



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

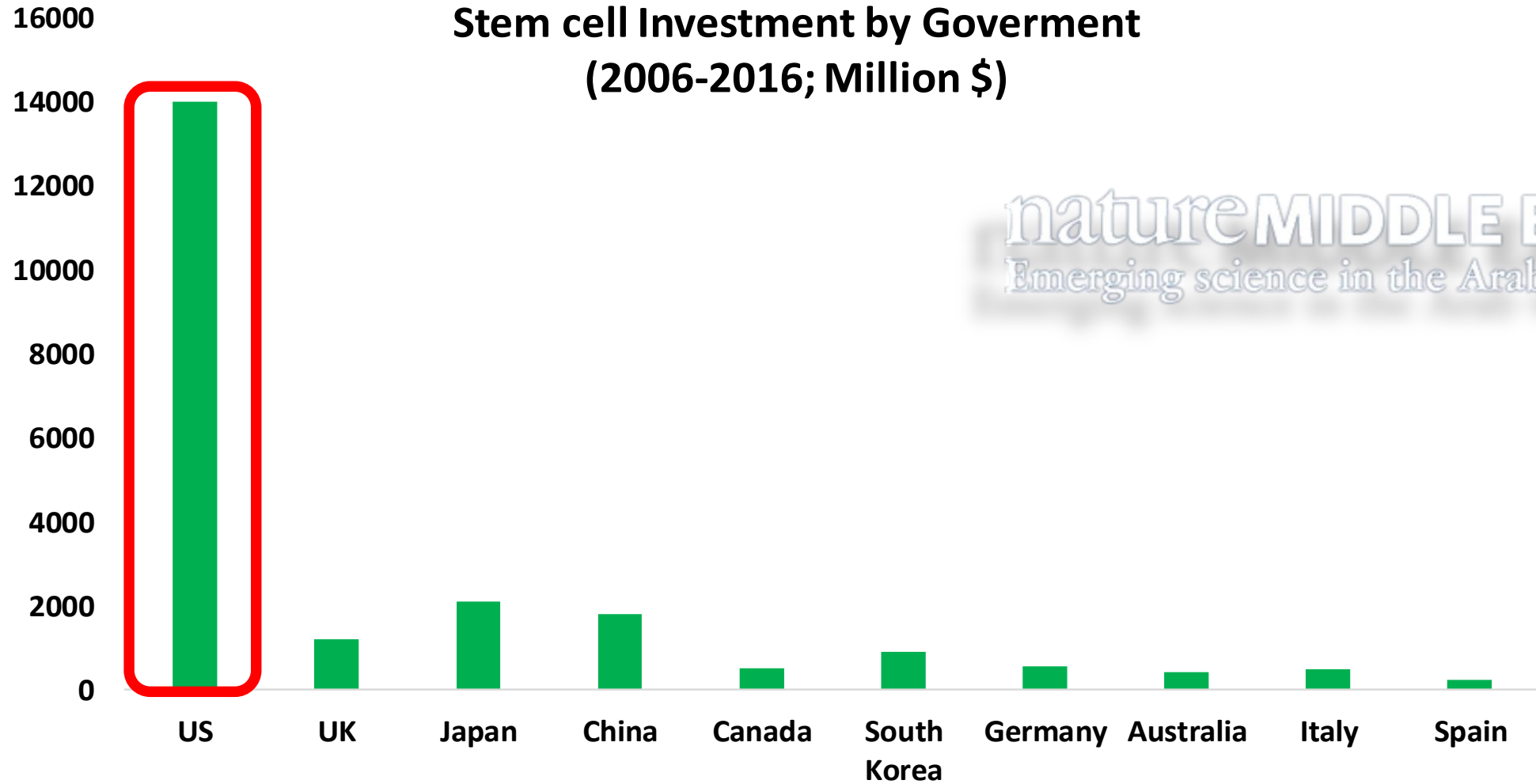
NK Cell  
Therapy

Lymphocyte  
Cell Therapy

# **Stem Cell & Regenerative Medicine**

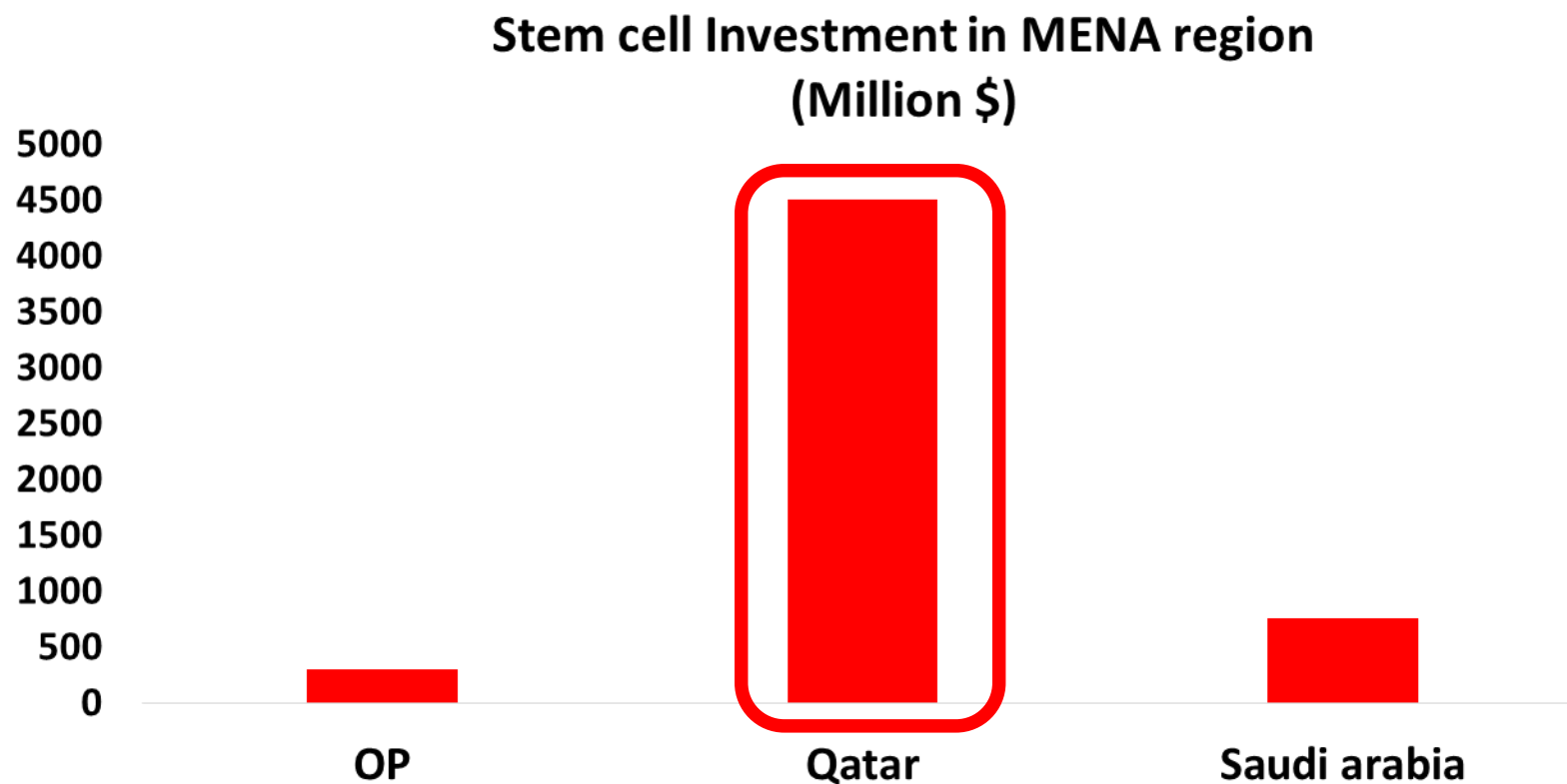
## **Global Market**

## Stem cell Investment by Government (2006-2016; Million \$)



nature MIDDLE EAST  
Emerging science in the Arab world







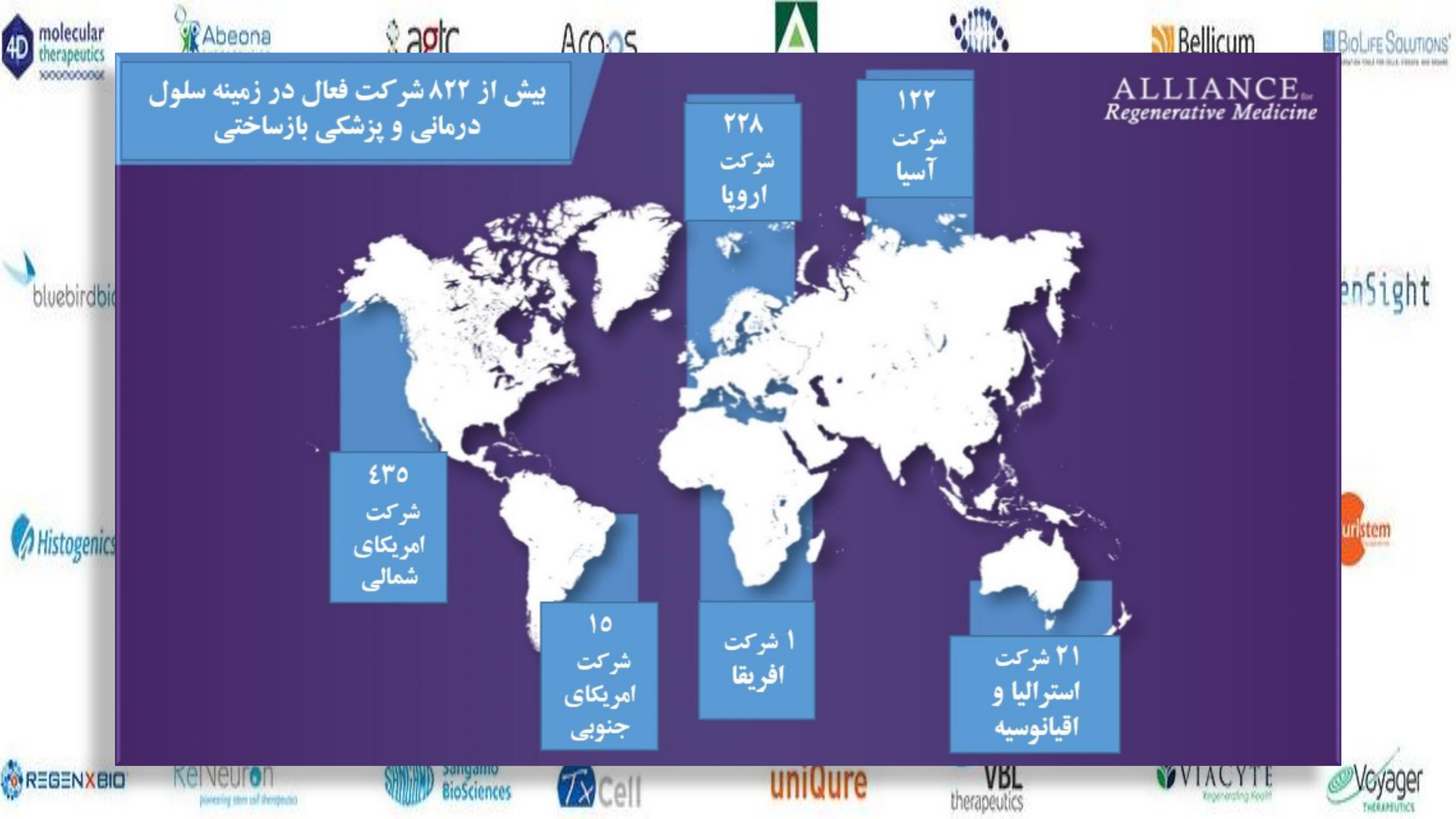
The Qatar Foundation will have a stem cell laboratory in the **US\$4.5 billion** Sidra Medical Centre, and will include a genetics and stem cell unit.

nature MIDDLE EAST  
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Council for development of the STEM cell sciences and technologies





یش از ۸۲۲ شرکت فعال در زمینه سلول  
درمانی و پزشکی بازساختی

ALLIANCE  
for  
Regenerative Medicine

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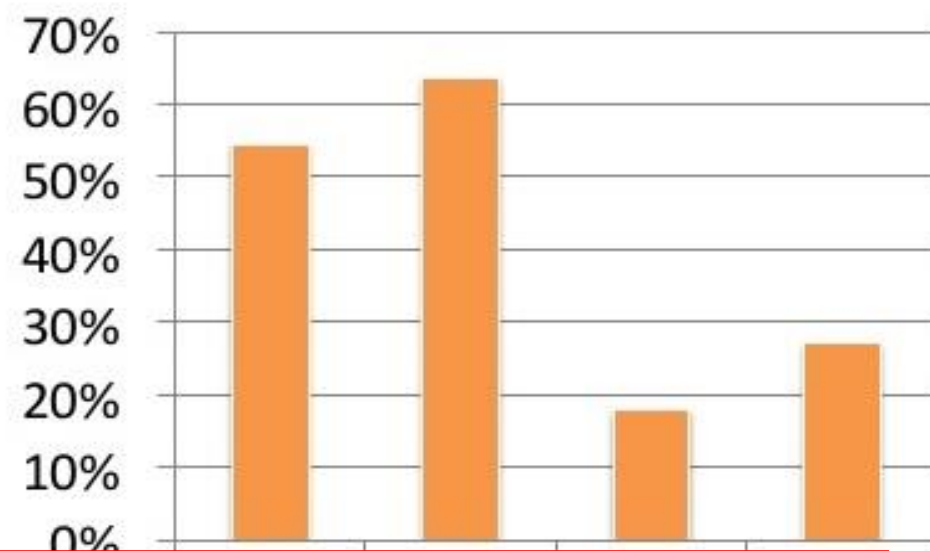
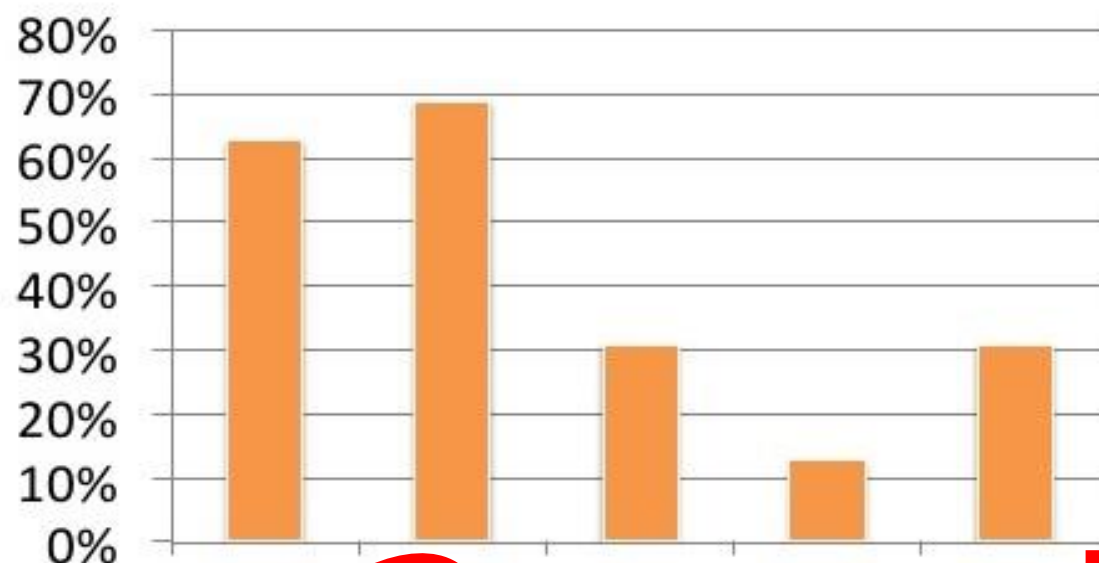
## Size of cell therapy market in some countries

| 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



Drug Discovery

Cell Therapies

Gene and Gene Modified CT

Tissue Engineering

Endogenous Activation

Autologous Stem Cells

Allogeneic Stem Cells

Primary Cells

Gene Modified Cells

**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**<sub>for</sub>  
*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

