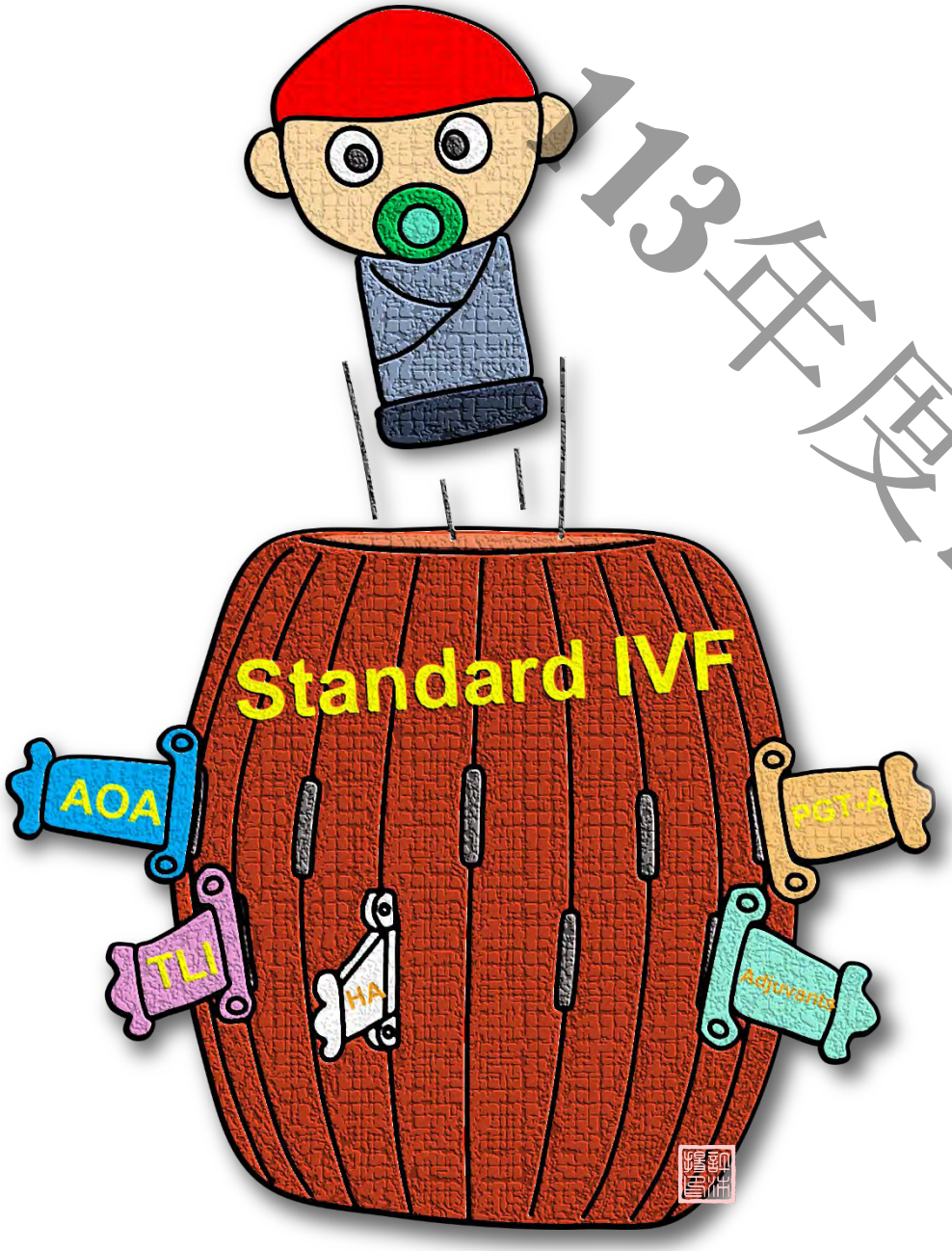


Rethink of “Add-ons” in ART

旭陽診所 許沛揚
Pei-Yang Hsu, MD, MPH
Email: phsu@jhsph.edu

2024/Mar 台灣婦產科醫學會113年會生殖內分泌 {SY49] 16:00-16:30

Disclosure

I have no conflict of interest to disclose.

今日主題

- 定義”Add-ons”(附加措施、附加物)
- 歐洲生殖醫學會對“Add-ons”的2023年最新建議選讀
- 倫理議題及性價考量
- Add-ons之外的根本問題
- 結論

定義“Add-ons”

- 人工生殖治療的**創新本質**，加上**受術夫妻的需求**，造就了新興療法的廣泛使用，即為”Add-ons”
- 這些補充選項可供患者在**標準生育程序之外**選擇，但通常會產生額外費用。
- 這些附加選項共同的目標是增進懷孕或活產率、減輕流產風險、加速達到懷孕的時間。
- 這些補充選項的**安全性**或**有效性的證據**，**通常有限或缺乏**。

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

110年接受人工生殖之受術妻年齡中位數達**39歲**

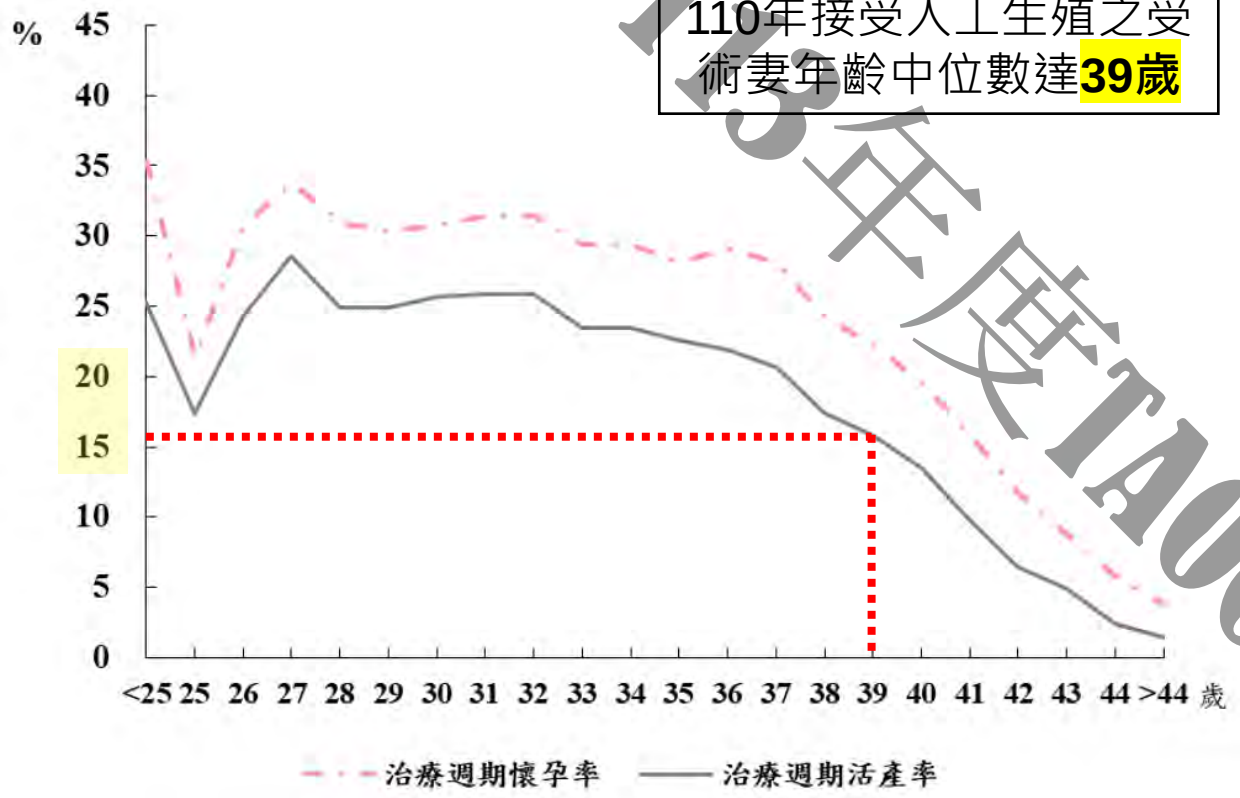
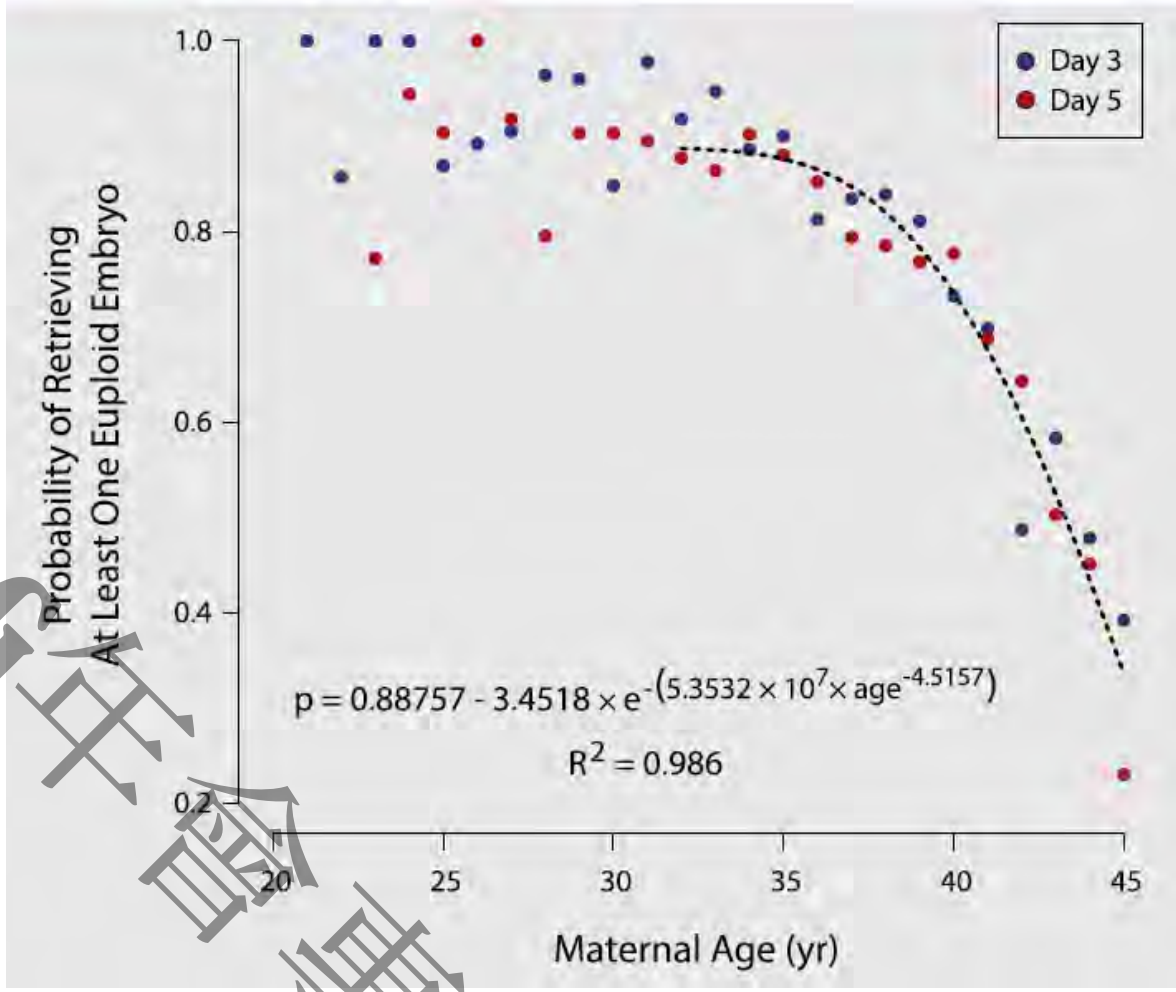


圖 9　110 年本國籍使用配偶精卵之人工生殖受術妻年齡與懷孕率及活產率關係
(母數：47,456 治療週期數)

FIGURE 4



試管嬰兒成功率與能否得到(染色體)正常之胚胎高度相關

Fertil Steril. 2016 May;105(5):1307-1313.
https://www.hpa.gov.tw/

How common is add-on use and how do patients decide whether to use them? A national survey of IVF patients

S. Lensen [1,*], K. Hammarberg [2,3], A. Polyakov [1,4,5], J. Wilkinson [6], S. Whyte [7,8,9,10], M. Peate [1], and M. Hickey [1]

Table II IVF add-ons used and whether they were associated with an additional cost.

Add-ons (n = 1590)	Used add-on		Paid extra for add-on	
Acupuncture[a]	692	(45.3)	681	(98.4)
Pre-implantation genetic testing for aneuploidy (PGT-A)	422	(27.6)	397	(94.1)
Chinese herbal medicine	397	(26.0)	390	(98.2)
Heparin (clexane)	377	(24.7)	272	(72.1)
Aspirin[a]	366	(24.0)	324	(88.5)
Timelapse imaging of embryos (Embryoscope)	358	(23.4)	98	(27.3)
EmbryoGlue (embryo transfer media, hyaluronan-containing transfer media)	341	(22.3)	203	(59.5)
Melatonin[a]	339	(22.2)	319	(94.1)
Prednisolone (corticosteroids, glucocorticoids)	334	(21.9)	302	(90.4)
Endometrial scratch (endometrial injury, pipelle)	264	(17.3)	192	(72.7)
Androgens (testosterone, DHEA, dehydroepiandrosterone, androderm patch)	204	(13.4)	150	(73.5)
Growth Hormone	180	(11.8)	133	(73.9)
Assisted hatching	120	(7.9)	54	(45.0)
Intralipid infusion	125	(8.2)	116	(92.8)
Physiological intracytoplasmic sperm injection (PICSI)	97	(6.4)	71	(73.2)
Intracytoplasmic morphologically selected sperm injection (IMSI)	88	(5.8)	43	(48.9)
Lipiodol flushing (poppy seed oil, lipiodol bathing)	86	(5.6)	67	(77.9)
Endometrial receptivity array (ERA)	53	(3.5)	47	(88.7)
GM-CSF culture media (Embryogen, Blastgen, Granulocyte-macrophage colony-stimulating factor culture media)	49	(3.2)	23	(46.9)
Artificial Oocyte Activation (Artificial oocyte activation calcium ionophore)	32	(2.1)	21	(65.6)
Viagra (vasodilators)	29	(1.9)	22	(75.9)
Meiotic spindle visualisation (Polscope, Oosight, Polarised light egg visualisation, Egg spindle visualisation)	23	(1.5)	8	(34.8)
Intravenous immunoglobulin (IVIG)	18	(1.2)	14	(77.8)
Platelet Rich Plasma intrauterine infusion or instillation	9	(0.6)	7	(77.8)
No add-ons used	274	(17.9)		
Missing	63	(4.0)		

澳洲, 線上問卷調查受術妻, 自2017至2020, 總計N=1590, 年齡中位數36歲

使用Add-ons的比例高達82%
種類多達24種

Hum Reprod. 2021 Jun 18;36(7):1854-1861.

Patient and professional perspectives about using in vitro fertilisation add-ons in the UK and Australia: a qualitative study

Sarah C Armstrong [1,2] Emily Vaughan [3] Sarah Lensen [4] Lucy Caughey [4] Cynthia M Farquhar [5] Allan Pacey [1] Adam H Balen [6] Michelle Peate [4] Elaine Wainwright [7,8]

問卷調查受術夫妻N=11(UK)+14(AU)及專家(醫師及胚胎師)N=24(UK)+25(AU),探討不同面相**使用Add-ons的驅使因素**

Professionals versus patients: who is driving add-on use?

- Patients' perspective:
  - A **professional opinion** (clinicians and also nurses or embryologists) was felt to be **the most influential reason for opting to** use add-ons
  - The importance of the professional opinion **also holds when the recommendation is to reject** an add-on
  - The need for adequate **counselling about the risks** to make an informed decision was deemed important by over **2/3 of participants**

是否選用附加措施仍很依賴專業建議，且希望知道風險

BMJ Open. 2023 Jul 26;13(7):e069146.

Human Fertilisation & Embryology Authority (HFEA)

There are five ratings that indicate whether a treatment add-on is effective at improving treatment outcomes for someone undergoing fertility treatment, according to evidence from studies. To make it easier to understand the scientific evidence for each treatment add-on we have a range of symbols and colours for each rated add-on below.

Ratings are determined by the* Scientific and Clinical Advances Advisory Committee (SCAAC), which is a subcommittee of the Authority. More information about the process for allocating and reviewing ratings can be found in the SCAAC meeting papers. The minutes of this decision-making process, and the specific evidence used to inform these decisions, can be found in the description for each treatment add-on.

*from 2013

On balance, findings from high quality evidence shows **this add-on is effective at improving the treatment outcome**.

On balance, it **is not clear whether this add-on is effective at improving the treatment outcome**. This is because there is conflicting moderate/high quality evidence – in some studies the add-on has been found to be effective, but in other studies it has not.

We cannot rate the effectiveness of this add-on at improving the treatment outcome as there is insufficient moderate/high quality evidence.

On balance, the evidence from moderate/high quality evidence shows that **this add-on has no effect on the treatment outcome**.

There are potential safety concerns and/or, on balance, the findings from moderate/high quality evidence shows that this **add-on may reduce treatment effectiveness**.

英國的HFEA於2023年更新了附加措施的燈號系統，便於識別證據力

https://www.hfea.gov.uk/treatments/treatment-add-ons

- Assisted Hatching
- Elective freeze all cycles
- Endometrial receptivity testing
- Endometrial scratching
- Hyaluronate enriched pre-transfer culture medium (e.g. EmbryoGlue)
- Immunological tests and treatments for fertility - Intralipids
- Immunological tests and treatments for fertility - Intravenous immunoglobulin (IVIG)
- Immunological tests and treatments for fertility - Steroids (Glucocorticoids)
- Intracytoplasmic morphologic sperm injection (IMSI)
- Intrauterine culture
- Physiological intracytoplasmic sperm injection (PICSI) – in use for patients having ICSI treatment for male factor infertility
- Pre-implantation genetic testing for aneuploidy (PGT-A)
- Time-lapse imaging and incubation

SCAAC
評分了13項附加措施，
對於增加活產
沒有

https://www.hfea.gov.uk/treatments/treatment-add-ons

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Cochrane Special Collections

In vitro fertilisation – effectiveness of add-ons

15 July 2021

In vitro fertilisation – effectiveness of add-ons

Hide preview ▲ 15 July 2021

As many as one in seven couples experience difficulty becoming pregnant [1], and many of them turn to fertility treatments for help. In vitro fertilisation (IVF) is generally considered the most advanced treatment option, and is recommended in many cases, regardless of the cause of subfertility.

Laboratory add-ons

Clinical add-ons

Add-ons for the endometrium

These Cochrane reviews found that none of the IVF add-ons are supported by high-quality evidence that the add-on is effective and safe. In most cases, the included studies suffered from limitations, such as risk of bias and small sample size, which result in uncertainty about whether the add-on is beneficial, harmful or has no effect – it was not possible to tell.

For three add-ons, there was some evidence of possible benefit, however the evidence was not high quality:

- **addition of hyaluronic acid to embryo transfer media**
- using an advanced sperm selection technique known as **hyaluronic acid binding**
- **injection of high doses of a pregnancy hormone (hCG)** into the womb near the time of embryo transfer

- ☒ 植入培養液加入HA
- ☒ PICSI
- ■ 植入前的IU hCG

https://www.cochranelibrary.com/collections/doi/SC000046/full

Good practice recommendations on add-ons in reproductive medicine

ESHRE aimed to develop clinically relevant and evidence-based recommendations focusing on the safety and efficacy of add-ons currently used in fertility procedures. The multidisciplinary working group formulated 42 recommendations across three sections;

- diagnosis and diagnostic tests,
- laboratory tests and interventions and
- clinical management.

