Immunologic evaluation AND treatment for recurrent pregnancy failure

IN THE NAME OF GOD

Maryam khoshkhui (MD)

Definition

- Recurrent spontaneous abortion (RSA) refers to spontaneous abortion that occurs for more than **three times** continuously between the patient and the same partner…

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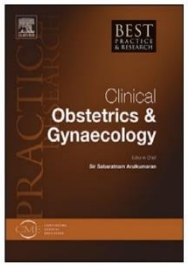

Immunotherapy for recurrent pregnancy loss

2019

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Original Article

Effect of immunotherapy on patients with unexplained recurrent spontaneous abortion

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Contributions: (I) Conception and design: J Chen, B Liu, Y Zhang, J Yang; (II) Administrative support: J Yang; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: J Chen, B Liu, Y Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Check for updates

The role of immunotherapy in in vitro fertilization and recurrent pregnancy loss: a systematic review and meta-analysis

2018

Chiara Achilli, M.D., Montserrat Duran-Retamal, M.D., Wael Saab, M.R.C.O.G, Paul Serhal, M.R.C.O.G, and Srividya Seshadri, M.D.

Centre for Reproductive and Genetic Health, London, United Kingdom

At present, it is generally believed that **immune factors** account for **60%** of unexplained recurrent spontaneous abortion (URSA), of which **alloimmune recurrent abortion is more common**, mainly due to the abnormal recognition of fetal paternal antigen by the mother , resulting in the **lack of maternal blocking antibody (BA),** other cellular and humoral immune abnormalities, embryo suffering from abnormal immune system attacking .

Diagnostic Criteria

Criteria for excluding other presumptive causes of RM are as follows:

(1) Normal karyotype of both parents

(2) Normal glucose tolerance test

(3) Normal uterine cavity as shown by hysterosalpingography, 3-D ultrasound, or hysteroscopy

(4) Normal thyroid function

(5) Normal serum prolactin

(6) Negative antiphospholipid (aPL) antibodies.

Diagnostic criteria

More recently, with the introduction of molecular technology to assess the genetic constitution of the embryo, immunotherapy is offered only to patients losing ***at least one euploid embryo***.

Imunomodulatory agents for Immunotherapy:

1) Active immunization with paternal leukocyte immunization

2)Passive immunization with Intravenous immunoglobulin (IVIg)

3)Intralipid

4)Filgrastim.

5)Glucocorticoid

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Active immunization with paternal leukocyte

Twenty mL Ficoll lymph separation solution was added into 50 mL centrifuge tube, then 20 mL anticoagulant venous blood was taken from the **patient's husband**, and slowly spread on the liquid surface of **lymphs separation**

The patients were inoculated at 6– 8 points on the medial side of the forearm once every 2 weeks, four times for a course.

After that, the patients returned to the hospital to detect the BA. If the antibody was **positive**, patients might become pregnant through natural or in vitro fertilization (IVF). If pregnancy, immunotherapy was still continued once every month for 4 times

Result Of Active immunization in LAI group

Table 4 Comparison in pregnancy rate, live rate and abortion rate between LAI group and control group

Subgroups	Treatment	Pregnancy	Live births	Abortions
Control group	IVF	82/154 (53.2%)[d]****	44 (53.7%)[d]****	15 (18.3%)[a]*
LAI group	IVF	130/134 (97.0%)	105 (80.8%)	11 (8.5%)
	Natural pregnancy	204/331 (61.6%)[e]****	150 (73.5%)	18 (8.8%)

[a], LAI for less than 4 *vs.* 4–6 times; [d], Control group *vs*. LAI group with IVF; [e], IVF *vs*. natural pregnancy in LAI group; *P<0.05; ****P<0.0001. LAI, lymphocyte active immunotherapy; IVF, in vitro fertilization.

Effect of immunotherapy on patients with unexplained recurrent spontaneous abortion Ann Palliat Med 2020

Imunomodulatory agents for Immunotherapy:

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Is there a Role of Intravenous Immunoglobulin in Immunologic Recurrent Pregnancy Loss?