**Total: 504**

Ph. I: 184

Ph. II: 286

Ph. III: 34

#### Cell Therapy

**Total: 586**

Ph. I: 174

Ph. II: 365

Ph. III: 47

#### Tissue Engineering

**Total: 24**

Ph. I: 6

Ph. II: 14

Ph. III: 4

ALLIANCE<sub>for</sub>  
*Regenerative Medicine*





## 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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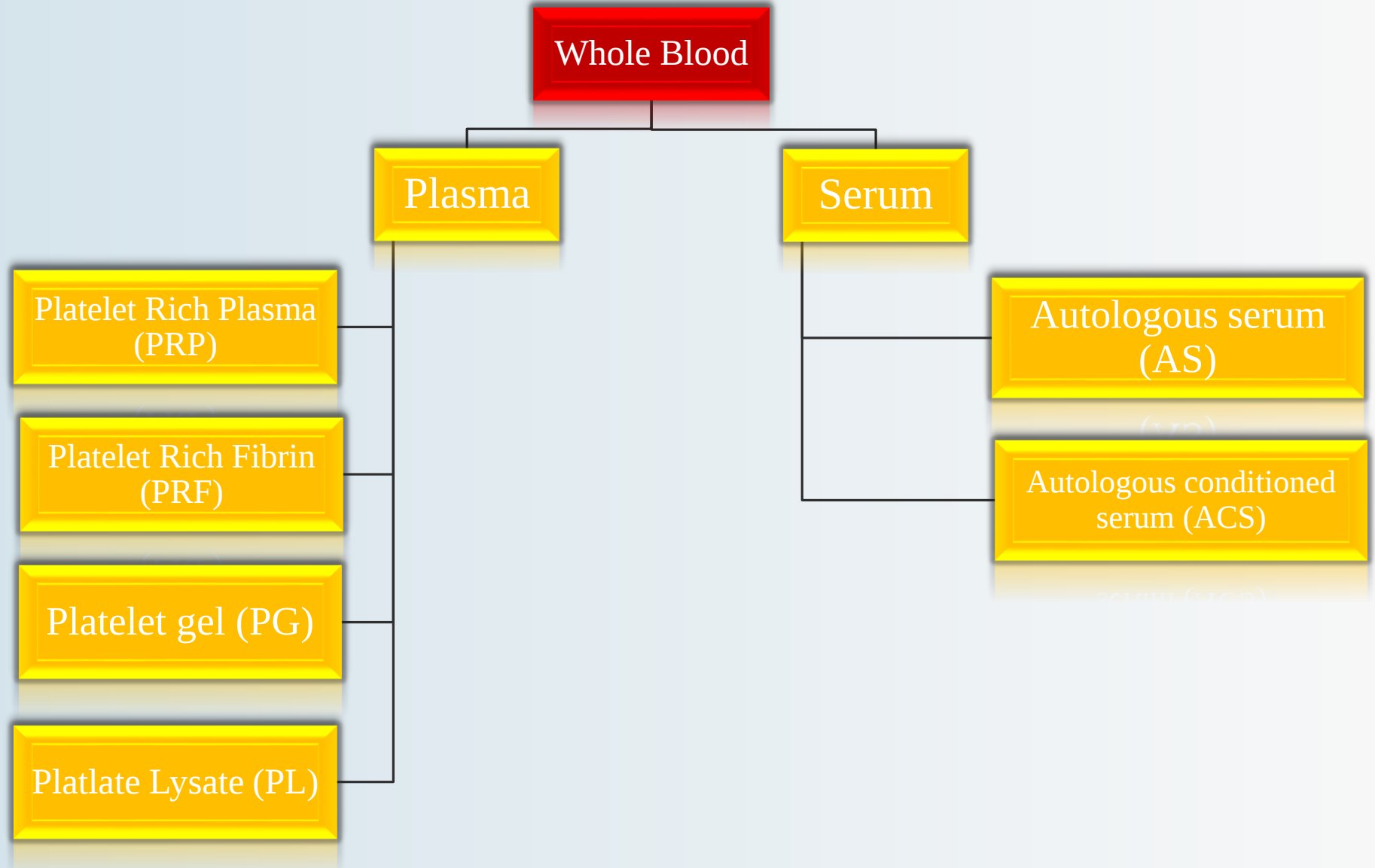
SVF

# Mature Cells

NK Cell  
Therapy

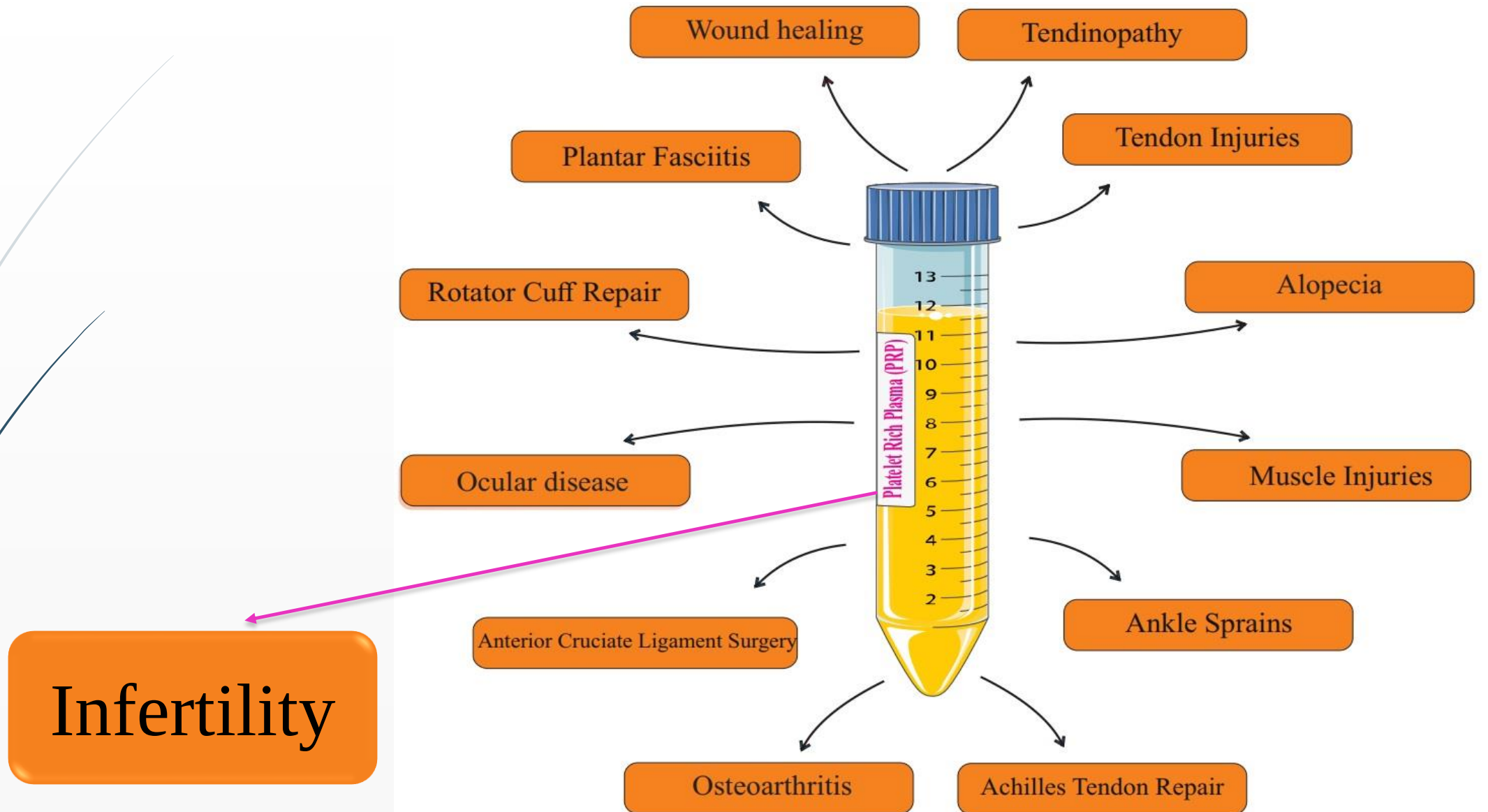
Lymphocyte  
Cell Therapy

## ➤ Hemoderivative Materials



# Platelet Rich Plasma (PRP)

## ➤ Clinical application of PRP





# 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., Grammatidis 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  $45.13 \pm 4.42$  years, had absence of menstrual cycle for  $4.88 \pm 1.13$  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  **$2.50 \pm 0.71$  follicles** of  **$15.20 \pm 2.05$  mm diameter**,  **$1.50 \pm 0.71$  oocytes** and  **$1.50 \pm 0.71$  MII oocytes**. All mature oocytes were inseminated by ICSI and the  **$1.50 \pm 0.71$  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

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

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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,<sup>a</sup> A. Gzgyan,<sup>b</sup> A. Feoktistov,<sup>c</sup> D. Niauri.<sup>d</sup> <sup>a</sup>Medical faculty, Saint-Petersburg State University, Saint-Petersburg, Russian Federation; <sup>b</sup>Saint-Petersburg State University, Saint-Petersburg, Russian Federation; <sup>c</sup>Medical group, Saint-Petersburg, Russian Federation; <sup>d</sup>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.

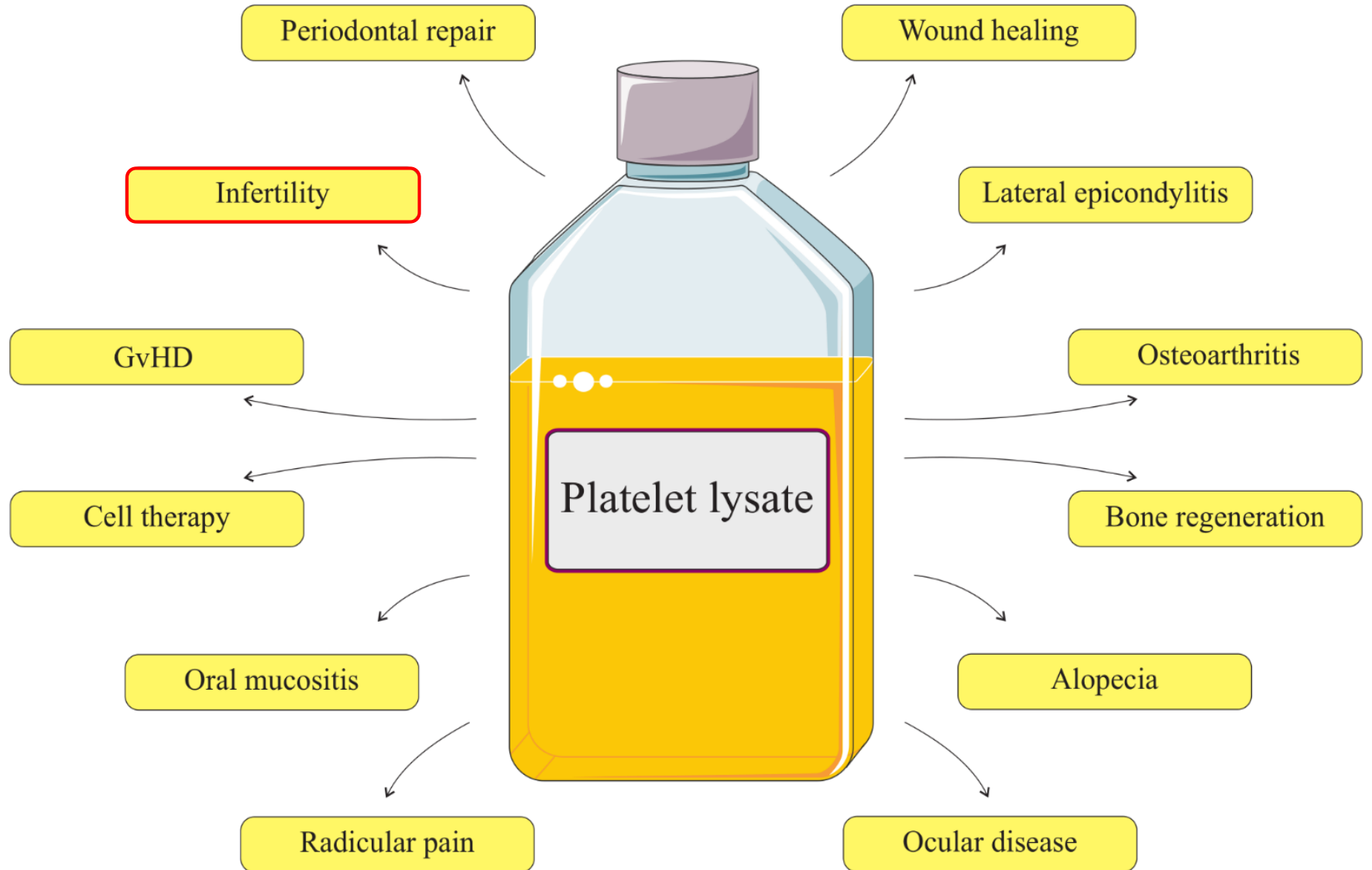
**CONCLUSIONS:** 1. The intrauterine perfusion with autologous PRP should be considered perspective, safe and cost-effective therapy method for patients with RIF. 2. PRP does not influence on pregnancy loss rate. 3. Further study is required.

