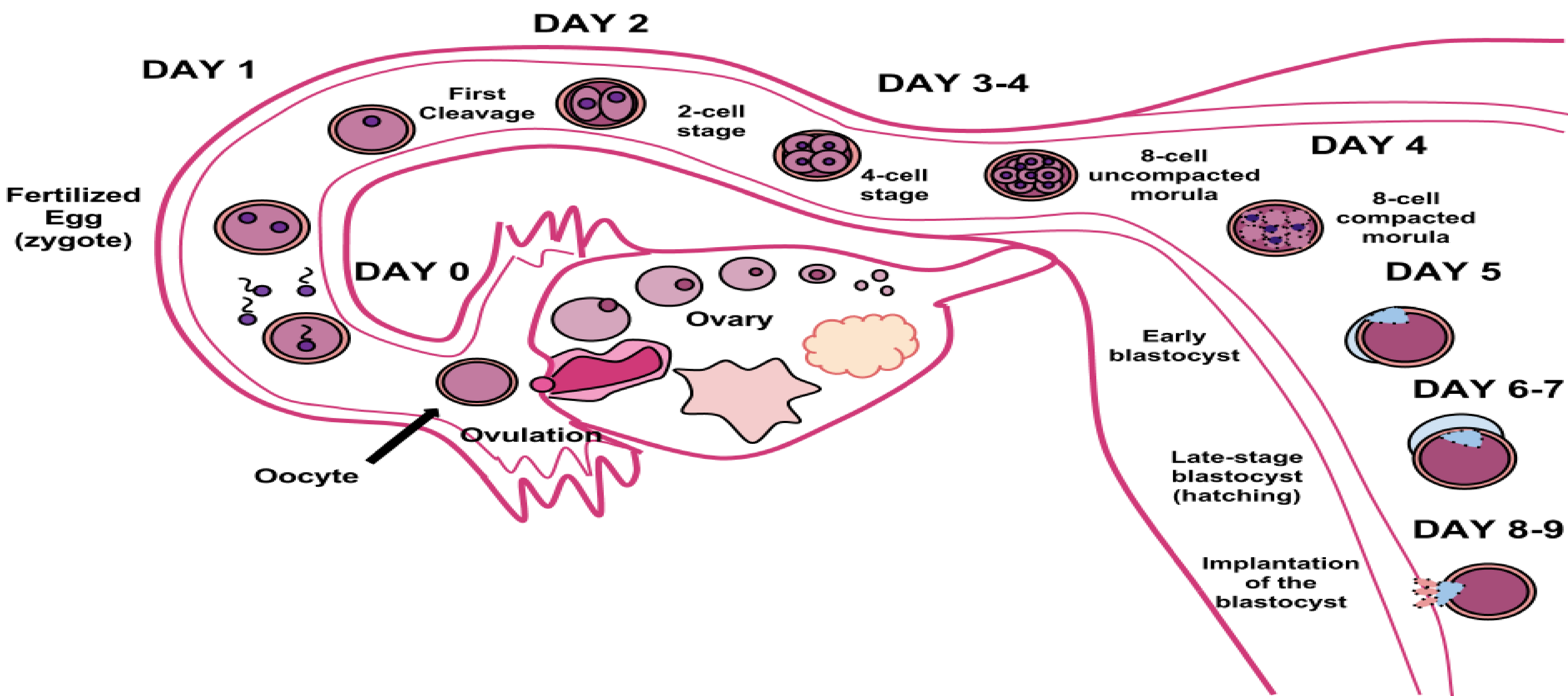
Outlines:

- **Implanation definition and requirements**
- **Endometrial phases**
- **Implanation phases**
- **Hormones**

Embryo Implantation

- embedding of the blastocyst in the endometrial stroma
- begins with the loss of the zona pellucida (hatching)
- 1-3 days after the morula (8 cells) enters uterine



