

PERSONA

Endometrium and implantation disorders

«Any of my statements are not a rule and express my own arguments»



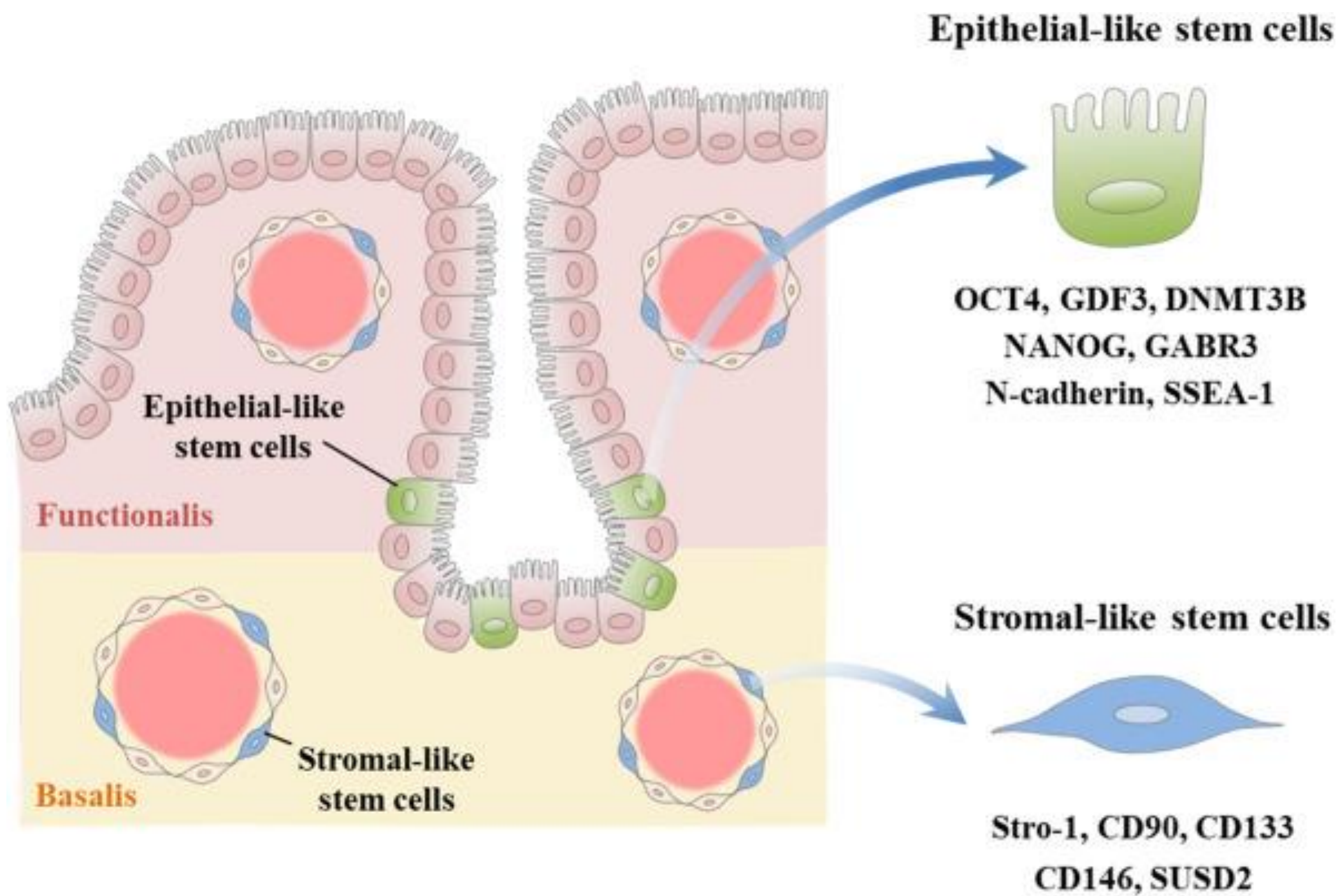
valiyev_ravil

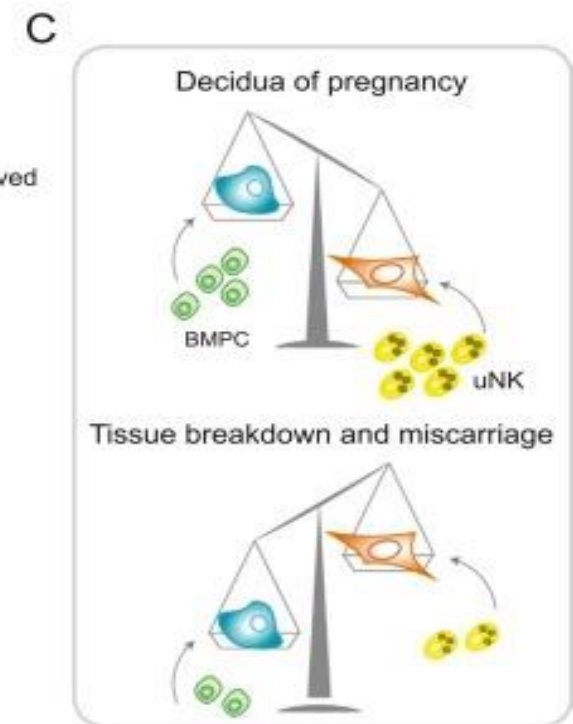
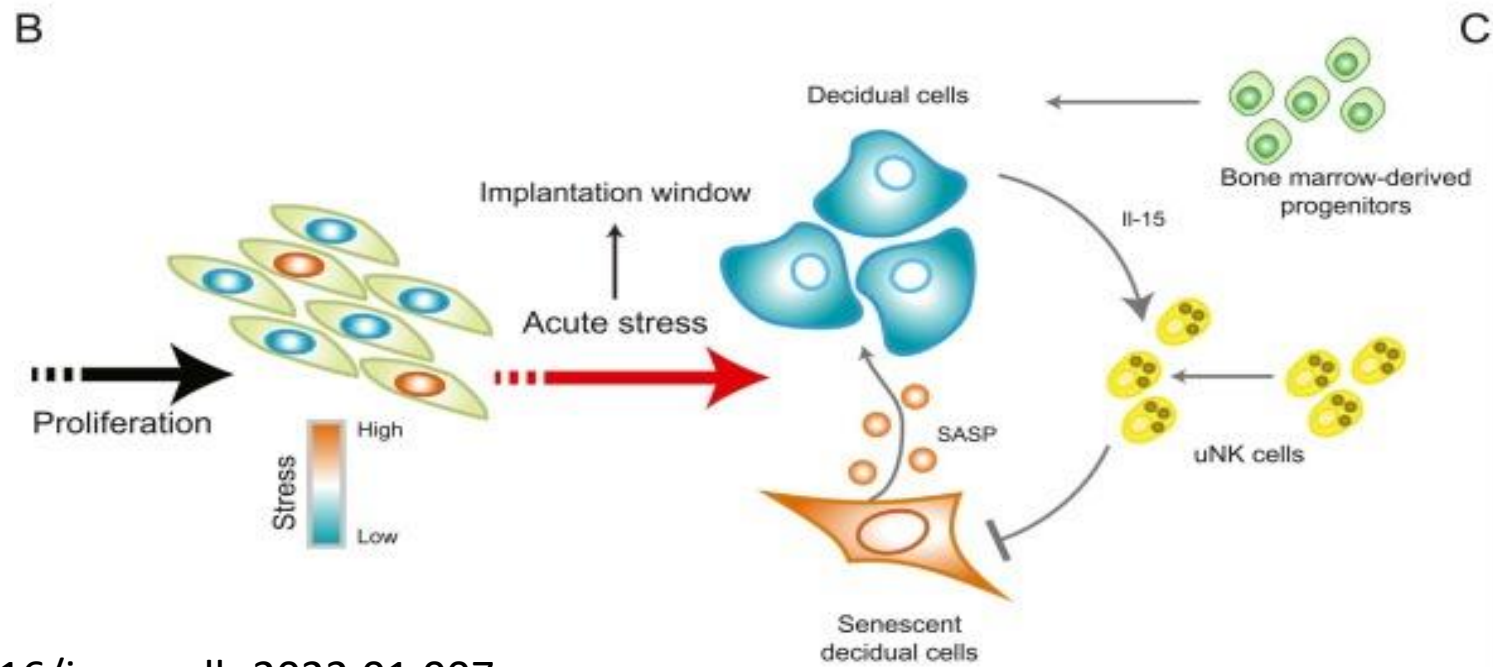
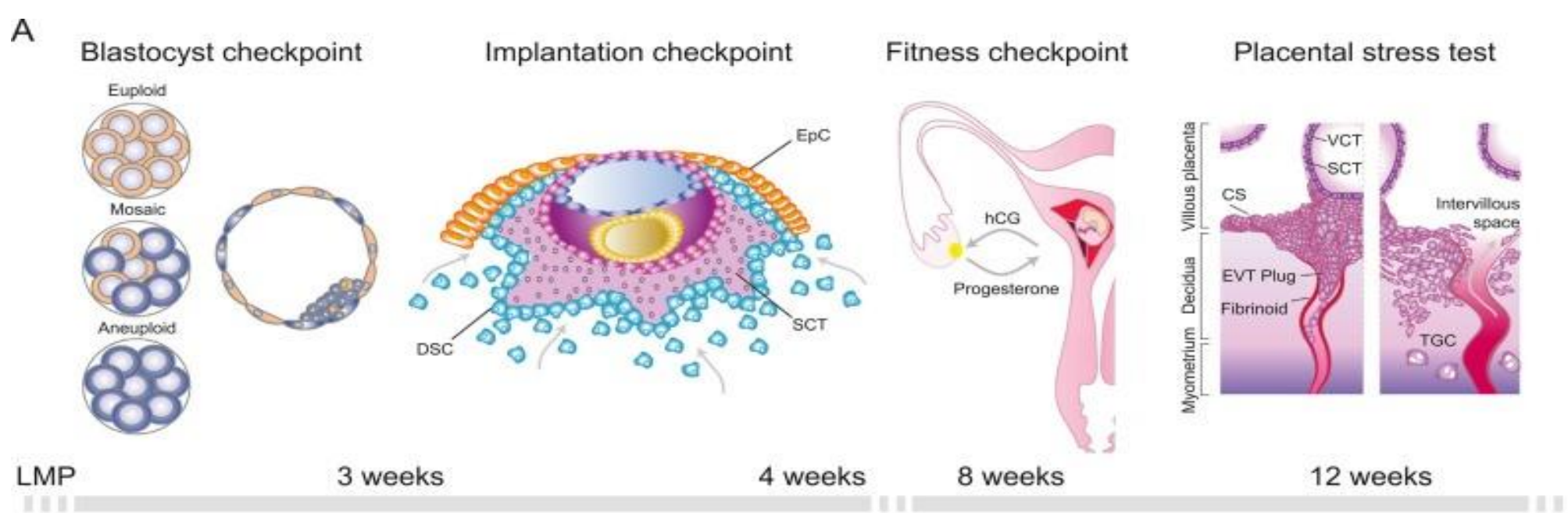
orcid.org/0000-0003-2526-4291



Conflict of interest. Exists.

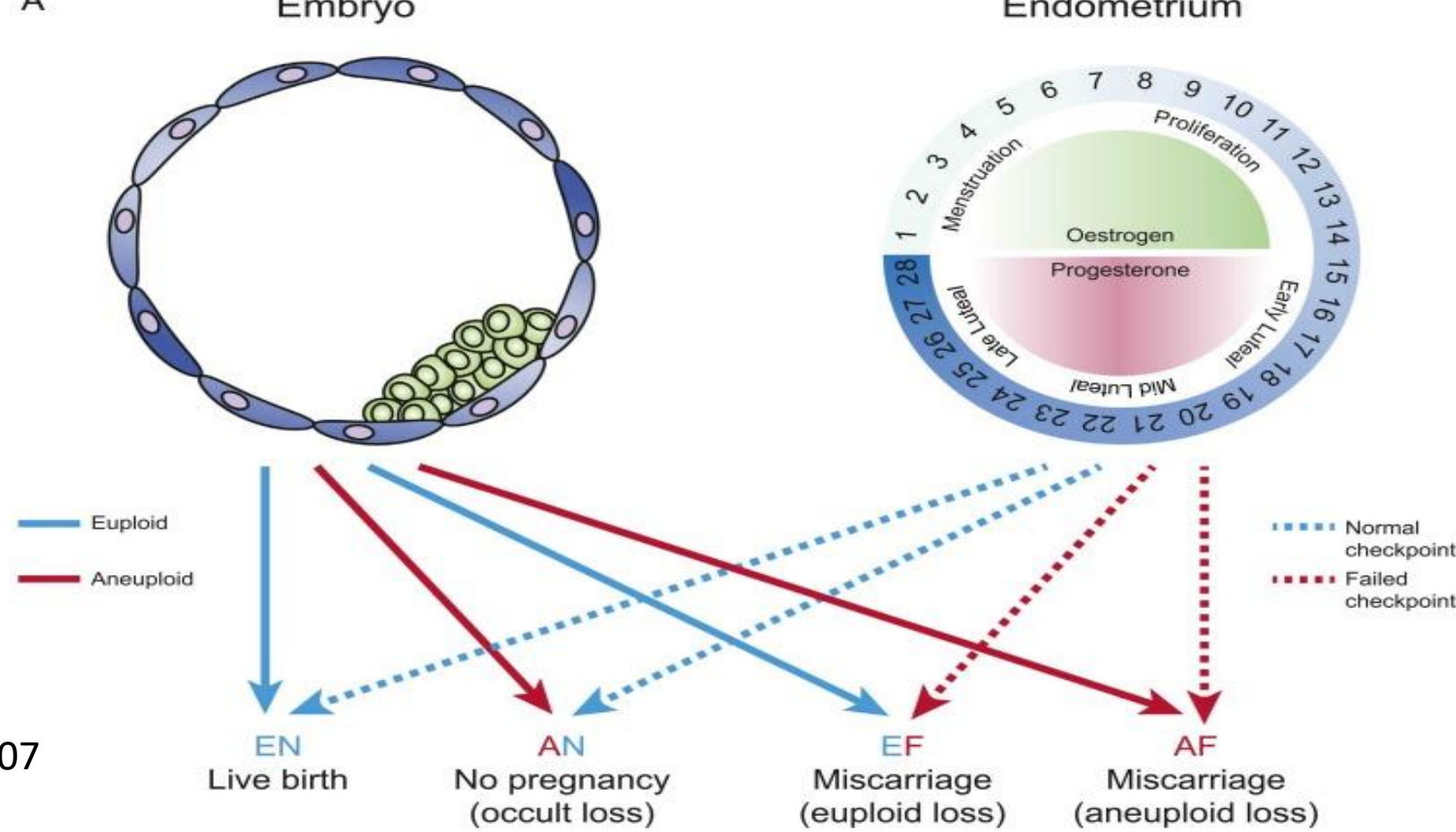
Эндометрий







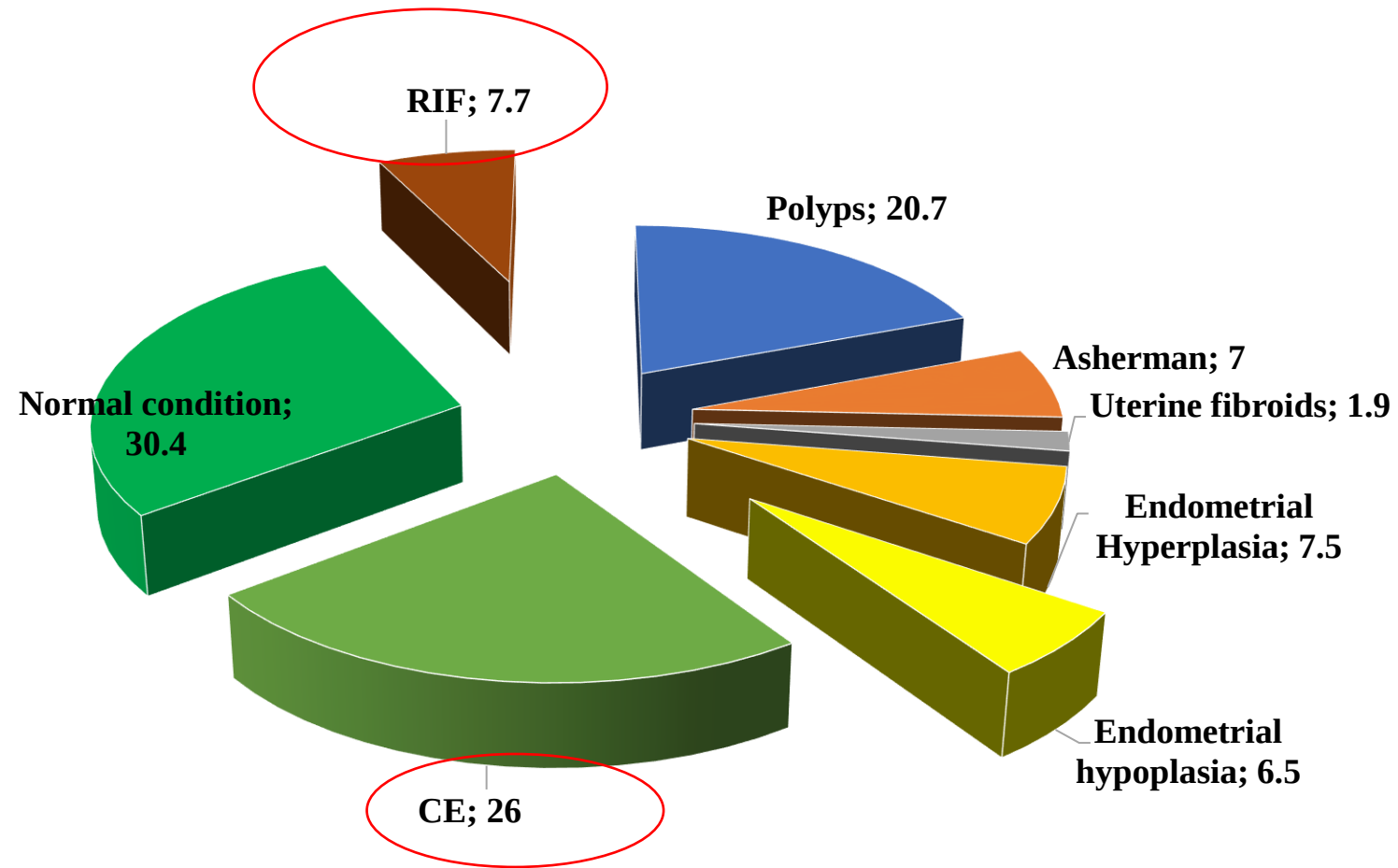
<https://doi.org/10.1016/j.semcd.2022.01.007>