## RESULTS OF PRP THERAPY ARE STEEL CONTROVERCIAL????

- Platelet Count
- WBC Count
- Patient Criteria

# Platelet Lysate (PL)

# ➤ Clinical application of Platelet Lysate



# Autologous Conditioned 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-1 $\beta$                                                         | 224 | UD                  | 7.9                  |
| IL-6                                                                 | 200 | UD                  | 28.7                 |
| TNF- $\alpha$                                                        | 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- $\beta$                                                         | 80  | 1165                | 97,939               |

# Adipose-Derived Tissue

## Nanofat

# Nano and Micro Fat





1A  
1B



2A  
2B



3A  
3B  
3C



4A  
4B



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# Stem Cells

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Nano fat

MSCs

# Mature Cells

PLI

Intrauterine  
Lymphocyte  
Therapy

# Terminology (Kolte et al., 2014)

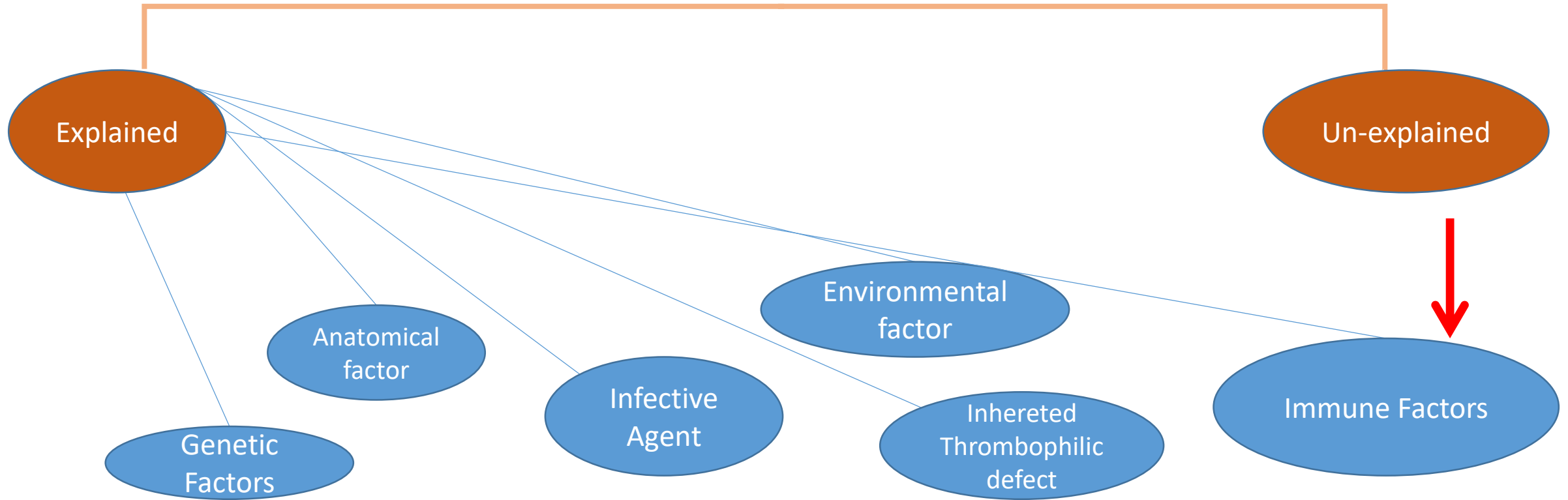
- **Recurrent Pregnancy Loss: RPL**
- **Habitual abortion**
- **Habitual miscarriage**
- **Recurrent abortion**
- **Recurrent Miscarriage: RM**

# Recurrent miscarriage (RM)

## Definition

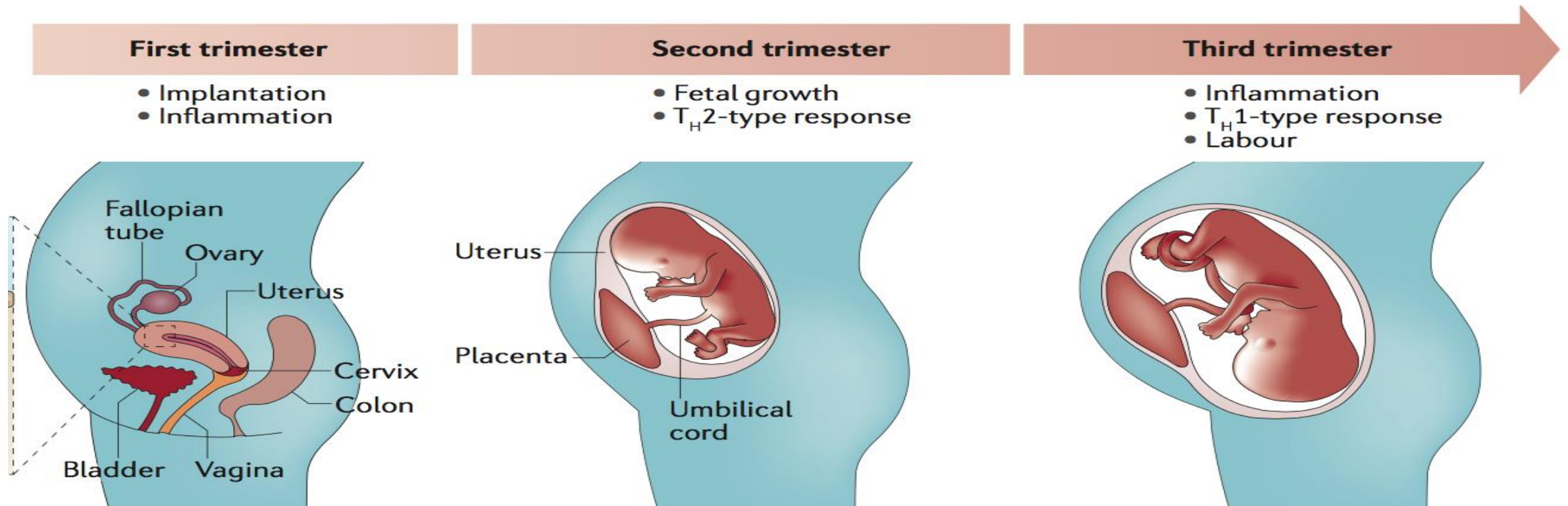
- RM is 3 or more consecutive, spontaneous pregnancy loss, under 20 weeks gestation from the last menstrual period, by the same partner
- The incidence of RM is variable range from 0.5% to 2.3%
- According to the guidelines of the American Society for Reproductive Medicine (ASRM) and European Society 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



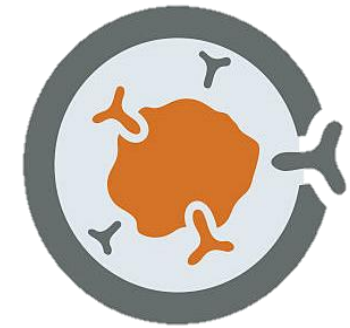
# Immunologic factors (Lim et al., 1996)

alteration in cellular immunity

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



**Autoimmune**



mediated by humoral

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

**Alloimmune**



# 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***

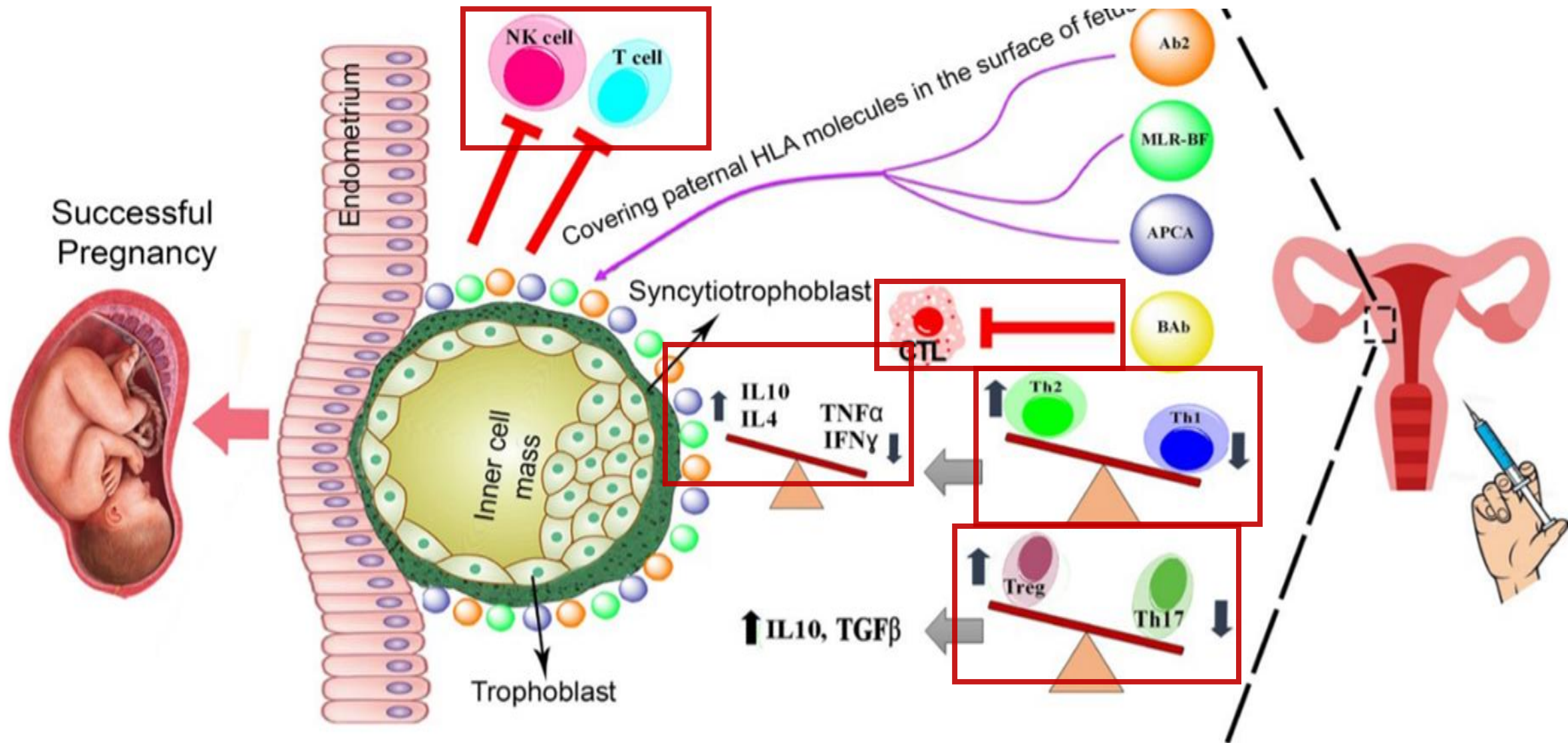
Immunosuppressive therapies for autoantibodies and to inappropriate cellular immunity toward the implanting fetus Includes:

- ***Corticosteroids***
- ***Intravenous Immunoglobulin (IVIG)***

## Immunosuppressing 02

## 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%)**



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

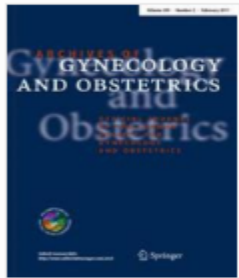
## Clinical trial studies on lymphocyte immunotherapy (LIT) in patients with recurrent pregnancy loss (RPL)

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

# Systematic review



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[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

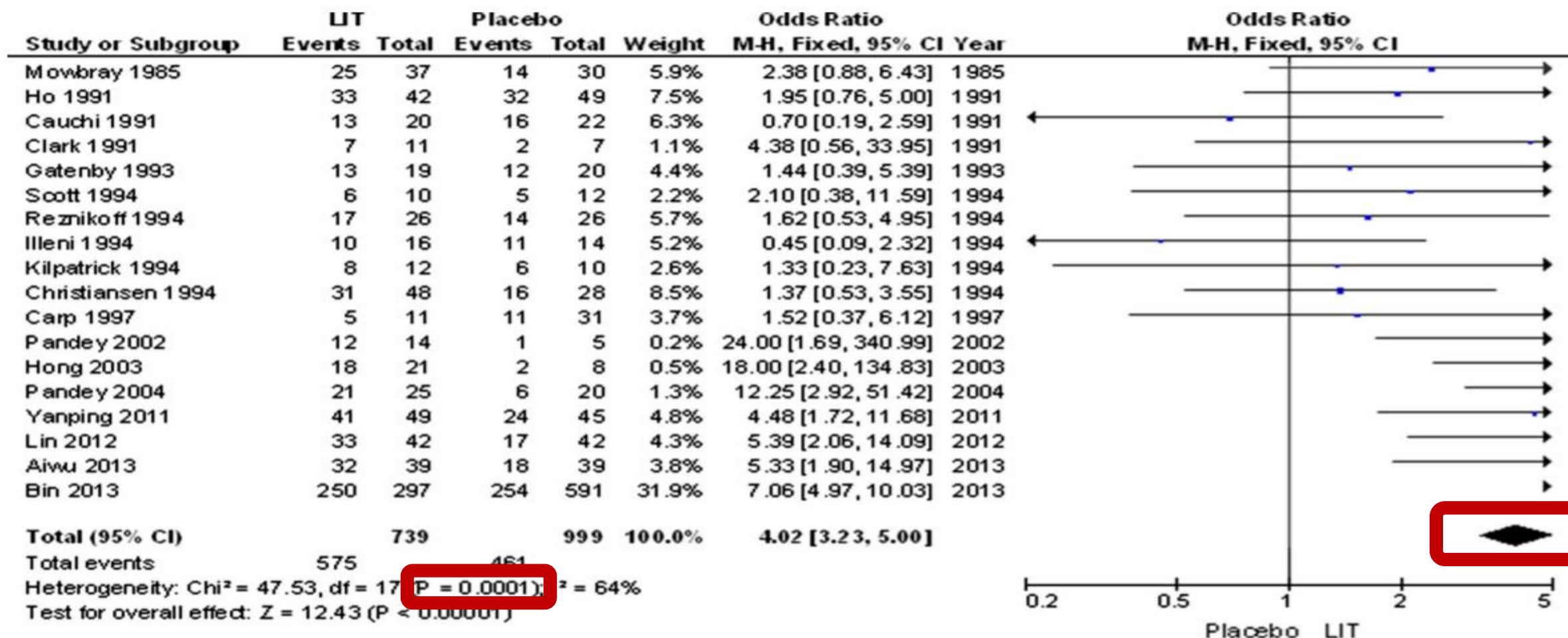
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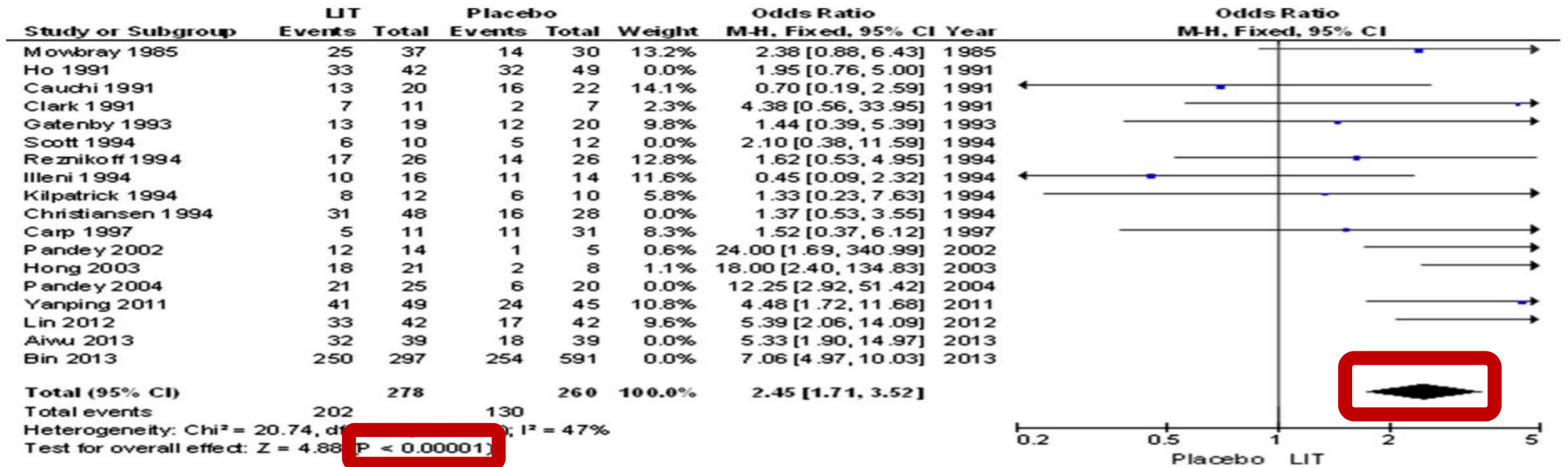
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Citations

# Pregnancy Rate



# Live Birth Rate





## SCHNELLER, HÖHER, EINFACHER DIE AKTUELLEN FAKTOR-NEWS

Virtuelles Hämophilie-Symposium  
25.09.2019

Mehr erfahren

DE19H00027



### Transfusion Medicine and Hemotherapy

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Original Article · Originalarbeit

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

Wegener S.<sup>a</sup> · Schnurstein K.<sup>a</sup> · Hansch S.<sup>b</sup> · Briese V.<sup>b</sup> · Sudik R.<sup>c</sup> · Wegener R.<sup>d</sup> · Busecke A.<sup>e</sup> · Müller H.<sup>e</sup>

 [Author affiliations](#)

Transfus Med Hemother 2006;33:501-507

<https://doi.org/10.1159/000096125>

**Table 4.** Results of active immunotherapy in repeated miscarriages

| AI time point               | Births<br>(A) | Abortions<br>(B) | No pregnancy<br>after AI<br>(C) | Successful pregnancy<br>after AI<br>(A/A+B) | Success rate<br>(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<br>(A) | Abortions<br>(B) | No pregnancy<br>after AI (C) | Successful<br>pregnancy<br>(A/A+B) | Success rate<br>(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.