} 分三大類

These recommendations offer valuable direction for healthcare professionals who are responsible for the care of patients undergoing ART treatment for infertility. Their purpose is to promote safe and effective ART treatment, enabling patients to make informed decisions based on realistic expectations. The good practice recommendations aim to ensure that patients are fully informed about the various treatment options available to them and the likelihood of any additional treatment or test to improve the chance of achieving a live birth.

Meet the working group


Kersti Lundin


Anja Pinborg


Janne G. Bentzen


Gurkan Bozdag


Thomas Ebner


Joyce Harper


Ashley Moffett


Sarah Norcross


Nikolaos Polyzos


Satu Rautakallio-Hokkanen


Ioannis Sfontouris


Karen Sermon


Nathalie Vermeulen


Nathalie Le Clef

27 tests/interventions, **42** recommendations

https://www.eshre.eu Hum Reprod. 2023 Nov 2;38(11):2062-2104.

European Recommendations for good practice in addition to an evidence-based guidelines programme: rationale and method of development

Nathalie Vermeulen,[1] Nathalie Le Clef,[1] Zdravka Veleva,[2] Arianna D'Angelo,[3] Kelly Tilleman[4]

Table 1 Comparison of the key features of guidelines and recommendations for good practice

	Recommendations for good practice	Evidence-based guidelines
Topic	Clinical/laboratory topics with significant uncertainty and variation in practice, which cannot be addressed as an evidence-based guideline	Clinical/laboratory topics for which there is sufficient evidence to answer key questions
Output	One or more papers published in a scientific journal	Full guideline published online + summary published in a scientific journal
	Patient version (if relevant) No patient version for technical recommendations	Patient version (if relevant)
	Implementation tools	Implementation tools
Supporting evidence	Expert opinion Any available evidence, but mostly limited to observational data based on a limited amount of cases	Systematics reviews, RCTs, observational data (on large case series) or lower quality evidence
Recommendations	Consensus-based	Primarily evidence-based
Development group	Working group	Guideline development group
	8–10 members	10–15 members
	Experts with hands-on expertise	Content experts Non-expert clinicians Patient representative Allied healthcare professionals
Time frame	12 months from the first meeting	18–24 months from the first meeting
External review	Strongly recommended*	Obligatory
	4 weeks	6 weeks

*External review can be irrelevant if a larger group of stakeholders was involved during consensus development.

Good Practice Recommendation 有別於實證指引，可能加入了較多的 Expert Opinion (實證證據力較低)

BMJ Evid Based Med. 2019 Feb;24(1):30-34.

Materials and methods

- 根據Manual for development of ESHRE good practice recommendations
- **14位臨床及2位方法學專家**，資料蒐集至**2022/Aug**，優先順序：systemic reviews及RCTs，輔以observational studies的相關資料

Table 1. Overview of the four standard phrases that were used for the formulation of the recommendations, and their implications.

Terminology	Implications
Recommended	The test/intervention can be applied to most patients or to those patient groups for whom it may be of relevance. The recommendation can be adopted as policy in most situations.
Can be considered	Can be applied after a thorough discussion of possible benefits and risks and with close monitoring, follow-up and evaluation.
Currently not recommended for routine clinical use	The test/intervention should not be applied routinely to patients at this stage, but this may change when more evidence on efficacy and safety becomes available. Optionally, the intervention can be applied to a specific patient group.
Not recommended	Based on safety concerns and/or lack of efficacy and/or lack of biological rationale, the test/intervention should not be applied to patients. Further evaluation of these tests/interventions can be done, but only in strict research settings.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

Intervention	Recommendation
Screening hysteroscopy	Can be considered in RIF
Endometrial receptivity tests	Not recommended
Immunology tests and treatments	Not (routinely) recommended
Artificial oocyte activation	Not routinely recommended Recommended in certain conditions
Mitochondrial replacement therapy	Not recommended
IVA of dormant follicles	Not recommended
IVM	Not routinely recommended
Sperm DNA testing and treatment	Not routinely recommended
Artificial sperm activation	Not recommended
Sperm evaluation and selection	Not routinely recommended Microfluidics can be considered
GF supplemented culture medium	Not recommended
Assisted hatching	Not recommended
Genetic testing and treatments	Not routinely recommended
Time-lapse imaging	Not recommended

3

11

Intervention	Recommendation
Platelet-rich plasma (IU or IO)	Not recommended
Duostim	Not routinely recommended
Adjuncts during ovarian stimulation	Not recommended
Intravaginal & intrauterine culture device	Not routinely recommended
Additions to transfer media (HA)	Is recommended
Endometrial scratching	Not routinely recommended
Flushing of the uterus	Not recommended
Stem cell Mobilization	Not recommended
Steroids	Not recommended
Elective freeze-all	Not routinely recommended
ICSI for non-male factor infertility	Not recommended
Antioxidant therapy	Not recommended
Complementary and alternative Medicine	Not recommended

13

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

Screening hysteroscopy in subfertile women and women undergoing assisted reproduction (Review)

Cochrane Library

Summary of findings 2. Screening hysteroscopy versus no hysteroscopy in women before IVF

Screening hysteroscopy versus no hysteroscopy in women before IVF

Patient or population: women before IVF treatment
Setting: academic and private clinics
Intervention: screening hysteroscopy
Comparison: no hysteroscopy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no hysteroscopy	Risk with hysteroscopy				
Live birth	221 per 1000	279 per 1000 (245 to 316)	RR 1.26 (1.11 to 1.43)	2745 (6 RCTs)	⊕⊕⊖⊖ low[a,b]	
Adverse events	0 per 1000	0 per 1000 (0 to 0)	Peto OR 7.47 (0.15 to 376.42)	1872 (4 RCTs)	⊕⊕⊖⊖ very low[a,c]	
Clinical pregnancy	278 per 1000	368 per 1000 (334 to 404)	RR 1.32 (1.20 to 1.45)	3750 (10 RCTs)	⊕⊕⊖⊖ low[a,d]	
Miscarriage	53 per 1000	53 per 1000 (35 to 79)	RR 1.01 (0.67 to 1.50)	1669 (3 RCTs)	⊕⊕⊖⊖ low[a,e]	

✓ **Sensitivity analysis done by pooling results from trials at low risk of bias showed no increase in LBR following a screening HSC (RR 0.99, 95% CI 0.82 to 1.18; 2 RCTs; participants = 1452; I^2 = 0%).**

Cochrane 2019：IVF前做子宮鏡可能增加LBR

Cochrane Database Syst Rev. 2019 Apr 16;4(4):CD012856.

Screening hysteroscopy in subfertile women and women undergoing assisted reproduction (Review)

Cochrane Library

Analysis 2.1. Comparison 2 Screening hysteroscopy versus no hysteroscopy in women before IVF, Outcome 1 Live birth.

Study or subgroup	Hysteroscopy n/N	No hysteroscopy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Unselected					
Juul Hare 2018	17/112	13/105		4.44%	1.23[0.63,2.4]
Subtotal (95% CI)	**112**	**105**		**4.44%**	**1.23[0.63,2.4]**
Total events: 17 (Hysteroscopy), 13 (No hysteroscopy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.55)					
2.1.2 First IVF					
Smit 2016	71/373	75/377		24.68%	0.96[0.72,1.28]
Elsetohy 2015	58/102	33/101		10.97%	1.74[1.25,2.41]
Subtotal (95% CI)	**475**	**478**		**35.65%**	**1.2[0.96,1.49]**
Total events: 129 (Hysteroscopy), 108 (No hysteroscopy)					
Heterogeneity: Tau^2=0; Chi^2=7.3, df=1(P=0.01); I^2=86.3%					
Test for overall effect: Z=1.63(P=0.1)					
2.1.3 Two or more IVF failures					
El-Toukhy 2016	102/350	102/352		33.65%	1.01[0.8,1.27]
Aghahosseini 2012	50/142	45/211		11.98%	1.65[1.17,2.32]
Rama Raju 2006	72/255	44/265		14.28%	1.7[1.22,2.37]
Subtotal (95% CI)	**747**	**828**		**59.91%**	**1.3[1.1,1.53]**
Total events: 224 (Hysteroscopy), 191 (No hysteroscopy)					
Heterogeneity: Tau^2=0; Chi^2=9.11, df=2(P=0.01); I^2=78.04%					
Test for overall effect: Z=3.12(P=0)					
Total (95% CI)	**1334**	**1411**		**100%**	**1.26[1.11,1.43]**
Total events: 370 (Hysteroscopy), 312 (No hysteroscopy)					
Heterogeneity: Tau^2=0; Chi^2=16.34, df=5(P=0.01); I^2=69.41%					
Test for overall effect: Z=3.52(P=0)					
Test for subgroup differences: Chi^2=0.35, df=1 (P=0.84), I^2=0%					

Favours no hysteroscopy 0.5 0.7 1 1.5 2 Favours hysteroscopy

篩檢性子宮鏡對2次以上IVF失敗者可能有較顯著好處

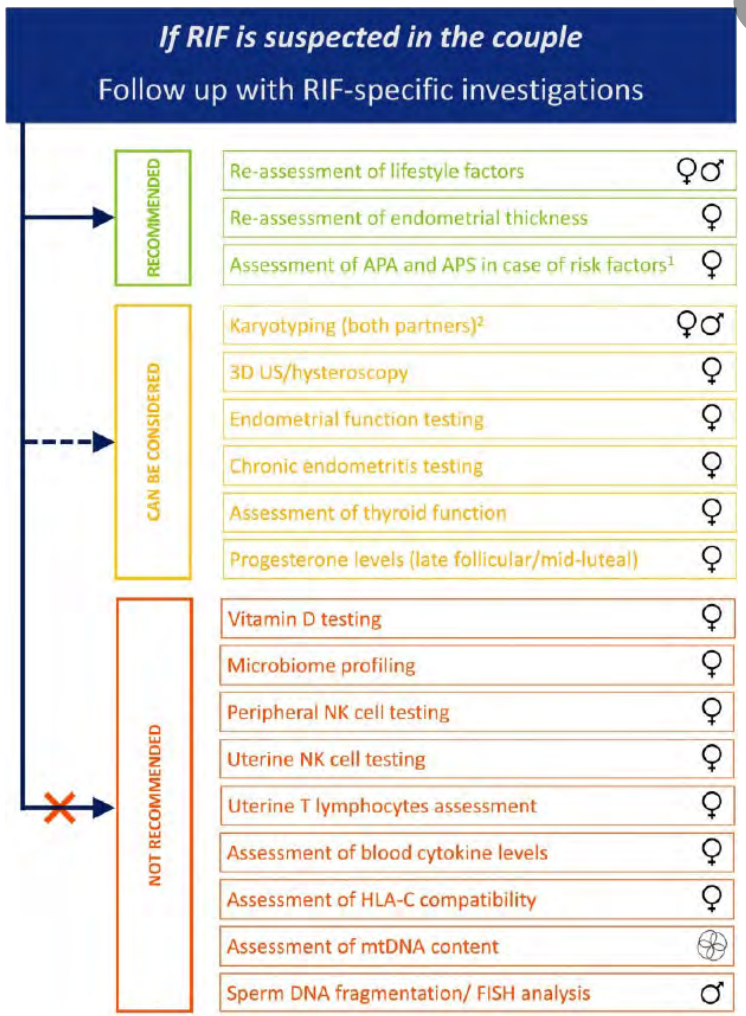
Safety

Four trials in the Cochrane review reported complications following hysteroscopy (odds ratio (OR) 7.47; 95% CI 0.15 to 376.42; 4 RCTs; n = 1872; I^2 N/A; very low-quality evidence); of these, three trials recorded no events in either group; in the fourth trial, one case of endometritis was reported (Kamath *et al.*, 2019).

Cochrane Database Syst Rev. 2019 Apr 16;4(4):CD012856.

ESHRE good practice recommendations on recurrent implantation failure†

ESHRE Working Group on Recurrent Implantation Failure, D. Cimadomo [1], M.J. de los Santos [2], G. Griesinger [3,4], G. Lainas [5], N. Le Clef [6], D.J. McLernon [7], D. Montjean [8], B. Toth [9], N. Vermeulen [6], and N. Macklon [10,*]



Hysteroscopy can be considered, especially when there is a suspicion of a uterine anomaly visualized on transvaginal ultrasound.

Intervention	Benefits versus harms (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR)[1]	Level of evidence for safety[1]	Considerations
Screening hysteroscopy	Unselected patients: no benefit on LBR RIF: might be beneficial effect on LBR No evidence of an effect on miscarriage rate Complications are minimal	⊕⊕◯◯	⊕⊕◯◯	/

Screening hysteroscopy is currently not recommended for routine clinical use.

Screening hysteroscopy can be considered in patients with recurrent implantation failure.

Hum Reprod. 2023 Nov 2;38(11):2062-2104. Hum Reprod Open. 2023 Jun 15;2023(3):hoad023.

A 5-year multicentre randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF

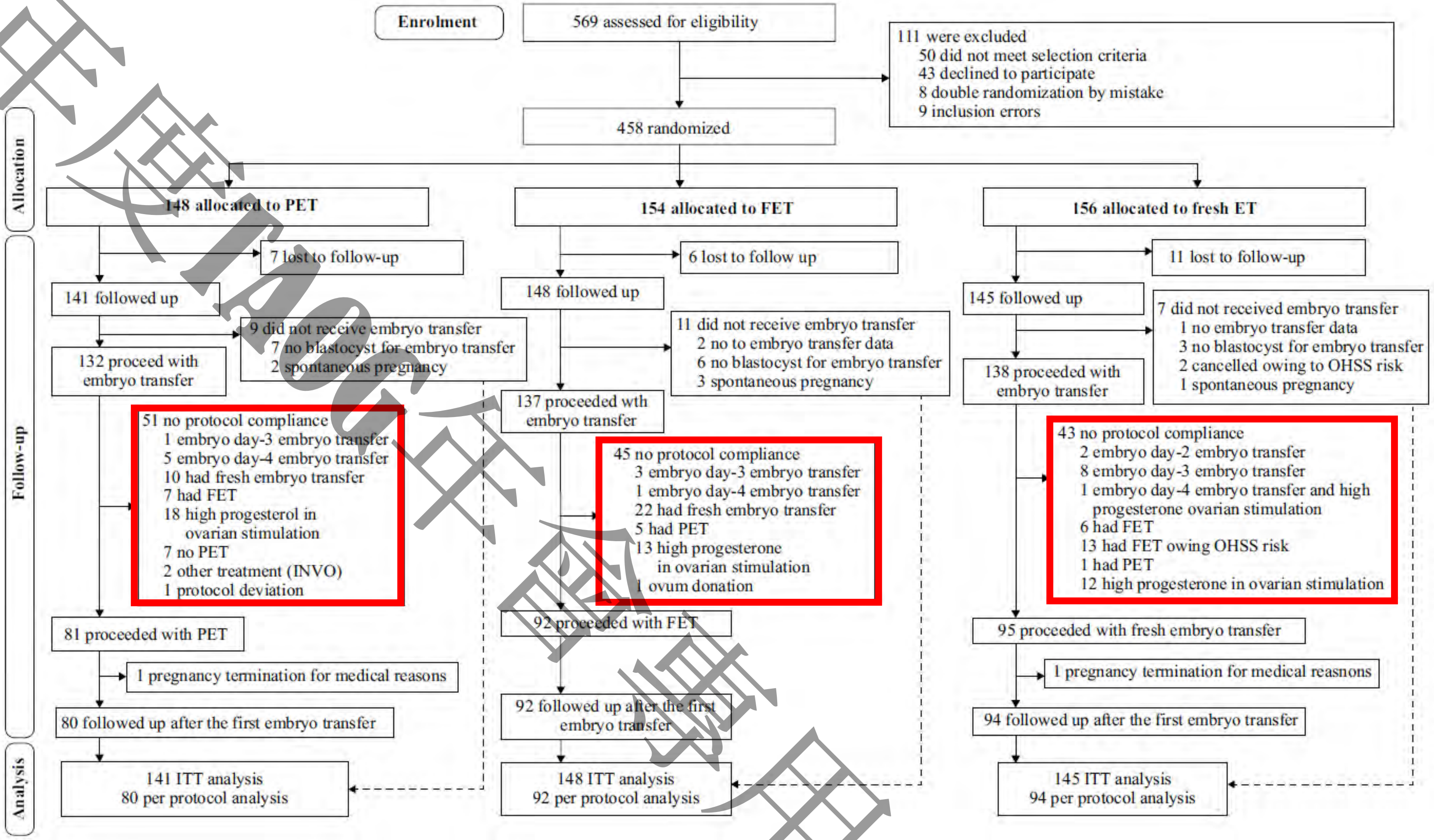
BIOGRAPHY

Professor Carlos Simón is Board Certified and Professor of Obstetrics and Gynaecology at the University of Valencia, Spain, and Senior Lecturer, Beth Israel Deaconess Medical Center Harvard University, Boston, USA. His main interest is the human embryonic implantation process, including the embryo, maternal endometrium, and the cross-communication between them.

Carlos Simón[1,2,4,*,†], Carlos Gómez[3,1], Sergio Cabanillas[4], Iavor Vladimirov[5], Gemma Castillón[6], Juan Giles[4], Kubra Boynukalin[7], Necati Findikli[7], Mustafa Bahçeci[7], Israel Ortega[8], Carmina Vidal[4], Miyako Funabiki[9], Alexandra Izquierdo[10], Lourdes López[10], Susana Portela[11], Nilo Frantz[12], Marcos Kulmann[12], Sagiri Taguchi[9], Elena Labarta[4], Francisco Colucci[13], Shari Mackens[14], Xavier Santamaría[6], Elkin Muñoz[11], Saúl Barrera[15], Juan Antonio García-Velasco[8], Manuel Fernández[16,17,18], Marcos Ferrando[19], María Ruiz[3], Ben W Mol[20], Diana Valbuena[2,3] for the ERA-RCT Study Consortium Group

2013/Nov-2017/Apr

~50% dropout



旭陽診所
Professor Chang Fertility Clinic

Reprod Biomed Online. 2020 Sep;41(3):402-415.

