

2025 ASRI guidelines for the treatment of RPL : a comparative review

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Background

- Definition: **≥ 2 spontaneous abortions** (1–5% of couples)
- Prevalence: 0.8-1.4 %
- Common causes: genetic, endocrine, uterine, APS
- Immune factors: NK cell dysfunction, Th1/Th2 imbalance, autoantibody positivity
- 73% of unexplained RPL have immune abnormalities

Immunologic Basis of RPL

- Pregnancy = dynamic immune state
- 1st & 3rd trimester: proinflammatory
- 2nd trimester: anti-inflammatory
- Imbalance → RPL, RIF, PE
- Positive AutoAb (ATA, ANA, aPL) : higher risk of pregnancy loss
- Endometrial biomarkers (uNK, Th1/Th2 ratio) guide therapy

Clinical burden of RPL

- Significant psychological & financial burden
- Repeated losses → anxiety, depression

Why guidelines matter

- Practice variation is wide
- Counseling challenges
- Need for evidence-based framework

Guidelines

Evaluation and treatment of recurrent pregnancy loss: a committee opinion

ESHRE guideline: recurrent pregnancy loss: an update in 2022[†]

**2025 American Society for Reproductive Immunology
Guidelines for the Treatment of Recurrent Pregnancy
Losses: Practice Recommendations From the ASRI Clinical
Reproductive Immunology Fellowship**

Evaluation and treatment of recurrent pregnancy loss: a committee opinion

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2025 American Society for Reproductive Immunology Guidelines for the Treatment of Recurrent Pregnancy Losses: Practice Recommendations From the ASRI Clinical Reproductive Immunology Fellowship

- 2012
- 정의 : ≥ 2 회
- 평가 : 유전, 자궁기형, 내분비, APS
- 치료
 - ✓ APS $\rightarrow$ aspirin + heparin
 - ✓ Uterine anomaly $\rightarrow$ surgery
 - ✓ Unexplained $\rightarrow$ no proven therapy
- 원인불명 RPL $\rightarrow$ 보수적 접근
- 10년 이상 업데이트 없음. 면역학적 부분 부족

Evaluation and treatment of recurrent pregnancy loss: a committee opinion

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- 2022
- 정의 (≥ 2 회 clinical miscarriage)
- 불필요 검사 배제
 - ✓ TSH only (no thyroid antibodies)
 - ✓ Parental karyotype (conditional)
 - ✓ Uterine imaging (3D US, hysteroscopy)
 - ✓ APS mandatory
- 치료 권고 (APS only, 면역치료 불권장)
- Psychosocial care, 생활습관 교정 강조
- Strength: strong evidence basis
- Limitation: less flexible for clinical practice

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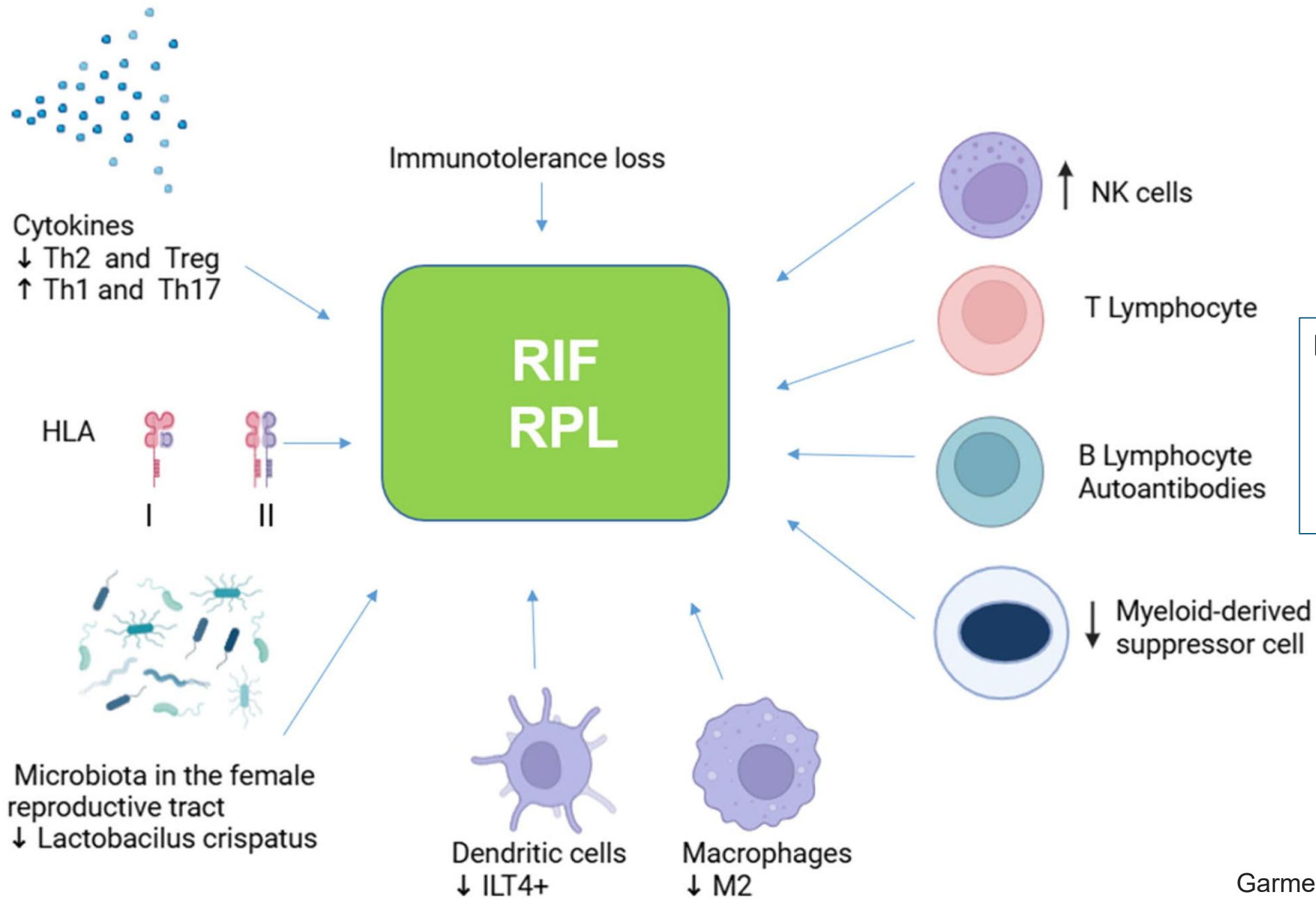
- 2025
- Guideline 목적 & 범위 (면역학적 focus)
- 정의 (≥ 2 회, 면역 기전 포함 고려)
- 평가
 - 기존 항목 (유전, 자궁, 내분비, APS)
 - 추가적 면역 marker (NK cell, Th1/Th2, cytokine profile 등)
- 치료 권고:
 - APS: heparin+aspirin
 - 면역치료:
 - ✓ IVIG
 - ✓ corticosteroid
 - ✓ TNF- α inhibitors
 - ✓ Intralipid

Purpose of ASRI Guideline

- Standardize immunotherapy for RPL
- Objectives: review evidence, assess risk/benefit, recommend clinical practice
- Developed by CRIF/ASRI (Clinical Reproductive Immunology Fellowship)

