

Repeated Implantation Failure. The New Evidence

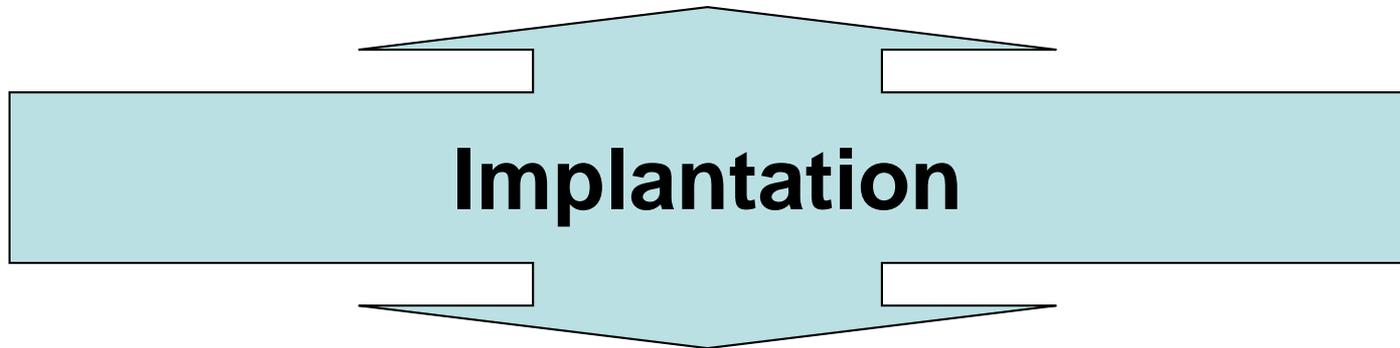


Antonis Makrigiannakis MD, PhD
Professor and Chairman
Dept of Ob/Gyn
University of Crete

Conflict of interest

- None

Embryo quality



Implantation

Endometrial receptivity

What is RIF

- **How many attempts?**
- How many embryos?
- Age?
- Embryo quality?
- Failure in the presence of potential obstacles?

RECURRENT IMPLANTATION FAILURE

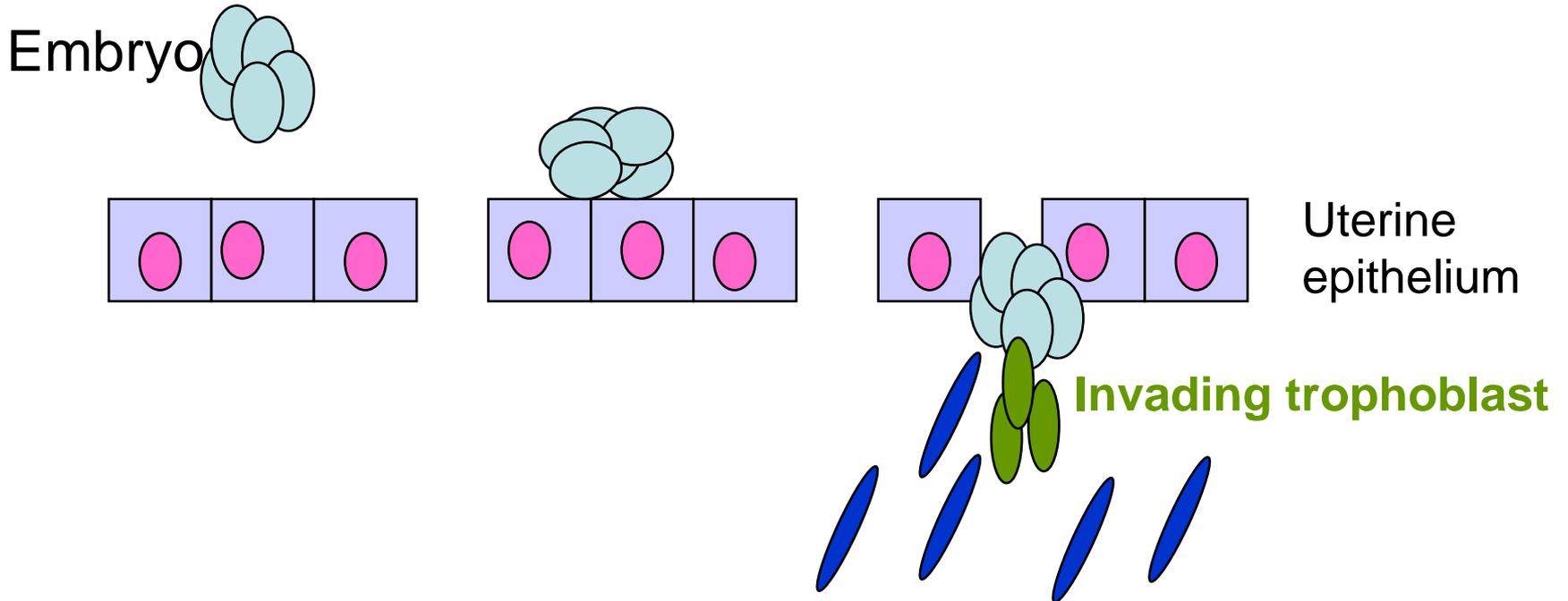
- Failure to achieve a pregnancy after 3 completed fresh IVF-ET cycles (Tan et al 2005)
- Failure of ≥ 10 embryos to implant
- In the era of SET/DET should the definition of RIF be revised

Implantation - key event in the establishment of pregnancy

Apposition

Adhesion

Invasion



Continuous process from conception to 22 weeks gestation

Implantation
Failure



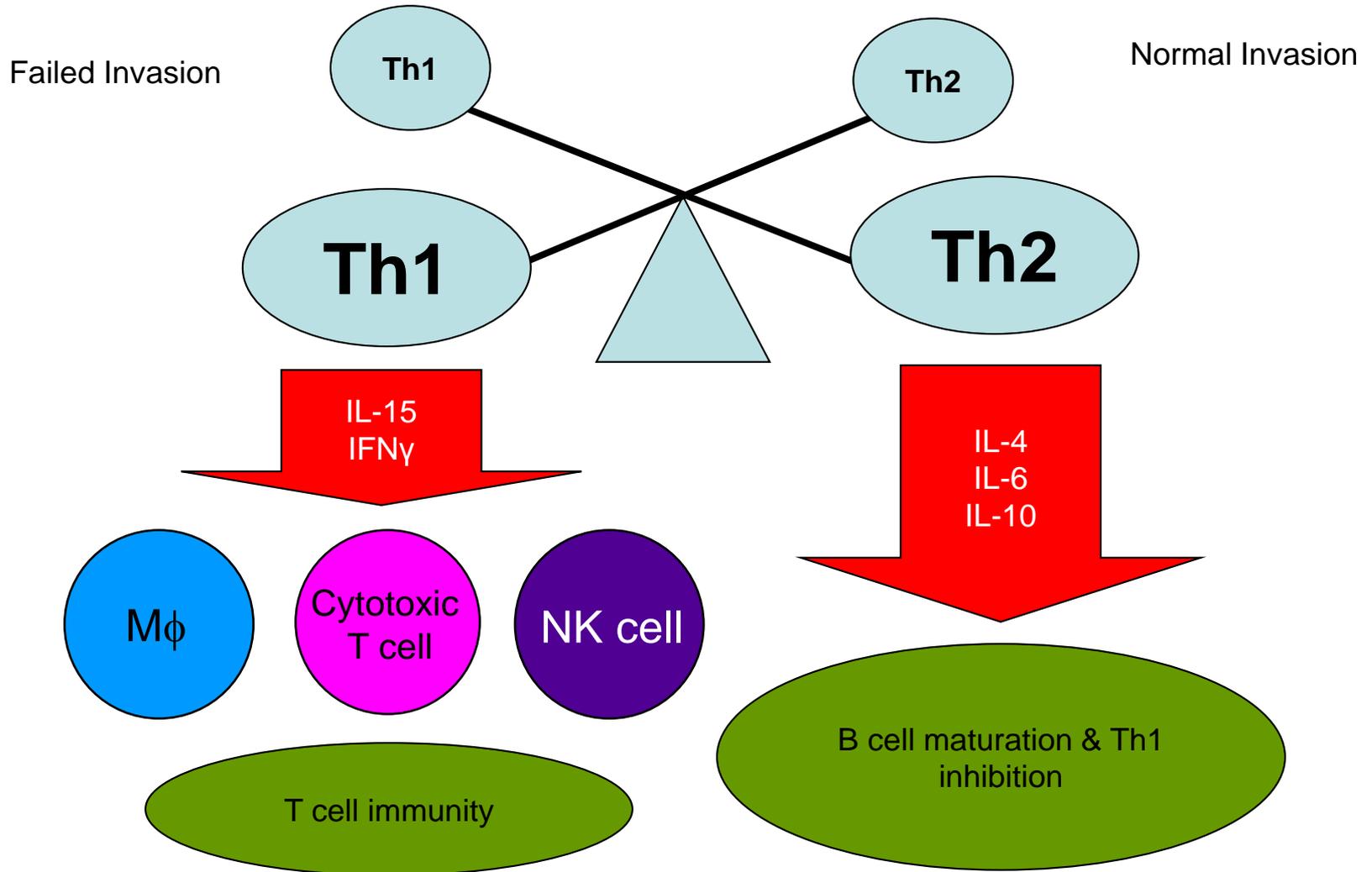
Early
Implantation

Miscarriages



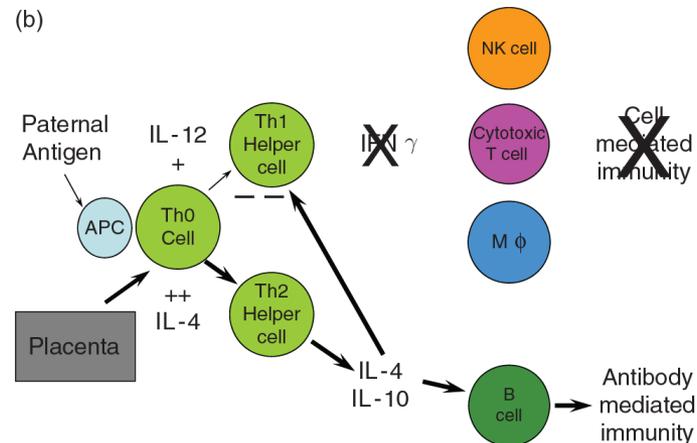
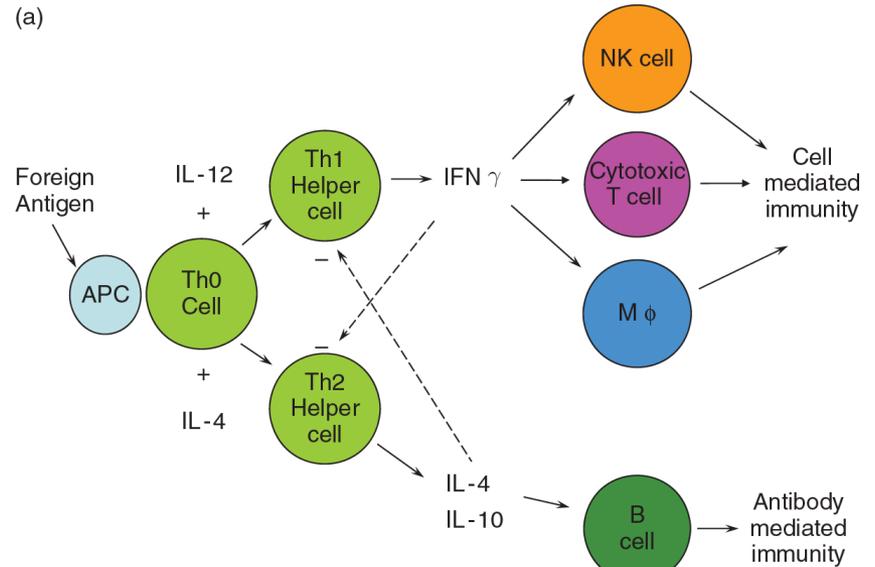
Late
Implantation &
placentation

The Th1/Th2 theory



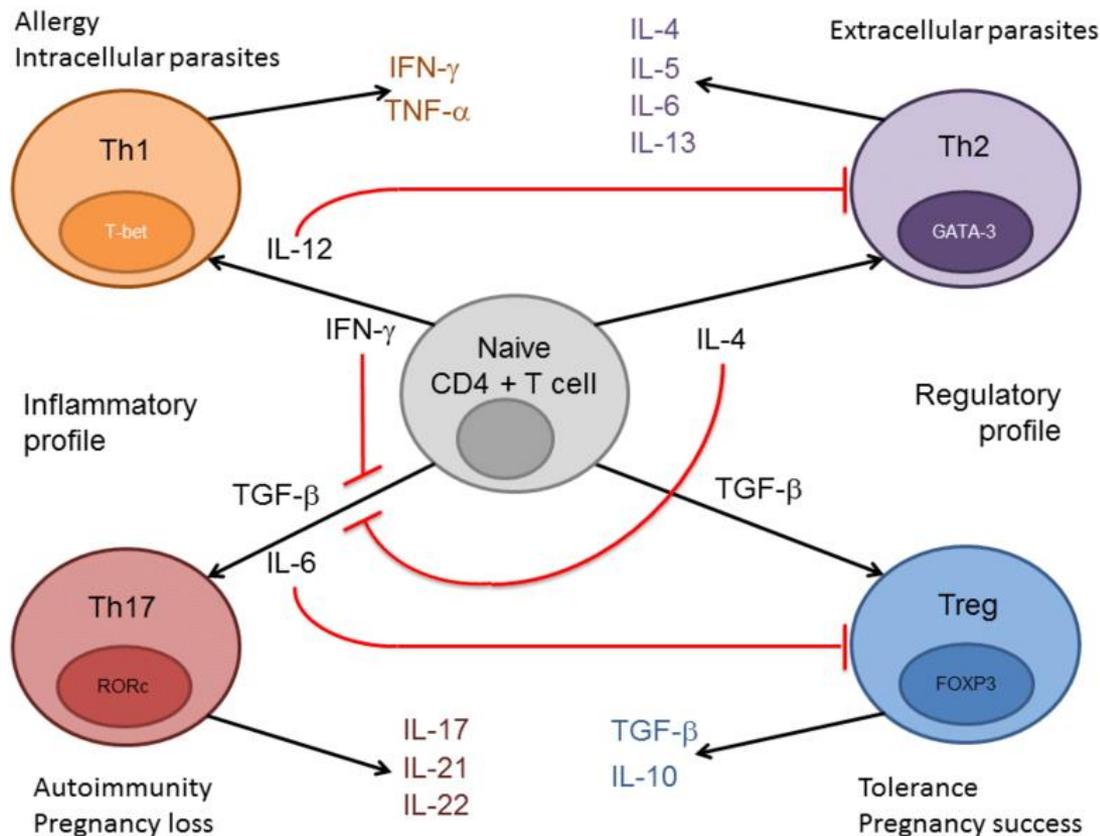
T cell profiling

The Th1 vs Th2 theory
Rather a simplified approach



T cell profiling

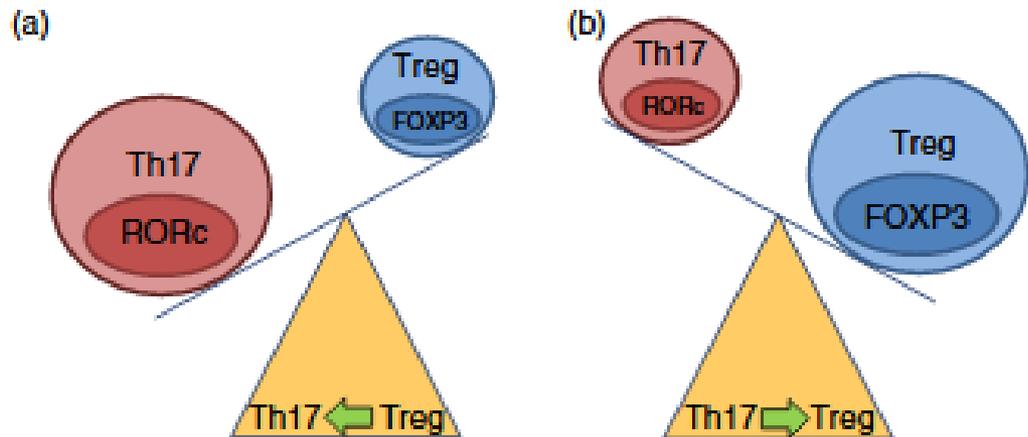
The role of Treg and Th17 immunity



The balance between Th17/Treg is defining immune tolerance during implantation

T cell profiling

The role of Treg and Th17 immunity



Pregnancy complications
(URPL, PE, PTB)
Autoimmunity
(SLE, RA, MS)