B

Predicted miscarriage rates*		Reported miscarriage rates		
checkpoint failure	miscarriage rate	previous miscarriages	Magnus <i>et al.</i> 2019 [5]	Coomarasamy <i>et al.</i> , 2020 [112] (95 % CI)
1 in 13	10.6 %	0	11.6 %	11.3 % (7-17)
2 in 13	20.6 %	1	19.8 %	17.0 % (9-27)
3 in 13	30.0 %	2	27.7 %	28.0 % (20-36) ‡
4 in 13	38.8 %	3	41.9 % †	
5 in 13	47.2 %	4		39.6 % (35-44)
6 in 13	55.0 %	5		47.2 % (36-58)
7 in 13	62.5 %	6		63.9 % (54-73) †

Structure of Endometrial pathologies (Persona 2018 – 2023)



Endometrial hyperplasia

JOINT GOC-SOGC CLINICAL PRACTICE GUIDELINE | VOLUME 41, ISSUE 12, P1789-

1800, DECEMBER 01, 2019

Guideline No. 390-Classification and Management of Endometrial Hyperplasia

Marie-Hélène Auclair, MDCM • Paul J. Yong, MD • Shannon Salvador, MD • Jackie Thurston, MD •

Terence (Terry) J. Colgan, MD • Alexandra Sebastianelli, MD  

DOI: <https://doi.org/10.1016/j.jogc.2019.03.025>

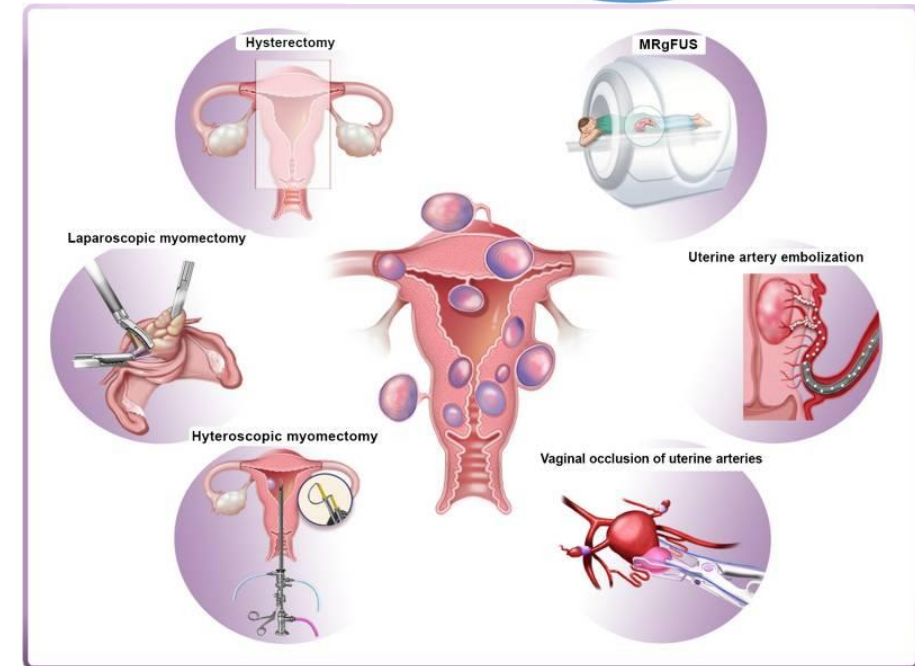
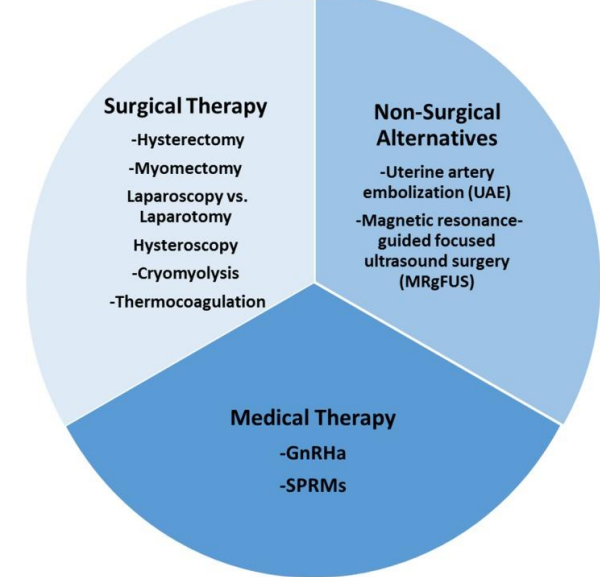
Uterine fibroids

SPECIAL ARTICLE | VOLUME 19, ISSUE 2, P152-171, MARCH 01, 2012

AAGL Practice Report: Practice Guidelines for the Diagnosis and Management of Submucous Leiomyomas

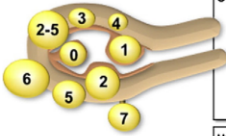
AAGL: *Advancing Minimally Invasive Gynecology Worldwide*

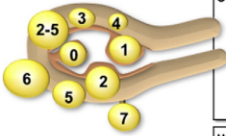
DOI: <https://doi.org/10.1016/j.jmig.2011.09.005>



Polyp			Coagulopathy
Adenomyosis			Ovulatory dysfunction
Leiomyoma	Submucosal		Endometrial
Malignancy & hyperplasia	Other		Iatrogenic
			Not yet classified

Leiomyoma subclassification system



	SM - Submucosal	0	Pedunculated intracavitary
		1	<50% intramural
		2	≥50% intramural
	O - Other	3	Contacts endometrium; 100% intramural
		4	Intramural
		5	Subserosal ≥50% intramural
		6	Subserosal <50% intramural
		7	Subserosal pedunculated
		8	Other (specify e.g. cervical, parasitic)

Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below 2-5 Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.
--	---

Endometrial polyps



International Journal of Surgery

Volume 43, July 2017, Pages 7-16



Review

The management of polyps in female reproductive organs

Vasilios Tanos MD, PhD (Professor in Obstetrics and Gynecology) ^{a, b} , Kelsey Elizabeth Berry ^{a, b} .

Removal of uterine polyps: clinical management and surgical approach

A. Ludwin , S. R. Lindheim, R. Booth & I. Ludwin

Pages 388-396 | Received 29 Mar 2020, Accepted 13 Jun 2020, Published online: 10 Jul 2020

Download citation <https://doi.org/10.1080/13697137.2020.1784870>



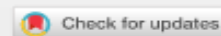
REVIEWS ON HYSTEROSCOPIC MANAGEMENT OF INTRAUTERINE PATHOLOGIES IN POSTMENOPAUSE

To treat or not to treat? An evidence-based practice guide for the management of endometrial polyps

K. K. Sheng & S. D. Lyons

Pages 336-342 | Received 23 Feb 2020, Accepted 01 Mar 2020, Published online: 04 Jun 2020

Download citation <https://doi.org/10.1080/13697137.2020.1742107>





«Thin endometrium»

Treatment options for endometrial hypoproliferation

Cakiroglu, Yigit^{a,b}; Tiras, Bulent^{a,b}; Franasiak, Jason^c; Seli, Emre^{c,d}

Current Opinion in Obstetrics and Gynecology 35(3):p 254-262,
June 2023. | DOI: 10.1097/GCO.0000000000000863

"To date, there is no consensus on the definition of a thin endometrium, with thresholds of 6, 7, or 8 mm being used in the literature."

Prevalence syndrome thin endometrium

A thin endometrium is encountered infrequently (2.4%) in assisted reproductive technology cycles

S. Sharma, 2016

Nova IVI Fertility, New Delhi, India

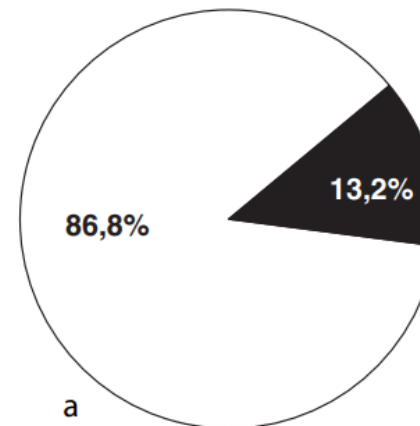
The incidence of thin endometrium in ART has been reported to be between 1.5 and 9.1%

K E Liu, 2018

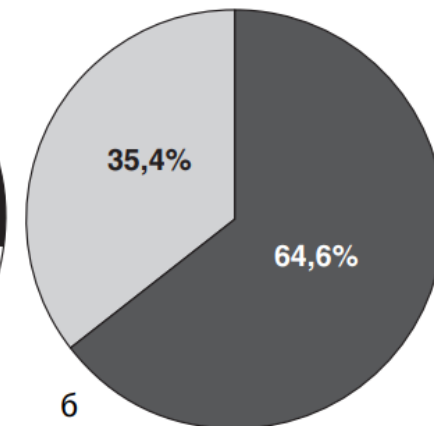
Краснопольская К.В. и др., 2016



25% beyond age forty in natural cycles.



- Нормальная толщина эндометрия (М-эхо 8 мм и более)
- Тонкий эндометрий (М-эхо менее 8 мм)



- Экстремально тонкий эндометрий (М-эхо 5 мм и менее)
- Умеренно тонкий эндометрий (М-эхо 6–7 мм)

The influence of endometrial thickness on the effectiveness of ART has been proven

[Fertil Steril](#). 2008 Oct;90(4):1272-4. Epub 2007 Oct 22.

Parabolic trend in endometrial thickness at embryo transfer in in vitro fertilization/intracytoplasmic sperm injection cases with clinical pregnancy evidence.

[Lamanna G](#)¹, [Scioscia M](#), [Lorusso F](#), [Serrati G](#), [Selvaqi LE](#), [Depalo R](#).

[Hum Reprod](#). 2009 Dec;24(12):3082-9. doi: 10.1093/humrep/dep303. Epub 2009 Sep 2.

Determinants of pregnancy rate in the donor oocyte model: a multivariate analysis of 450 frozen-thawed embryo transfers.

[Dessolle L](#)¹, [Daraï E](#), [Cornet D](#), [Rouzier R](#), [Coutant C](#), [Mandelbaum J](#), [Antoine JM](#).

— Author information

1 Service de gynécologie obstétrique et médecine de la reproduction, Hôpital TENON, 75020 Paris, France. lionel.dessolle@tnn.aphp.fr

[J Assist Reprod Genet](#). 2014 Sep;31(9):1189-94. doi: 10.1007/s10815-014-0297-x. Epub 2014 Aug 10.

The outcome of infertility treatment in patients undergoing assisted reproductive technology after conservative therapy for endometrial cancer.

[Fujimoto A](#)¹, [Ichinose M](#), [Harada M](#), [Hirata T](#), [Osuga Y](#), [Fujii T](#).

— Author information

1 Department of Obstetrics and Gynecology, Sanraku Hospital, 2-5, Kanda-Surugadai, Chiyoda-ku, Tokyo, Japan, 101-8326, fujimoto-ky@umin.ac.jp.



[J Hum Reprod Sci](#). 2016 Jan-Mar; 9(1): 3–8.
doi: [10.4103/0974-1208.178632](https://doi.org/10.4103/0974-1208.178632)

PMCID: PMC4817285
PMID: [27110071](https://pubmed.ncbi.nlm.nih.gov/27110071/)

The endometrium in assisted reproductive technology: How thin is thin?

[Nalini Mahajan](#) and [S. Sharma](#)

Fertility and Sterility.

April 2020

Endometrial thickness is associated with incidence of small-for-gestational-age infants in fresh in vitro fertilization–intracytoplasmic sperm injection and embryo transfer cycles

Zizhen Guo, M.D

Pregnancy complications and outcomes for singleton births based on endometrial thickness.

Outcomes	EMT ≤7.5 mm (n = 132)	7.5 < EMT ≤12 mm (n = 2,166)	EMT > 12 mm (n = 859)	P value
Gestational age (wk)	38.69 ± 1.97	39.09 ± 1.51	39.08 ± 1.80	NS ^a
PTD (<37 wk), n (%)	13 (9.8)	130 (6.0)	64 (7.5)	NS ^b
VPTD (<32 wk), n (%) ^{c,d}	3 (2.3)	11 (0.5)	13 (1.5)	.004 ^e
Birth weight (kg) ^{c,d}	3.25 ± 0.56	3.38 ± 0.51	3.39 ± 0.53	.020 ^f
SGA, n (%) ^d	11 (8.3)	111 (5.1)	32 (3.7)	.046 ^b
LGA, n (%)	17 (12.9)	427 (19.7)	178 (20.7)	NS ^b
Male gender, n (%)	70 (53.0)	1,126 (52.0)	469 (54.6)	NS ^b
Cesarean delivery, n (%)	88 (66.7)	1,440 (66.5)	534 (62.2)	NS ^b
Placenta previa, n (%)	0	22 (1.0)	13 (1.5)	NS ^c
Placental abruption, n (%)	0	4 (0.2)	5 (0.6)	NS ^e
Hypertensive disorders, n (%) ^g	10 (7.6)	89 (4.1)	36 (4.2)	NS ^b
GDM, n (%)	13 (9.8)	178 (8.2)	76 (8.8)	NS ^b

Note: Values are presented as mean ± standard deviation or n (%); ANOVA = analysis of variance; EMT = endometrial thickness; GDM = gestational diabetes mellitus; LGA = large for gestational age (>90%); NS = not statistically significant; PTD = preterm delivery (<37 weeks); SGA = small for gestational age (defined <10%); VPTD = very preterm delivery (<32 weeks);

^a Welch's ANOVA.

^b Fisher's exact square test.

^c Statistically significant differences between EMT ≤7.5 mm and EMT >12 mm groups.

^d Fisher's exact test.

^e Hyperintensive disorders include pre-eclampsia, preeclampsia, and eclampsia.

^f Fisher's exact test.

^g Fisher's exact test.