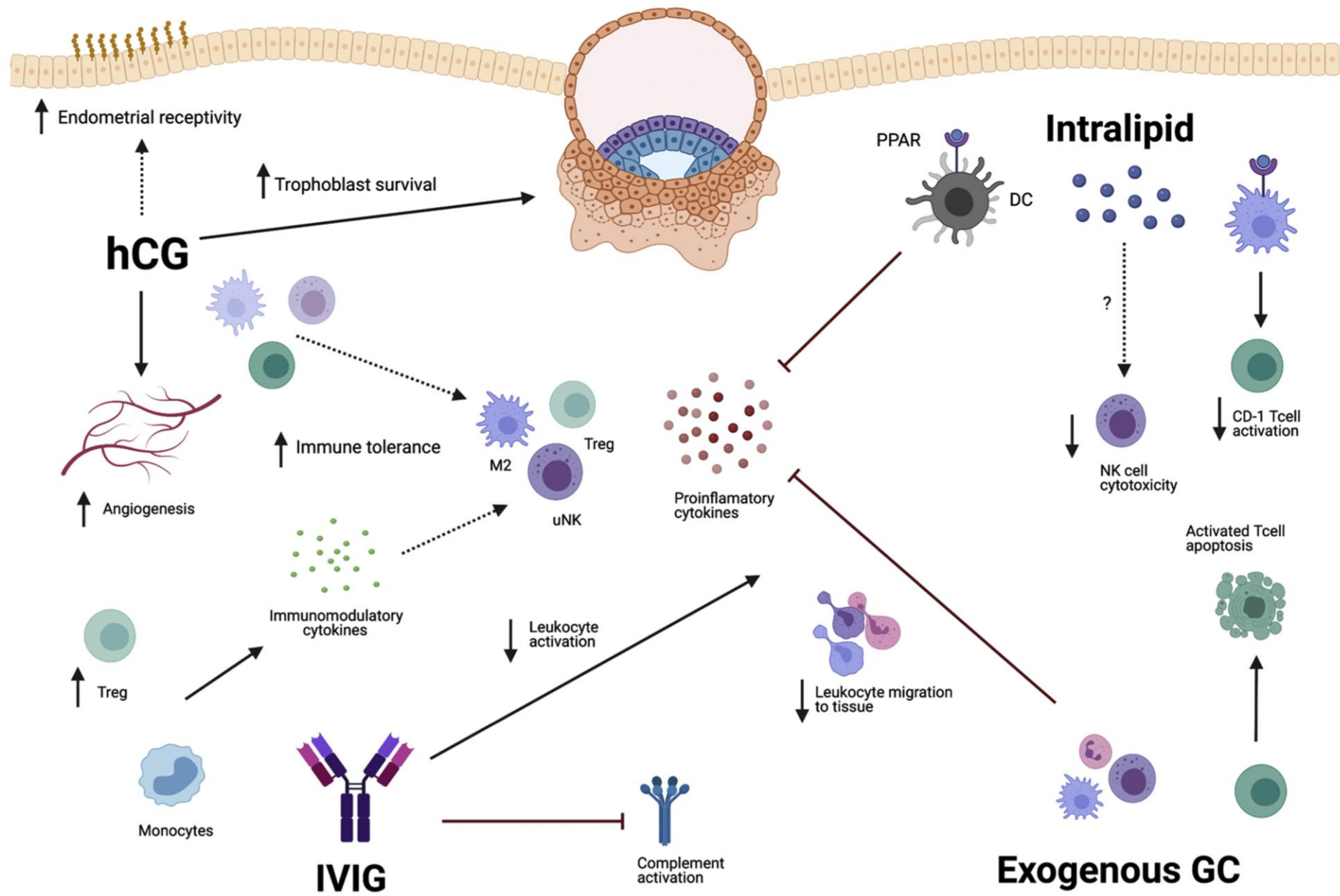
Methodology

- AGREE II and GRADE-based process
- Databases: PubMed, EMBASE, Cochrane
- Criteria: ≥ 2 losses, immune abnormality $\pm$ unexplained
- Endpoints: Live birth rate (LBR), miscarriage rate (MR)
- 11 immunotherapies reviewed



Immunologic workup

- ✓ aPL, ANA, ATA
- ✓ Pb NK cell, uNK cell
- ✓ Th1/Th2 cytokine ratio, Treg/Th17 ratio



Genest G et al. Fertil Steril Rev. 2022

Corticosteroids

- Suppress aberrant immune activation
 - Inhibit T-cell activation, proliferation, and survival
 - Downregulate proinflammatory cytokines (IL-2, TNF- α , IFN- γ)
 - Shift Th1 $\rightarrow$ Th2 balance toward a tolerogenic immune state
- Modulate uterine immune microenvironment
 - Decrease endometrial NK cell numbers and cytotoxicity
 - Promote Th2 cytokine secretion and tolerogenic macrophage (M2) differentiation
 - Enhance decidual immune tolerance and implantation stability

Corticosteroids

Author (year)	Included studies	Inclusion criteria	Treated Group	Control Group	RR / OR (95% CI, p-value)	Conclusion
Dan et al. (2015)	2 (all RCT)	uRPL (≥ 3 consecutive MR) High levels of uNK cells ($\geq 5\%$)	66/88 (75.0%)	42/88 (47.7%)	RR 1.58 (1.23–2.02, p<0.001)	LBR ↑
Mekinian et al. (2016)	4 (all RCT)	uRPL (≥ 3 consecutive MR) No immune test (3 RCTs) High levels of uNK cells ($\geq 5\%$, 1 RCT)	149/199 (74.9%)	57/201 (28.4%)	OR 7.99 (5.01–12.73, p<0.001)	LBR ↑
Ma et al. (2022)	2 (1 RCT)	uRPL (≥ 3 consecutive MR) ANA+ (titer>1:80, 1 non-RCT) High levels of uNK cells ($\geq 5\%$, 1 RCT)	160/179 (89.4%)	44/63 (69.8%)	OR 2.45 (1.11–5.44, p=0.03)	LBR ↑

Corticosteroids

Safety and Possible side effects

- Risk of Preterm delivery, LBW, PE (evidence low)
- No effect on GDM
- No increased risk of teratogenicity (cleft palate, congenital heart defects)