Uterine anatomic abnormalities

Endometrial thickness and receptivity

Thrombophilia and connective tissue disease

Immunologic factor

Embryonic  
Factors

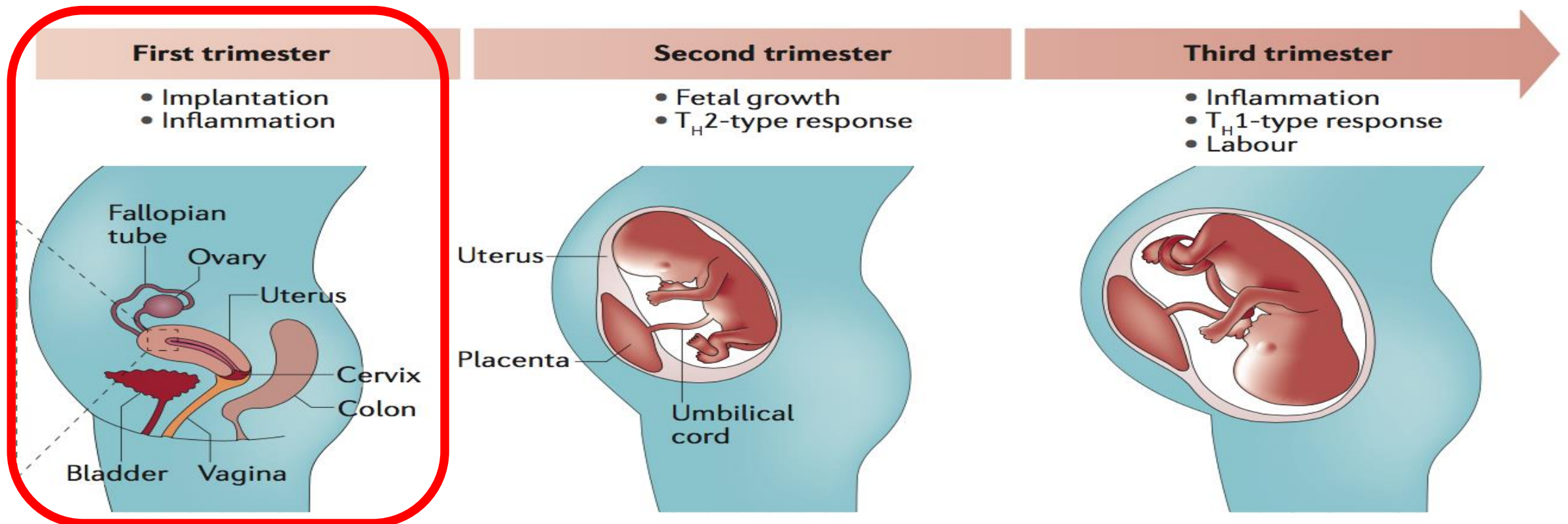
Genetic factor (Karyotype)

Assuming the embryo ceases to develop in utero

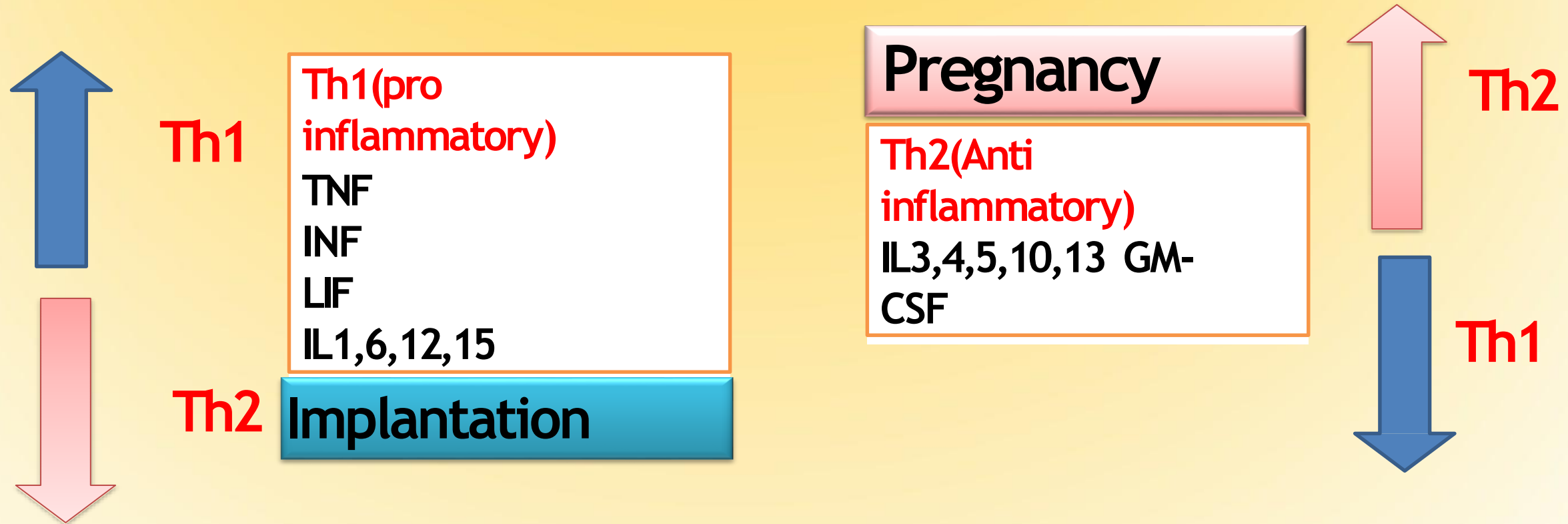
Maternal  
Factors

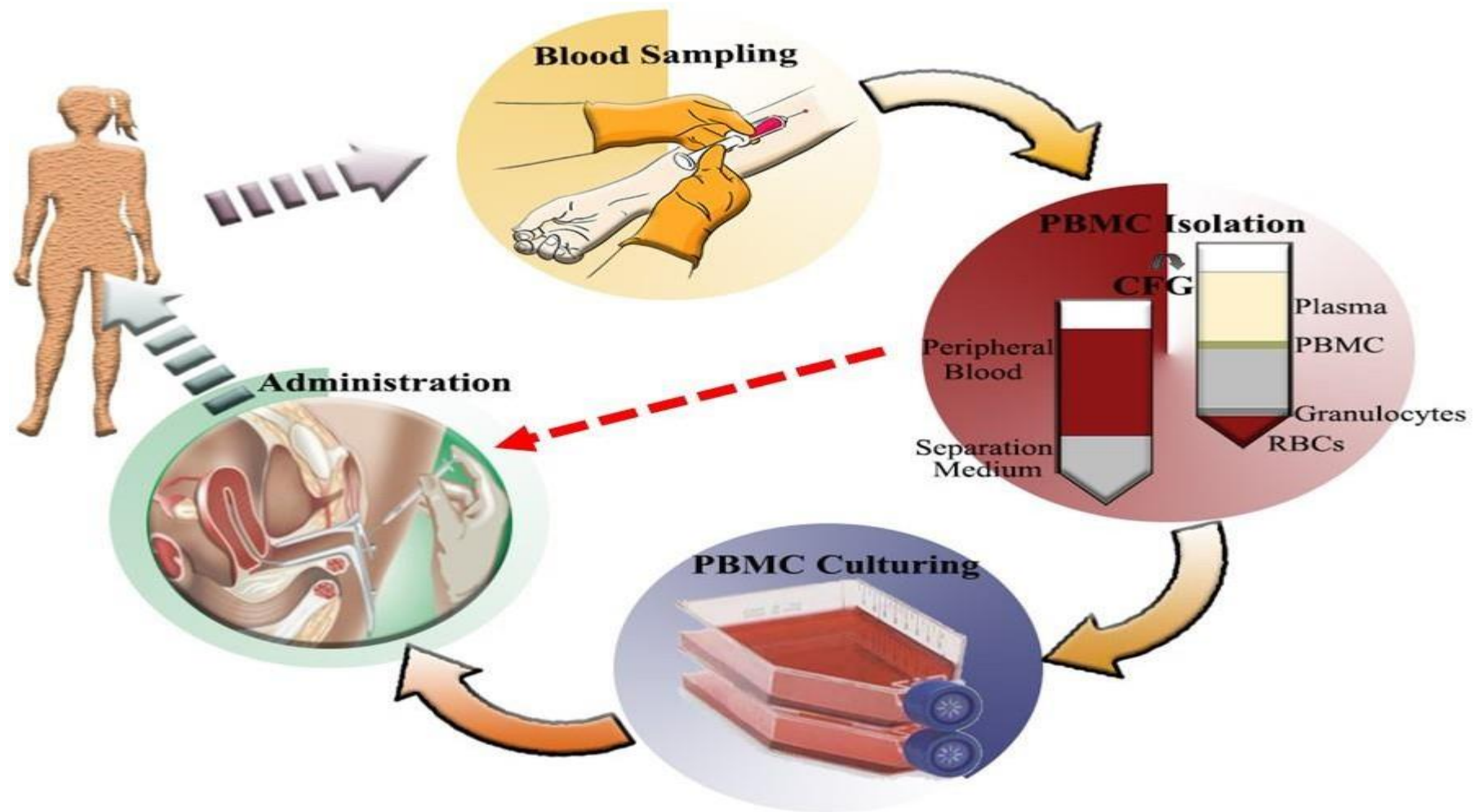
# A successful pregnancy : a dynamic immunologic process

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**







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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<sup>a</sup>, Maryam Razavi<sup>b</sup>, Mahroo Rezaeinejad<sup>c</sup>, Safoura Rouholamin<sup>d</sup>, Amir Almasi-Hashiani<sup>e</sup>, Reihaneh Pirjani<sup>f</sup>, Mahdi Sepidarkish<sup>g,\*</sup>

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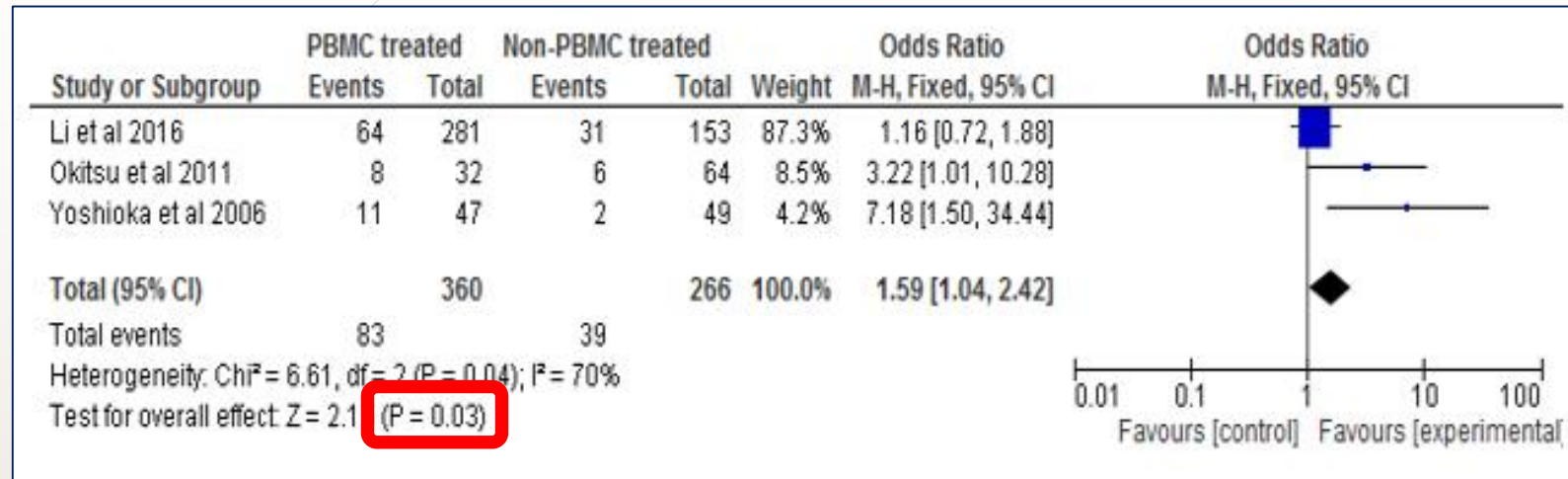
<sup>d</sup> Department of Obstetrics and Gynecology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

<sup>e</sup> Department of Epidemiology, School of Health, Arak University of Medical Sciences, Arak, Iran

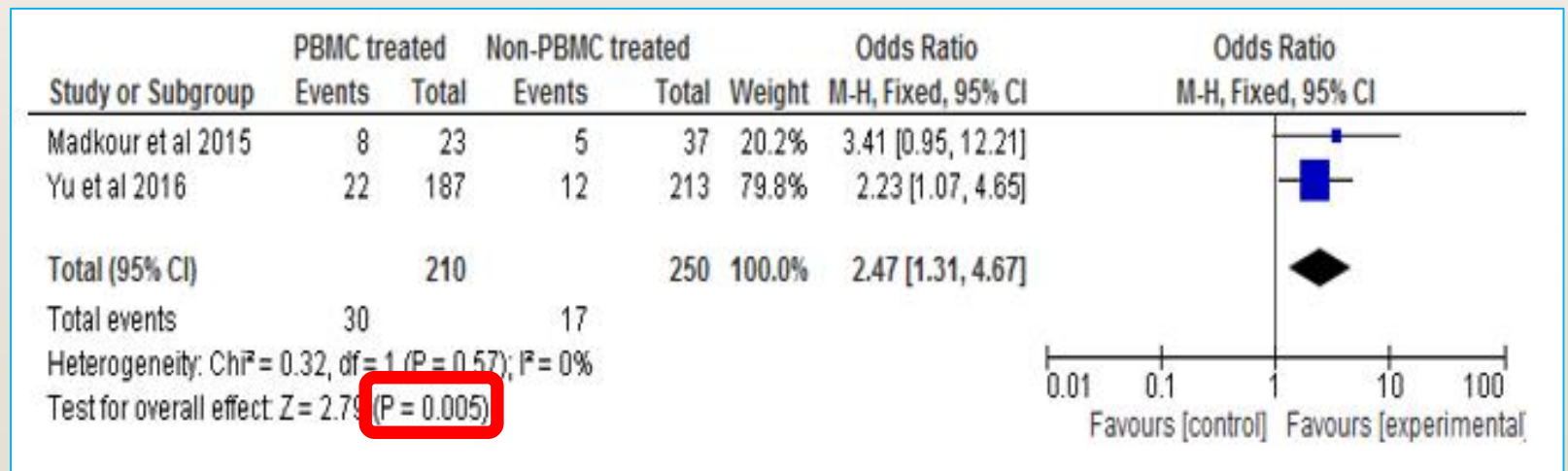
<sup>f</sup> Obstetrics and Gynecology Department, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran

