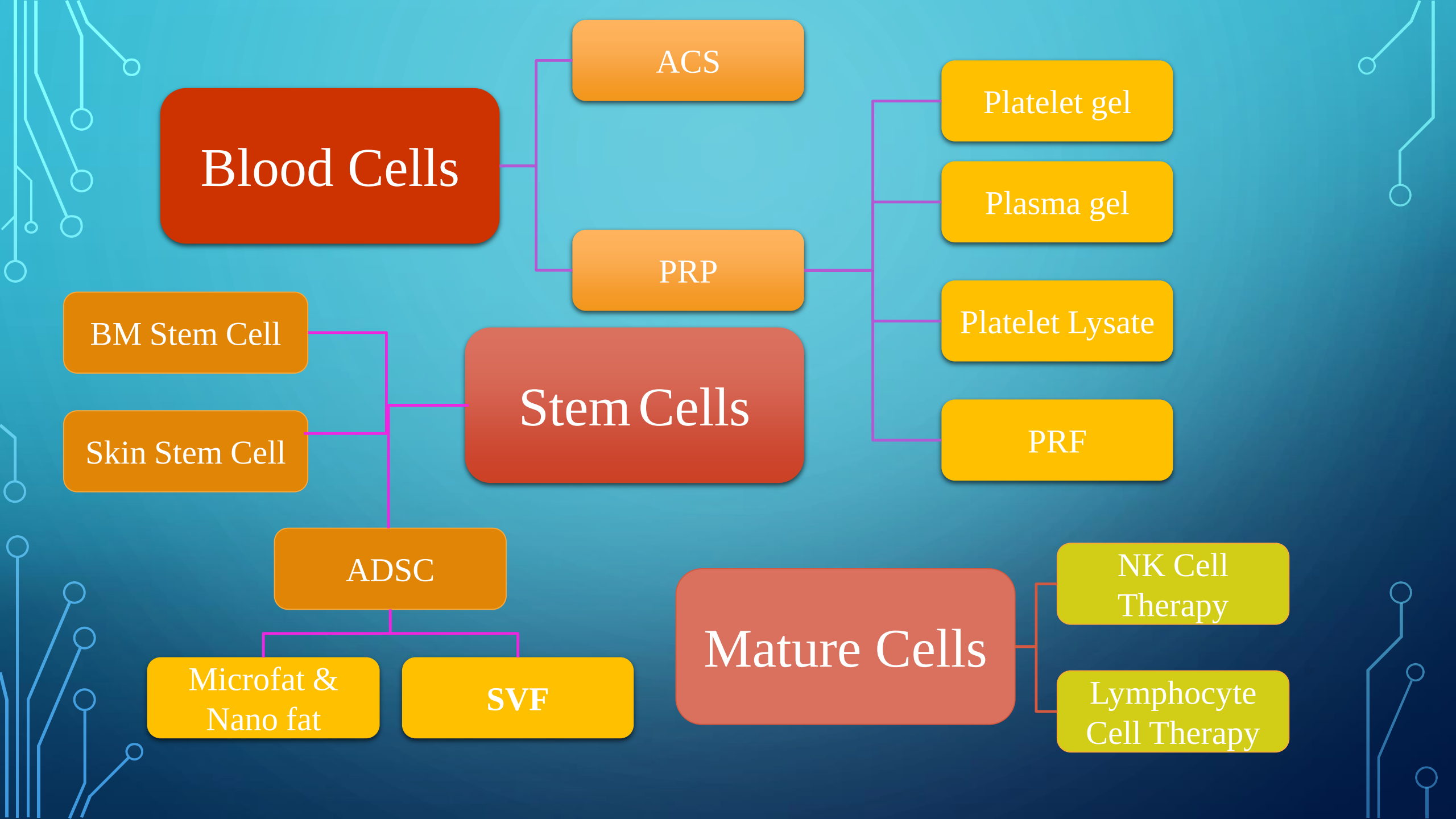
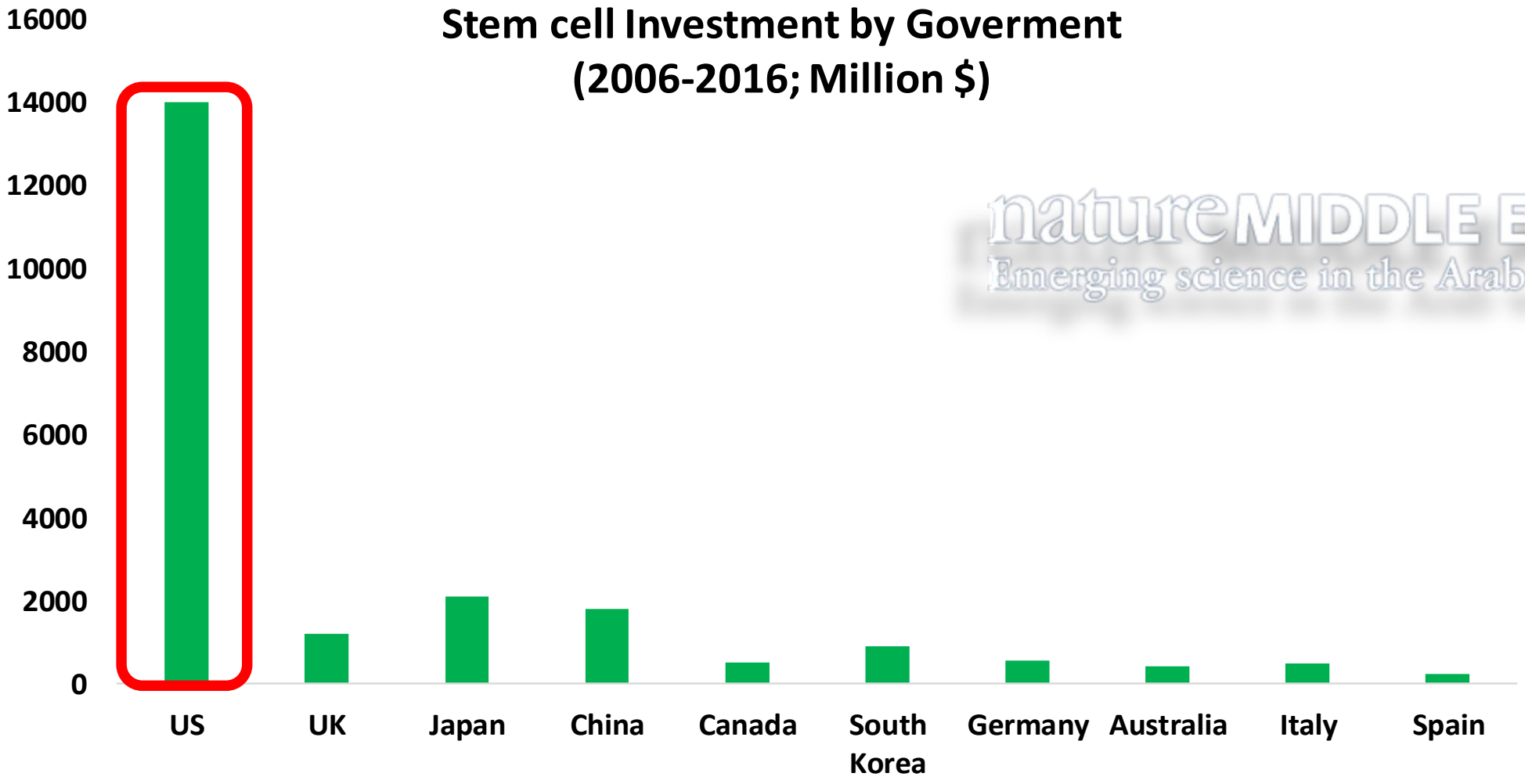
IN THE NAME OF GOD

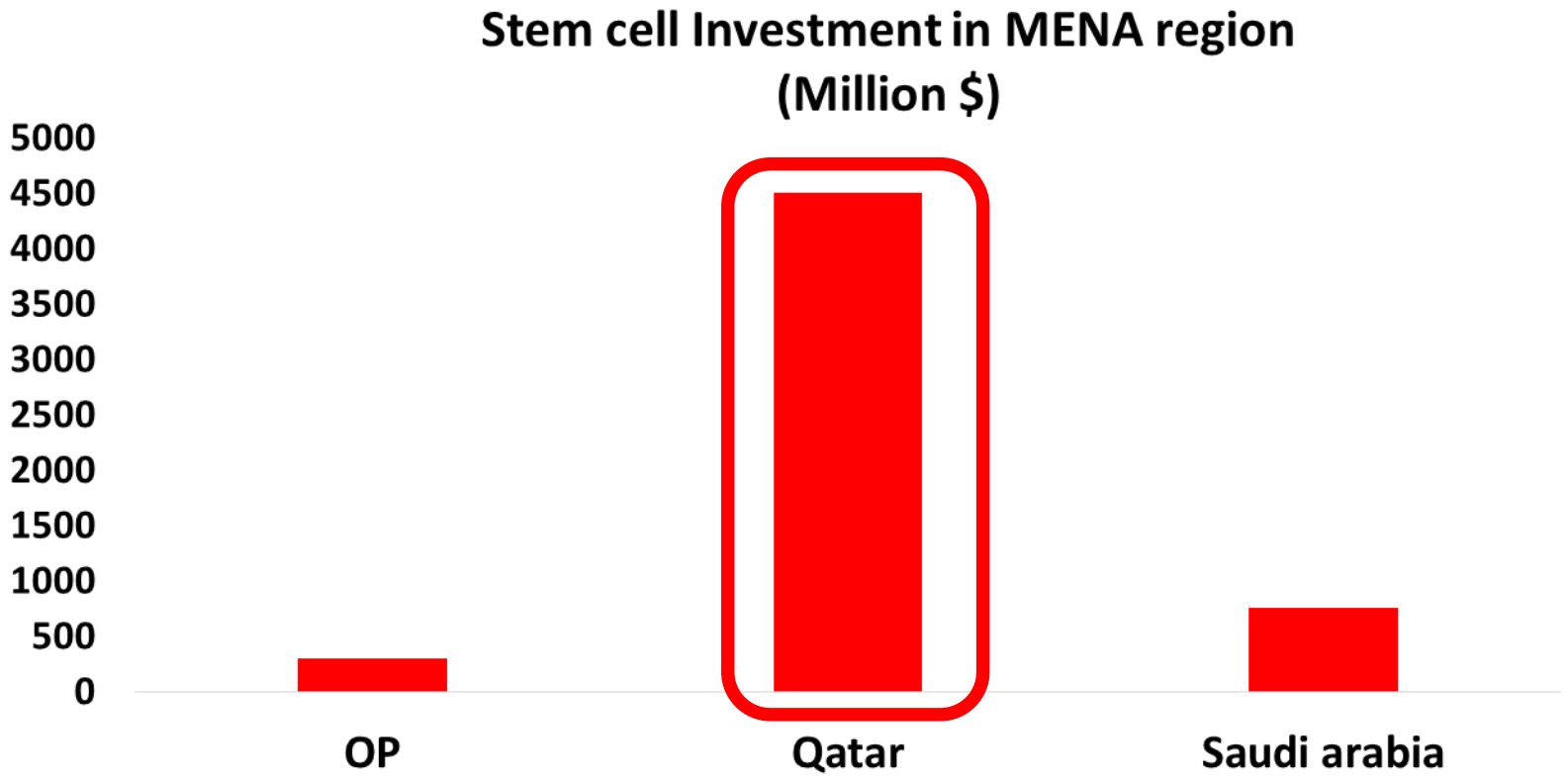

Blood Cells
ACS
PRP
Platelet gel
Plasma gel
Platelet Lysate
PRF
Stem Cells
BM Stem Cell
Skin Stem Cell
ADSC
Microfat & Nano fat
SVF
Mature Cells
NK Cell Therapy
Lymphocyte Cell Therapy

Stem Cell & Regenerative Medicine

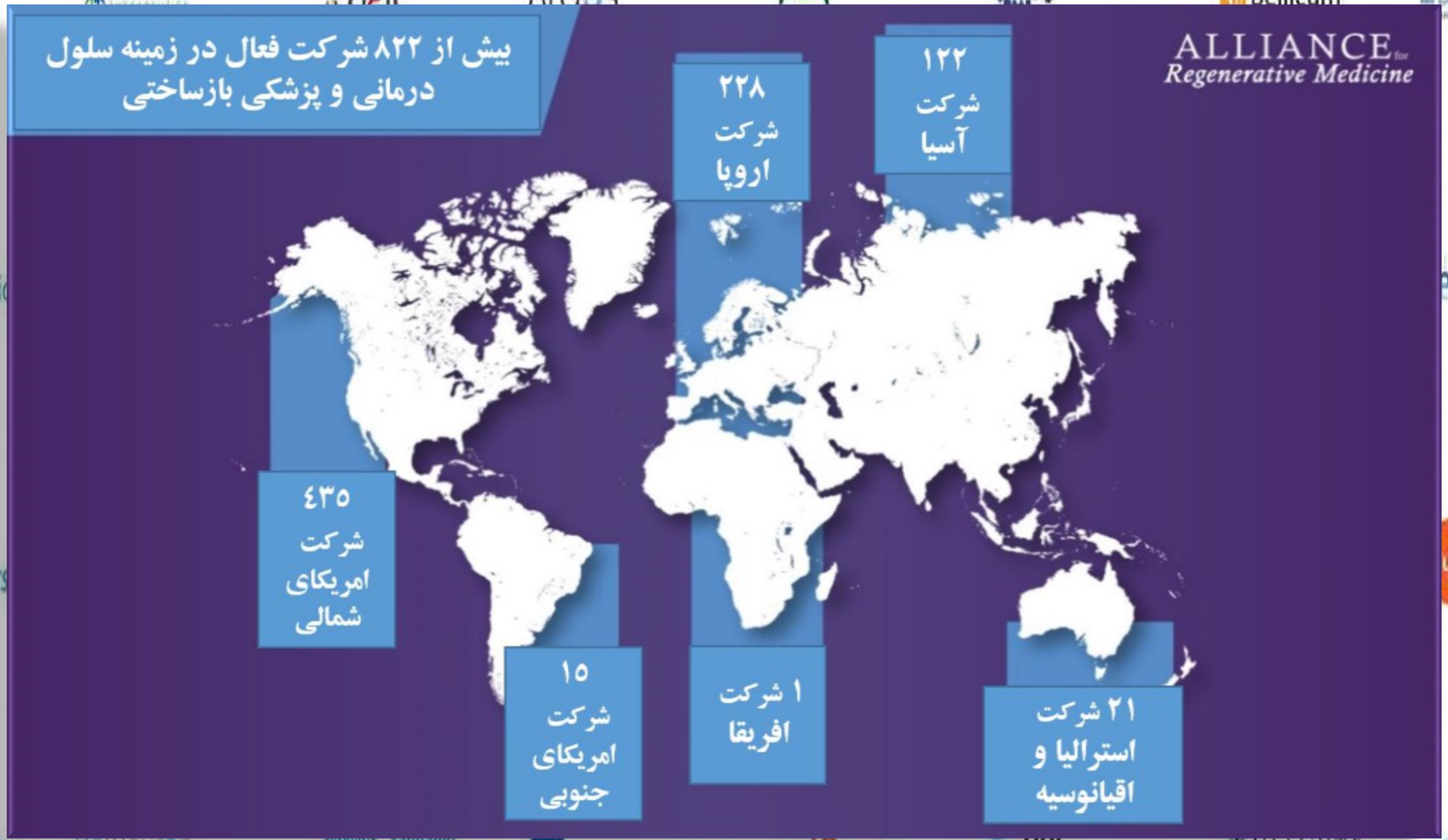
Global Market

Stem cell Investment by Goverment (2006-2016; Million $)




Stem cell Investment in MENA region
(Million $)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
OP
Qatar
Saudi arabia

The Qatar Foundation will have a stem cell laboratory in the **US$4.5 billion** Sidra Medical Centre, and will include a genetics and stem cell unit.

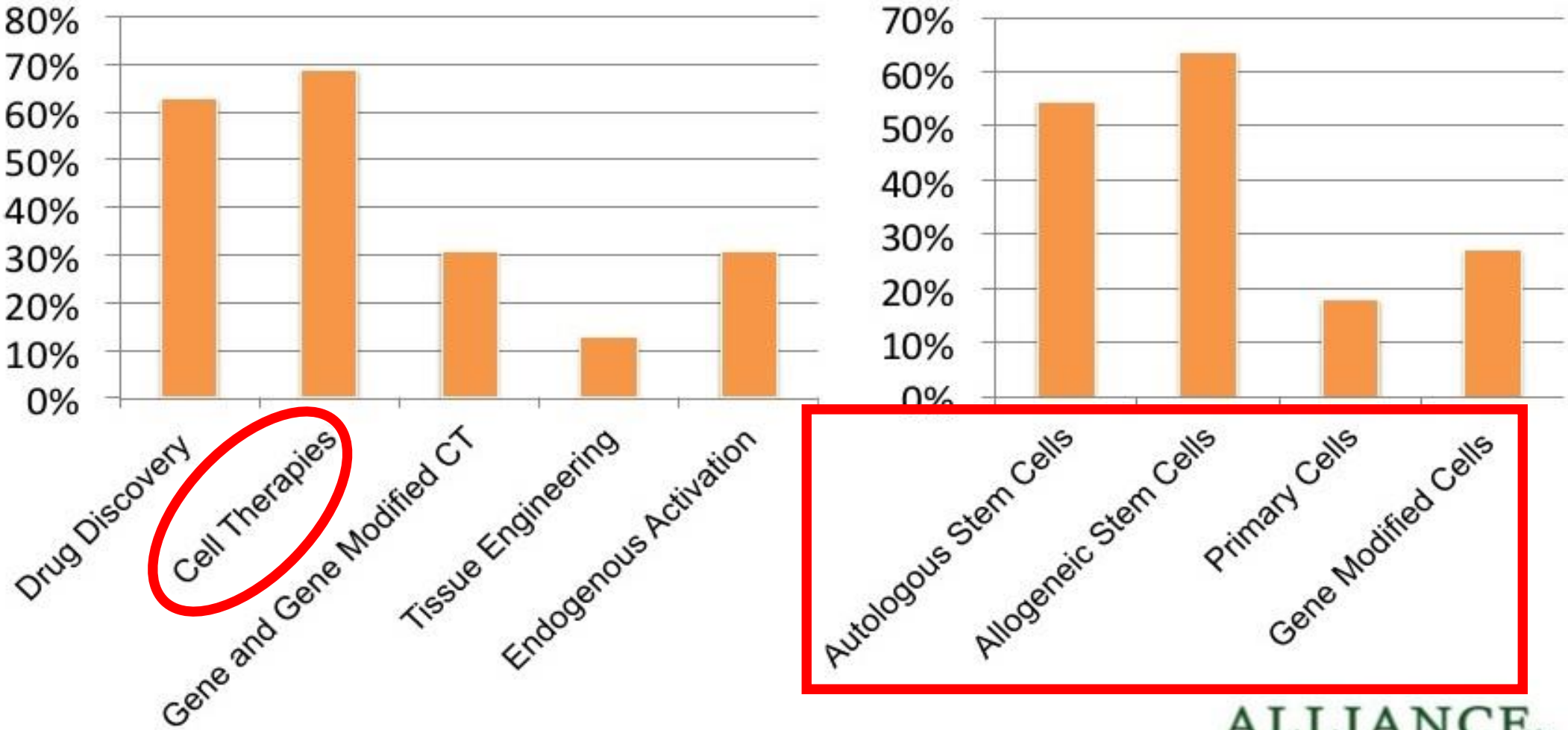

بیش از ۸۲۲ شرکت فعال در زمینه سلول درمانی و پزشکی بازساختی
ALLIANCE for Regenerative Medicine
۱۲۲ شرکت آسیا
۲۲۸ شرکت اروپا
۴۳۵ شرکت امریکای شمالی
۱۵ شرکت امریکای جنوبی
۱ شرکت افریقا
۲۱ شرکت استرالیا و اقیانوسیه

Size of cell therapy market in some countries

Country	No of Clinics	No of Patients
China	> 400	> 50,000
United State	> 350	> 30,000
Russia	> 150	> 20,000
Japan	> 20	> 10,000
India	> 60	> 15,000
South Korea	> 15	> 8,000

Some disciplines have recognized that science based innovation involving a necessary clinical trials stage is not the only available model of innovation.