Successful pregnancy
(Tolerance of fetal alloantigens)
Self tolerance
(Tolerance of self antigens)

Treg immune profile favors immune suppression and therefore pregnancy

Th17 immune profile favors immune reactions and therefore it is considered against pregnancy

Novel approaches to modulate endometrial receptivity

TREATMENTS OF PROVEN BENEFIT



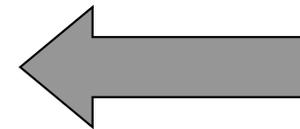
Endometrium : hysteroscopy
salpingectomy

Does endometrial scratching promote
implantation and live birth rates
in patients with RIF?

Possible mechanisms

No.	Description	Families	Accession no.	Fold increase	P
1	KIAA0367	Antiapoptosis	NM_015225	5.7/3.2	<.01
2	BCL2/adenovirus E1B 19kDa interacting protein 3-like (BNIP3L)	Antiapoptosis	NM_004331	2.5	<.01
3	Dual oxidase 1 (DUOX1)	Cell communication/ signal transduction	NM_017434 NM_175940	10.3	<.01
4	Annexin A3 (ANXA3)	Cell communication/ signal transduction	NM_005139	2.3	<.01
5	Crystallin, alpha B (CRYAB)	Cell communication/ signal transduction	NM_001885	3.1	<.01
6	Galanin (Gal)	Cell communication/ signal transduction	NM_015973	5.2	<.01
7	Cystatin SN (CST1)	Cell communication/ signal transduction	NM_001898	3.4	<.01
8	A disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 8 (ADAMTS8)	Extracellular matrix/ proteolysis	NM_007037	2.6/6.9	<.01
9	Cysteine-rich secretory protein 3 (CRISP3)	Cell adhesion molecules	NM_006061	8.7	.0178
10	Tissue factor pathway inhibitor 2 (TFPI2)	Immune/wound response	NM_006528	5.0	.0164
11	Toll-like receptor 5 (TLR5)	Immune/wound response	NM_003268	2.5	<.01
12	Uroplakin 1B (UPK1B)	Cell surface/ membrane	NM_006952	7.4/6.7	<.01
13	ADFP	Cell surface/ membrane	NM_001122	2.3	<.01
14	LAMP2	Cell surface/ membrane	NM_002294	2.1	<.01
15	MUC1	Cell surface/ membrane	NM_013995 NM_001018016 NM_001018017 NM_001018021 NM_002456	2.1	.029

Genes up-regulated by endometrial biopsy

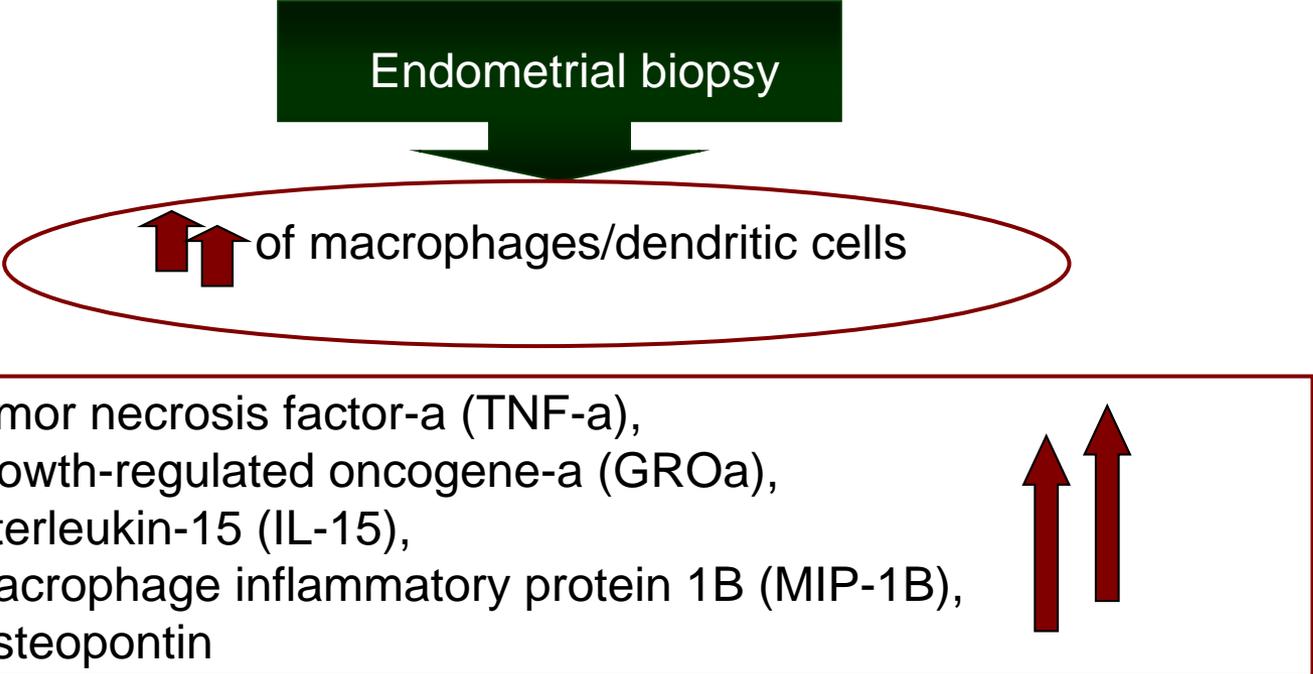


Up-regulation of receptivity molecules

Kalma et al.Fertil Steril 2009;91:1042

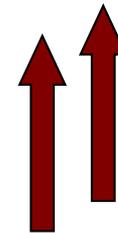
Local injury of the endometrium induces an inflammatory response that promotes successful implantation

Endometrial biopsy



↑↑ of macrophages/dendritic cells

- tumor necrosis factor- α (TNF- α),
- growth-regulated oncogene- α (GRO α),
- interleukin-15 (IL-15),
- macrophage inflammatory protein 1B (MIP-1B),
- Osteopontin



A positive correlation was found between the levels of macrophages/dendritic cells, MIP-1B expression, and TNF- α expression & the pregnancy outcome.



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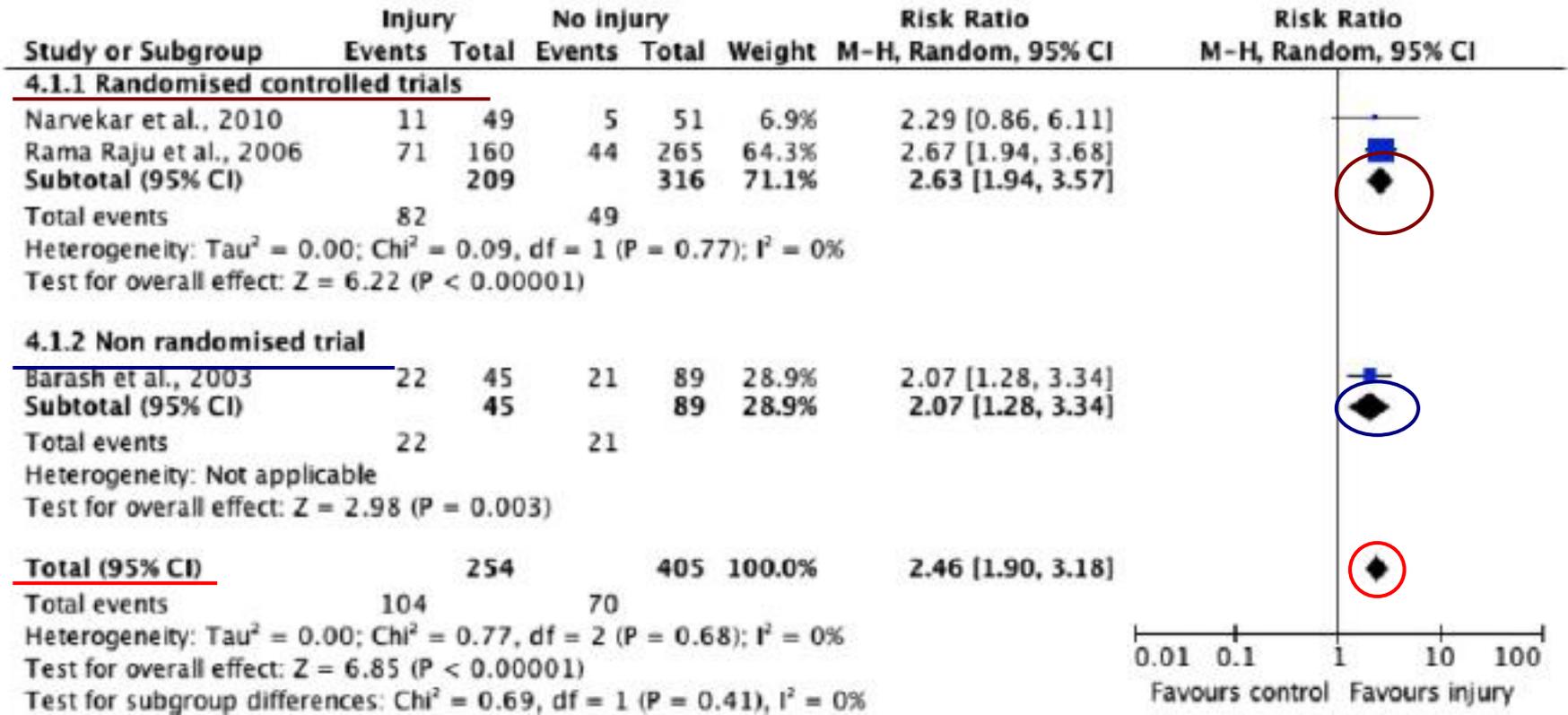
REVIEW

Endometrial injury to overcome recurrent embryo implantation failure: a systematic review and meta-analysis

Neelam Potdar ^{a,*}, Tarek Gelbaya ^b, Luciano G Nardo ^c

^a Leicester Fertility Centre, University of Leicester and University Hospitals of Leicester, Leicester, UK; ^b Leicester Fertility Centre, University Hospitals of Leicester, Leicester, UK; ^c Reproductive Medicine and Surgery Unit, Gynhealth, Manchester, UK

Randomized & non randomized trials for endometrial injury & control groups : Live birth rate



Endometrial injury improves live birth rate



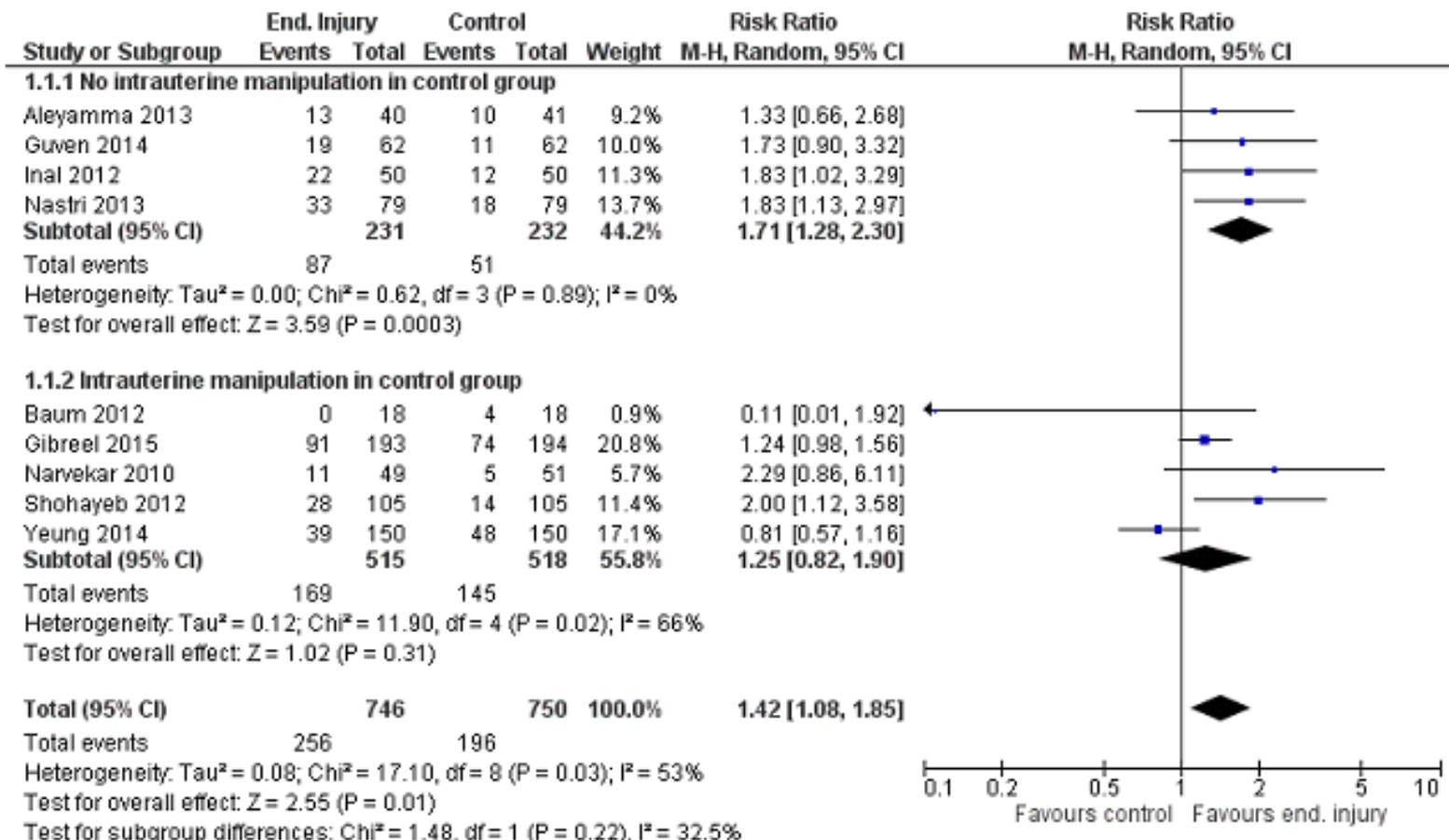
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Cochrane Database of Systematic Reviews

Endometrial injury in women undergoing assisted reproductive techniques (Review)

Nastri CO, Lensen SF, Gibreel A, Raine-Fenning N, Ferriani RA, Bhattacharya S, Martins WP

Endometrial scratching is beneficial to live birth and ongoing pregnancy rates



**However after:
a stringent interpretation
and new data....**



Endometrial injury in women with RIF: Recent RCTs show no significant impact on success rates

Variable	LEI (n = 60)	Control (n = 60)	p value
Embryo transfer(n) (Mean ± SD)	3 ± 1.8	3 ± 1.2	0.432
endometrial thickness (mm) (Mean ± SD)	3.3 ± 7.2	8 ± 4.1	0.351
Clinical Pregnancy (n, %)			
Abortion	5 (8.3%)	7 (11.7%)	0.457
Live birth	14 (23.3%)	13 (21.6%)	
Ectopic pregnancy	1 (1.7%)	0	
Blighted ovum	1 (1.7%)	0	

J Fam Reprod Health 2016; 10(3): 108-114

Comparison of outcomes variable between the study groups^a.