Table 1

Possible mechanisms of intravenous immunoglobulin (IVIg) in the prevention of recurrent pregnancy loss (RPL).

Mechanism
Reduce autoantibodies
Neutralize autoantibodies
Decrease NK cell activity
Control the secretion of cytokines
Suppress the binding and activation of complement
Modulate and blockade of Fc receptor
Inhibit FcγRIIb signaling in macrophages
Increase the clearance of pathogenic antibody by FcRn
Suppress superantigens
Regulate adhesion molecules on B- and T lymphocytes
Increase apoptosis of activated cytotoxic lymphocytes

Which patients may benefit from IVIG?

1)In presence of auto antibodies such as antiTPO

2)Increase NK cell

3) Increase Th1/Th2

4)Increase TNF/IL10

5)Evidence of Immunologic abortion

Thyroid disease during pregnancy

- Thyroid disease is **one of the most frequent endocrine** conditions in women of childbearing age.

- The most common cause of thyroid dysfunction is **thyroid autoimmunity (TAI).**TAI is defined as the presence of antithyroid antibodies (ATA), specifically thyroid peroxidase antibodies (TPO-Ab) and/or thyroglobulin antibodies (Tg-Ab).

- With a prevalence of 5%-20%, TAI is the **most common autoimmune condition** in women of reproductive age.

Anti TPO antibody

In 1990, an association between thyroid antibody positivity and spontaneous miscarriage was first reported.

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Anti-thyroid peroxidase antibody positivity during early pregnancy is associated with **pregnancy complications** and **maternal morbidity in later life**

A higher prevalence of TPO-Ab in women with RM has been found in several studies, varying from 19% to 36%.

Clinical and Experimental Medicine
https://doi.org/10.1007/s10238-020-00663-y

ORIGINAL ARTICLE

Check for updates

Thyroid peroxidase in human endometrium and placenta: a potential target for anti-TPO antibodies

Reyhane Rahnama[1] · Ahmad-Reza Mahmoudi[2] · Somayeh Kazemnejad[3] · Mansour Salehi[4] · Ataollah Ghahiri[5] · Haleh Soltanghoraee[6] · Sedigheh Vafaei[7] · Abbas Rezaei[1] · Amir Hassan Zarnani[7,8,9]

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- Endometrial samples were taken from normal women, and placenta tissues were collected after full-term caesarian section. Expression of TPO messenger RNA (mRNA) was investigated by qRT-PCR.
- In addition, polyclonal anti-TPO antibodies were produced and the expression of TPO protein in mentioned tissues was evaluated by immunohistochemistry and Western blot analysis
- TPO expression in endometrium and placenta may explain higher frequency of abortion and infertility in patients with thyroid autoimmunity

Am J Reprod Immunol. 1998 Apr;39(4):223-5.

The use of combined heparin/aspirin and immunoglobulin G therapy in the treatment of in vitro fertilization patients with antithyroid antibodies.

Sher G[1], Maassarani G, Zouves C, Feinman M, Sohn S, Matzner W, Chong P, Ching W.

Author information

- It appears that in patient that have Anti TPO more than 3 fold of upper limit of normal(usually >300), IVIg may be helpful

Which patients may benefit from IVIG?

1)In presence of auto antibodies such as antiTPO

2)Increase NK cell

3) Increase Th1/Th2

4)Increase TNF/IL10

5)Evidence of Immunologic abortion

Am J Reprod Immunol. 2013 Dec;70(6):434-47. doi: 10.1111/aji.12170.

Intravenous immunoglobulin treatment for repeated IVF/ICSI failure and unexplained infertility: a systematic review and a meta-analysis.

Li J[1], Chen Y, Liu C, Hu Y, Li L.

Author information

Am J Reprod Immunol. 2012 Jul;68(1):75-84. doi: 10.1111/j.1600-0897.2012.01135.x. Epub 2012 Apr 18.

Intravenous immunoglobulin treatment increased live birth rate in a Spanish cohort of women with recurrent reproductive failure and expanded CD56(+) cells.