Where Pharma is Investing in Regenerative Medicine



Survey Participants: *Allergan, Amgen, Baxter, Biogen Idec, Boehringer Ingelheim, Celgene, Eli Lilly, GSK, Johnson & Johnson, Merck Serono, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi-Genzyme, Shire*

ALLIANCE for Regenerative Medicine

Gene and Cellular Therapies and Other Regenerative Medicine Products – Q2 2017 Clinical Trials

899
Clinical trials underway worldwide by mid-year 2017

Ph. I: 284
Ph. II: 539
Ph. III: 76

Number of Clinical Trials Utilizing Specific RM/AT Technology: Q2 2017

Gene Therapy & Gene-Modified Cell Therapy	Cell Therapy	Tissue Engineering
Total: 504	**Total: 586**	**Total: 24**
Ph. I: 184	Ph. I: 174	Ph. I: 6
Ph. II: 286	Ph. II: 365	Ph. II: 14
Ph. III: 34	Ph. III: 47	Ph. III: 4

ALLIANCE for Regenerative Medicine

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

A to Z Index | Follow FDA | En Español

Search FDA

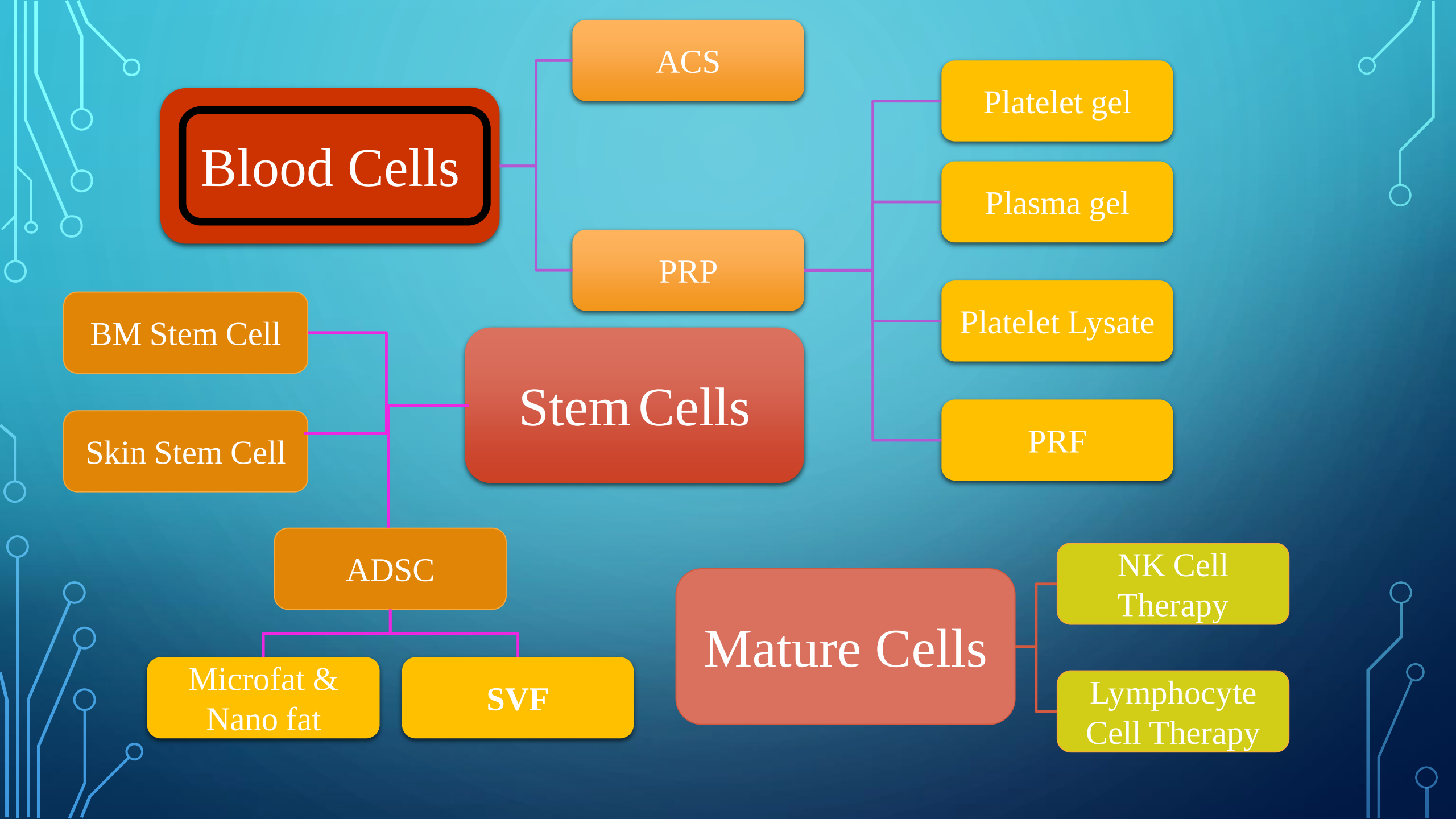
CAR T-Cell Therapy Approved for Children and Young Adults with Leukemia

On August 30, the FDA approved a type of CAR T-cell therapy for certain children and young adults with a form of ALL.

The treatment, Tisagenlecleucel (Kymriah™), is the first CAR T-cell therapy to receive FDA approval.

Manufactured CAR T cells ready for infusion into a patient

Credit: Penn Medicine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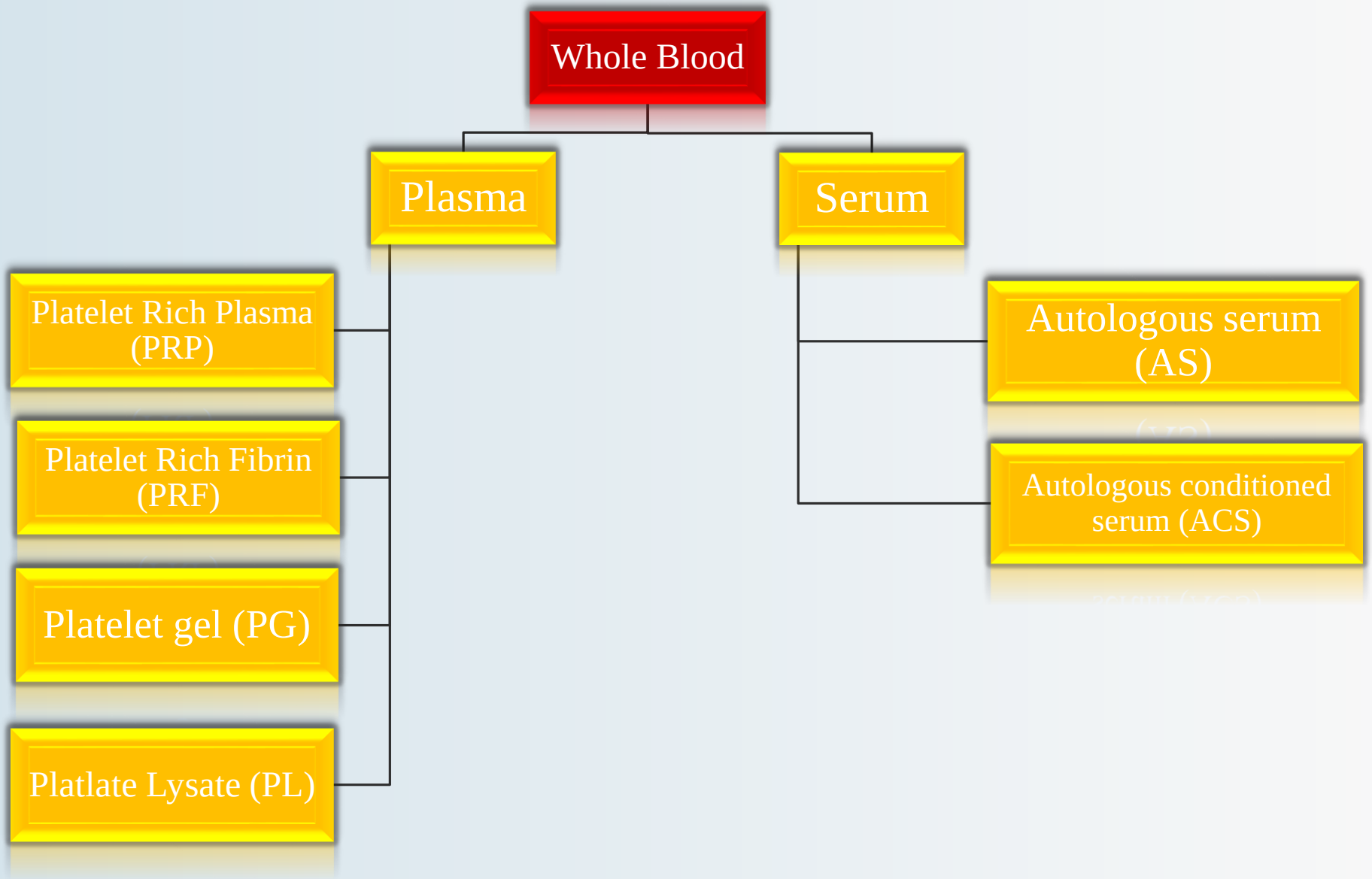
Microfat & Nano fat
SVF
Mature Cells
NK Cell Therapy
Lymphocyte Cell Therapy

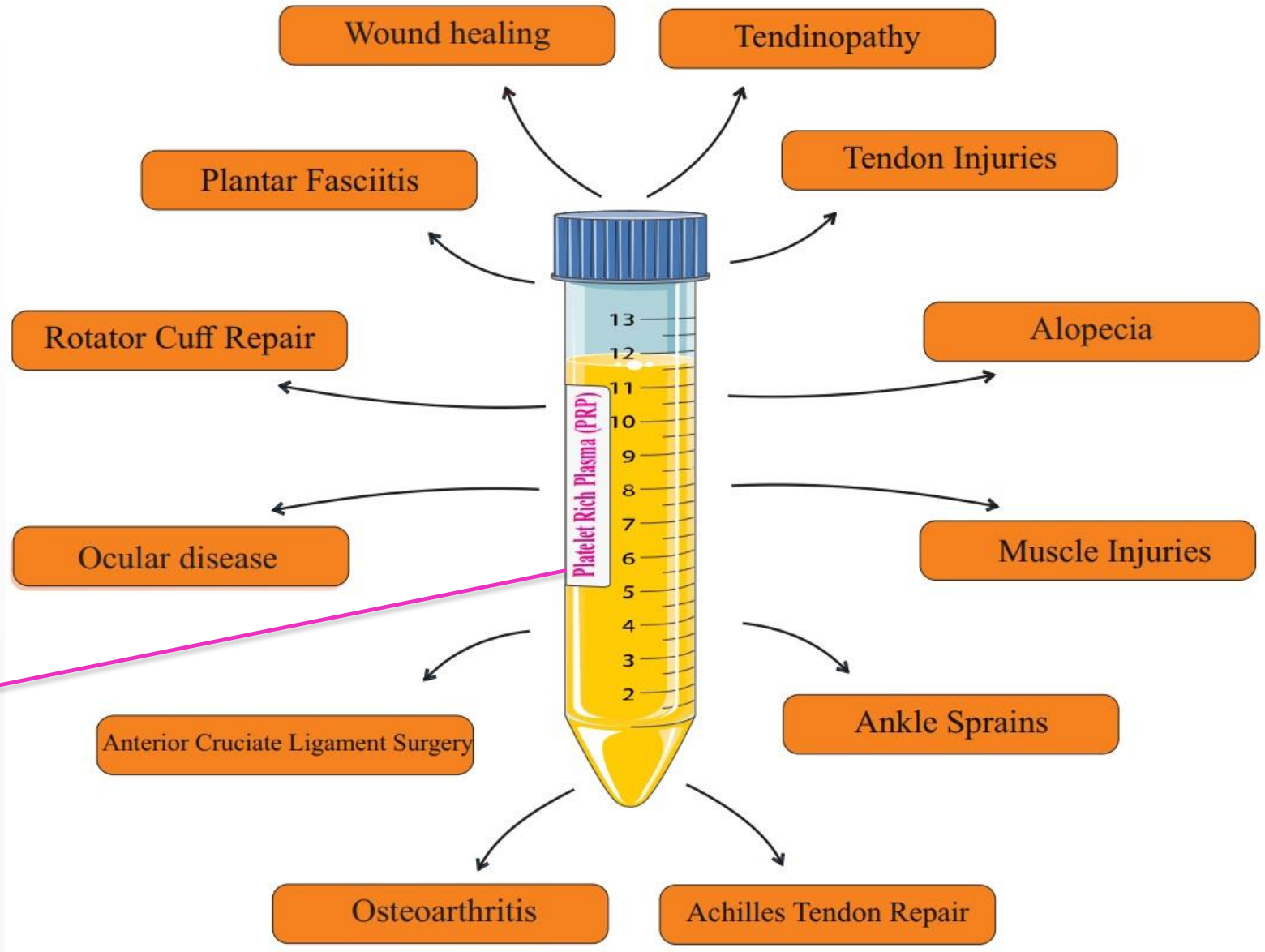
➢ Hemoderivative Materials



Platelet Rich Plasma

(PRP)

➢ Clinical application of PRP



Infertility

Ovarian rejuvenation and folliculogenesis reactivation in peri-menopausal women after autologous platelet-rich plasma treatment

P-401

Pantos K., Nitsos N., Kokkali G., Vaxevanoglou T., Markomichali C., Pantou A., Grammatis M., Lazaros L., Sfakianoudis K.

Centre for Human Reproduction, Genesis Athens Hospital, Chalandri-Athens, Greece

Material & Methods

Subjects

- Eight peri-menopausal women undergoing PRP treatment constituted the study population. All subjects, aged 45.13±4.42 years, had absence of menstrual cycle for 4.88±1.13 months.
- The FSH, LH, E_2 and AMH levels were determined before the PRP treatment and at monthly intervals after the PRP treatment in order to monitor the ovarian function. The presence of developing follicles was confirmed by ultrasound scan.

Results

- The successful ovarian rejuvenation was confirmed by the menstrual cycle restoration **1-3** months after the ovarian PRP treatment.
- The subsequent oocyte retrievals were successful in all cases, resulting in **2.50±0.71 follicles** of **15.20±2.05 mm diameter**, **1.50±0.71 oocytes** and **1.50±0.71 MII oocytes**. All mature oocytes were inseminated by ICSI and the **1.50±0.71 resultant embryos** were cryopreserved at 2pn stage until transfer. To date, no embryo transfer has been performed.

PRP Therapy for Rejuvenation of Ovary in Delhi

What is Ovarian Rejuvenation?

Platelet-rich plasma is a concentrate of platelet-rich plasma protein acquired from whole blood. It is prepared by a method called double centrifugation method, by this method the concentration of platelet is four to five times the normal value. For the treatment, it is prepared from your own blood (autologous), hence it has no side effects.

PRP Treatment for Ovarian Insufficiency

What is ovarian insufficiency?

Request a Call Back

Name

Email

Phone Number

For

Country Code Country Name

Int J Reprod BioMed Vol. 14. No. 10. pp: 625-628, October 2016

Original article

Effects of autologous platelet-rich plasma on implantation and pregnancy in repeated implantation failure: A pilot study

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Department of Obstetrics and Gynecology, Preventive Gynecology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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Tel: (+98) 9123164282
Email: nazari@sbmu.ac.ir

Received: 22 August 2016
Accepted: 28 September 2016

Abstract

Background: Repeated implantation failure (RIF) is a major challenge in reproductive medicine and despite several methods that have been described for management, there is little consensus on the most effective one.

Objective: This study was conducted to evaluate the effectiveness of platelet-rich plasma in improvement of pregnancy rate in RIF patients.

Materials and Methods: Twenty women with a history of RIF who were candidates for frozen-thawed embryo transfer were recruited in this study. Intrauterine infusion of 0.5 ml of platelet-rich plasma that contained platelet 4-5 times more than peripheral blood sample was performed 48 hrs before blastocyst transfer.

Results: Eighteen participants were pregnant with one early miscarriage and one molar pregnancy. Sixteen clinical pregnancies were recorded and their pregnancies are ongoing.

Conclusion: According to this study, it seems that platelet-rich plasma is effective in improvement of pregnancy outcome in RIF patients.

Key words: *Platelet-rich plasma, Implantation, Fertilization in Vitro, Pregnancy rate, Repeated implantation failure.*

RANDOMIZED CONTROLLED TRIAL EVALUATING EFFICACY OF AUTOLOGOUS PLATELET -RICH PLASMA THERAPY FOR PATIENTS WITH RECURRENT IMPLANTATION FAILURE.

D. Obidniak,[a] A. Gzgzyan,[b] A. Feoktistov,[c] D. Niauri.[d] [a]Medical faculty, Saint-Petersburg State University, Saint-Petersburg, Russian Federation; [b]Saint-Petersburg State University, Saint-Petersburg, Russian Federation; [c]Medical group, Saint-Petersburg, Russian Federation; [d]OB/GYN, Saint-Petersburg, Russian Federation.

OBJECTIVE: to evaluate if the intrauterine perfusion (IP) with autologous platelet-rich plasma (PRP) enhances frozen-thawed embryo transfer effectiveness in patients with repeated implantation failure (RIF).

DESIGN: Study type: Interventional. Study Design: randomized controlled study. Intervention Model: Parallel Assignment. Masking: open-label.

MATERIALS AND METHODS: After obtaining institutional review board approval, 90 women aged 28 - 39 years were involved Matching criteria: RIF, normal karyotype, absence of uterine factors of infertility, absence of chromosomal abnormalities in previous pregnancy. 2 groups of patients: study group (N = 45): single IP with 2.0 ml of autologous PRP; control group: no therapy (N = 45). Endometrium preparation was carried out according to standardized protocol of hormone replacement therapy. PRP preparation is carried out using patented tubes "Plasmolifting" (patent #2494788). Primary outcome measures were clinical pregnancy rate and implantation rate. Secondary outcome measures were pregnancy loss rate, endometrial thickness and adverse event.

RESULTS: The clinical pregnancy rate was higher in the study group (53.3% vs 24.4%) (*OR* = 3.63, 95 % *CI* 1.48-8.90, $p < 0,01$). The implantation rate differed significantly: in the study group it revealed 40.5% ; in the control group - 20.9% (*OR* = 2.43, 95 % *CI* 1.13-5.21, $p < 0,05$). The endometrium thickness was significantly higher in the study group (*OR* = 2.91, 95 % *CI* 1.37-7.21, $p < 0,05$). The pregnancy rate loss did not differ between groups. No adverse event was noted.

CONCLUSIONS: 1. The intrauterine perfusion with autologous PRP should be considered perspective, safe and cost-effective therapy method for patients with RIF. 2. PRP does not influence on pregnancy loss rate. 3. Further study is required.

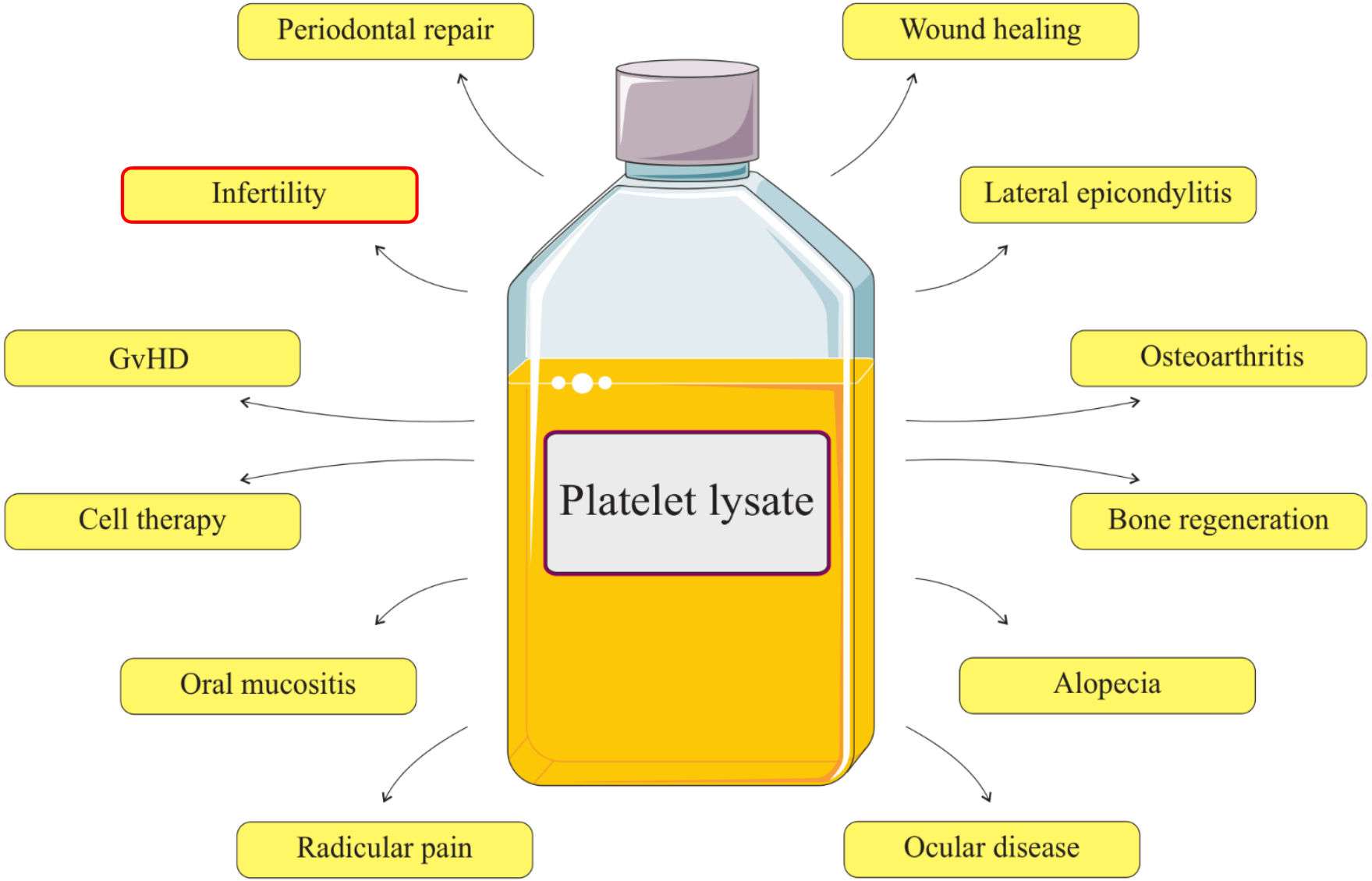
RESULTS OF PRP THERAPY ARE STEEL CONTROVERCIAL????