Fertilization = Sperm + Ovum

↓

Zygote

↓

Cleavage formation

↓

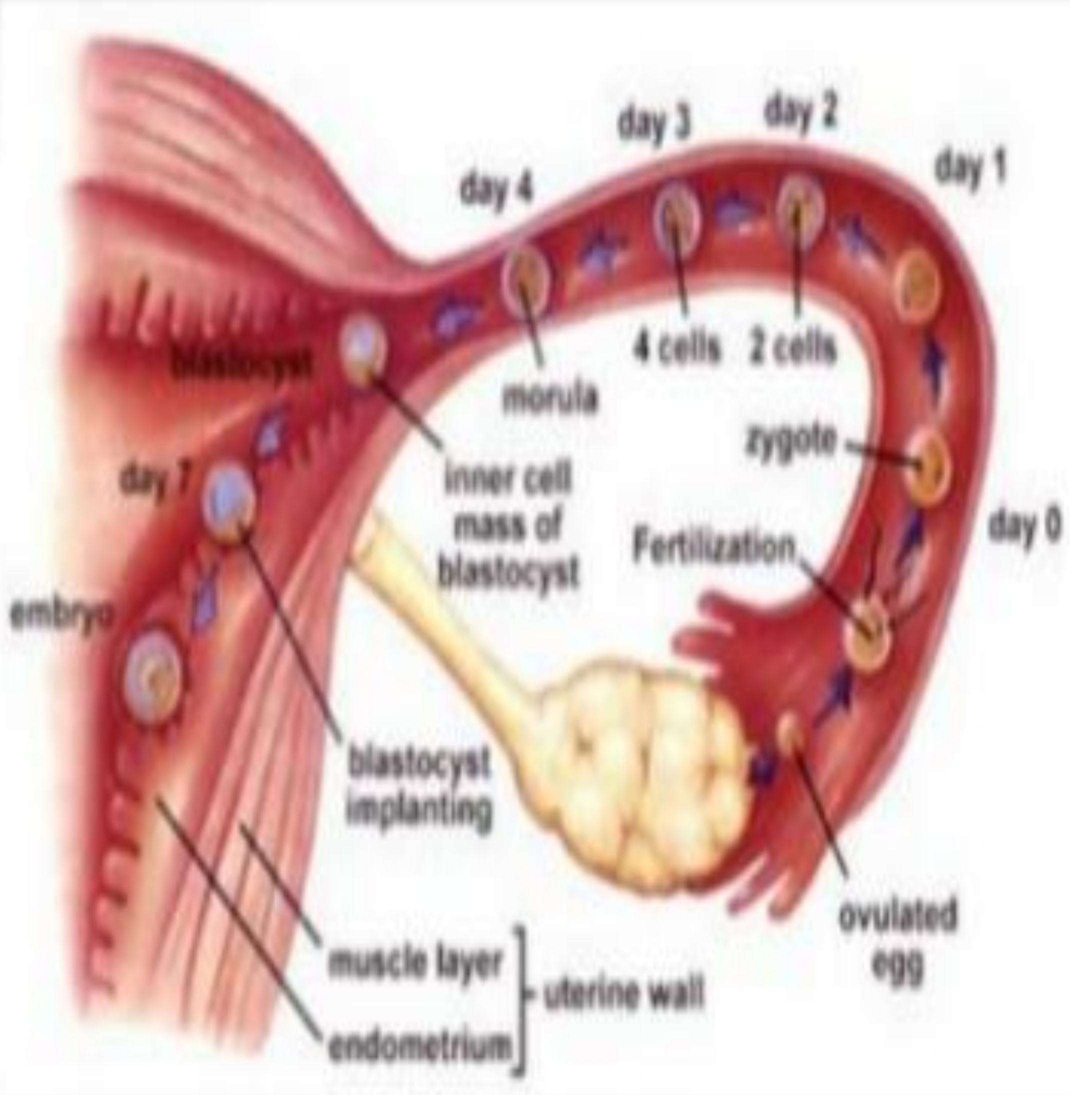
Compaction of morula

↓

Blastocyst

↓

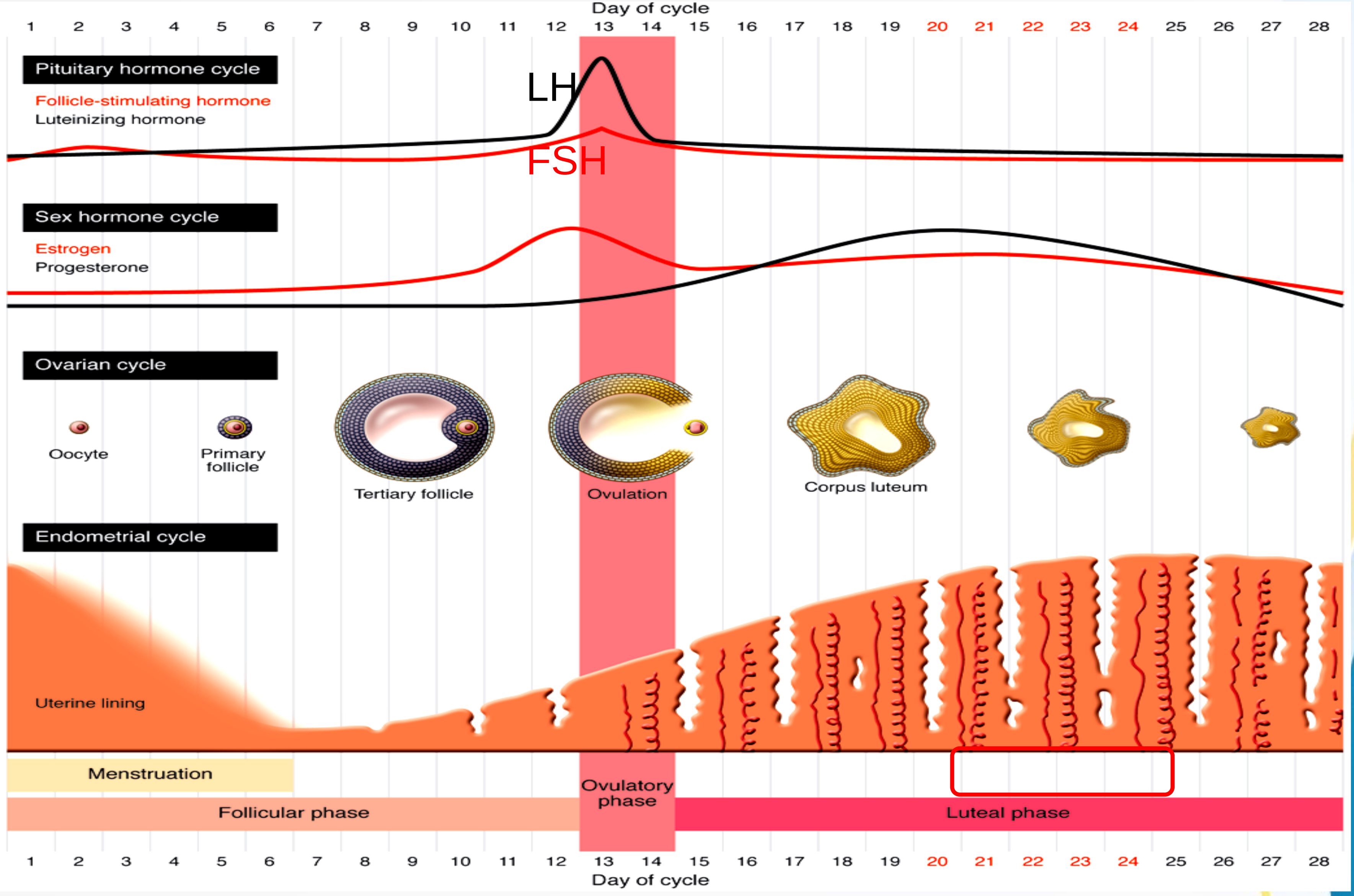
Implantation



Implantation requires:

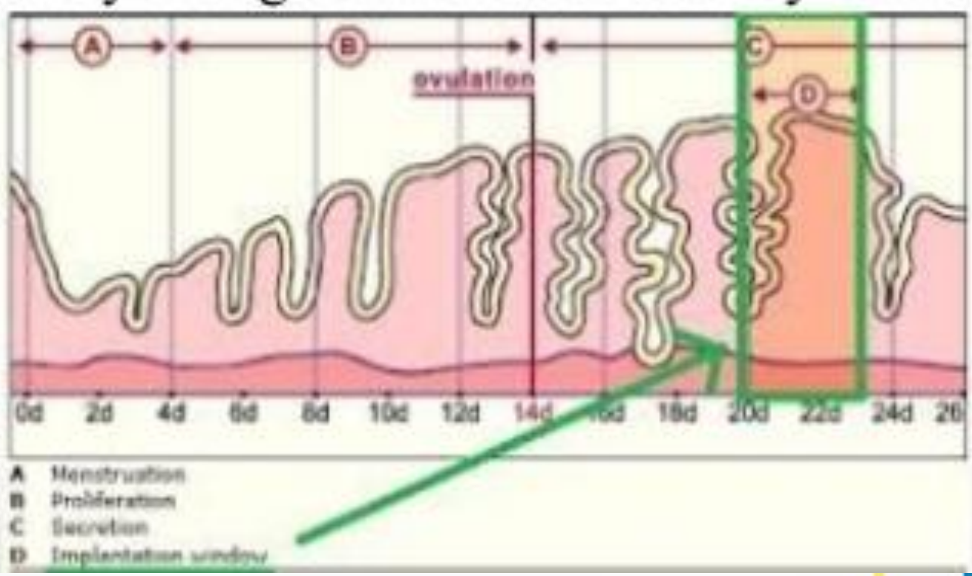
- **A Receptive endometrium**
- **A functionally normal embryo**
- **Adequate cross communication between them (harmonious synchronization of a large cast of biochemical and molecular players and regulatory endocrine, paracrine, autocrine, and juxtacrine modulators that needs cell-cell and cell-matrix interactions**