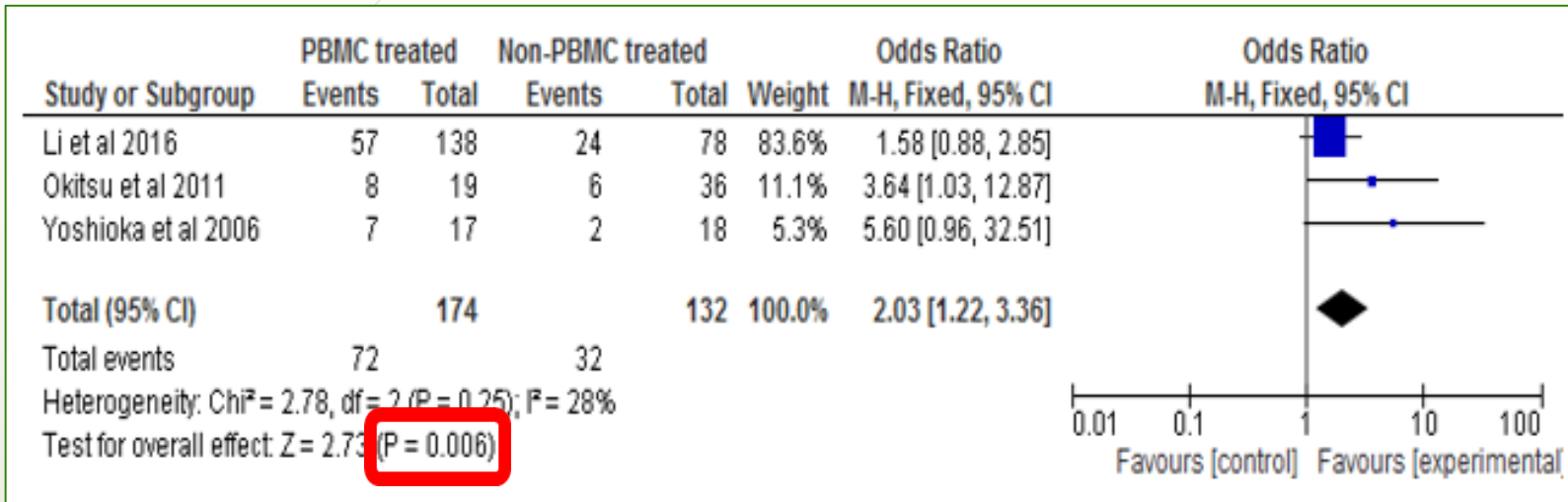
<sup>g</sup> Department of Epidemiology and Reproductive Health, Reproductive Epidemiology Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran

**Implantation  
rate  
Quasi-exp  
studies**



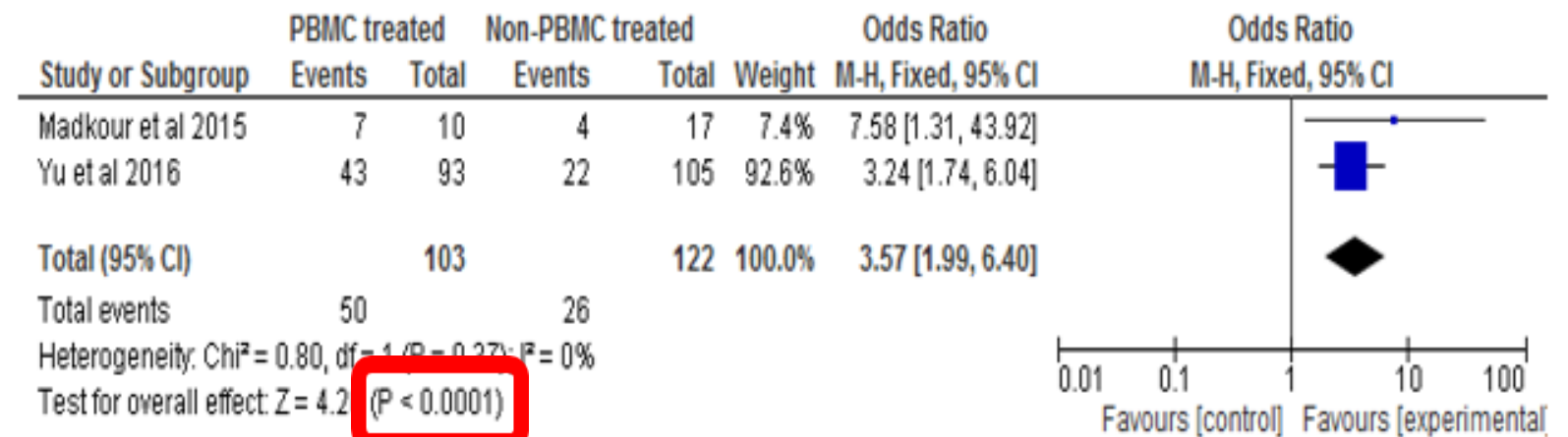
**Implantation  
rate  
In RCTs**

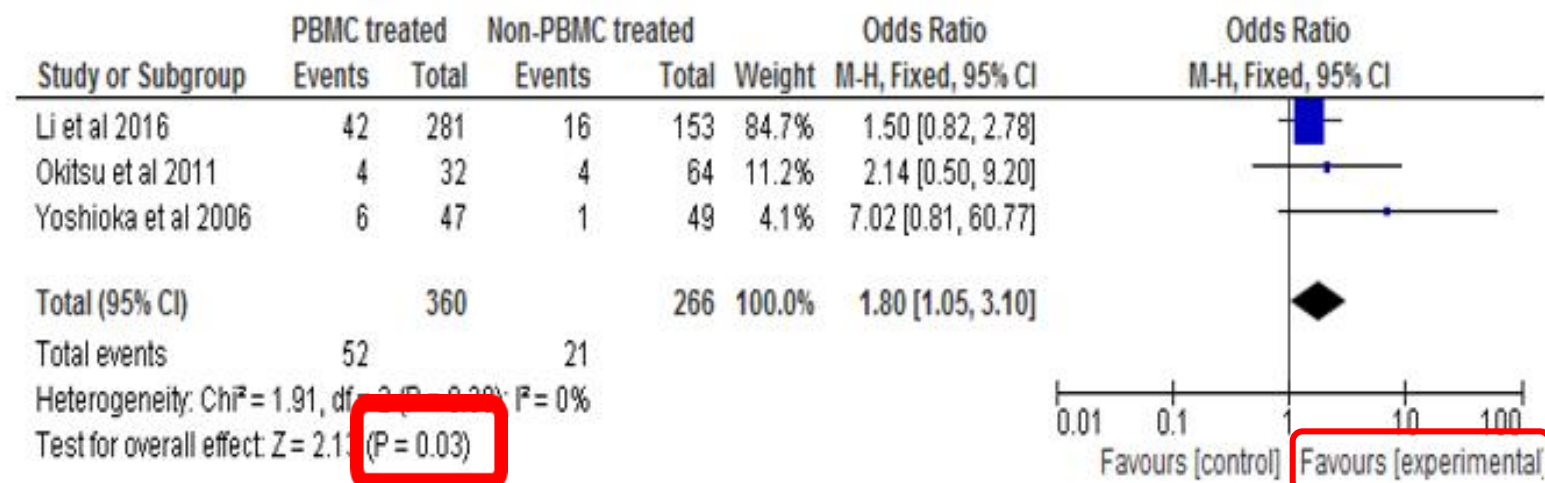




**Pregnancy  
rate  
In quasi-exp  
studies**

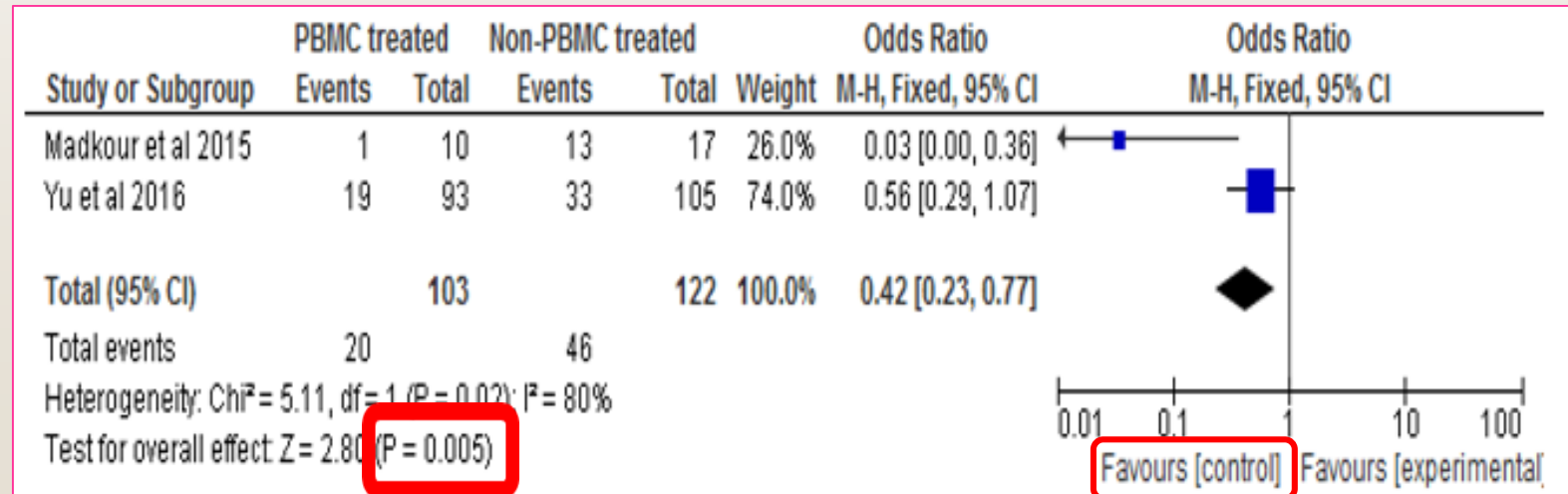
**Pregnancy  
rate  
In RCTs**





**Live birth  
rate  
In quasi-exp  
studies**

**Miscarriage  
rate  
In RCTs**



# Introduction



## *ClinicalTrials.gov PRS* *Protocol Registration and Results System*

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Showing: 1 record

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

KEY: Results Delayed Results Study Documents PRS Review  
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Iranian Registry of Clinical Trials - **Beta version**

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فارسی «

[Protocol summary](#)

[General information](#)

[Secondary Ids](#)

[Ethics committees](#)

[Health conditions studied](#)

[Primary outcomes](#)

[Secondary outcomes](#)

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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 ▼