Corticosteroids

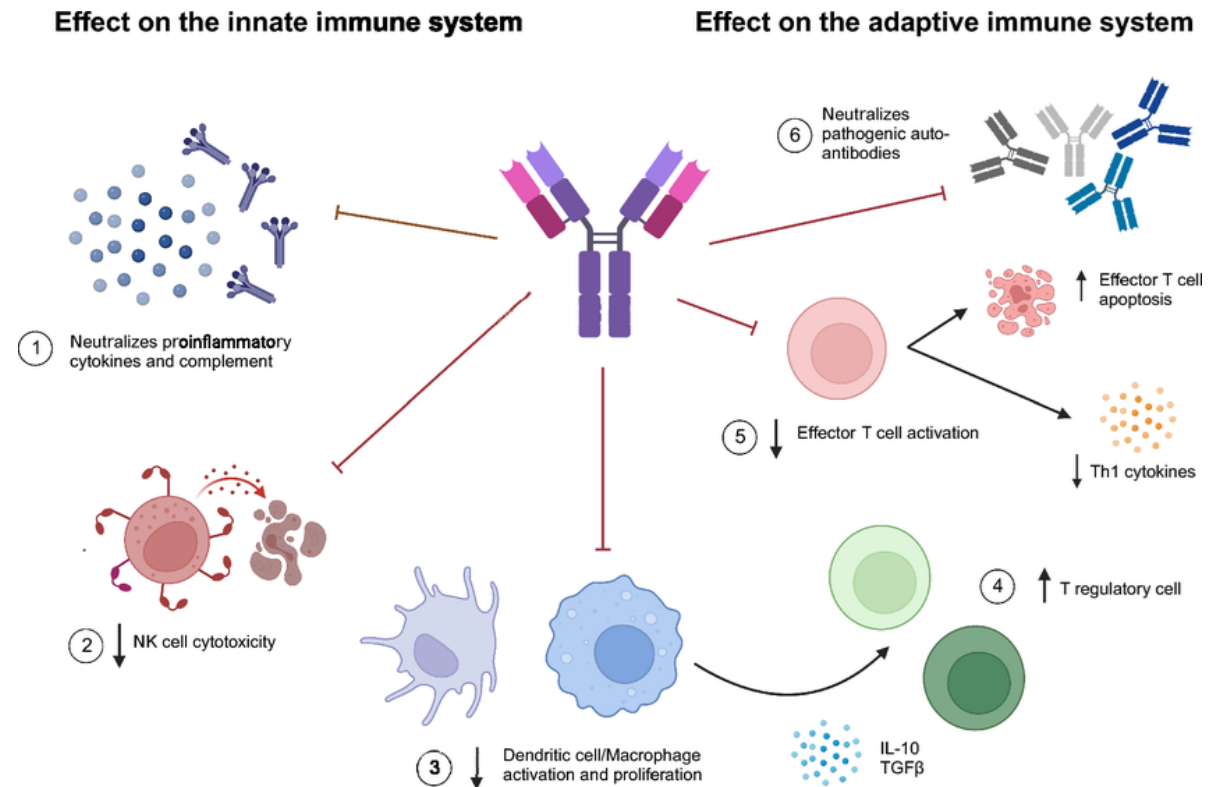
- Recommendation
 - ✓ uNK cells>5%, ANA+, other autoAb+: strongly recommended
 - ✓ If no immune abnormalities conditional recommendation
 - ✓ Dose: Prednisone 5–20mg/day
 - ✓ Duration: Preconception–1st trimester

ESHRE 2022 recommendation

APS 를 동반한 RPL 에서 임신율 향상 보이지 않아 권고하지 않음(Strong). 일부 소규모/바이오마커 선택군에서 신호는 있으나, 과거 고용량 장기투여의 조산·고혈압·당뇨 위험 등 안전성 우려로 보류. 추가 RCT 필요.

IVIg

- Immunodeficiency, neonatal alloimmune thrombocytopenia, APS, ITP
- Mechanism: modulate both innate and adaptive immune response
- Replenish IgG Ab, elicit active immune response



Author, year	Studies	Case	Control	RR / OR (95% CI, p-value)	Conclusion
Christiansen et al., 2005	7 (all RCT)	29/52 (55.8%)	18/42 (42.9%)	OR 1.60 (0.70 to 3.66)	No improve LBR
Hutton et al., 2007	8 (all RCT)	105/172 (61.0%)	95/173 (54.9%)	OR 1.28 (0.78 to 2.12)	No improve LBR
Ata et al., 2011	6 (all RCT)	88/139 (63.3%)	87/133 (65.4%)	OR 0.92 (0.55 to 1.54)	No improve LBR
Wong et al., 2014	7 (all RCT)	92/159 (57.9%)	85/144 (59.0%)	OR 0.98 (0.61 to 1.58)	No improve LBR
Egerup et al. 2015	11 (all RCT)	107/265 (40.4%)	113/266 (42.5%)	RR 0.92 (0.75 to 1.12)	No improve LBR
Wang, et al., 2016	11 (all RTC)	202/297 (68.0%)	151/285 (53.0%)	RR 1.25 (1.00 to 1.56)	Improve LBR
Achilli et al., 2018	05 (all RTC)	29/79 (36.7%)	21/78 (26.9%)	OR 1.56 (0.79 to 3.09)	No improve LBR
Roepke et al., 2018	5 (all RCT)	91/136 (66.9%)	85/137 (62.0%)	RR 1.07 (0.91 to 1.26)	No improve LBR
Christiansen et al., 2019	13 (all RCT)	219/325 (67.4%)	173/312 (55.4%)	RR 1.20 (1.06 to 1.37)	Improve LBR
Woon et al., 2020	3 (all non-RCT)	140/152 (92.1%)	35/91 (38.5%)	RR 2.31 (1.66 to 3.21)	Improve LBR
Parhizkar et al., 2022	5 (3 non-RCT and 2 Cohort)	99/114 (86.8%)	44/102 (43.1%)	OR 8.64 (4.36 to 17.15)	Improve LBR
Habets et al., 2022	8 (all non-RCT)	244/284 (85.9%)	74/194 (38.1%)	RR 1.98 (1.44 to 2.73)	Improve LBR
Shi et al., 2022	13 (all RCT)	312/461 (67.7%)	183/402 (45.5%)	OR 2.30 (1.23 to 4.30)	Improve LBR

Preconception start, ≥ 4 RPL, NK cell $\uparrow$, autoantibody+
 $\rightarrow$ IVIG use improves LBR

Modified intention-to-treat population					Fisher's exact test	
	Time at the start of administration	Administration	Ongoing pregnancy at 22 weeks of gestation– no./total no. (%)	95% CI	p-value	Odds ratio (95% CI)
Ongoing pregnancy at 22 weeks of gestation	4 or 5 weeks	Placebo	9/28 (32.1)	15.9–52.4	0.004	5.40 (1.79-16.30)
		IVIG	23/32 (71.9)	53.3–86.3		
	6 weeks	Placebo	8/10 (80.0)	44.4–97.5	0.23	0.29 (0.05-1.82)
		IVIG	8/15 (53.3)	26.6–78.7		
	Time at the start of administration	Administration	Live births– no./total no. (%)	95% CI	p-value	Odds ratio (95% CI)
Live birth	4 or 5 weeks	Placebo	9/28 (32.1)	15.9–52.4	0.02	4.03 (1.37-11.84)
		IVIG	21/32 (65.6)	46.8–81.4		
	6 weeks	Placebo	8/10 (80.0)	44.4–97.5	0.23	0.26 (0.04-1.82)
		IVIG	8/15 (53.3)	26.6–78.7		

Table 4: Time of treatment initiation and pregnancy outcome.