Window of Implantation: A unique moment for embryo-uterine signaling



Window of Implantation

- The implantation window is a short interval during the mid-secretory phase, when the endometrium is most receptive to blastocyst implantation.
- It begins on days 20–24 of an ideal menstrual cycle and lasts less than 48hrs. Integrins are the markers for WOI.
- During the WOI, the endometrium which has been primed by **estrogen** and **progesterone** is characterized by changes that are collectively termed **Endometrial receptivity**.



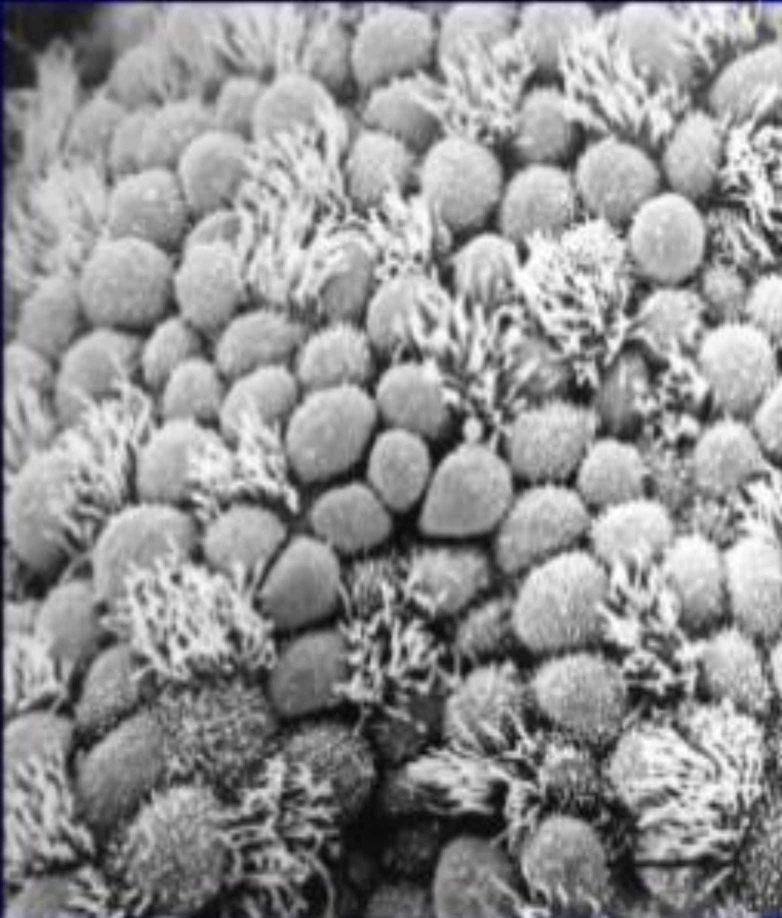
Preparation for Implantation

I. The change from proliferative to secretory endometrium

- At the time of implantation
  - ✓The endometrium is 10-14 mm thick
  - ✓Secretory activity has reached a peak
- This change is the histologic expression of many biochemical and molecular events.

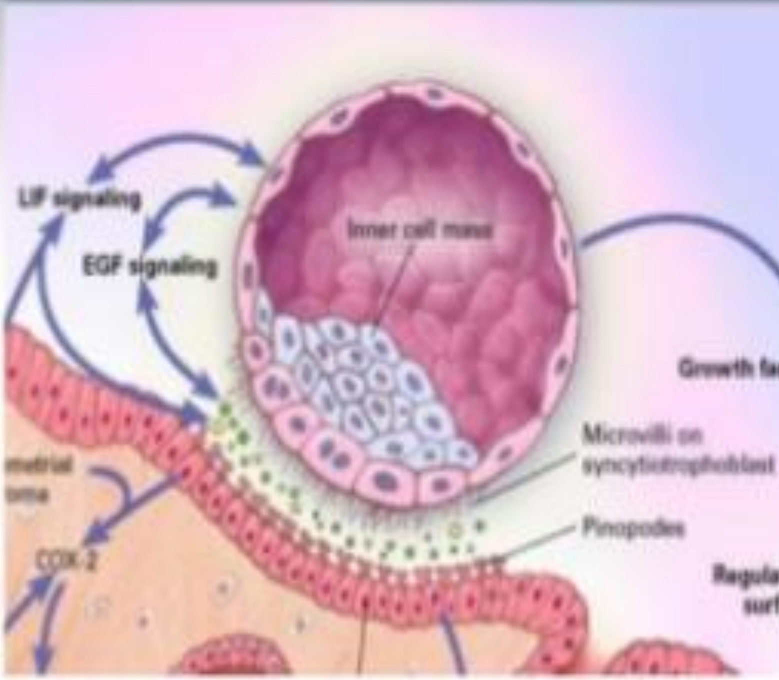
II. Endometrial receptivity

- ✓heralded by the progesterone-induced formation of pinopodes
- ✓pinopodes absorb fluid from the uterine cavity forcing the blastocyst to be in contact with the endometrial epithelium.
- ✓The window of endometrial receptivity: 20-24 of a 28-day normal cycle.