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### Protocol summary

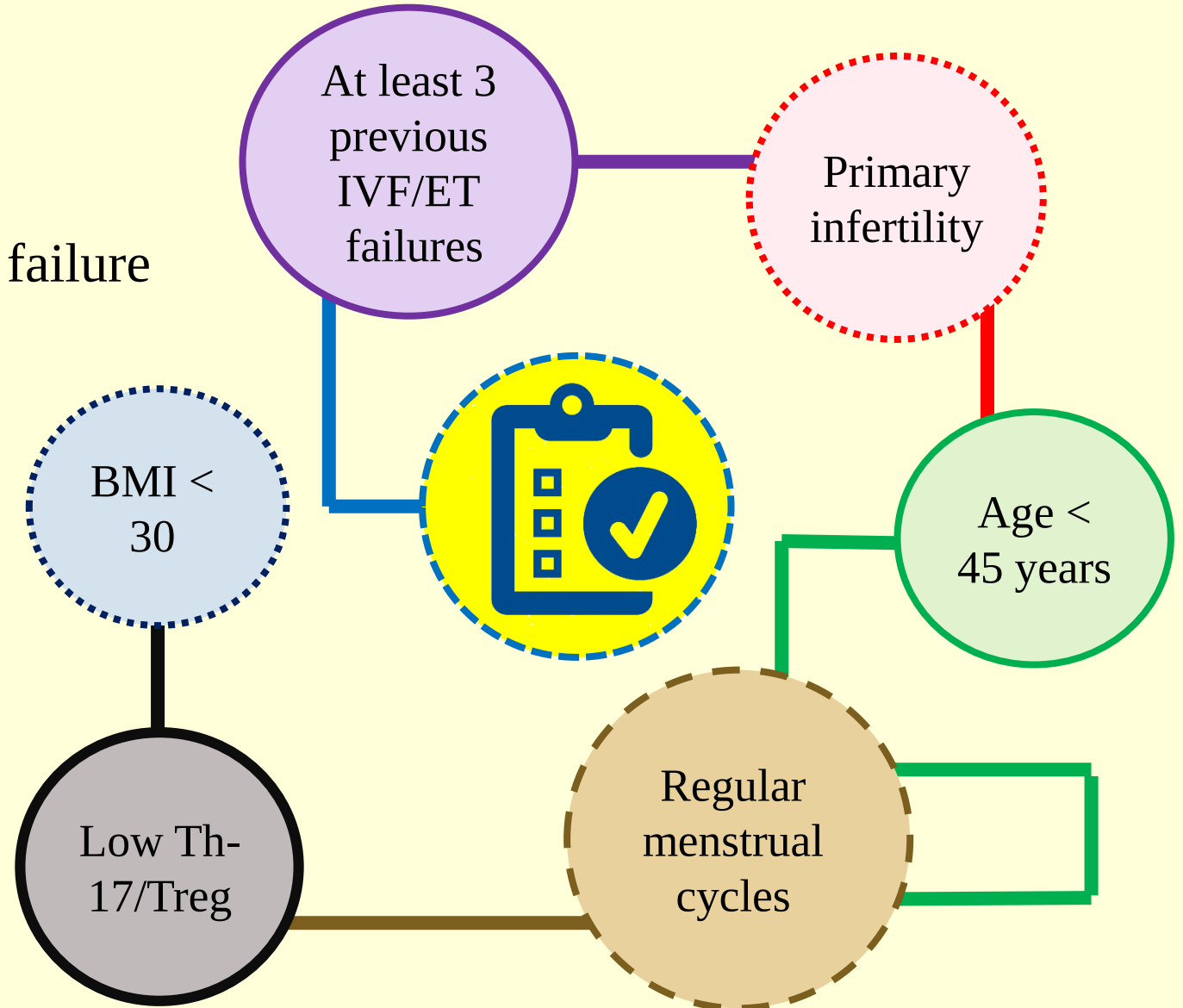
#### Summary

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

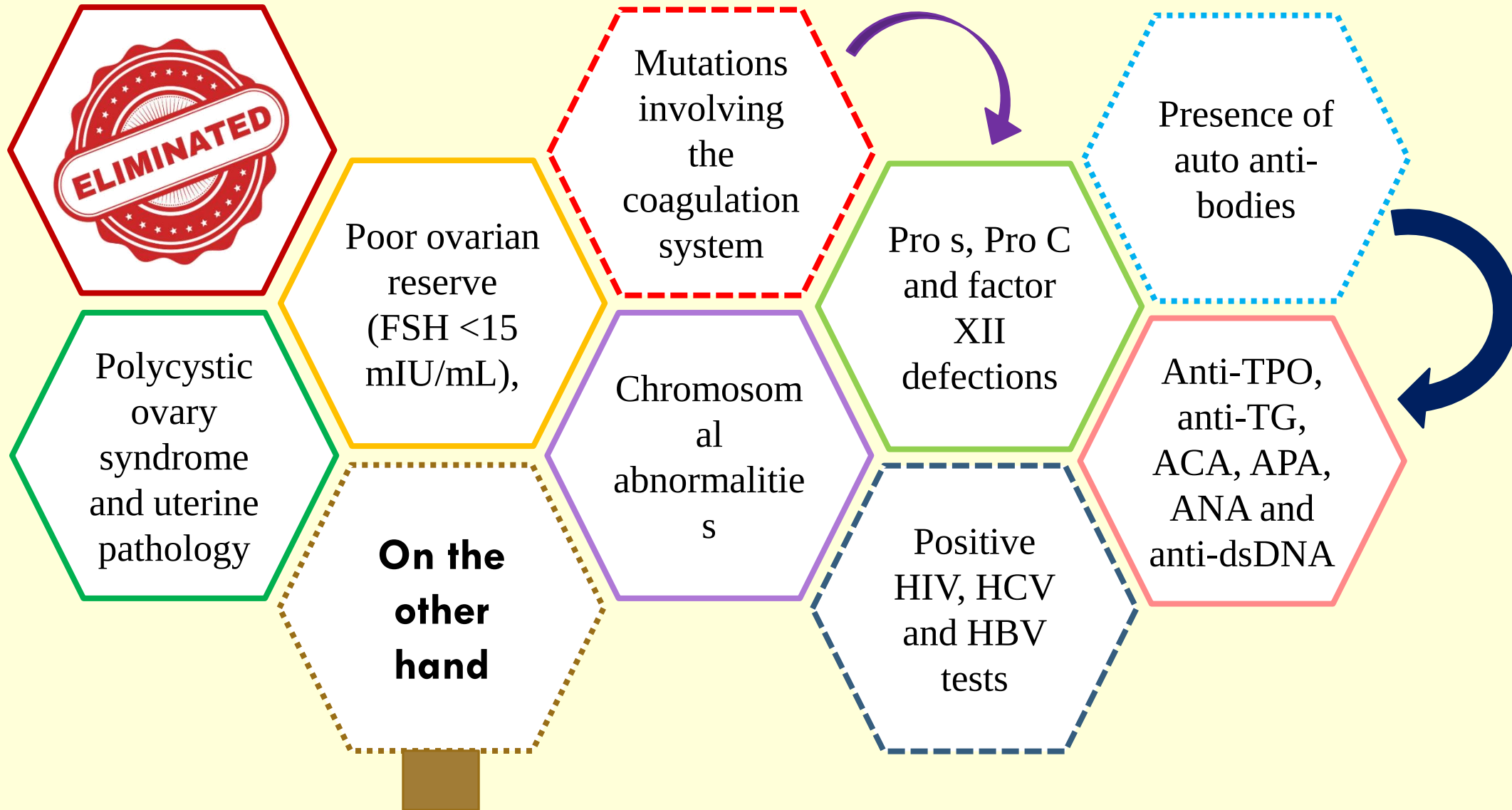
# Methods

## *Subject and Study design*

- 248 patients with the history of IVF failure



# Methods



# Methods

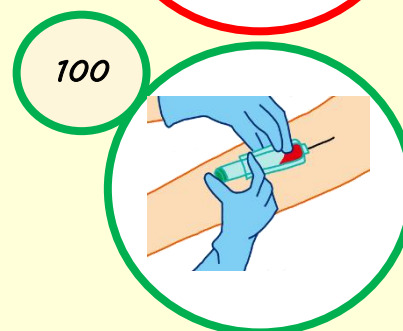
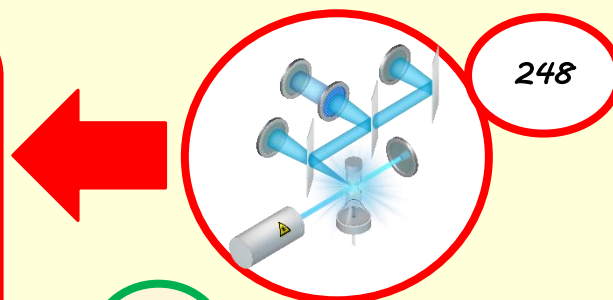
21



## Flow cytometry

10 ml

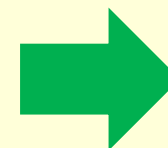
For Th-17, Treg and Th-17/Treg



## Blood Sampling

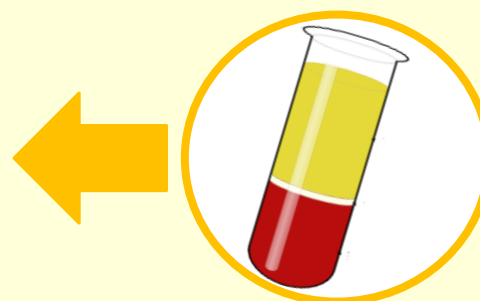
20 mL

Five days before ET



## PBMCs Isolation

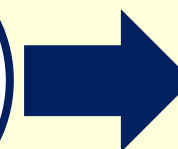
Using Ficoll-Paque



## PBMCs Culturing

20-30 $\times$ 10<sup>6</sup> PBMCs were suspended  
in 8 ml CM10

At the presence hCG (10 IU/mL.day)  
for 48 hours

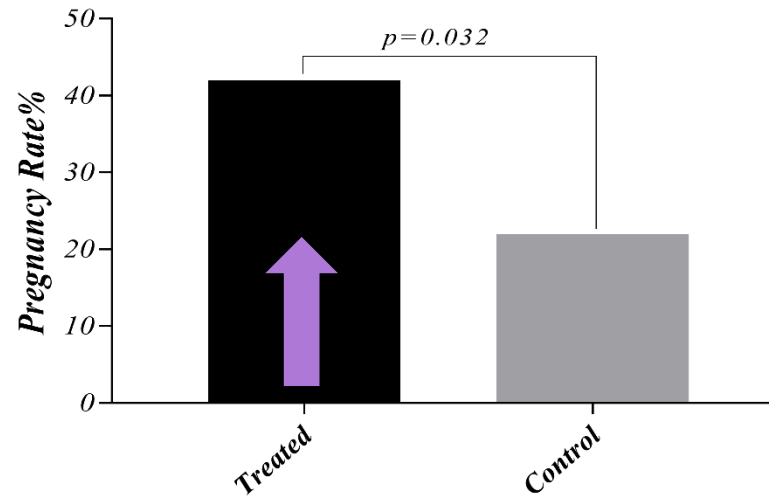


# *Pregnancy Outcomes*

# Results

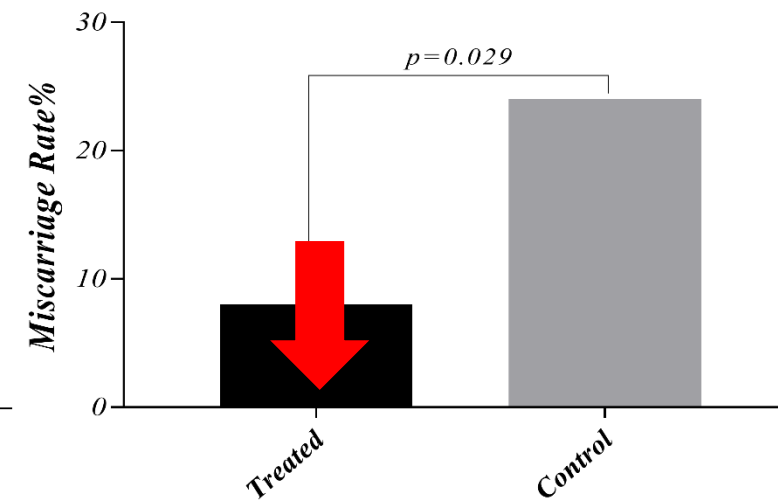
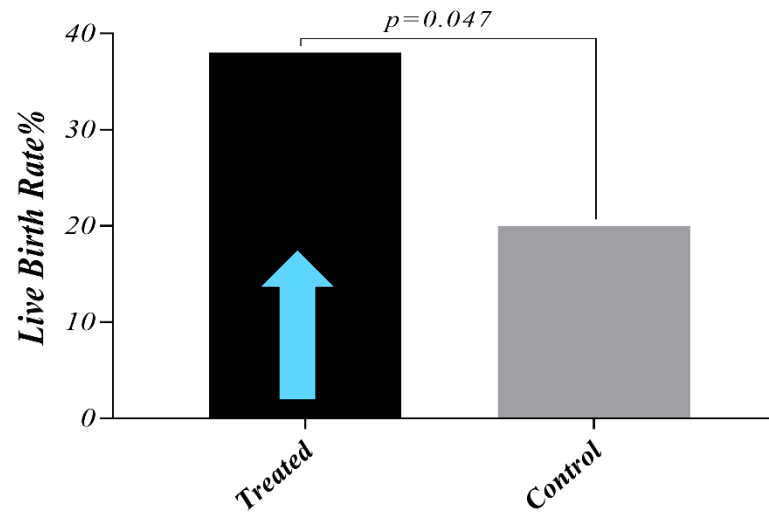


Pregnancy  
rate



■ Treated (RIF patients with  
PBMCs therapy)  
■ Control (RIF patients  
with PBS injection)

Miscarriage  
rate



# Results



**TABLE 4. Clinical outcome of the patients in the PBMC-treated and control groups**

|                          | Treated RIF<br>Patients% N=50 | Control group%<br>N=50 | P value |
|--------------------------|-------------------------------|------------------------|---------|
| <b>Pregnancy Rate%</b>   | 42%                           | 22%                    | 0.032   |
| <b>Live Birth Rate%</b>  | 38%                           | 20%                    | 0.047   |
| <b>Miscarriage Rate%</b> | 8%                            | 24%                    | 0.029   |