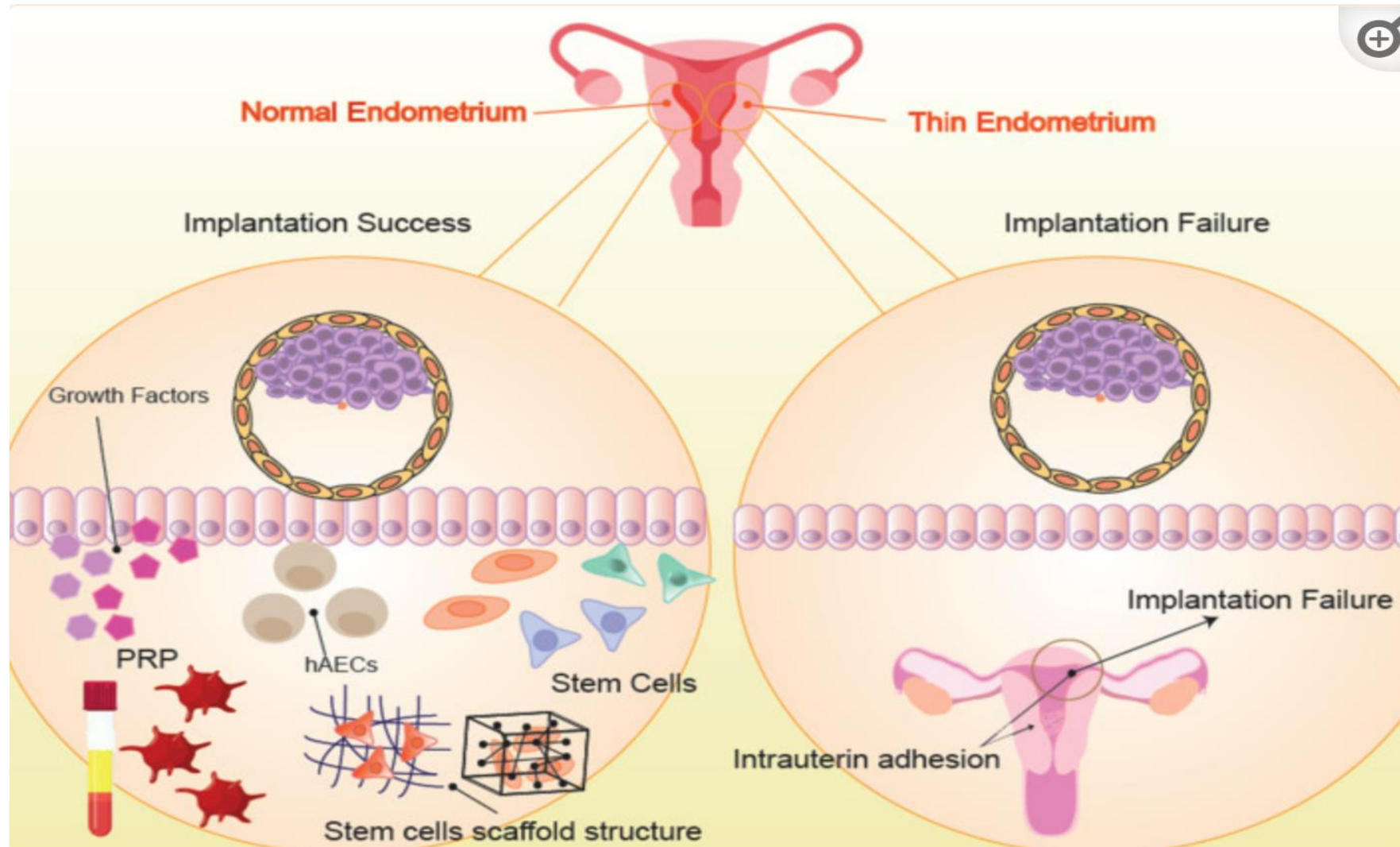
Endometrial thickness is associated with incidence of small-for-gestational-age infants in fresh in vitro fertilization–intracytoplasmic sperm injection and embryo transfer cycles

A thin endometrium can increase the risk of various pregnancy complications. specifically focusing on low birth weight, preeclampsia, and abnormal placentation.

ЭҚҰ/ ИКСИ бағдарламаларында жұқа эндометриясы бар гестациялық жасына қарай салмағы төмен сәбилердің туу қаупі 2 есе артады. Преэклампсия және ҚОПМБ қаупі

Treatment

<https://doi.org/10.1186/s13287-021-02698-8>



Treatment

[Front Endocrinol \(Lausanne\)](#). 2023; 14: 1102706.

PMCID: PMC10014925

Published online 2023 Mar 1. doi: [10.3389/fendo.2023.1102706](#)

PMID: [36936160](#)

Hormone replacement therapy alone or in combination with tamoxifen in women with thin endometrium undergoing frozen-thawed embryo transfer: A retrospective study

[Qingqing Shi](#),^{1,2,3,†} [Chenyang Huang](#),^{1,2,3,†} [Jingyu Liu](#),^{1,2,3,†} [Yifan Li](#),^{1,2,3} [Na Kong](#),^{1,2,3} [Jie Mei](#),^{1,2,3}
[Xiaoyue Shen](#),^{1,2,3} [Yanxin Sun](#),^{1,2,3} [Feifei Lu](#),^{1,2,3} [Haixiang Sun](#),^{✉1,2,3,*} and [Guijun Yan](#)^{✉1,2,3,*}

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
---	---	---	---	---	---	---	---	---	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----

эстрадиол 6-8 mg трансдермально

Тамоксифен 10 mg 2 раза в день

Micronized progesterone 300-600mg
Dihydrosterone 30 mg

PERSONA
Efficiency
60%

Treatment

[Int J Fertil Steril](#). 2022 Oct-Dec; 16(4): 251–255.

Published online 2022 Oct 12. doi: [10.22074/IJFS.2022.541389.1210](#)

PMCID: PMC9627013

PMID: [36273309](#)

Growth Hormone: A Potential Treatment of Patients with Refractory Thin Endometrium: A Clinical Trial Study

[Soghra Hosseini Aghdam](#), M.D.,^{1,2} [Alyeh Ghasemzadeh](#), M.D.,^{1,2,*} [Laya Farzadi](#), M.D.,^{1,2} [Kobra Hamdi](#), M.
[Nazli Navali](#), M.D.,^{1,2} [Parvin Hakimi](#), M.D.,^{1,2} [Marayam Baradaran-Binazir](#), Ph.D.,³ [Mohammad Nouri](#), Ph.D.
[Amir Fattahi](#), Ph.D.,^{1,4,*} and [Ralf Dittrich](#), Ph.D.⁵

^{1,2}

Randomized Controlled Trial

> [Afr J Reprod Health](#). 2023 Mar;27(3):32-39.

doi: [10.29063/ajrh2023/v27i3.4](#).

Effectiveness of growth hormone in promoting endometrial growth in patients with endometrial dysplasia in frozen embryo transfer

[Yong Wu](#)¹, [Yuan Tian](#)¹, [Lili Zhang](#)¹, [Li Zeng](#)¹, [Ying Wang](#)¹, [Ruifeng Shao](#)¹, [Chihua He](#)¹

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
---	---	---	---	---	---	---	---	---	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----

эстрадиол 6-8 mg трансдермально



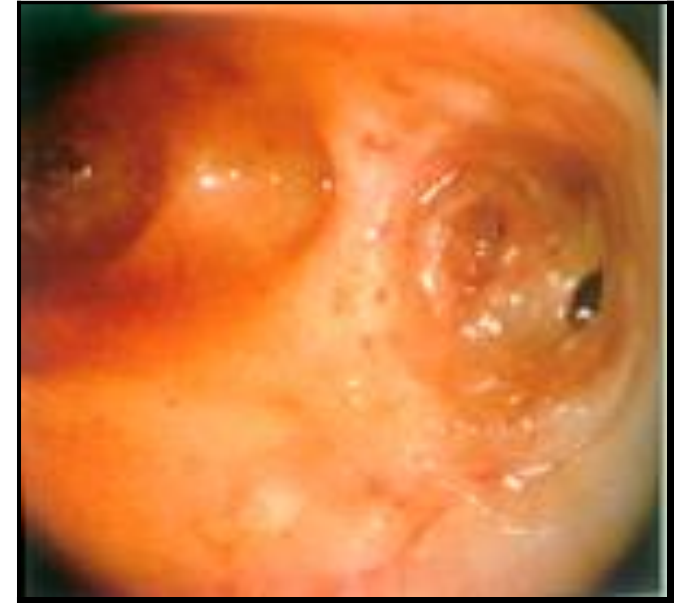
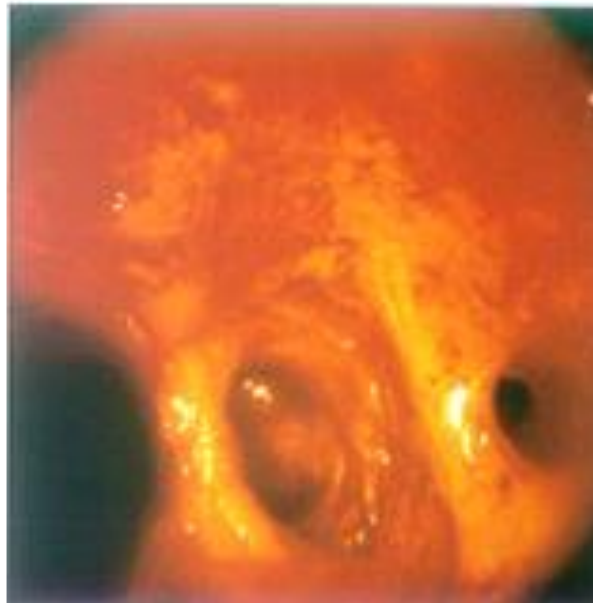
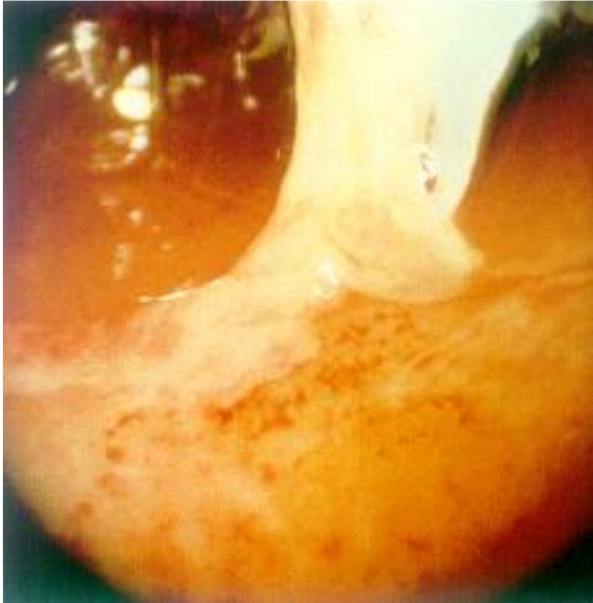
PERSONA

Efficiency 70% - Be careful!!!!

Гормон роста 2 mg 1 раза в
день

Micronized progesterone
300-600mg
Dihydrosterone 30 mg

The cause of thin endometrium is iatrogenic (surgical) with manipulation Asherman's syndrome



Dissection of synechiae of the uterine cavity

- ✓ Stage 1 - destruction with a hysteroscope
- ✓ Stage 2- microscissors or electrosurgery
- ✓ 3 and 4 Stage microscissors or electrosurgical dissection under ultrasound or laparoscopic control

Postoperative management.

- ❑ Prescription of oral estrogen-containing contraceptives for 2-3 months (evidence base group A)
- ❑ Құрамында эстроген бар контрацептивтерді 2-3 айға тағайындау (дәлелдемелік топ А)
- ❑ /Антибактериалды терапия/Antibacterial Therapy
- ❑ Control hysteroscopy after 10 – 21 days
10-21 күннен кейін қайта гистероскопия
- ❑ Физикалық қорғану әдістерін қолдану
Using barrier methods

Операциядан кейінгі кезең

Additions to antibiotic therapy



ХГЧ жатырішілік енгізу Intrauterine administration of hCG

- Promotes embryonic invasion by coordinating cytokine secretion – leads to increased expression of E2 and P, C3, and NOTCH1 – Literature data is controversial.



Гранулоциттер колониясын ынталандырушы фактор

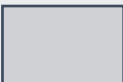
Granulocyte Colony-Stimulating Factor

- Data from randomized controlled trials indicate minimal harm and potential benefit



Тромбоциттерге бай плазма Enriched platelet plasma

The largest randomized controlled trial (RCT) involved 138 patients and requires reassessment due to the suboptimal control group. The remaining studies are observational and hold only historical interest



Өсу гормоны

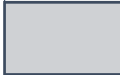
Growth hormone

- It affects VEGF, LIF, and integrins in the endometrium—its use is currently under development.



Scratching эндометрия

- "The latest RCT (1364 patients) by Lensen S. in 2019 showed no advantages."



Культуральды сұйықтығының супернатанты "Supernatant of culture fluid"

- "There is no convincing evidence of a positive effect on clinical pregnancy rates with a thin endometrium."



Эндометриоз және жұқа эндометрий бар науқастарда Летрозол қолдану

Letrozole in patients with endometriosis and thin endometrium- Restores integrin expression – increases (like alpha-GnRH) clinical pregnancy rates



Преднизолонды жатыр ішіне еңгізу

Intrauterine administration of prednisone lacks evidence

Treatment after dissection of the adhesions of the uterine cavity



Cause of thin endometrium, RIF – chronic endometritis

Chronic Endometritis

This disease is characterized by disruption of intercellular interactions, sclerosis of the stroma around the vessels, changes in tissue angioarchitecture and ischemia; an important role in early reproductive losses is played by an imbalance of growth factors, proteases and their inhibitors, causing remodeling of the uterine mucosa with progressive collagenogenesis and atrophy of the glandular apparatus – which leads to endometrial hypoplasia.

According to R. Friedman and J. Hamu, chronic endometritis as a manifestation of hypoplasia occurs in 22% of patients in the IVF program, in 14% of unexplained infertility and in 23.6% of women with miscarriages in the first trimester and in 50% of patients with secondary infertility .

Prevalence rates of chronic endometritis according to literature data.

Prevalence rates of chronic endometritis according to the literature.

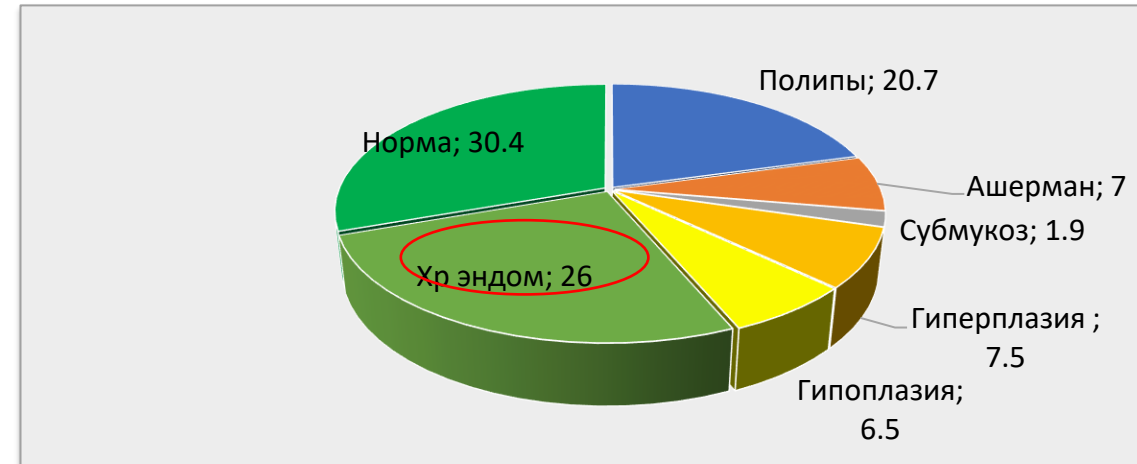
Population	Prevalence	References
Infertile women	0.2–56.8%	Wild (1986) , Sahmay et al. (1995) , Féghali et al. (2003) , Polisseni et al. (2003) , Cicinelli et al. (2005) , Chen et al. (2016) and Cicinelli et al. (2018)
Recurrent implantation failure	14–67.5%	Johnston-MacAnanny et al. (2010) , Cicinelli et al. (2015) , Bouet et al. (2016) , Kitaya et al. (2017) , and Zhang et al. (2019)
Recurrent miscarriage	9.3–67.6%	Kitaya (2011) , Zolghadri et al. (2011) , Cicinelli et al. (2014) , McQueen et al. (2014) , and Bouet et al. (2016)
Abnormal uterine bleeding	1.4–52%	Kitaya et al. (2018) and Song et al. (2018)
Patients with endometrial polyps	28–92.6%	Cicinelli et al. (2019) , Kuroda et al. (2020) , and Guo et al. (2021)

Данные
PERSONA -
26%

Созылмалы эндометрит - ісіну, стромалық жасушалардың тығыздығының жоғарылауы, эпителий жасушалары мен строма арасындағы жетілу диссоциациясы және плазмалық жасушалардың стромалық инфильтрациясы бар эндометрия шырышты қабатының локализацияланған қабынуы.