- ≥4 miscarriages, 400 mg/kg/day × 5일간, 임신 4-6주차
- 4-5주차 시작 시, 유산력 6회 이상 시: OPR, LBR ↑
- 경증 이상반응 (46%) : 간수치 상승 (18%), 두통/발열/피부발진 등
- 주산기 결과
 - 조산 (<37주): 44.8% vs 5.9% ($p=0.007$)
 - FGR (태아성장제한): 34.5% vs 0% ($p=0.008$)
 - Congenital anomaly: 4/29 (14.3%) vs 0/17 ($p=0.28$, 유의하지 않음)

IVIG

Recommendations

- ✓ IVIG treatment for RPL has moderate evidence to improve LBR
- ✓ Particularly, initiated prior to pregnancy, high no. of RPL, immune abnormalities
- ✓ Dose: 200–400 mg/kg q1–3 weeks
- ✓ Duration : from periconception and throughout pregnancy

ESHRE 2022 recommendation

The use of repeated and high doses of Ivlg very early in pregnancy may improve live birth rate in women with 4 or more unexplained RPL

Conditional ⊕⊕■

Lymphocyte Immunotherapy (LIT)

- Active immunotherapy using partner or a third party lymphocyte to promote maternal immunomodulation
- Mechanism: Produce blocking Ab, Th1/Th2 balance, T reg↑ , NK cytotoxicity ↓
- 22 RCTs → 68% positive, OR 1.45–3.74
- Side effects : redness/swelling at injection site, fatigue, HIV transmission

Lymphocyte Immunotherapy (LIT)

Recommendations

- ✓ LIT is banned in US by the FDA
- ✓ Conditional for RPL in other countries
- ✓ Low to moderate evidence to increase LBR in uRPL
- ✓ Strict infection control & antibody confirmation required

ESHRE 2022 recommendation

Lymphocyte immunization therapy should not be used as treatment for unexplained RPL as it has no significant effect and there may be serious adverse effects.

Strong



Intravenous Lipid Emulsion (ILE)

- Mechanism: PPAR C activation → ↓NK cytotoxicity

	Before treatment (%)	After treatment(%)	Pregnancy(%)	<i>P</i> -Value
Intralipid group(n=79)	26.1±4.9	24.4±5.6	18.7±6.3	<i>P</i> <0.001
IVIg group (n=81)	26.7±5.2	23.6±6.3	19.8±5.3	<i>P</i> <0.001
<i>P</i> -value	0.669			

Changes in pNK cell numbers

Table 2 Summary table showing intralipid outcomes across all the included studies, stratified by total trials, randomized control trials only, vs reproductive pregnancy loss only and vs IVIG, the odds ratio (OR) generated in each meta-analysis and the 95% CI generated.

Outcome	Studies	Participants	OR (95% CI)
Vs control (all studies included)			
Clinical pregnancy	9	1869	1.64 (1.31, 2.04)
Live birth	8	1068	2.36 (1.75, 3.17)
Miscarriage	5	542	0.20 (0.14, 0.30)
Implantation rate	2	912	2.97 (2.05, 4.29)
Vs control (all patients, RCTs only)			
Clinical pregnancy	4	402	1.83 (1.19, 2.80)
Live birth	5	763	2.17 (1.54, 3.05)
Vs control (RPL cases only, all studies included)			
Clinical pregnancy	3	428	1.17 (0.78, 1.74)
Live birth	3	529	2.67 (1.79, 3.98)
Miscarriage	3	361	0.24 (0.14, 0.30)
Vs IVIG (all studies included)			
Live birth	2	634	1.02 (0.74, 1.40)

- IR ↑ (OR 2.97, 2.05-4.29, $I^2=0\%$)
- LBR ↑, MR ↓ in RPL

Intravenous Lipid Emulsion (ILE)

Recommendation

- ✓ ILE improves LBR of women with RPL (low evidence)
- ✓ ILE may increase LBR in women with uRPL without embryological factors, particularly those with positive immune markers (pbNK cell ↑, Th1 cytokine ↑)

ESHRE 2022 recommendation

There is insufficient evidence to recommend intralipid therapy for improving live birth rate in women with unexplained RPL.

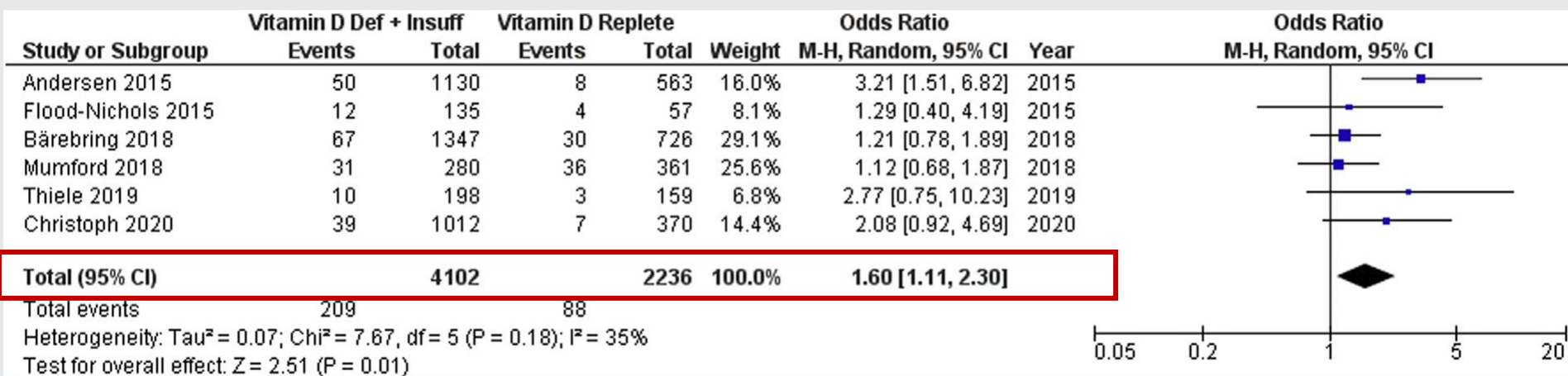
Strong



Vitamin D

- Trophoblast invasion, spiral artery remodeling, immune modulation
- Mechanism
 - ✓ Suppresses proinflammatory immune cells (Th1, B, NK) and cytokines (IL-2, TNF- α , IFN- γ)
 - ✓ Enhances tolerogenic cytokines (IL-4, IL-10, VEGF, G-CSF)
 - ✓ $\uparrow$ Treg, $\downarrow$ Th17 $\rightarrow$ restores immune tolerance
 - ✓ Inhibits NK cytotoxicity, modulates TLR4 expression
 - ✓ Enhances endometrial receptivity via glycodelin, IGFBP-1, and glucose regulation

FIGURE 3



Comparison of the risk of miscarriage by vitamin D deficient + insufficient and sufficient status. Forest plot summarizing the results of the meta-analysis comparing the risk of miscarriage in women with deficient and insufficient levels of vitamin D combined and women with sufficient levels of vitamin D. CI = confidence interval; M-H = Mantel-Haenszel.

Tamblyn. Vitamin D and miscarriage. Fertil Steril 2022.

- Vit D deficient vs sufficient/ insufficient vs sufficient : MR ↑
- Low or insufficient vitamin D → higher miscarriage risk
- Preventive effect of vitamin D supplementation = inconclusive

Tamblyn JA et al. Fertil Steril. 2022

Vitamin D

- Recommendations

- ✓ Women with RPL are at an increased risk of having low vitamin D levels.
- ✓ There is moderate evidence that vitamin D deficiency is associated with RPL.
- ✓ Low evidence that vitamin D supplementation increases the LBR of women with RPL.
- ✓ Preconception assessment of serum 25(OH)D is strongly recommended.
- ✓ Dose : vitamin D3 2000–4000 IU/day is recommended to achieve at least serum 25(OH)D level ≥ 30 ng/mL (≥ 75 nmol/L).