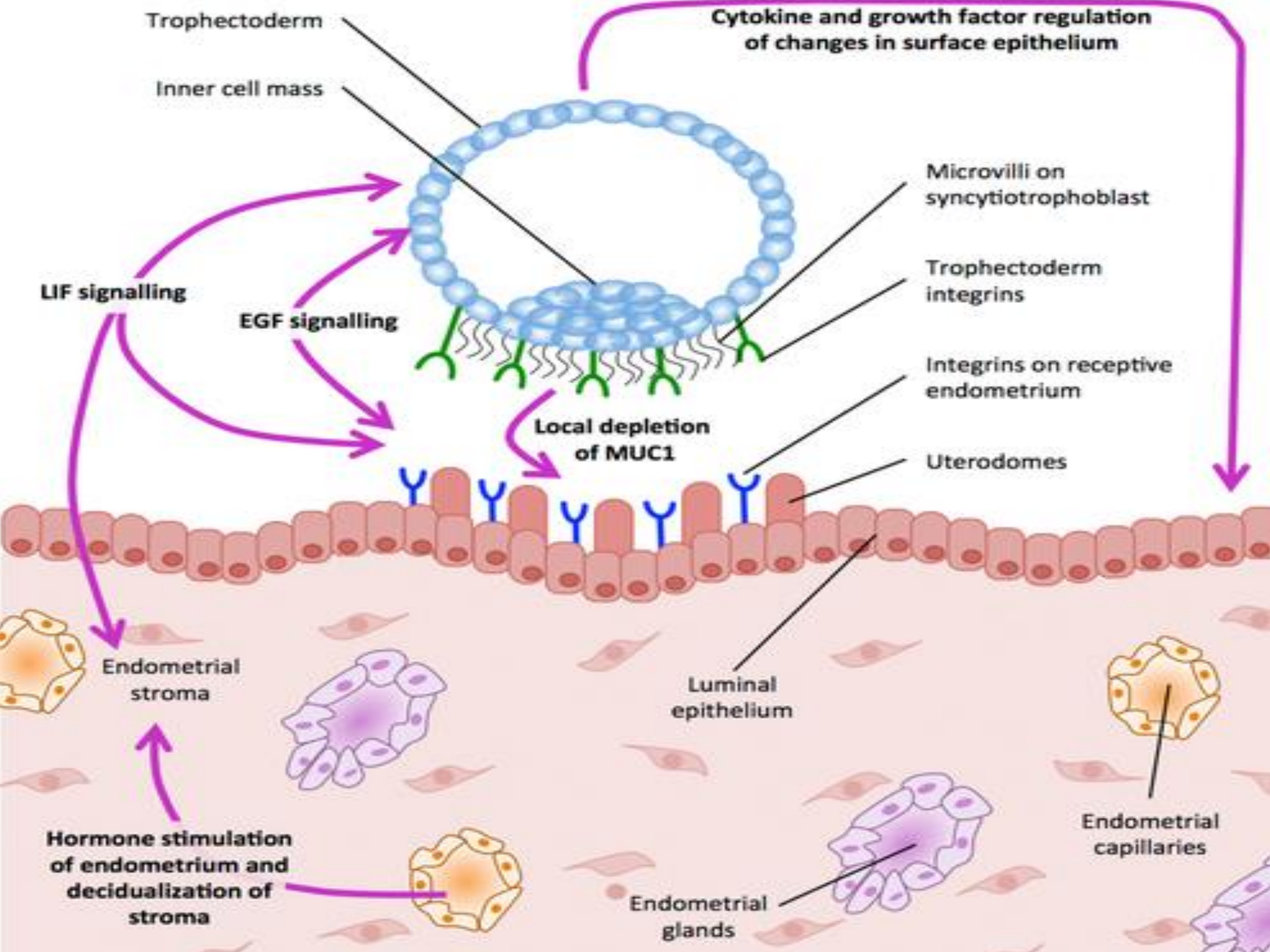


Pinopods

- Pinopods are bleb-like protrusions found on the apical surface of the endometrial epithelium
- Appear only during implantation.
- They appear progesterone dependent.
- Pinopods absorb the fluid from the uterine cavity forcing the blastocyst to be in contact with the endometrial epithelium.



- They are the morphological markers for endometrial receptivity and implantation.


Trophectoderm
Cytokine and growth factor regulation of changes in surface epithelium
Inner cell mass
Microvilli on syncytiotrophoblast
Trophectoderm integrins
LIF signalling
EGF signalling
Integrins on receptive endometrium
Local depletion of MUC1
Uterodomes
Endometrial stroma
Luminal epithelium
Hormone stimulation of endometrium and decidualization of stroma
Endometrial capillaries
Endometrial glands

Decidualization

- Decidualization is a biological transformation by which the endometrial stromal cells (fibroblast -like) differentiate into a highly specialized secretory epithelioid cell type, termed decidual cells.
- Decidualization occurs during the late secretory phase (D23-28) and is a pre-requisite for successful blastocyst implantation.
- FUNCTIONS OF DECIDUAL CELLS:
  - **Controlled Trophoblast Invasion:** Decidua forms a local micro environment to promote trophoblast attachment & invasion as well as limit the extent of aggressive invasion.
  - **Protection of Conceptus from Maternal Immune Rejection:** Acts as a gate keeper that controls immune tolerance during pregnancy by blocking T cells that would otherwise attack the developing conceptus.

Preparation for Implantation

❖Endometrium

The change from proliferative to secretory endometrium and transforming endometrial fibroblasts into specialized secretory decidual cells resulted in decidualization under many underlying biochemical and molecular events orchestrated by progesterone

Decedualization:

- ❖ Confers immune tolerance
- ❖ Regulates trophoblast invasion
- ❖ Nourishes peri-implantation conceptus
- ❖ Protects the peri-implantation conceptus against a variety of physiologic stressors

Implantation phases:

❖ Apposition phase

Embryo finds a location in which to implant, being guided to a specific area in the maternal endometrium.