- Platelet Count
- WBC Count
- Patient Criteria

Platelet Lysate

(PL)

➢Clinical application of Platelet Lysate



Autologous Conditined Serum

(ACS)

A)

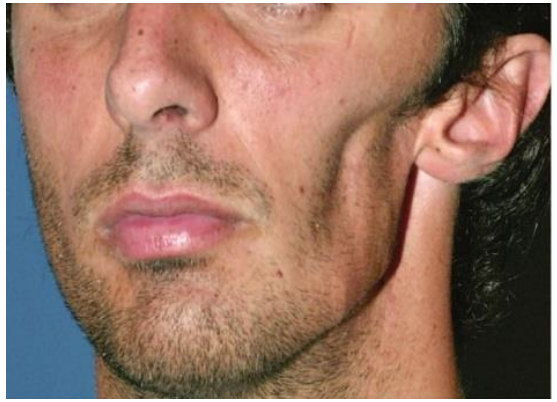
Cytokines and growth factors present in autologous conditioned serum

Cytokine	N	Basal Concentration	Concentration in ACS
IL-1Ra	224	236	2015
IL-1β	224	UD	7.9
IL-6	200	UD	28.7
TNF-α	92	UD	10.1
IL-10	92	UD	33.4
FGF-2	92	14.6	26.6
VEGF	92	61	508.6
HGF	92	431	1339
IGF-1	92	86,000	117,209
PDGF AB	92	205	39,026
TGF-β	80	1165	97,939

Adipose-Derived Tissue

Nanofat

Nano and Micro Fat



1A

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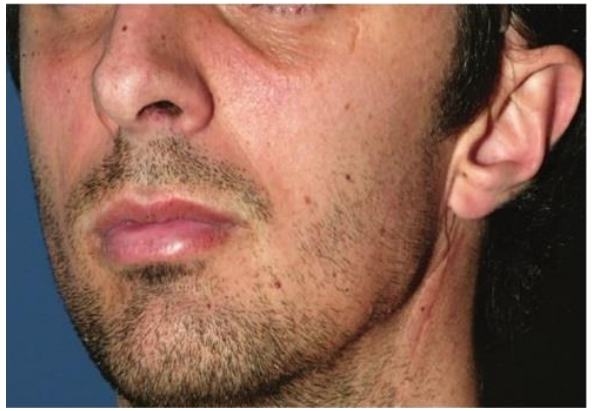

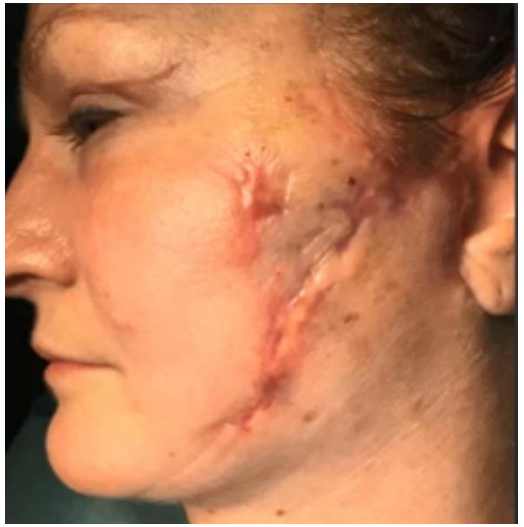

2A

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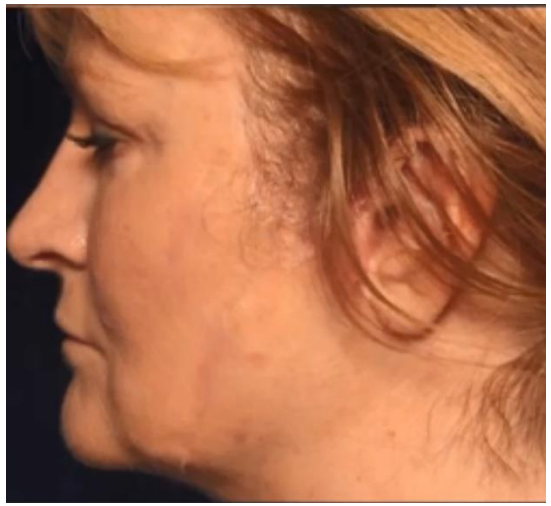
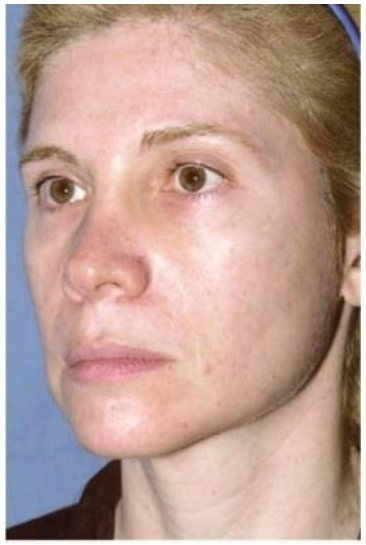
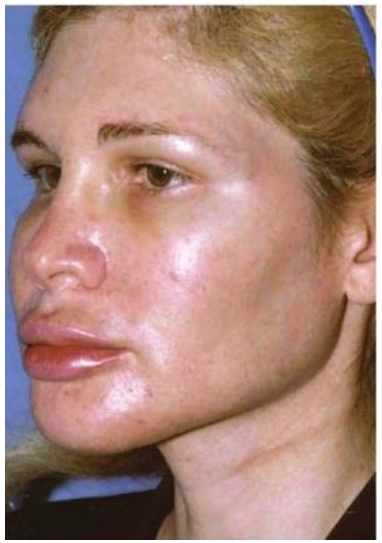
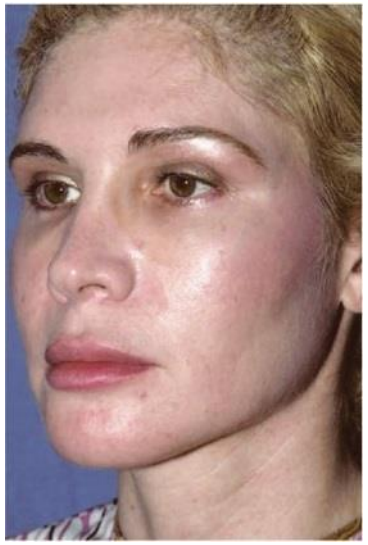




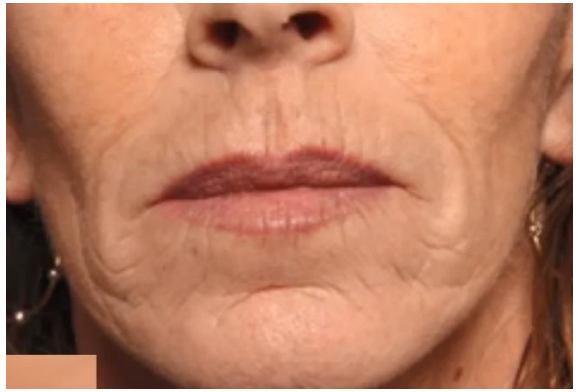




3A

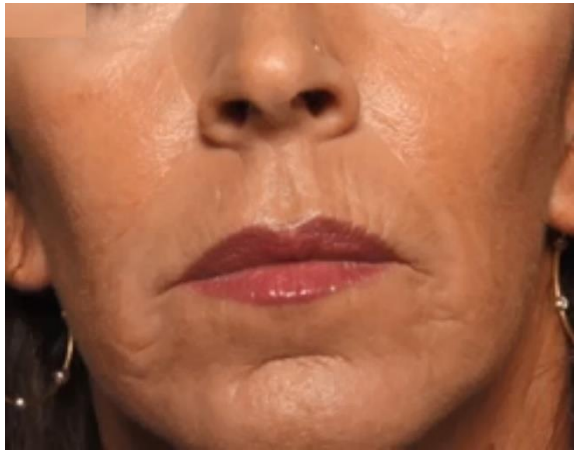
3B

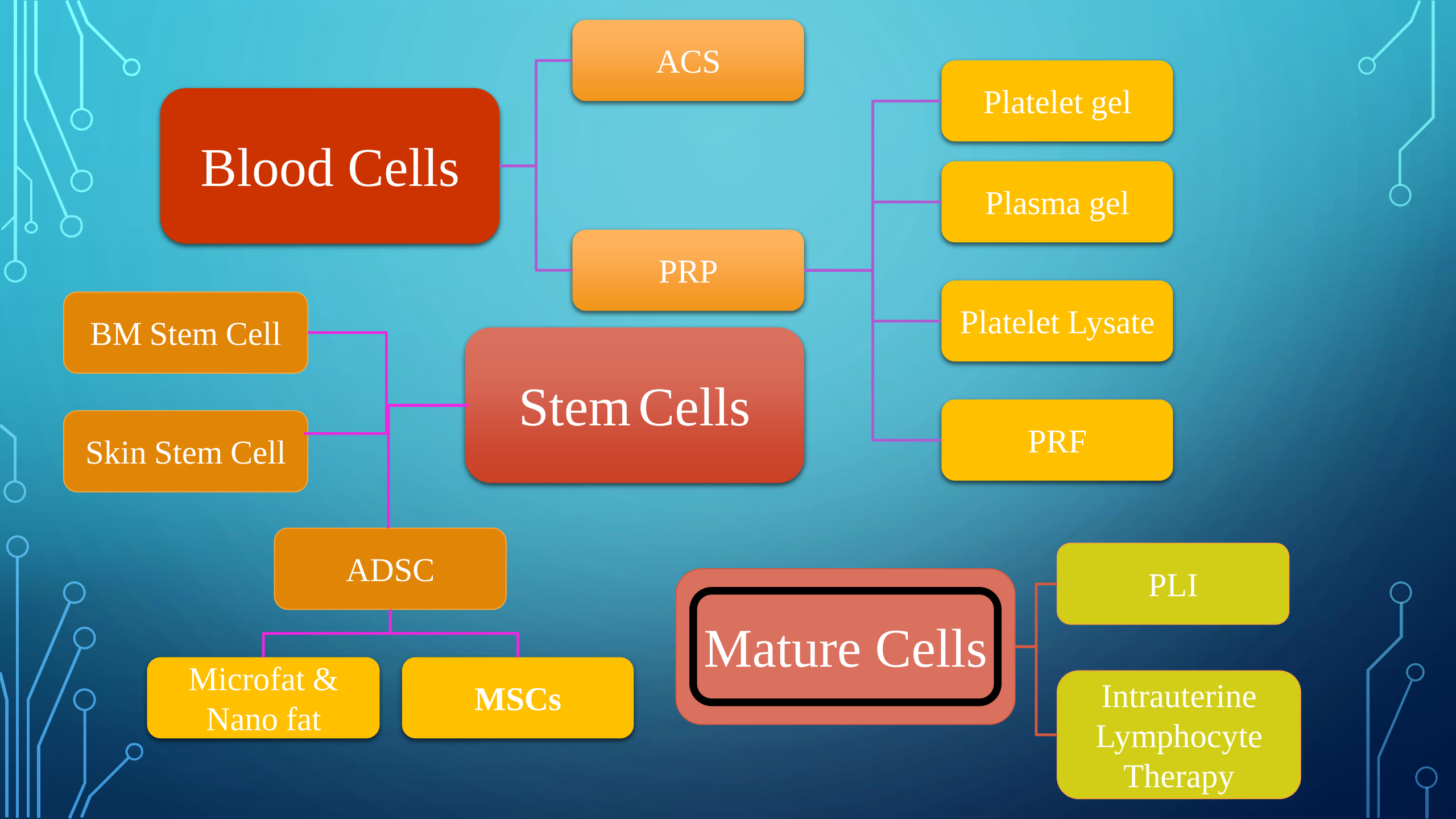
3C



4A

4B

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Skin Stem Cell
ADSC
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MSCs
Mature Cells
PLI
Intrauterine Lymphocyte Therapy

Terminology (Kolte et al., 2014)

- **Recurrent Pregnancy Loss: RPL**
- **Habitual abortion**
- **Habitual miscarriage**
- **Recurrent abortion**
- **Recurrent Miscarriage: RM**

Recurrent miscarriage (RM)

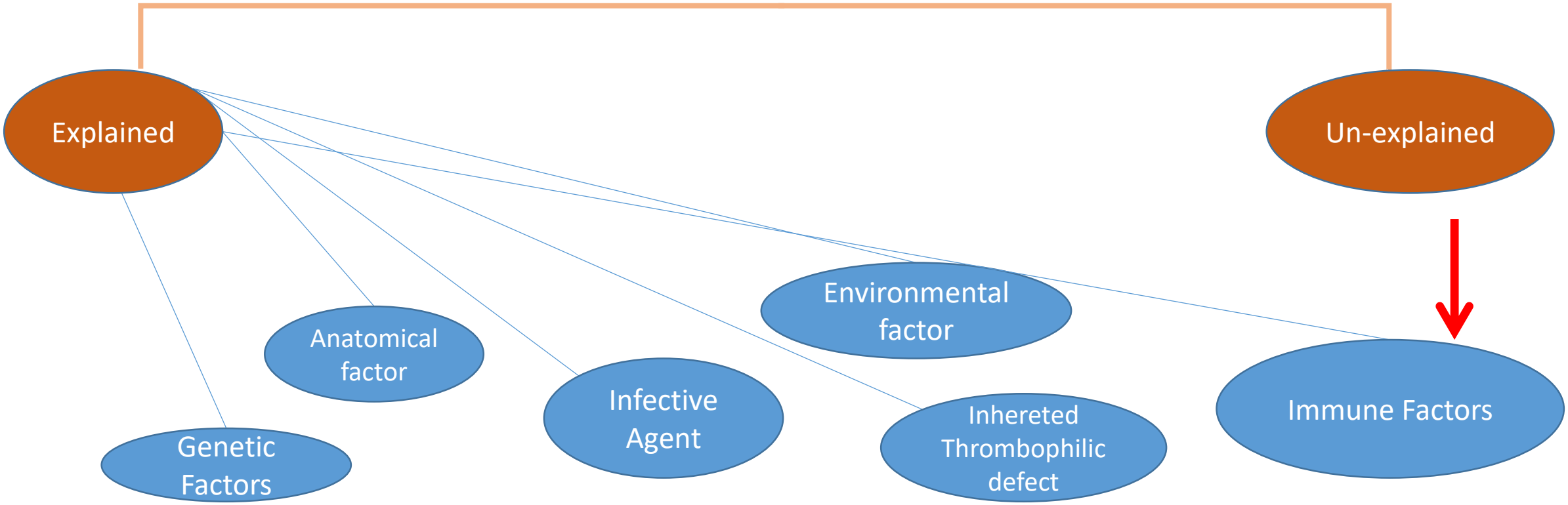
Definition

- RM is 3 or more consecutive, spontaneous pregnancy loss, under 20 weeks gestation from the last menstrual period, by the same partner

- The incidence of RM is variable range from 0.5% to 2.3%

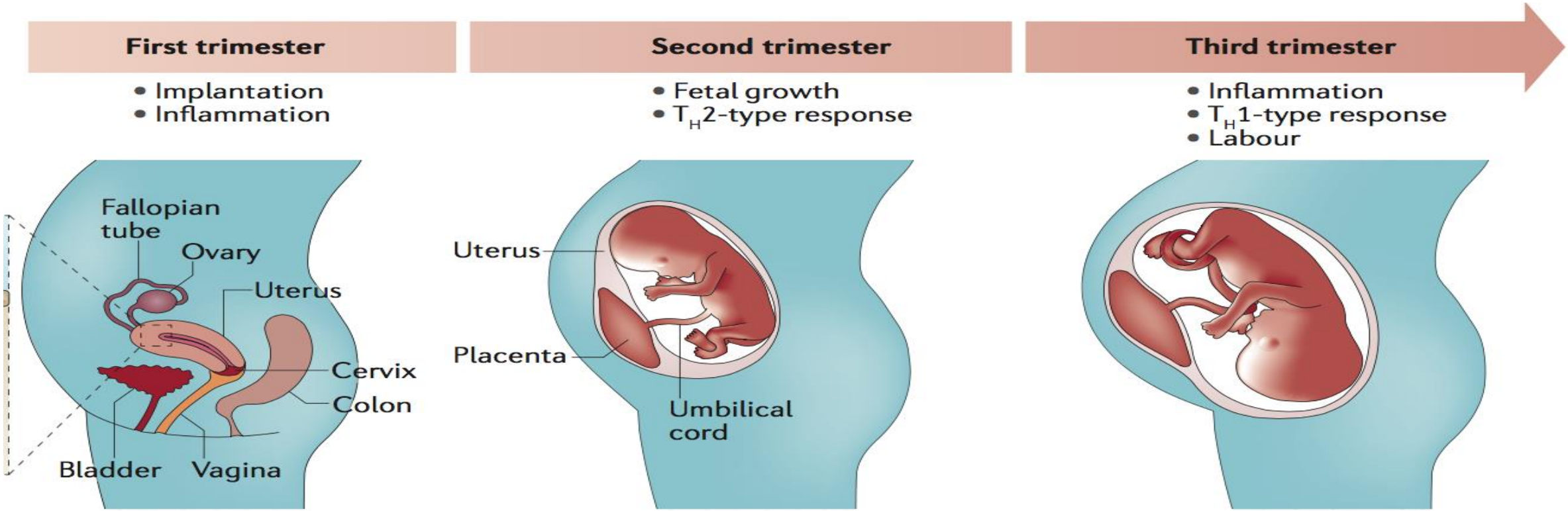
- According to the guidelines of the American Society for Reproductive Medicine (ASRM) and European Society of Human Reproduction and Embryology (ESHRE), the cause of RM is diagnosed in only half of patients. Therefore, reproductive immunology can help to uncover a considerable number of idiopathic RM

Possible causes



A successful pregnancy : a dynamic immunologic process

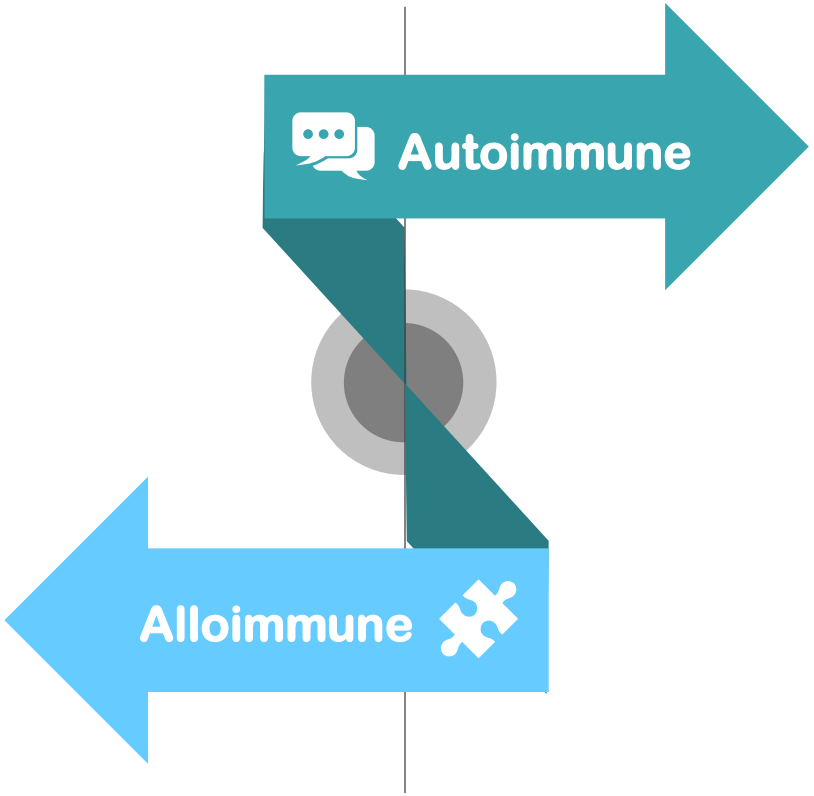
Depends on the ability of the maternal immune system to change and adapt to each specific developmental stage

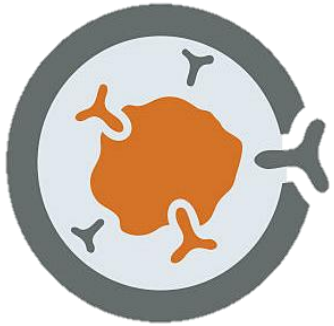


Immunologic factors (Lim et al., 1996)

alteration in cellular immunity

Alloimmune-(Immunity against non self)
An abnormal maternal immune response to fetus or placenta