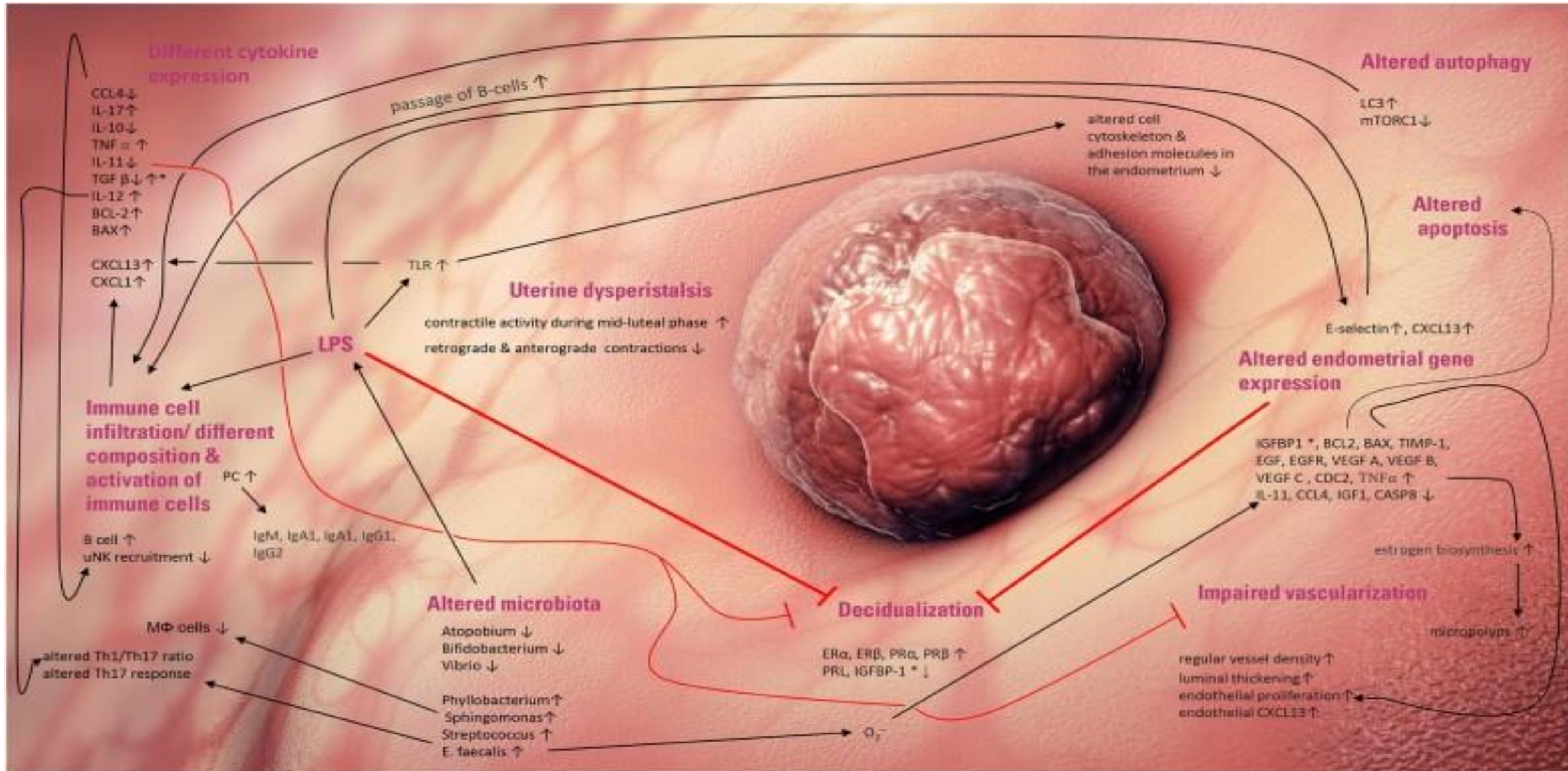
СЭ таралуы бедеу әйелдерде 2,8-56,8%, имплантацияның қайталама сәтсіздігі (RIF) бар әйелдерде 14-67,5% және қайталама түсіктері бар әйелдерде 9,3-67,6% құрайды.

- A. The incidence of chronic endometritis (CE) ranges widely from 2.8% to approximately 86.5%, as reported by various studies.
- B. Chronic endometritis occurs in 22% of patients in IVF programs, 14% of those with unexplained infertility, and 23.6% of women with first-trimester miscarriages



Chronic endometritis (CE) is a condition associated with a disruption in the harmonious coexistence of microorganisms and the immune system in the endometrium. Changes in the endometrial microenvironment affect its sensitivity to receptors, which can impede normal implantation

A simplified illustration of the proposed mechanisms of the influence of chronic endometritis on female fertility

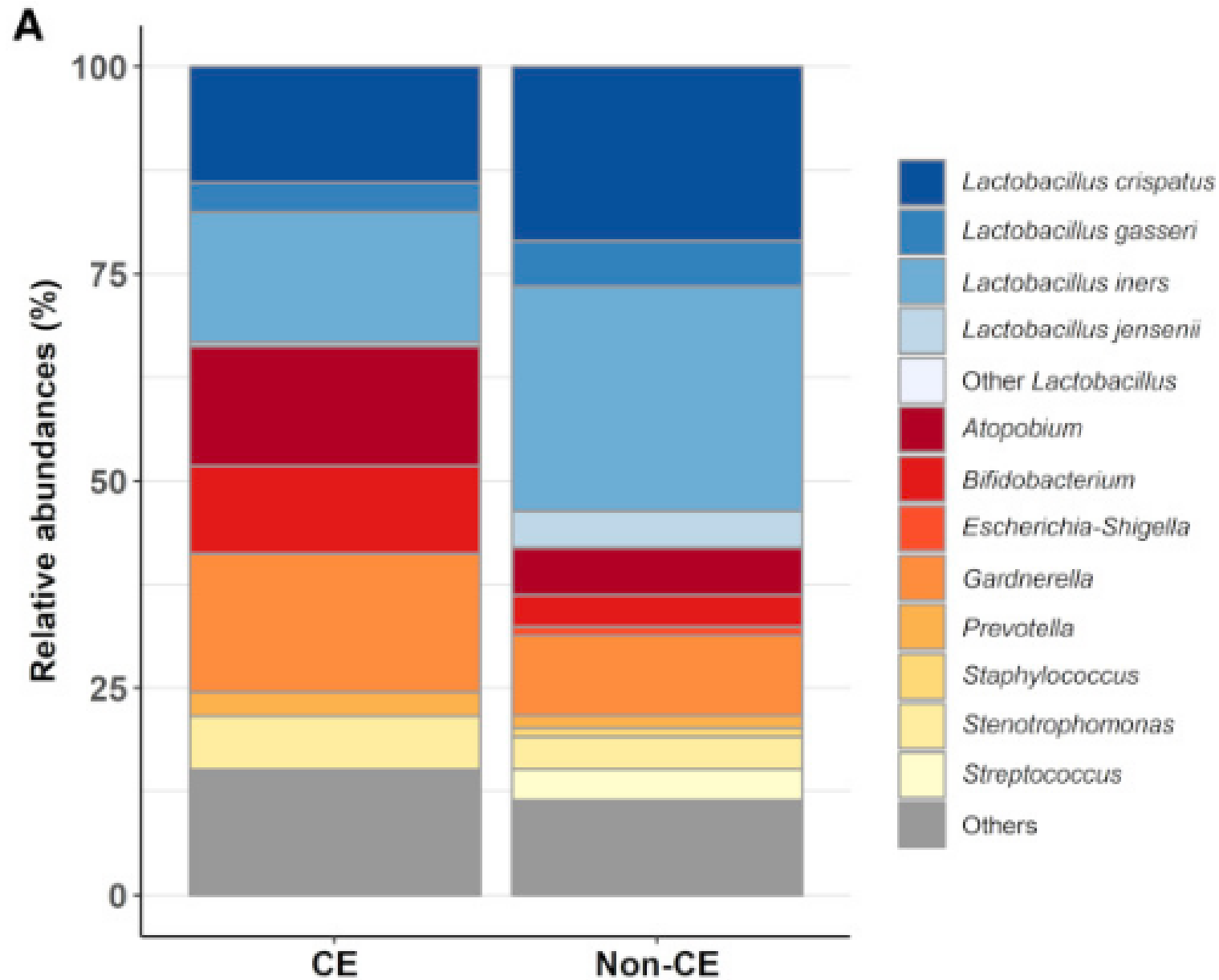


Пути инфицирования полости матки

лимфогенная диссеминация



**Вклад ЖКТ в формирование
микробиоты полости матки
составляет до 40%**



Diagnosis

- Hysteroscopy and endometrial biopsy with determination of CD138+
- Sensitivity of the hysteroscopy method: PERSONA – 89%

Fertility
and Sterility



• 2019 Apr;

Correlation between hysteroscopy findings and chronic endometritis

[Dongmei Song¹](#), [Tin-Chiu Li²](#), [Yun Zhang³](#)

diagnostic accuracy from 59,3% to 82,8% respectively



2020. Evaluating Chronic Endometritis in Women with Recurrent Implantation Failure and Recurrent Pregnancy Loss by Hysteroscopy and Immunohistochemistry

• [Mahvash Zargar, MD, PhD](#)

The diagnostic accuracy of hysteroscopy in diagnosing CE was 86,36%, 87,30%, 70,37% and 94,82%

Treatment



Patients with Mycoplasma and Ureaplasma infections are treated with Josamycin (2 g/day for 12 days), and Minocycline (200 mg/day for 12 days) is prescribed for patients with resistance. Combination of ceftriaxone (250 mg, single dose, intramuscular injection), doxycycline (200 mg/day for 14 days) and metronidazole (1000 mg/day for 14 days) for primary treatment

Fertility and Sterility.

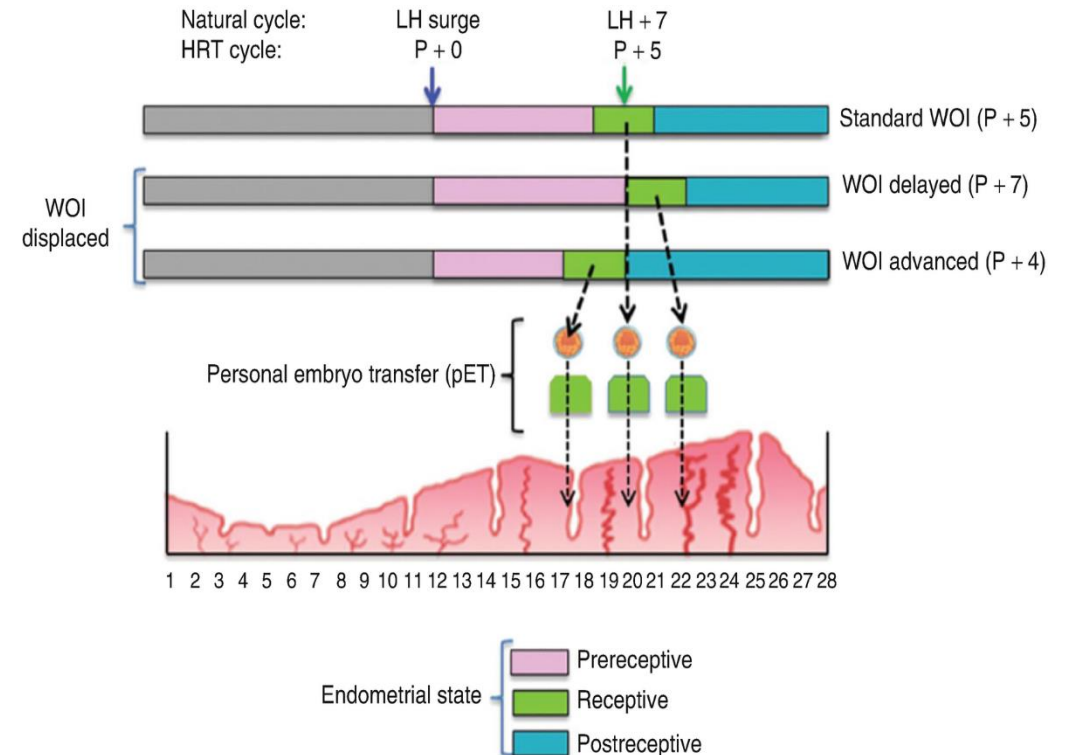
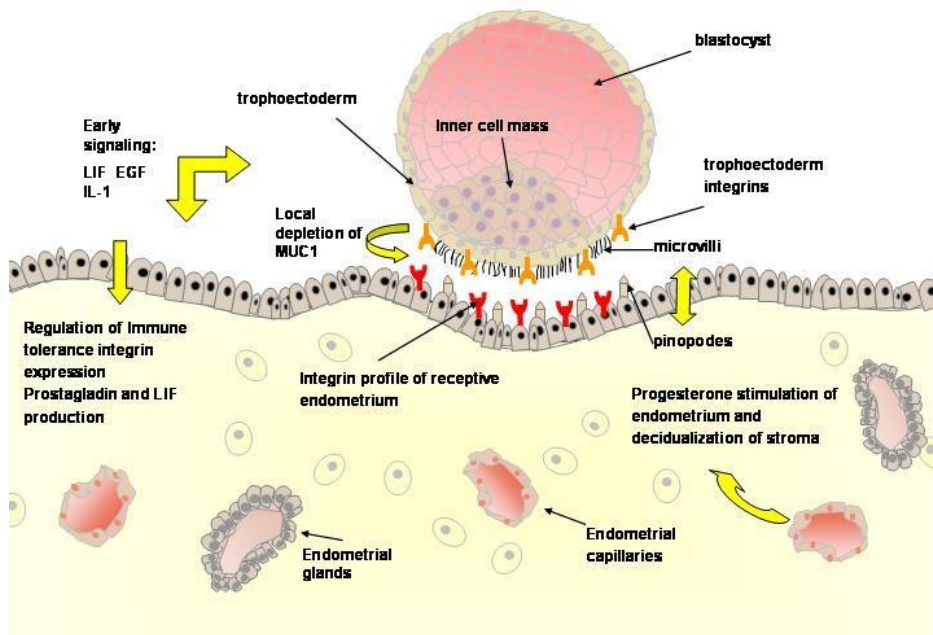


McQueen DB, Bernardi LA, Stephenson MD. showed that 70% of cases of HE were cured with a regimen of 100 mg doxycycline twice daily for 14 days.

- **Own data – "combined" therapy for chronic endometritis – effectiveness of 72%.**

Recurrent implantation failure

The effectiveness of ART is directly related to solving the key problem of reproductive medicine - identifying the period of endometrial receptivity («window of implantation» WOI)