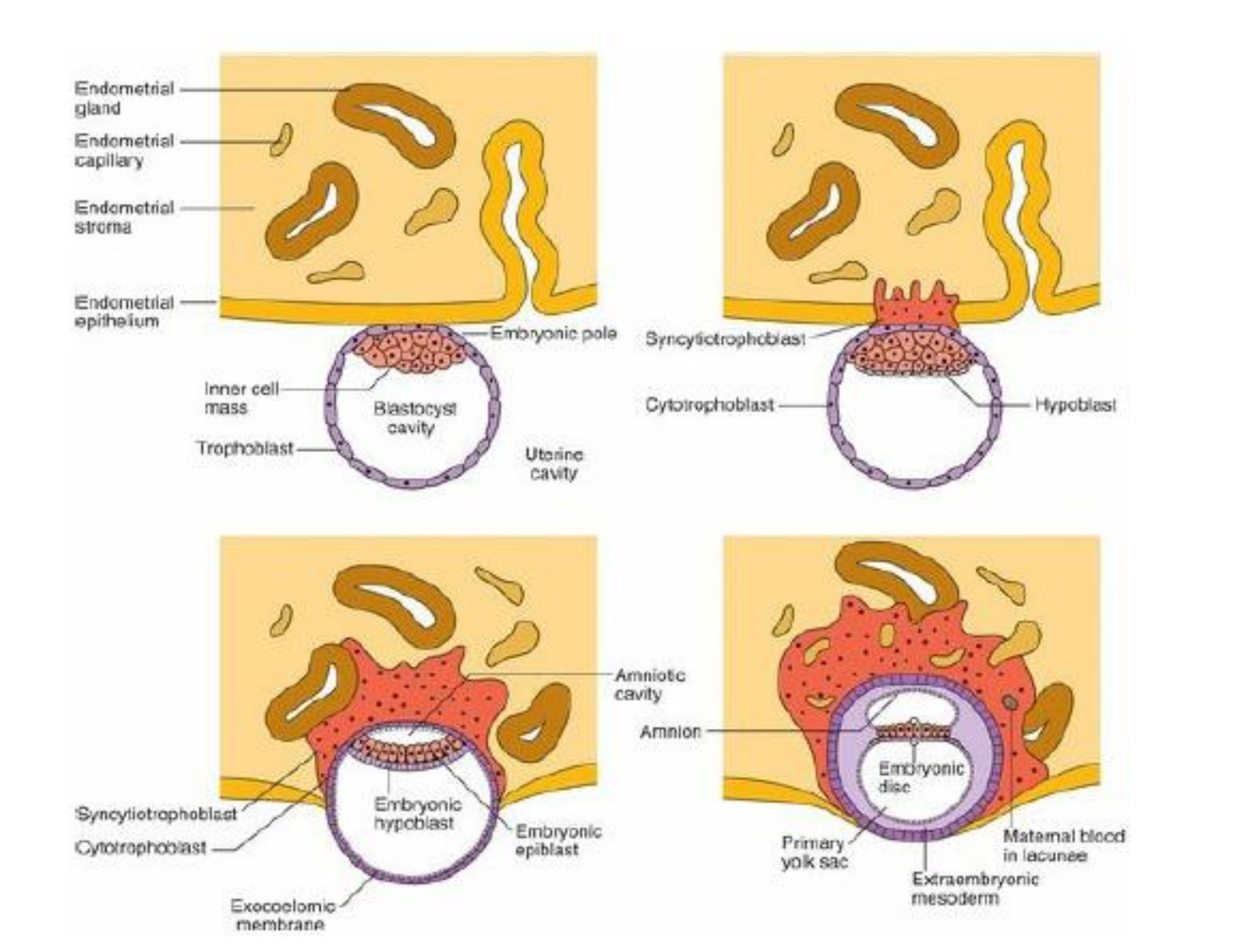
❖ Adhesion phase

- Direct contact between the endometrial epithelium (EE) and the trophectoderm (TE)
- Integrins, Selectins, Trophinin, Laminin, Fibronectin, Ephrin

❖ Invasion phase

Trophoblast reaches the basement membrane and passes the endometrial stroma and reaches the uterine vessels.

Implantation



Stages of Implantation

HATCHING - blastocyst gets released from zona pellucida

⬇

ADPLANTATION - blastocyst slowly "rolls" on surface, aligns with the ICM close to the epithelium.

⬇

APPOSITION -

III. A dialogue between endometrium and the early embryo.

1. Early pregnancy factor (EPF)

- ✓ detected in the maternal circulation within 1-2 days after fertilization.
- ✓ prior to implantation is produced by the ovary in response to a signal from the embryo.
- ✓ After implantation is derived from the embryo.
- ✓ has immunosuppressive properties