Moraru M[1], Carbone J, Alecsandru D, Castillo-Rama M, García-Segovia A, Gil J, Alonso B, Aguarón A, Ramos-Medina R, Martínez de María J, Oliver-Miñarro D, Rodríguez-Mahou M, Ortega V, Caballero P, Meliá E, Vidal J, Cianchetta-Sivori M, Esteban C, Vargas-Henny L, Dale J, Ortiz-Quintana L, Fernández-Cruz E, Sánchez-Ramón S.

Author information

Method of study

157women with previous recurrent miscarriage and/or recurrent implantation failure after *IVF* were consecutively studied.

64 patients with $CD56^+$ cell expansion, **no** apparent underlying disease and who maintained their desire to conceive were selected.

40 of them received IVIG during pregnancy.

Results

- Overall, the clinical pregnancy rate for the women under IVIG therapy was **92.5%** and the live birth rate was **82.5%.**
- Significantly lower pregnancy and live birth rates (25% and 12.5%) were observed for the patients with recurrent pregnancy loss and NK/NKT-like cells expansion without IVIG.
- After **three** cycles of IVIG, NK cell percentages **decreased** significantly and these values persisted throughout gestation.

Conclusion

IVIG therapy for women with RRF **and** NK or NKT-like cell expansion was a safe and **beneficial** therapeutic strategy that associated with high clinical pregnancy and live birth rates.

In the absence of immunological screening, beneficial effects of IVIG in preventing recurrent reproductive failure (RRF) have not been reported.

Am J Reprod Immunol. 2011 Nov;66(5):394-403. doi: 10.1111/j.1600-0897.2011.01018.x. Epub 2011 May 30.

Elevated preconception CD56+ 16+ and/or Th1:Th2 levels predict benefit from IVIG therapy in subfertile women undergoing IVF.

Winger EE[1], Reed JL, Ashoush S, El-Toukhy T, Ahuja S, Taranissi M.

Author information

•Problem

We sought to answer two questions:

- First, is there a group of patients who benefit from IVIG in IVF?

- Second, can this group of patients be identified by preconception blood testing?

Conclusion

- In patients with **normal** Th1:Th2 and **normal** $CD56^+$ cell levels, IVF success rates were not further improved with IVIG therapy.
- IVIG may be a useful treatment option for patients with previous IVF failure and preconception Th1:Th2 and/or NK elevation.

Preconception immune testing may be a critical tool for determining which patients will benefit from IVIG therapy.

See 1 citation found by title matching your search:

Am J Reprod Immunol. 2010 Mar 1;63(3):263-5. doi: 10.1111/j.1600-0897.2009.00790.x. Epub 2010 Jan 8.

CD3-CD56+CD16+ natural killer cells and improvement of pregnancy outcome in IVF/ICSI failure after additional IVIG-treatment.

Heilmann L[1], Schorsch M, Hahn T.

Author information

2010

Heilmann; 2010;

- **Problem**

Which percent of NK cell is harmful ????

The purpose of this retrospective, observational study was to investigate whether additional treatment with IVIG increased the rate of successful pregnancies after repeated implantation failure (RIF).

Method of study

A total of 188 women with 226 treatment cycles between 2007 and 2009 were evaluated for IVIG therapy.

The percentage of NK cells was measured two times before a new embryo transfer (only women with NK cell percentages ***>12%*** were included) and after embryo transfer at a positive pregnancy test.

Conclusion

In a subgroup of RIF-patients with high level of $CD56^+$ $CD16^+$ NK-cells the additional application of IVIG leads to a favorable pregnancy outcome

Dosage of IVIG

- 250-300 mg/kg or 20 gram monthly till 12-20 wk

for nl pregnancy

For IVF :10-15 days before transfer then after positive pregnancy test

IVIG side effects

- As many as 25% of IVIG recipients experience a systemic side effect related to their infusion.

TABLE 55.6 Tolerability related immunoglobulin adverse events.

Common	Less common
Migrainoid headache Myalgia Malaise Fatigue	Fever Diarrhea Rash Cough Chest tightness Sinus tenderness

IVIG side effects

TABLE 55.8 Severe systemic side effects of immunoglobulin therapy.