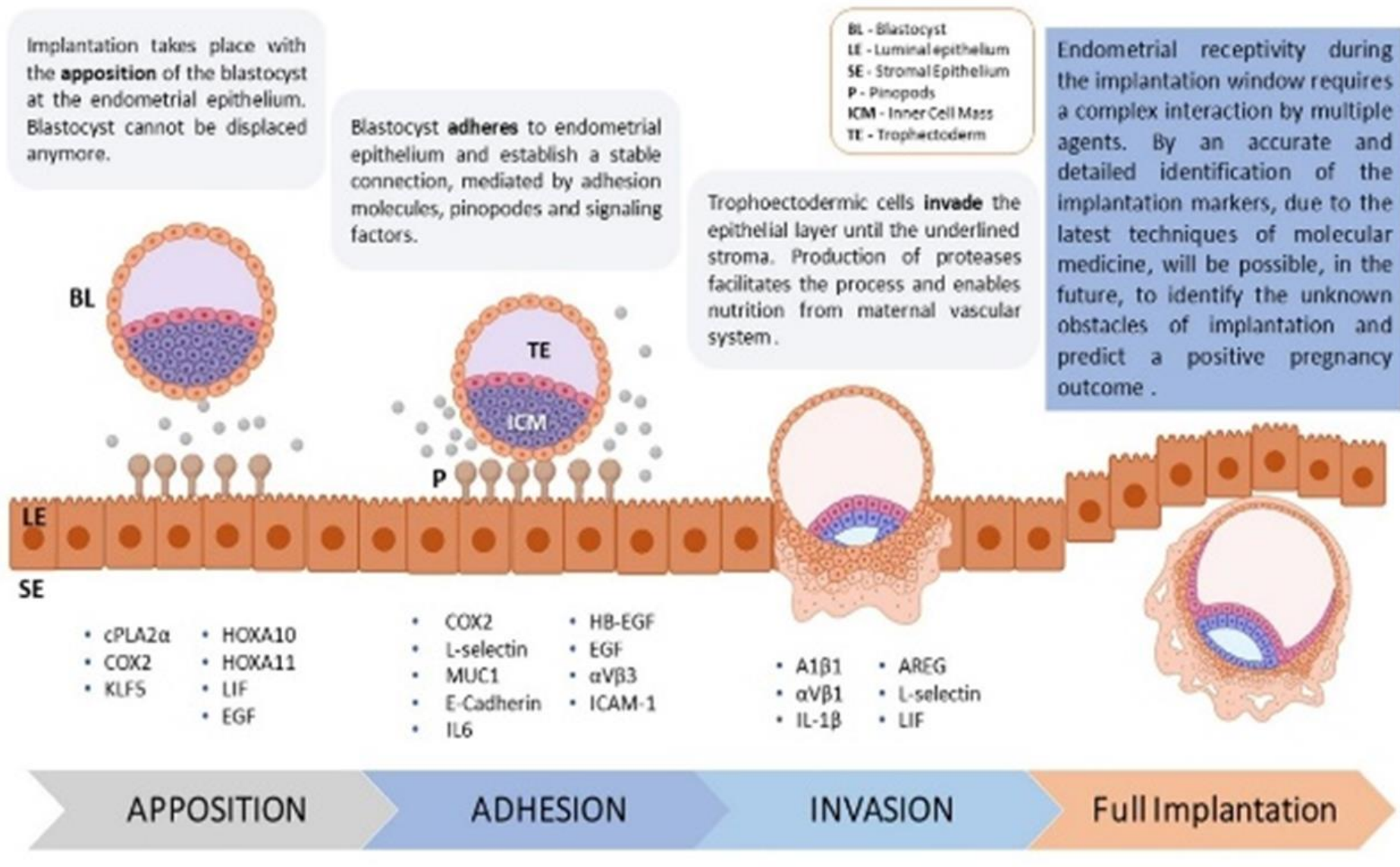
MAIN ACTORS BEHIND THE ENDOMETRIAL RECEPTIVITY AND SUCCESSFUL IMPLANTATION

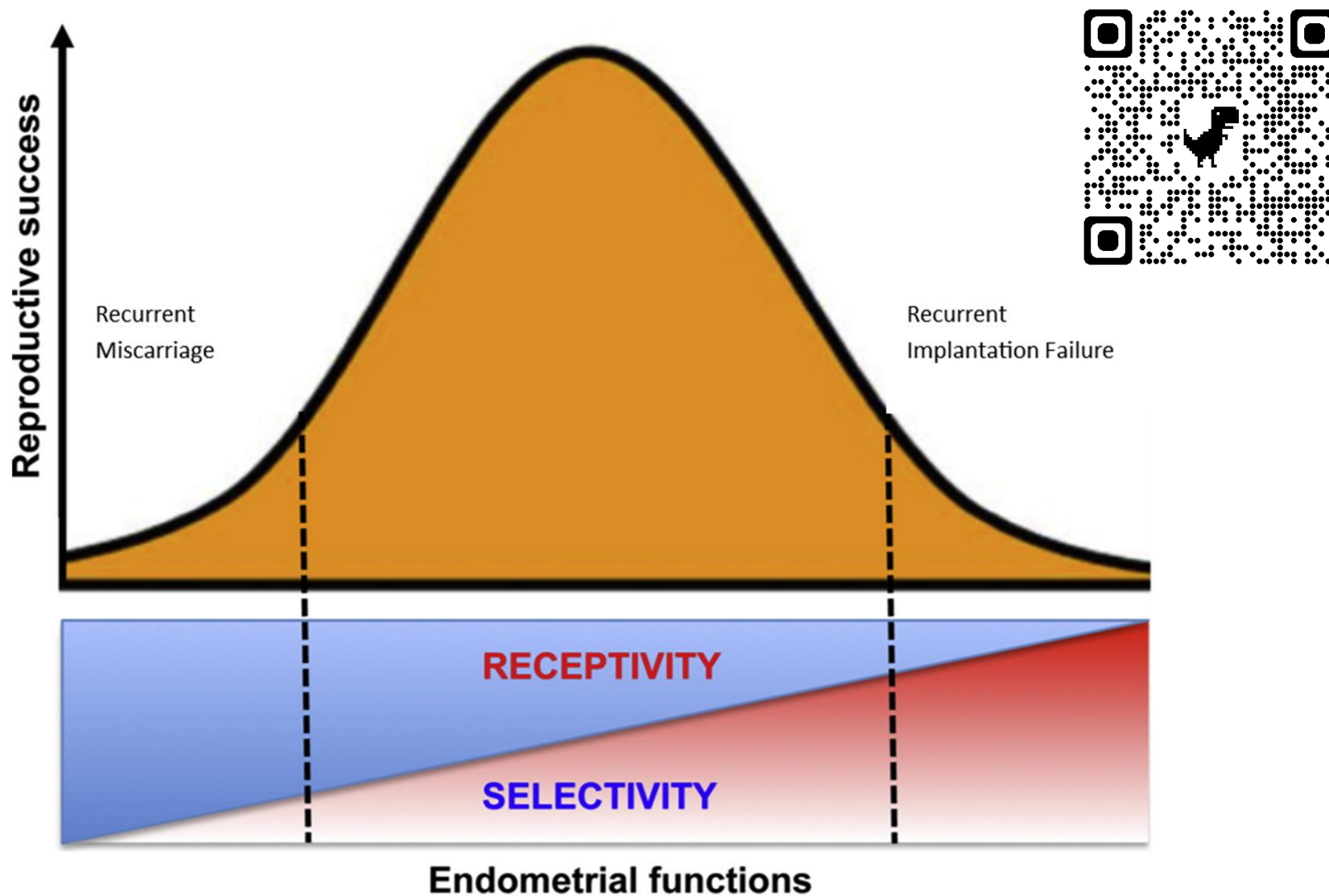
Implantation takes place with the **apposition** of the blastocyst at the endometrial epithelium. Blastocyst cannot be displaced anymore.

Blastocyst **adheres** to endometrial epithelium and establish a stable connection, mediated by adhesion molecules, pinopodes and signaling factors.

Trophoectodermic cells **invade** the epithelial layer until the underlined stroma. Production of proteases facilitates the process and enables nutrition from maternal vascular system.

Endometrial receptivity during the implantation window requires a complex interaction by multiple agents. By an accurate and detailed identification of the implantation markers, due to the latest techniques of molecular medicine, will be possible, in the future, to identify the unknown obstacles of implantation and predict a positive pregnancy outcome.





Schematic representation of the possible clinical consequences of an imbalance between the selective and receptive functions of the decidualized endometrium. While excessive receptivity and poor selectivity may result in inadequate implantation of low-viable embryos, which may manifest as recurrent early pregnancy loss and recurrent implantation failure.

Recurrent implantation failure (RIF)) ESHRE

	Maternal age	Implantation rate / pregnancy rate ¹	Cumulative likelihood of implantation for each embryo transfer (embryos of unknown euploidy)						RIF THRESHOLD of >60%
			FIRST ET (n=1)	SECOND ET (n=2)	THIRD ET (n=3)	FOURTH ET (n=4)	FIFTH ET (n=5)	SIXTH ET (n=6)	
Embryos of unknown euploidy	<35	31,5	31,5	53,1	<u>67,9</u>	78,0	84,9	89,7	Intervene after 3 ETs
	35-39	25,9	25,9	45,1	59,3	<u>69,9</u>	77,7	83,4	Intervene after 4 ETs
	≥40	15	15,0	27,8	38,6	47,8	55,6	<u>62,3</u>	Intervene after 6 ETs
Euploid embryos	<35	68,4	<u>68,4</u>	90,0	96,8	99,0	99,7	99,9	Intervene after 2 ETs
	35-40	64,1	<u>64,1</u>	87,1	95,4	98,3	99,4	99,8	Intervene after 2 ETs
	>40	58,0	58,0	<u>82,4</u>	92,6	96,9	98,7	99,5	Intervene after 2 ETs

1

Epidemiology

8 – 33% - Recurrent Implantation Failure-update overview on etiology, diagnosis, treatment and future directions. Asher Bashiri. Reprod Biol Endocrinol. 2018;

50% of embryo transfers were asynchronous in women <35 years old, which is significantly lower compared to 68.1%, which were asynchronous in women >35 years old. (Shapiro B.S 2016)

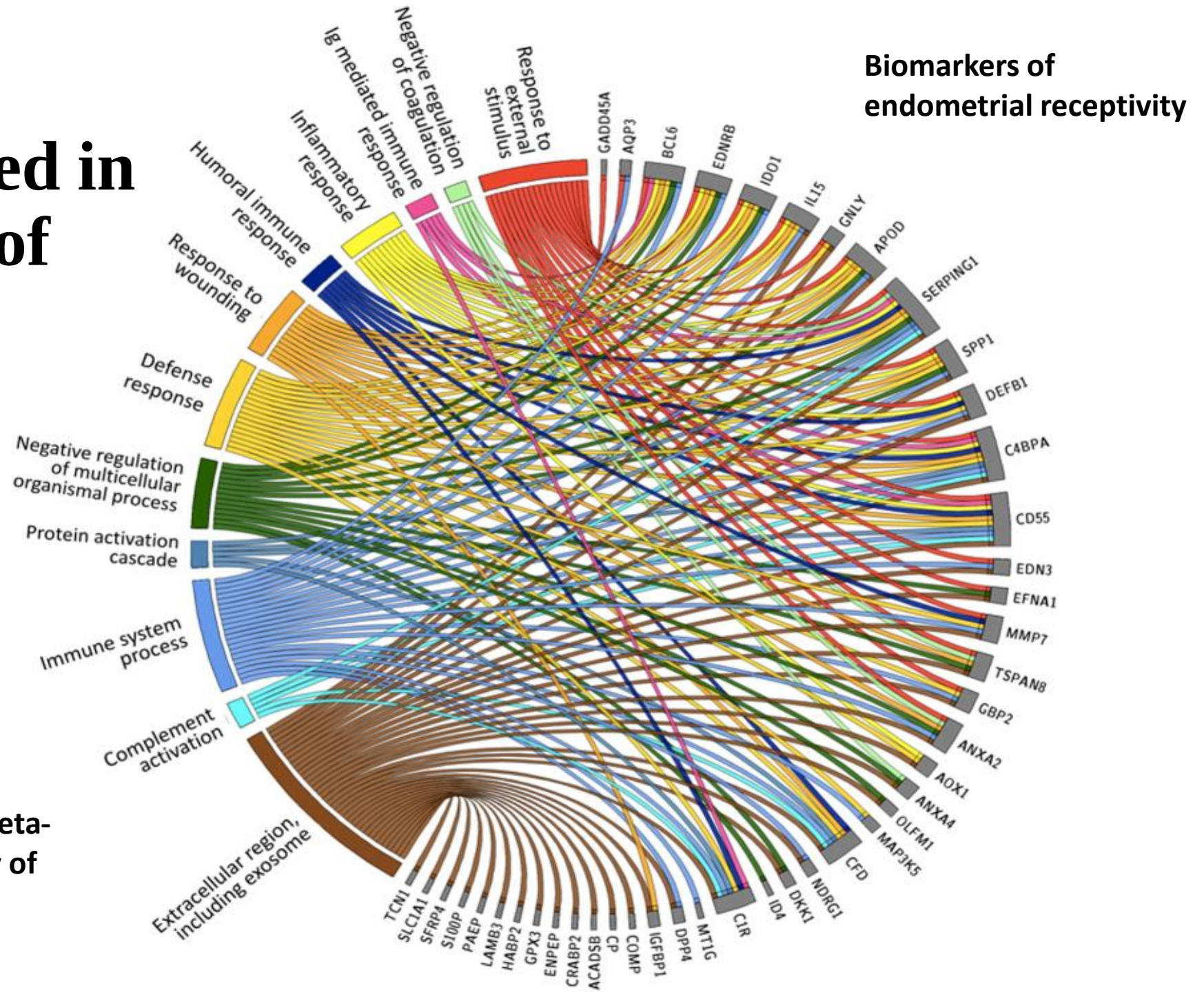
Biochemical pregnancy is actually not uncommon, and its reported incidence ranges from 8 to 33% in the general population, including those who become pregnant spontaneously (Maesawa Y, et al.. 2015 r.)

Pregnancy loss is common, occurring in 30% of conceptions and 10% of clinically recognized pregnancies.(Wilcox AJ. et al. 2013)

RIF – PERSONA (CGH) – 10% - 2016; 8% - 2017; 7,7% - 2018.... We are expecting 5% from 2023

Factors involved in the formation of the receptive endometrium

Meta-signature of human endometrial receptivity: a meta-analysis and validation study of transcriptomic biomarkers.
Signe Altmäe, 2017



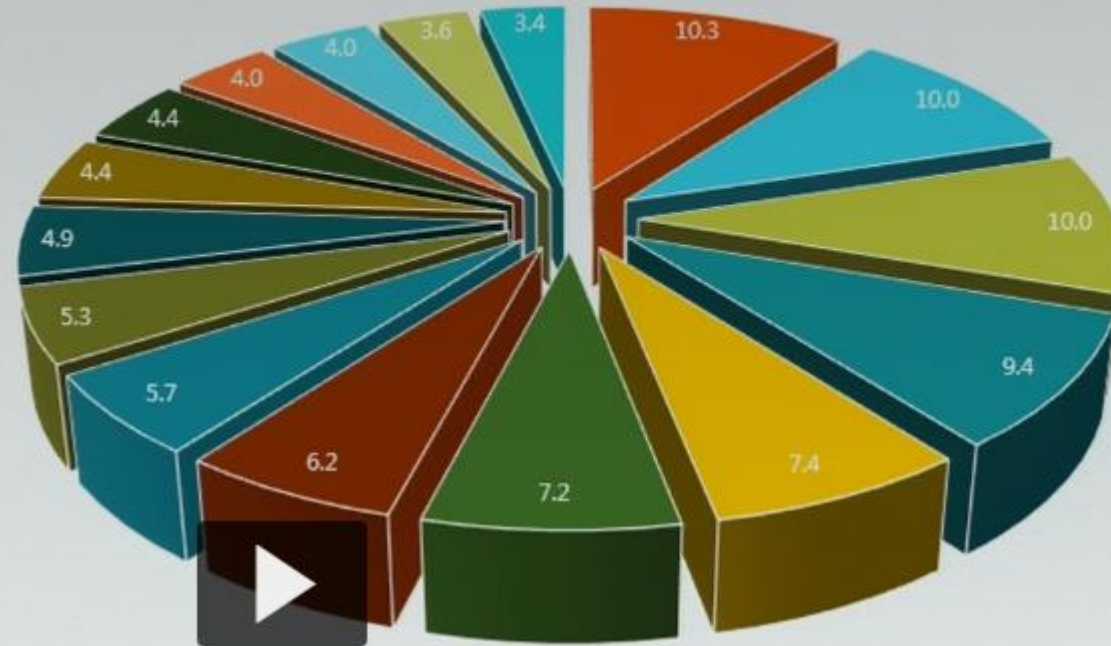
Regulatory genes

RNA-Seq GO analysis



*Used GO Slim analysis on
differentially regulated
genes.*

*Complete deregulation of
basic cell responses including
proliferation, differentiation,
transport, signalling and cell
cycle related processes.*



- Signal transduction
- Metabolic process
- Cell differentiation
- Response to stress
- Apoptosis/Cell death
- Cell proliferation
- Immune system process
- Locomotion

- Anatomical structure development
- Biosynthetic process
- Transport
- Protein modification process
- Small molecule metabolic process
- Catabolic process
- Cell cycle
- Cellular component assembly

ORIGINAL ARTICLE | VOLUME 118, ISSUE 4, P724-736, OCTOBER 2022

 Download Full Issue

 PDF [789 KB]

 Figures

ORIGINAL

 Do

Use of the endometrial receptivity array to guide personalized embryo transfer after a failed transfer attempt was associated with a lower cumulative and per transfer live birth rate during donor and autologous cycles

Mauro Cozzolino, M.D.   • Patricia Díaz-Gimeno, Ph.D. • Antonio Pellicer, M.D., Ph.D. • Nicolas Garrido, M.Sc., Ph.D.

Published: September 04, 2022 • DOI: <https://doi.org/10.1016/j.fertnstert.2022.07.007> •

 Check for updates

REFLECTION

 Downl

End of an endometrial receptivity array?

Marika Raff, M.D. • Emily Jacobs, M.D. • Brad Van Voorhis, M.D.

Published: September 05, 2022 • DOI: <https://doi.org/10.1016/j.fertnstert.2022.07.031> •

 Check for updates

 PlumX Metrics

be Claim

 Advanced search

 Request



Endometrial diagnostic methods in Kazakhstan

- CD 138 (Syndecan 1), CD 20 (B-cell marker), CD 8 (T cells)
- LIF -Leukemia inhibitory factor (HILDA)
- Pinopode
- E2 and P4 receptors
- Integrin $\alpha v \beta 3$

Over 4 years, 3484 patients were examined using 15607 different IHCs.