TABLE 3 REPRODUCTIVE OUTCOMES AT FIRST EMBRYO TRANSFER AND CUMULATIVE OUTCOMES DURING 1-YEAR FOLLOW-UP: INTENTION-TO-TREAT ANALYSIS

	PET (*n* = 141)	FET (*n* = 148)	Fresh embryo transfer ET (*n* = 145)	PET versus FET		PET versus fresh embryo transfer	
				Relative risk (95% CI)	*P*-value	Relative risk (95% CI)	*P*-value
Transfers, *n*	132	137	138				
Pregnancy rate, *n* (%)	83 (58.9)	73 (49.3)	84 (57.9)	1.19 (0.96 to 1.48)	0.12	1.02 (0.84 to 1.24)	0.9
Implantation rate, *n* (%)	88/201 (43.8)	80/220 (36.4)	97/225 (43.1)	1.20 (0.95 to 1.52)	0.14	1.02 (0.82 to 1.26)	0.92
Live birth rate *n* (%)	57 (40.4)	51 (34.5)	64 (44.1)	1.17 (0.87 to 1.58)	0.33	0.92 (0.70 to 1.20)	0.55
Singleton	49/57 (86)	40/51 (78.4)	45/64 (70.3)	1.1 (0.92 to 1.31)	0.32	1.22 (1.01 to 1.48)	0.049
Multiple (all twins)	8/57 (14)	11/51 (21.6)	19/64 (29.7)	0.65 (0.28 to 1.49)	0.32	0.47 (0.22 to 1)	0.049
Clinical miscarriages, *n* (%)	17/83 (20.5)	11/73 (15.1)	5/84 (5.9)	1.36 (0.68 to 2.71)	0.41	3.44 (1.33 to 8.90)	0.006
Biochemical pregnancies, *n* (%)	7/83 (8.4)	9/73 (12.3)	11/84 (13.1)	0.68 (0.27 to 1.74)	0.44	0.64 (0.26 to 1.58)	0.46
Ectopic pregnancies, *n* (%)	1/83 (1.2)	1/73 (1.4)	1/84 (1.2)	0.88 (0.06 to 13.82)	1	1.01 (0.06 to 15.92)	1
Elective termination of pregnancy, *n* (%)	1/83 (1.2)	0/73 (0.0)	1/84 (1.2)				
Neonatal mortality, *n* (%)	0/83 (0.0)	1/73 (1.4)	0/84 (0.0)				
Live birth lost to follow-up, *n* (%)	0 (0.0)	0 (0.0)	2/84 (2.4)				
Patients with additional embryo transfers, *n* (%)	57 (40.4)	57(38.5)	42 (28.9)	1.05 (0.79-1.40)	0.81	1.40 (1.01 to 1.93)	0.047
Total additional cycles and transfers, *n*	150	130	110				
Cumulative transfers, *n*	282	267	248				
Pregnancies from additional embryo transfers, *N*	49	45	33				
Cumulative pregnancy rate, *n* (%)	132/141 (93.6)	118/148 (79.7)	117/145 (80.7)	1.17 (1.07 to 1.29)	0.0005	1.16 (1.06 to 1.27)	0.0013
Cumulative live birth rate, *n* (%)	88/141 (62.4)	82/148 (55.4)	85/145 (58.6)	1.13 (0.93 to 1.37)	0.23	1.06 (0.88 to 1.28)	0.55
Singleton	75/88 (85.2)	67/82 (81.7)	58/85 (68.2)	1.04 (0.91 to 1.19)	0.54	1.25 (1.06 to 1.48)	0.011
Multiple (all twins)	13/88 (14.8)	15/82 (18.3)	27/85 (31.8)	0.81 (0.41 to 1.59)	0.54	0.47 (0.26 to 0.84)	0.011
Cumulative clinical miscarriages, *n* (%)	24/132 (18.2)	17/118 (14.4)	5/117 (4.3)	1.26 (0.71 to 2.23)	0.49	4.26 (1.68 to 10.79)	0.0006
Cumulative biochemical pregnancies, *n* (%)	19/132 (14.4)	16/118 (13.6)	23/117 (19.7)	1.06 (0.57 to 1.97)	1	0.73 (0.42 to 1.27)	0.31
Cumulative ectopic pregnancies, *n* (%)	1/132 (0.8)	1/118 (0.8)	1/117 (0.9)	0.89 (0.06 to 14.14)	1	0.89 (0.06 to 14.02)	1
Transfers per patient	2.63 ± 1.14	2.28 ± 0.70	2.62 ± 0.73	0.35 (–0.4 to 0.4)	0.1	0.01 (–0.43 to 0.45)	1

TABLE 4 REPRODUCTIVE OUTCOMES AT THE FIRST EMBRYO TRANSFER AND CUMULATIVE OUTCOMES DURING 1-YEAR FOLLOW-UP: PER PROTOCOL ANALYSIS

	PET (*n* = 80)	FET (*n* = 92)	Fresh embryo transfer (*n* = 94)	PET versus FET		PET versus fresh embryo transfer	
				Relative risk (95% CI)	*P*-value	Relative risk (95% CI)	*P*-value
Pregnancy rate, *n* (%)	58 (72.5)	50 (54.3)	55 (58.5)	1.33 (1.06 to 1.68)	0.01	1.24 (1 to 1.54)	0.057
Implantation rate, *n* (%)	63/110 (57.3)	60/139 (43.2)	58/150 (38.6)	1.33 (1.03 to 1.70)	0.03	1.48 (1.14 to 1.92)	0.004
Live birth rate, *n* (%)	45 (56.2)	39 (42.4)	43 (45.7)	1.33 (0.98 to 1.80)	0.09	1.23 (0.92 to 1.65)	0.17
Singleton	40/45 (88.9)	30/39 (76.9)	33/43 (76.7)	1.16 (0.95 to 1.41)	0.16	1.16 (0.95 to 1.41)	0.16
Multiple (all twins)	5/45 (11.1)	9/39 (23.1)	10/43 (23.2)	0.48 (0.18 to 1.32)	0.16	0.48 (0.18 to 1.28)	0.16
Clinical miscarriages, *n* (%)	9/58 (15.5)	7/50 (14)	3/55 (5.4)	1.11 (0.44 to 2.76)	1	2.84 (0.81 to 9.97)	0.13
Biochemical pregnancies, *n* (%)	4/58 (6.9)	4/50 (8)	8/55 (14.5)	0.86 (0.23 to 3.27)	1	0.47 (0.15 to 1.49)	0.23
Ectopic pregnancies, *n* (%)	0 (0.0)	0 (0.0)	1 (1.8)				
Patients with surplus embryo transfers, *n* (%)	19 (23.7)	16 (17.4)	4 (4.2)				
Total surplus embryo transfers, *n*	39	18	10				
Cumulative transfers, *n*	119	110	104				
Pregnancies from surplus embryo transfers, *n*	18	15	4				
Cumulative pregnancy rate, *n* (%)	76/80 (95)	65/92 (70.6)	59/94 (62.8)	1.34 (1.17 to 1.55)	<0.0001	1.51 (1.28 to 1.78)	<0.0001
Cumulative live birth rate, *n* (%)	57 (71.2)	51 (55.4)	46 (48.9)	1.28 (1.02 to 1.62)	0.04	1.46 (1.13 to 1.87)	0.003
Singleton	51/57 (89.5)	41/51 (80.4)	34/46 (73.9)	1.11 (0.95 to 1.31)	0.28	1.21 (1 to 1.47)	0.066
Multiple (all twins)	6/57 (10.5)	10/51 (19.6)	12/46 (26.1)	0.54 (0.21 to 1.37)	0.28	0.40 (0.16 to 0.99)	0.066
Cumulative clinical miscarriages, *n* (%)	10/76 (13.2)	8/65 (12.3)	3/59 (5.1)	1.07 (0.45 to 2.55)	1	2.59 (0.75 to 8.99)	0.15
Cumulative biochemical pregnancies, *n* (%)	9/76 (11.8)	6/65 (9.2)	9/59 (15.3)	1.28 (0.48 to 3.41)	0.78	0.78 (0.33 to 1.83)	0.62
Cumulative ectopic pregnancies, *n* (%)	0 (0.0)	0 (0.0)	1/59 (1.7)				
Transfers per patient	3.05 ± 1.51	2.13 ± 0.34	3.5 ± 1.29	0.92 (–0.11 to 1.97)	0.09	–0.45 (–2.13 to 1.24)	1

ERA/pET對活產率沒影響

Reprod Biomed Online. 2020 Sep;41(3):402-415.

JAMA | Original Investigation

Effect of Timing by Endometrial Receptivity Testing vs Standard Timing of Frozen Embryo Transfer on Live Birth in Patients Undergoing In Vitro Fertilization

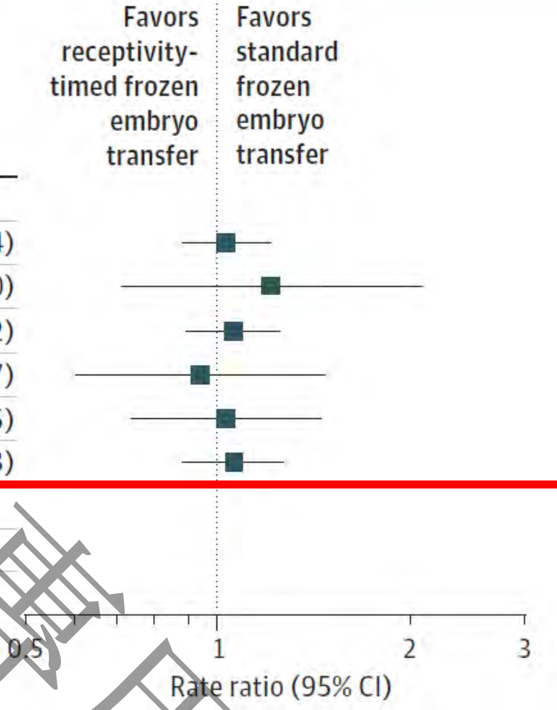
A Randomized Clinical Trial

Nicole Doyle, MD, PhD; Samad Jahandideh, PhD; Micah J. Hill, DO; Eric A. Widra, MD; Michael Levy, MD; Kate Devine, MD

RCT, all received ERA (**non-selection design**), 30-40y, PGT-A; exclusion: TESE, RIF (>2 ET failure before), RPL (≥2 loss), BMI>40; N = 767

Figure 2. Frozen Embryo Transfer Results

	No. (%) Receptivity-timed frozen embryo transfer	No. (%) Standard frozen embryo transfer	Absolute between-group difference, % (95% CI)	Rate ratio (95% CI)	*P* value
Total patients	381	386			
Biochemical pregnancy[a]	294 (77.2)	307 (79.5)	-2.3 (-8.2 to 3.5)	0.97 (0.83-1.14)	.48
Biochemical pregnancy loss[b,c]	29 (9.9)	25 (8.1)	-1.8 (-2.8 to 6.4)	1.21 (0.71-2.10)	.55
Clinical pregnancy[d]	262 (68.8)	281 (72.8)	-4.0 (-10.4 to 2.4)	0.94 (0.80-1.12)	.25
Clinical pregnancy loss[c,e]	36 (13.7)	41 (14.6)	0.9 (-6.8 to 5.0)	0.94 (0.60-1.47)	.87
Total pregnancy loss[f]	65 (22.1)	66 (21.5)	-0.6 (-6.0 to 7.2)	1.03 (0.73-1.45)	.93
Live birth[g]	223 (58.5)	239 (61.9)	-3.4 (-10.3 to 3.5)	0.95 (0.79-1.13)	.38
Ectopic pregnancy	3	1			
Therapeutic abortion	1	0			
Stillbirth	2	1			



嚴謹的RCT：ERA/pET對活產率沒影響

旭陽診所
Professor Chang Fertility Clinic

JAMA. 2022 Dec 6;328(21):2117-2125. IF 120.7 (2023)

JAMA | Original Investigation

Effect of Timing by Endometrial Receptivity Testing vs Standard Timing of Frozen Embryo Transfer on Live Birth in Patients Undergoing In Vitro Fertilization
A Randomized Clinical Trial

Nicole Doyle, MD, PhD; Samad Jahandideh, PhD; Micah J. Hill, DO; Eric A. Widra, MD; Michael Levy, MD; Kate Devine, MD

RCT, 30-40y, PGT-A, all received ERA (**non-selection design**)
Exclude: TESE, RIF (>2 ET failure before), RPL (≥2 loss), BMI>40 ➔ 767 randomized.

	Receptivity testing recommended ≥24-h adjustment				
Total patients	123	120			
Biochemical pregnancy[a]	92 (74.8)	99 (82.5)	−7.7 (−18.0 to 2.6)	0.91 (0.68-1.20)	.19
Biochemical pregnancy loss[b]	14 (15.2)	4 (4.0)	11.2 (2.9 to 19.5)	3.77 (1.24-11.44)	.02
Clinical pregnancy[c]	76 (61.8)	94 (78.3)	−16.5 (−27.8 to −5.2)	0.79 (0.58-1.07)	.01
Clinical pregnancy loss[d]	9 (11.8)	18 (19.1)	−7.3 (−18.1 to 3.5)	0.62 (0.28-1.38)	.28
Total pregnancy loss[e]	23 (25.0)	22 (22.2)	−2.8 (−9.4 to 15.0)	1.13 (0.6-2.02)	.78
Live birth[f]	67 (54.5)	76 (63.3)	−8.8 (−21.1 to 3.5)	0.86 (0.63-1.19)	.20

子族群ERA/pET反而有較低臨床懷孕率及較高化學懷孕率

JAMA. 2022 Dec 6;328(21):2117-2125. IF 120.7 (2023)

Intervention	Benefits versus harms (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR)[1]	Level of evidence for safety[1]	Considerations	Recommendation
Endometrial receptivity tests	No effect on LBR, inconclusive effect on cLBR No data on safety, biopsy procedure can be painful	⊕⊕◯◯	No data	Clinical and methodological heterogeneity in patient populations (number of previously failed cycles), reported comparisons and unit of analysis (per couple or per cycle)	The presently available endometrial receptivity tests are **not recommended**.

Recommendation

Robust data on the efficacy of endometrial receptivity tests are lacking. Additionally, the existing tests do not account for the intricate interplay between the endometrium and the embryo, including the timing, location, and depth of the biopsy procedure.

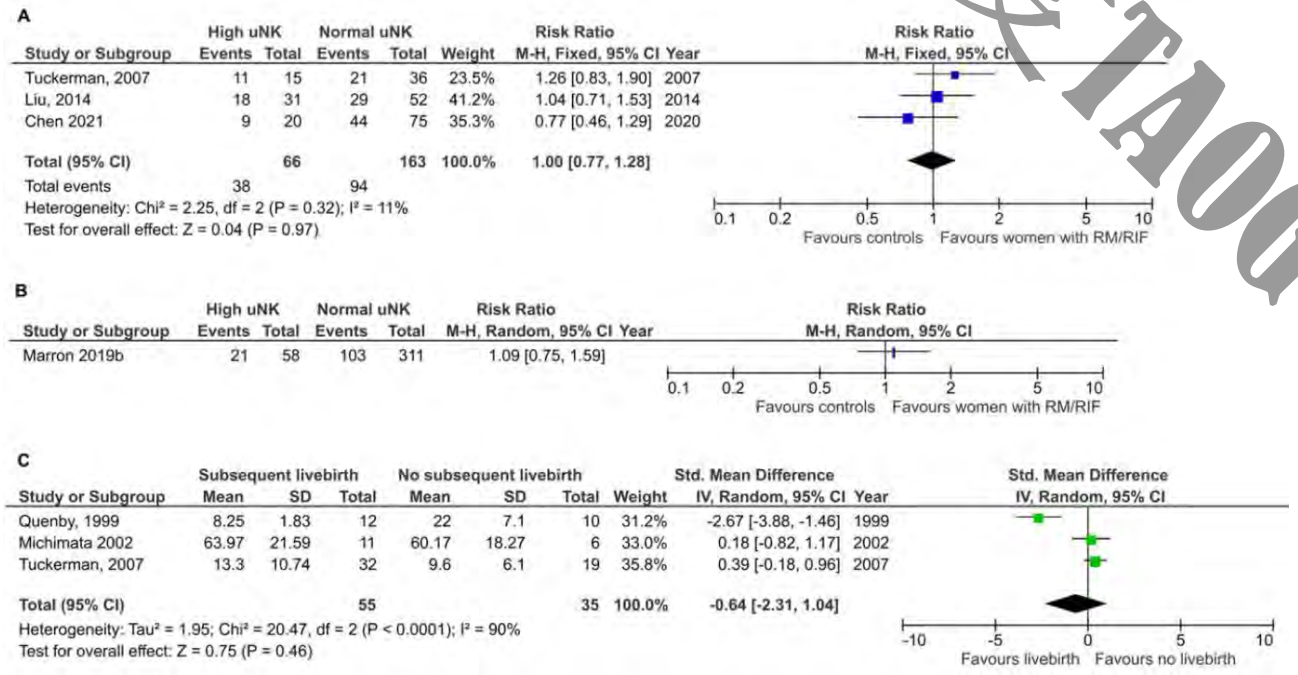
The presently available endometrial receptivity tests are not recommended.

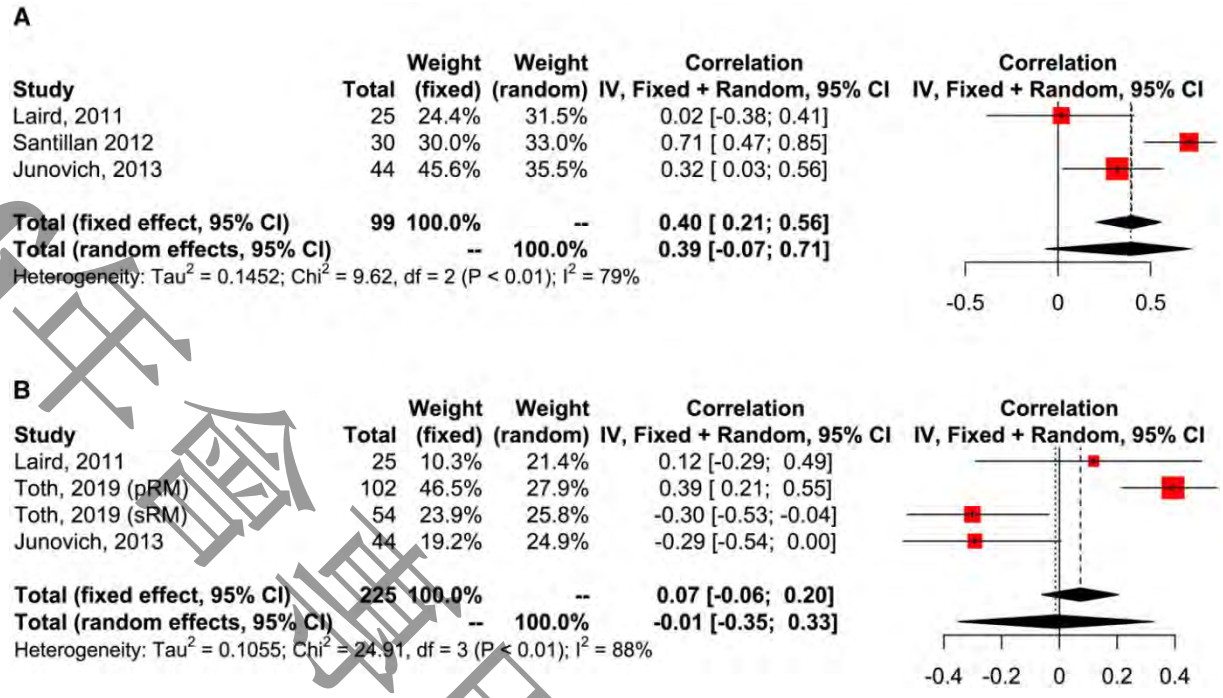
human reproduction update

Number and function of uterine natural killer cells in recurrent miscarriage and implantation failure: a systematic review and meta-analysis

Ee Von Woon [1,2,*], Orene Greer [1], Nishel Shah [1], Dimitrios Nikolaou [2], Mark Johnson [1], and Victoria Male [1]