ESHRE 2022 recommendation

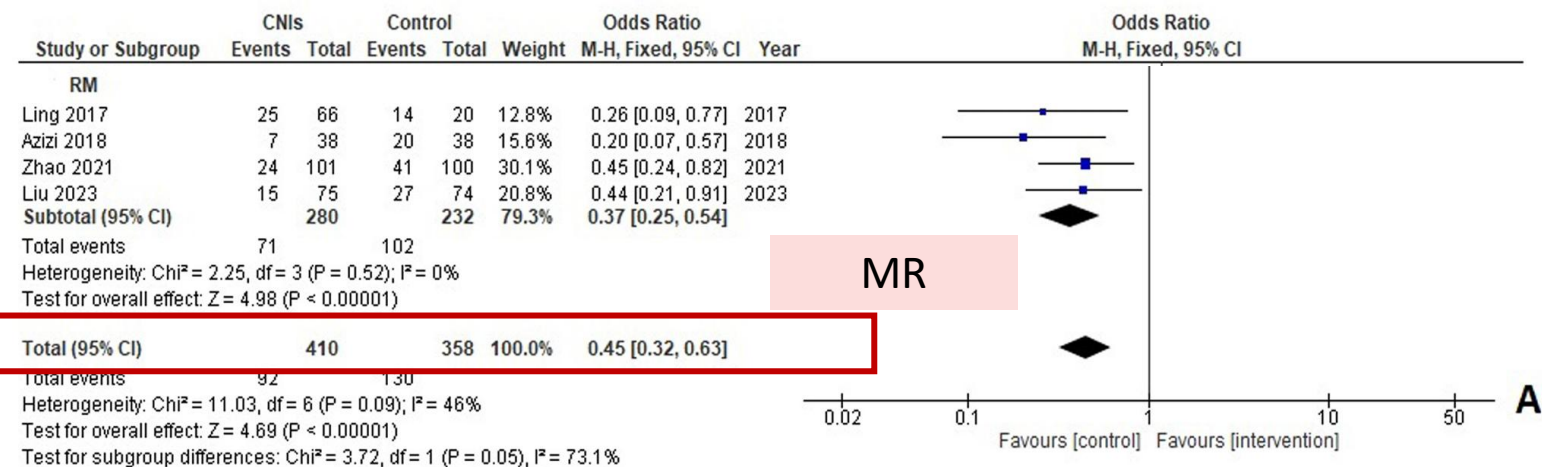
Preconception counselling in women with RPL could include the general advice to consider prophylactic vitamin D supplementation.

GPP

Testing of vitamin D status is not recommended for women with RPL.

Calcineurin Inhibitors (CNI)

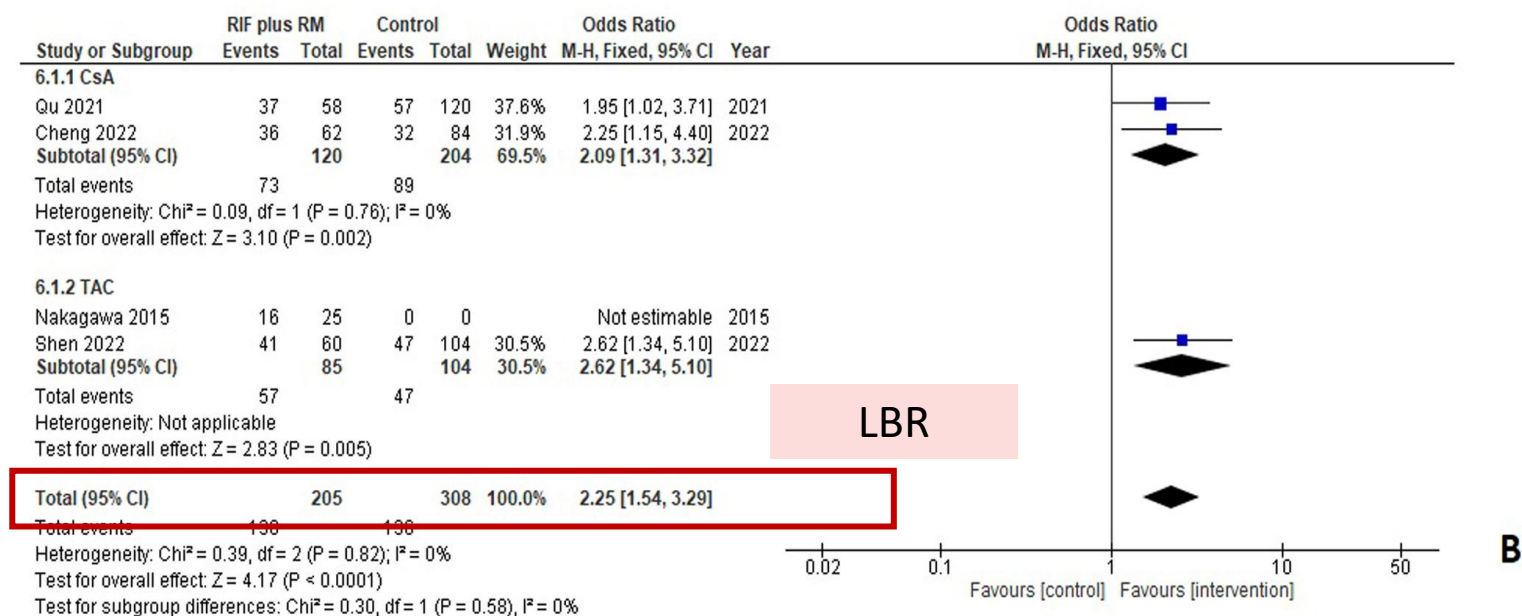
- Immunosuppressant : Tacrolimus, cyclosporine
 - Similar immune rejection mechanisms to organ transplant.
 - CNIs may restore tolerance and improve implantation when Th1/Th2 imbalance or NK-cell activation is present.
- Mechanism: Th1/Th2 rebalance
- Use in immune-abnormal RPL (Th1/Th2↑, CD56+/CD57+ ↑)



- MR↓, LBR↑

Recommendation

- ✓ There is low-level evidence (concerning a small number of studies) that tacrolimus and cyclosporine treatment improve LBR in women with RPL and immune abnormalities



G-CSF

- Anti inflammatory, angiogenic
- Endometrial decidualization, regulation of trophoblastic development, placental metabolism, angiogenesis를 통해 implantation 에 관여
- Mechanism: Treg recruitment, angiogenesis, stimulate Th2 cytokines
- Side effects: bone/muscle pain, headaches, tiredness, fatigue