Serious systemic side effect	Risk factor
Renal injury or failure	• Carbohydrate containing products, particularly sucrose • Underlying renal compromise • Increasing age • Diabetes
Thrombosis	• Activated factor 11a contamination • Previous thrombotic event • Thrombophilia • Hyperviscosity (e.g., monoclonal gammopathy, macroglobulinemia) • Increasing age
Hemolysis	• Elevated antibody titers against blood group antigens A and B
Aseptic meningitis	• History of migraine headache
Transfusion related lung injury (TRALI)	• No known risk factors

Reprod Med Biol

NK cell abnormality and its treatment in women with reproductive failures such as recurrent pregnancy loss, implantation failures, preeclampsia, and pelvic endometriosis

Atsushi Fukui,[1] Mai Kamoi,[1] Ayano Funamizu,[1] Kohei Fuchinoue,[1] Hitomi Chiba,[1] Megumi Yokota,[1] Rie Fukuhara,[1] and Hideki Mizunuma[1]

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NKp46, one of the natural cytotoxicity receptors (NCRs), is a unique marker that functions in NK cell cytotoxicity and cytokine production. Expression of NKp46 on NK cells is lower in women with recurrent pregnancy loss and pregnancy-induced hypertension

Evaluation of NKp46 on peripheral blood NK cells may provide a means of screening for reproductive abnormalities

Which patients may benefit from IVIG?

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2)Increase NK cell

3) Increase Th1/Th2

4)Increase TNF/IL10

5)Evidence of Immunologic abortion

Case Presentation

1398/06/28

ISO 9001:2015 IQC

ISO 10003:2014 IQC

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Medical Genetics

Immunoassay - Endocrine

	Result	Unit	Reference Interval
Anti-Mullerian Hormone	0.76	ng/mL	< 0.3 : Low ovarian reserve function (POF) 0.3 - 0.7 : Lower Borderline 0.7 - 5.0 : Normal ovarian reserve function 5 - 7.0 : Upper Borderline > 7.0 : Consistent with PCOS
Homocysteine	9.2	µM/L	Age <60y : 5 - 15

Immunoassay - Cancer Biomarker

	Result	Unit	Reference Interval
CA-125	18.9	U/mL	Adults <35 Verify High Result in next 14 days by the same method. Body Fluids: Not Established.

Vitamin Assay

	Result	Unit	Reference Interval
25-OH-Vitamin D (CLIA)	13.3	ng/mL	Deficient..... <10 Insufficient..... 10 - 29 Sufficient..... 30 - 70 Potential Intoxication. >100

mmunohematology - Flow cytometry

	Result	Unit		Reference Interval
Lymph gate	19	%		
CD5	63.3	%Lymph		42-82
CD16	20	%Lymph	H	5 - 19
CD 19	6.5	%Lymph		3 - 14
CD56	19.8	%Lymph	H	3 - 15
CD16+CD56 Dual	17.2	%Lymph		Not available
HLA-DR	13.4	%Lymph		3-15

Bahar Lab Director

Imunomodulatory agents for Immunotherapy:

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Intralipid

Intralipid decreases NK cytotoxicity both in vitro and in vivo

Filagrastim

G-CSF has been reported to promote the mobilization and proliferation of lymphocytes, dendritic cells, and Treg cells

Glucocorticoids

Glucocorticoids can exert a range of positive effects that would be expected to promote establishment of early pregnancy, such as suppression of uterine NK cells and promotion of trophoblast proliferation and invasion

Check for updates

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Chiara Achilli, M.D., Montserrat Duran-Retamal, M.D., Wael Saab, M.R.C.O.G, Paul Serhal, M.R.C.O.G, and Srividya Seshadri, M.D.

Centre for Reproductive and Genetic Health, London, United Kingdom

2018

Therefore, currently and based on the available literature, immunotherapy should only be used in the context of research and should not be used in routine clinical practice to improve reproductive outcomes. However, better-designed RCTs with better patient selection are strongly needed to finally address the role of the immunomodulators currently available.

Thanks your
attention