*All studies included were judged as having moderate to serious risk of bias





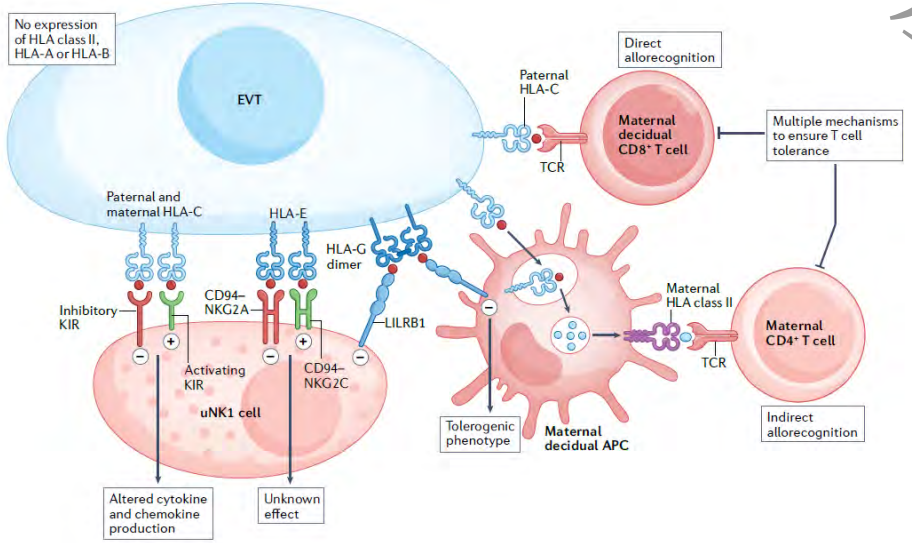
uNK高或正常與LBR無關

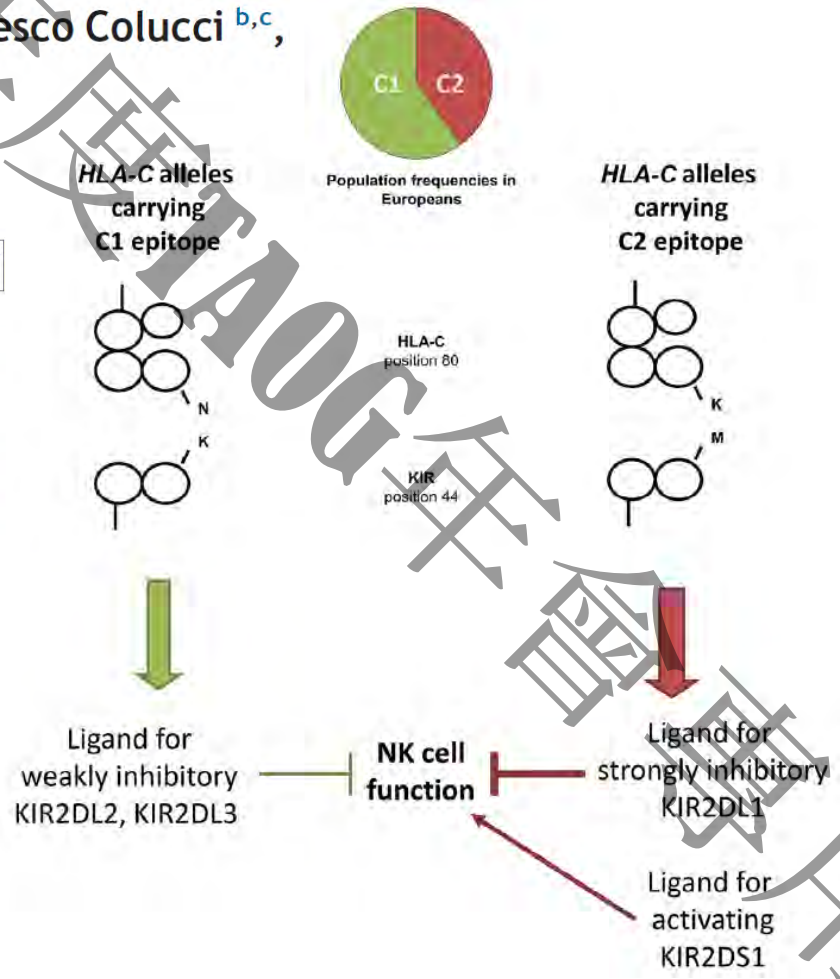
uNK與pNK無顯著相關

Hum Reprod Update. 2022 Jun 30;28(4):548-582.

Variation of maternal *KIR* and fetal *HLA-C* genes in reproductive failure: too early for clinical intervention

Ashley Moffett [a,b,*,1], Olympe Chazara [a,b], Francesco Colucci [b,c], Martin H Johnson [b,d]





uNK藉由KIR與HLA-C產生抑制或促進的細胞激素

學理上可行，但：

- 多數為小型的的觀察性研究
- 主要與Preeclampsia連結
- 研究設計控制變因多
- 分析KIR多型性尚未標準化

因此作者結論：
KIR/HLA genotyping尚未具備臨床使用條件

Reprod Biomed Online. 2016 Dec;33(6):763-769.

Intervention		Benefits versus harms (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR)[1]	Level of evidence for safety[1]	Considerations	Recommendation
Immunology tests and treatments	Immunology tests	Benefit on LBR or miscarriage rate is unclear due to lack of understanding of the mechanisms Harms: misinformation	⊕◯◯◯	No data	No rationale for these tests, no standardization	Peripheral blood tests for immune parameters and uNK-cell testing are **not recommended**. KIR and HLA genotyping is **currently not recommended for routine clinical use.**

Peripheral blood tests for immune parameters and uNK-cell testing are not recommended.

KIR and HLA genotyping is currently not recommended for routine clinical use.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

Evidence for the effectiveness of immunologic therapies in women with subfertility and/or undergoing assisted reproduction

Pedro Melo, M.D., M.Sc.,[a] Teresa Thornton, M.B.Ch.B.,[b] Arri Coomarasamy, M.D.,[b] and Ingrid Granne, D.Phil.[c]
[a] Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, United Kingdom; [b] Jersey General Hospital, St Helier, Jersey, United Kingdom; and [c] Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, United Kingdom

TABLE 2

Summary of findings of included randomized controlled trials for the outcome of ongoing pregnancy or live birth.

Intervention	Anticipated absolute effects (95% CI): Risk with placebo or no intervention	Risk with intervention	Risk ratio (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
Aspirin	230/1,000	239/1,000 (186–305)	RR, 1.04 (0.81–1.33)	1319 (6 RCTs)	⨁⨁⨁◯ Moderate[a]
Subcutaneous heparin	173/1,000	269/1,000 (139–520)	RR, 1.55 (0.80–3.00)	386 (3 RCTs)	⨁◯◯◯ Very low[a,b,c]
Corticosteroids	208/1,000	260/1,000 (154–437)	RR, 1.25 (0.74–2.10)	449 (5 RCTs)	⨁⨁◯◯ Low[a,b]
Aspirin plus corticosteroids	329/1,000	424/1,000 (319–562)	RR, 1.29 (0.97–1.71)	395 (1 RCT)	⨁⨁◯◯ Low[a,d]
Intrauterine G-CSF	138/1,000	210/1,000 (153–290)	RR, 1.52 (1.11–2.10)	844 (5 RCTs)	⨁⨁◯◯ Low[a,b]
Subcutaneous G-CSF	350/1,000	532/1,000 (269–1,000)	RR, 1.52 (0.77–3.00)	52 (1 RCT)	⨁◯◯◯ Very low[a,b,e]
Intralipid	140/1,000	250/1,000 (133–469)	RR, 1.78 (0.95–3.34)	244 (2 RCTs)	⨁◯◯◯ Very low[a,b,e]
IVIG	120/1,000	154/1,000 (38–619)	RR, 1.28 (0.32–5.16)	51 (1 RCT)	⨁⨁◯◯ Low[a,e]
r-hLIF	292/1,000	137/1,000 (70–265)	RR, 0.47 (0.24–0.91)	150 (1 RCT)	⨁⨁◯◯ Low[a,e]
PBMCs	160/1,000	325/1,000 (213–497)	RR, 2.03 (1.33–3.10)	312 (2 RCTs)	⨁◯◯◯ Very low[a,b,e]

作者結論：對於多種免疫治療都缺乏高品質證據

Fertil Steril. 2022 Jun;117(6):1144-1159.

Intervention		Benefits versus harms (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR)[1]	Level of evidence for safety[1]	Considerations	Recommendation
Immunology tests and treatments	Immunology treatments	Benefit on LBR and miscarriage rate are unclear Significant safety concerns	⊕⊕◯◯	No data	No rationale for these treatments, no standardization	Immunomodulating treatments, such as Intralipid, IVIG, rh-LIF, PBMCs, and anti-TNF, are **not recommended**.

Recommendation

Immunomodulating treatments, such as Intralipid, IVIG, rh-LIF, PBMCs, and anti-TNF, lack biological rationale, and evidence of clinical benefit. Additionally, potential serious side effects have been reported in other patient populations.

Immunomodulating treatments, such as Intralipid, IVIG, rh-LIF, PBMCs, and anti-TNF, are not recommended.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

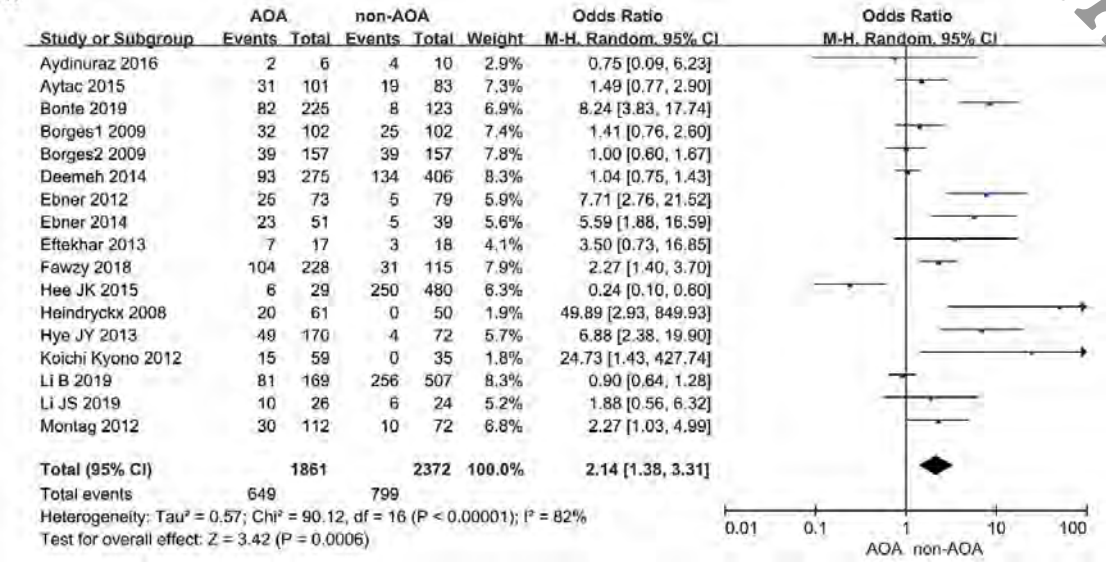
Assisted Oocyte Activation With Calcium Ionophore Improves Pregnancy Outcomes and Offspring Safety in Infertile Patients: A Systematic Review and Meta-Analysis

*Yinghua Shan†, Huishan Zhao†, Dongmei Zhao†, Jianhua Wang, Yuanqing Cui and Hongchu Bao**

Reproductive Medicine Centre, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, China

Search up to Feb 2022, **5 RCTs,**
9 prospective studies, 8 retrospective studies

A



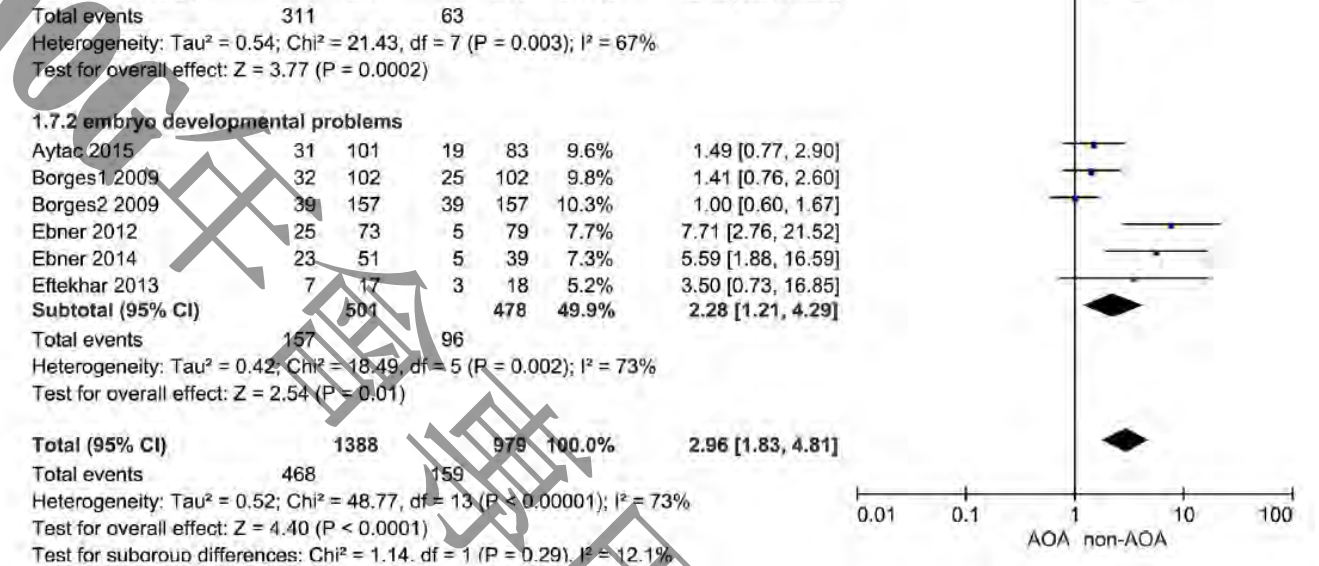
Study or Subgroup	AOA Events	AOA Total	non-AOA Events	non-AOA Total	Weight	Odds Ratio M-H, Random, 95% CI
Aydinuraz 2016	2	6	4	10	2.9%	0.75 [0.09, 6.23]
Aytac 2015	31	101	19	83	7.3%	1.49 [0.77, 2.90]
Bonte 2019	82	225	8	123	6.9%	8.24 [3.83, 17.74]
Borges1 2009	32	102	25	102	7.4%	1.41 [0.76, 2.60]
Borges2 2009	39	157	39	157	7.8%	1.00 [0.60, 1.67]
Deemeh 2014	93	275	134	406	8.3%	1.04 [0.75, 1.43]
Ebner 2012	25	73	5	79	5.9%	7.71 [2.76, 21.52]
Ebner 2014	23	51	5	39	5.6%	5.59 [1.88, 16.59]
Eftekhar 2013	7	17	3	18	4.1%	3.50 [0.73, 16.85]
Fawzy 2018	104	228	31	115	7.9%	2.27 [1.40, 3.70]
Hee JK 2015	6	29	250	480	6.3%	0.24 [0.10, 0.60]
Heindryckx 2008	20	61	0	50	1.9%	49.89 [2.93, 849.93]
Hye JY 2013	49	170	4	72	5.7%	6.88 [2.38, 19.90]
Koichi Kyono 2012	15	59	0	35	1.8%	24.73 [1.43, 427.74]
Li B 2019	81	169	256	507	8.3%	0.90 [0.64, 1.28]
Li JS 2019	10	26	6	24	5.2%	1.88 [0.56, 6.32]
Montag 2012	30	112	10	72	6.8%	2.27 [1.03, 4.99]
Total (95% CI)		**1861**		**2372**	**100.0%**	**2.14 [1.38, 3.31]**
Total events	649		799			

Heterogeneity: Tau² = 0.57; Chi² = 90.12, df = 16 (P < 0.00001); I² = 82%
Test for overall effect: Z = 3.42 (P = 0.0006)

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
AOA non-AOA

FIGURE 2 | **(A)** Forest plot of pregnancy rate between AOA treatment and non-AOA treatment patient groups using calcium ionophore. **(B)** The subgroup analysis of pregnancy rate between AOA treatment and non-AOA treatment patient groups.

B



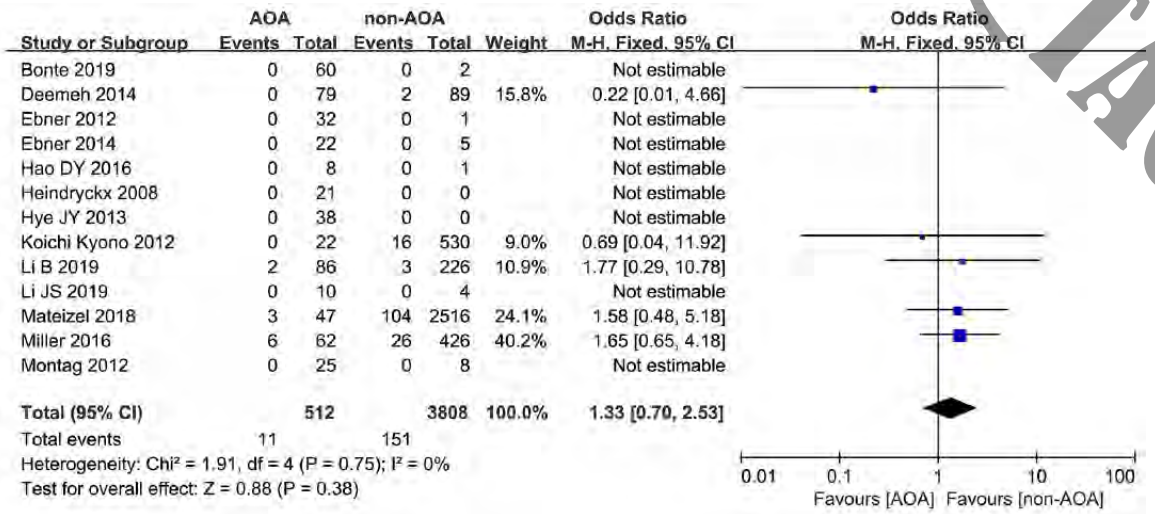
Study or Subgroup	AOA Events	AOA Total	non-AOA Events	non-AOA Total	Weight	Odds Ratio M-H, Random, 95% CI
1.7.1 previous ICSI cycles of no or low fertilization						
Aydinuraz 2016	1	6	4	10	2.9%	0.30 [0.02, 3.63]
Bonte 2019	82	225	8	123	9.0%	8.24 [3.83, 17.74]
Fawzy 2018	104	228	31	115	10.4%	2.27 [1.40, 3.70]
Heindryckx 2008	20	61	0	50	2.3%	49.89 [2.93, 849.93]
Hye JY 2013	49	170	4	72	7.5%	6.88 [2.38, 19.90]
Koichi Kyono 2012	15	59	0	35	2.3%	24.73 [1.43, 427.74]
Li JS 2019	10	26	6	24	6.7%	1.88 [0.56, 6.32]
Montag 2012	30	112	10	72	8.9%	2.27 [1.03, 4.99]
Subtotal (95% CI)		**887**		**501**	**50.1%**	**3.79 [1.90, 7.59]**
Total events	311		63			
Heterogeneity: Tau² = 0.54; Chi² = 21.43, df = 7 (P = 0.003); I² = 67%						
Test for overall effect: Z = 3.77 (P = 0.0002)						
1.7.2 embryo developmental problems						
Aytac 2015	31	101	19	83	9.6%	1.49 [0.77, 2.90]
Borges1 2009	32	102	25	102	9.8%	1.41 [0.76, 2.60]
Borges2 2009	39	157	39	157	10.3%	1.00 [0.60, 1.67]
Ebner 2012	25	73	5	79	7.7%	7.71 [2.76, 21.52]
Ebner 2014	23	51	5	39	7.3%	5.59 [1.88, 16.59]
Eftekhar 2013	7	17	3	18	5.2%	3.50 [0.73, 16.85]
Subtotal (95% CI)		**501**		**478**	**49.9%**	**2.28 [1.21, 4.29]**
Total events	157		96			
Heterogeneity: Tau² = 0.42; Chi² = 18.49, df = 5 (P = 0.002); I² = 73%						
Test for overall effect: Z = 2.54 (P = 0.01)						
Total (95% CI)		**1388**		**979**	**100.0%**	**2.96 [1.83, 4.81]**
Total events	468		159			
Heterogeneity: Tau² = 0.52; Chi² = 48.77, df = 13 (P < 0.00001); I² = 73%						
Test for overall effect: Z = 4.40 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.14, df = 1 (P = 0.29), I² = 12.1%						

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
AOA non-AOA

作者結論：使用Calcium Ionphore顯著改善ICSI低受精率者

Front Physiol. 2022 Jan 24:12:751905.