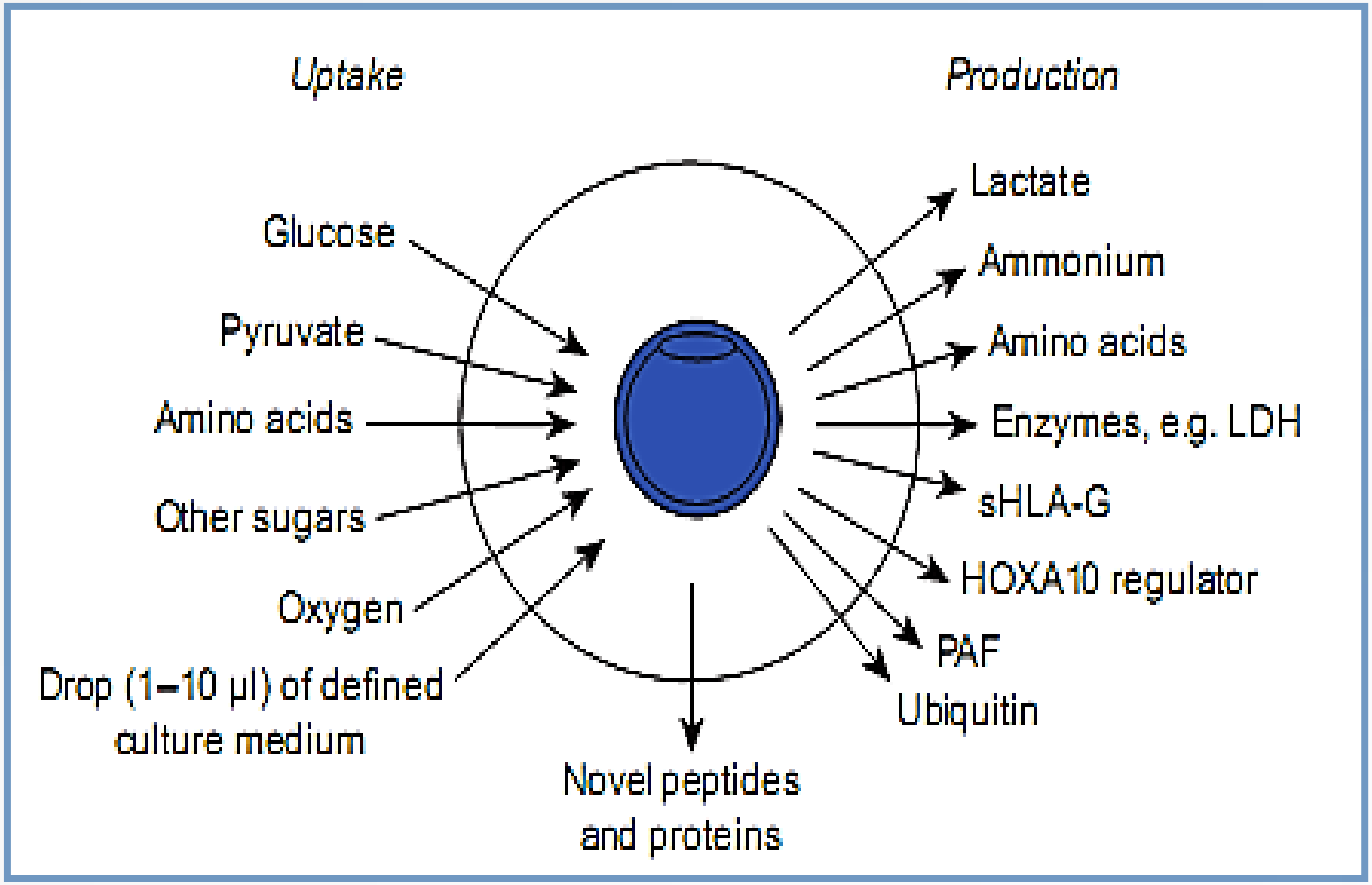
2. HCG

- ✓Secreted by blastocysts
- ✓beginning days 7-8 after fertilization
- ✓enhancing steroid secretion from corpus luteum

3. Prostaglandin E_2

- ✓Secreted by secretory endometrial epithelial cells
- ✓synthesis is increased at the implantation site

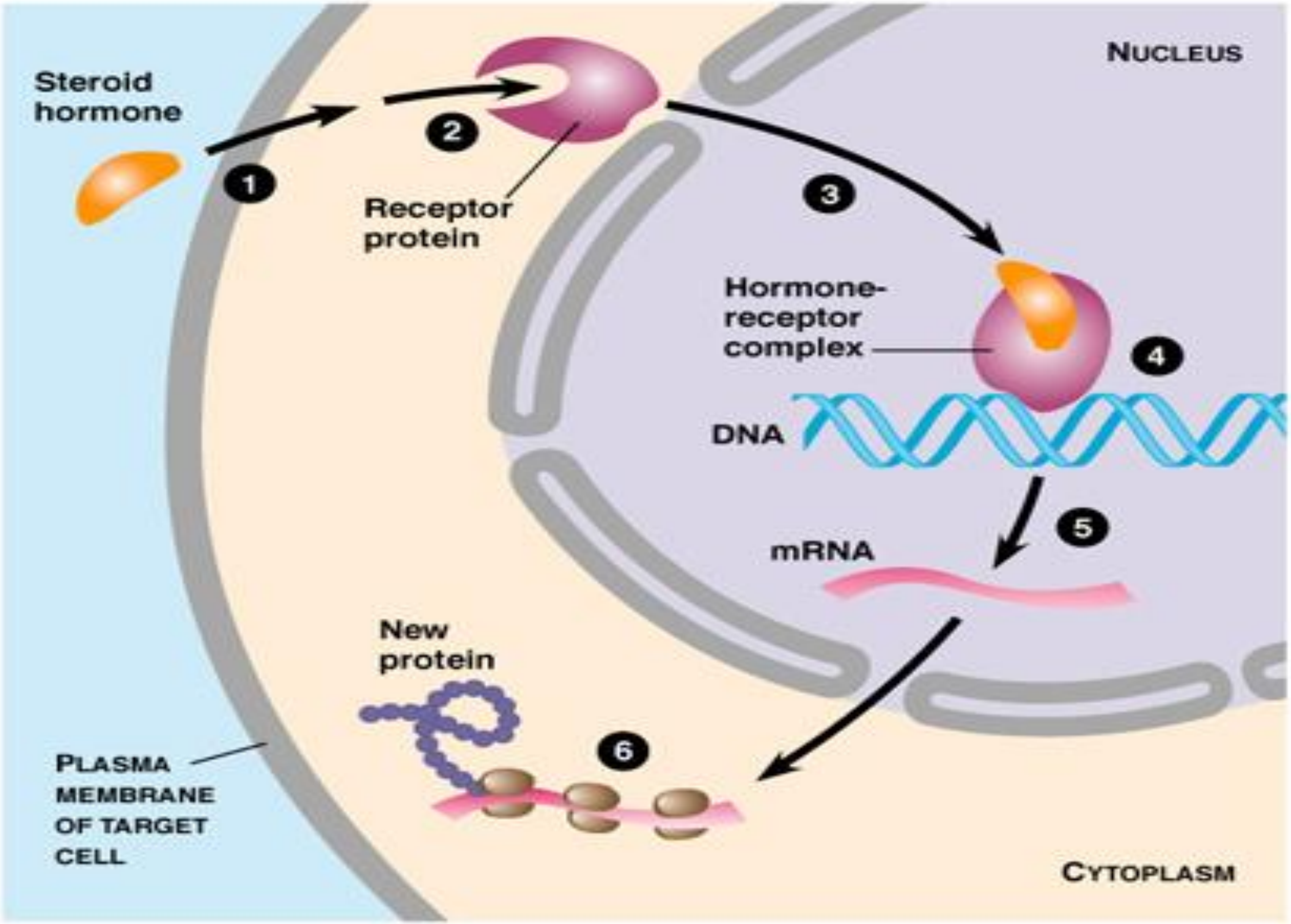
Embryo secretions



Endometrial sensing

- The endometrium rejects a genetically abnormal embryo or fetus
- In humans, endometrial stromal cells have been shown in vitro in a coculture model to respond selectively to low-quality embryos by inhibiting the secretion of key implantation factors
- A significant pregnancy loss resulting from preimplantation embryonic death is considered to be a selection process leading to the survival of superior embryos for implantation.

Estrogen and Progesterone



Estrogen

- Concentration of estrogen within a very narrow range determines the duration of the window of uterine receptivity in mice.

- Uterine receptivity remains open for an extended period at lower estrogen levels but rapidly closes at higher levels accompanied by aberrant uterine expression of implantation-related genes.

Progesterone

- Decidualization is under maternal control and initiated during the midsecretory phase of each cycle in response to elevated progesterone.

- Several progesterone receptor-regulated genes such as Ihh, Bmp2, Wnt4, Hoxa10, and Hand2 are essential for implantation and decidualization.