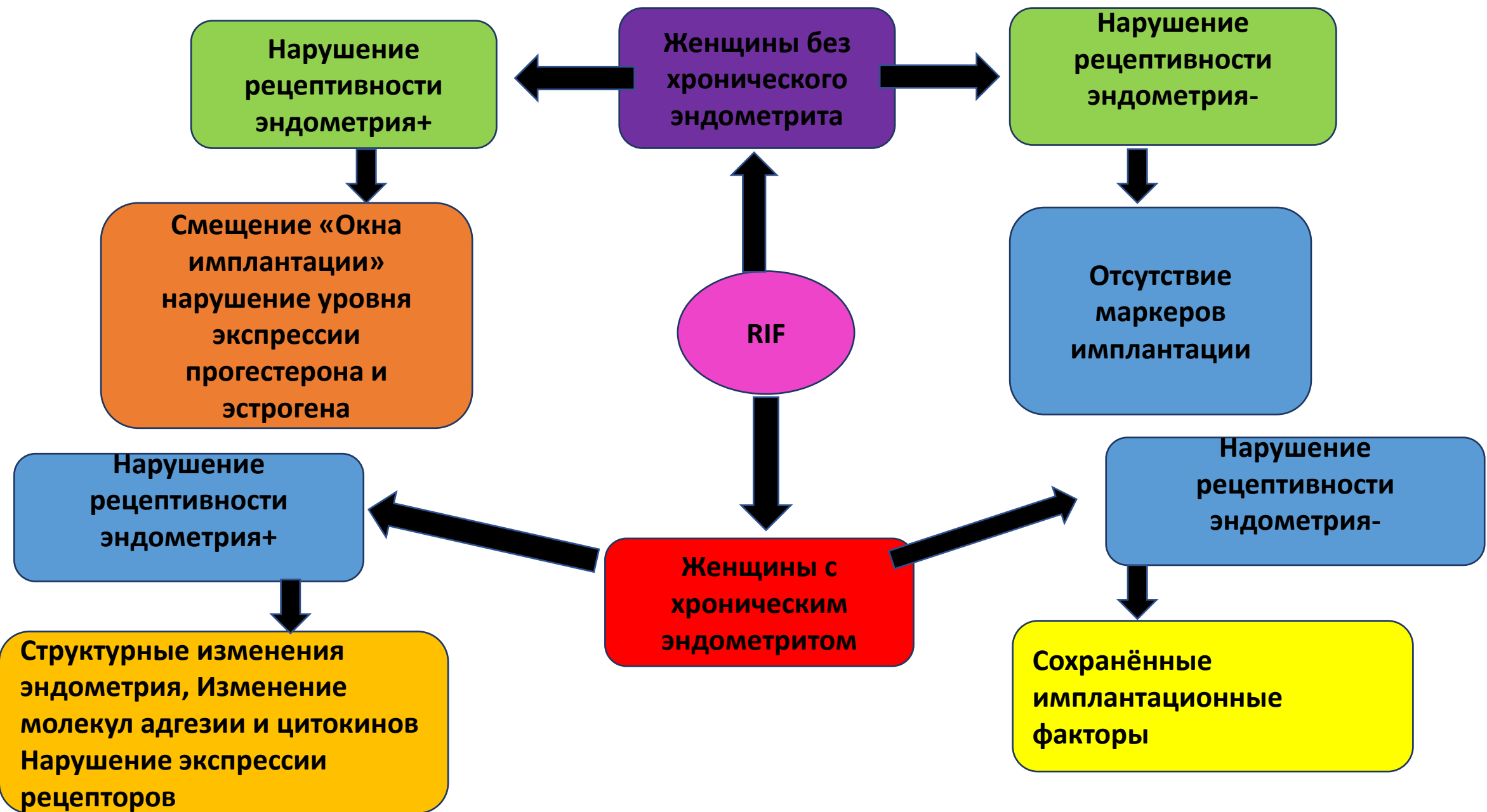
If RIF is suspected in the couple

Follow up with RIF-specific investigations

ESHRE – 2023 год

RECOMMENDED	Re-assessment of lifestyle factors	♀♂
	Re-assessment of endometrial thickness	♀
	Assessment of APA and APS in case of risk factors ¹	♀
CAN BE CONSIDERED	Karyotyping (both partners) ²	♀♂
	3D US/hysteroscopy	♀
	Endometrial function testing	♀
	Chronic endometritis testing	♀
	Assessment of thyroid function	♀
	Progesterone levels (late follicular/mid-luteal)	♀
NOT RECOMMENDED	Vitamin D testing	♀
	Microbiome profiling	♀
	Peripheral NK cell testing	♀
	Uterine NK cell testing	♀
	Uterine T lymphocytes assessment	♀
	Assessment of blood cytokine levels	♀
	Assessment of HLA-C compatibility	♀
	Assessment of mtDNA content	⊗
	Sperm DNA fragmentation/ FISH analysis	♂

1. Endometrial receptivity: Decreased (LIF); Changes in $\alpha v\beta 3$, $\alpha 4\beta 1$ and $\alpha 1\beta 1$ levels during the implantation window (integrins)
2. P4 level (3) FET not less 10 ng/mL



"Not everything is straightforward... Do you need anything presented in the form of graphs?"

Смещение «Окна имплантации» нарушение уровня экспрессии прогестерона и эстрогена

тегі, аты, әкесінің аты (фамилия, имя, отчество) _____ Жынысы: ер, әйел (астын сызыңыз) (Пол: (муж, жен подчеркнуть))

3. Науқастың туылған күні (Дата рождения пациента) 02.10.1990 _____ Қызмет көрсету тобы (группа обслуживания) _____

4. Азаматтық (гражданство) Республика Казахстан _____ ПАТАЛОГО-АНАТОМИЧЕСКИЙ ОТДЕЛ, ПАТОЛОГО-АНАТОМ ОТДЕЛЕНИЕ, ПАРАКЛИНИКА, АО "ЦКБ"

5. Бөлімше (Отделение) _____ Дәрігердің тегі, аты, әкесінің аты (Ф.И.О. врача) Даирбекова Ж.,врач-патологоанатом(ПАТАЛОГО-АНАТОМИЧЕСКИЙ ОТДЕЛ)

6. Жолдаманы жасаған күні, айы, жылы мен сағаты (Дата и время создания направления) 04.12.2023 12:11 _____

7. Материалдың лабораторияға түскен күні мен уақыты (дата и время поступления материала в лабораторию) 04.12.2023 12:18 _____

8. Биопсияның түрі (диагностикалық,жедел биопсия, операциялық материал) Вид биопсии(диагностическая,срочная биопсия, операционный материал) _____

9. Кесектер саны (Количество кусочков) 1 _____ Блоктардың саны (количество блоков) 1 _____ Бояу әдістемесі (Методика окраски) _____

10. Макро және микроскопиялық сипаттау (Макро-и микроскопическое описание):
Гистологическое исследование (окраска Г-Э): №187 В препарате единичный мелкий фрагмент эндометрия ранней стадии фазы секреции. Покровный эндометриальный эпителий представлен в единичном поле зрения в виде мелкого обрывка, с набухшими клетками, без бугорковых выпячиваний. В присланном материале покровный эпителий малочислен бугорковых выпячиваний развитых пиноподий в умеренном количестве.
Иммуногистохимическое исследование: LIF -35% окрашенных клеток, с умеренно выраженной экспрессией - 4 балла (норма 10 баллов);
CD138 в строме эндометрия - единичные клетки с умеренно выраженной экспрессией, до 1 клетки в поле зрения (при увеличении микроскопа 40x0.65; в норме - отрицательно)

P4 - 6

3. Науқастың туылған күні (Дата рождения пациента) 02.10.1990 _____ Қызмет көрсету тобы (группа обслуживания) _____

4. Азаматтық (гражданство) Республика Казахстан _____ ПАТАЛОГО-АНАТОМИЧЕСКИЙ ОТДЕЛ, ПАТОЛОГО-АНАТОМ ОТДЕЛЕНИЕ, ПАРАКЛИНИКА, АО "ЦКБ"

5. Бөлімше (Отделение) _____ Дәрігердің тегі, аты, әкесінің аты (Ф.И.О. врача) Даирбекова Ж.,врач-патологоанатом(ПАТАЛОГО-АНАТОМИЧЕСКИЙ ОТДЕЛ)

6. Жолдаманы жасаған күні, айы, жылы мен сағаты (Дата и время создания направления) 05.12.2023 11:16 _____

7. Материалдың лабораторияға түскен күні мен уақыты (дата и время поступления материала в лабораторию) 05.12.2023 11:33 _____

8. Биопсияның түрі (диагностикалық,жедел биопсия, операциялық материал) Вид биопсии(диагностическая,срочная биопсия, операционный материал) _____

9. Кесектер саны (Количество кусочков) 1 _____ Блоктардың саны (количество блоков) 1 _____ Бояу әдістемесі (Методика окраски) _____

10. Макро және микроскопиялық сипаттау (Макро-и микроскопическое описание):
Гистологическое исследование (окраска Г-Э): №1197 В препарате разрозненные фрагменты эндометрия средней стадии фазы секреции. Покровный эндометриальный эпителий с анличием бугорковых выпячиваний развитых пиноподий в умеренном количестве.
Иммуногистохимическое исследование: LIF -75-78% окрашенных клеток, с умеренно выраженной экспрессией - 8 баллов (норма 10 баллов)

P4 - 8

Отсутствие маркеров имплантации

Гистологическое исследование (окраска Г-Э): №685 В препарате мелкие фрагменты эндометрия средней стадии фазы пролиферации с очагами фиброзирования стромы, выраженных вокруг желез. В покровном эндометриальном эпителие определяются единичные клеточные выросты.

Иммуногистохимическое исследование: LIF 15% окрашенных клеток, с умеренно выраженной экспрессией-2 балла (норма 10 баллов);
CD138 в строме эндометрия —очагово расположенные клетки с умеренно выраженной экспрессией, до 2 клеток в поле зрения (при увеличении микроскопа 40x0,65; в норме — отрицательно);
CD8 в строме эндометрия —очагово и диффузно расположенные клетки с умеренно выраженной экспрессией, до 18-27 клеток в поле зрения; (при увеличении микроскопа 40x0,65; в норме — до 10 клеток);
CD20 в строме эндометрия —очагово расположенные клетки с умеренно выраженной экспрессией, до 4 клеток в поле зрения (при увеличении микроскопа 40x0,65; в норме — до 3 клеток);

Маркер	H-score-тест
ER в железах эндометрия	Неравномерно от 300 до 270
ER в строме эндометрия	Неравномерно от 270 до 210
PR в железах эндометрия	Неравномерно от 300 до 270
PR в строме эндометрия	Неравномерно от 270 до 240

Иммуногистохимическое исследование: LIF -25% окрашенных клеток, с умеренно выраженной экспрессией-3 балла (норма 10 баллов);
CD138 в строме эндометрия — отрицательная реакция (в норме — отрицательно);

Маркер	H-score-тест
ER в железах эндометрия	Неравномерно от 300 до 270
ER в строме эндометрия	Материал скудный-равномерно 270
PR в железах эндометрия	Равномерно 240
PR в строме эндометрия	Материал скудный-равномерно 300

Нарушение рецептивности эндометрия-

Иммуногистохимическое исследование (ИГХ) реакция проводилась дважды, так как в первой реакции выраженный фоновый дефект): **LIF** –65-70% окрашенных клеток, с умеренно выраженной экспрессией-8 баллов (норма 10 баллов);

CD138 в строме эндометрия – очагово расположенные клетки с умеренно выраженной экспрессией, до 4-6 клеток в поле зрения (при увеличении микроскопа 40x0,65; в норме – отрицательно);

CD8 в строме эндометрия – диффузно и очагово расположенные клетки с умеренно выраженной экспрессией, до 30-38 клеток в поле зрения (при увеличении микроскопа 40x0,65; в норме – до 10 клеток);

CD20 в строме эндометрия – очагово расположенные клетки с умеренно выраженной экспрессией, до 6-8 клеток в поле зрения (при увеличении микроскопа 40x0,65; в норме – до 3 клеток);

Маркер	H-score-тест
ER в железах эндометрия	Неравномерно от 300 до 240
ER в строме эндометрия	Неравномерно от 270 до 210
PR в железах эндометрия	Неравномерно от 300 до 240
PR в строме эндометрия	Неравномерно от 270 до 240

Гистологическое исследование (окраска Г-Э): В препарате фрагмент эндометрия ранней стадии фазы секреции с очагами разрастания фиброзной ткани в строме. В покровном эндометриальном эпителие функционального слоя эндометрия определяются развивающиеся пиноподии, не менее 60% от общей площади поверхности.

Иммуногистохимическое исследование: **LIF** –80% окрашенных клеток, с умеренно выраженной экспрессией-8 баллов (норма 10 баллов);

CD138 в строме эндометрия – очагово расположенные клетки с умеренно выраженной экспрессией, до 6-9 клеток в поле зрения (при увеличении микроскопа 40x0,65; в норме – отрицательно).

CD8 в строме эндометрия – диффузно и очагово расположенные клетки с умеренно выраженной экспрессией, до 36-40 клеток в поле зрения (при увеличении микроскопа 40x0,65; в норме – до 10 клеток);

CD20 в строме эндометрия – очагово расположенные клетки с умеренно выраженной экспрессией, до 8-10 клеток в поле зрения (при увеличении микроскопа 40x0,65; в норме – до 3 клеток);

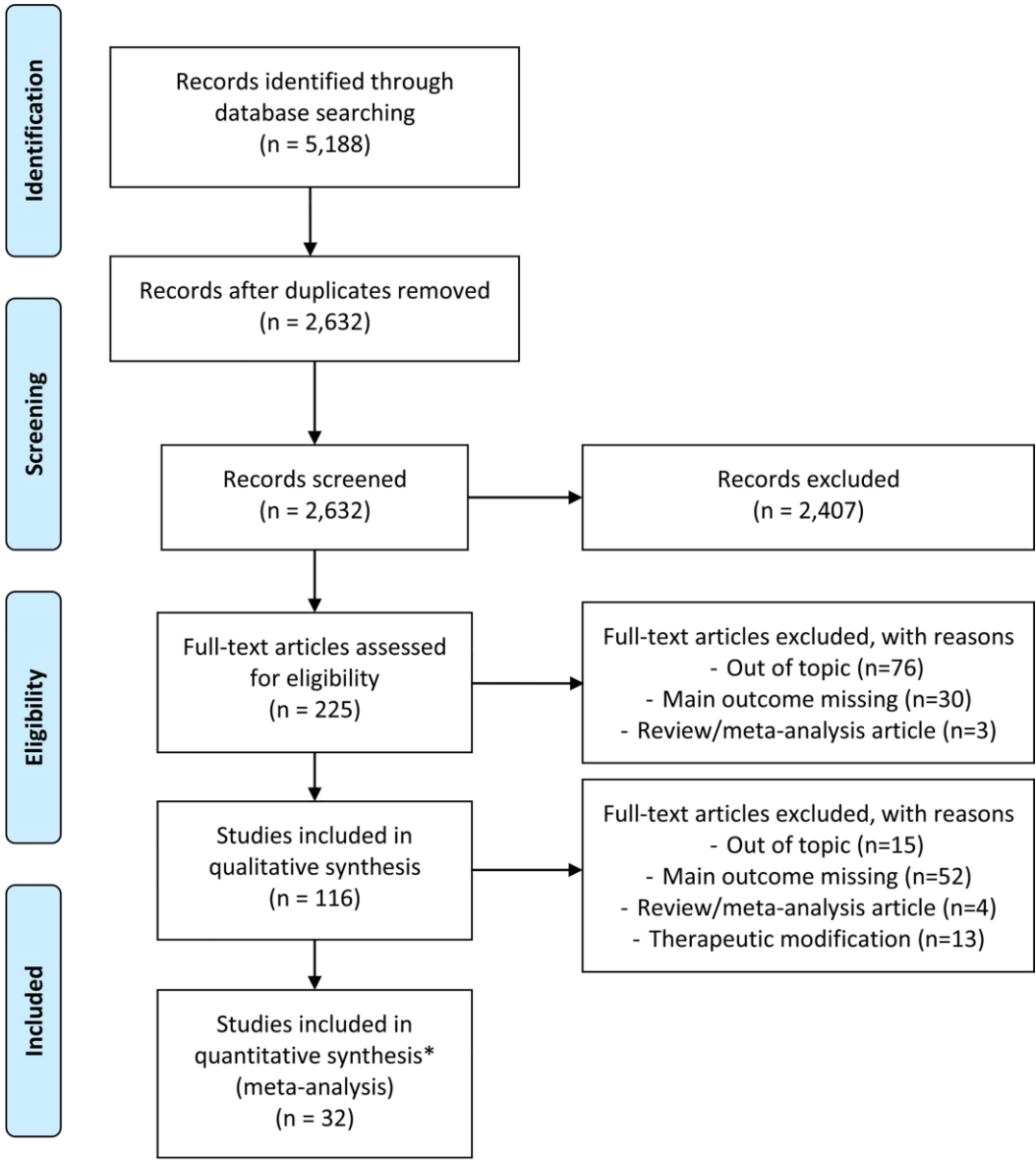
Basic postulates

- CE (minimal stromal fibrosis) – does not affect pregnancy, may affect gestation
- CE (stromal fibrosis) – leads to infertility due to a decrease in integrins and LIF – treatment
- After treatment of CE, the implantation window was restored - no problem
- After CE treatment, the implantation window has not been restored - treatment (or waiting up to 6 months - 1.5 years)
- After treatment with CE, the implantation window was restored with a shift in the time period +4 to + 8-9 from P4 – PET (or waiting up to 6 months - 1.5 years)