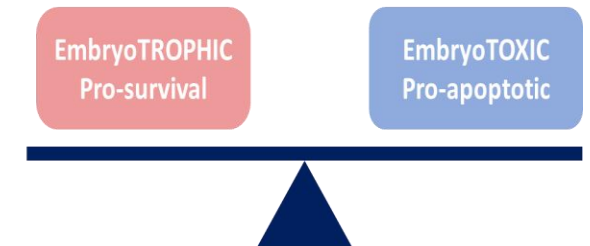
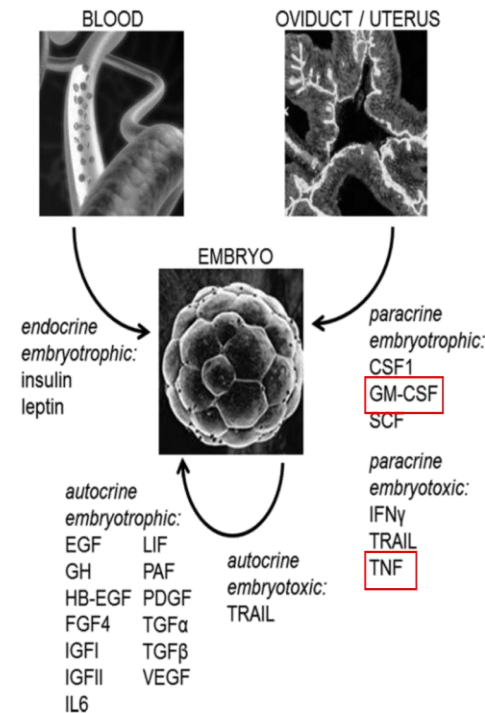
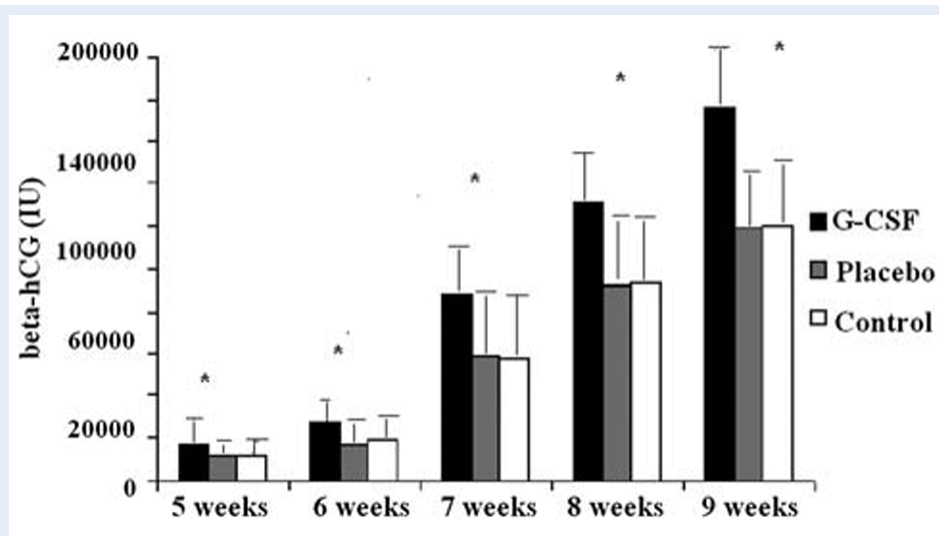


Table II Results of the study in patients treated with G-CSF and controls (placebo)

	G-CSF	Placebo	P-value
Number of live births (%)	29 (82.8)	16 (48.5)	0.0061
Number of miscarriages (%)	6 (17.2)	17 (51.5)	0.0061
Gestational week of miscarriage (mean $\pm$ SD)	6.0 $\pm$ 1.1	6.2 $\pm$ 1.0	0.6989
Newborn weight (g, mean $\pm$ SD)	3050 $\pm$ 220	3125 $\pm$ 240	0.3098
Side effects			
Skin rash	1	0	0.5147
Leukocytosis	2	0	0.2617
Pregnancy complication*	0	1	0.3535

*Pre-eclampsia.



- G-CSF group에서 LBR $\uparrow$, MR $\downarrow$
- b-hCG $\uparrow$

Scarpellini F, Sbracia M. Hum Reprod. 2009

Efficacy and safety of recombinant human granulocyte colony-stimulating factor in patients with unexplained recurrent spontaneous abortion: A systematic review and meta-analysis

Fangxiang Mu, Jiumei Huang, Xianghui Zeng, Ling Liu, Fang Wang^{*}

연구	디자인	Inclusion Criteria	G-CSF 용량·투여법·시기	주요 결과	결론
Jin S. et al. 2020	RCT	≥2회 uRPL (30/30)	300 µg/mL IU, 1회 배란일	PR 87.7% vs 57.7% (p<0.05)	PR↑
Eapen A. et al. 2019	RCT	≥3회 uRPL (76/74)	1 µg/kg/week SC 배란 후부터 임신 5-9주까지	PR 59.2% vs 68.9% LBR 59.2% vs 64.9%	효과 없음, AEs↑
Zafardoust S. et al 2017	RCT	≥3회 uRPL (23/27)	300 µg/mL IU, 1 회 배란일	PR 17.4% vs 11.1%	긍정적 경향
Fu J. et al. 2015	RCT	≥2회 uRPL (85/83)	5 µg/kg/day SC × 5일 배란기~착상기	PR 85.9% vs 68.7% (p<0.05)	PR, LBR↑
Santjohanser C. et al 2013	CCS	≥2회 uRPL (49/78)	5 µg/kg/day SC QD or QOD 배란 후~임신 확인 시까지	PR 46.9% vs 25.6%	효과 없음
Scarpellini & Sbracia 2009	RCT	≥3회 uRPL (35/33)	1 µg/kg/day SC 배란 후부터 임신 12주까지	LBR 82.8% vs 42.5% (p<0.05)	LBR↑

LBR↑ (RR 1.35) but heterogeneous

G-CSF

- Recommendation
 - ✓ Conflicting evidence for G-CSF as a treatment for uRPL
 - ✓ New RCTs are needed

ESHRE 2022 recommendation

There is no evidence to recommended G-CSF in women with unexplained RPL.

Strong

⊕⊕⊕■

Anti-TNF Therapy

- Used for autoimmune inflammatory diseases (RA, AS, PsA, IBD) refractory to conventional immunosuppressants
- Mechanism: TNF- α blockade $\rightarrow$ improve Th1/Treg balance
- RCT
 - Combined treatment with adalimumab and IVIG significantly improved implantation, clinical pregnancy, and live birth rates
 - Etanercept treatment significantly increased live birth rates and reduced TNF- α levels and NK cell activity in women with ≥ 4 RPL

Winger et al. 2009

Fu J et al. 2019

Anti-TNF Therapy

- Recommendations
 - ✓ Conflicting data for using anti-TNF as a monotherapy for RPL
 - ✓ New RCTs are needed
 - ✓ Screen for latent TB before use

Heparin + ASA

- Mechanism: anticoagulation + trophoblast protection
- APS: LMWH+ASA → LBR↑
- Inherited thrombophilia : insufficient evidence
- uRPL without APS: inconclusive evidence

Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent pregnancy loss

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<https://doi.org/10.1002/14651858.CD012852.pub2>

• aPL 양성인 RPL 환자

비교	RR, 95% CI	결과	근거수준
Aspirin(ASA) vs placebo	LBR 0.94, 0.71–1.25	차이없음	매우 낮음
Heparin+ASA vs ASA	LBR : 1.27, 1.09–1.49 MR : 0.48, 0.32–0.71	LBR 증가 MR 감소	낮음
LMWH+ASA vs ASA/ UFH+ASA vs ASA	1.20, 1.04–1.38 / 1.74, 1.28–2.35	LBR 증가	낮음
LMWH vs ASA	LBR 1.2, 1.00–1.43	LBR 증가	
LMWH+ASA vs UFH+ASA	LBR : 1.44, 0.80–2.62 MR : 0.53, 0.28–0.99	MR 감소	

Antiphospholipid 양성 RPL에서는 LMWH + ASA 사용군에서 LBR을 높이고 MR을 줄일 가능성이 있음.