# Blood Cells

ACS

PRP

Platelet gel

Plasma gel

Platelet Lysate

PRF

BM Stem Cell

Skin Stem Cell

# Stem Cells

ADSC

Microfat &  
Nano fat

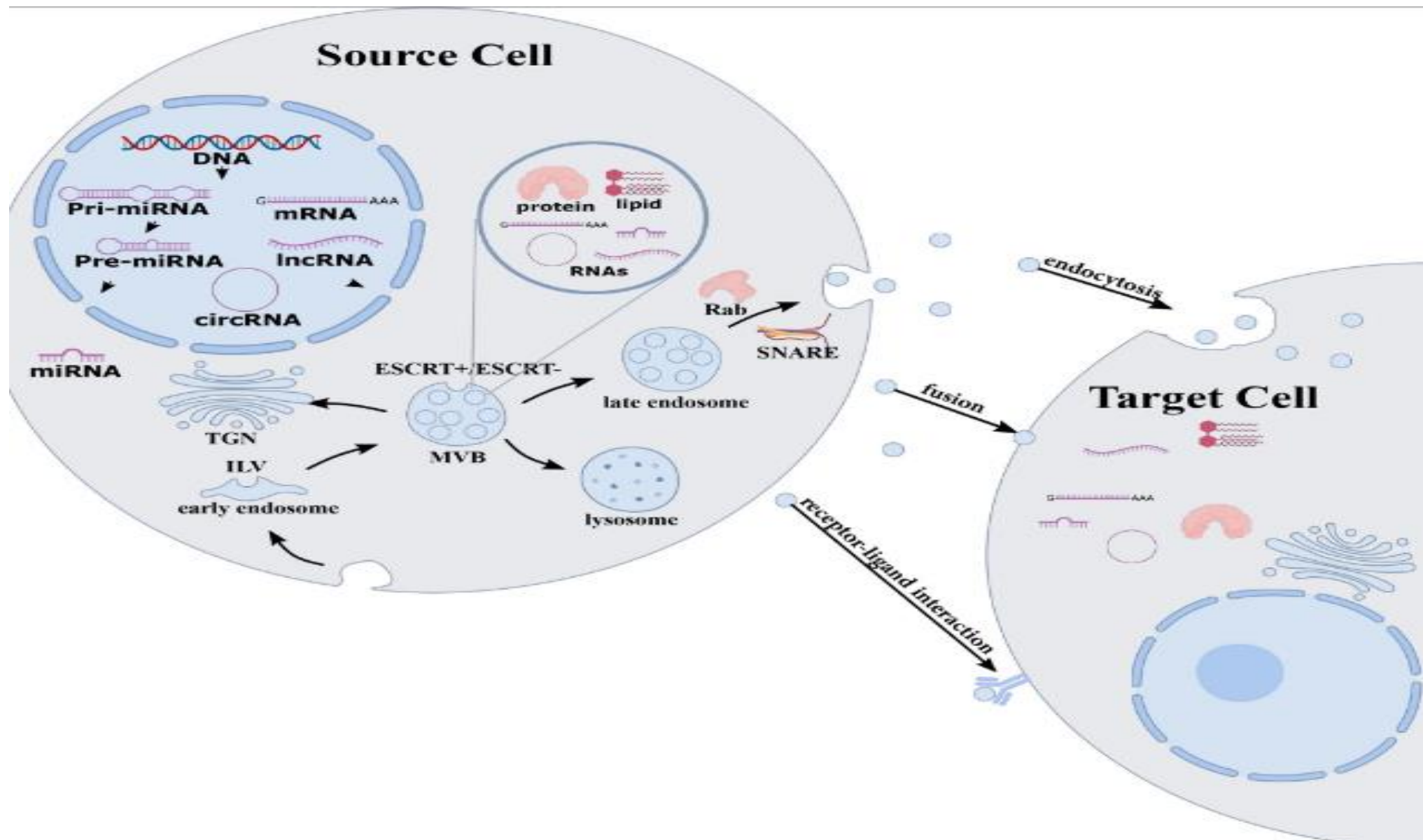
MSCs

# Mature Cells

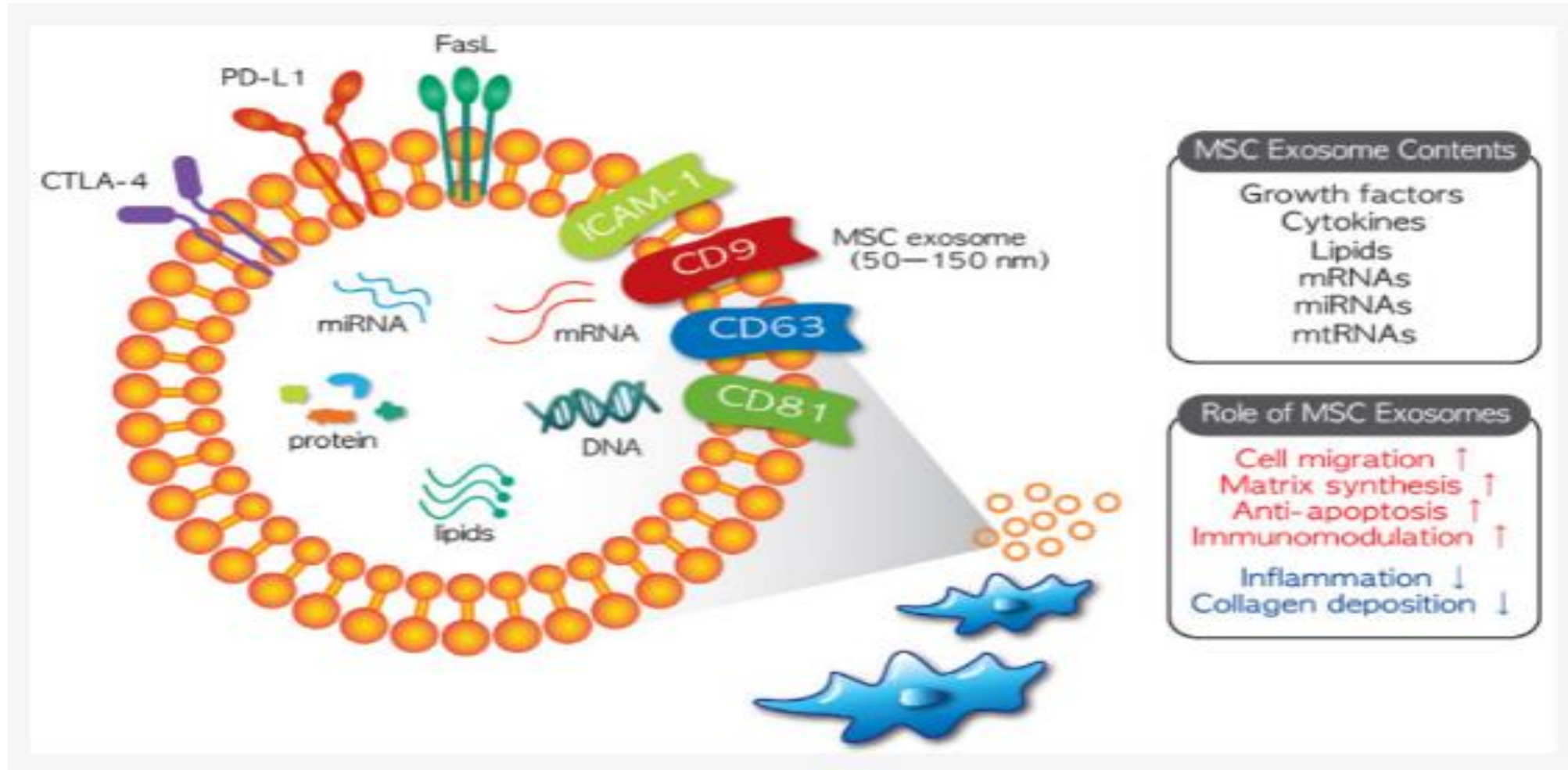
PLI

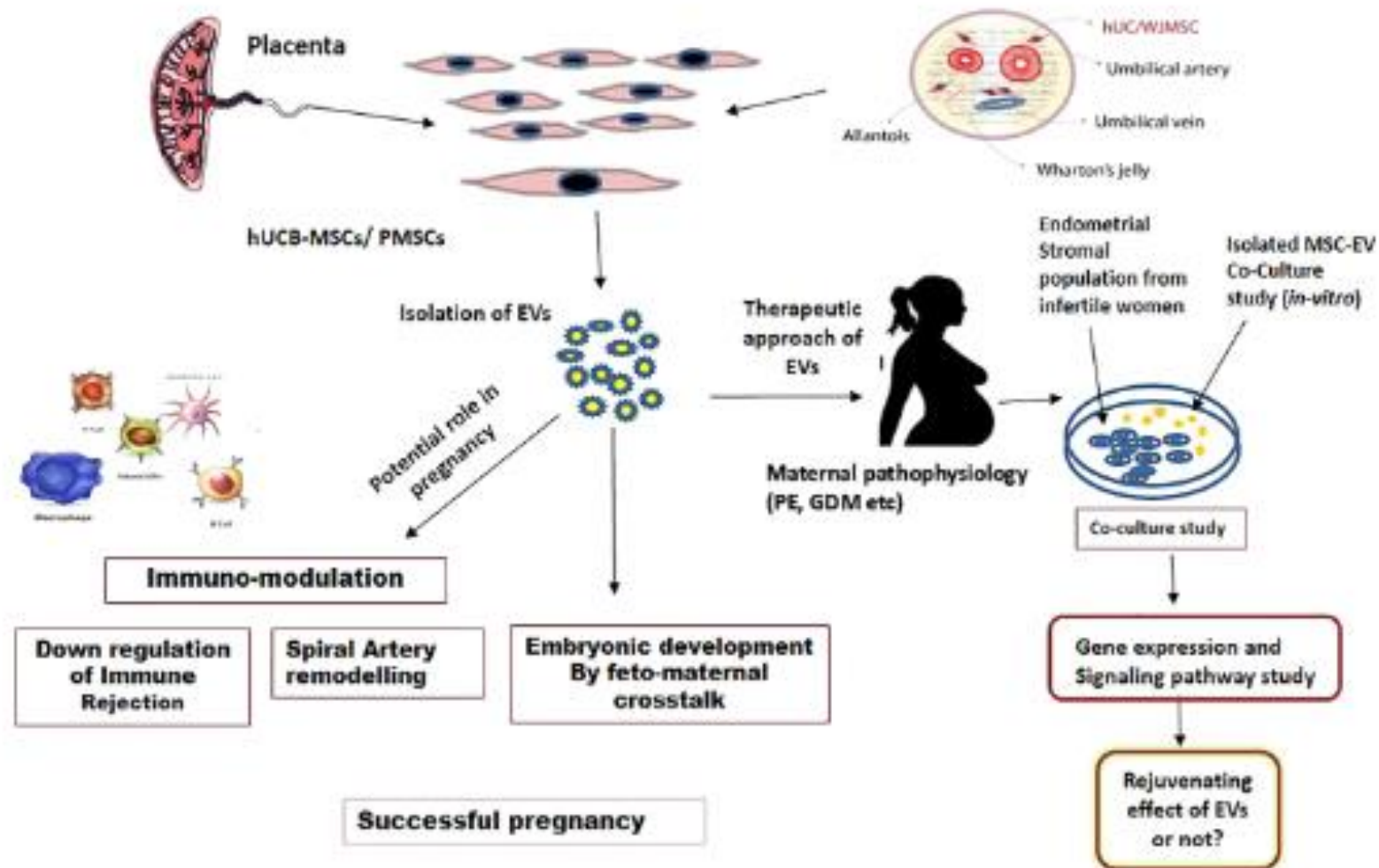
Intrauterine  
Lymphocyte  
Therapy

# Exosome And Female Infertility

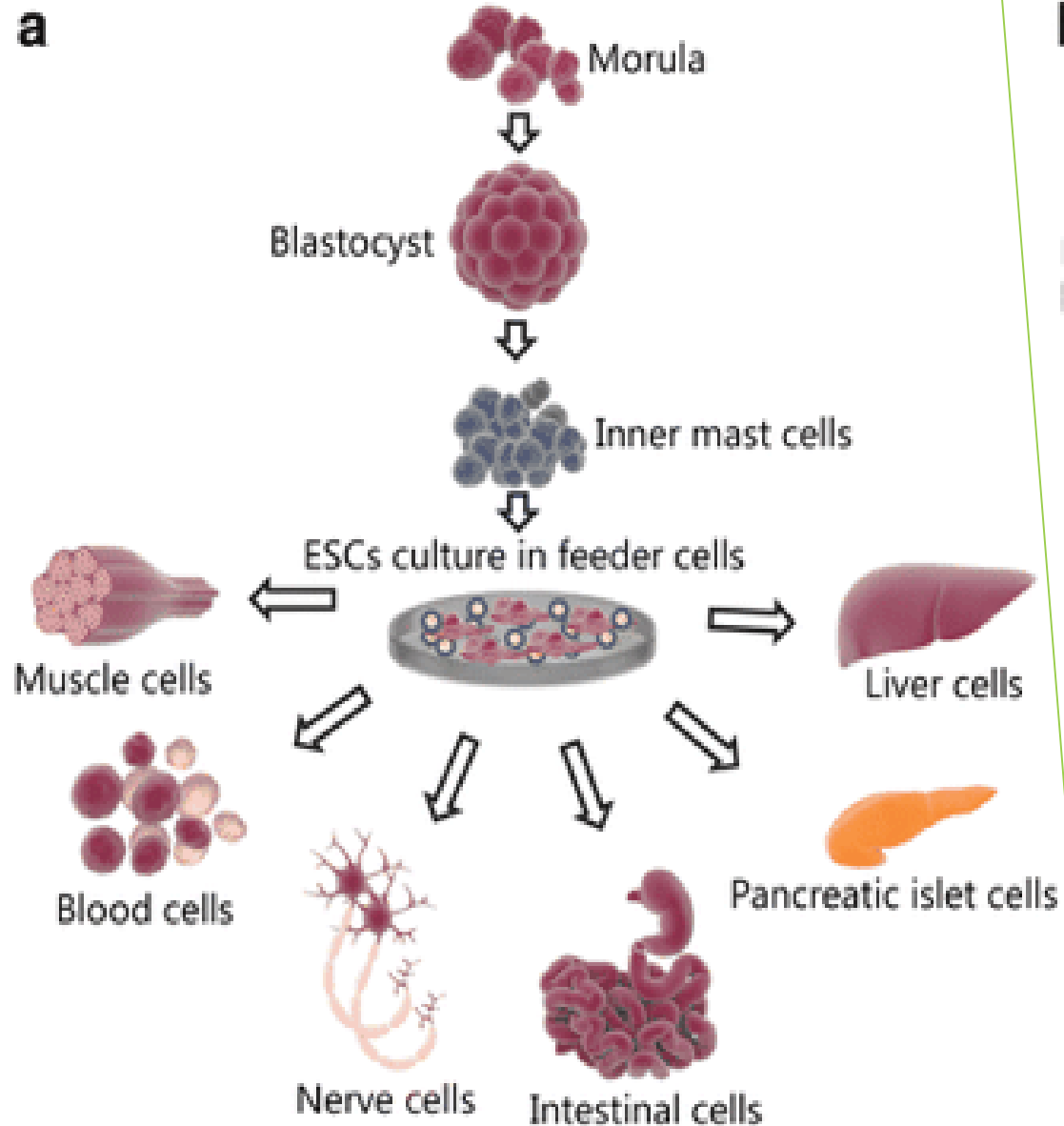


# Human Umbilical Cord mesenchymal Stem Cell exosome

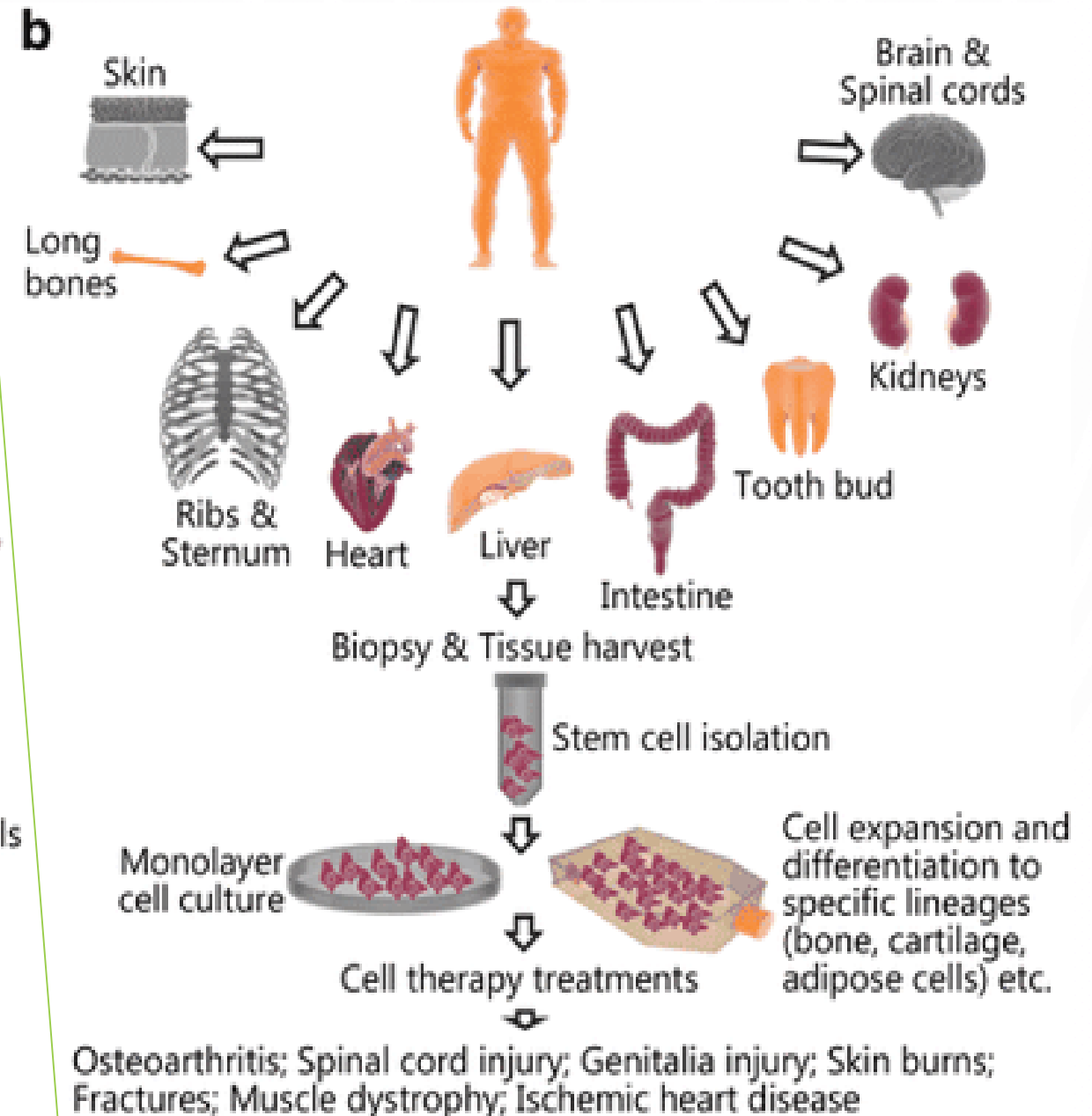




## ➤ Embryonic Source



## ➤ 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

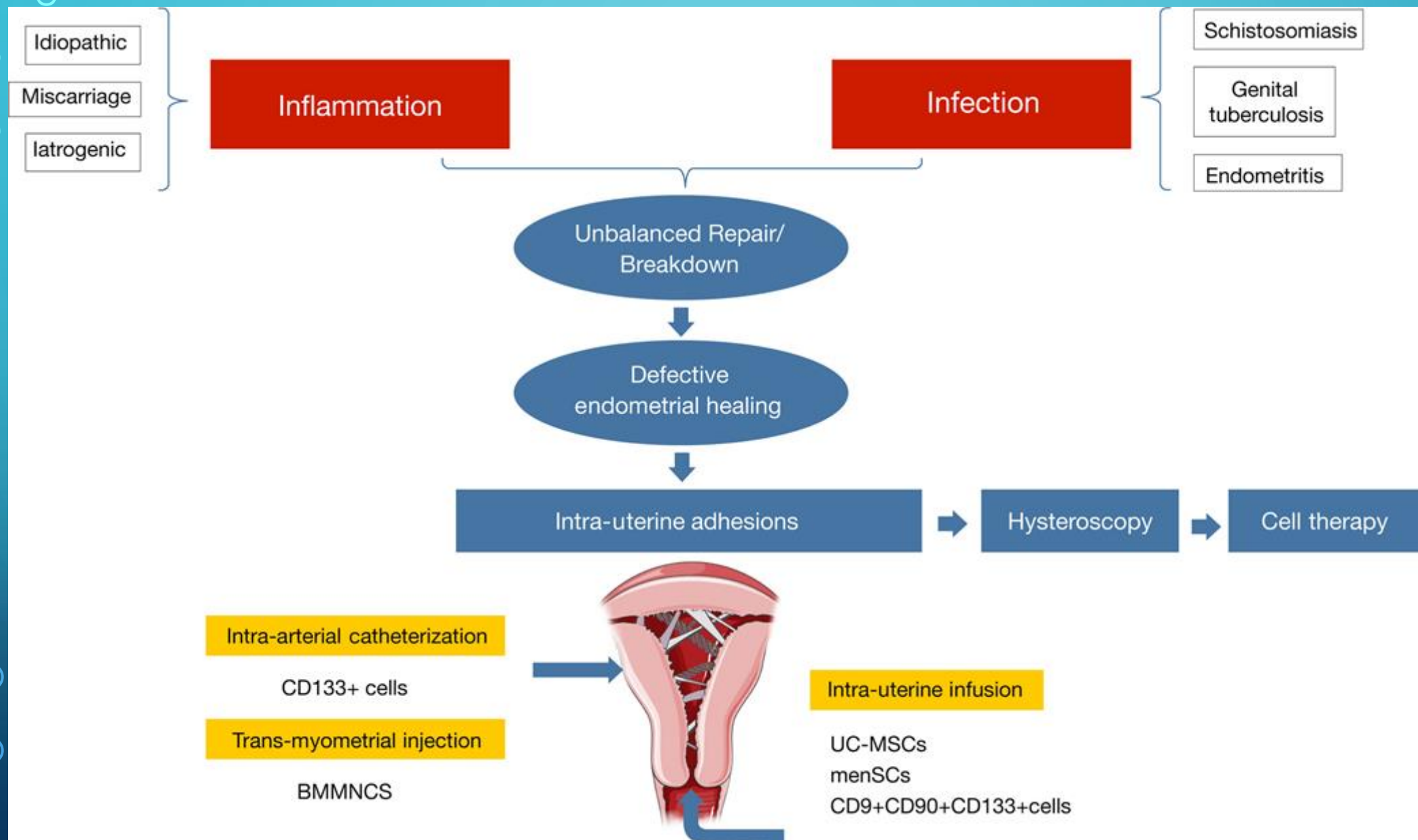


- Optic Nerve Damage
- Retinitis Pigmentosa
- Macular degeneration
- Stargardt / Macular Dystrophy
- Glaucoma Disease

## Other Applications



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



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

Xavier Santamaria<sup>1,2,†</sup>, Sergio Cabanillas<sup>3,†</sup>, Irene Cervelló<sup>1</sup>,  
Cristina Arbona<sup>4</sup>, Francisco Raga<sup>5</sup>, Jaime Ferro<sup>3</sup>, Julio Palmero<sup>6</sup>,  
Jose Remohí<sup>1,3</sup>, Antonio Pellicer<sup>1,3</sup>, and Carlos Simón<sup>1,3,7,8,\*</sup>

<sup>1</sup>Fundación Instituto Valenciano de Infertilidad (FIVI), Department of Obstetrics & Gynecology, School of Medicine, Valencia University and Instituto Universitario IVI/INCLIVA, Valencia, Spain <sup>2</sup>Instituto Valenciano Infertilidad (IVI) Barcelona, Barcelona, Spain <sup>3</sup>Instituto Valenciano Infertilidad (IVI) Valencia, Valencia, Spain <sup>4</sup>Department of Hematology, Hospital ClÚnico Universitario/INCLIVA, Valencia, Spain <sup>5</sup>Department of Obstetrics & Gynecology, Hospital ClÚnico Universitario/INCLIVA, Valencia, Spain <sup>6</sup>Department of Radiology, Hospital ClÚnico Universitario/INCLIVA, Valencia, Spain <sup>7</sup>Department of Obstetrics & Gynecology, Stanford University School of Medicine, Stanford University, Stanford, California <sup>8</sup>Igenomix, Parc Científic Valencia University, Paterna, Valencia, Spain

\*Correspondence address. E-mail: carlos.simon@ivi.es

Submitted on August 22, 2015; resubmitted on January 29, 2016; accepted on February 4, 2016

**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 II               | 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 performed                 | 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 II               | Stage I                        | Not performed                 | 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, hysteroscopy; hm, hysteroscopic myomectomy; Im, 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<sup>+</sup> 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 cm<sup>3</sup> of a saline suspension of the selected CD133<sup>+</sup> cells (containing 42–200 × 10<sup>6</sup> cells, mean (123.56 × 10<sup>6</sup>) was two injected through each uterine artery into the spiral arterioles.