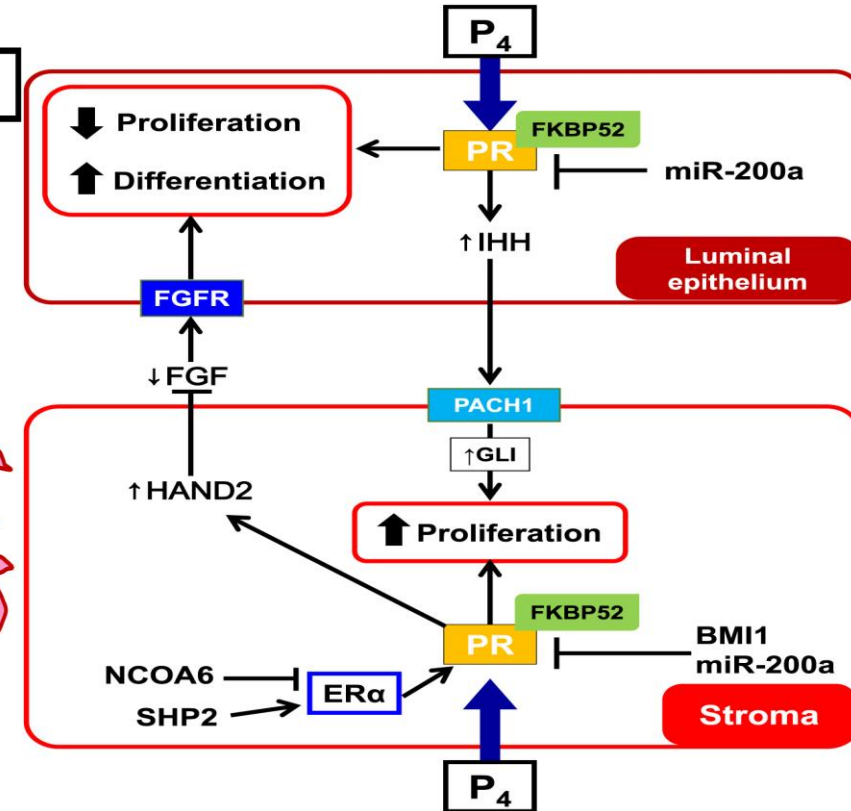
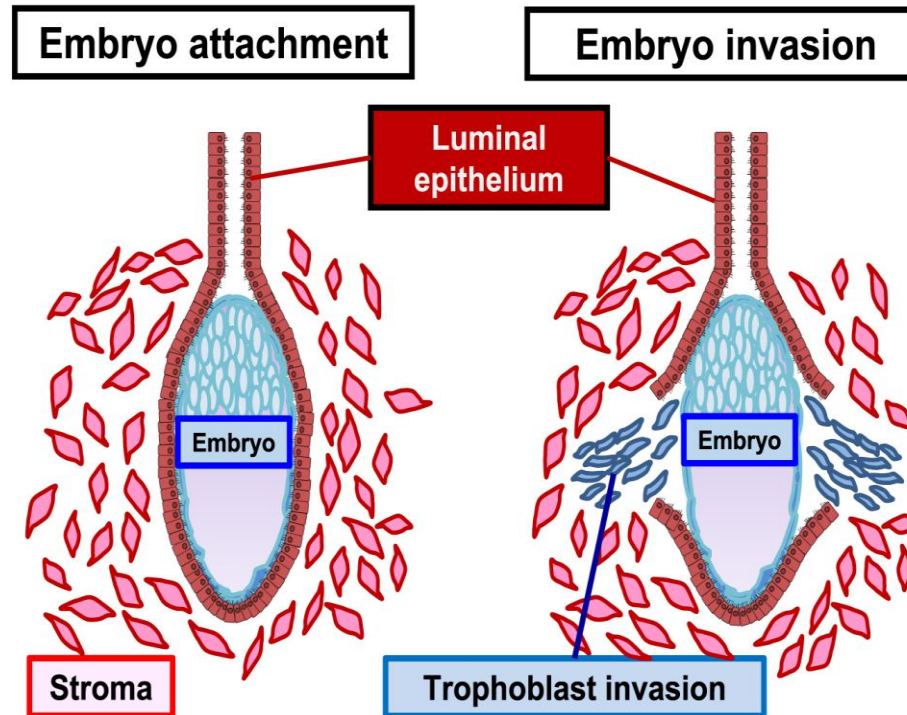
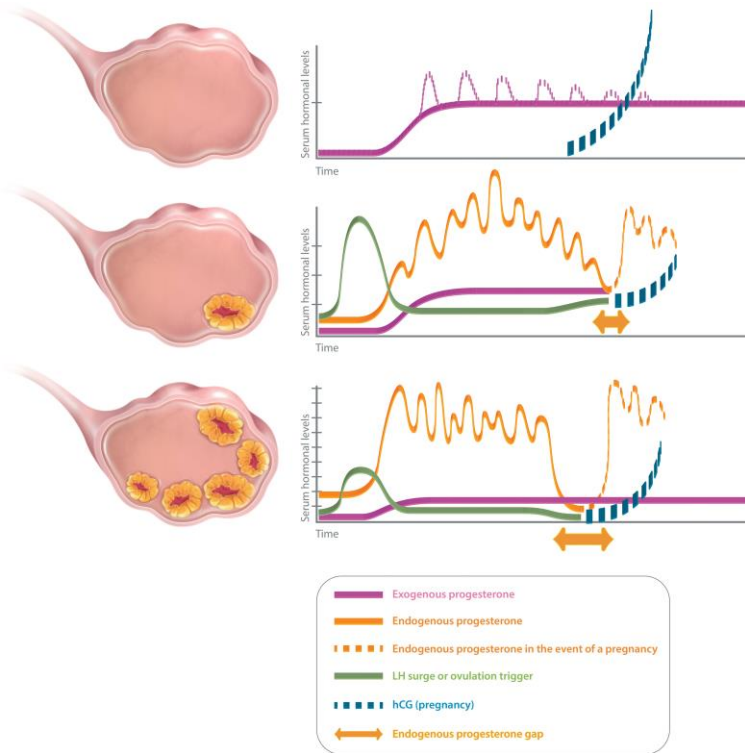
Low Luteal Serum Progesterone Levels Are Associated With Lower Ongoing Pregnancy and Live Birth Rates in ART: Systematic Review and Meta-Analyses

main statements



* regardless of the number of corpora lutea

What is already known

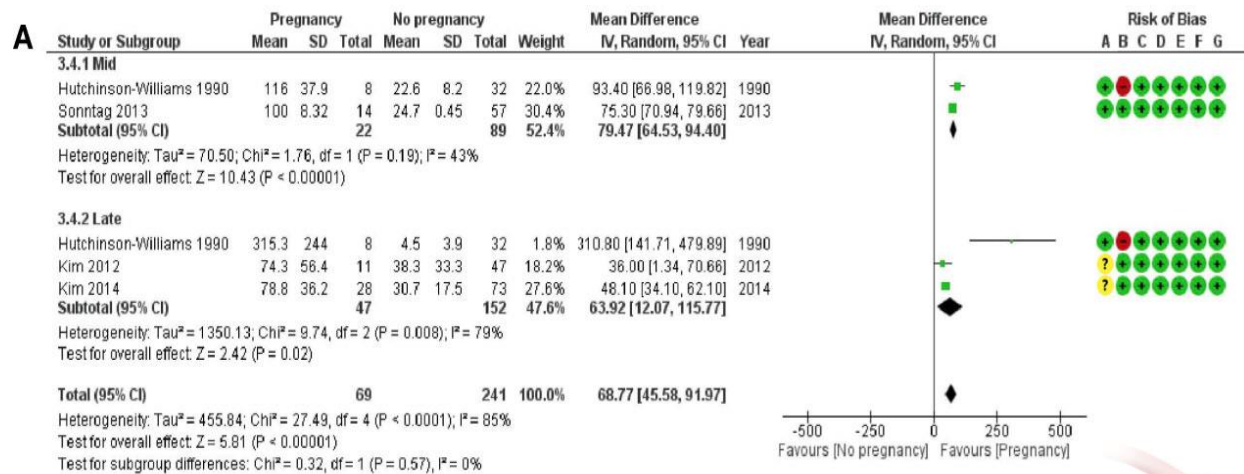


https://www.jstage.jst.go.jp/article/endocrj/66/3/66_EJ18-0431/_article

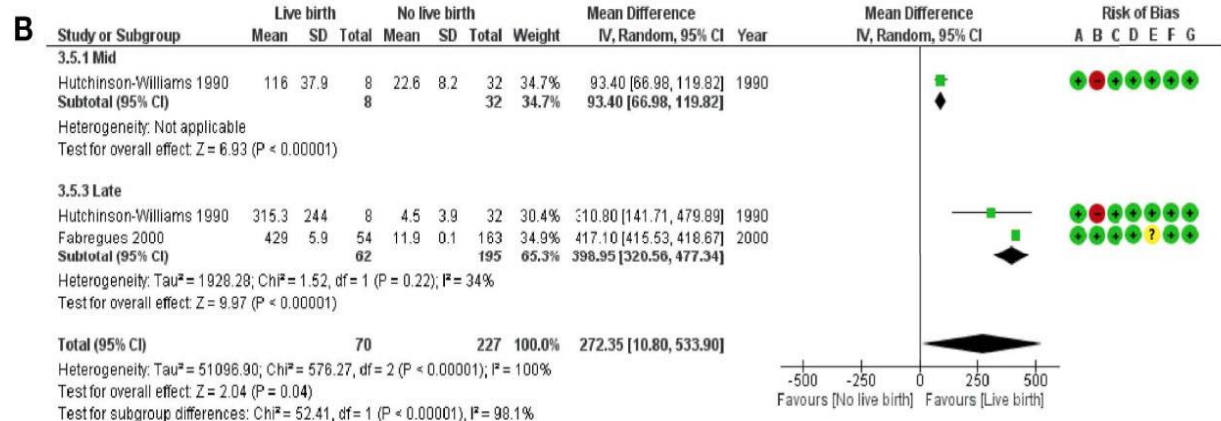
Embryo transfers performed 160 ± 4 hours after the hCG trigger or onset of the LH surge (estimated equivalent to 120 ± 4 hours after ovulation) were associated with a significantly higher LBR (relative risk (RR) 1.21, 95% CI 1.04–1.41).

<https://academic.oup.com/humrep/article-abstract/37/12/2797/6777824?redirectedFrom=fulltext&login=false>

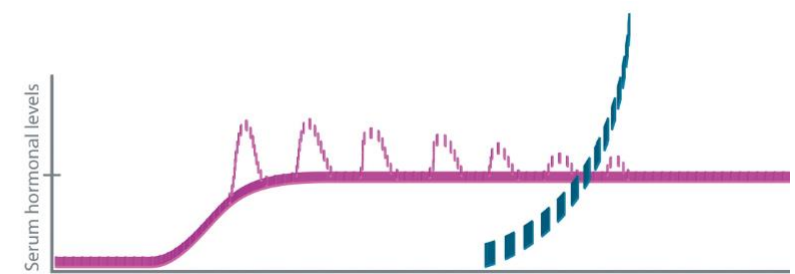
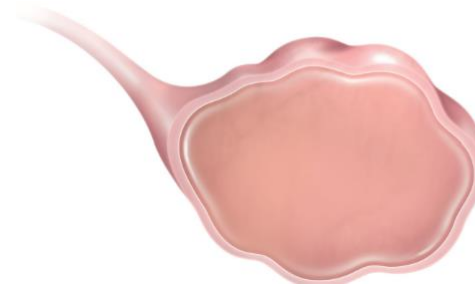
Group «FET HRT (vaginal progesterone)»



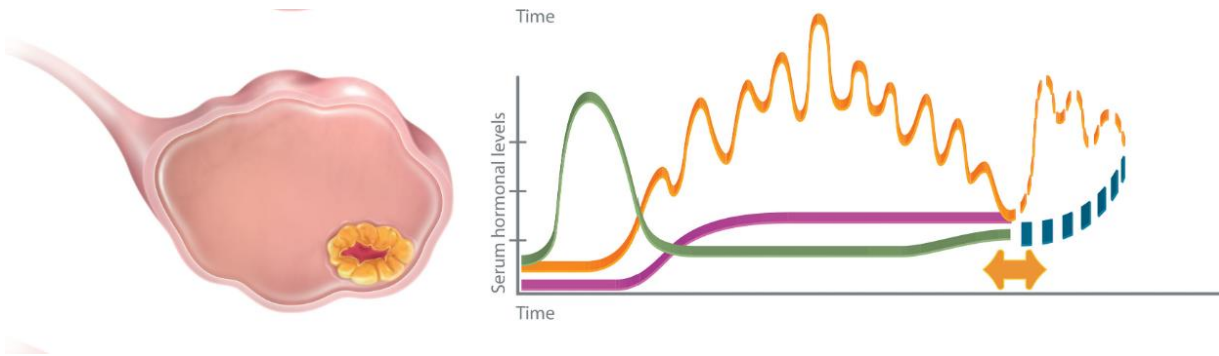
In most studies using vaginal progesterone, the optimal concentration of luteal progesterone is between 8 and 15 ng/ml Injection form – more than 10 ng/ml?; more than 20 ng/ml??
Progesterone deficiency – RIF or Miscarriage



progesterone concentration 1 day before embryo transfer above 15 ng/ml and/or estradiol concentration above 150 pg/ml



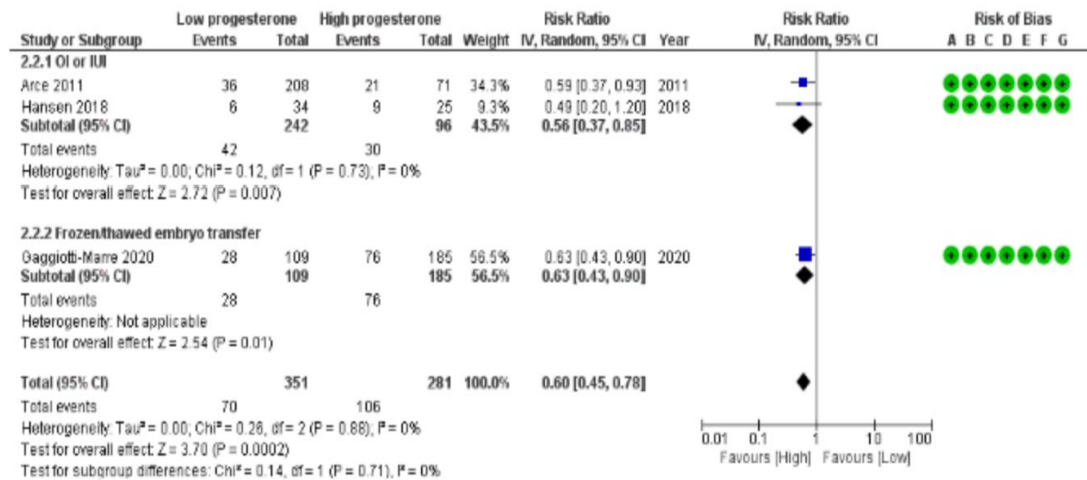
Group «one or few corpora lutea»



The combination of measurement of the serum LH peak and the early rise in serum luteal progesterone may be an interesting option for clinicians wishing to optimize the timing of natural cycle frozen-thaw embryo transfer

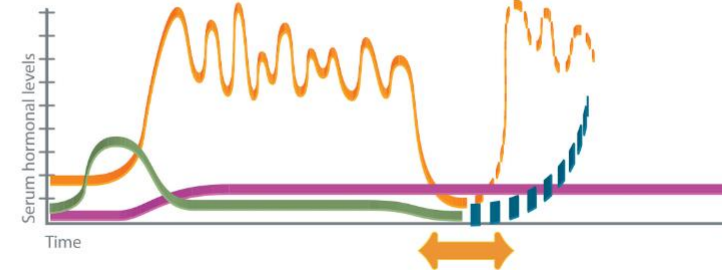
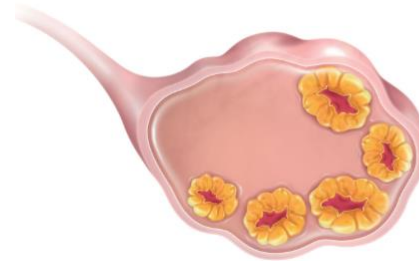
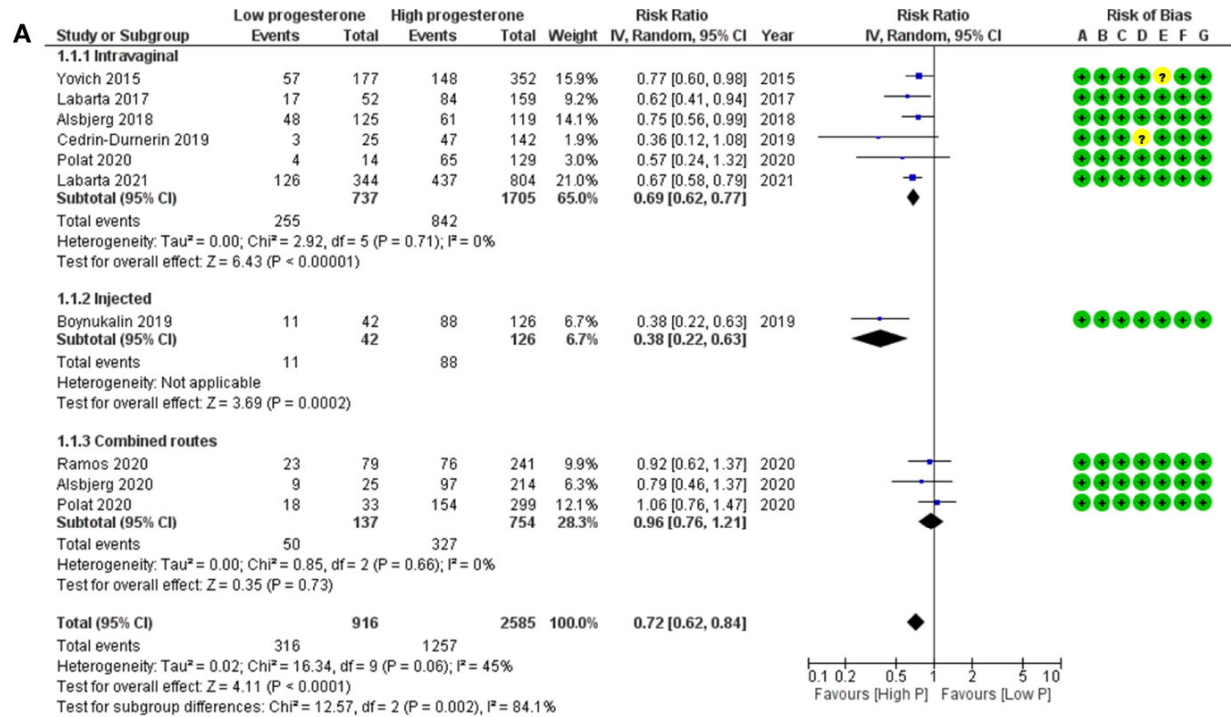
Supplemental Figure 2: Forest plot of studies “one or few corpora lutea” according to the transfer type for live birth.