Hamulyak EN et al. Cochrane Database Syst Rev. 2020

Heparin + ASA

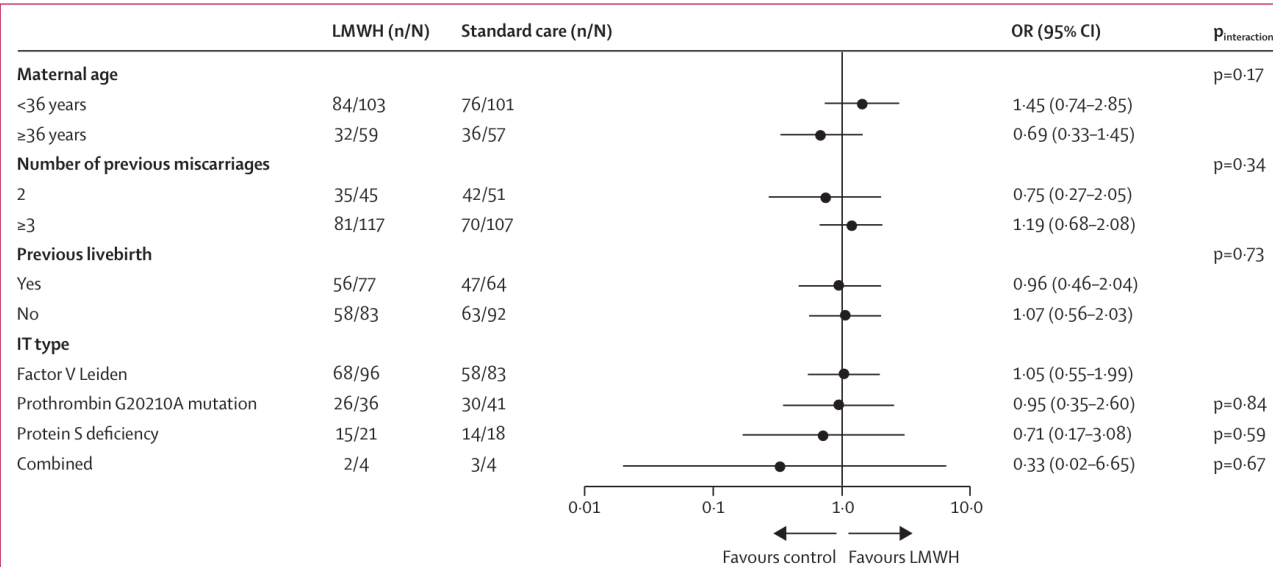
- Inherited thrombophilia

Author, year	Outcome	Case	Control	RR / OR, 95% CI	Conclusion
De Jong et al. 2014	LMWH vs. ASA	119	120	1.08, CI = 0.93-1.26, p=0.3	No Difference in LBR
	LMWH vs. CTL	231	222	1.23, CI 0.84-1.81, p =0.29	No Difference in LBR
	LMWH+ ASA vs. CTL	161	161	1.01, CI 0.87-1.16, p =0.94	No Difference in LBR
Skeith, et al 2016	LBR	201/238	159/245	0.81, 0.55-1.19, p=0.28	No difference in LBR
Liu et al 2021	MR	30,254		Factor V: 2.44, 1.96–3.03	Genetic thrombophilias increase the risk of SABs
				PGM: 2.08, 1.61–2.68	
				Protein S: 3.45, 1.15–10.35	

	LMWH (n=162)	Standard care (n=158)	Unadjusted analysis*	Adjusted analysis†	Absolute risk difference
Livebirth	116 (72%)	112 (71%)	1.04 (0.64 to 1.68); p=0.99	1.08 (0.65 to 1.78); p=0.77	0.7% (95% CI -9.2% to 10.6%)
Pregnancy loss	46 (28%)	46‡ (29%)	..	..	..

Data are n (%) unless stated otherwise. LMWH=low-molecular-weight heparin. *Odds ratio (95% CI) and χ^2 test p value with continuity correction. †Odds ratio (95% CI) and p value logistic regression adjusted for maternal age (<36 years, ≥ 36 years), number of miscarriages (2, ≥ 3), tertiary or non-tertiary centre, and randomising country (UK, Netherlands), with the standard surveillance group as the reference group. ‡One set of triplets in the standard care group was counted as a livebirth as two of the three fetuses were livebirths; the other was terminated at 8+3 weeks' gestation. This termination has not been counted in this table.

Table 2: Pregnancy outcome (livebirth rates)



- International, open-label RCT
- Enoxaparin 40mg SC daily
- 임신테스트 양성 후 7주 이내 시작, 분만 시까지 지속
- LMWH는 반복유산 + 유전성 thrombophilia 여성에서 LBR을 개선하지 않음
- 연령, 유산횟수, 이전 livebirth 유무, thrombophilia 종류에 따른 차이 없음
- 유전성 혈전성향 검사를 위한 선별검사 및 LMWH의 사용 권장하지 않음.

Quenby S et al. Lancet. 2023

Heparin + ASA

Recommendations

- ✓ Heparin + ASA during pregnancy may increase the LBR in RPL women with persistent aPL when compared with aspirin treatment alone.
- ✓ Excluding APS, conflicting data for heparin treatment for uRPL with or without thrombophilia.
- ✓ LMWH and aspirin are recommended for patients with APS throughout pregnancy and postpartum.
- ✓ Further research for dose, duration, and patient selection is needed.

ESHRE 2022 recommendation

For women who fulfil the laboratory criteria of APS and a history of three or more pregnancy losses, we suggest administration with low-dose aspirin (75 to 100 mg/day) starting before conception, and a prophylactic dose heparin (UFH or LMWH) starting at date of a positive pregnancy test, over no treatment.

Conditional ⊕■■■

The GDG suggests offering anticoagulant treatment for women with two pregnancy losses and APS, only in the context of clinical research.

GPP

Recommendation

Heparin or low dose aspirin are not recommended, as there is evidence that they do not improve live birth rate in women with unexplained RPL.