Intervention	Benefits versus harms (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR)[1]	Level of evidence for safety[1]	Considerations	Recommendation
Artificial oocyte activation	Beneficial in patients with previous fertilization failure or low fertilization rate and embryo developmental problems Safety to be considered (mechanism unclear), but not reported	⊕⊕◯◯	⊕⊕◯◯	Current studies show variation in ionophore stimulus with respect to concentration, exposure time, and number of exposures.	Artificial oocyte activation is **currently not recommended for routine clinical use**. Artificial oocyte activation is **recommended** for complete activation failure (0% 2PN), very low fertilization (<30% fertilization), or globozoospermia.



congenital birth defect rate between AOA treatment and non-AOA treatment patient groups using calcium ionophore.

Recommendation

There is evidence suggesting the effectiveness of AOA in certain situations such as complete activation failure (0% 2PN), very low fertilization (<30% fertilization), or globozoospermia. However, it is crucial to maintain continuous monitoring and assessment of the long-term effects and safety of children born through this procedure. Further research in this field is strongly encouraged and necessary.

Artificial oocyte activation is currently not recommended for routine clinical use.

Artificial oocyte activation is recommended for complete activation failure (0% 2PN), very low fertilization (<30% fertilization), or globozoospermia.

Fertil Steril. 2022 Jun;117(6):1144-1159.

Intervention		Benefits versus harms (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR)[1]	Level of evidence for safety[1]	Considerations	Recommendation
Mitochondrial replacement therapy		Few data, no benefit on LBR No data on safety	⊕◯◯◯	No data	In some cases, the acceptors' mtDNA haplotype takes over the donors' mtDNA	Mitochondrial replacement therapy to affect oocyte quality is **not recommended**.
***In vitro* activation of dormant follicles**		No comparative studies Safety, adverse effects, and long-term effects: no data	⊕◯◯◯	No data	For POI patients, options are limited.	*In vitro* activation of dormant follicles is **not recommended**.
IVM	Clinical IVM	No comparative studies Abnormal fertilization and development arrest reported	⊕◯◯◯	No data	It has been suggested that IVM encompasses a lower financial and emotional burden as compared to standard IVF/ICSI.	Clinical IVM and rescue-IVM or natural cycle IVF/M are **currently not recommended for routine clinical use**.
	Rescue IVM	LBR is lower, effect on miscarriage rate is unclear, most studies report increased miscarriages/decreased implantation. Safety of rescue IVM is questionable since these oocytes commonly have meiotic defects and are of poor quality.	⊕◯◯◯	⊕◯◯◯	/	
Artificial sperm activation		Higher LBR/CPR No data on safety Malformations reported in animal studies	⊕◯◯◯	⊕◯◯◯	/	Artificial sperm activation is **currently not recommended for routine clinical use**. Artificial sperm activation is **recommended** for patients with primary or secondary total asthenozoospermia which are not the result of axonemal structure defects.

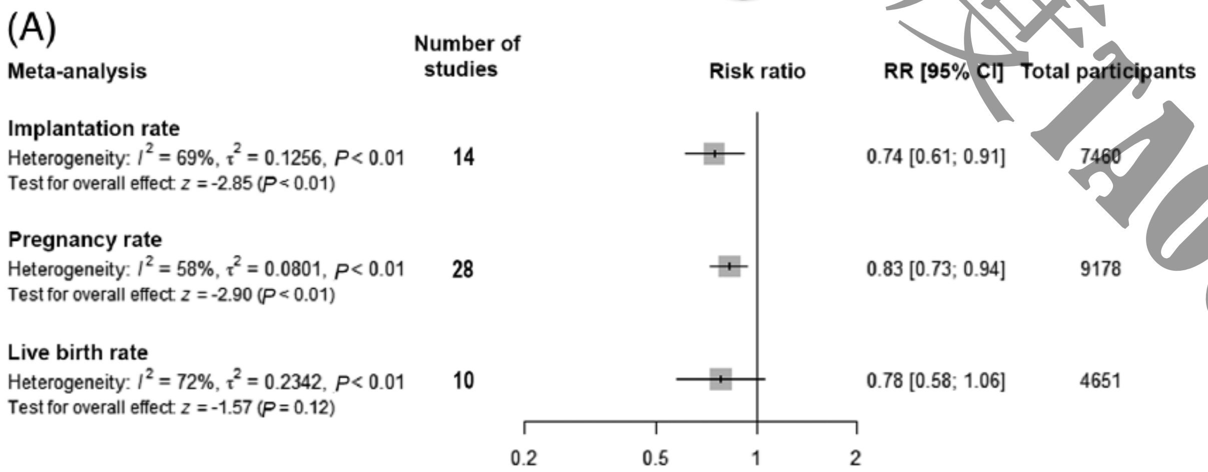
⊕◯◯◯, body of evidence is of very low quality (few observational data)

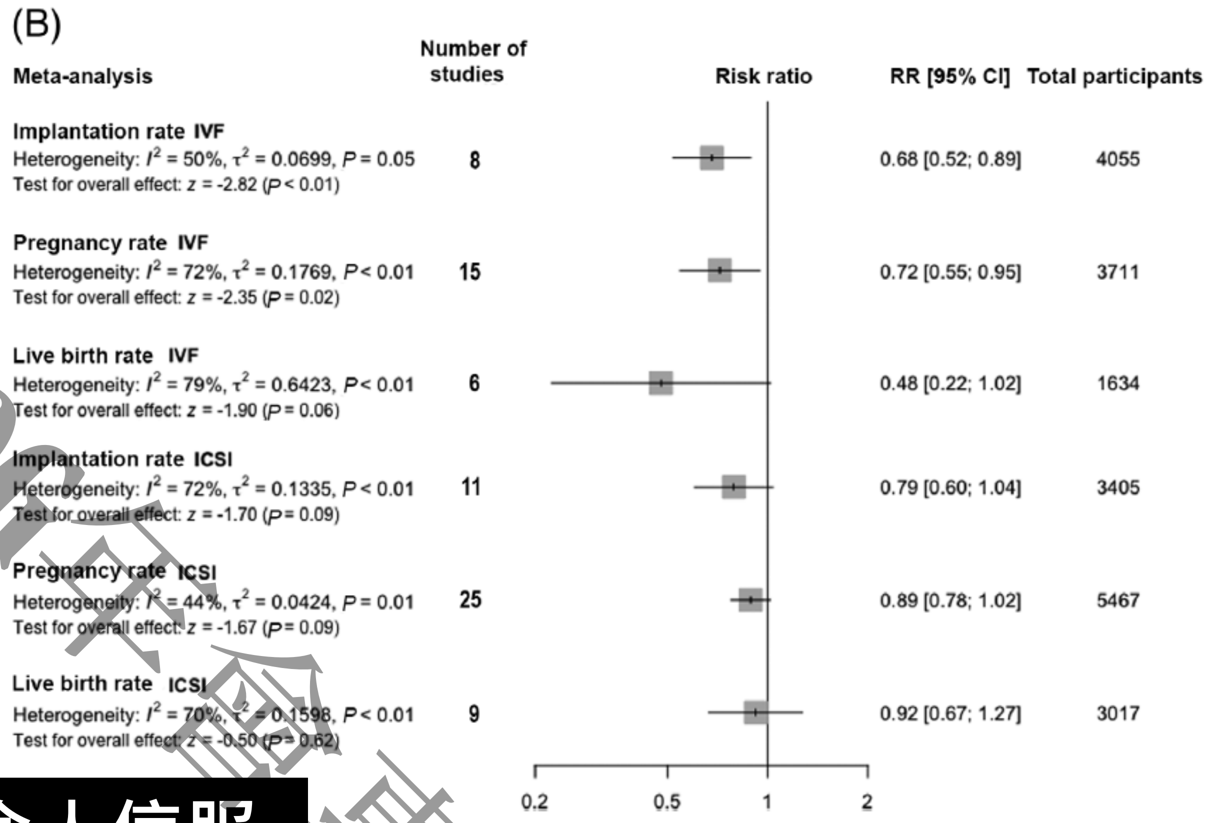
Hum Reprod. 2023 Nov 2;38(11):2062-2104.

Clinical implications of sperm DNA damage in IVF and ICSI: updated systematic review and meta-analysis

Jordi Ribas-Maynou[1,2]*, Marc Yeste[1,2], Nerea Becerra-Tomás[3,4,5,6], Kenneth I. Aston[7], Emma R. James[7,8] and Albert Salas-Huetos[7,†]*

Search up to Mar 2020, 32 studies included (IVF N=18, ICSI N=27)





作者結論SDF與IVF預後有關，但難令人信服

GPR認為：SDF預測懷孕或活產預後的效用仍未被確立(Inconclusive)

Hum Reprod. 2023 Nov 2;38(11):2062-2104.   Biol Rev Camb Philos Soc. 2021 Aug;96(4):1284-1300.

Safety

No safety issues have been reported.

Recommendation

There is insufficient evidence for the relevance of SDF tests to predict pregnancy or guide treatment decisions. Further research in this field is strongly recommended to enhance our understanding and knowledge.

Sperm DNA damage testing is currently not recommended for routine clinical use.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

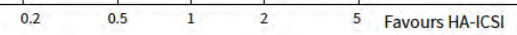
★ Advanced sperm selection techniques for assisted reproduction (Review)

Lepine S, McDowell S, Searle LM, Kroon B, Glujovsky D, Yazdani A

Cochrane Library

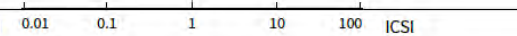
Analysis 1.1. Comparison 1 Hyaluronic acid sperm selection (HA-ICSI) versus ICSI, Outcome 1 Live birth per woman randomly assigned.

Study or subgroup	HA-ICSI n/N	ICSI n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Majumdar 2013	22/71	21/80		5.38%	1.18[0.71,1.96]
Miller 2019	379/1381	346/1371		94.62%	1.09[0.96,1.23]
Total (95% CI)	**1452**	**1451**		**100%**	**1.09[0.97,1.23]**
Total events: 401 (HA-ICSI), 367 (ICSI)					
Heterogeneity: Tau²=0; Chi²=0.1, df=1(P=0.76); I²=0%					
Test for overall effect: Z=1.43(P=0.15)					



Analysis 1.2. Comparison 1 Hyaluronic acid sperm selection (HA-ICSI) versus ICSI, Outcome 2 Miscarriage per woman randomly assigned.

Study or subgroup	HA-ICSI n/N	ICSI n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Majumdar 2013	3/71	7/80		6.28%	0.48[0.13,1.8]
Miller 2019	60/1381	96/1371		91.96%	0.62[0.45,0.85]
Troya 2015	1/47	2/55		1.76%	0.59[0.05,6.25]
Total (95% CI)	**1499**	**1506**		**100%**	**0.61[0.45,0.83]**
Total events: 64 (HA-ICSI), 105 (ICSI)					
Heterogeneity: Tau²=0; Chi²=0.13, df=2(P=0.94); I²=0%					
Test for overall effect: Z=3.19(P=0)					



使用HA Binding做精蟲選擇對活產率無影響，但可能減少流產率

Safety

No safety issues have been shown. However, the manufacturer's recommendation that the optimal temperature for sperm HBA binding is 30°C should be taken into consideration when performing ICSI using the PICSI dish. There are a variety of available commercial products which select sperm based on HA receptor expression.

Recommendation

The sperm hyaluronic binding assay has limited clinical value with regard to the prediction of fertilization or pregnancy, or guiding of treatment selection, which is further hampered by limitations in the standardization of the test. The method may offer an advantage in some categories of patients. Similarly, PICSI, as a sperm selection method, may have little or no effect on live birth or CPR.

Sperm hyaluronic binding assay is currently not recommended for routine clinical use.

Physiological ICSI is currently not recommended for routine clinical use.

Cochrane Database Syst Rev. 2019 Jul 30;7(7):CD010461.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

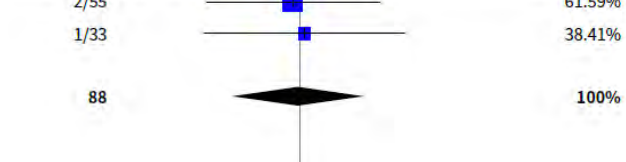
Advanced sperm selection techniques for assisted reproduction (Review)

Lepine S, McDowell S, Searle LM, Kroon B, Glujovsky D, Yazdani A

Cochrane Library

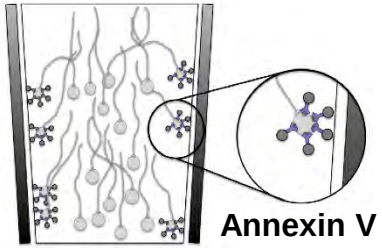
Analysis 3.1. Comparison 3 Magnetic-activated cell sorting (MACS) versus ICSI, Outcome 1 Live birth per woman randomly assigned.

Study or subgroup	MACS n/N	ICSI n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ziarati 2018	12/29	7/33		100%	1.95[0.89,4.29]
Total (95% CI)	**29**	**33**		**100%**	**1.95[0.89,4.29]**
Total events: 12 (MACS), 7 (ICSI)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.66(P=0.1)					



Analysis 3.2. Comparison 3 Magnetic-activated cell sorting (MACS) versus ICSI, Outcome 2 Miscarriage per woman randomly assigned.

Study or subgroup	MACS n/N	ICSI n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Troya 2015	1/33	2/55		61.59%	0.83[0.08,8.84]
Ziarati 2018	1/29	1/33		38.41%	1.14[0.07,17.39]
Total (95% CI)	**62**	**88**		**100%**	**0.95[0.16,5.63]**
Total events: 2 (MACS), 3 (ICSI)					
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.87); I²=0%					
Test for overall effect: Z=0.06(P=0.96)					



Annexin V magnetic selection

使用MAC做精蟲選擇對活產或流產率無影響 (very low-quality evidence)

Safety

There are no data available regarding the safety of using MACS.

Recommendation

There is insufficient evidence of an impact of MACS on pregnancy and LBRs compared to traditional sperm preparation methods.

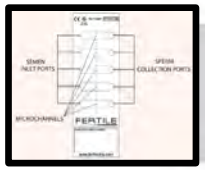
Magnetic-activated cell sorting is currently not recommended for routine clinical use.

Cochrane Database Syst Rev. 2019 Jul 30;7(7):CD010461.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

Prospective randomized controlled study of a microfluidic chip technology for sperm selection in male infertility patients

Şirin Aydın | Esra Bulgan Kılıçdağ | Pınar Çağlar Aytaç | Tayfun Çok | Erhan Şimşek | Bülent Haydardedeoğlu



ZyMōt FERTILITY, INC.

	Fertile chip ($n = 64$)	Control group ($n = 64$)	p
Fertilization rate (%)	60.84 ± 19.10	57.88 ± 20.39	0.41
Total number of embryos after ICSI (n)*	6.16 ± 3.99	7.77 ± 4.78	**0.045***
Total number of grade 1 embryos after ICSI (n)	1.84 ± 2.15	2.13 ± 2.46	0.47
Total number of grade 2 embryos after ICSI (n)	2.36 ± 6.97	1.87 ± 2.40	0.59
Total number of grade 3 embryos after ICSI (n)*	1.84 ± 2.68	3.04 ± 3.95	**0.046***
Number of transferred embryos (n)	1.44 ± 0.50	1.39 ± 0.49	0.59
Transferred grade 1 embryo (n)	0.83 ± 0.65	0.75 ± 0.61	0.48
Transferred grade 2 embryo (n)	0.53 ± 0.73	0.53 ± 0.73	1.0
Transfer day			
Third day (n)	28 (44.4%)	19 (30.3%)	0.34
Fourth day (n)	1 (1.6%)	3 (4.8%)	
Fifth day (n)	33 (52.4%)	40 (63.5%)	
Sixth day (n)	1 (1.6%)	1 (1.6%)	
Number of patients with surplus embryo after transfer (n)	37 (58.7%)	35 (55.6%)	0.85

*$p < 0.05$. Bold values indicates statistical significant.

TABLE 4 Pregnancy outcome

	Fertile chip ($n = 64$)	Control group ($n = 64$)	p
Implantation rate, %	50 ± 44	31 ± 43	**0.02***
Pregnancy rate/ cycles, % (n)*	62.5 (40/64)	45.3 (29/64)	**0.038***
Chemical pregnancy rate, % (n)	3.2 (2/40)	8.1 (5/29)	0.22
Abortion rate, % (n)	8.1 (5/40)	3.2 (2/29)	0.22
Multiple pregnancy rate, % (n)	4.8 (3/40)	1.6 (1/29)	0.30
Clinical pregnancy rate, % (n)	59.4 (38/64)	35.9 (23/64)	**0.006***
Live birth rate/ cycle % (n)	46.8(29/62)	25(16/64)	**0.009***

小規模RCT顯示，Microfluidic chip選精蟲對活產有幫助

Andrologia. 2022 Jul;54(6):e14415.

Recommendation

While a single small RCT has demonstrated a small increase in LBR, an observational study showed no benefit of using microfluidics for sperm selection. Further research is required to validate these findings and provide a more robust evidence base before making widespread recommendations.

Microfluidics can be considered.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction (Review)

Teixeira DM, Miyague AH, Barbosa MAP, Navarro PA, Raine-Fenning N, Nastri CO, Martins WP

Cochrane Library

Summary of findings for the main comparison.

Regular (ICSI) compared with ultra-high magnification (IMSI) for assisted reproduction

Patient or population: couples undergoing assisted reproduction treatment

Setting: fertility clinics

Intervention: sperm selection under ultra-high magnification (IMSI)

Comparison: sperm selection under regular magnification (ICSI)

13 RCTs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	ICSI	IMSI			
Live birth per allocated couple	243 per 1000	269 per 1000 (216 to 337)	RR 1.11 (0.89 to 1.39)	929 (5 studies)	⊕⊖⊖⊖ very low[a,b]
Miscarriage per allocated couple	70 per 1000	75 per 1000 (54 to 103)	RR 1.07 (0.78 to 1.48)	2297 (10 studies)	⊕⊖⊖⊖ very low[b,c]
Miscarriage per clinical pregnancy	230 per 1000	207 per 1000 (157 to 276)	RR 0.90 (0.68 to 1.20)	783 (10 studies)	⊕⊖⊖⊖ very low[b,c]
Clinical pregnancy per allocated couple	320 per 1000	394 per 1000 (355 to 438)	RR 1.23 (1.11 to 1.37)	2775 (13 studies)	⊕⊖⊖⊖ very low[c,d,e]
Congenital abnormalities per live birth	No studies reported on this outcome				

IMSI比之ICSI對活產率無影響

The method of IMSI can be time-consuming and impacts workflow, especially in laboratories that do not use the method routinely.

Safety

There are no data available regarding the safety of using IMSI.

Recommendation

Based on the current available data, there is uncertainty regarding the clinical benefit of IMSI compared to conventional ICSI. Further research in this field is necessary to gain a better understanding of the potential benefits of IMSI as well as its implications.

Intracytoplasmic morphologic sperm injection is currently not recommended for routine clinical use.