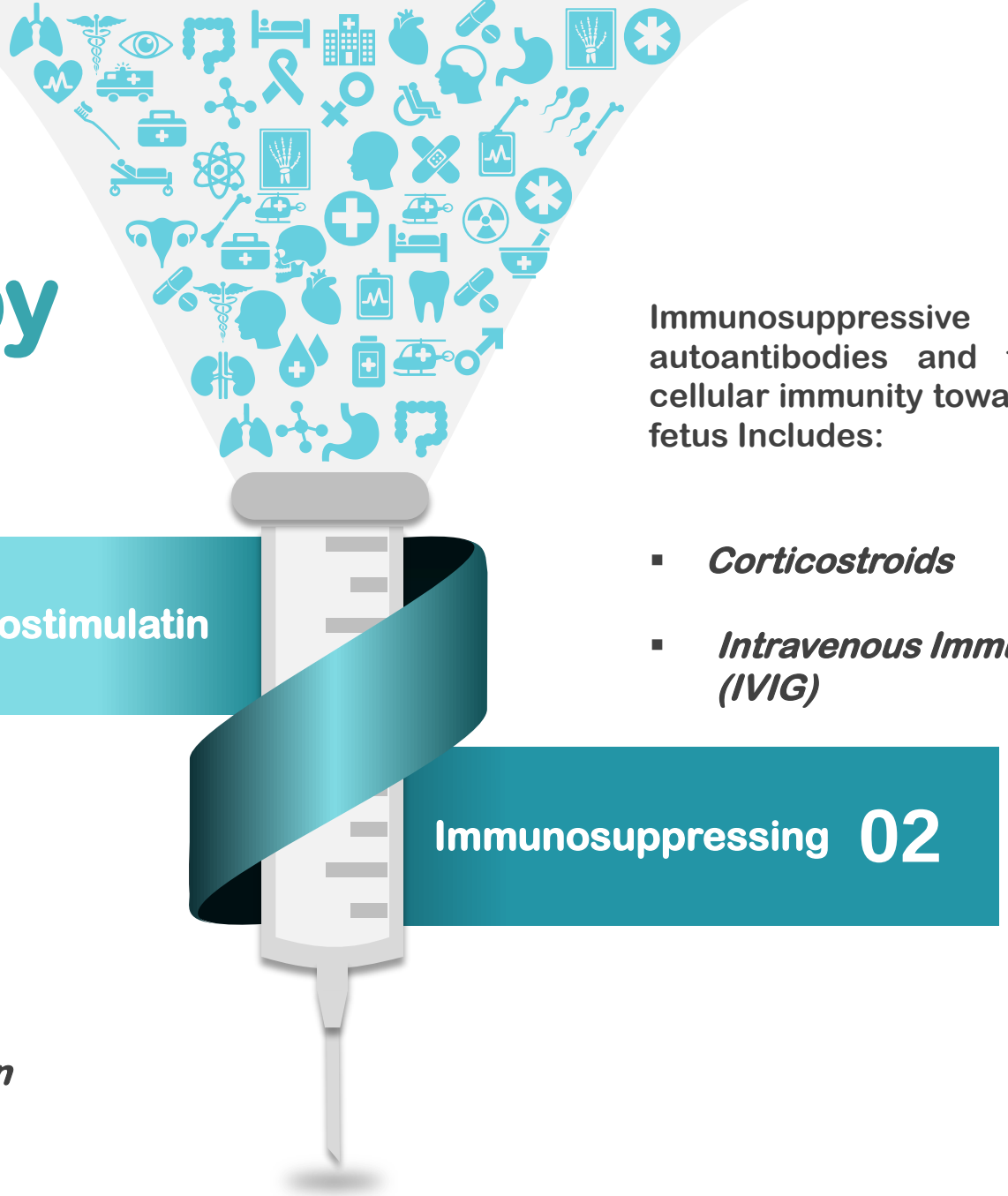


mediated by humoral factors

Autoimmune-(immunity against self)
Either antiphospholipid antibodies or other auto antibodies (Systemic Lupus Erythmatosus)

Immunotherapy

(Porter et al., 2006)



01 Immunostimulating

Includes:

- ***Leukocyte immunization:***
  - Stimulation of the maternal immune system using alloantigens on either paternal or pooled donor leukocytes
  - It poses significant risk to both the mother and her fetus.
- ***Trophoblast membrane immunization***
- ***Third party donor immunization***

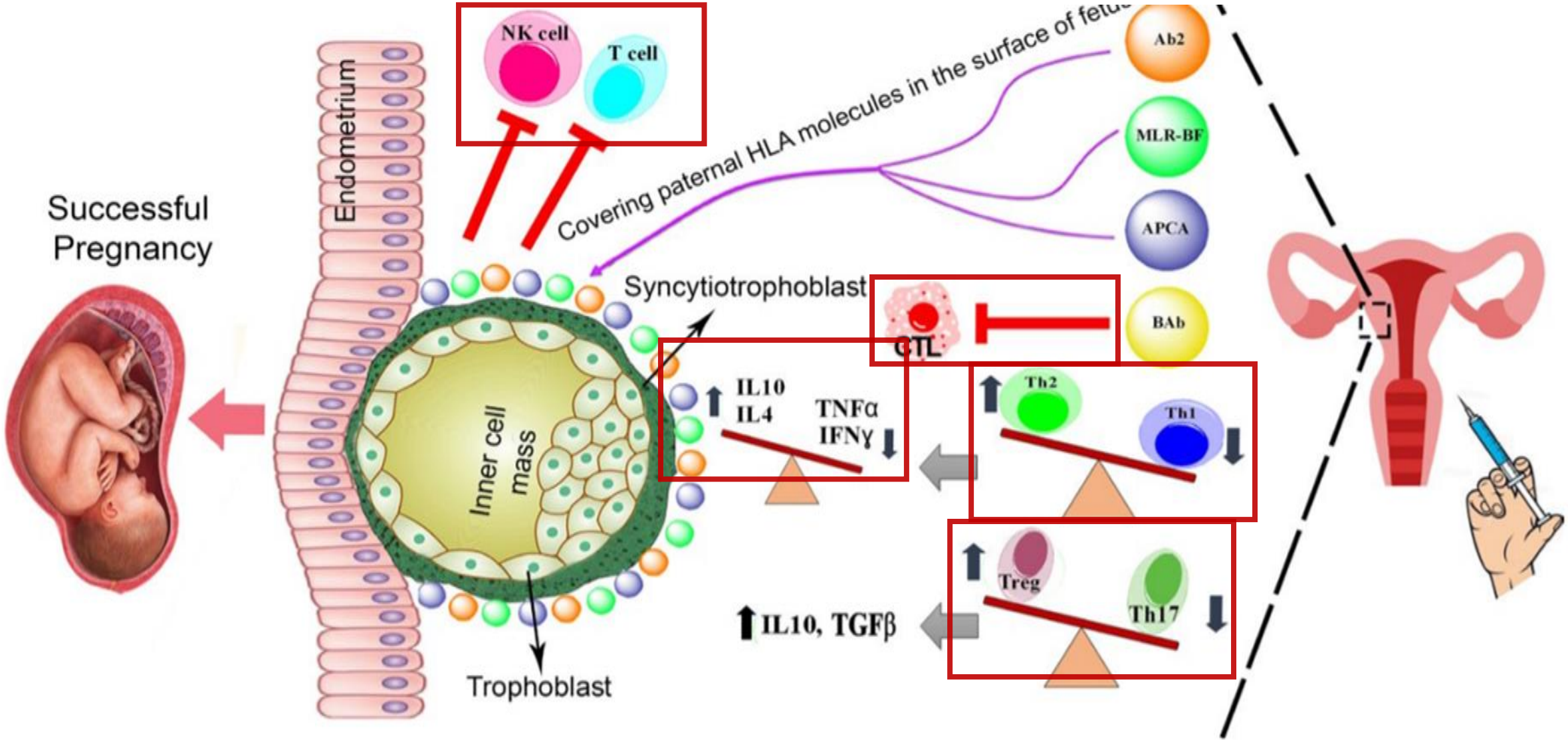
Immunosuppressing 02

Immunosuppressive therapies for autoantibodies and to inappropriate cellular immunity toward the implanting fetus Includes:

- ***Corticostroids***
- ***Intravenous Immunoglobulin (IVIG)***

APCA and Blocking Abs

- ✓ blocking antibodies (BA) inhibit mixed lymphocyte reaction and are also anti-mitogenic in nature.
- ✓ Mixed lymphocyte reaction blocking antibodies are specific to the husband's lymphocytes.
- ✓ During normal pregnancy and after lymphocyte immunotherapy **blocking antibodies** are developed.
- ✓ positive rate of **APCA** was significantly higher in recurrent spontaneous abortion (RSA) **women with successful pregnancy (82.4%) compared to the abortion group (10%)**


Successful Pregnancy
Endometrium
NK cell
T cell
Covering paternal HLA molecules in the surface of fetus
Ab2
MLR-BF
APCA
BAb
Syncytiotrophoblast
CTL
IL10
IL4
TNFα
IFNγ
Th2
Th1
Inner cell mass
Treg
Th17
IL10, TGFβ
Trophoblast

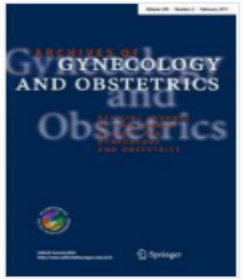
Times, doses and Type of injection of Lymphocyte immunotherapy

Ref	Time of infusion	Dose of lymphocyte per treatment	Site and type of injection
Gatenby et al[155]	2 times with 4-6 weeks of intervals	40 × 10^6 PBML	Intradermal into the forearms
Hasegawa et al[156]	2 times with 4 weeks of intervals	1 × 10^8 lymphocyte/mL (NS)	Intradermal
Agrawal et al[146]	6 times with 4 weeks of intervals	5 × 10^6 lymphocyte/mL (NS)	Intradermal into the forearms
Pandey et al[44]	Maximum of 6 times with 4 weeks of intervals (stopped when MLR-Bf ≥30 was achieved)	5 × 10^6 lymphocyte/mL (NS)	Intradermal, intramuscular subcutaneous and intravenous routes at four separate sites on the forearms
Gharesifard et al[36]	Maximum of 3 times with 5 weeks of intervals	100-200 × 10^6 Mononuclear cells	Forearms
Wu et al[100]	4 times with 3 weeks intervals, (maintained the therapy every 6 weeks before the pregnancy)	2-3 × 10^7 lymphocyte/mL (NS)	Intradermal
Gharesifard et al[140]	Maximum of 3 times with 5 weeks of intervals	50-100 × 10^6 mononuclear cells	Not mentioned
Cavalante et al[119]	3 times with 3 weeks intervals (booster immunization every 3 months while attempting pregnancy)	80-100 × 10^6 lymphocyte	Intradermal into the forearms
Motak et al[157]	2-6 times before the planned pregnancy with 2 weeks of intervals	100-277 × 10^6 lymphocyte	Subcutaneously in eight places on the upper lateral surface of both forearms
Liu et al[120]	3 times with 3 weeks intervals before pregnancy and 2 times with 8 weeks intervals after the conception	1 × 10^7 PBMC	Intradermal

Clinical trial studies on lymphocyte immunotherapy (LIT) in patients with recurrent pregnancy loss (RPL)

Studies	Year	Autologous LIT (AL)	Paternal LIT (PL)	Third-party LIT (TPL)	Pregnancy outcome	Possible mechanism of action
Ramhorst et al[107]	2000	No	Yes	No	N = 92 treated and 37 control Pregnancy: 58% vs 46%	Production of MLR-BFs
Motak-Pochrzęst[89]	2015	No	Yes	No	N = 100 treated (RPL and/or RIF) Pregnancy: 44% Live birth: 30%	Alteration in the levels of TNF-α, IFN-γ, IL-4, IL-10 as well as PBL profile and NK cell activity
Cavalcante et al[119]	2015	No	Yes	No	N = 106 treated Pregnancy: 100% Live birth: 77.35%	Not evaluated
Chen et al[159]	2016	No	Yes	No	N = 380 treated Pregnancy: 89.7%	Not evaluated
Liu et al[120]	2017	No	Yes	No	N = 46 treated (URPL) Pregnancy: 67.18% Live birth: 74.42%	Reduction of Th1 Enhancement of Th2 Increasing of TGFβ

Systematic review



Archives of Gynecology and Obstetrics
February 2017, Volume 295, Issue 2, pp 511–518 | Cite as

Lymphocyte immunotherapy in the treatment of recurrent miscarriage: systematic review and meta-analysis

Authors | Authors and affiliations

Marcelo Borges Cavalcante, Manoel Sarno, Edward Araujo Júnior, Fabricio Da Silva Costa, Ricardo Barini

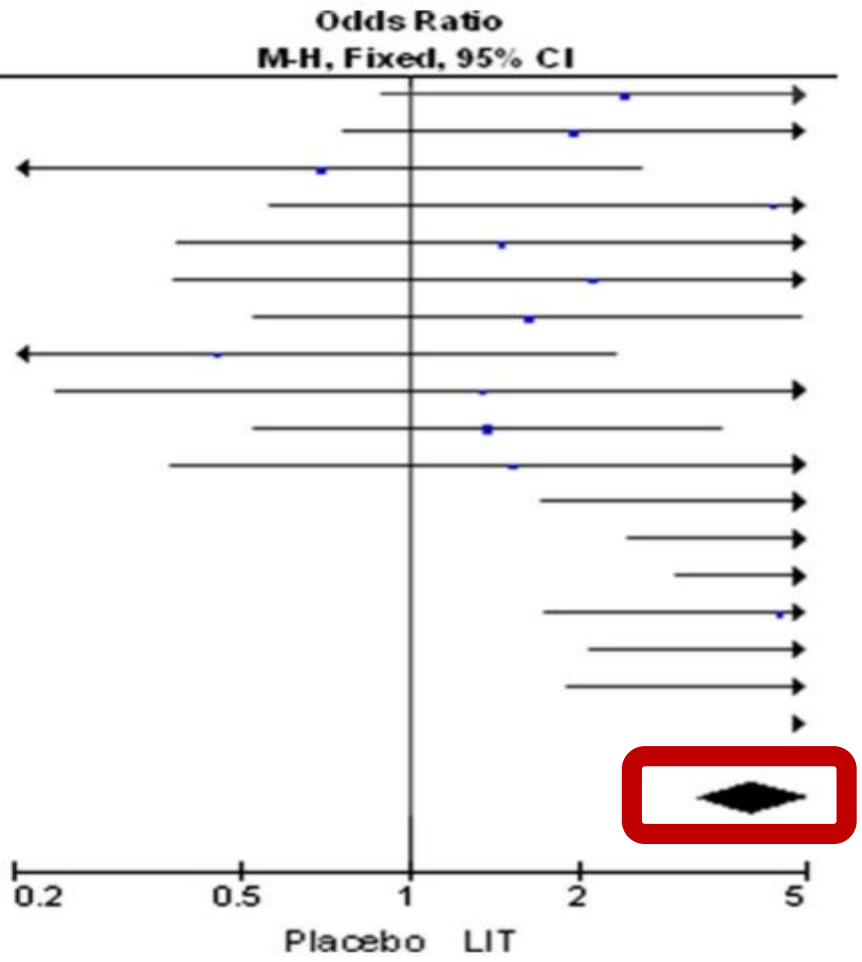
Gynecologic Endocrinology and Reproductive Medicine
First Online: 21 December 2016

Pregnancy Rate

Study or Subgroup	LIT Events	LIT Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Mowbray 1985	25	37	14	30	5.9%	2.38 [0.88, 6.43]	1985
Ho 1991	33	42	32	49	7.5%	1.95 [0.76, 5.00]	1991
Cauchi 1991	13	20	16	22	6.3%	0.70 [0.19, 2.59]	1991
Clark 1991	7	11	2	7	1.1%	4.38 [0.56, 33.95]	1991
Gatenby 1993	13	19	12	20	4.4%	1.44 [0.39, 5.39]	1993
Scott 1994	6	10	5	12	2.2%	2.10 [0.38, 11.59]	1994
Reznikoff 1994	17	26	14	26	5.7%	1.62 [0.53, 4.95]	1994
Illeni 1994	10	16	11	14	5.2%	0.45 [0.09, 2.32]	1994
Kilpatrick 1994	8	12	6	10	2.6%	1.33 [0.23, 7.63]	1994
Christiansen 1994	31	48	16	28	8.5%	1.37 [0.53, 3.55]	1994
Carp 1997	5	11	11	31	3.7%	1.52 [0.37, 6.12]	1997
Pandey 2002	12	14	1	5	0.2%	24.00 [1.69, 340.99]	2002
Hong 2003	18	21	2	8	0.5%	18.00 [2.40, 134.83]	2003
Pandey 2004	21	25	6	20	1.3%	12.25 [2.92, 51.42]	2004
Yanping 2011	41	49	24	45	4.8%	4.48 [1.72, 11.68]	2011
Lin 2012	33	42	17	42	4.3%	5.39 [2.06, 14.09]	2012
Aiwu 2013	32	39	18	39	3.8%	5.33 [1.90, 14.97]	2013
Bin 2013	250	297	254	591	31.9%	7.06 [4.97, 10.03]	2013
Total (95% CI)		**739**		**999**	**100.0%**	**4.02 [3.23, 5.00]**	
Total events	575		461				

Heterogeneity: Chi² = 47.53, df = 17 (P = 0.0001); ² = 64%

Test for overall effect: Z = 12.43 (P < 0.00001)

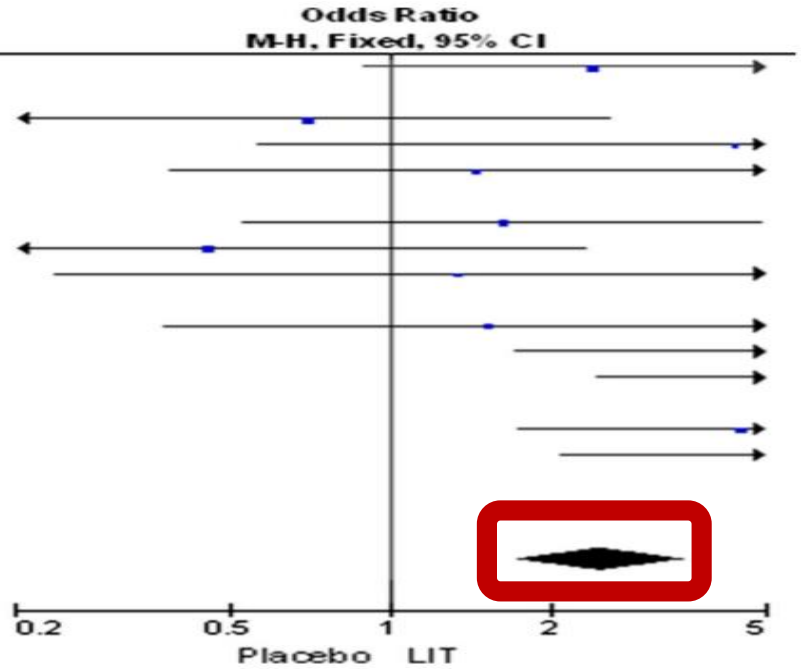


Live Birth Rate

Study or Subgroup	LIT Events	LIT Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Mowbray 1985	25	37	14	30	13.2%	2.38 [0.88, 6.43]	1985
Ho 1991	33	42	32	49	0.0%	1.95 [0.76, 5.00]	1991
Cauchi 1991	13	20	16	22	14.1%	0.70 [0.19, 2.59]	1991
Clark 1991	7	11	2	7	2.3%	4.38 [0.56, 33.95]	1991
Gatenby 1993	13	19	12	20	9.8%	1.44 [0.39, 5.39]	1993
Scott 1994	6	10	5	12	0.0%	2.10 [0.38, 11.59]	1994
Reznikoff 1994	17	26	14	26	12.8%	1.62 [0.53, 4.95]	1994
Illeni 1994	10	16	11	14	11.6%	0.45 [0.09, 2.32]	1994
Kilpatrick 1994	8	12	6	10	5.8%	1.33 [0.23, 7.63]	1994
Christiansen 1994	31	48	16	28	0.0%	1.37 [0.53, 3.55]	1994
Carp 1997	5	11	11	31	8.3%	1.52 [0.37, 6.12]	1997
Pandey 2002	12	14	1	5	0.6%	24.00 [1.69, 340.99]	2002
Hong 2003	18	21	2	8	1.1%	18.00 [2.40, 134.83]	2003
Pandey 2004	21	25	6	20	0.0%	12.25 [2.92, 51.42]	2004
Yanping 2011	41	49	24	45	10.8%	4.48 [1.72, 11.68]	2011
Lin 2012	33	42	17	42	9.6%	5.39 [2.06, 14.09]	2012
Aiwu 2013	32	39	18	39	0.0%	5.33 [1.90, 14.97]	2013
Bin 2013	250	297	254	591	0.0%	7.06 [4.97, 10.03]	2013
Total (95% CI)		**278**		**260**	**100.0%**	**2.45 [1.71, 3.52]**	
Total events	202		130				

Heterogeneity: Chi² = 20.74, df [illegible]; I² = 47%

Test for overall effect: Z = 4.88 (P < 0.00001)



Transfusion Medicine and Hemotherapy

Free Access

Original Article · Originalarbeit

Immunotherapy with Paternal Lymphocytes for Recurrent Miscarriages and Unsuccessful in vitro Fertilization Treatment

Wegener S.[a] · Schnurstein K.[a] · Hansch S.[b] · Briese V.[b] · Sudik R.[c] · Wegener R.[d] · Busecke A.[e] · Müller H.[e]

Author affiliations

Transfus Med Hemother 2006;33:501-507
https://doi.org/10.1159/000096125

Table 4. Results of active immuno-therapy in repeated miscarriages

AI time point	Births (A)	Abortions (B)	No pregnancy after AI (C)	Successful pregnancy after AI (A/A+B)	Success rate (A/A+B+C)
Preconceptional (n = 142)	101	16	25	86% (101/117)	71% (101/142)
In ≥3 miscarriages (n = 49)	(36)	(6)	(7)	86% (36/42)	73% (36/49)
In early pregnancy (n = 35)	31	4	–	89% (31/35)	89% (31/35)
Overall (n = 177)	132	20	25	87% (132/152)	75% (132/177)

Table 7. Results of active immunotherapy after unsuccessful IVF treatment (data from 47 patients)

Births (A)	Abortions (B)	No pregnancy after AI (C)	Successful pregnancy (A/A+B)	Success rate (A/A+B+C)
12	4	31	75% (12/16)	36 % (12/47)

The effect of PBMC-therapy on pregnancy rate in recurrent implantation failure (RIF) patients

Rif

Recurrent implantation failure may be defined as failure of implantation in at least three consecutive IVF attempts, in which 1–2 embryos of high grade quality are transferred in each cycle

It is estimated that approximately 10% of women seeking IVF treatment will experience this particular problem

Implantation failure is related to either maternal factors or embryonic causes.