Strong ⊕⊕⊕■

Hydroxychloroquine (HCQ)

- Mechanism: TLR inhibition, anti-inflammatory, antithrombotic
- Cost effective
- Evidence
 - HCQ reversed antiphospholipid antibody–mediated suppression of first-trimester trophoblast invasion and differentiation, normalizing cytokine and angiogenic factor expression.
Albert et al. AJRI 2014
 - Among women with APS-related recurrent spontaneous abortion, regimens combining HCQ with low-dose aspirin and heparin achieved higher live-birth rates.
Mekinian et al. 2017, Ye et al 2017

Hydroxychloroquine (HCQ)

Recommendations

- ✓ Low level evidence for HCQ treatment for uRPL
- ✓ HCQ can be considered for uRPL women with autoimmunity (APS, SLE, RA, aPL+ etc) or placental inflammatory diseases, who failed 1st line treatment.
- ✓ Dose: 100–200 mg BID
- ✓ Duration : maintain through pregnancy/postpartum

Cochrane Central Register of Controlled Trials

Hydroxychloroquine for prevention of recurrent miscarriage: results of BBQ study, a french multicentre randomised placebo-controlled trial

Pasquier E

Human reproduction (Oxford, England), 2025, 40, i13 | added to CENTRAL: 31 August 2025 | 2025 Issue 8

<https://doi.org/10.1093/humrep/deaf097.022>

hCG

- Mechanism: decidualization, angiogenesis, immune tolerance
- Cochrane (5 studies): MR↓ trend (RR 0.51)
- Recommendation
 - ✓ Low level of evidence that the injection of hCG prevents pregnancy loss
 - ✓ Lack of high-quality evidence, uncertain benefit

ESHRE 2022 recommendation

There is insufficient evidence to recommend the use of hCG to improve live birth rate in women with RPL and luteal phase insufficiency.

Conditional ⊕⊕■

No	면역치료	근거 수준	권고 요약	권장 용량·투여 시기	주요 대상군 / 비고
1	Corticosteroids	Moderate	uRPL 여성 중 면역이상($\uparrow$ uNK $\geq$ 5%, ANA+, autoAb+)에서 권고 면역이상 없는 경우 조건부 권고.	Prednisone 또는 prednisolone 10–20 mg/day. 임신 전부터 1삼분기까지 유지.	면역 이상 (ANA+, uNK>5%)이 있는 경우 효과적.
2	IVIG	Moderate	면역이상(pbNK $\uparrow$, Th1/Th2 불균형, 자가면역 양성) 및 $\geq$ 4회 RPL 여성에서 권고.	200–400 mg/kg IV, 임신 전 시작, 1–3 주 간격, 임신 중 지속.	고비용.
3	LIT	Low–Moderate	허용국가에서는 uRPL 여성에 조건부 권고. anti-paternal Ab seroconversion 확인 필수.	파트너 림프구 100 million/dose, 피내주사 임신 전·임신 중	미국(FDA) 금지. 감염예방지침 필수.
4	ILE	Low	면역이상(pbNK cytotoxicity $\uparrow$, Th1 cytokine $\uparrow$) 여성에서 LBR $\uparrow$ 가능성.	20% soybean oil 기반 ILE, 용량 다양. 임신 전 또는 초임기 1–2회.	비용 낮고 안전성 양호.
5	Vitamin D	Moderate (RPL의 연관성) Low (보충효과)	비타민 D 결핍은 RPL 위험 $\uparrow$. 보충 시 면역조절 효과 있으나 LBR 향상 근거 낮음.	Vitamin D3 2000–4000 IU/day, 임신 전 혈중 25(OH)D > 30 ng/mL 유지.	결핍 고위험군(아프리카계, 북위지역) 평가 필수.
6	Calcineurin Inhibitors	Low	Th1/Th2 ratio $\uparrow$, CD56+/CD57+ NK cell $\uparrow$ 등 면역이상 여성에서 LBR $\uparrow$ 보고. 더 많은 연구 필요.	Tacrolimus 0.5–2 mg/day (개별화), 임신 전부터 시작.	Th1/Th2 ratio 기반 용량조절 권장.
7	G-CSF	Conflicting	uRPL에서 효과 불확실. 일부 연구 LBR $\uparrow$ 보고 있으나 결과 불일치.	rhG-CSF 1 μ g/kg SC, 배란 후 6일째~임신 9주까지.	더 많은 RCT 필요.
8	Anti-TNF	Conflicting	단독요법 근거 불충분. 일부 연구에서 refractory innate immune RPL에서 LBR $\uparrow$.	Etanercept 25 mg/week SC, 임신 전후 투여.	자가면역 질환 치료제, 감염 스크리닝 필수.
9	Heparin + ASA	Moderate (APS) Conflicting (uRPL)	APS 여성에서 LMWH + ASA $\rightarrow$ LBR $\uparrow$ uRPL에는 근거 불충분.	LMWH + ASA 75–100mg po qd, 임신 초~분만 후 지속.	Thrombotic APS $\rightarrow$ 치료용량 Obstetric APS $\rightarrow$ 예방용량
10	Hydroxychloroqui ne	Low	uRPL 여성 중 자가면역질환(APS, SLE, RA) 혹은 autoAb 양성자에게 고려 가능.	HCQ 100–200 mg BID, 임신 전·임신 중·산후 지속.	보조요법으로 사용 가능.
11	hCG	Low	hCG 주사로 유산 예방 근거 불충분. 일부 RCT에서 MR $\downarrow$ 경향.	Urinary or recombinant hCG IM 또는 IU 주입 배란 후 또는 임신 초기 반복투여.	대규모 고품질 연구 필요.

ASRI 2025

- **Definition**
- ≥ 2 miscarriages
- Immune mechanisms considered
- **Evaluation – General**
- Genetic, uterine, endocrine, APS
- Same as previous guidelines
- **Evaluation – Immune factors**
- NK cell activity
- Th1/Th2 cytokine ratio
- Other biomarkers (research-based)

• Strengths	• Limitations
• First guideline to systematically define immunotherapy for RPL • Provides practical recommendations for 11 immunotherapies • Establishes standardized terminology and dosing protocols • Integrates immune-based patient selection criteria (e.g., NK, Th1/Th2, autoantibodies)	• Low to moderate evidence quality for most therapies • High heterogeneity among included studies • Limited RCTs and small sample sizes • Cost and accessibility issues for treatments (e.g., IVIG, CNIs) • Lacks long-term safety and cost-effectiveness data

학회	정의	검사 권고	치료 권고	특징
ASRM (2012)	≥2회 임상적 유산 (연속 여부 무관)	- 부모 핵형검사- 자궁기형 평가 (자궁조영술/sonoHSG/자궁내시경) - 내분비(갑상선, 당뇨) - 항인지질항체 검사	- APS에 한해 aspirin+heparin - 자궁기형 교정 - 원인불명은 보조치료 근거 부족	가장 보수적, update 없음
ESHRE (2022)	≥2회 임상적 유산	- 유전자: 부모 핵형검사 (조건부) - 자궁기형: 3D US/자궁내시경- 내분비: TSH만 권장 (항TPO 항체 불필요) - APS 필수 검사	- APS에서만 항응고치료 - 면역치료(IVIG, Intralipid 등) 권고하지 않음 - 심리적 지원 강조	evidence-based 세분화, 불필요 검사 최소화
ASRI (2025)	≥2회 임상적 유산 (특히 면역 원인 강조)	- NK cell, Th1/Th2 balance 등 면역 marker 고려 가능 (연구 맥락) - APS 필수	- APS: aspirin+heparin - 면역 관련 치료: IVIG, corticosteroid, intralipid, TNF-α inhibitor 등 조건부 권고	최초로 면역치료 권고 를 구체적으로 정리한 가이드라인

Take home message

- >70% of RPL involve immune abnormalities
- Highest evidence: corticosteroids, IVIG
- Immune-targeted therapy effective in selected patients
- Precision-based immunotherapy emphasized

Severance

With the Love of God, Free Humankind from Disease and Suffering