Variables	Intervention group n = 55 (%)	Control group n = 56 (%)	P value	OR	95% CI
Live Birth rate	14(25.45)	12(21.42)	0.6	1.25	0.52-3.02
Clinical pregnancy	15(27.27)	13(23.21)	0.6	1.24	0.53-2.93
Pregnancy test	22(40.00)	17(30.35)	0.2	1.53	0.70-3.35

^a Denominators include all those who were recruited for the study (Intention to treat analysis).

European Journal of Obstetrics & Gynecology and Reproductive Biology 214 (2017) 109–114



Endometrial scratching in women with implantation failure after a first IVF/ICSI cycle; does it lead to a higher live birth rate? The SCRaTCH study: a randomized controlled trial (NTR 5342)

N. E. van Hoogenhuijze^{1*}, H. L. Torrance¹, F. Mol², J. S. E. Laven³, E. Scheenjes⁴, M. A. F. Traas⁵, C. Janssen⁶, B. Cohlen⁷, G. Teklenburg⁷, J. P. de Bruin⁸, R. van Oppenraaij⁹, J. W. M. Maas¹⁰, E. Moll¹¹, K. Fleischer¹², M. H. van Hooff¹³, C. de Koning¹⁴, A. Cantineau¹⁵, C. B. Lambalk¹⁶, M. Verberg¹⁷, M. Nijs¹⁸, A. P. Manger¹⁹, M. van Rumste²⁰, L. F. van der Voet²¹, A. Preys-Bosman²², J. Visser²³, E. Brinkhuis²⁴, J. E. den Hartog²⁵, A. Sluijmer²⁶, F. W. Jansen²⁷, W. Hermes²⁸, M. L. Bandel²⁹, M. J. Pelinck³⁰, J. van Disseldorp³¹, M. van Wely³², J. Smeenk³³, Q. D. Pieterse³⁴, J. C. Boxmeer³⁵, E. R. Groenewoud³⁶, M. J. C. Eijkemans¹, J. C. Kasius¹ and F. J. M. Broekmans¹

van Hoogenhuijze *et al.* *BMC Women's Health* (2017) 17:47

Does intrauterine administration of PBMCs
promote implantation & pregnancy rates
in patients with RIF?

Intrauterine administration of autologous peripheral blood mononuclear cells promotes implantation rates in patients with repeated failure of IVF–embryo transfer

Intrauterine administration of autologous PBMCs promote **clinical pregnancy, implantation and live birth rates** in patients with repeated failure of IVF-embryo transfer

41.2% vs 11.1% and 23.4% vs 4.1% and 35.3% vs 5.5%

Proposed mechanisms for PBMC actions within the uterine cavity

- Activated PBMC that are administered into the uterine cavity can induce adequate **endometrial differentiation** for embryo implantation.
- PBMC can evoke favorable **inflammatory reactions** in the uterine cavity, for example, secreting proteases that may effectively change the function or structure of surface molecules expressed on the endometrial luminal epithelial cells.
- PBMC may move from the uterine cavity toward the endometrial stromal tissue, **creating a leading pathway** for subsequent embryo attachment and invasion

J. Mamm. Ova Res. 26, 122–128, 2009

J. Reprod. Immunol. 81, 1–8., 2009

Issues to be addressed

- What is the biological impact?
- When is the appropriate time to administer the PBMCs?
- Should PBMCs be pre-treated with HCG?
- Apart from RIF?
- **Differential (Better) Activation of PBMCs?**

DOES INTRAUTERINE ADMINISTRATION
OF PBMCs PRETREATED WITH CRH
PROMOTE IMPLANTATION RATES IN
PATIENTS WITH RIF?



Corticotropin-releasing hormone promotes blastocyst implantation and early maternal tolerance

A. Makrigiannakis^{1,2,3}, E. Zoumakis^{1,4}, S. Kalantaridou^{3,4}, C. Coutifaris⁵, A. N. Margioris¹, G. Coukos⁵, K. C. Rice⁶, A. Gravanis^{1,*} and G. P. Chrousos^{4,*}

Repeated implantation failure: a new potential treatment option

Antonis Makrigiannakis*, Moncef BenKhalifa[†], Thomas Vrekoussis[‡], Sami Mahjub[§], Sophia N. Kalantaridou[‡] and Timur Gurgan[¶]

*Department of Obstetrics and Gynecology, Medical School, University of Crete, Heraklion, Greece, [†]Reproductive Medicine & Medical Cytogenetics, Regional University Hospital & Medical School, Picardie University Jules Verne, Amiens, France, [‡]Department of Obstetrics and Gynecology, Medical School, University of Ioannina, Ioannina, Greece, [§]Elyssa IVF Center, Tunis, Tunisia, [¶]Department of Obstetrics and Gynecology, Medical School, Hacettepe University, Ankara, Turkey

Eur J Clin Invest 2015; 45 (4): 380–384

REPEATED IMPLANTATION FAILURE: A NEW APPROACH

Table 2 Overview of the studies using PBMC for improving clinical pregnancy rate after blastocyst transfer in women with RIF

	Embryo type	Intervention	Participants (n)	Clinical pregnancy rate	Outcome significance
Yoshioka <i>et al.</i> , [9]	Blastocyst	HCG-treated PBMC	17	42.1% (7/17)	Significant
Okitsu <i>et al.</i> , [15]	Blastocyst	Untreated PBMC	13	46.1% (6/13)	Not significant
Current study	Blastocyst	CRH-treated PBMC	45	44.4% (20/45) *	Significant

* $P < 0.001$



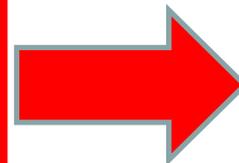
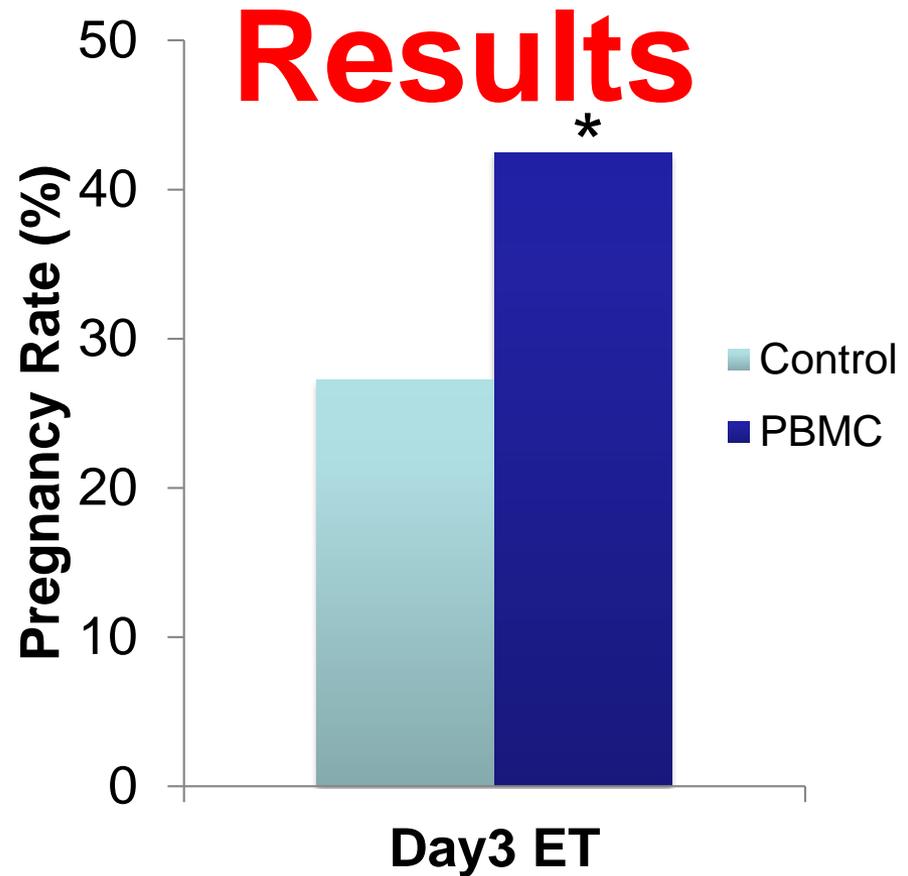
Intrauterine CRH-treated PBMC in repeated implantation failure

Antonis Makrygiannakis¹  | Thomas Vrekoussis¹ | Fanourios Makrygiannakis¹ | Halil Ruso² | Sophia N. Kalantaridou³ | Timur Gurgan⁴

TABLE 2 Results of our crossover studies investigating the role of intrauterine administration of CRH-treated PBMC, as a treatment strategy in women with RIF (day 5-blastocyst transfer and day 3-cleavage stage embryo transfer)

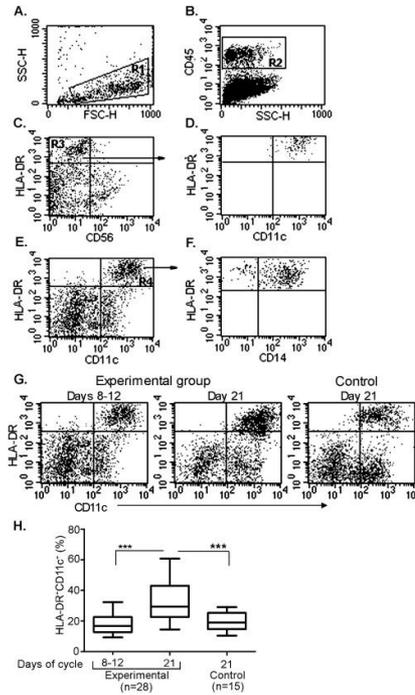
	Participants (n)	Timepoint of intervention	Embryo stage (Day of embryo transfer)	Clinical pregnancy rate	Outcome
Makrygiannakis et al ¹⁴	45	Day 2	Blastocyst (Day 5)	20/45 (44.4%)	Significant
Current study	26	Day 2	Cleavage embryos (Day 3)	15/26 (57.69%)	Significant

	PBMC Group (n=93)	Control Group (n=99)	P value
Maternal Age	34.19	34.09	ns
Previous Cycles	3.13	3.45	ns
Endometrial Thickness on HCG day (mm)	9.71	9.5	ns
Av. Number of Oocytes	8.73	7.93	ns
Av. Number of MII oocytes	6.94	5.97	ns
Fertilisation (%)	84.02	85.22	ns
Grade 1 Embryos on D3 (%)	52.6	51.56	ns
Av. Number of ET embryos	1.8	1.9	ns
Clinical Pregnancy Rate (%)	42.00	24.27	0.01
Abortion Rate (%)	17.94	41.67	0.01
Live Birth Rate (%)	34.40	14.14	0.01