Maternal Factors

Uterine anatomic abnormalities

Endometrial thickness and receptivity

Thrombophilia and connective tissue disease

Immunologic factor

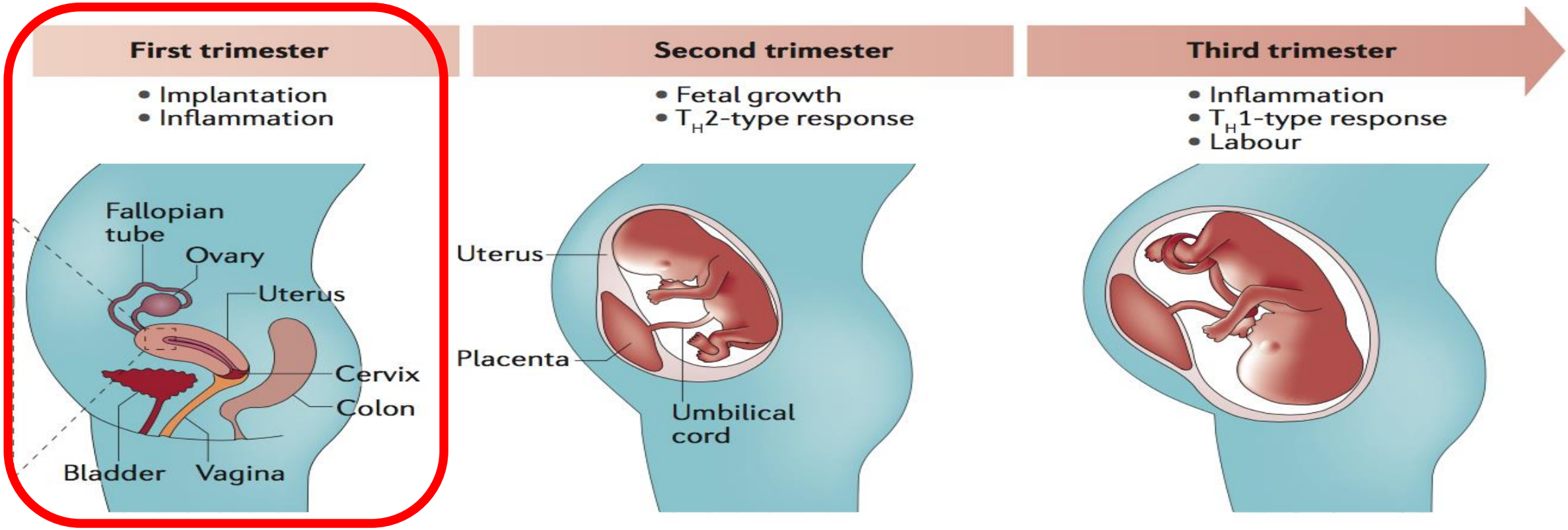
Embryonic Factors

Genetic factor (Karyotype)

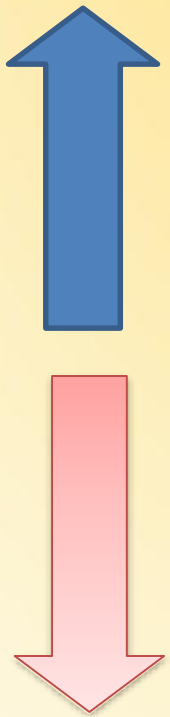
Assuming the embryo ceases to develop in utero

A successful pregnancy : a dynamic immunologic process

Depends on the ability of the maternal immune system to change and adapt to each specific developmental stage



Maternal immune systems seems to be involved in establishment and maintenance of pregnancy through **Th1/Th2 profile balance**



Th1

Th1(pro inflammatory)

TNF

INF

LIF

IL1,6,12,15

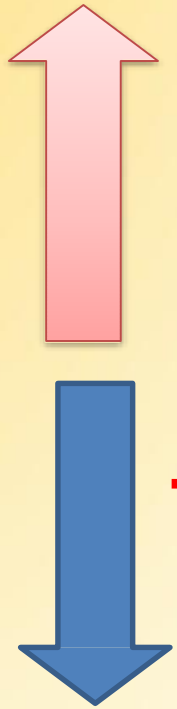
Th2

Implantation

Pregnancy

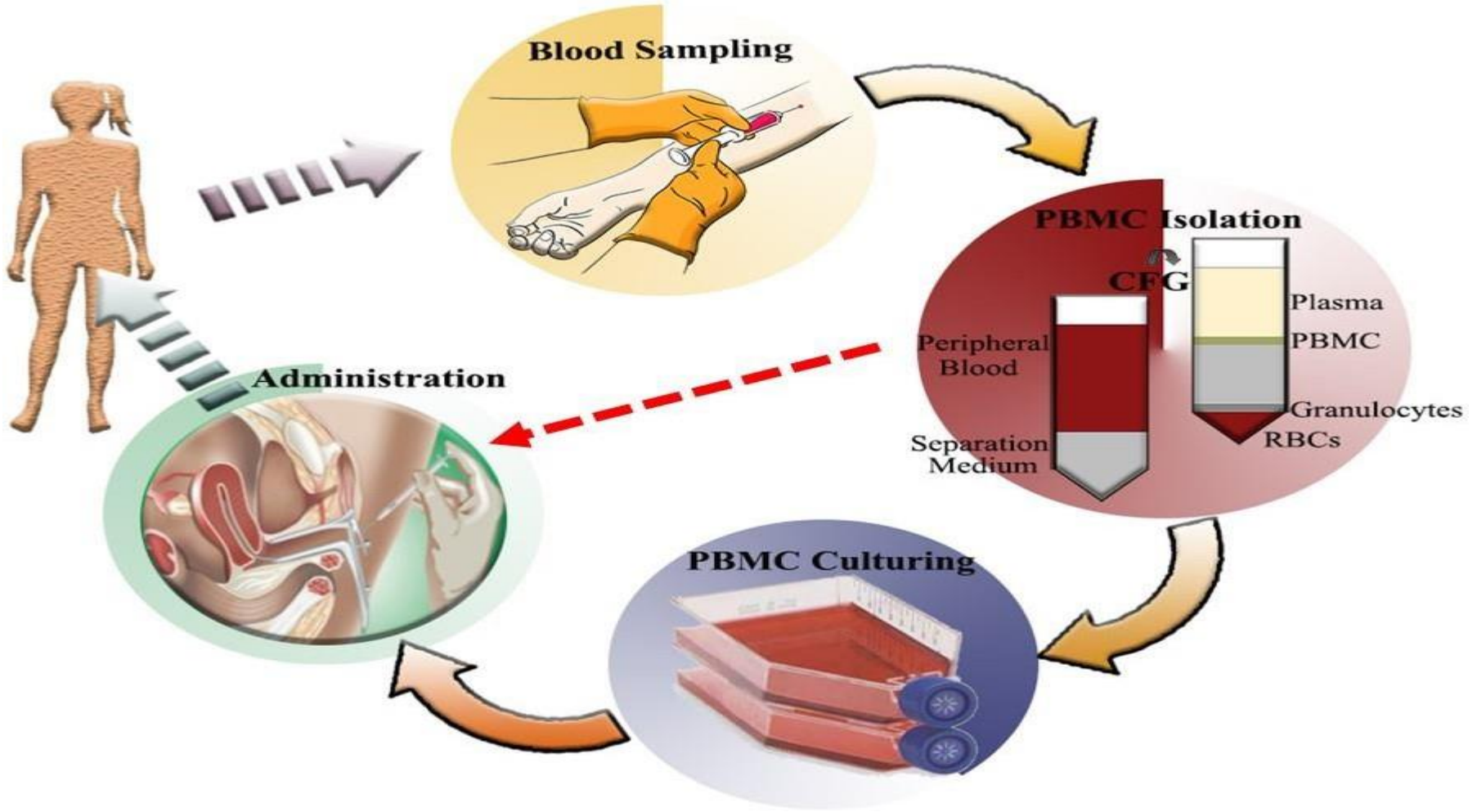
Th2(Anti inflammatory)

IL3,4,5,10,13 GM-CSF



Th2

Th1


Blood Sampling
PBMC Isolation
CFG
Plasma
PBMC
Granulocytes
RBCs
Peripheral Blood
Separation Medium
Administration
PBMC Culturing

Journal of Reproductive Immunology 131 (2019) 50–56

Contents lists available at ScienceDirect

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

Review article

Intrauterine administration of autologous peripheral blood mononuclear cells in patients with recurrent implantation failure: A systematic review and meta-analysis

Arezoo Maleki-Hajiagha[a], Maryam Razavi[b], Mahroo Rezaeinejad[c], Safoura Rouholamin[d], Amir Almasi-Hashiani[e], Reihaneh Pirjani[f], Mahdi Sepidarkish[g,*]

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[f] Obstetrics and Gynecology Department, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran
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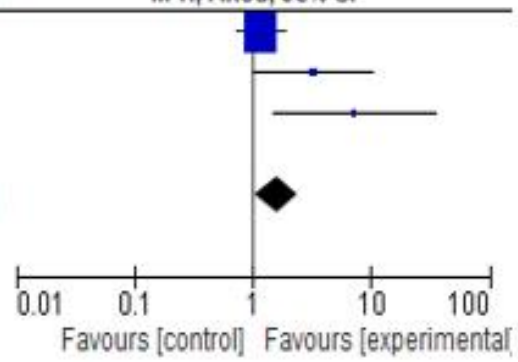
Study or Subgroup	PBMC treated Events	Total	Non-PBMC treated Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Li et al 2016	64	281	31	153	87.3%	1.16 [0.72, 1.88]
Okitsu et al 2011	8	32	6	64	8.5%	3.22 [1.01, 10.28]
Yoshioka et al 2006	11	47	2	49	4.2%	7.18 [1.50, 34.44]
Total (95% CI)		360		266	100.0%	**1.59 [1.04, 2.42]**
Total events	83		39			

Heterogeneity: Chi² = 6.61, df = 2 (P = 0.04); I² = 70%

Test for overall effect: Z = 2.1 (P = 0.03)



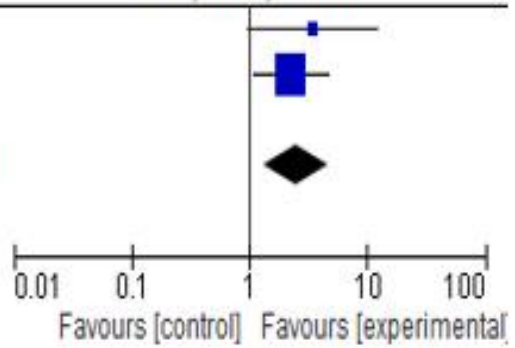
Implantation rate Quasi-exp studies

Implantation rate In RCTs

Study or Subgroup	PBMC treated Events	Total	Non-PBMC treated Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Madkour et al 2015	8	23	5	37	20.2%	3.41 [0.95, 12.21]
Yu et al 2016	22	187	12	213	79.8%	2.23 [1.07, 4.65]
Total (95% CI)		210		250	100.0%	**2.47 [1.31, 4.67]**
Total events	30		17			

Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%

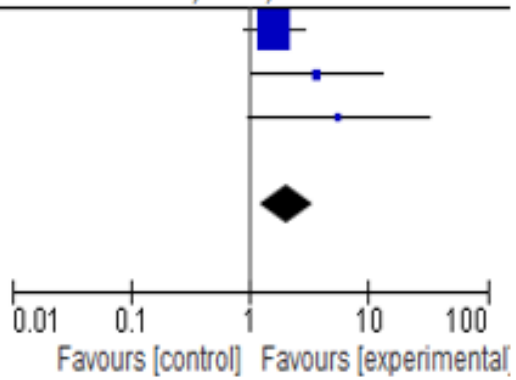
Test for overall effect: Z = 2.79 (P = 0.005)



Study or Subgroup	PBMC treated Events	Total	Non-PBMC treated Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Li et al 2016	57	138	24	78	83.6%	1.58 [0.88, 2.85]
Okitsu et al 2011	8	19	6	36	11.1%	3.64 [1.03, 12.87]
Yoshioka et al 2006	7	17	2	18	5.3%	5.60 [0.96, 32.51]
Total (95% CI)		**174**		**132**	**100.0%**	**2.03 [1.22, 3.36]**
Total events	72		32			

Heterogeneity: Chi² = 2.78, df = 2 (P = 0.25); I² = 28%

Test for overall effect: Z = 2.73 (P = 0.006)



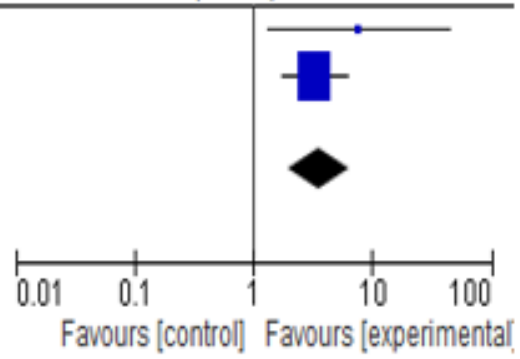
Pregnancy rate In quasi-exp studies

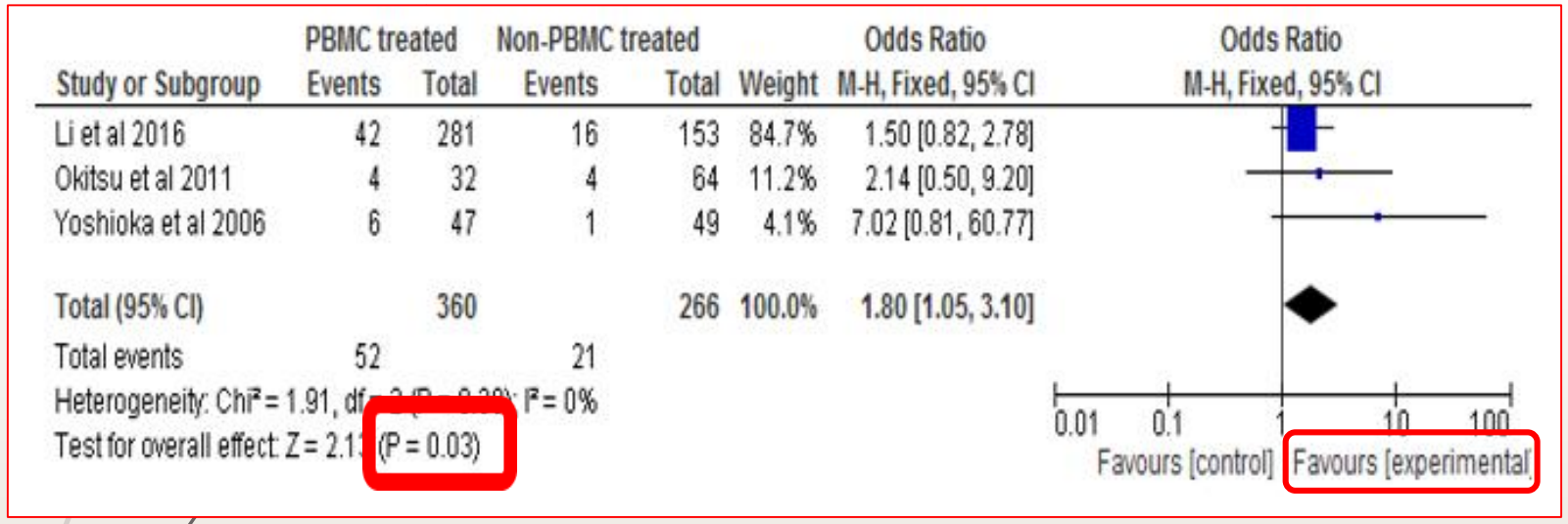
Pregnancy rate In RCTs

Study or Subgroup	PBMC treated Events	Total	Non-PBMC treated Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Madkour et al 2015	7	10	4	17	7.4%	7.58 [1.31, 43.92]
Yu et al 2016	43	93	22	105	92.6%	3.24 [1.74, 6.04]
Total (95% CI)		**103**		**122**	**100.0%**	**3.57 [1.99, 6.40]**
Total events	50		26			

Heterogeneity: Chi² = 0.80, df = 1 (P = 0.37); I² = 0%

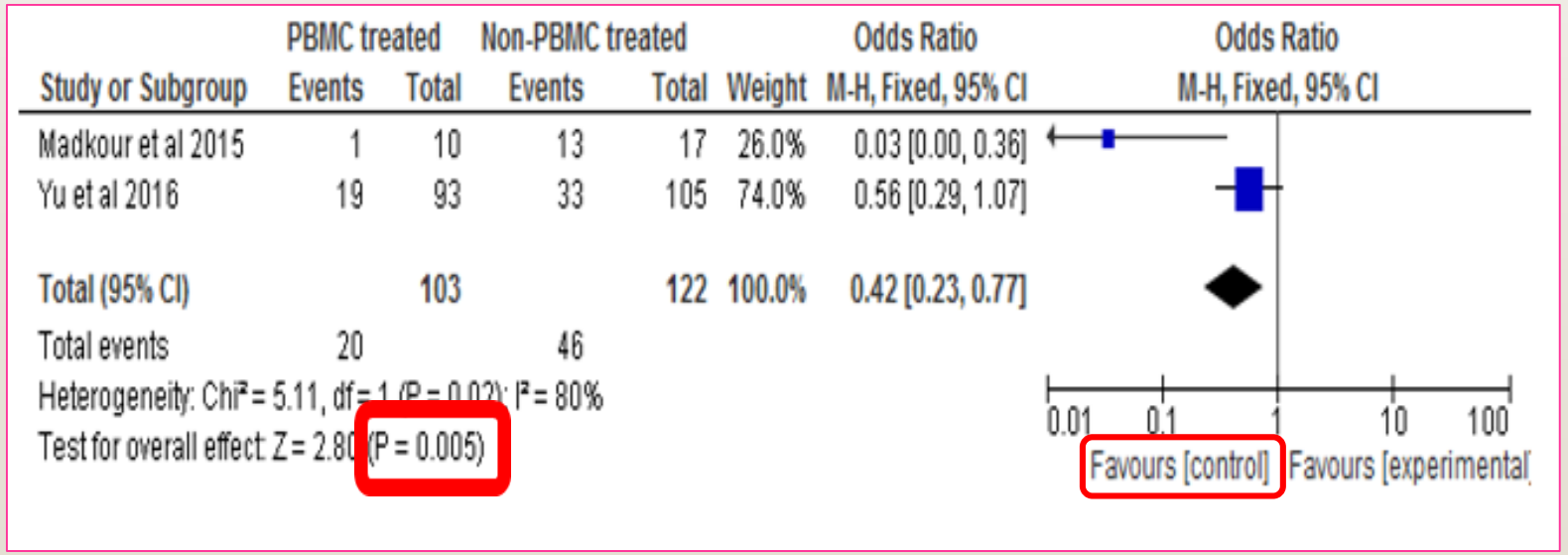
Test for overall effect: Z = 4.2 (P < 0.0001)





Live birth rate In quasi-exp studies

Miscarriage rate In RCTs



Introduction

ClinicalTrials.gov PRS
Protocol Registration and Results System

Contact ClinicalTrials.gov PRS
Org: SCARM User: YousefiM Logout

Showing: 1 record

	Protocol ID	ClinicalTrials.gov ID	Brief Title	Record Status	Last Update	Responsible Party
Open	SCARM-infertility-004	NCT03267797	hCG-activated PBMC-therapy in RIF Patients	In Progress	07/09/2019 09:28	[Sponsor]

KEY: R Results DR Delayed Results D Study Documents PR PRS Review
U XML Upload NP No longer public PRS Review Comments

IRCT Iranian Registry of Clinical Trials - Beta version

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- Protocol summary
- General information
- Secondary Ids
- Ethics committees
- Health conditions studied
- Primary outcomes
- Secondary outcomes
- Intervention groups
- Recruitment centers

Intrauterine administration of autologous hCG-activated peripheral blood mononuclear cells improves pregnancy outcomes in patients with recurrent implantation failure; a double-blind randomized control trial study