TABLE 1. Identification of implantation-related genes in the mouse

Progesterone-responsive	Estrogen-responsive	
	Up-regulated	Down-regulated
Alkaline phosphatase	Arachidonate 15-lipoxygenase	BM-90/fibulin
Amphiregulin	ATFx	EIG 180 (ethanol-induced gene)
Apg-2 (chaperone)	Cytosolic adenylate kinase	Glutathione *S*-transferase, θ-2
Carbonic anhydrase II	GADD45 protein	Hereditary hemochromatosis-like protein
Cathepsin F	Glutamyl-tRNA synthetase	Hoxd4
CCAAT/enhancer binding protein β	Guanine nucleotide regulatory protein	HS1-binding protein 3
Chondroitin sulfate proteoglycan 2	Heat shock protein, 105 kDa	Intracisternal A particles
Claudin-7	Hexokinase II, exon 1	Leptin receptor
Complement C1q B chain	IL-1 receptor, type 11	Norrie disease homolog
Cyclin-dependent kinase inhibitor 1C	Mitochondrial stress-70 protein	P glycoprotein 3
Dickkopf-3	NAD-dependent methylenetetrahydrofolate dimethyl cyclohydrolase	Ras-related protein (DEXRAS1)
Follistatin		Thioether *S*-methyltransferase
Glutathione-*S*-transferase	NM23 metastatic-associated protein	Xeroderma pigmentosum, complementation group C
Histidine decarboxylase	Nuclear autoantigenic sperm protein	
Hoxa 11	p45 MAPK kinase	
IGF binding protein-3	Procollagen, type VI, α 2	
IL-13 receptor, 2	Protein kinase inhibitor p58	
Keratin complex 1	RAB geranylgeranyl transferase	
Lactotransferrin	RAMP3	
Leukocyte 12/15 lipoxygenase	Ran GTPase	
LRG-21	RAN GTPase-activating protein 1	
Membrane metalloendopeptidase	RNAse L inhibitor (Mu-RLI)	
Metallothionein 1	Small proline-rich protein 2F	
Norrie disease homolog	Splicing factor, arginine/serine-rich 10	
Osteoblast-specific factor 2	Squalene epoxidase	
Peptidylarginine deiminase	Squalene synthase	
Procollagen type V 2	Type VI collagen, α 3	
Procollagen type XV		
Ras-like GTP-binding protein Rem		
Small proline-rich protein 2F		
Snail homolog		
Spermidine synthase		
Squalene synthase		
Tissue factor pathway inhibitor		

The results of different mouse uterine microarray experiments were compared to identify commonly detected genes. Progesterone-responsive genes were pooled from several disparate approaches (253, 375, 377), whereas estrogen-induced genes were grouped by their response pattern (375, 379).

Endometrial Receptivity Array (ERA)

Win-Test (Window Implantation Test)

Publication of Indian Society of Assisted Reproduction
Journal of Human Reproductive Sciences
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Current issue
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J Hum Reprod Sci. 2015 Jul-Sep; 8(3): 121–129.
doi: 10.4103/0974-1208.165153
PMCID: PMC4601169
PMID: 26538853

Endometrial receptivity array: Clinical application

Reproductive Medicine and Biology
Open Access

ORIGINAL ARTICLE | Open Access

Efficacy of the endometrial receptivity array for repeated implantation failure in Japan: A retrospective, two-centers study

Tomoko Hashimoto, Masae Koizumi, Masakazu Doshida, Mayumi Toya, Eri Sagara, Nao Oka, Yukiko Nakajo, Nobuya Aono, Hideki Igarashi, Koichi Kyono

First published: 27 June 2017 | https://doi.org/10.1002/rmb2.12041 | Citations: 14