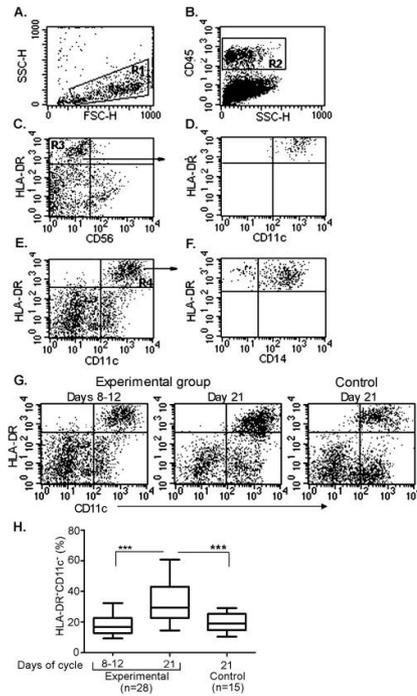


$P < 0.05$

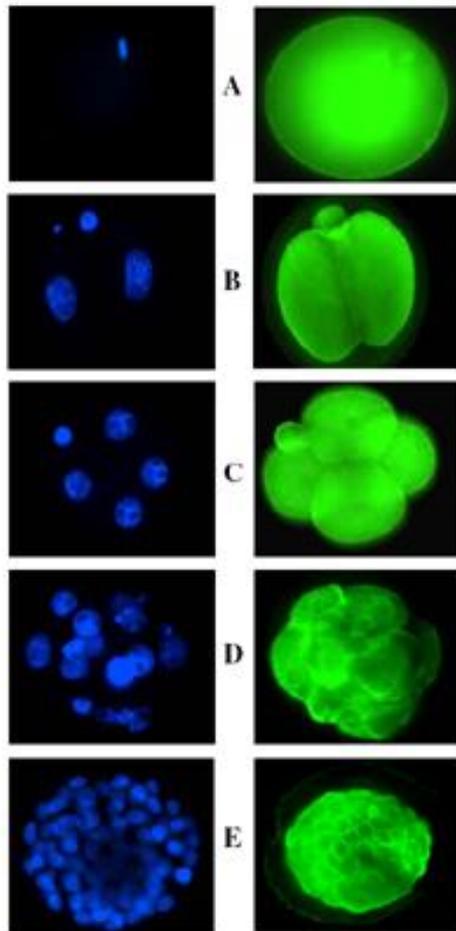
CRH induces IL 6



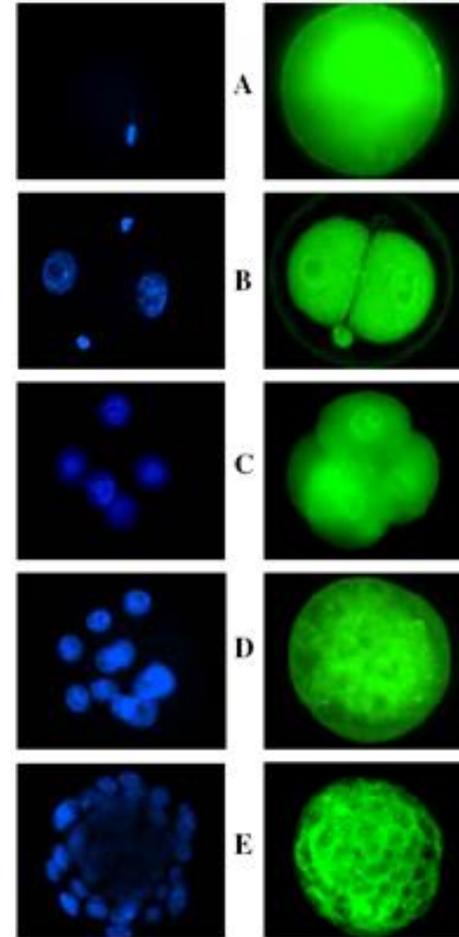
CRH decreases IFN



CRH & development of embryos



CRH expression in embryo

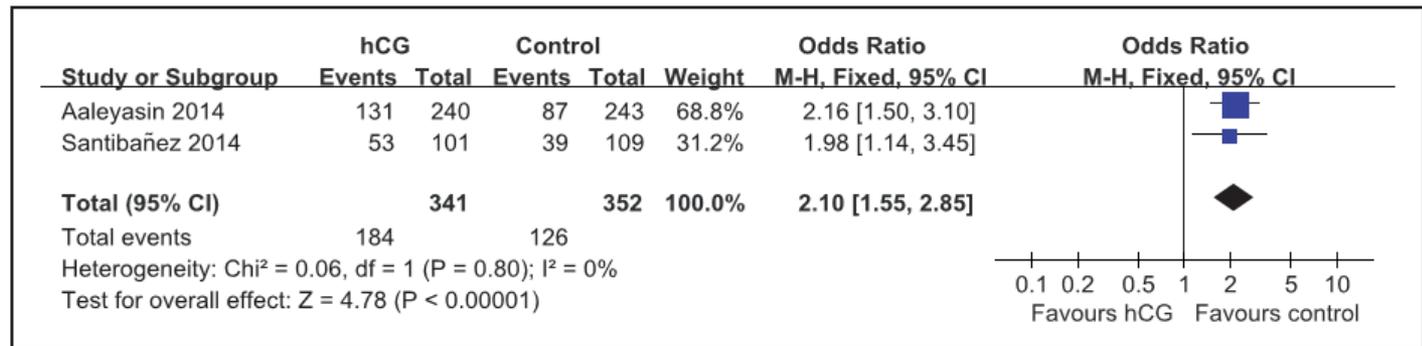


CRHR1 expression in embryo

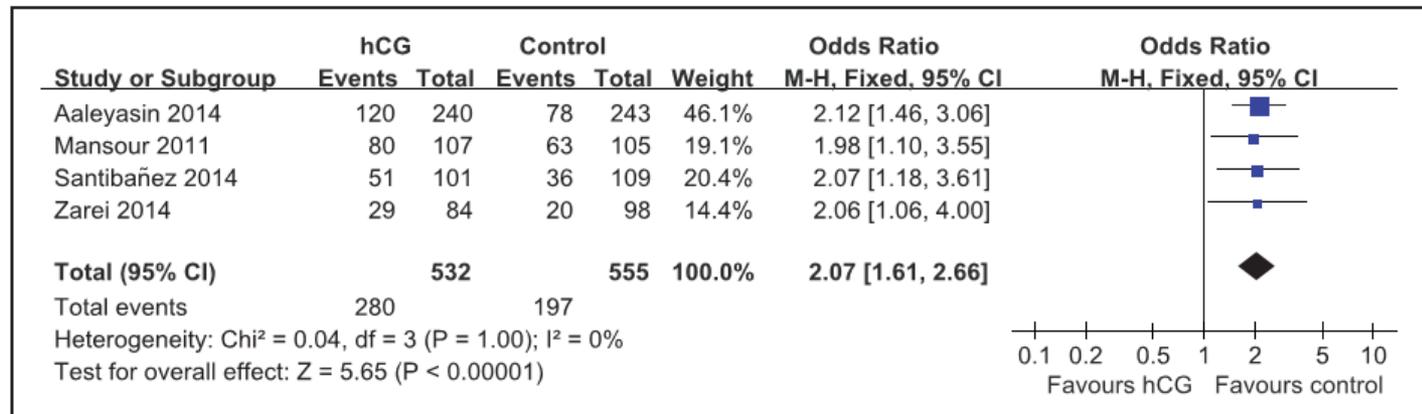
**DOES INTRAUTERINE ADMINISTRATION
OF HCG PROMOTE IMPLANTATION
RATES IN PATIENTS WITH RIF?**

Ye et al 2015: HCG significantly increases biochemical and pregnancy rates

Biochemical pregnancy rate



Clinical pregnancy rate



RESEARCH

Open Access



Intrauterine administration of human chorionic gonadotropin does not improve pregnancy and live birth rates independently of blastocyst quality: a randomised prospective study

Barbara Wirleitner^{1*}, Maximilian Schuff¹, Pierre Vanderzwalmen^{1,2}, Astrid Stecher¹, Jasmin Okhowat¹, Libor Hradecký³, Tomáš Kohoutek³, Milena Králícková⁴, Dietmar Spitzer⁵ and Nicolas H. Zech¹

However concurrent evidence on blastocyst transfer did not support this finding



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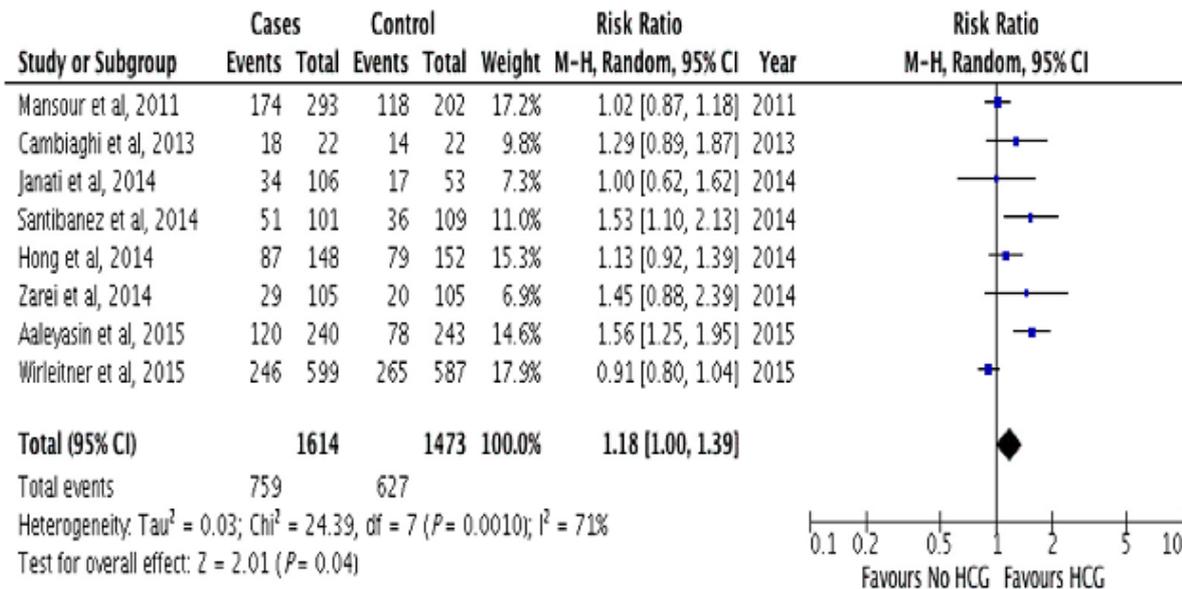
REVIEW

The effect of intrauterine HCG injection on IVF outcome: a systematic review and meta-analysis



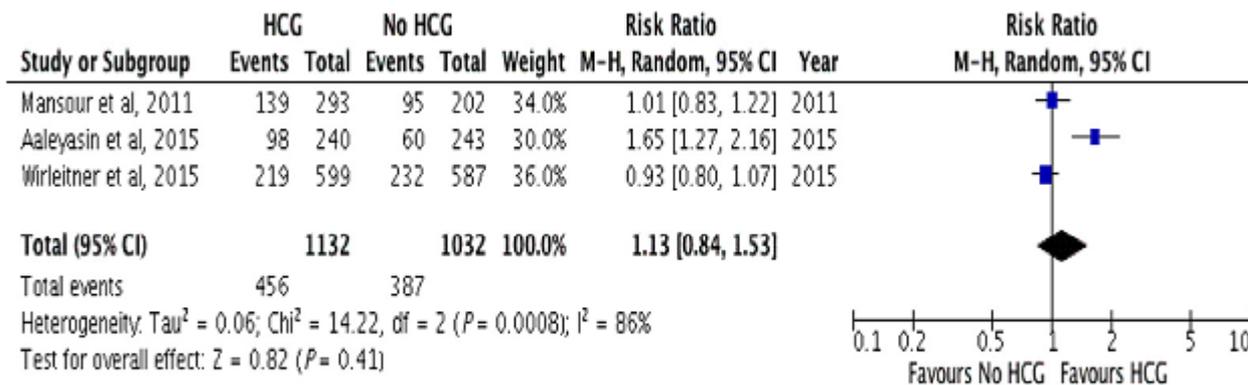
A Osman ^{a,b,*}, J Pundir ^c, M Elsherbini ^b, S Dave ^c, T El-Toukhy ^a, Y Khalaf ^a

^a Assisted Conception Unit, Guys Hospital, Great Maze Pond SE1 9RT, UK; ^b Faculty of Medicine, Cairo University, Al-Saray Street, El Manial Cairo 11956, Egypt; ^c Centre of reproductive medicine, St Bartholomew's Hospital, Bart's Health, London EC1A 7BE, UK



No impact of HCG administration on Clinical & Live Birth rates

Clinical pregnancy rates for intrauterine HCG administration versus no HCG.



Live birth rates for intrauterine HCG administration versus no HCG.



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Intrauterine administration of human chorionic gonadotropin (hCG) for subfertile women undergoing assisted reproduction (Review)

Craciunas L, Tsampras N, Coomarasamy A, Raine-Fenning N

Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD011537.

DOI: 10.1002/14651858.CD011537.pub2.

Currently meta-analysis: impossible

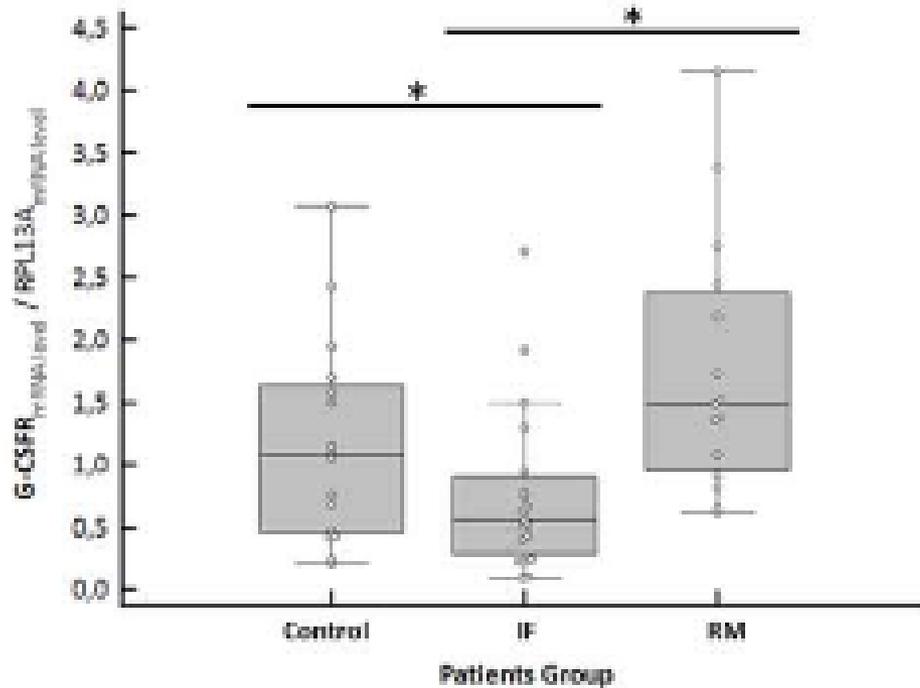
- For the analyses of live birth and clinical pregnancy, there was considerable heterogeneity (I^2 greater than 75%).
- Exploration for the sources of heterogeneity identified two key pre-specified variables as important determinants:
 - stage of ET (cleavage versus blastocyst stage)
 - Dose of IC-hCG (less than 500 international units (IU) versus 500 IU or greater).

Future Management of RIF?

- **GM-CSF**



G-CSF is deregulated in RIF and RM



A randomized clinical trial of endometrial perfusion with granulocyte colony-stimulating factor in in vitro fertilization cycles: impact on endometrial thickness and clinical pregnancy rates

David H. Barad, M.D.,^{a,b} Yao Yu, Ph.D.,^{a,b} Vitaly A. Kushnir, M.D.,^{a,b} Aya Shohat-Tal, Ph.D.,^{a,b} Emanuela Lazzaroni, M.S.,^{a,b} Ho-Joon Lee, Ph.D.,^{a,b} and Norbert Gleicher, M.D.^{a,b}

^a The Center for Human Reproduction (CHR), and ^b Foundation for Reproductive Medicine, New York, New York

No effect in older women undergoing IVF

The role of G-CSF in RIF

Outcomes	Subgroups analysis	Fixed/Random model
		Pooled relative risk (95% CI)
Implantation	Thin endometrium/RIF	1.887 (1.256,2.833)
	Normal IVF	0.750 (0.447,1.258)
	Overall	1.461 (0.801,2.664)
Biochemical pregnancy	Thin endometrium/RIF	2.385 (1.414,4.023)
	Normal IVF	0.888 (0.562,1.403)
	Overall	1.426 (0.795,2.559)
Clinical pregnancy	Thin endometrium/RIF	2.312 (1.444,3.701)
	Normal IVF	0.993 (0.611,1.616)
	Overall	1.563 (1.122,2.176)

NA: Not applicable.