More options ▾ View older revisions

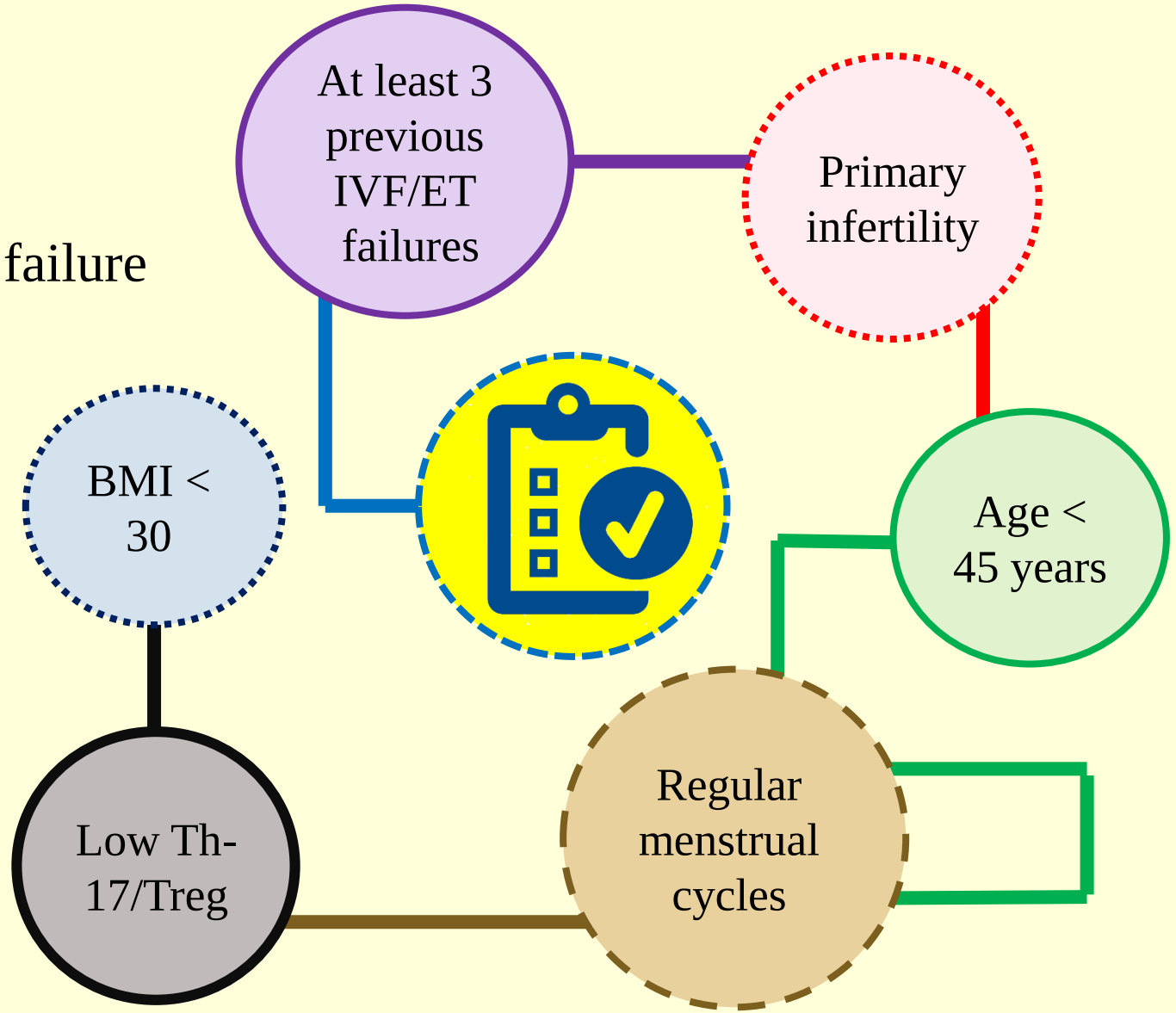
Protocol summary

Summary	The aim of our study is to select patients with repeated implantation failure (RIF) based on immunological disorders and their treatment with

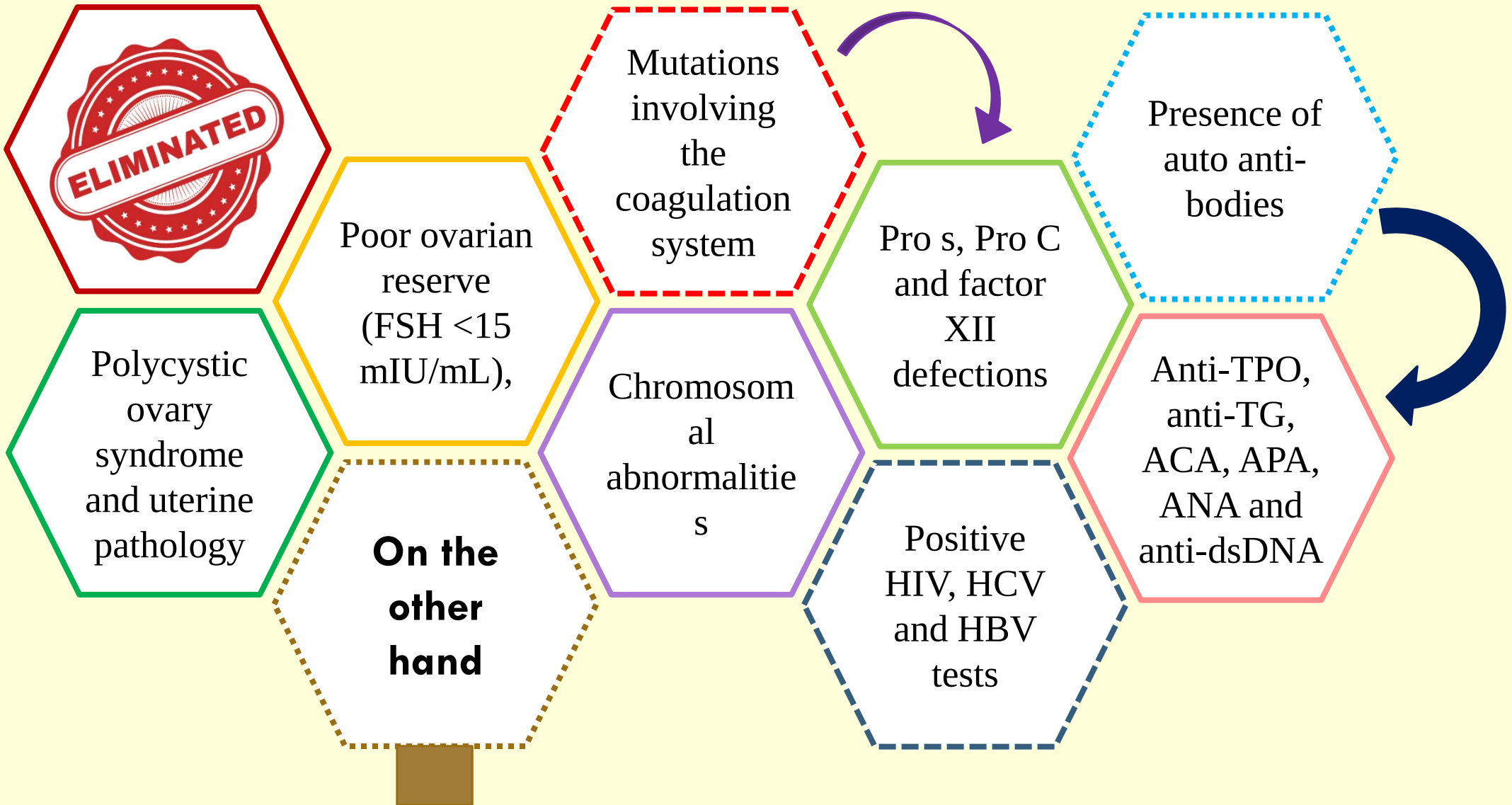
Methods

Subject and Study design

- 248 patients with the history of IVF failure



Methods

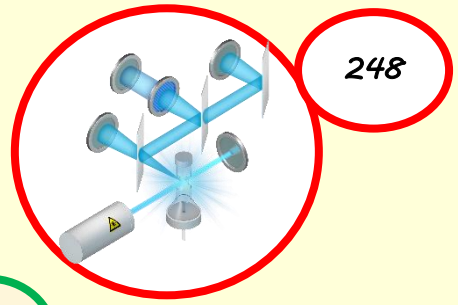

ELIMINATED
Mutations involving the coagulation system
Presence of auto anti-bodies
Poor ovarian reserve (FSH <15 mIU/mL),
Pro s, Pro C and factor XII defections
Polycystic ovary syndrome and uterine pathology
Chromosomal abnormalities
Anti-TPO, anti-TG, ACA, APA, ANA and anti-dsDNA
On the other hand
Positive HIV, HCV and HBV tests

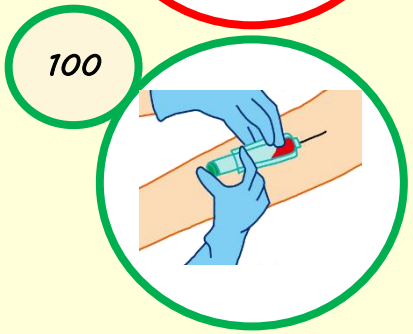
Methods

Flow cytometry

10 ml

For Th-17, Treg and Th-17/Treg





Blood Sampling

20 mL
Five days before ET

PBMCs Isolation

Using Ficoll-Paque

PBMCs Culturing

20-30×10^6 PBMCs were suspended in 8 ml CM10
At the presence hCG (10 IU/mL.day) for 48 hours

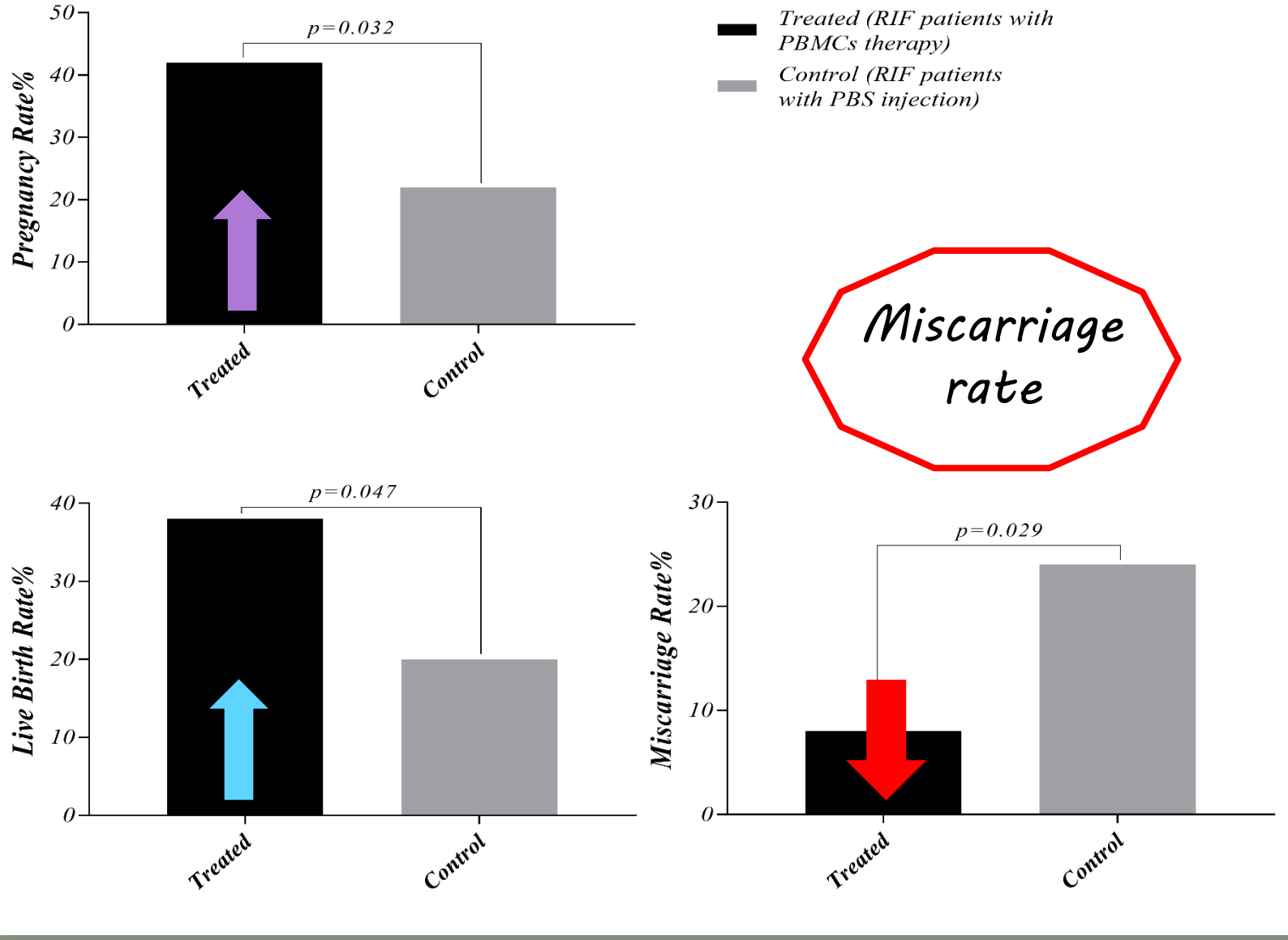
Pregnancy Outcomes

Results

Pregnancy rate

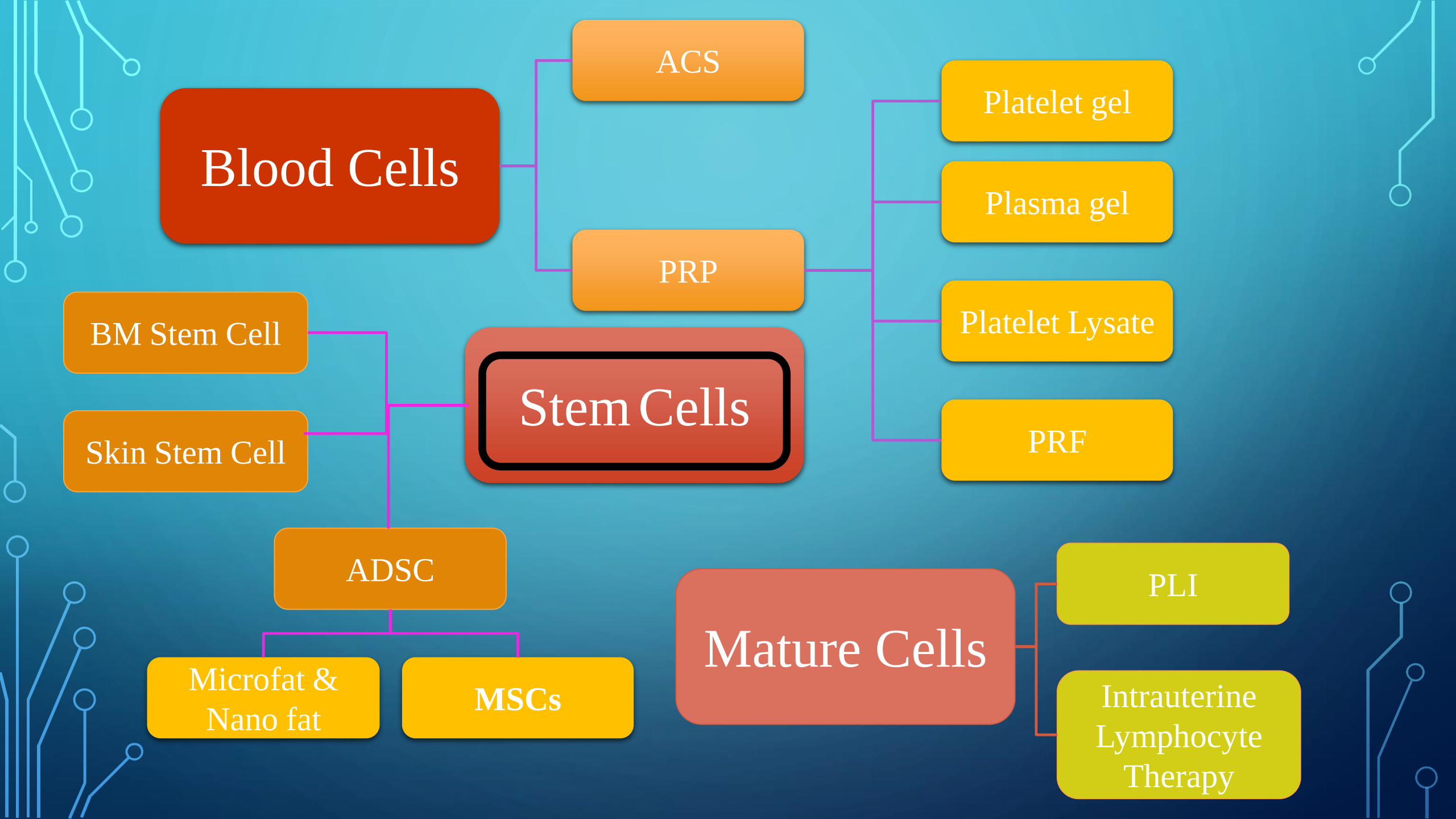
Live birth rate

Miscarriage rate

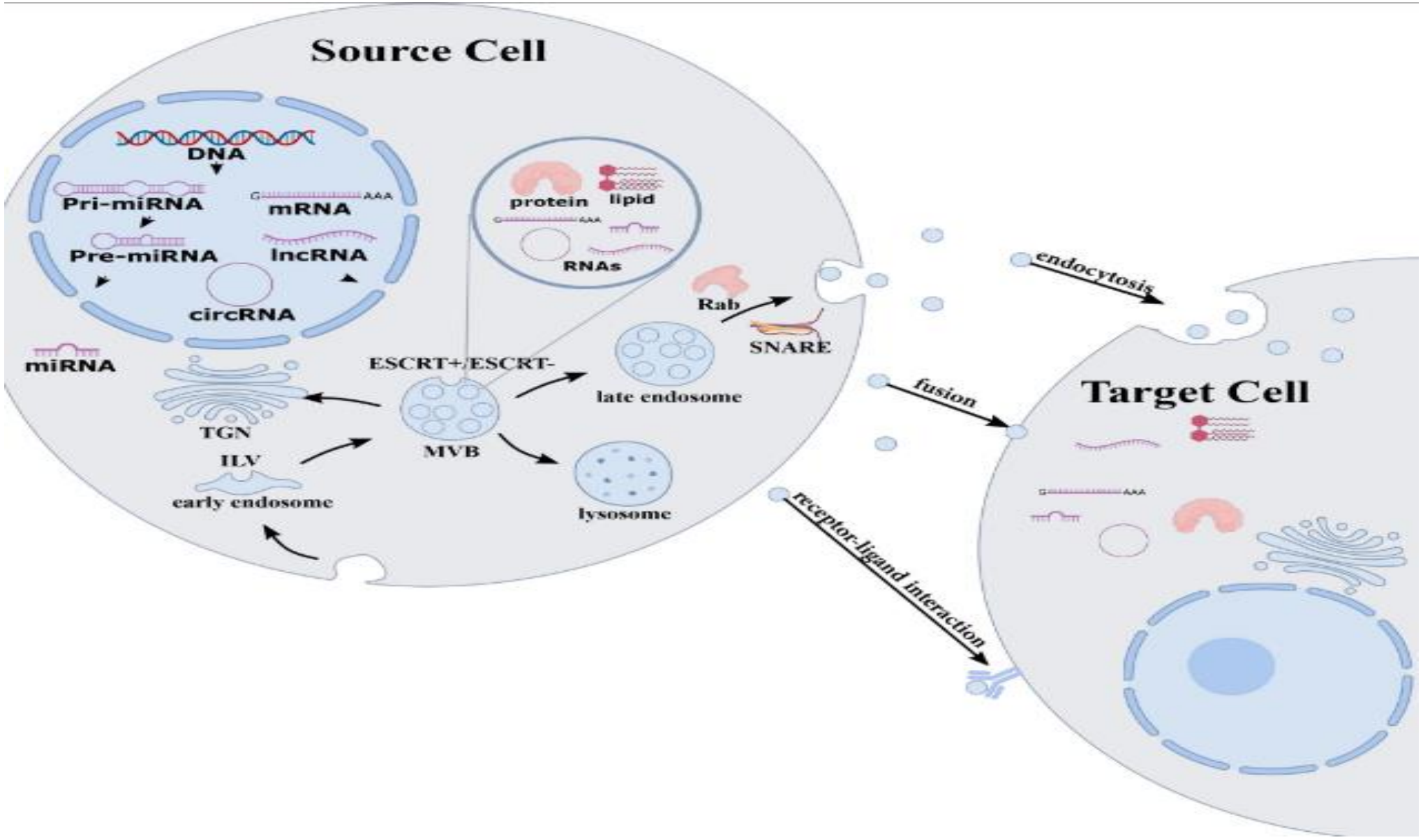


Results

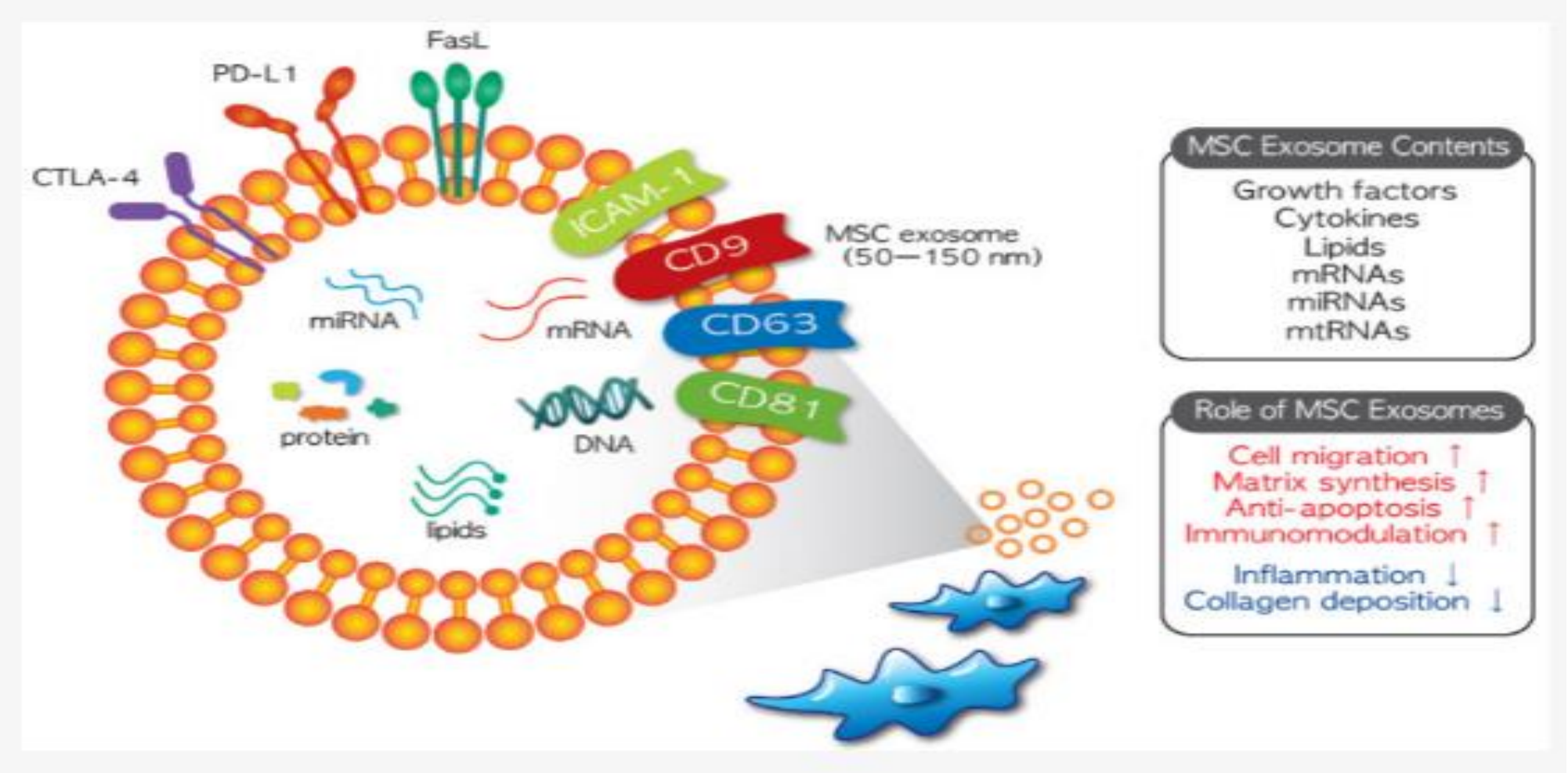
TABLE 4. Clinical outcome of the patients in the PBMC-treated and control groups			
	Treated RIF Patients% N=50	Control group% N=50	P value
Pregnancy Rate%	42%	22%	0.032
Live Birth Rate%	38%	20%	0.047
Miscarriage Rate%	8%	24%	0.029