Original article

The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment

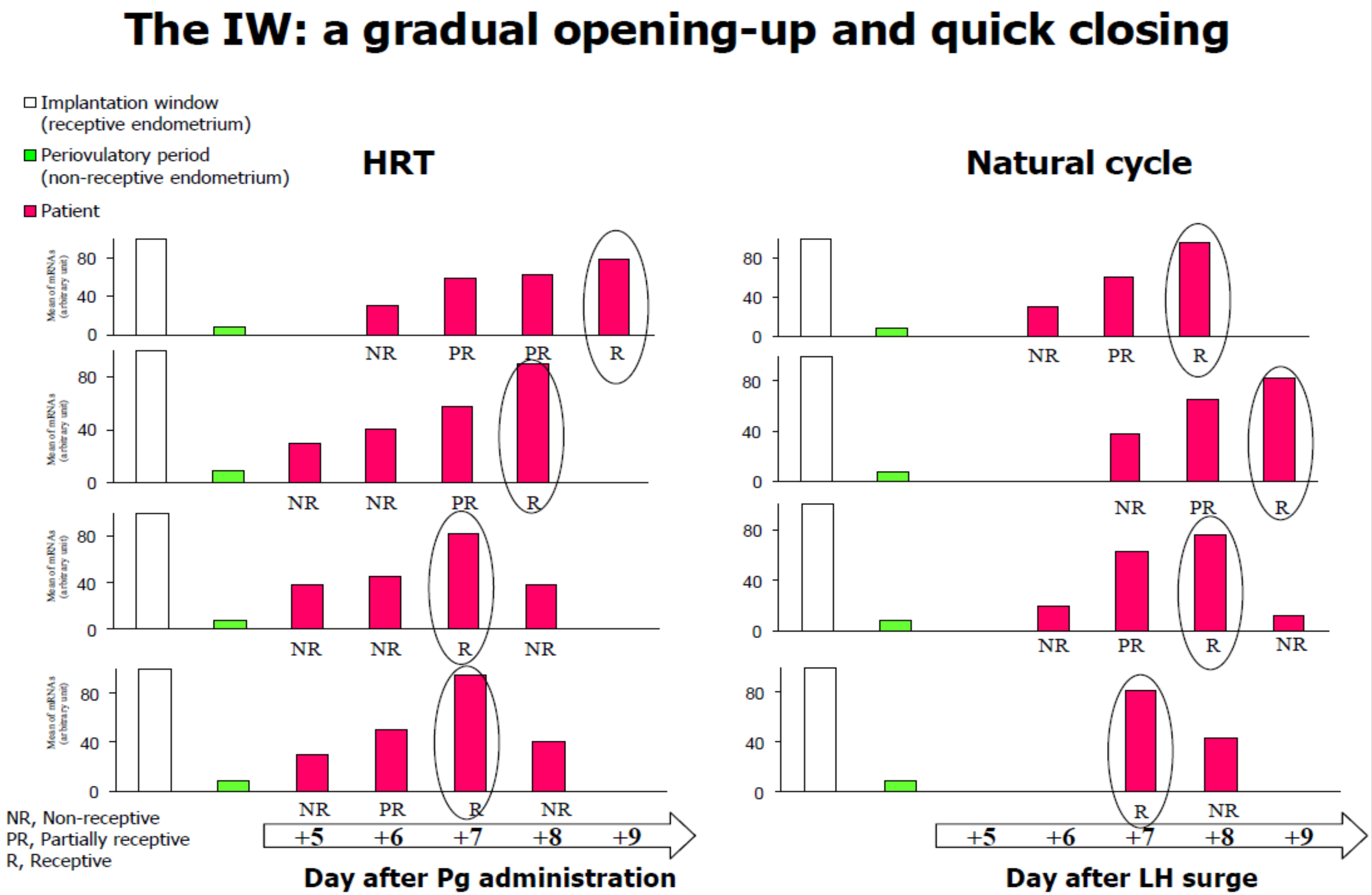
ty, Stanford,

Review | Open Access | Published: 05 August 2019

15 years of transcriptomic analysis on endometrial receptivity: what have we learnt?

Soumaya Messaoudi, Imane EL Kasmi, Amelie Bourdiec, Kimberley Crespo, Laurence Bissonnette, Cecile

Win test

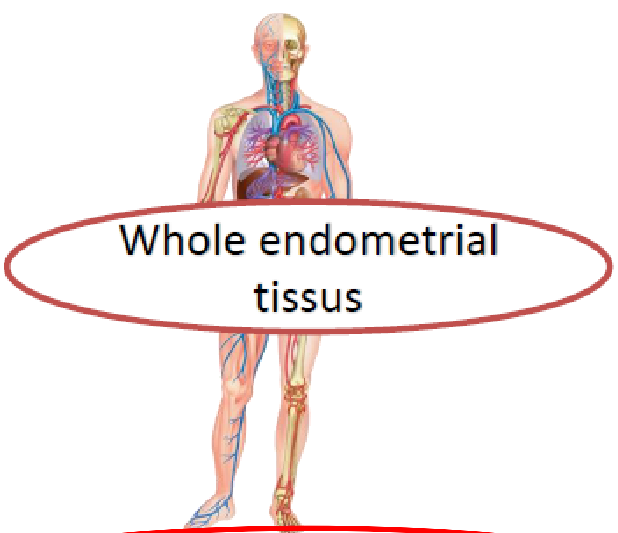


The IW: a gradual opening-up and quick closing
Implantation window (receptive endometrium)
Periovulatory period (non-receptive endometrium)
Patient
HRT
Natural cycle
Mean of mRNAs (arbitrary unit)
80
40
0
NR PR PR R
NR NR PR R
NR NR R NR
NR PR R NR
NR PR R
NR PR R
NR PR R NR
R NR
NR, Non-receptive
PR, Partially receptive
R, Receptive
+5 +6 +7 +8 +9
Day after Pg administration
+5 +6 +7 +8 +9
Day after LH surge

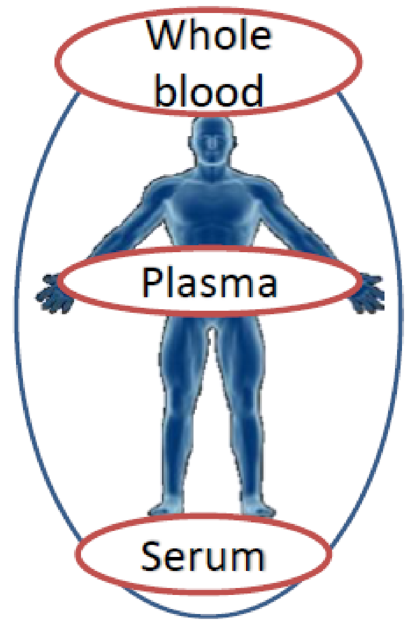
Toward a new generation of the Win-Test:
non-invasive endometrial receptivity test

Objective: avoid to perform an endometrial biopsy

Tissue



Bloodstream ?



Circulating microRNAs as biomarkers of human endometrial receptivity: myth or reality ?

New generation of Win-Test (Window Implantation Test)

Human Reproduction Update Advance Access published June 27, 2014
Human Reproduction Update, Vol.0, No.0 pp. 1–19, 2014
doi:10.1093/humupd/dmu031

human reproduction update

Cell-free nucleic acids as non-invasive biomarkers of gynecological cancers, ovarian, endometrial and obstetric disorders and fetal aneuploidy

S. Traver[1], S. Assou[1,2], E. Scalici[1,2], D. Haouzi[1], T. Al-Edani[1,2], S. Belloc[3], and S. Hamamah[1,2,4,*]

Hum. Reprod. Advance Access published July 30, 2013
Human Reproduction, Vol.0, No.0 pp. 1–12, 2013
doi:10.1093/humrep/det301

human reproduction ORIGINAL ARTICLE Reproductive biology

MicroRNAs: new candidates for the regulation of the human cumulus–oocyte complex

S. Assou[1,2], T. Al-edani[1,2], D. Haouzi[2], N. Philippe[2], C.-H. Lecellier[3], D. Piquemal[4], T. Commes[2,4], O. Aït-Ahmed[2], H. Dechaud[1,2,5], and S. Hamamah[1,2,5,*]

Human Rep
doi:10.1093/humrep/deu238

human reproduction ORIGINAL ARTICLE Embryology

Cell-free DNA in human follicular fluid as a biomarker of embryo quality

E. Scalici[1,2,3,†], S. Traver[1,†], N. Molinari[4], T. Mullet[2,3], M. Monforte[3], E. Vintejoux[3], and S. Hamamah[1,2,3,*]

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SCIENTIFIC REPORTS

OPEN

Circulating microRNAs in follicular fluid, powerful tools to explore *in vitro* fertilization process

Received: 24 July 2015
Accepted: 08 April 2016

E. Scalici[1,2,3], S. Traver[1], T. Mullet[1,2], N. Molinari[4], A. Ferrières[3], C. Brunet[3], S. Belloc[5] & S. Hamamah[1,2,3]

PLOS ONE

RESEARCH ARTICLE

Cell-free DNA in Human Follicular Microenvironment: New Prognostic Biomarker to Predict in vitro Fertilization Outcomes

Sabine Traver, Elodie Scalici, Tiffany Mullet, Nicolas Molinari, Claire Vincens, Samir Hamamah

The End