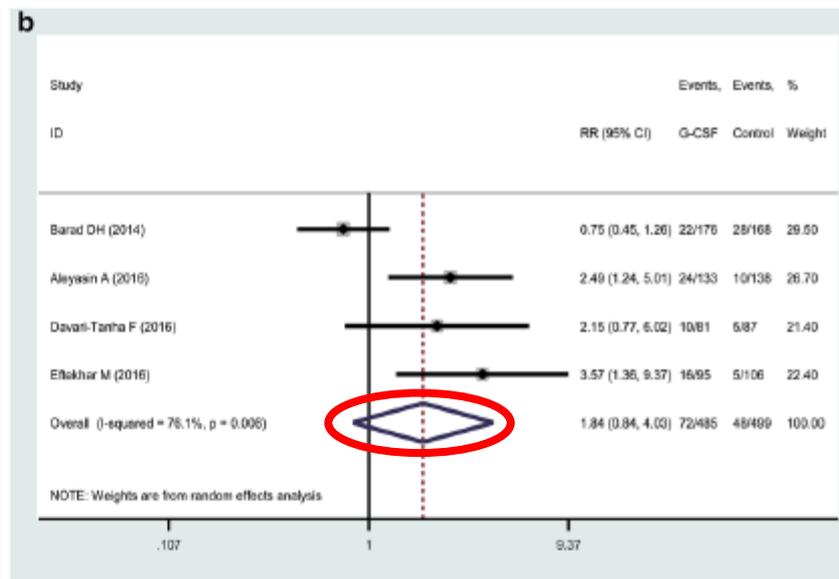
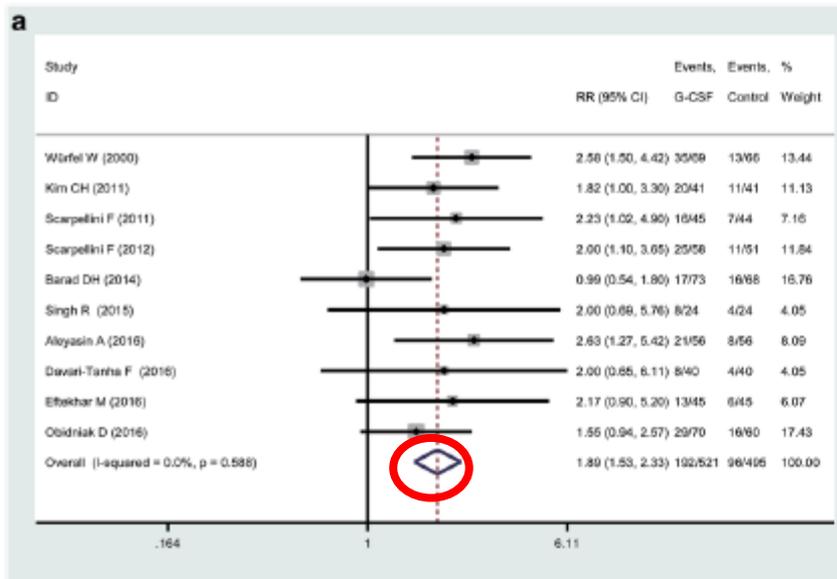
G-CSF seems to be effective only in case of thin endometrium / RIF

REVIEW



Therapeutic role of granulocyte colony-stimulating factor (G-CSF) for infertile women under in vitro fertilization and embryo transfer (IVF-ET) treatment: a meta-analysis

Ling Zhang¹ · Wei-Hai Xu¹ · Xiao-Hua Fu¹ · Qiong-Xiao Huang¹ · Xiao-Yan Guo¹ · Lin Zhang¹ · Shi-Shi Li¹ · Jing Zhu¹ · Jing Shu¹



Future Management of RIF?

- **Intralipids**

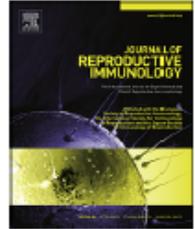




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journal homepage: www.elsevier.com/locate/jri



Intralipid® may represent a new hope for patients with reproductive failures and simultaneously an over-immune endometrial activation



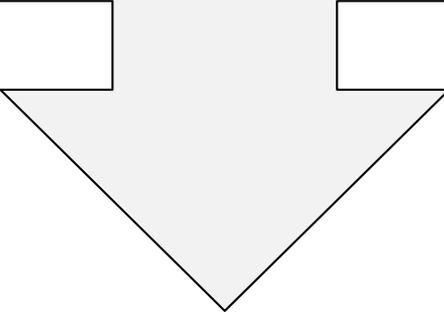
Nathalie Lédée^{a,b,*}, Claudine Vasseur^c, Marie Petitbarat^a, Lucie Chevrier^a, Katia Vezmar^{a,b,c,d}, Geraldine Dray^b, Sandra Chenière^b, Annina Lobersztajn^b, Dominique Vitoux^a, Guy Nino Cassuto^b, Gérard Chaouat^d

Conclusions: Double blind placebo versus Intralipid® studies should be conducted. Intralipid® may be an option to explore in RIF patients who exhibit an over-immune activation of uNK cells.

Intralipid therapy for recurrent implantation failure: new hope or false dawn?

N. Shreeve^{a,*}, K. Sadek^b

Journal of Reproductive Immunology 93 (2012) 38–40



Need for RCT

The role of GH in RIF

	GH Patients	Non-GH Patients	Positive Controls	P Value
Endometrial thickness (mm) mean (SD)	9.3 (1.5)	8.6 (1.0)	9.4 (1.7)	0.046
No. of embryos obtained	7.9 (2.2)	8.2 (1.5)	8.3 (1.3)	0.643
Embryos transferred				0.036 ^a
1	2 (5.7%)	0 (0%)	5 (14.3%)	
2	26 (74.3%)	27 (77.1%)	27 (77.1%)	
3 (%)	7 (20.0%)	8 (22.9%)	3 (8.6%)	
β -hCG (positive)	19 (54.3%)	6 (17.1%)	26 (74.3%)	<0.001 ^{a,b}
Heartbeat (positive)	18 (51.4%)	6 (17.1%)	25 (71.4%)	<0.001 ^{a,b}
No. of sacs				<0.001 ^{a,b}
1	13 (37.1%)	4 (11.4%)	17 (48.6)	
2	6 (7.1%)	2 (5.7%)	9 (25.7)	
Delivery (yes)	18 (51.4%)	6 (17.1%)	24 (68.6%)	<0.001 ^{a,b}
Babies born				<0.001 ^{a,b}
1	14 (40.0%)	5 (14.3%)	16 (45.7%)	
2	4 (11.4%)	1 (2.9%)	8 (22.9%)	

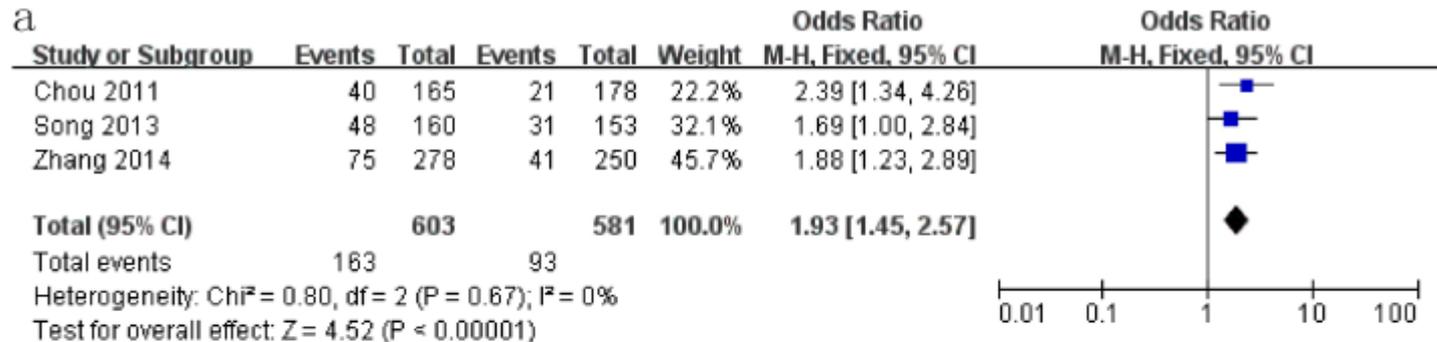
^aSignificant differences between non-GH patients *vs.* positive controls in a multiple-comparison–adjusted *post hoc* test.

^bSignificant differences between non-GH patients *vs.* GH patients in a multiple-comparison–adjusted *post hoc* test.

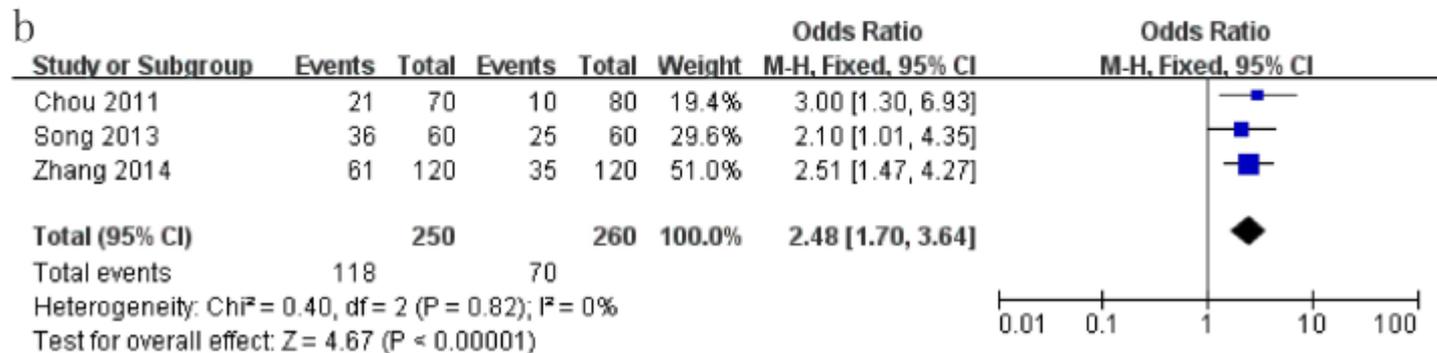
**GH administration improves IVF success rates in women
with RIF**

The role of atosiban in RIF

Implantation rate

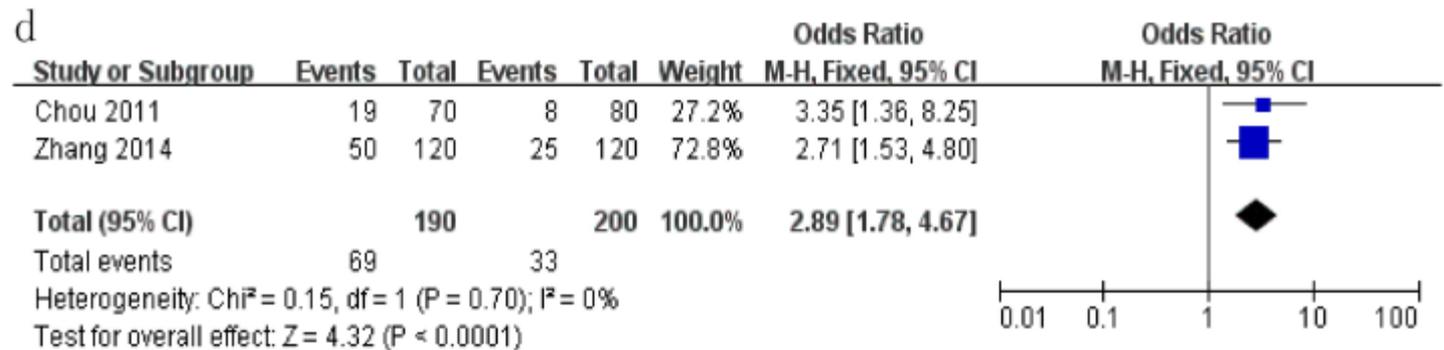


Clinical pregnancy rate



Atosiban administration improves implantation and clinical pregnancy rates in women with RIF

The role of atosiban in RIF



Live Birth
rate

Atosiban administration improves live birth rates in women with RIF

HOW TO PREDICT IMPLANTATION

- Embryo
- **Endometrium**

Endometrial receptivity: Prediction via gene expression profiles

SCIENTIFIC REPORTS

OPEN

An endometrial gene expression signature accurately predicts recurrent implantation failure after IVF