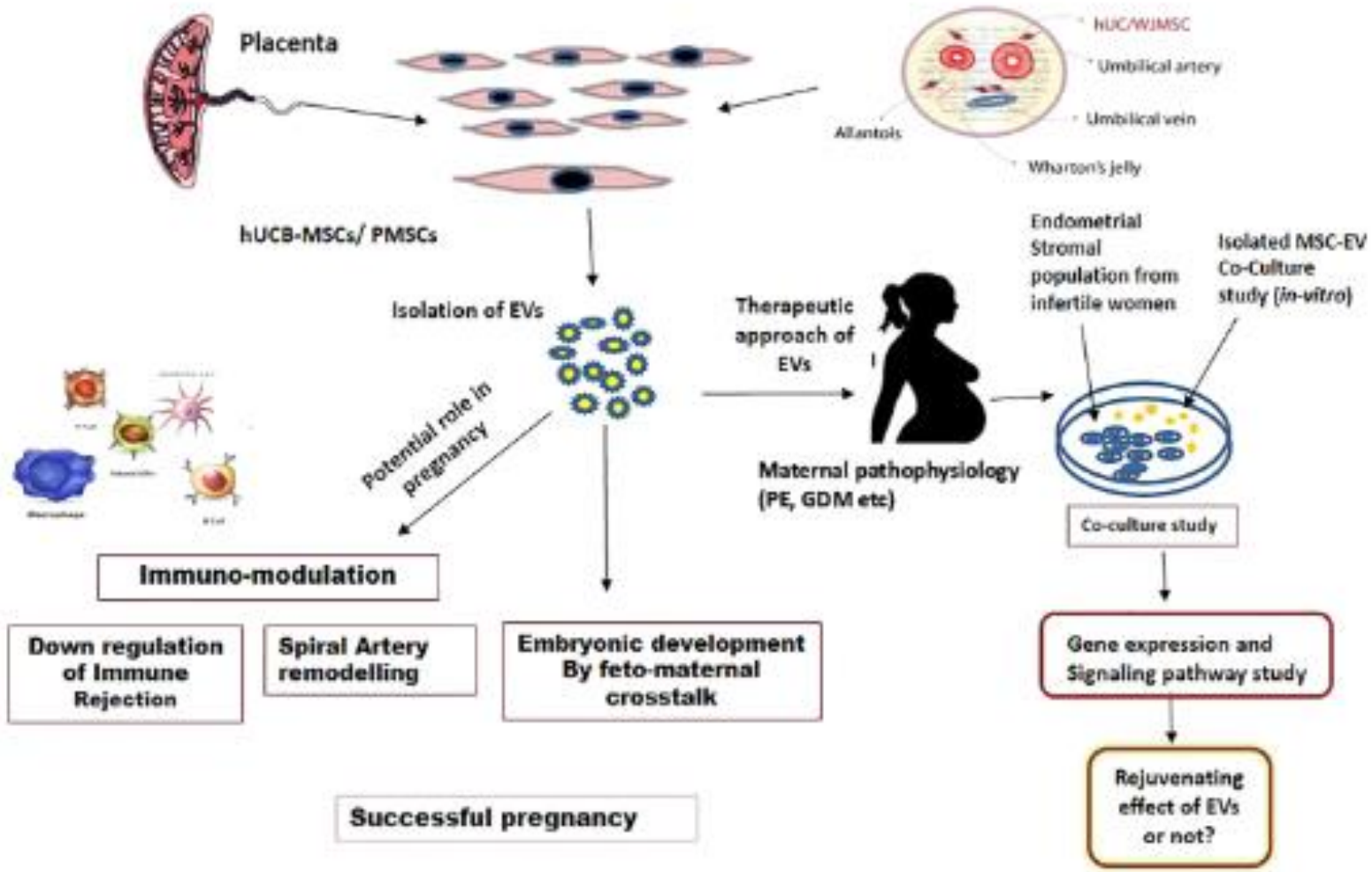

Blood Cells
ACS
PRP
Platelet gel
Plasma gel
Platelet Lysate
PRF
Stem Cells
BM Stem Cell
Skin Stem Cell
ADSC
Microfat & Nano fat
MSCs
Mature Cells
PLI
Intrauterine Lymphocyte Therapy

Exosome And Female Infertility

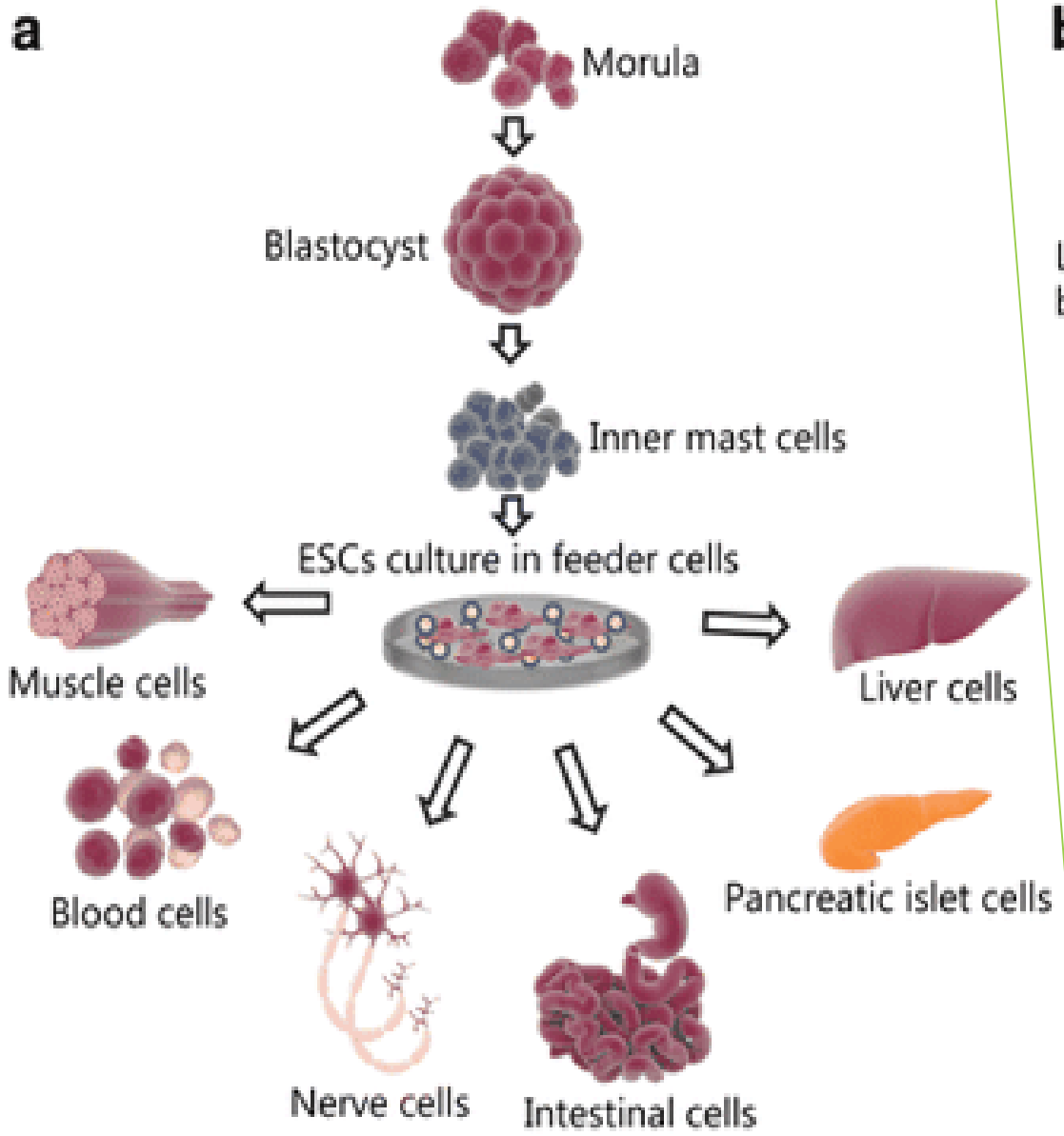


Human Umbilical Cord mesanchymal Stem Cell exosome

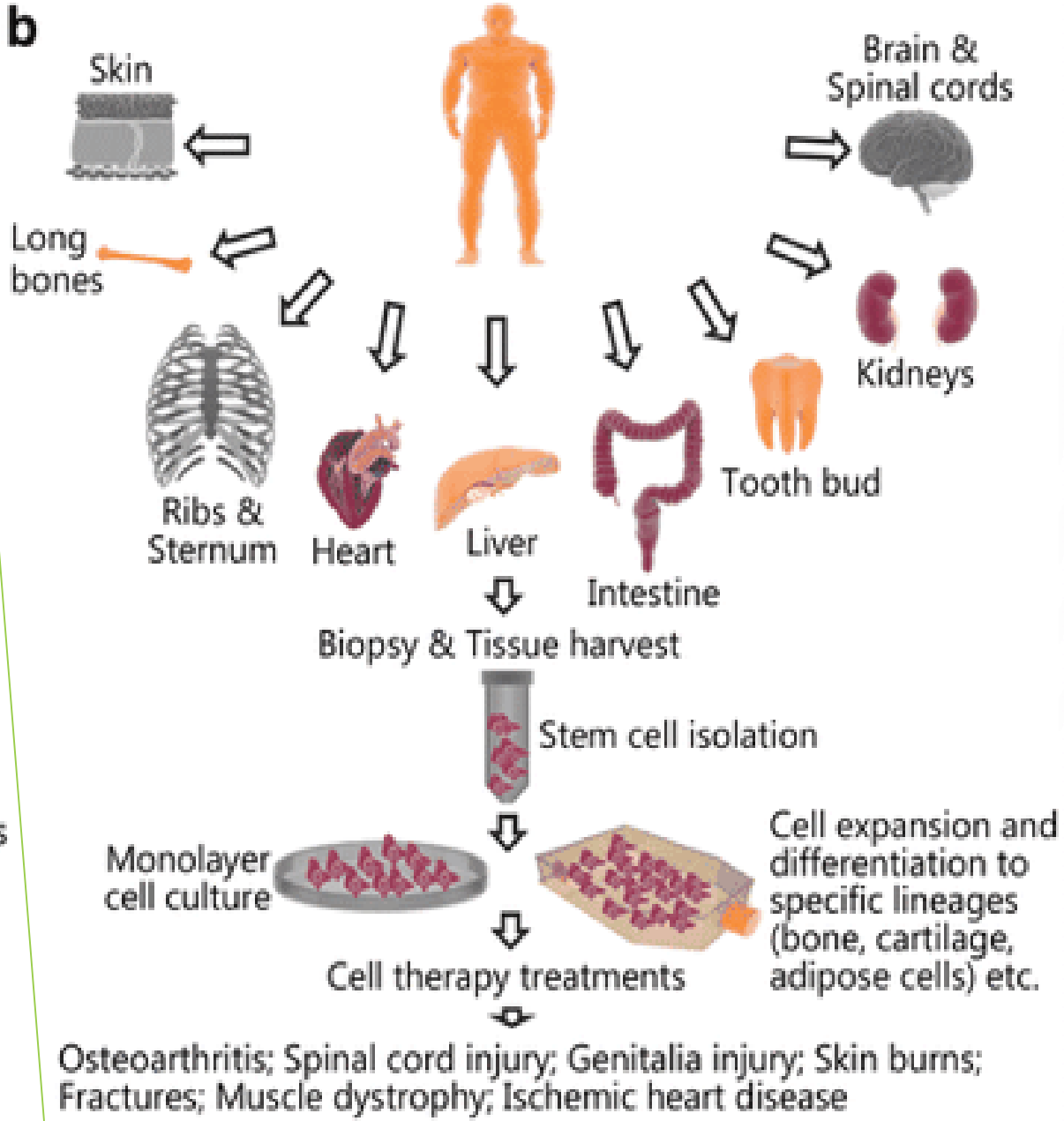



Placenta
hUC/WJMSC
Umbilical artery
Umbilical vein
Allantois
Wharton's jelly
hUCB-MSCs/ PMSCs
Isolation of EVs
Therapeutic approach of EVs
Endometrial Stromal population from infertile women
Isolated MSC-EV Co-Culture study (in-vitro)
Potential role in pregnancy
Maternal pathophysiology (PE, GDM etc)
Co-culture study
Immuno-modulation
Down regulation of Immune Rejection
Spiral Artery remodelling
Embryonic development By feto-maternal crosstalk
Gene expression and Signaling pathway study
Rejuvenating effect of EVs or not?
Successful pregnancy

➢ Embryonic Source



➢ Adult Source



➢Stem Cell Therapy

Orthopaedics Applications

- Non-union / Delayed Union Fracture
- Osteonecrosis or Avascular Necrosis (AVN)
- Knee cartilage defect
- Rheumatoid Arthritis (RA)

Neuro Applications

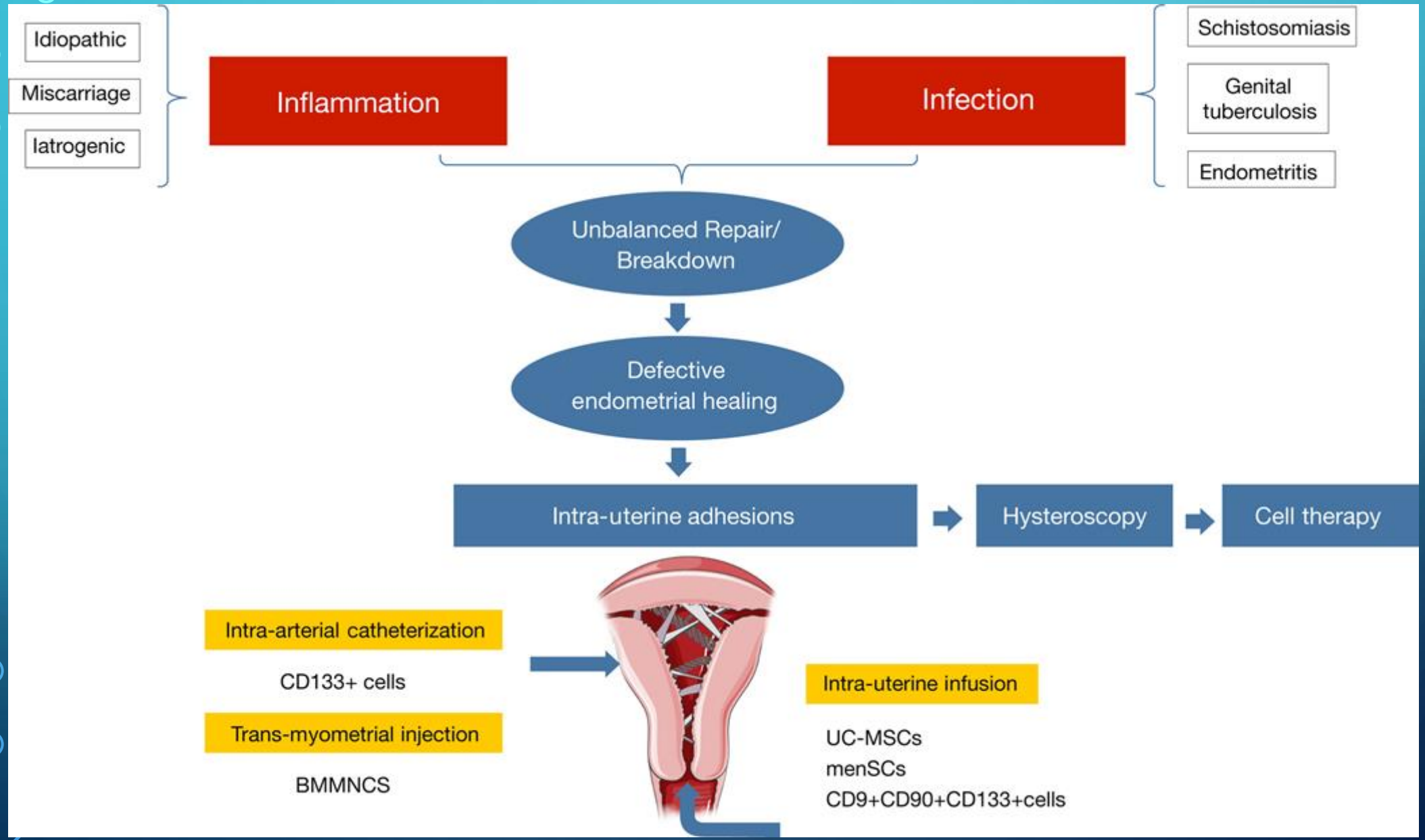
- Spinal Cord injury
- Spinal Fusion Treatment
- Cerebral Palsy
- Autism
- Motor Neuron Disease
- Multiple Sclerosis
- Parkinson's Disease
- Alzheimer's / Dementia Disease
- Cerebellar Atrophy
- Cerebellar Ataxia
- Spinal Muscular Atrophy
- Down Syndrome

Eye Applications

- Optic Nerve Demage
- Retinitis Pigmentosa
- Macular degeneration
- Stargardt / Macular Dystrophy
- Glaucoma Disease

Other Applications

- Diabetes (Type 1 & 2)
- Accute / Chronic Liver Disease
- Muscular Dystrophy
- Acute / Chronic Kidney Disease
- Peripheral Arterial Disease
- Myocardial Infarction
- Lung Disease
- Erectile Dysfunction
- Anti-Aging Treatment
- Scleroderma Disease


Idiopathic
Miscarriage
Iatrogenic
Inflammation
Infection
Schistosomiasis
Genital tuberculosis
Endometritis
Unbalanced Repair/ Breakdown
Defective endometrial healing
Intra-uterine adhesions
Hysteroscopy
Cell therapy
Intra-arterial catheterization
CD133+ cells
Trans-myometrial injection
BMMNCS
Intra-uterine infusion
UC-MSCs
menSCs
CD9+CD90+CD133+cells

Human Reproduction, Vol.31, No.5 pp. 1087–1096, 2016
Advanced Access publication on March 22, 2016 doi:10.1093/humrep/dew042

human reproduction

ORIGINAL ARTICLE *Reproductive biology*

Autologous cell therapy with CD133+ bone marrow-derived stem cells for refractory Asherman's syndrome and endometrial atrophy: a pilot cohort study

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PARTICIPANTS/MATERIALS, SETTING, METHODS: After the initial hysteroscopic diagnosis, BMDSC mobilization was performed by granulocyte-CSF injection, then CD133+ cells were isolated through peripheral blood aphaeresis to obtain a mean of 124.39 million cells (range 42–236), which were immediately delivered into the spiral arterioles by catheterization. Subsequently, endometrial treatment after stem cell therapy was assessed in terms of restoration of menses, endometrial thickness (by vaginal ultrasound), adhesion score (by hysteroscopy), neoangiogenesis and ongoing pregnancy rate. The study was conducted at Hospital Clínico Universitario of Valencia and IVI Valencia (Spain).

MAIN RESULTS AND THE ROLE OF CHANCE: All 11 AS patients exhibited an improved uterine cavity 2 months after stem cell therapy. Endometrial thickness increased from an average of 4.3 mm (range 2.7–5) to 6.7 mm (range 3.1–12) ($P = 0.004$). Similarly, four of the five EA patients experienced an improved endometrial cavity, and endometrial thickness increased from 4.2 mm (range 2.7–5) to 5.7 mm (range 5–12) ($P = 0.03$). The beneficial effects of the cell therapy increased the mature vessel density and the duration and intensity of menses in the first 3 months, with a return to the initial levels 6 months after the treatment. Three patients became pregnant spontaneously, resulting in one baby boy born, one ongoing pregnancy and a miscarriage. Furthermore, seven pregnancies were obtained after fourteen embryo transfers, resulting in three biochemical pregnancies, one miscarriage, one ectopic pregnancy, one baby born and one ongoing pregnancy.