Risks of bias legend: A, confounding; B, selection of participants; C, classification of intervention; D, deviations from intervention; E, missing data; F, measurement of outcome; G, selection of reported results.

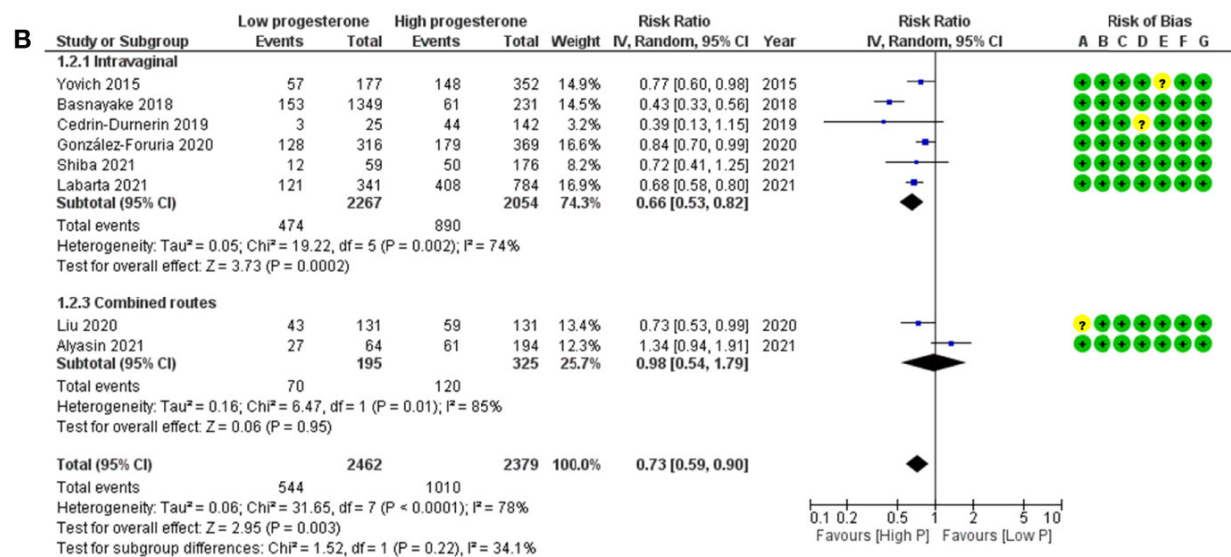


In natural cycles or in stimulated cycles with one or more corpora lutea, the interpretation of serum progesterone levels is challenging, as its secretion fluctuates widely throughout the day, with variations up to eightfold within 90 minutes, becoming more pronounced from the mid to late luteal phase. Women with low luteal progesterone levels had a significantly lower likelihood of live birth in cycles with one or more corpora lutea (OR, 95% CI: 0.60, 0.45–0.78) compared to women with high luteal progesterone levels.

Group «one or few corpora lutea»

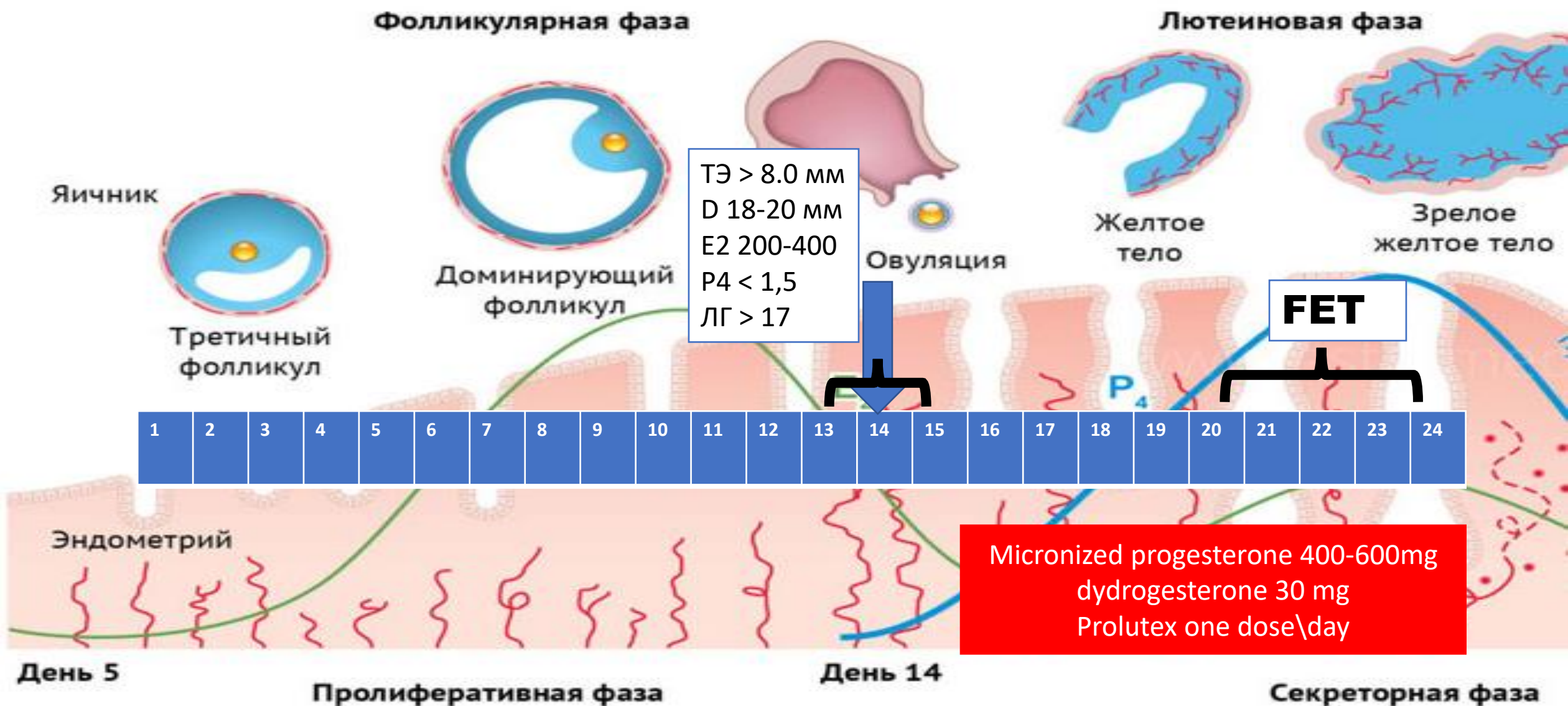


When comparing the groups with ongoing pregnancy and without pregnancy (95% CI), the progesterone concentration was 68.8 (45.6–92.0) ng/mL.

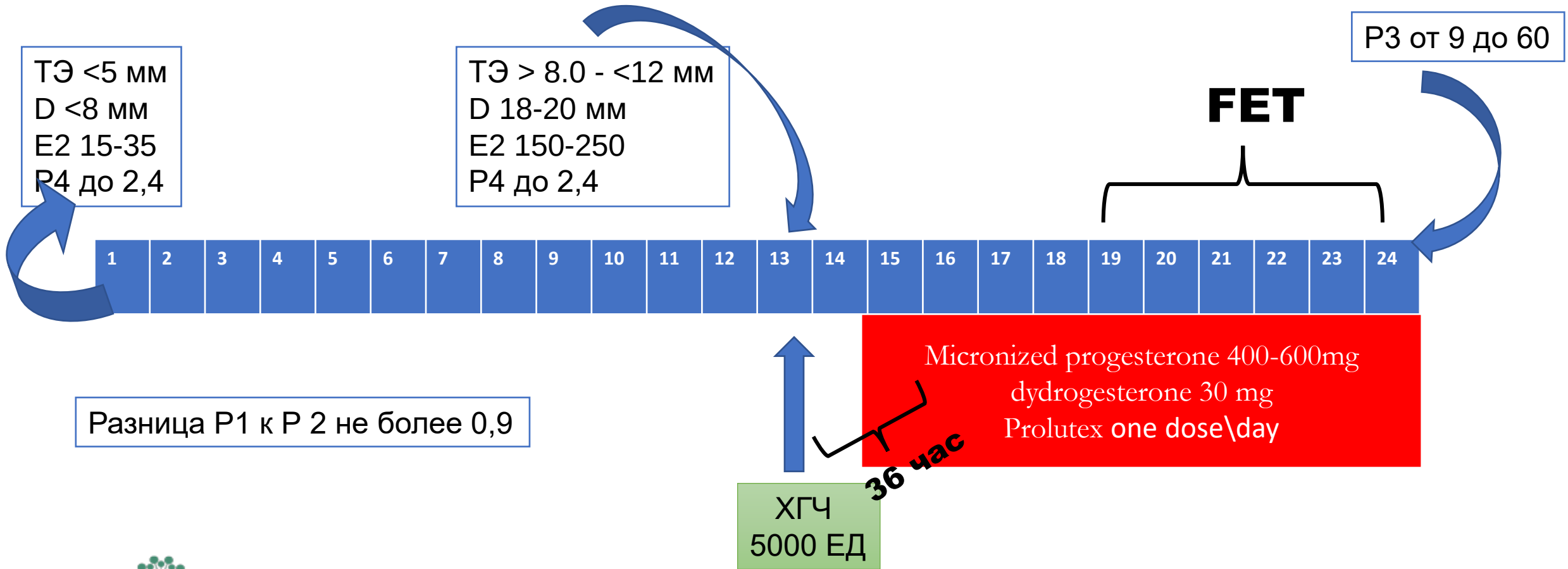


When comparing the live birth groups with the non-live birth groups (95% CI), the progesterone concentration was 272.4 (10.8–533.9) ng/mL.

Natural Cycle



Modified natural cycle





HRT- FET

ТЭ <4.0
Е2 от 10-60
Р4 до 2,4

ТЭ $\geq 8.0 < 12$
Е2 120-200
Р4 до 2,4

FET

Р3 от 10 до 60



Р1 к Р2 не более 0,9, лучше с отрицательной регрессией

Micronized progesterone 300-600mg
dydrogesterone 30 mg
Prolutex one dose\day

GnRH-a in HRT

TЭ < 4.0MM
E2 < 20
P4 < 1

TЭ ≥ 9.0 < 12
E2 200-400
P4 < 1,9

P3 от 12 до 60

FET



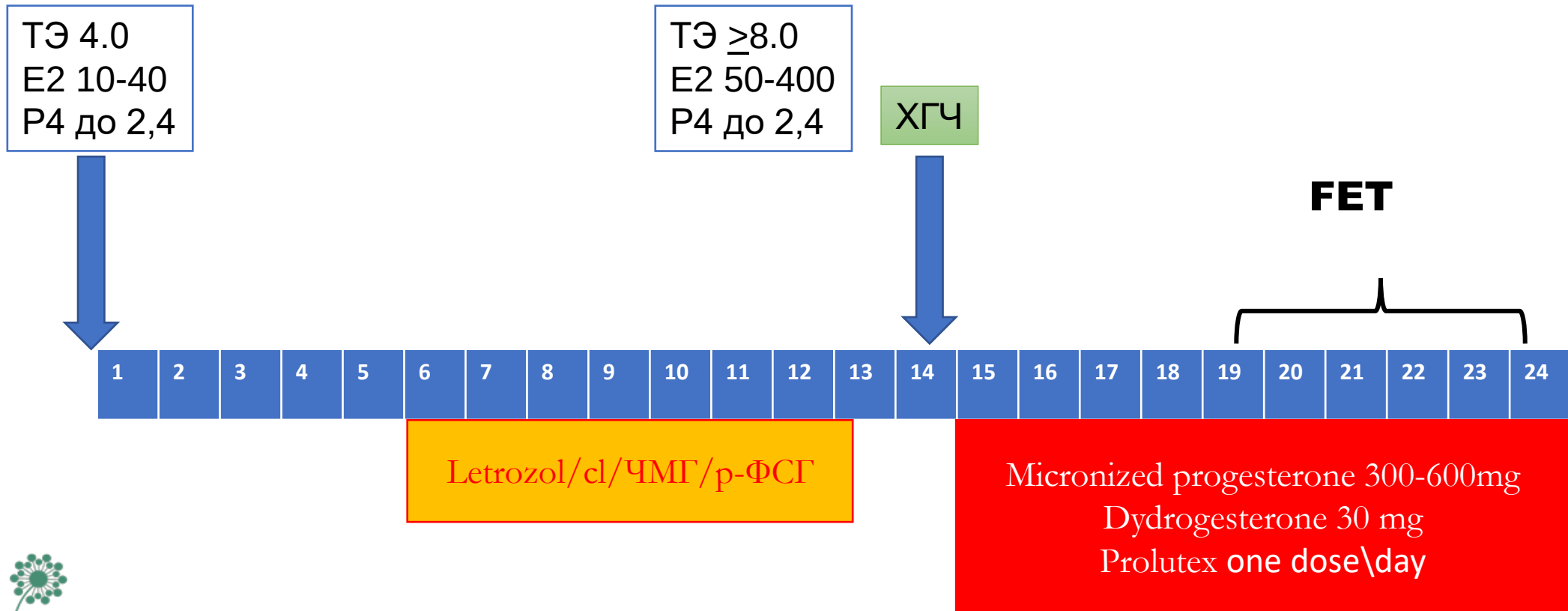
эстрадиол 2-12 mg

А-ГнРГ

19-22
Д.м.ц.

Micronized progesterone 300-600mg
Dydrogesterone 30 mg
Prolutex one dose\day

Mild-OS cycle for FET



Supplemental Table 2: GRADE tables for (A) « No corpus luteum », (B) « One or few corpora lutea » and (C) « Several corpora lutea »



(A)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty of evidence (GRADE)
Ongoing pregnancy	Low	High	Moderate	High	Moderate	⊕⊕
Live birth	Low	Moderate	High	High	Moderate	⊕⊕
Miscarriage	Low	Low	High	High	Low	⊕⊕

(B)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty of evidence (GRADE)
Live birth	Low	Moderate	Low	Low	Low	⊕⊕⊕

(C)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty of evidence (GRADE)
Ongoing pregnancy	Low	Moderate	Very low	Moderate	Very low	⊕
Live birth	Low	Moderate	Very low	Moderate	Very low	⊕



Выводы

Low levels of luteal progesterone had a significantly adverse effect on ongoing pregnancy and live birth rates in artificial cycles without a corpus luteum (CL), in cycles with one or more CLs, and possibly in stimulated cycles with multiple CLs

Unfortunately, the optimal progesterone threshold for combined administration routes has not yet been studied, and it is currently difficult to assess for oral dydrogesterone, which does not cross-react with progesterone measurements.

A recent study did not show a correlation between luteal serum progesterone levels and endometrial receptivity as assessed by the ERA test (Labarta E, Sebastian-Leon P, Devesa-Peiro A, Celada P, Vidal C, Giles J, et al. Analysis of Serum and Endometrial Progesterone in Determining Endometrial Receptivity. Hum Reprod (2021) 36:2861–70. doi: 10.1093/humrep/deab184). The underlying mechanism is not yet clearly defined and may involve more than just an "abnormal" implantation window.

It is also important to consider the possibility of progesterone absorption issues in some patients, especially in cases of recurrent implantation failure (RIF). Serum progesterone levels can vary depending on the assay used for its determination. Progesterone levels can indeed fluctuate over time, which is related to the method of administration and metabolism of the luteal support used (exogenous progesterone), as well as the pulsatile secretion of CL (endogenous progesterone).