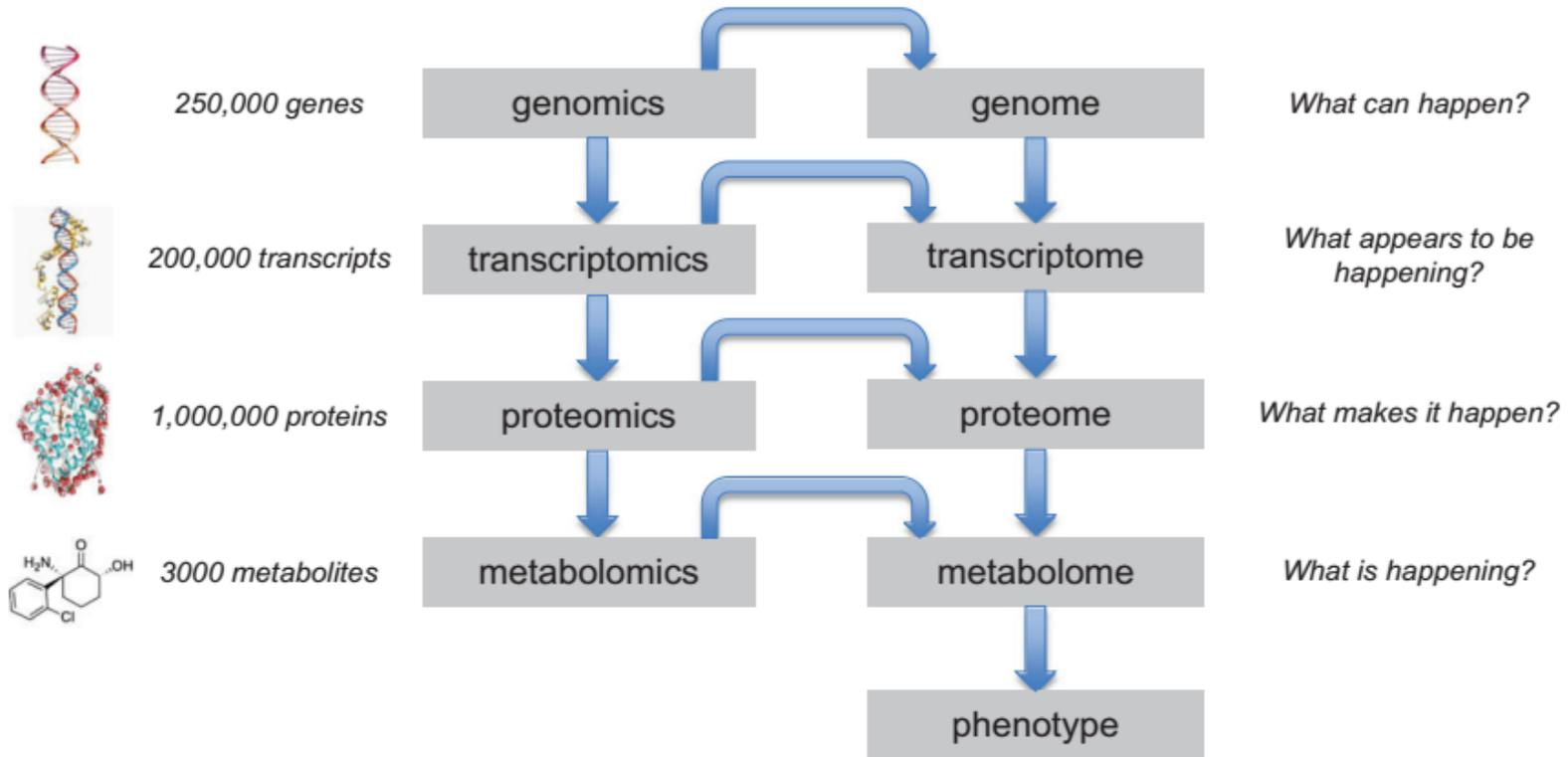
Received: 04 August 2015

Accepted: 11 December 2015

Published: 22 January 2016

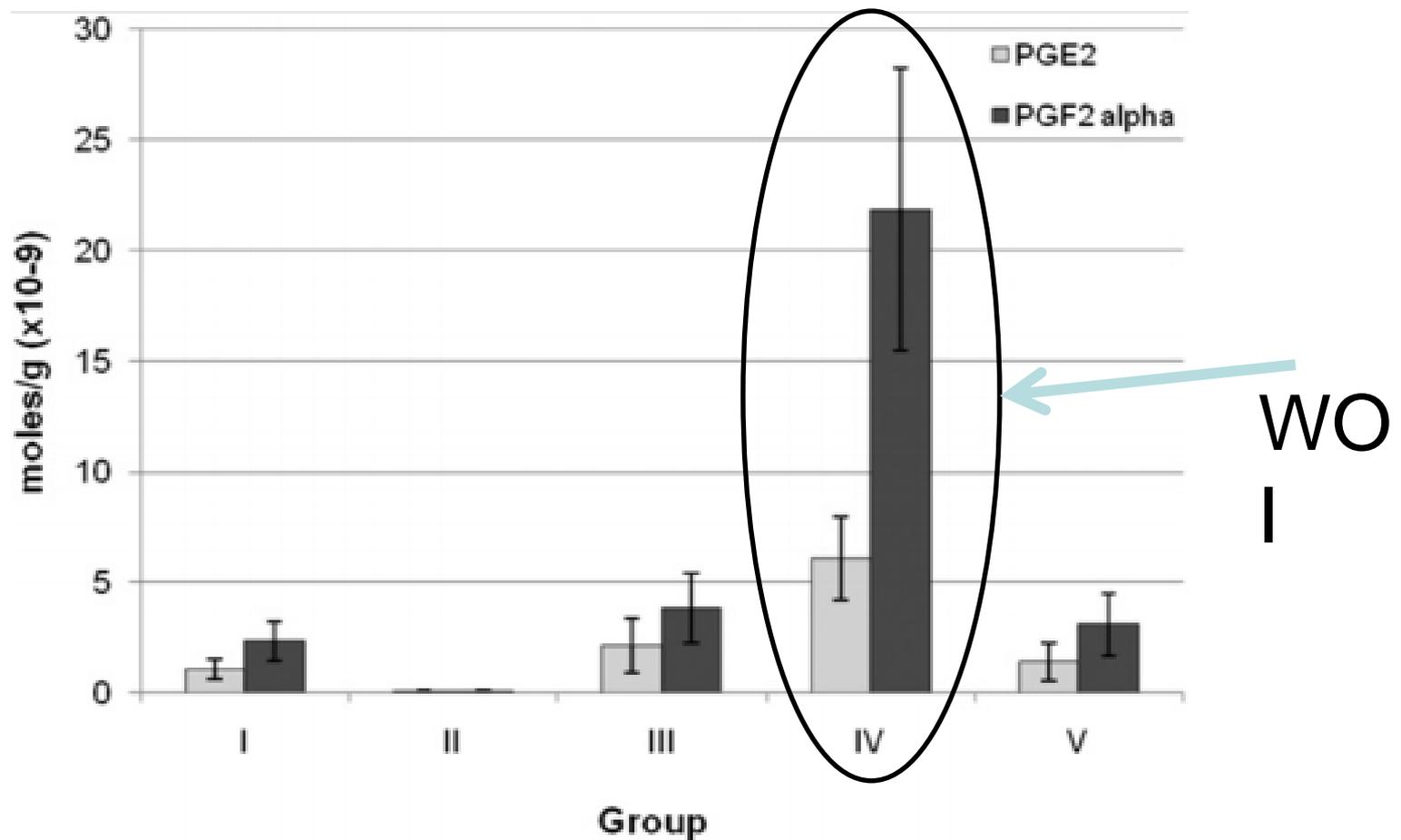
Yvonne E. M. Koot^{1,*}, Sander R. van Hooff^{2,*}, Carolien M. Boomsma¹, Dik van Leenen², Marian J. A. Groot Koerkamp², Mariëtte Goddijn³, Marinus J. C. Eijkemans^{1,4}, Bart C. J. M. Fauser¹, Frank C. P. Holstege^{2,*} & Nick S. Macklon^{1,5,*}

The role of –omics in implantation research

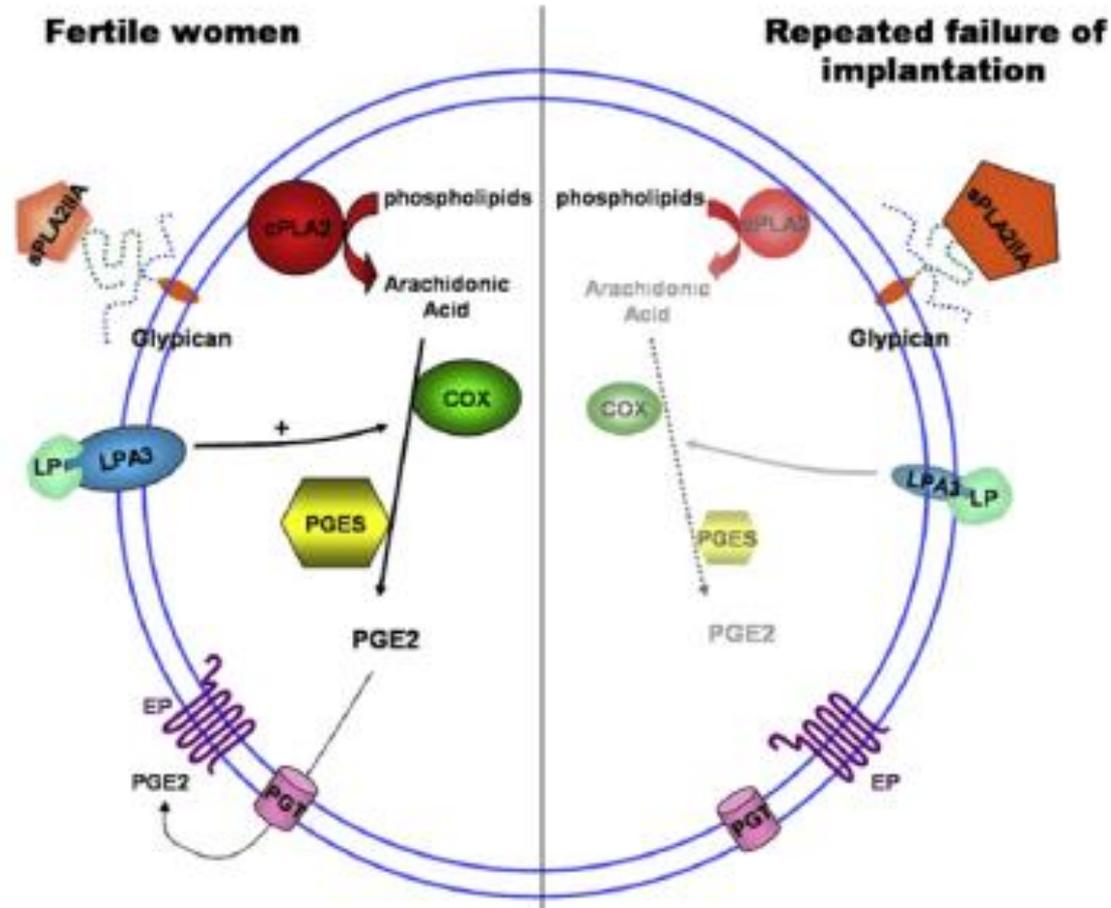


Lipidomics in implantation

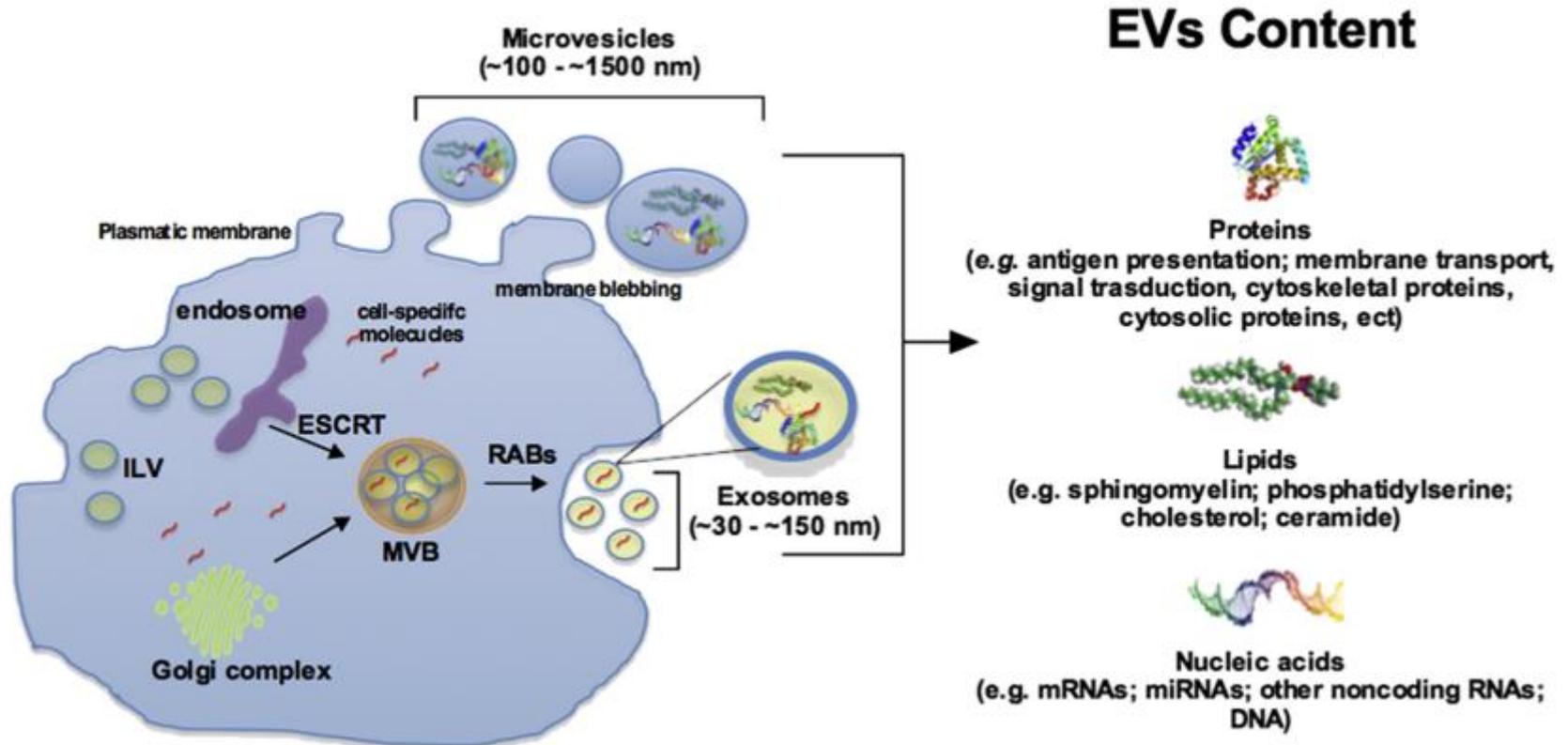
Differential expression of PGs during the menstrual cycle: a lipidomics example



Disrupted PG synthesis in RIF



The role of exosomes: a liquid biopsy for endometrial assessment?



MicroRNAs in implantation

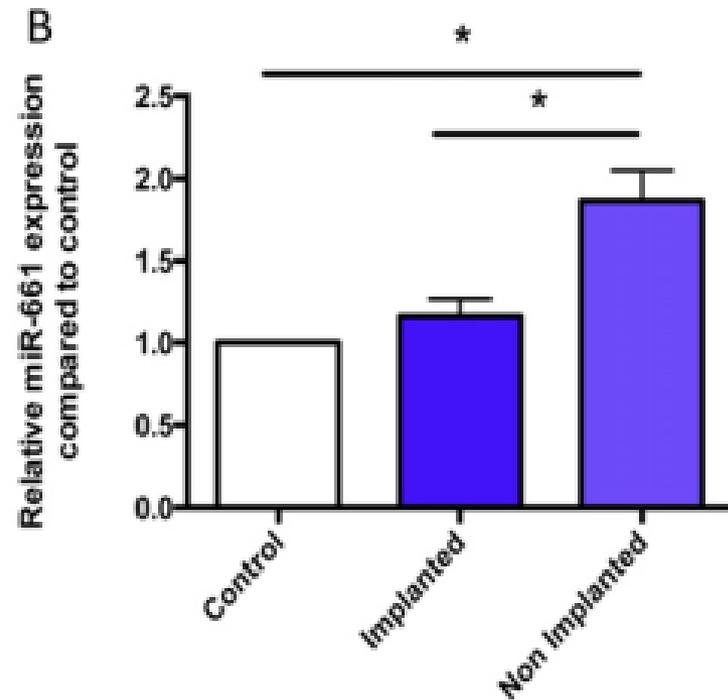
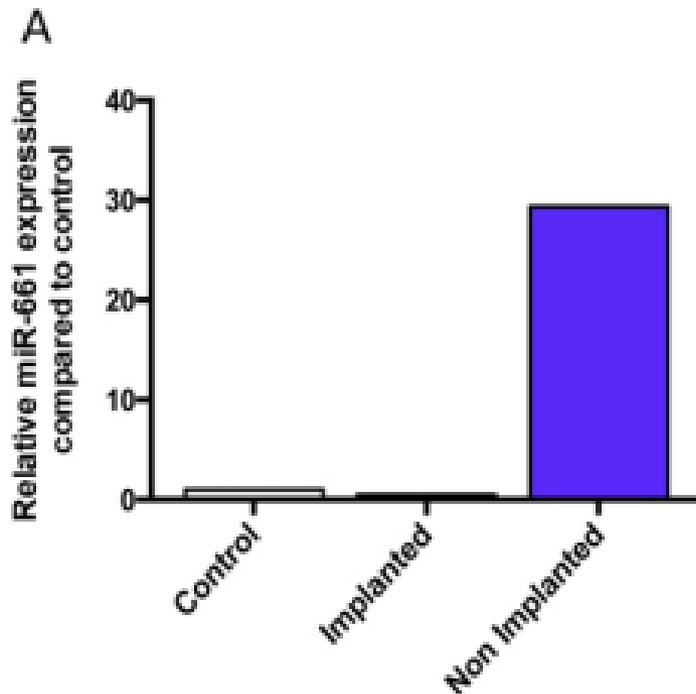
Table 1 Summary of miRNAomic Studies on Endometria at Different Phases of the Reproductive Cycle

Species	Time of sampling	Tissue	miRNA families/cluster			
			Let-7	miR-200	miR-30	miR-17-92
Mice	Day 1 versus Day 4 of pregnancy	Uterine tissue	✓	✓		✓
Mice	Day 1 versus Day 5 of pregnancy	Uterine luminal epithelium at implantation site	✓	✓	✓	
Rat	Day 4 versus Day 5 of pregnancy	Uterine tissue	✓	✓	✓	✓
Mice	Activated versus delayed implanting	Uterine tissue	✓	✓	✓	✓
Mice	Day 5 of pregnancy	Uterine tissue at implantation site and inter-implantation	✓			✓
Mice	Day 5 of pregnancy	Uterine tissue at implantation site and inter-implantation	✓	✓	✓	✓
Human	Late proliferative versus Mid-secretory	Endometrial epithelial cells from women with no history of infertility			✓	
Human	LH + 2 versus LH + 7	Endometrial aspirate from fertile women	✓		✓	
Human	LH + 2 versus LH + 7	Endometrial biopsies from women with regular cycle			✓	

LH + 2: 2 days after luteinizing hormone surge in natural cycle (pre-receptive).