Table I Clinical characteristics and outcome of patients with AS.

Patient	Preoperative menstrual history	Etiology of Asherman	Prior repair attempts	Age	Maximum preoperative endometrial thickness (mm)	Hysteroscopy			Post-operative menstrual history	Maximum post-operative endometrial thickness (mm)	Pregnancy outcome
						First look before cell therapy	Second look after cell therapy	Third look after cell therapy			
1	Scant spotting	D&C	h/s × 6	39	4.5	AS Stage III	Stage II	Stage I	Regular with HRT	5.2	No
2	Scant spotting	D&C	None	30	4	AS Stage III	Stage II	Stage I	Regular with HRT	6.5	No
3	Scant spotting	D&C	h/s × 2	43	4.5	AS Stage II	Stage I	Stage I	Regular with HRT	7	Yes, BP
4	Amenorrhea	D&C	h/s × 5	37	4.5	EA + AS Stage II	Stage I	Stage I	Regular with HRT	6.1	No
6	Scant spotting	Unexplained	h/s × 1	45	5	EA + AS Stage I	Stage I	Uterine cavity normalized	Regular with HRT	5	No
7	Scant spotting	D&C	h/s × 9	34	3.5	EA + AS Stage II	Stage I	Stage I	Regular with HRT		Yes, SP premature rupture of membranes at 17 weeks
8	Amenorrhea	D&C; IUD (LNG 5 years)	h/s × 1	35	3.5	EA + AS	Stage I	Stage I	Regular with HRT	7.1	No transfer. All abnormal embryos
9	Scant spotting	D&C	none	40	4.7	AS Stage III	Stage I	Not	Regular with HRT	12	Yes, SP ongoing First trimester pregnancy
11	Scant spotting	Im	h/s × 2	40	5	AS Stage I	Stage I	Not performed	Regular with HRT	6	Yes, ongoing first trimester pregnancy
13	Scant spotting	D&C; Im	None	43	3	EA + AS	Stage I	Not	Regular with HRT	8 mm	Yes, EP
15	Scant spotting	D&C	h/s × 2	32	5	AS Stage II	Uterine cavity normalized	Not performed	Regular with HRT	6.8	Baby born, 39.4 weeks, 2860 g

D&C, dilatation/curettage; POF, premature ovarian failure; h/s, histeroscopy; hm, histeroscopic myomectomy; lm, laparotomic myomectomy; AS, Asherman's syndrome; EA, endometrial atrophy; BP, biochemical pregnancy; EP, ectopic pregnancy; SP, spontaneous pregnancy; ART, assisted reproductive treatment; LNG, levonorgestrel; HRT, hormone replacement therapy; The Asherman Syndrome Classification by 'The American Fertility Society classification of intrauterine adhesions, 1988'.

- **Delivery of BMDSCs**

After successful CD133+ isolation, patients were referred to the radiology department of HCU, where cell delivery to the endometrial stem cell niche via intra-arterial catheterization was performed using a technique routinely performed for embolization of fibroids. The common femoral artery was approached using the Seldinger technique in which a 4 F introducer allowed catheterization of both hypogastric arteries with an angiographic catheter curve and a guide Terumo 0.035 in. Through the latter catheter, a 2.5 F microcatheter with a guide (0.014 in) was introduced to catheterize the uterine artery to the most distal spiral arterioles that the microcatheter could reach. Once the catheter position was stabilized and verified, 15 cm3 of a saline suspension of the selected CD133+ cells (containing 42–200 × 106 cells, mean (123.56 × 106) was two injected through each uterine artery into the spiral arterioles.

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RESEARCH Open Access

Allogeneic cell therapy using umbilical cord MSCs on collagen scaffolds for patients with recurrent uterine adhesion: a phase I clinical trial

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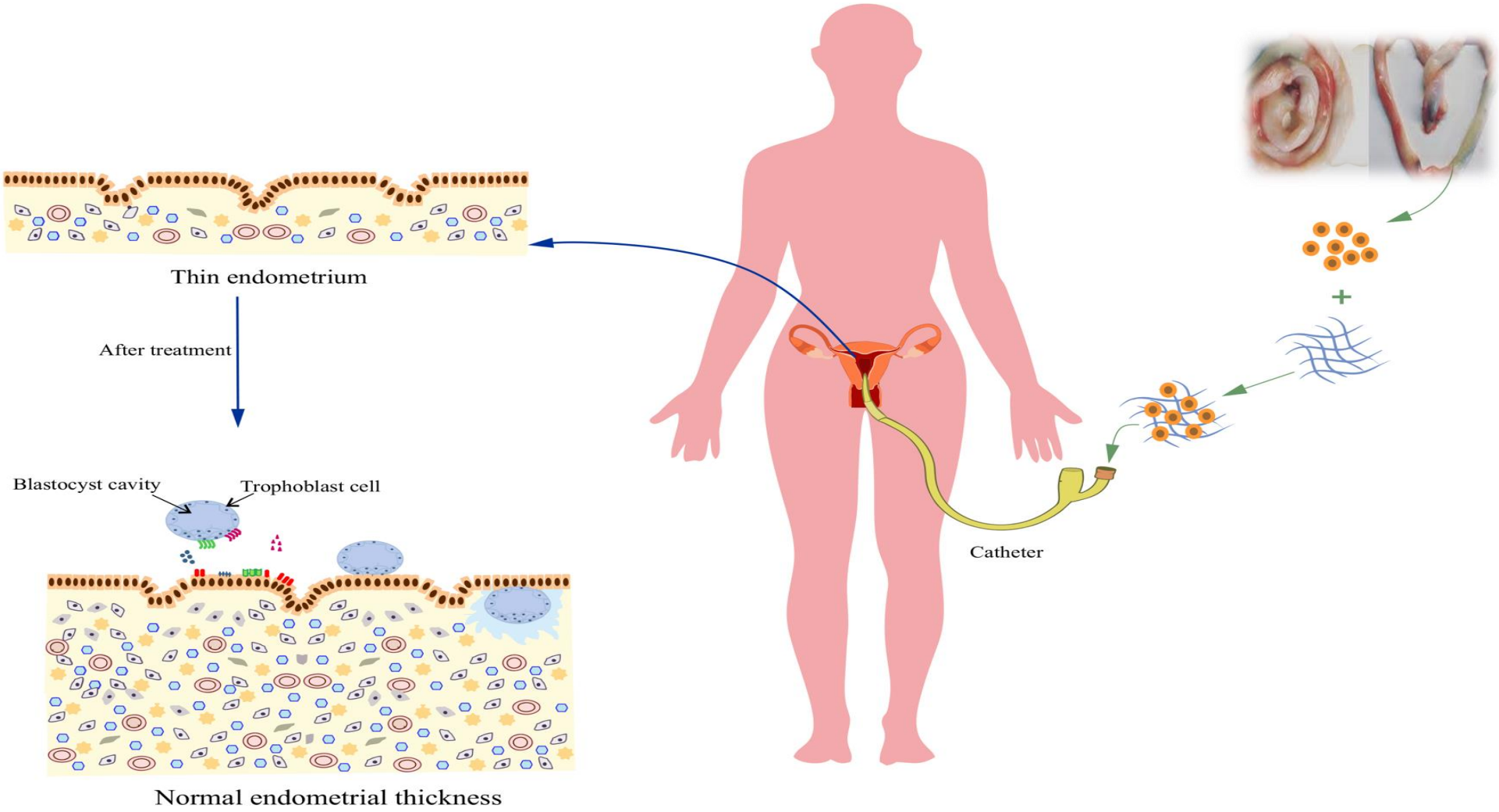
- **Preparation of the UC-MSC /collagen complex**

The regeneration-induced functional complex was made as follows: a 4 cm × 6 cm collagen scaffold with pores of 20–200 μm in diameter (Zhenghai Biotechnology Company, Shandong, China) was rinsed with xeno-free MSC culture medium (MesenCult™ MSC Basal Medium, Stemcell Technologies, Vancouver, Canada), excess fluid was aspirated, and a suspension of 1 × 107 (about 4.2 ×105/cm2) UC-MSCs was dripped uniformly onto the scaffold. The cell-seeded scaffold was incubated in humid air consisting of 5% CO2 at 37 °C for 1 h before transplantation

- **Hysteroscopic operations**

Two experienced gynecologists using ultrasound guidance performed the hysteroscopic operations. The endometrial adhesions were separated using non-electrified micro scissors until an anatomical uterine cavity with slight staxis was observed. The UC-MSC/collagen scaffold complex was spread onto an 18F Foley catheter and placed into the uterine cavity, and then an infill catheter bulb containing 3 ml of saline was used to attach the scaffold to the inner wall of uterine cavity. After 12 h, the catheter was removed after withdrawing saline in the bulb. The procedure was performed following 10 days of 6 mg/day Progynova (estradiol) (menstrual period day 13). Continuous administration of the same dosage of Progynova, lasting for 30 days following the operation, and 60 mg of progesterone was injected on the 30th day post-operation. Then, the hormone replacement therapy was stopped, and patients returned to a natural menstrual cycle.

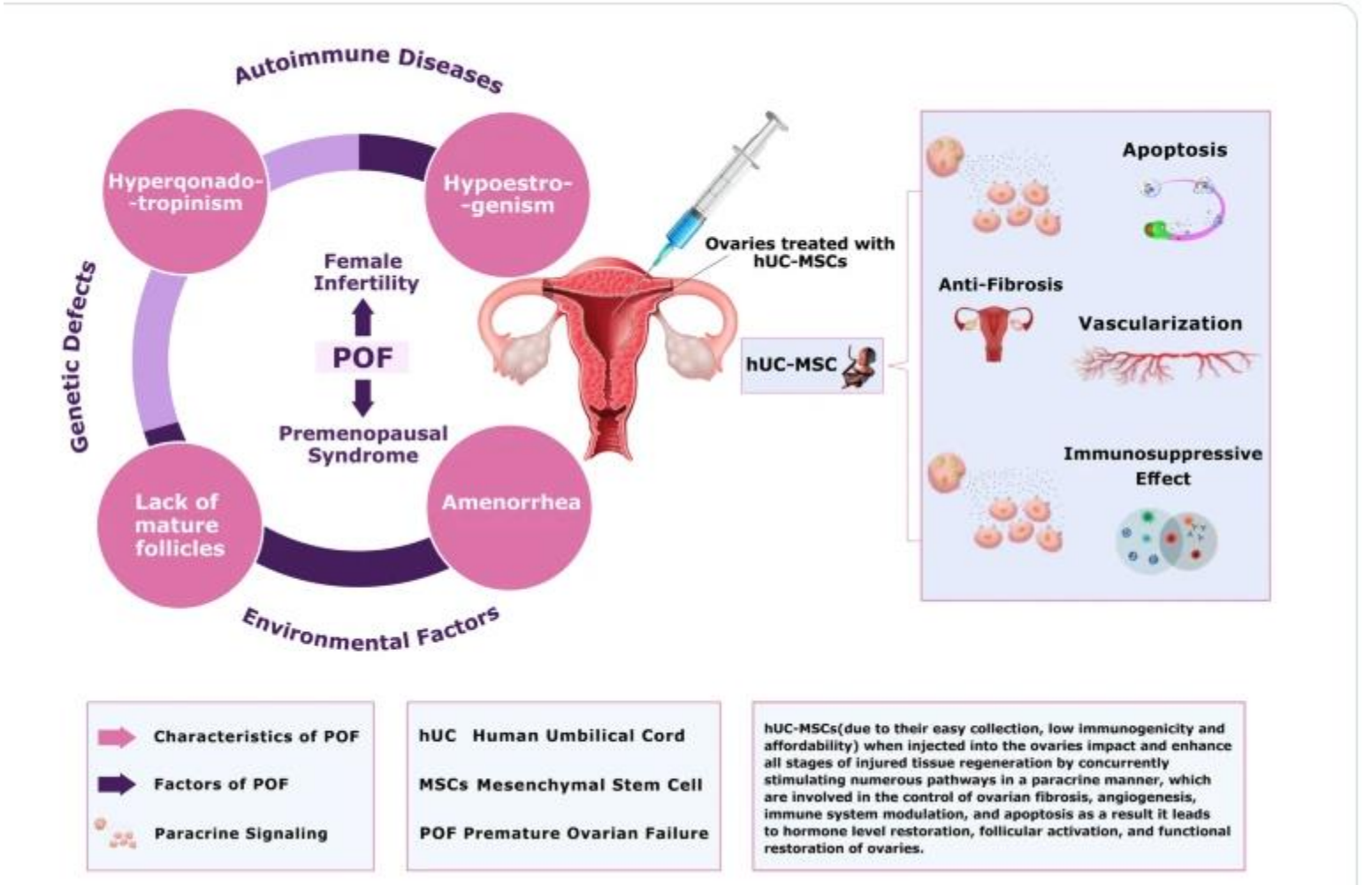
scanning

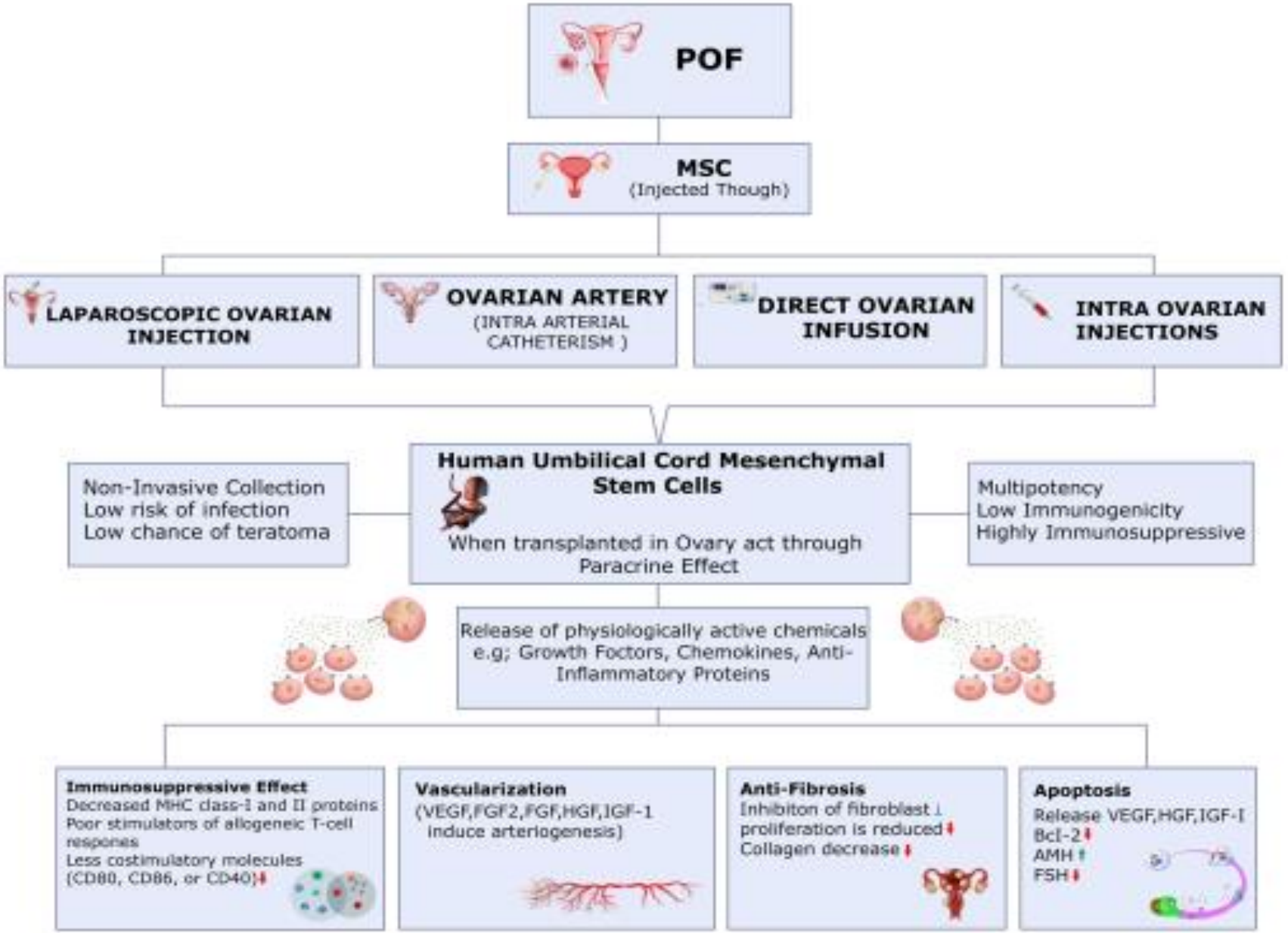

Thin endometrium
After treatment
Blastocyst cavity
Trophoblast cell
Normal endometrial thickness
Catheter
Collagen scaffold
BMSCs
Chemokine
Chemokine receptors
L-selectin
LIF
LIF Reseptor
Pinopodes

Results

The average maximum endometrial thickness, measured in 25 patients, increased from 4.46 ± 0.85 mm to 5.74 ± 1.20 mm Among them, three patients became pregnant after ET (Patient Nos. 10, 17, and 18), seven patients became pregnant spontaneously (Patient Nos. 1, 4, 5, 15, 19, 20, and 23), and two patients experienced failed ET (Patient Nos. 3 and 16)

In total, ten patients became pregnant by the end of 30-month follow-up period.(the end of August 2017)


Autoimmune Diseases
Hyperqonado-
-tropinism
Hypoestro-
-genism
Genetic Defects
Female
Infertility
POF
Premenopausal
Syndrome
Lack of
mature
follicles
Amenorrhea
Environmental Factors
Ovaries treated with
hUC-MSCs
hUC-MSC
Apoptosis
Anti-Fibrosis
Vascularization
Immunosuppressive
Effect
Characteristics of POF
Factors of POF
Paracrine Signaling
hUC Human Umbilical Cord
MSCs Mesenchymal Stem Cell
POF Premature Ovarian Failure
hUC-MSCs(due to their easy collection, low immunogenicity and affordability) when injected into the ovaries impact and enhance all stages of injured tissue regeneration by concurrently stimulating numerous pathways in a paracrine manner, which are involved in the control of ovarian fibrosis, angiogenesis, immune system modulation, and apoptosis as a result it leads to hormone level restoration, follicular activation, and functional restoration of ovaries.


POF
MSC
(Injected Though)
LAPAROSCOPIC OVARIAN INJECTION
OVARIAN ARTERY
(INTRA ARTERIAL CATHETERISM)
DIRECT OVARIAN INFUSION
INTRA OVARIAN INJECTIONS
Human Umbilical Cord Mesenchymal Stem Cells
When transplanted in Ovary act through Paracrine Effect
Non-Invasive Collection
Low risk of infection
Low chance of teratoma
Multipotency
Low Immunogenicity
Highly Immunosuppressive
Release of physiologically active chemicals e.g; Growth Foctors, Chemokines, Anti-Inflammatory Proteins
Immunosuppressive Effect
Decreased MHC class-I and II proteins
Poor stimulators of allogeneic T-cell responses
Less costimulatory molecules (CD80, CD86, or CD40)
Vascularization
(VEGF,FGF2,FGF,HGF,IGF-1 induce arteriogenesis)
Anti-Fibrosis
Inhibiton of fibroblast proliferation is reduced
Collagen decrease
Apoptosis
Release VEGF,HGF,IGF-I
Bcl-2
AMH
FSH

Participant Group/Arm	Intervention/Treatment
Experimental: UCA-PSC Subsequent to isolation and culture of UCA-PSCs, UCA-PSCs (GMP grade, from Clinical Center for Stem Cell Research of the Affiliated Drum Tower Hospital of Nanjing University Medical School, licensed by the National Institute for China Food and Drug Control) were injected into the ovaries of patients with hormone replacement treatment, which consisted of Premarin (0.625 mg/days on days 1 through 25) combined with Provera (10 mg/day for 10 days a month with monthly withdrawal bleeding).	Procedure: transplantation of human UCA-PSCs or WJ-MSCs into ovaries of POF patients • After vaginal sterilization, TVUS-guided transplantation was performed by the senior-level medical physician B Wang), using a SIEMENS ACUSON ANTANES premium edition system (SIEMENS AG Healthcae Sector, Erlangen, Germany), equipped with a 6-10 MHz probe. The solution (a total number of 2×10^7cells, 1×10^7 /400 μL for unilateral ovarian injection) was injected into the ovary by using 21G PTC needles (Hakko Medical Co, Japan) under TVUS guiance. Each patent received up to three transplantations.
Experimental: WJ-MSC Subsequent to isolation and culture of WJ-MSCs, WJ-MSCs (GMP grade, from Clinical Center for Stem Cell Research of the Affiliated Drum Tower Hospital of Nanjing University Medical School, licensed by the National Institute for China Food and Drug Control) were injected into the ovaries of patients with hormone replacement treatment, which consisted of Premarin (0.625 mg/days on days 1 through 25) combined with Provera (10 mg/day for 10 days a month with monthly withdrawal bleeding).	Procedure: transplantation of human UCA-PSCs or WJ-MSCs into ovaries of POF patients • After vaginal sterilization, TVUS-guided transplantation was performed by the senior-level medical physician B Wang), using a SIEMENS ACUSON ANTANES premium edition system (SIEMENS AG Healthcae Sector, Erlangen, Germany), equipped with a 6-10 MHz probe. The solution (a total number of 2×10^7cells, 1×10^7 /400 μL for unilateral ovarian injection) was injected into the ovary by using 21G PTC needles (Hakko Medical Co, Japan) under TVUS guiance. Each patent received up to three transplantations.

"Thank you for your attention"