Cochrane Database Syst Rev. 2020 Feb 21;2(2):CD010167.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

Growth factor-supplemented embryo culture medium

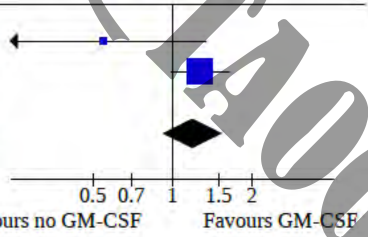
GM-CSF (granulocyte macrophage colony-stimulating factor) supplementation in culture media for women undergoing assisted reproduction (Review)

Armstrong S, MacKenzie J, Woodward B, Pacey A, Farquhar C

Cochrane Library

Analysis 1.1. Comparison 1: GM-CSF-supplemented culture medium versus culture medium not supplemented with GM-CSF, Outcome 1: Live birth

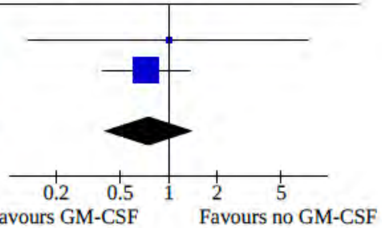
Study or Subgroup	GM-CSF Events	GM-CSF Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Rose 2020	11	50	17	50	11.1%	0.55 [0.23 , 1.33]
Ziebe 2013	168	654	145	678	88.9%	1.27 [0.99 , 1.64]
Total (95% CI)		**704**		**728**	**100.0%**	**1.19 [0.93 , 1.52]**
Total events:	179		162			



Heterogeneity: Chi² = 3.19, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1: GM-CSF-supplemented culture medium versus culture medium not supplemented with GM-CSF, Outcome 2: Miscarriage

Study or Subgroup	GM-CSF Events	GM-CSF Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Rose 2020 (1)	2	50	2	50	7.7%	1.00 [0.14 , 7.39]
Ziebe 2013	17	654	24	678	92.3%	0.73 [0.39 , 1.37]
Total (95% CI)		**704**		**728**	**100.0%**	**0.75 [0.41 , 1.36]**
Total events:	19		26			



Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable

Summary of findings 1. GM-CSF-supplemented culture media compared to culture media not supplemented with GM-CSF for women undergoing assisted reproduction

GM-CSF-supplemented culture media compared to culture media not supplemented with GM-CSF for women undergoing assisted reproduction

Patient or population: women undergoing assisted reproduction
Setting: fertility clinics
Intervention: GM-CSF-supplemented culture media
Comparison: culture medium not supplemented with GM-CSF

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with culture media not supplemented with GM-CSF	Risk with GM-CSF-supplemented culture media			
Live birth or ongoing pregnancy	Study population		OR 1.19 (0.93 to 1.52)	1432 (2 RCTs)	⊕⊕◯◯ LOW 1 2
	223 per 1000	254 per 1000 (210 to 303)			
Miscarriage	Study population		OR 0.75 (0.41 to 1.36)	1432 (2 RCTs)	⊕⊕◯◯ LOW 3
	36 per 1000	27 per 1000 (15 to 48)			
Clinical pregnancy	Study population		OR 1.16 (0.93 to 1.45)	1532 (3 RCTs)	⊕⊕◯◯ LOW 1 4
	263 per 1000	293 per 1000 (250 to 342)			

Recommendation

There is insufficient evidence for both the efficacy and safety of using culture media supplemented with GM-CSF. Further research is needed to better understand the potential benefits and risks associated with culture media supplements.

Growth factor-supplemented embryo culture medium is not recommended.

Cochrane Database Syst Rev. 2020 Jul 16;7(7):CD013497.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

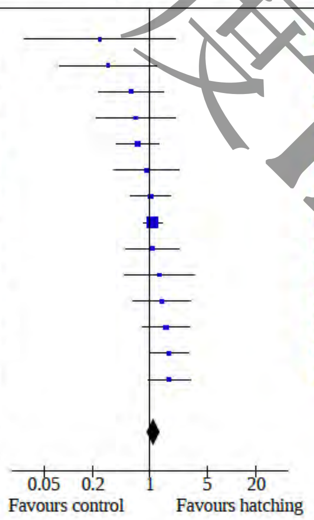
Assisted hatching on assisted conception (in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI)) (Review)

Lacey L, Hassan S, Franik S, Seif MW, Akhtar MA

Cochrane Library

Figure 4. Forest plot of comparison: 1 Live birth rate, outcome: 1.1 Live birth per woman randomised.

Study or Subgroup	Assisted hatching Events	Assisted hatching Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Hurst 1998	2	13	3	7	1.2%	0.24 [0.03 , 2.03]	+	?	?	?	+	+
Germond 2004	3	84	8	74	3.1%	0.31 [0.08 , 1.20]	+	?	?	+	+	+
Balakier 2009	13	45	16	39	4.5%	0.58 [0.24 , 1.45]	+	?	+	+	+	+
Safari 2017	7	30	10	32	2.8%	0.67 [0.22 , 2.07]	?	?	?	-	-	-
Shi 2016	29	82	42	96	9.3%	0.70 [0.38 , 1.29]	?	?	-	+	?	+
Lanzendorf 1998	12	41	15	48	3.6%	0.91 [0.37 , 2.26]	+	?	+	+	?	+
Sagoskin 2007	55	121	37	82	9.0%	1.01 [0.58 , 1.78]	+	?	?	?	+	+
Ge 2008	156	487	144	473	37.0%	1.08 [0.82 , 1.41]	+	?	+	+	+	+
Hellebaut 1996	21	60	20	60	4.8%	1.08 [0.51 , 2.29]	+	?	-	?	+	+
Razi 2013	10	90	8	92	2.6%	1.31 [0.49 , 3.49]	+	?	+	+	+	+
Petersen 2005	17	75	13	75	3.7%	1.40 [0.62 , 3.13]	+	?	?	+	+	+
Cohen 1992	34	69	26	68	4.9%	1.57 [0.80 , 3.10]	+	?	+	?	+	+
Nada 2018	40	158	25	150	7.1%	1.69 [0.97 , 2.97]	+	?	?	-	-	?
Wan 2014	39	96	29	102	6.2%	1.72 [0.95 , 3.11]	?	?	?	?	+	?
Total (95% CI)		**1451**		**1398**	**100.0%**	**1.09 [0.92 , 1.29]**						
Total events:	438		396									



Heterogeneity: Chi² = 16.31, df = 13 (P = 0.23); I² = 20%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

14 RCTs, N = 2849; low-quality evidence

Summary of findings 1. Assisted hatching compared to no assisted hatching for women undergoing assisted conception

Assisted hatching compared to no assisted hatching for women undergoing assisted conception

Patient or population: women undergoing assisted conception
Setting: clinic
Intervention: assisted hatching
Comparison: no assisted hatching

Outcomes	Anticipated absolute effects* (95% CI): Risk with no assisted hatching	Anticipated absolute effects* (95% CI): Risk with assisted hatching	Relative effect (95% CI)	№. of participants (studies)	Quality of evidence (GRADE)	Comments
Live births per woman randomised	283 per 1000	301 per 1000 (267 to 338)	OR 1.09 (0.92 to 1.29)	2849 (14 RCTs)	⊕⊕⊝⊝ LOW[a]	
Multiple pregnancy rate per woman randomised	91 per 1000	121 per 1000 (102 to 144)	OR 1.38 (1.13 to 1.68)	4308 (18 RCTs)	⊕⊕⊝⊝ LOW[b]	
Clinical pregnancy rate per woman randomised	322 per 1000	363 per 1000 (341 to 387)	OR 1.20 (1.09 to 1.33)	7249 (39 RCTs)	⊕⊕⊝⊝ LOW[b]	
Miscarriage rate per woman randomised	53 per 1000	60 per 1000 (44 to 81)	OR 1.13 (0.82 to 1.56)	2810 (17 RCTs)	⊕⊝⊝⊝ VERY LOW[c]	

作者結論:

- AH可能些許**增加CPR**，尤其在**Poor prognosis**的個案較顯著；對活產率的影響仍不確定
- AH可能**增加多胞胎率** (low-quality evidence)

Recommendation

Assisted hatching has no significant impact on LBR. In addition, there may be risks to AH such as higher rates of multiple pregnancies and monozygotic twinning.

Assisted hatching is not recommended.

旭陽診所
Professor Chang Fertility Clinic

Cochrane Database Syst Rev. 2021 Mar 17;3(3):CD001894.
Hum Reprod. 2023 Nov 2;38(11):2062-2104.

The role of assisted hatching in in vitro fertilization: a guideline

Practice Committee of the American Society for Reproductive Medicine

部分狀況例如為了 **準備PGT-A的切片於是在D3或D5做AH**, 或為了**冷凍胚胎前使胚胎塌陷**, 這些是屬於**常規使用**, 不在本指引的討論範圍.

DOES AH IMPROVE LIVE BIRTH RATES WITH FRESH EMBRYO TRANSFER? ARE THERE SUBSETS OF PATIENTS WHO BENEFIT?

Recommendation

- Laser-AH should not be routinely recommended for all patients undergoing IVF. There are insufficient data to make a recommendation for selected groups, such as patients with poor prognosis. (Strength of evidence: B/C; strength of recommendation: moderate.)

DOES AH INCREASE MONOZYGOTIC TWINNING?

DOES AH IMPROVE LIVE BIRTH RATES WITH FROZEN EMBRYO TRANSFERS? ARE THERE SUBSETS OF PATIENTS WHO BENEFIT?

Recommendation

- There are insufficient data to make a recommendation for laser-AH in FET cycles. (Strength of evidence: B; strength of recommendation: moderate.)

Recommendation

- There is insufficient evidence to definitely conclude that AH is associated with MZT, as the outcome is rare and the available studies have conflicting findings. (Strength of evidence: B; strength of recommendation: moderate.)

Fertil Steril. 2022 Jun;117(6):1177-1182.

Table 3. Overview of the studies published to date that compare PGT-A with conventional IVF treatment.

RCT	Patients	Controls	Embryo biopsy	Genetic platform	LBR (unless otherwise indicated)	Miscarriage rate
Yang *et al.* (2012b)	55 good-prognosis patients, 1st IVF cycle Age: 31.2 ± 2.5	48 controls Age: 31.5 ± 2.7	Blastocyst	aCGH	Higher[1] 38/55 (69.1%) vs 20/48 (41.7%) (P = 0.009) (per ET)	No difference 1/55 (2.6%) vs 2/48 (9.1%) (P = 0.597)
Forman *et al.* (2013)	89 single euploid blastocyst transfer, normal ovarian reserve, ≤1 previous IVF failure Age: 35.1 ± 3.9	86 double blastocyst transfer Age: 34.5 ± 4.7	Blastocyst	qPCR	No difference[2] 60.7% vs 65.1% (RR 0.9; 95% CI 0.7 to 1.2) (per ET)	Not reported
Scott *et al.* (2013)	134 blastocysts/ 72 patients with normal ovarian reserve, ≤1 previous IVF failure Age: 32.2 ± 0.5	163 blastocysts/ 83 patients Age: 32.4 ± 0.5	Blastocyst	qPCR	Higher 61/72 (84.7%) vs 56/83 (67.5%) (RR 1.26; 95% CI 1.06 to 1.53; P = 0.01) (per ET)	No difference 7/61 (11.5%) vs 14/70 (20.0%); P = 0.2)
Rubio *et al.* (2017)	538 Day 3 embryos from 138 patients Age: 38–41	581 Day 3 embryos/ 140 patients Age: 38–41	Day 3	aCGH	No difference 44/138 (31.9%) vs 26/140 (18.6%) (OR 2.381, 95% CI 1.343 to 4.223)	Lower 1/37 (2.7%) vs 16/41 (39.0%) (OR 0.06, 95% CI 0.008 to 0.48)
Verpoest *et al.* (2018)	205 patients (177 transfers) Age: 38.6 ± 1.4	191 patients (249 transfers) Age: 38.6 ± 1.4	Polar body	aCGH	No difference 50/205 (24%) vs 45/ 191(24%) (RR 1.06; 95% CI 0.75 to 1.50; P = 0.75) (per patient)	Lower 14/205 (7%) vs 27/ 191 (14%) (RR 0.48; 95% CI 0.26 to 0.90; P = 0.02)
Munné *et al.* (2019)	330 patients undergoing IVF with at least two blastocysts that could be biopsied Age: 33.7 ± 3.59	331 patients undergoing IVF with at least two blastocysts that could be biopsied Age: 33.8 ± 3.58	Blastocyst	NGS	No difference[3] 137/274 (50%) vs 143/313 (46%) (per ET) per ITT (per patient): 138/ 330 (41.8%) vs 144/ 331 (43.5%)	No difference 27/274 (9.9%) vs 30/ 313 (9.6%)
Yan *et al.* (2021)	606 women with three or more good-quality blastocysts Age: 29.1 ± 3.6	606 women with three or more good-quality blastocysts Age: 29.2 ± 3.5	Blastocyst	NGS	Lower (per patient) 458/606 (77.2%) vs 496/606 (81.8%) (absolute difference, −4.6 percentage points; 95% CI −9.2 to −0.0; P < 0.001)	Lower 8.7% and 12.6%, (RR 0.69; 95% CI 0.49 to 0.98)

GPR評論：

- **PGT-A並未顯著增加第一次植入後活產率**
- **但目前共識是，PGT-A作為一個檢查，”活產”並非評估有效性的適切指標，而應為”流產率”或”達到懷孕時間”**
- **性價分析認為PGT-A對於AMA且有高數量囊胚時，可藉由減少無效植入而節省費用**

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

Recommendation

The current available data for PGT-A using current methodology for genetic analysis indicate limited improvement in LBR. The supposition that PGT-A reduces miscarriages or time-to-pregnancy in specific patient groups, such as those with advanced maternal age, is based on *post hoc* analyses (Munné *et al.*, 2019) and requires further investigation to establish its validity.

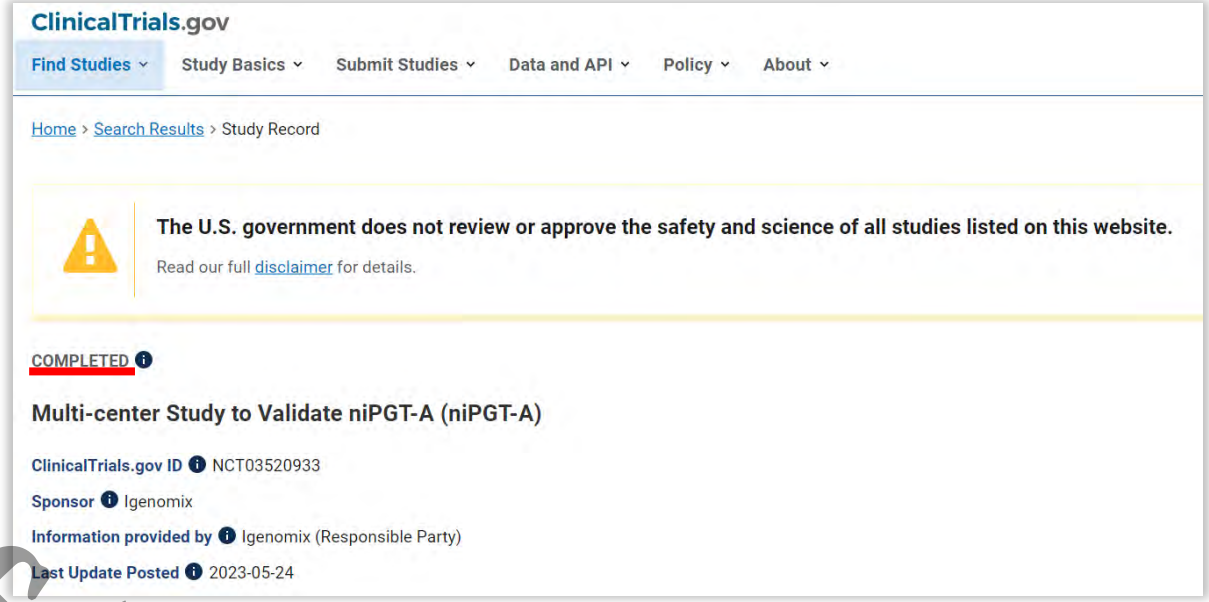
Pre-implantation genetic testing for aneuploidy is currently not recommended for routine clinical use.

human reproduction update

Non-invasive preimplantation genetic testing (niPGT): the next revolution in reproductive genetics?

Megan Leaver[1], and Dagan Wells[1,2,*]

- Uncertainty over the optimal method
- Questions concerning the reliability and clinical utility of the data produced
- PGT based upon blastocentesis or SCM samples should, at present, only be carried out in the context of **pre-clinical studies** and carefully designed clinical pilot investigations
- Further studies should be encouraged



Recommendation

At present, niPGT is to be considered in the research phase. Further studies and validation are needed before considering its widespread use in clinical practice.

Non-invasive PGT is currently not recommended for routine clinical use.

Hum Reprod Update. 2020 Jan 1;26(1):16-42.

Time-lapse systems for embryo incubation and assessment in assisted reproduction (Review)

Armstrong S, Bhide P, Jordan V, Pacey A, Farquhar C

Cochrane Library

比較培養環境

Summary of findings for the main comparison. TLS with conventional morphological assessment of still TLS images compared to conventional incubation and assessment for embryo incubation and assessment in assisted reproduction

TLS with conventional morphological assessment of still TLS images compared to conventional incubation and assessment for embryo incubation and assessment in assisted reproduction

Patient or population: couples undergoing assisted reproductive technology
Setting: fertility clinic
Intervention: TLS with conventional morphological assessment of still TLS images
Comparison: conventional incubation and assessment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with conventional incubation and assessment	Risk with TLS with conventional morphological assessment of still TLS images				
Live birth	333 per 1,000	267 per 1,000 (190 to 361)	OR 0.73 (0.47 to 1.13)	440 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	
Miscarriage	37 per 1,000	83 per 1,000 (28 to 222)	OR 2.25 (0.84 to 6.02)	440 (2 RCTs)	⊕⊕⊖⊖ Low[b]	

作者結論：

- 目前證據並未顯示TLS與傳統培養箱的差別

比較軟體選胚

Summary of findings 2. TLS utilising embryo selection software compared to TLS with conventional morphological assessment of still TLS images for embryo incubation and assessment in assisted reproduction

TLS utilising embryo selection software compared to TLS with conventional morphological assessment of still TLS images for embryo incubation and assessment in assisted reproduction

Patient or population: couples undergoing assisted reproductive technology
Setting: fertility clinic
Intervention: TLS utilising embryo selection software
Comparison: TLS with conventional morphological assessment of still TLS images

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TLS with conventional morphological assessment of still TLS images (trial design 2)	Risk with TLS utilizing embryo selection software				
Live birth	0 per 1000	0 per 1000	not estimable	0 RCTs		
Miscarriage	54 per 1,000	74 per 1,000 (35 to 147)	OR 1.39 (0.64 to 3.01)	463 (2 RCTs)	⊕⊖⊖⊖ Very low[a]	
Stillbirth	0 per 1000	0 per 1000	not estimable	0 RCTs		
Clinical pregnancy	537 per 1,000	529 per 1,000 (437 to 622)	OR 0.97 (0.67 to 1.42)	463 (2 RCTs)	⊕⊕⊖⊖ Low[b]	

綜合比較

Summary of findings 3. TLS utilising embryo selection software compared to conventional incubation and assessment for embryo incubation and assessment in assisted reproduction

TLS utilising embryo selection software compared to conventional incubation and assessment for embryo incubation and assessment in assisted reproduction

Patient or population: couples undergoing ART
Setting: fertility clinic
Intervention: TLS utilising embryo selection software
Comparison: conventional incubation and assessment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with conventional incubation and assessment	Risk with TLS utilising embryo selection software				
Live birth	381 per 1,000	461 per 1,000 (365 to 586)	OR 1.21 (0.96 to 1.54)	1017 (2 RCTs)	⊕⊖⊖⊖ Very low[a]	
Miscarriage	94 per 1,000	70 per 1,000 (48 to 101)	OR 0.73 (0.49 to 1.08)	1351 (3 RCTs)	⊕⊖⊖⊖ Very low[b]	
Stillbirth	0 per 1000	0 per 1000	not estimable	0 RCTs		
Clinical pregnancy	545 per 1,000	584 per 1,000 (530 to 635)	OR 1.17 (0.94 to 1.45)	1351 (3 RCTs)	⊕⊖⊖⊖ Very low[c]	

Cochrane Database Syst Rev. 2019 May 29;5(5):CD011320.