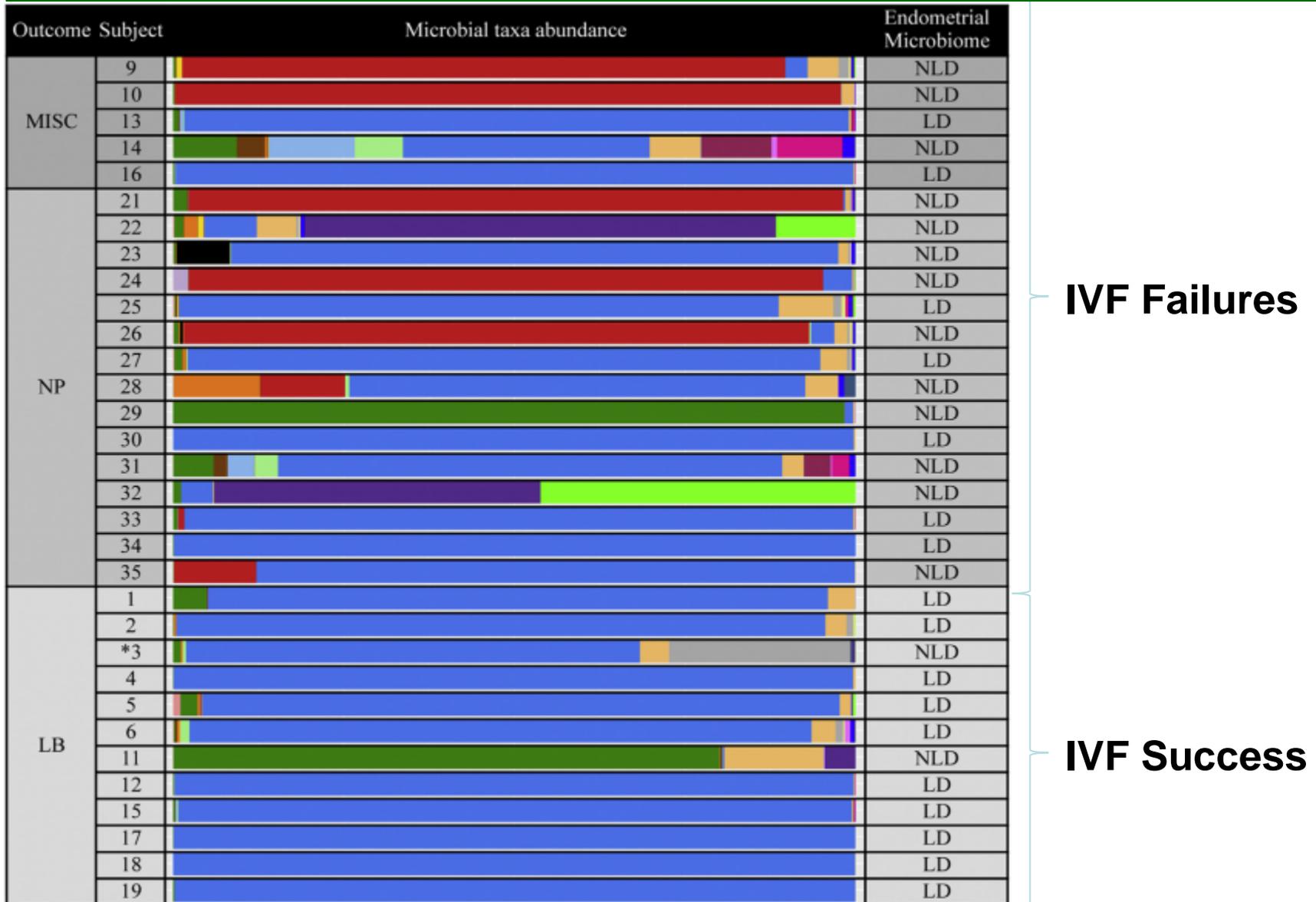
LH + 7: 7 days after luteinizing hormone surge in natural cycle (receptive).

The role of MiR661 in implantation

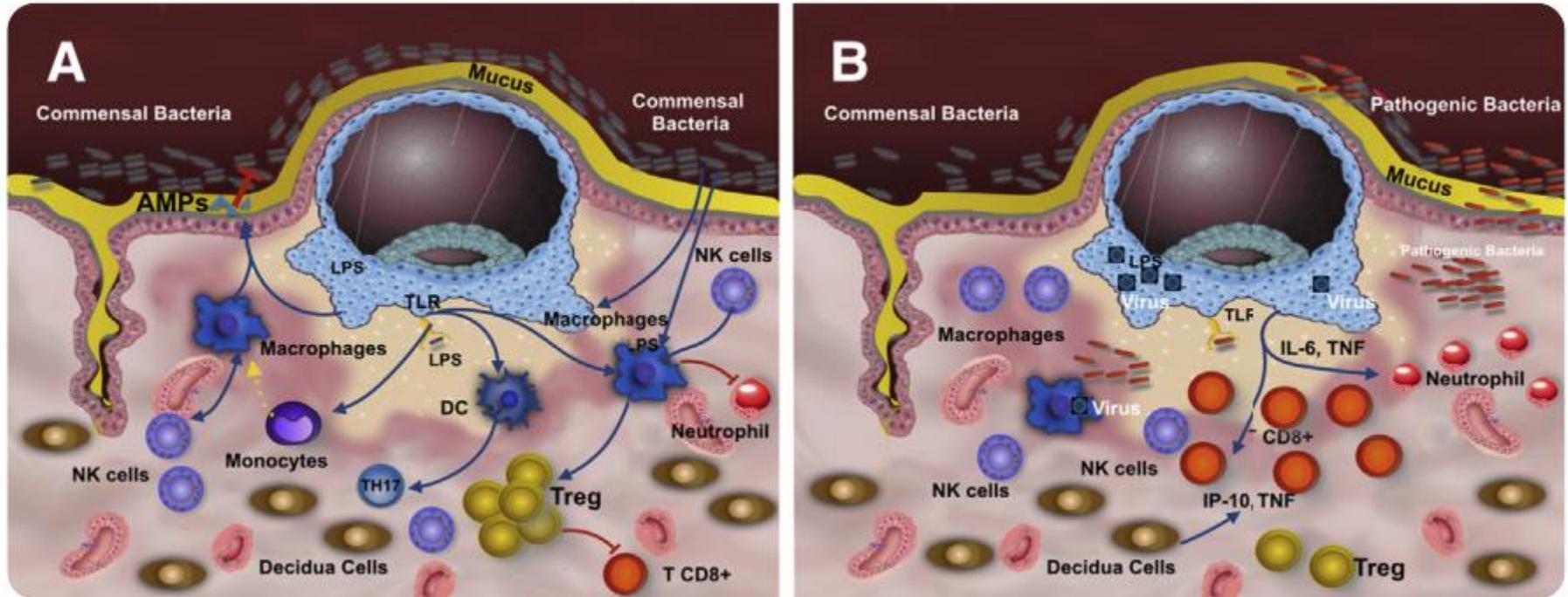


Vaginal microbiome as a predictor of successful implantation

IVF Success is significantly related to Lactobaccilus profile



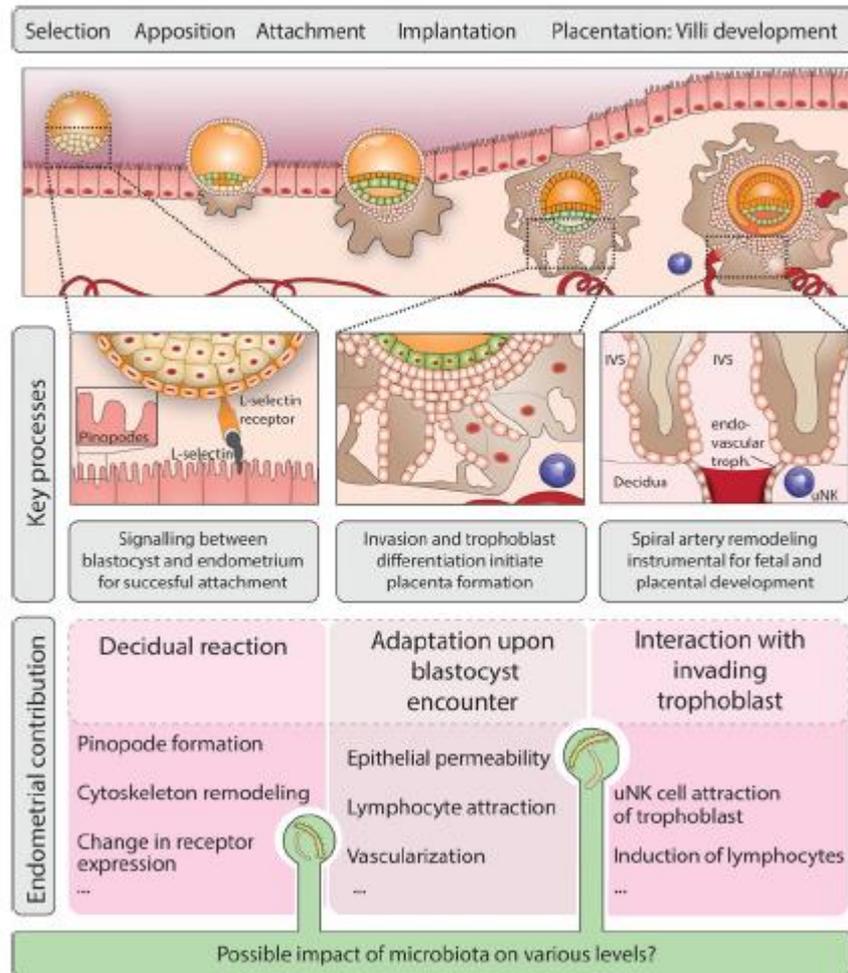
Hypothesis on Dysbiosis



Pathogenic bacteria induce TNFa and CD8 cell activity

How uterine microbiota might be responsible for a receptive, fertile endometrium

Marilen Benner, Gerben Ferwerda, Irma Joosten and Renate G. van der Molen 



Autoimmunity, systemic inflammation, and their correlation with repeated implantation failure and recurrent miscarriage: Is chronic endometritis the missing piece of the jigsaw?

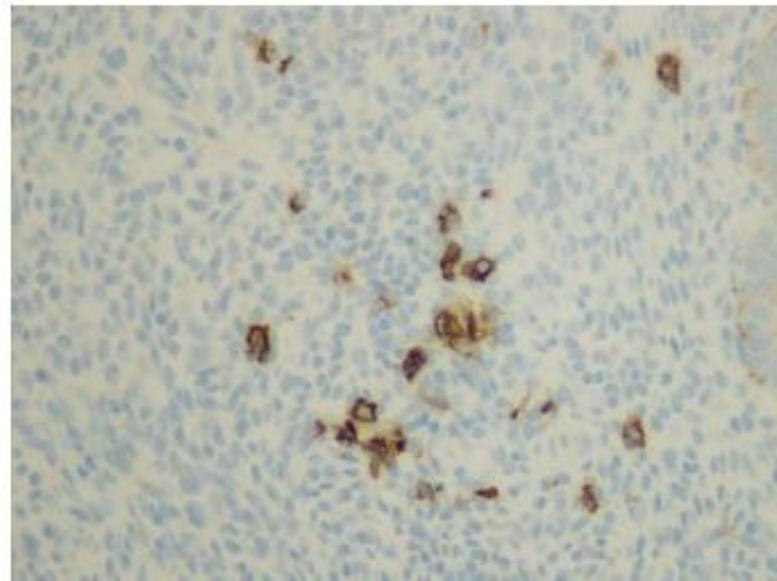


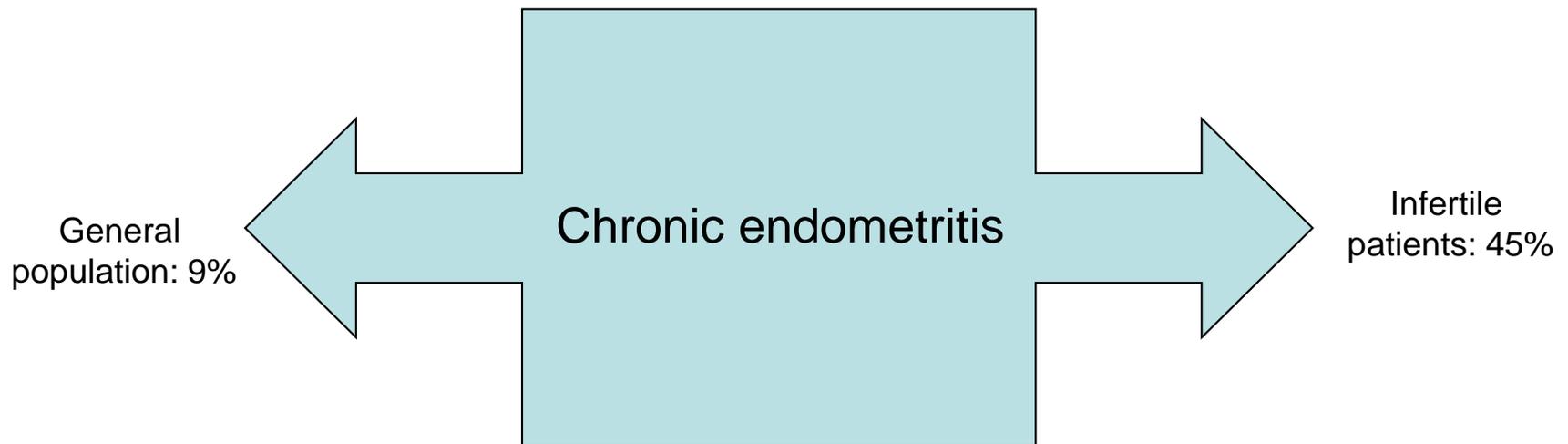
Fig. 1 Histology of chronic endometritis defined by the presence of CD138 staining plasma cells.