RESEARCH

Open Access

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



Yun Cao<sup>1†</sup>, Haixiang Sun<sup>1†</sup>, Hui Zhu<sup>1†</sup>, Xianghong Zhu<sup>1</sup>, Xiaoqiu Tang<sup>1</sup>, Guijun Yan<sup>1</sup>, Jingmei Wang<sup>1</sup>, Donghui Bai<sup>2</sup>, Juan Wang<sup>2</sup>, Liu Wang<sup>2</sup>, Qi Zhou<sup>2</sup>, Huiyan Wang<sup>1</sup>, Chengyan Dai<sup>1</sup>, Lijun Ding<sup>1</sup>, Biyun Xu<sup>1</sup>, Yan Zhou<sup>4</sup>, Jie Hao<sup>2\*</sup>, Jianwu Dai<sup>3\*</sup> and Yali Hu<sup>1,5\*</sup> 

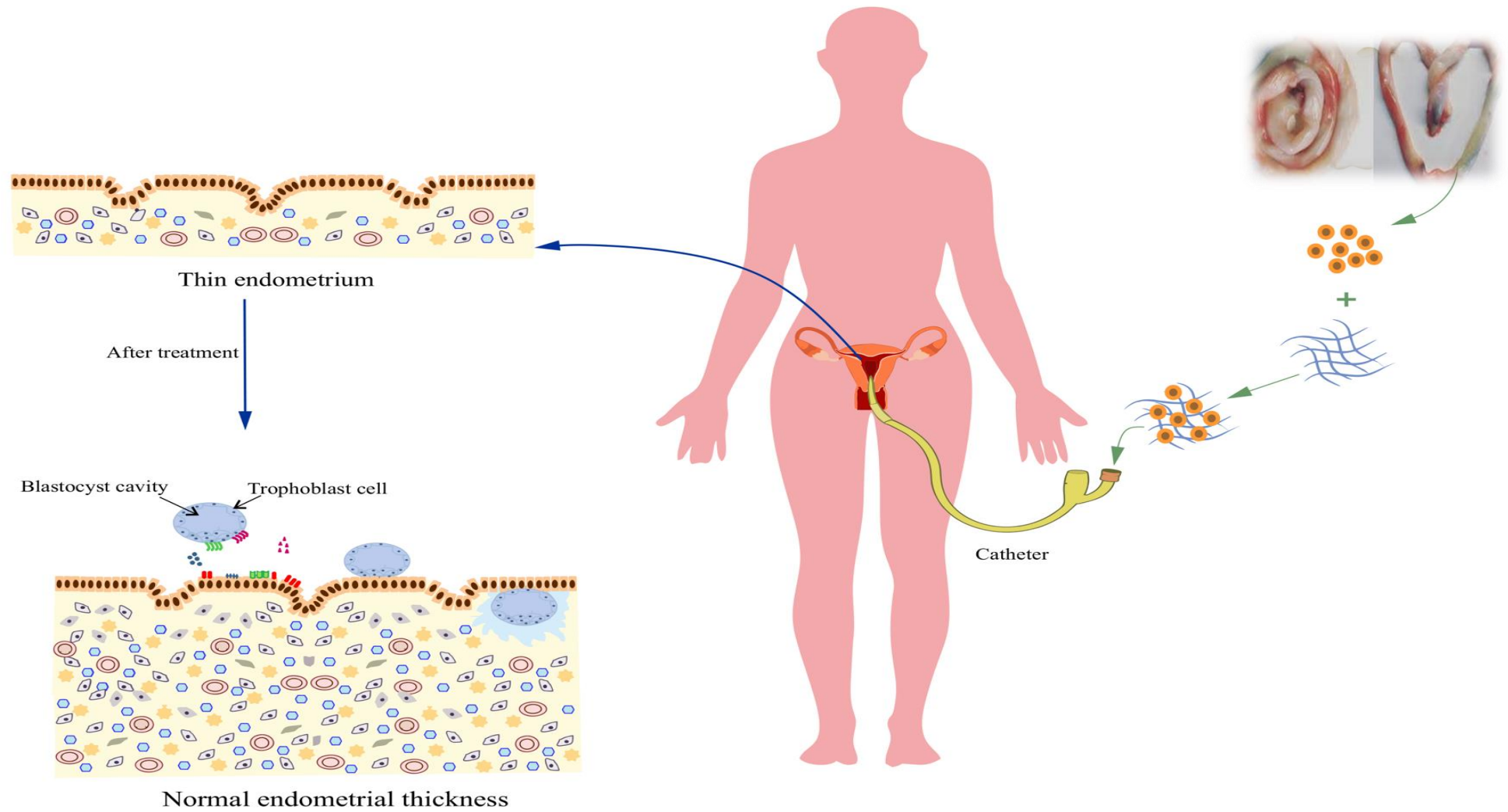
- **Preparation of the UC-MSc /collagen complex**

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  $1 \times 10^7$  (about  $4.2 \times 10^5/\text{cm}^2$ ) UC-MSCs was dripped uniformly onto the scaffold. The cell-seeded scaffold was incubated in humid air consisting of 5% CO<sub>2</sub> 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

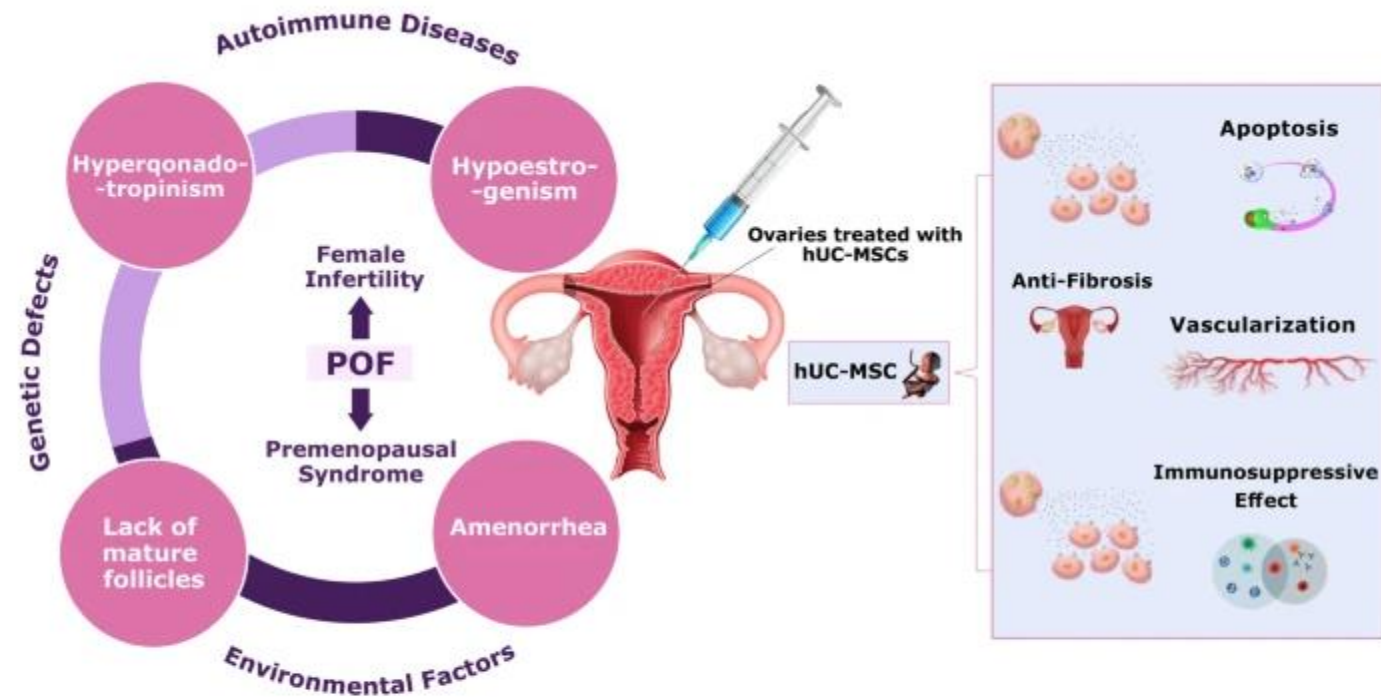


## Results

The average maximum endometrial thickness, measured in 25 patients, increased from  $4.46 \pm 0.85 \text{ mm}$  to  $5.74 \pm 1.20 \text{ mm}$ . 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)

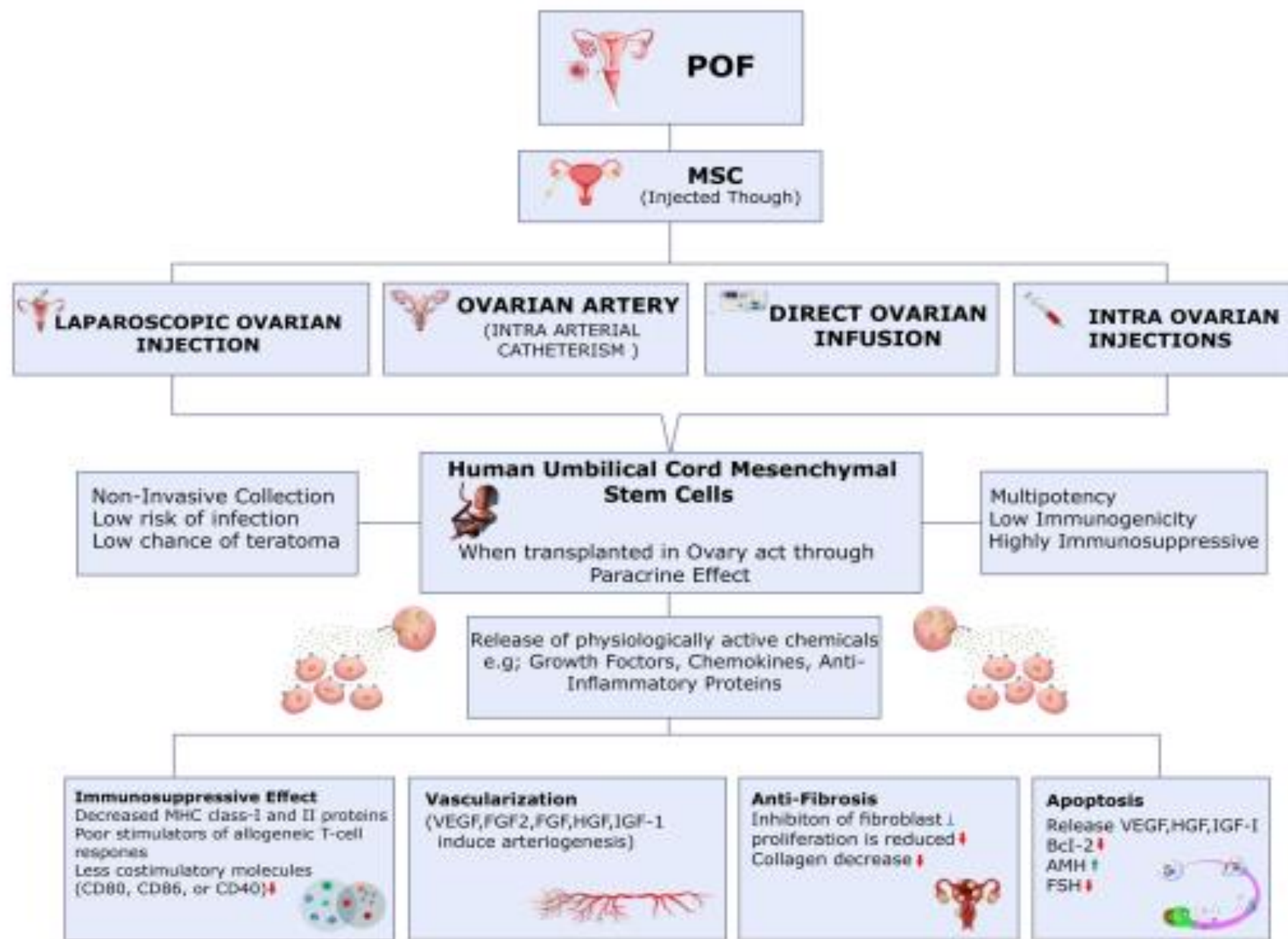
In total, **ten** patients became pregnant by the end of 30-month follow-up period.( the end of August 2017)





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.



| Participant Group/Arm ❶                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Intervention/Treatment ❶                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Experimental: UCA-PSC</p> <p>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).</p> | <p>Procedure: transplantation of human UCA-PSCs or WJ-MSCs into ovaries of POF patients</p> <ul style="list-style-type: none"> <li>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 Healthcare Sector, Erlangen, Germany), equipped with a 6-10 MHz probe. The solution (a total number of <math>2 \times 10^7</math> cells, <math>1 \times 10^7</math> / 400 <math>\mu</math>L for unilateral ovarian injection) was injected into the ovary by using 21G PTC needles (Hakko Medical Co, Japan) under TVUS guidance. Each patient received up to three transplantations.</li> </ul> |
| <p>Experimental: WJ-MSC</p> <p>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).</p>    | <p>Procedure: transplantation of human UCA-PSCs or WJ-MSCs into ovaries of POF patients</p> <ul style="list-style-type: none"> <li>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 Healthcare Sector, Erlangen, Germany), equipped with a 6-10 MHz probe. The solution (a total number of <math>2 \times 10^7</math> cells, <math>1 \times 10^7</math> / 400 <math>\mu</math>L for unilateral ovarian injection) was injected into the ovary by using 21G PTC needles (Hakko Medical Co, Japan) under TVUS guidance. Each patient received up to three transplantations.</li> </ul> |

*"Thank you for your attention"*