Clinical outcomes of uninterrupted embryo culture with or without time-lapse-based embryo selection versus interrupted standard culture (SelecTIMO): a three-armed, multicentre, double-blind, randomised controlled trial

D C Kieslinger, C G Vergouw, L Ramos, B Arends, M H J M Curfs, E Slappendel, E H Kostelijk, M H E C Pieters, D Consten, M O Verhoeven, D E Besselink, F Broekmans, B J Cohlen, J M J Smeenk, S Mastenbroek, C H de Koning, Y M van Kasteren, E Moll, J van Disseldorp, E A Brinkhuis, E A M Kuijper, W M van Baal, H G I van Weering, P J Q van der Linden, M H Gerards, P M Bossuyt, M van Wely, C B Lambalk

Netherland, From 2016, **largest TL RCT studies**, **N=1731**, <42 y, avg 34 y/o, TLE (TL + EEVA) vs TLR (TL + routine morphology) vs Control, Fresh D3 ET + FET w/i 12 mo

	TLE group	TLR group	Control group	TLE vs TLR		TLR vs control		TLE vs control	
				OR (95% CI)	AD (95% CI)	OR (95% CI)	AD (95% CI)	OR (95% CI)	AD (95% CI)
Cumulative results (intention to treat)									
Cumulative positive hCG rate	357/577 (61·9%)	355/579 (61·3%)	357/575 (62·1%)	1·02 (0·81 to 1·30)	0·56 (−5·78 to 6·89)	0·96 (0·76 to 1. 22)	−0·77 (−7·11 to 5·57)	0·99 (0·78 to 1·26)	−0·22 (−6·56 to 6·13)
Cumulative clinical pregnancy rate	328/577 (56·9%)	336/579 (58·0%)	328/575 (57·0%)	0·95 (0·76 to 1·20)	−1·19 (−7·63 to 5·26)	1·04 (0·82 to 1·32)	0·99 (−5·47 to 7·44)	0·99 (0·78 to 1·25)	−0·20 (−6·66 to 6·26)
Cumulative OPR	293/577 (50·8%)	295/579 (51·0%)	284/575 (49·4%)	0·99 (0·79 to 1·25)	−0·17 (−6·69 to 6·35)	1·06 (0·84 to 1·33)	1·56 (−4·96 to 8·08)	1·06 (0·84 to 1·33)	1·39 (−5·14 to 7·92)
Cumulative livebirth rate	281/577 (48·7%)	280/579 (48·4%)	277/575 (48·2%)	1·01 (0·81 to 1·28)	0·34 (−6·17 to 6·86)	1·01 (0·80 to 1·27)	0·19 (−6·33 to 6·71)	1·02 (0·81 to 1·29)	0·53 (−6·00 to 7·05)
Cumulative miscarriage rate	92/577 (15·9%)	94/579 (16·2%)	100/575 (17·4%)	0·98 (0·71 to 1·34)	−0·29 (−5·13 to 4·55)	0·92 (0·68 to 1·25)	−1·16 (−6·00 to 3·69)	0·90 (0·66 to 1·23)	−1·45 (−6·29 to 3·40)
Fresh embryo transfer results (intention to treat)									
Positive hCG rate	217/577 (37·6%)	213/579 (36·8%)	233/575 (40·5%)	1·03 (0·82 to 1·31)	0·82 (−5·51 to 7·1)	0·85 (0·67 to 1·08)	−3·73 (−10·01 to 2·0)	0·88 (0·70 to 1·12)	−2·91 (−9·26 to 3·43)
Clinical pregnancy rate	199/577 (34·5%)	200/579 (34·5%)	206/575 (35·8%)	1·00 (0·78 to 1·27)	−0·05 (−6·27 to 6·16)	0·94 (0·74 to 1·20)	−1·28 (−7·50 to 4·94)	0·94 (0·74 to 1·20)	−1·34 (−7·56 to 4·89)
OPR	171/577 (29·6%)	170/579 (29·4%)	180/575 (31·3%)	1·01 (0·79 to 1·31)	0·28 (−5·70 to 6·25)	0·91 (0·71 to 1·17)	−1·94 (−4·04 to 7·93)	0·92 (0·72 to 1·19)	−1·67 (−7·65 to 4·32)
Livebirth rate	164/577 (28·4%)	163/579 (28·2%)	175/575 (30·4%)	1·01 (0·78 to 1·31)	0·27 (−5·64 to 6·18)	0·90 (0·69 to 1·15)	−2·28 (−8·20 to 3·64)	0·91 (0·70 to 1·17)	−2·01 (−7·94 to 3·91)
Miscarriage rate	49/577 (8·5%)	46/579 (7·9%)	54/575 (9·4%)	1·08 (0·71 to 1·64)	0·55 (−3·11 to 4·20)	0·80 (0·55 to 1·80)	−1·45 (−5·11 to 2·21)	0·89 (0·60 to 1·34)	−0·90 (−4·56 to 2·76)

作者結論：

- **使用TLS，活產率或累積活產率或到達懷孕時間，與傳統培養箱均無顯著差異**

Lancet. 2023 Apr 29;401(10386):1438-1446.

human reproduction open

ESHRE PAGES

Good practice recommendations for the use of time-lapse technology†

ESHRE Working group on Time-lapse technology, Susanna Apter[1], Thomas Ebner[2], Thomas Freour[3], Yves Guns[4], Borut Kovacic[5], Nathalie Le Clef[6], Monica Marques[7], Marcos Meseguer[8], Debbie Montjean[9], Ioannis Sfontouris[10], Roger Sturmey[11], and Giovanni Coticchio[12,*]

- TLI has **NOT been shown to improve LBRs**
- A tool for **research, teaching, standardizing assessment, facilitating laboratory workflows** and **quality control**
- These functions are not considered an add-on

Safety

Kirkegaard *et al.* (2012) reported no difference in safety between TLI and embryo culture in conventional benchtop incubators.

Recommendation

Incubators that utilize TLI have been demonstrated to be a convenient and effective tool for observing the continuous development of embryos. However, the use of TLI, with or without embryo selection software, has not shown conclusive evidence of improving the LBR or the time-to-pregnancy.

Time-lapse imaging is not recommended as a tool to improve live birth rates.

Intervention		Benefits versus harms (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR)[1]	Level of evidence for safety[1]	Considerations	Recommendation
Platelet-rich plasma	Intrauterine PRP administration	Evidence of benefit on CPR, no evidence of an effect on miscarriage rate No evidence of harm	⊕◯◯◯	⊕◯◯◯	Current studies include a small sample size and heterogenous study population in addition to different dosages of PRP	Intrauterine administration of platelet-rich plasma is **not recommended**.
	Intraovarian PRP administration	Mostly uncontrolled studies, no data on effect on LBR or miscarriage rate No evidence of harm	No data	No data		Intraovarian administration of platelet-rich plasma is **not recommended**.
Duostim		No data of benefit on LBR or miscarriage rate Harms are expected to be similar to standard OS	No data	No data	An RCT comparing duostim with two conventional stimulations has not been performed to date	Duostim is **currently not recommended for routine clinical use**.
Intravaginal and intrauterine culture device	Intravaginal culture device	No evidence of a benefit on LBR No data on harms	⊕◯◯◯	No data	An embryologist and an IVF lab are still required	Intravaginal or intrauterine culture devices are **currently not recommended for routine clinical use**.
	Intrauterine culture device	One small study showing no benefit on LBR No data on harms	⊕◯◯◯	No data		

Recommendation

While the available data regarding intrauterine PRP in the context of ART show promise, it is important to acknowledge the significant issues related to their quality and the overall lack of safety data. Further investigation and well-designed studies are necessary to assess the efficacy and ensure the safety of this procedure before considering its use in routine clinical practice.

Intrauterine administration of platelet-rich plasma is not recommended.

Recommendation

Currently, there is a lack of RCTs or controlled studies that demonstrate the efficacy of intraovarian PRP. Furthermore, the available data regarding the safety of intraovarian PRP in the context of ART are limited. Further investigation and well-designed studies are necessary to assess its efficacy and ensure its safety before considering its use in routine clinical practice.

Intraovarian administration of platelet-rich plasma is not recommended.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

human reproduction open
ESHRE PAGES

ESHRE guideline: ovarian stimulation for IVF/ICSI†

The ESHRE Guideline Group on Ovarian Stimulation,

Is the addition of adjuvants in OS meaningful in terms of efficacy and safety?

Routine use of adjuvant metformin before and/or during OS is not recommended with the GnRH antagonist protocol for women with PCOS. (Tso *et al.*, 2014; Jacob *et al.*, 2016)	Strong ⊕⊕◯◯
Use of adjuvant GH before and/or during OS is probably not recommended for poor responders. (Duffy *et al.*, 2010; Li *et al.*, 2017)	Conditional ⊕⊕◯◯
Use of testosterone before OS is probably not recommended for poor responders. (Nagels *et al.*, 2015)	Conditional ⊕⊕⊕◯
Use of dehydroepiandrosterone before and/or during OS is probably not recommended for poor responders. (Nagels *et al.*, 2015)	Conditional ⊕⊕⊕◯
Use of aspirin before and/or during OS is not recommended in the general IVF/ICSI population and for poor responders. (Siristatidis *et al.*, 2016)	Strong ⊕⊕⊕◯
Use of sildenafil before and/or during OS is not recommended for poor responders. (Ataalla *et al.*, 2017)	Strong ⊕◯◯◯
There is no evidence, i.e. controlled studies or randomised controlled studies (RCTs), addressing the efficacy and safety of adjuvant indomethacin use, to support a recommendation on the use of indomethacin during OS.	

Recommendation

The current evidence does not support the routine use of adjuncts such as metformin, growth hormone, testosterone, DHEA, aspirin, indomethacin, and sildenafil before or during ovarian stimulation. Furthermore, there are serious safety concerns with the use of some of these adjuncts, such as sildenafil. However, the use of these adjuncts based on individual patient characteristics or in specific clinical circumstances may warrant further investigation. Further research is needed to better understand the efficacy and safety of these adjuncts in the context of ovarian stimulation.

Adjuncts (metformin, growth hormone, testosterone, DHEA, aspirin, indomethacin, and sildenafil) before or during ovarian stimulation are not recommended.

Hum Reprod Open. 2020 May 1;2020(2):hoaa009.

Hyaluronic acid in embryo transfer media for assisted reproductive technologies (Review)

Heymann D, Vidal L, Or Y, Shoham Z

Cochrane Library

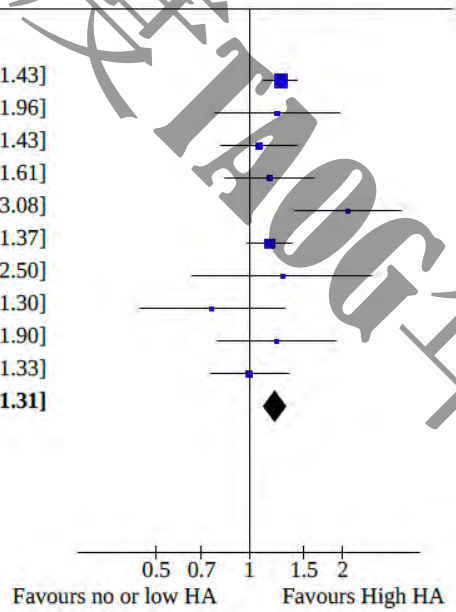
Analysis 1.1. Comparison 1: High versus low or no hyaluronic acid, Outcome 1: Live birth rate

Study or Subgroup	High HA Events	High HA Total	No or low HA Events	No or low HA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 High vs low or no hyaluronic acid						
Balaban 2011	310	639	247	643	36.4%	1.26 [1.11 , 1.43]
Fancsovits 2011	30	103	23	97	3.5%	1.23 [0.77 , 1.96]
Fancsovits 2015 (1)	69	208	62	201	9.3%	1.08 [0.81 , 1.43]
Hazlett 2008	49	116	39	107	6.0%	1.16 [0.83 , 1.61]
Kandari 2019	55	153	29	168	4.1%	2.08 [1.41 , 3.08]
Kleijkers 2016	184	417	159	419	23.4%	1.16 [0.99 , 1.37]
Korošec 2007 (2)	12	36	12	46	1.6%	1.28 [0.65 , 2.50]
Morbeck 2007	14	41	19	42	2.8%	0.75 [0.44 , 1.30]
Simon 2003	22	40	18	40	2.7%	1.22 [0.79 , 1.90]
Yung 2019	70	275	70	275	10.3%	1.00 [0.75 , 1.33]
Subtotal (95% CI)		**2028**		**2038**	**100.0%**	**1.21 [1.11 , 1.31]**
Total events:	815		678			

Heterogeneity: Chi² = 13.40, df = 9 (P = 0.15); I² = 33%

Test for overall effect: Z = 4.57 (P < 0.00001)

Test for subgroup differences: Not applicable



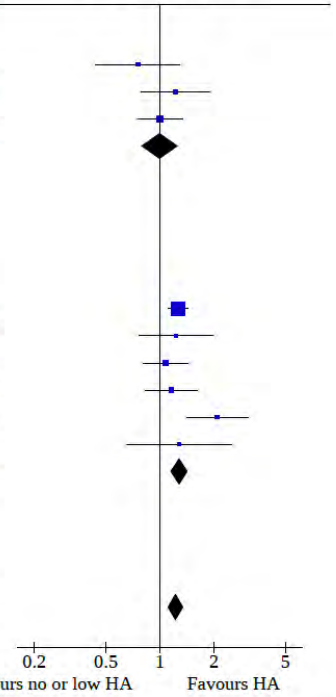
Footnotes

(1) Unpublished data retrieved after contacting authors, first cycle data

(2) Only fresh embryo transfer data

Analysis 1.3. Comparison 1: High versus low or no hyaluronic acid, Outcome 3: Live birth rate (grouped by frozen-thawed or fresh embryos)

Study or Subgroup	HA Events	HA Total	Low or no HA Events	Low or no HA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Frozen-thawed embryos						
Morbeck 2007	14	41	19	42	3.6%	0.75 [0.44 , 1.30]
Simon 2003	22	40	18	40	3.5%	1.22 [0.79 , 1.90]
Yung 2019	70	275	70	275	13.5%	1.00 [0.75 , 1.33]
Subtotal (95% CI)		**356**		**357**	**20.6%**	**0.99 [0.80 , 1.24]**
Total events:	106		107			
Heterogeneity: Chi² = 1.84, df = 2 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
1.3.2 Fresh embryos						
Balaban 2011	310	639	247	643	47.5%	1.26 [1.11 , 1.43]
Fancsovits 2011	30	103	23	97	4.6%	1.23 [0.77 , 1.96]
Fancsovits 2015 (1)	69	208	62	201	12.2%	1.08 [0.81 , 1.43]
Hazlett 2008	49	116	39	107	7.8%	1.16 [0.83 , 1.61]
Kandari 2019	55	153	29	168	5.3%	2.08 [1.41 , 3.08]
Korošec 2007	12	36	12	46	2.0%	1.28 [0.65 , 2.50]
Subtotal (95% CI)		**1255**		**1262**	**79.4%**	**1.28 [1.15 , 1.41]**
Total events:	525		412			
Heterogeneity: Chi² = 7.76, df = 5 (P = 0.17); I² = 36%						
Test for overall effect: Z = 4.73 (P < 0.00001)						
Total (95% CI)		**1611**		**1619**	**100.0%**	**1.22 [1.11 , 1.34]**
Total events:	631		519			
Heterogeneity: Chi² = 13.17, df = 8 (P = 0.11); I² = 39%						
Test for overall effect: Z = 4.21 (P < 0.0001)						
Test for subgroup differences: Chi² = 4.06, df = 1 (P = 0.04), I² = 75.4%						



作者結論: HA用於新鮮週期(分裂期或囊胚)植入可能增加活產率 (Moderate-quality evidence)

Cochrane Database Syst Rev. 2020 Sep 2;9(9):CD007421.

Recommendation

Current data indicate that addition of HA as an adherence compound in ET media in IVF treatment increases LBR following fresh transfers, without a significant effect on adverse outcomes. No effect was seen following frozen ETs. The higher multiple PRs after the use of HA-supplemented transfer medium should be further investigated.

Hyaluronic acid addition to transfer media is recommended. Monitoring of the multiple pregnancy rate is still advisable.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

Endometrial injury in women undergoing in vitro fertilisation (IVF) (Review)

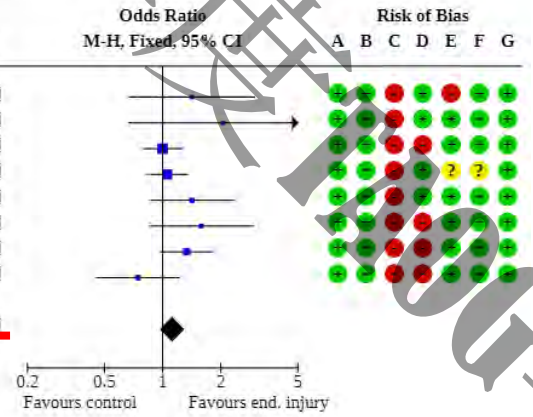
Lensen SF, Armstrong S, Gibreel A, Nastri CO, Raine-Fenning N, Martins WP

Cochrane Library

Analysis 1.1. Comparison 1: Endometrial injury versus control, Outcome 1: Live birth per woman randomised (studies at low risk of selection bias and other bias)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Berntsen 2020	20	122	13	107	2.8%	1.42 [0.67 , 3.01]
Hilton 2019	13	25	9	26	1.0%	2.05 [0.66 , 6.31]
Lensen 2019	180	690	176	674	32.0%	1.00 [0.78 , 1.27]
Metwally 2020	201	523	195	525	29.2%	1.06 [0.82 , 1.36]
Olesen 2019	47	151	37	153	6.2%	1.42 [0.85 , 2.35]
Polanski 2015	40	80	31	80	3.8%	1.58 [0.84 , 2.96]
van Hoogenhuijze 2020	110	472	88	474	16.4%	1.33 [0.97 , 1.83]
Yeung 2014	39	150	48	150	8.6%	0.75 [0.45 , 1.23]
Total (95% CI)		**2213**		**2189**	**100.0%**	**1.12 [0.98 , 1.28]**
Total events:	650		597			

Heterogeneity: Chi² = 8.23, df = 7 (P = 0.31); I² = 15%
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Summary of findings 1. Endometrial injury compared to control in women undergoing assisted reproductive techniques

Endometrial injury compared to control in women undergoing assisted reproductive techniques

Patient or population: women undergoing assisted reproductive techniques
Setting: clinic
Intervention: endometrial injury
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI) Risk with control	Anticipated absolute effects* (95% CI) Risk with Endometrial injury	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Live birth per woman randomised (studies at low risk of selection bias and other bias)	273 per 1,000	296 per 1,000 (269 to 324)	OR 1.12 (0.98 to 1.28)	4402 (8 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Live birth per woman randomised: sensitivity analysis (no high risk)	254 per 1,000	278 per 1,000 (177 to 409)	OR 1.13 (0.63 to 2.03)	229 (1 RCT)	⊕⊕⊖⊖ LOW [2,3]	
Live birth per woman randomised: sensitivity analysis (including all studies)	Meta-analysis not undertaken		-	7792 (29 RCTs)	⊕⊖⊖⊖ VERY LOW [4,5]	
Miscarriage per woman randomised (studies at low risk of selection bias and other bias)	60 per 1,000	53 per 1,000 (42 to 68)	OR 0.88 (0.68 to 1.13)	4402 (8 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Miscarriage per woman randomised: sensitivity analysis (no high risk)	53 per 1,000	61 per 1,000 (21 to 166)	OR 1.17 (0.38 to 3.58)	229 (1 RCT)	⊕⊕⊖⊖ LOW [2,3]	
Miscarriage per woman randomised: sensitivity analysis (including all studies)	54 per 1,000	56 per 1,000 (46 to 67)	OR 1.03 (0.85 to 1.25)	8092 (30 RCTs)	⊕⊕⊖⊖ LOW [4]	
Clinical pregnancy per woman randomised (studies at low risk of selection bias and other bias)	323 per 1,000	340 per 1,000 (312 to 370)	OR 1.08 (0.95 to 1.23)	4402 (8 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Clinical pregnancy per woman randomised: sensitivity analysis (no high risk)	307 per 1,000	339 per 1,000 (229 to 472)	OR 1.16 (0.67 to 2.02)	229 (1 RCT)	⊕⊕⊖⊖ LOW [2,3]	
Clinical pregnancy per woman randomised: sensitivity analysis (including all studies)	Meta-analysis not undertaken		-	8786 (37 RCTs)	⊕⊖⊖⊖ VERY LOW [4,5]	

作者結論：

- 不確定內膜傷害能否改善活產率
- 相關臨床試驗38個納入分析，異質性高，且尚有未完成之試驗，不建議再開啟新研究

Cochrane Database Syst Rev. 2021 Jun 10;6(6):CD009517.