Am J Reprod Immunol 2017; **77**: e12597;

American Journal of Reproductive Immunology **75** (2016) 672–677

Endometrial microbiota—new player in town

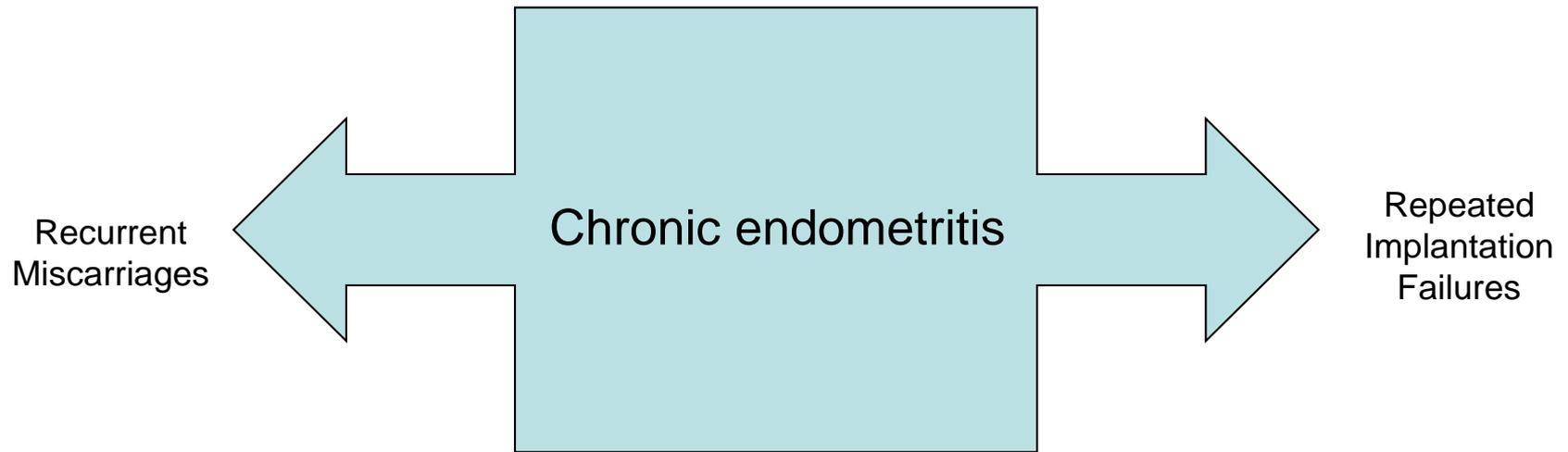
Inmaculada Moreno, Ph.D.^{a,b} and Jason M. Franasiak, M.D., T.S. (A.B.B.)^{c,d}



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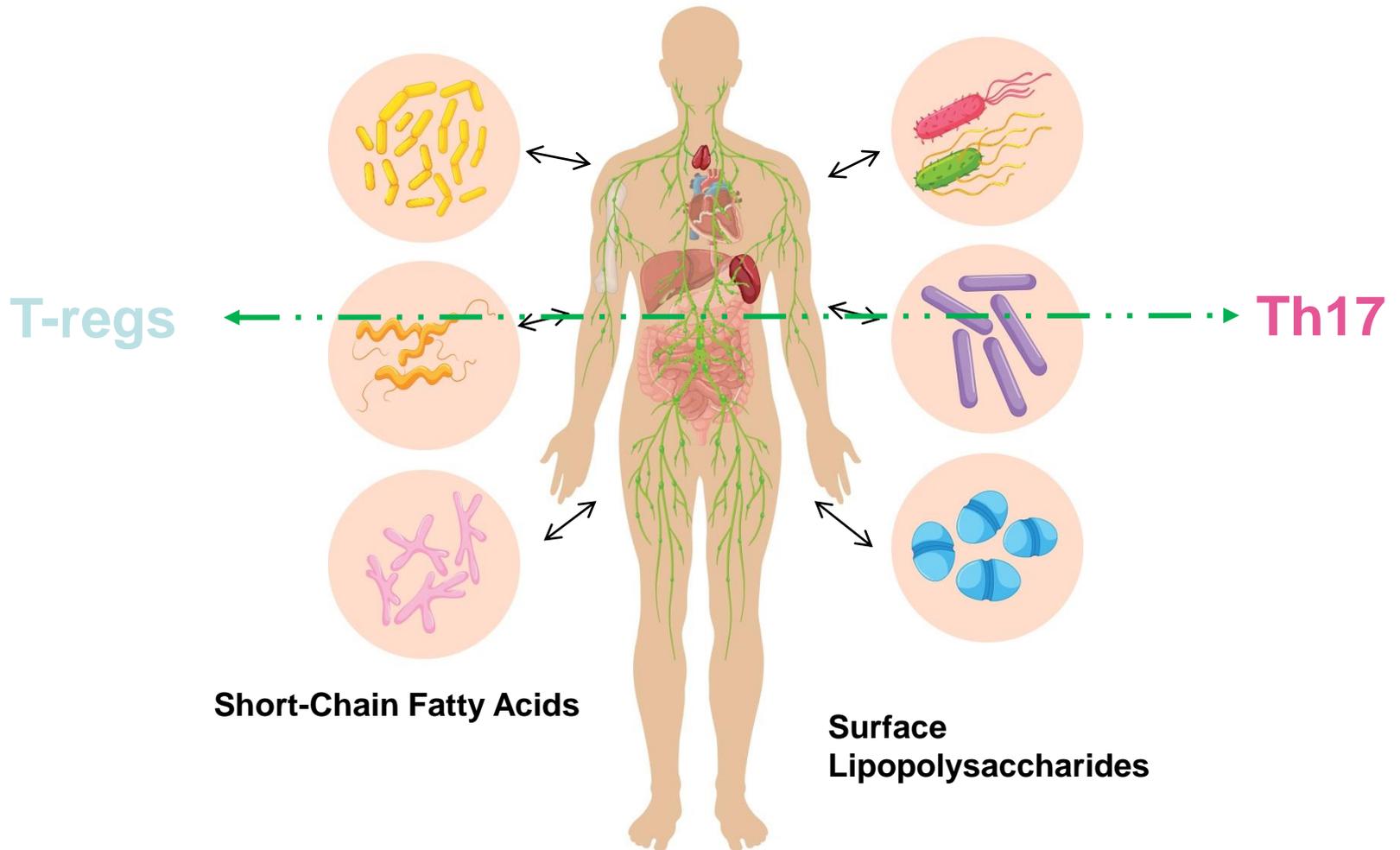
Endometrial microbiota—new player in town

Inmaculada Moreno, Ph.D.^{a,b} and Jason M. Franasiak, M.D., T.S. (A.B.B.)^{c,d}



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How can Microbiota affect the Immune System?



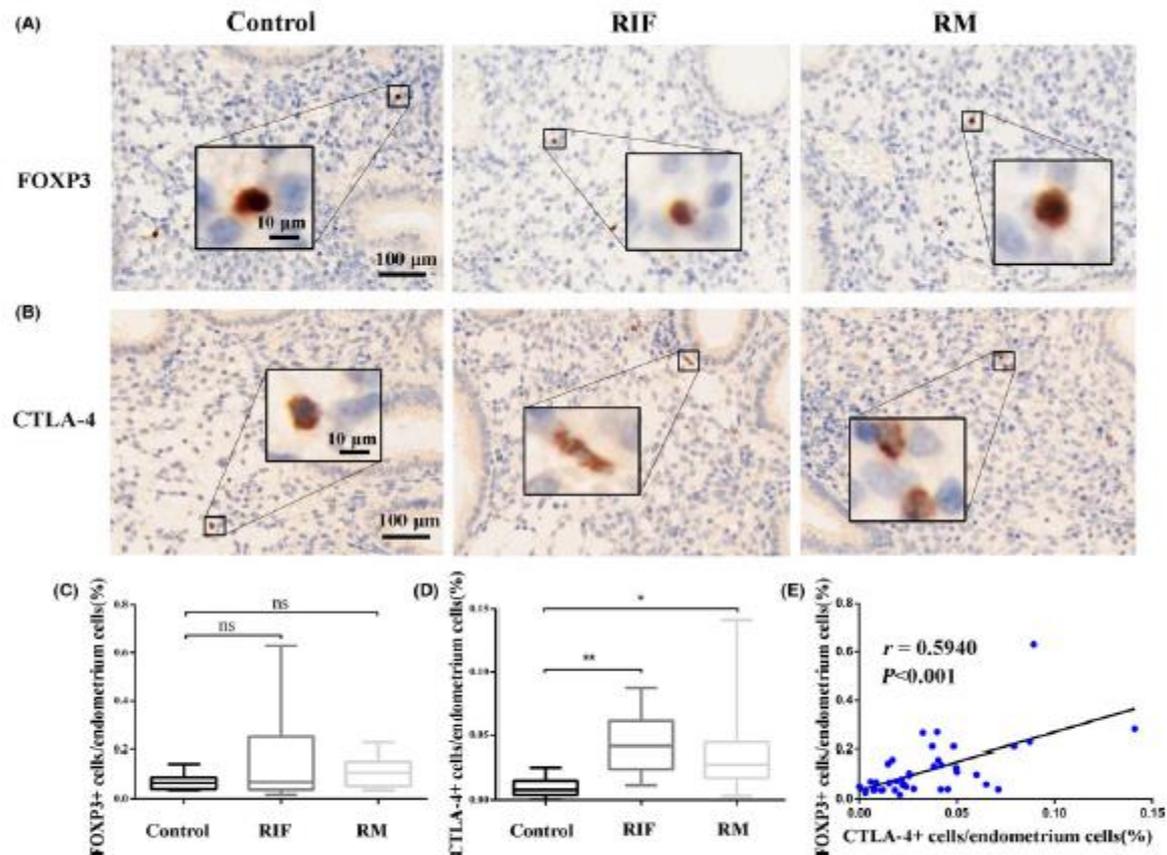
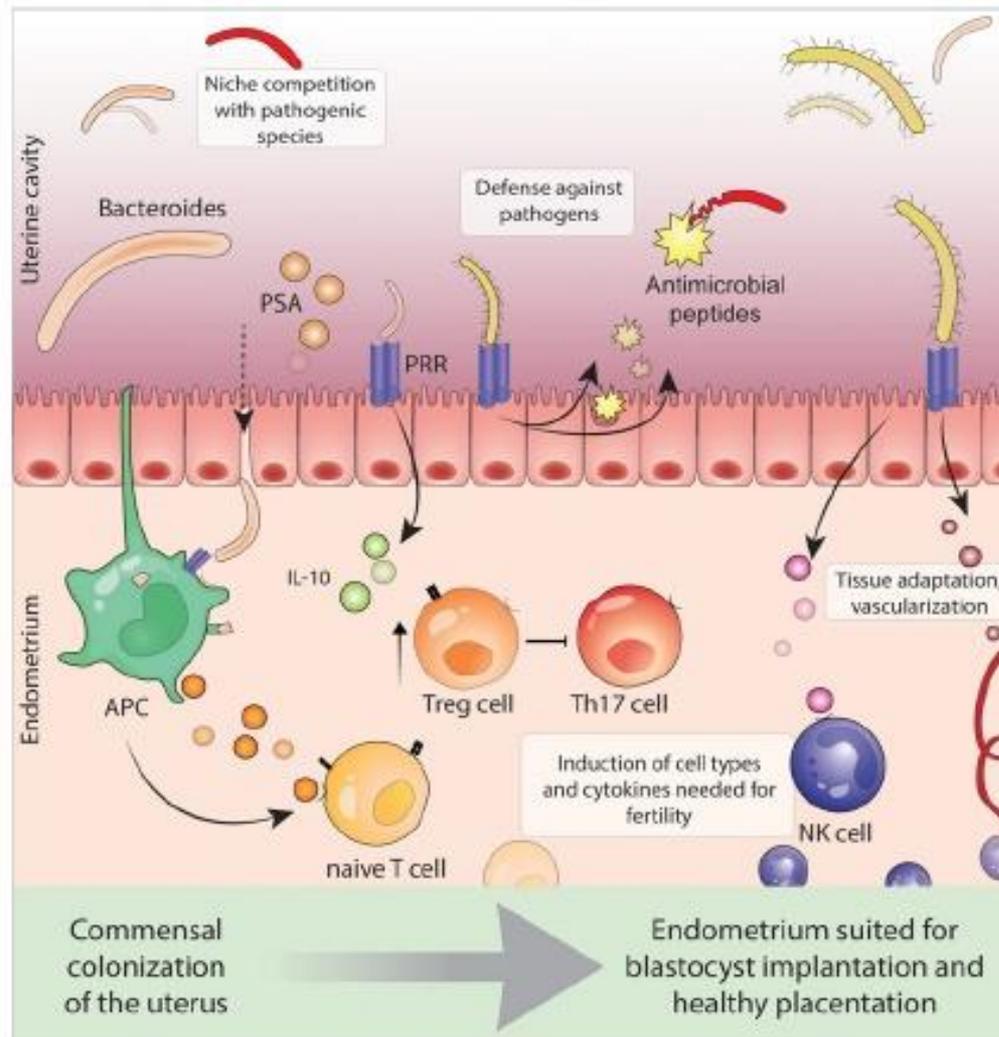


FIGURE 3 Immunohistochemical staining of FOXP3 and CTLA-4-positive endometrial cells in control, repeated implantation failure (RIF), and recurrent miscarriage (RM) women. (A-D) Representative immunohistochemistry and bar chart data showing percentages of endometrial FOXP3⁺ and CTLA-4⁺ cells in control (n=8), RIF (n=16), and RM (n=16) women in their mid-luteal phase. (E) Spearman correlations of FOXP3⁺ and CTLA-4⁺ cells in the endometrium of the three groups. *P<.05, **P<.01. Scale bars=100 μm, with insets=10 μm

Uterine microbiota may contribute to healthy endometrium physiology.



Conclusions



- Local endometrial injury, HCG, PBMC and PBMC & CRH, use may improve pregnancy outcomes in women with unexplained RIF

- ?? How it works: not entirely known (**Inflammation**)

- **Use under approved clinical trials with appropriate patient consent**

- Need for appropriate randomized trials comparing **standardized research interventions** with **no intervention** in a **well-defined RIF patient population**

Conclusions



CSF-1 , GH and Atosiban are still to be used only under strict research protocols.

Intralipids needs both basic science and observational evidence to support a clinical trial



THANK YOU!