Recommendation

Even though the most recent Cochrane meta-analysis included 37 RCTs, there is still uncertainty regarding the effect of endometrial scratching on LBR owing to large heterogeneity among studies in methodology and timing of the intervention. Subgroup analyses also failed to identify patient groups that would benefit from endometrial scratching.

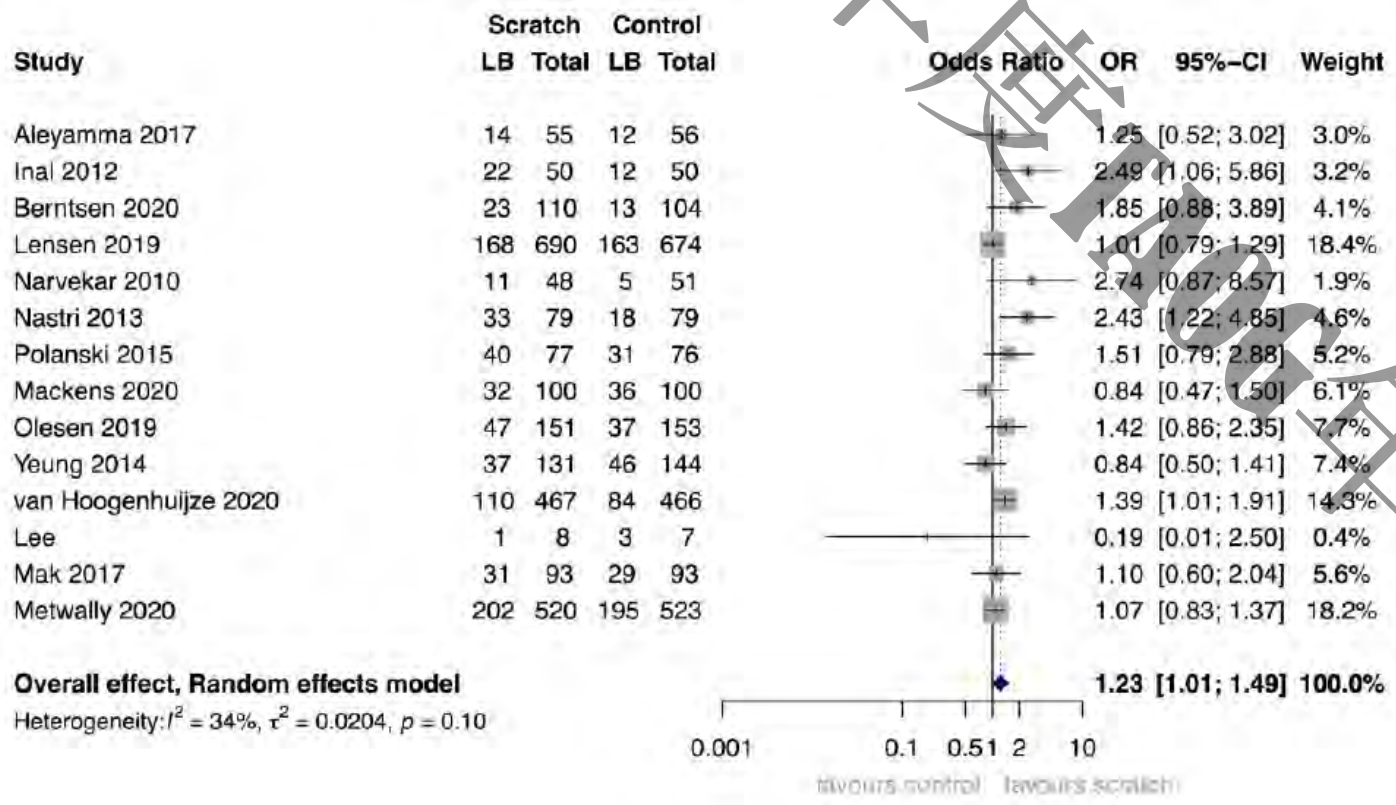
Endometrial scratching is currently not recommended for routine clinical use.

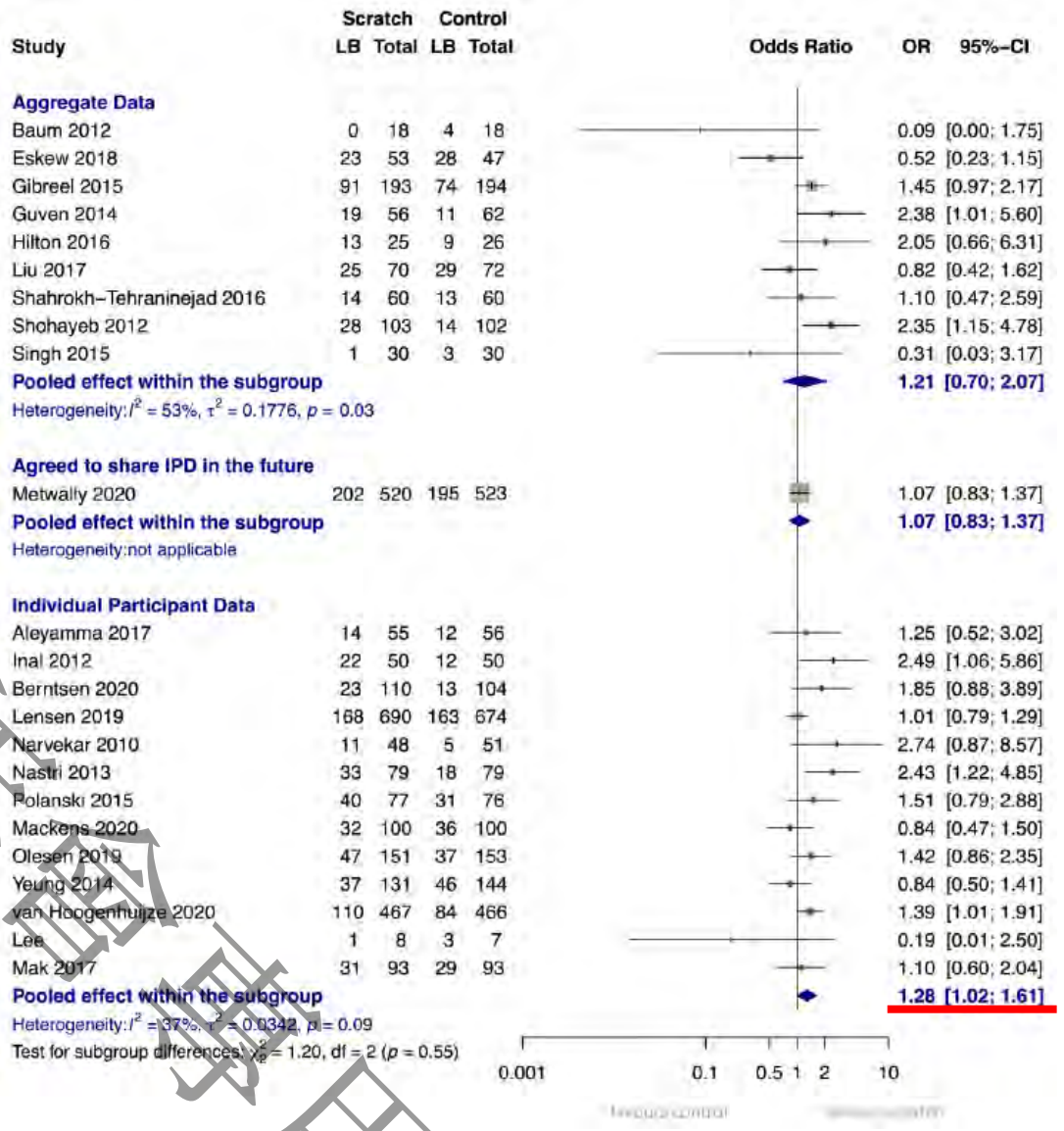
Hum Reprod. 2023 Nov 2;38(11):2062-2104.

OXFORD human reproduction update

Endometrial scratching in women undergoing IVF/ICSI: an individual participant data meta-analysis

Nienke E. van Hoogenhuijze[1,*], Gemma Lahoz Casarramona[2], Sarah Lensen[3], Cindy Farquhar[4], Mohan S. Kamath[5], Aleyamma T. Kunjummen[5], Nick Raine-Fenning[6,7], Sine Berntsen[8,9], Anja Pinborg[10], Shari Mackens[11], Zeynep Ozturk Inal[12], Ernest H.Y. Ng[13], Jennifer S.M. Mak[14], Sachin A. Narvekar[15], Wellington P. Martins[16], Mia Steengaard Olesen[17], Helen L. Torrance[1], Ben W. Mol[18,19], Marinus J.C. Eijkemans[20], Rui Wang[18], and Frank J.M. Broekmans[1]





作者結論: 內膜搔刮可能有幫助，但使用時機及方法尚未確立

Hum Reprod Update. 2023;29(6):721-740.

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

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

Cochrane Library

Summary of findings for the main comparison. Intrauterine administration of hCG for women undergoing assisted reproduction

Intrauterine administration of hCG for women undergoing assisted reproduction

Patient or population: subfertile women undergoing assisted reproduction
Setting: assisted reproduction units
Intervention: intrauterine human chorionic gonadotropin (hCG)
Comparison: no intrauterine hCG

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no hCG	Risk with intrauterine human chorionic gonadotropin (hCG)			
Live birth Cleavage stage: hCG < 500 IU Follow-up: mean 40 weeks	495 per 1000	376 per 1000 (287 to 500)	RR 0.76 (0.58 to 1.01)	280 (1 RCT)	⊕⊝⊝⊝ VERY LOW[a,b]
Cleavage stage: hCG ≥ 500 IU Follow-up: mean 40 weeks	273 per 1000	428 per 1000 (360 to 510)	RR 1.57 (1.32 to 1.87)	914 (3 RCTs)	⊕⊕⊕⊝ MODERATE[c]
Blastocyst stage: hCG ≥ 500 IU Follow-up: mean 40 weeks	369 per 1000	340 per 1000 (296 to 384)	RR 0.92 (0.80 to 1.04)	1666 (2 RCTs)	⊕⊕⊕⊝ MODERATE[c]
Miscarriage Follow-up: mean 40 weeks	58 per 1000	60 per 1000 (47 to 78)	RR 1.04 (0.81 to 1.35)	3927 (11 RCTs)	⊕⊝⊝⊝ VERY LOW[c,d]
Clinical pregnancy Cleavage stage: hCG < 500 IU Follow-up: mean 12 weeks	579 per 1000	509 per 1000 (405 to 637)	RR 0.88 (0.70 to 1.10)	280 (1 RCT)	⊕⊝⊝⊝ VERY LOW[a,d]
Cleavage stage: hCG ≥ 500 IU Follow-up: mean 12 weeks	307 per 1000	458 per 1000 (406 to 517)	RR 1.49 (1.32 to 1.68)	2186 (12 RCTs)	⊕⊕⊕⊝ MODERATE[c]
Blastocyst stage: hCG ≥ 500 IU Follow-up: mean 12 weeks	422 per 1000	418 per 1000 (359 to 485)	RR 0.99 (0.85 to 1.15)	2091 (4 RCTs)	⊕⊕⊕⊝ MODERATE[c]
Complications Follow-up: mean 40 weeks	Other complications reported in the included studies were ectopic pregnancy (4 RCTs; N = 1073; 4 events overall), heterotopic pregnancy (1 RCT; N = 495; 1 event), intrauterine death (3 RCTs; N = 1078; 22 events), and triplets (1 RCT; N = 48; 3 events). No evidence shows a difference between groups, but events were too few for any conclusions to be drawn.		-	1764 (7 RCTs)	⊕⊝⊝⊝ VERY LOW[c,d]

作者結論: 分裂期植入+IC hCG ≥500 IU可能可以增加LBR (moderate quality evidence)

Recommendation

Current evidence for the efficacy of intrauterine administration of hCG is conflicting. The evidence for its benefits in specific patient subgroups is also inconclusive. Considering the safety concerns, further studies are necessary.

Intrauterine administration of hCG is not recommended.

Cochrane Database Syst Rev. 2018 Oct 20;10(10):CD011537.

Intervention		Benefits versus harms (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR)[1]	Level of evidence for safety[1]	Considerations	Recommendation
Flushing of the uterus	Intrauterine administration of hCG	Some benefit for cleavage stage (not blastocyst) transfer at >500 IU No evidence of harm	⊕⊕⊕◯	⊕◯◯◯	Timing of administration, dosage of hCG and timing of embryo transfer differed between studies.	Intrauterine administration of hCG is **not recommended**.
	Intrauterine administration of G-CSF	RIF: No evidence of benefit on LBR Thin endometrium: may improve LBR (1 RCT) Very few side effects reported	⊕⊕◯◯	⊕◯◯◯	/	Intrauterine administration of granulocyte colony-stimulating factor is **not recommended**.
	Endometrial administration of embryo culture supernatant	No evidence of benefit on LBR or miscarriage rate No evidence of harm	⊕◯◯◯	⊕◯◯◯	In several studies, it was unclear how the culture media were administered, by injection or as a uterine infusion.	Endometrial administration of embryo culture supernatant is **not recommended**.
	Endometrial exposure to seminal plasma	No evidence of a benefit on LBR or miscarriage rate Complications: no evidence of an effect on multiple pregnancy rate, potential risk of allergic reaction	⊕⊕◯◯	⊕⊕◯◯	Available evidence is very heterogenous with regards to the inclusion/exclusion criteria of patients, and the interventions	Endometrial exposure to seminal plasma is **not recommended**.
Stem cell mobilization	Stem cell therapy for POI or DOR	Available evidence comes from case reports and uncontrolled studies with very little information on the actual procedures and long-term follow-up is lacking	No data	No data		Stem cell therapy for premature ovarian insufficiency, diminished/poor ovarian reserve or thin endometrium is **not recommended**.
	Stem cell therapy for thin endometrium		No data	No data		

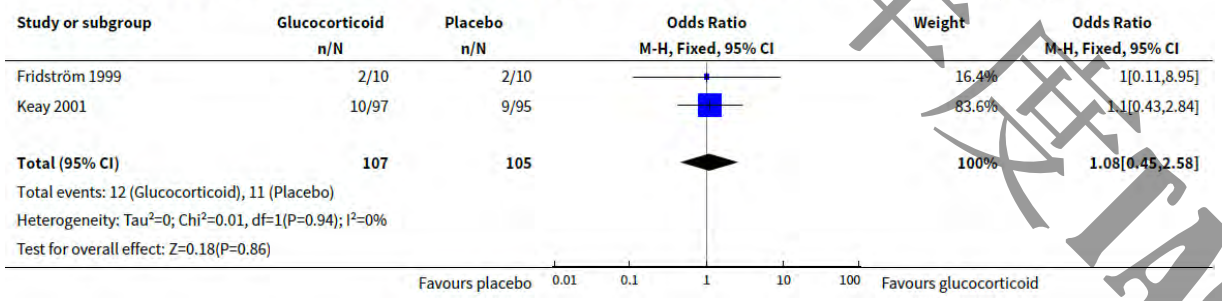
Hum Reprod. 2023 Nov 2;38(11):2062-2104.

Glucocorticoid supplementation during ovarian stimulation for IVF or ICSI (Review)

Kalampokas T, Pandian Z, Keay SD, Bhattacharya S

Cochrane Library

Analysis 1.1. Comparison 1 Glucocorticoid supplementation vs placebo, Outcome 1 Live birth rate.



Summary of findings for the main comparison. Glucocorticoid supplementation versus placebo for IVF or ICSI

Glucocorticoid supplementation versus placebo for IVF or ICSI

Patient or population: Patients undergoing IVF or ICSI
Settings: Infertility clinics in University/Teaching hospitals
Intervention: Glucocorticoid supplementation during ovarian stimulation
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Placebo	Corresponding risk Glucocorticoid supplementation				
Live birth rate	147 per 1000	157 per 1000 (72 to 308)	OR 1.08 (0.45 to 2.58)	212 (2 studies)	⊕⊕⊝⊝ low[1]	
Clinical pregnancy rate per woman/couple	236 per 1000	343 per 1000 (233 to 473)	OR 1.69 (0.98 to 2.90)	310 (2 studies)	⊕⊕⊝⊝ low[1]	
Multiple pregnancy rate per woman/couple	Only one event (in the glucocorticoid group)		OR 3.32 (0.12 to 91.60)	20 (1 study)	⊕⊝⊝⊝ very low[1,2]	
Miscarriage rate per woman	See footnote[3]		OR 1.00 (0.05 to 18.57)	20 (1 study)	⊕⊝⊝⊝ very low[1,2]	
OHSS per woman	Not reported in the included studies					
Side-effects per woman	Not reported in the included studies					

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

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.

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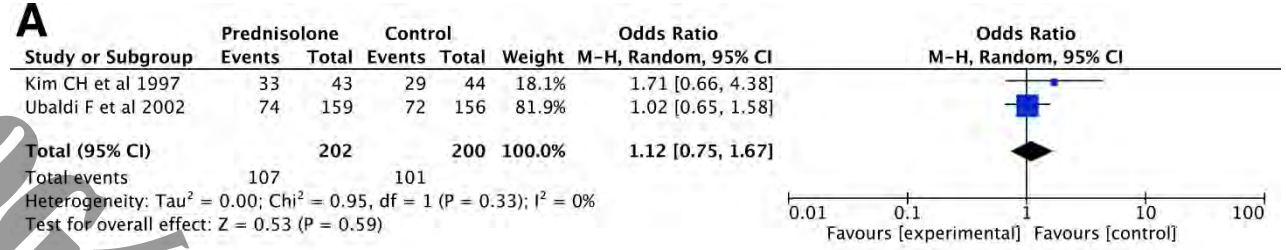


類固醇於刺激周期使用沒有幫助，並須考量潛在風險

Fertil Steril. 2018 Nov;110(6):1089-1100.
Cochrane Database Syst Rev. 2017 Mar 27;3(3):CD004752.

Recommendation

While there is some indication of potential benefits in patients with autoimmune disease, it is important to note that the existing data on the use of glucocorticoids in ART is limited and based on small, non-controlled studies with inconsistent criteria.

Glucocorticoids are not recommended in ART. 

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

Fresh versus frozen embryo transfers in assisted reproduction (Review)

Zaat T, Zagers M, Mol F, Goddijn M, van Wely M, Mastenbroek S

Cochrane Library

8 RCTs

全胚冷凍對累積活產率無影響

Summary of findings 1. Fresh compared to frozen embryo transfer (cumulatively) in assisted reproduction

Fresh compared to frozen embryo transfer (cumulatively) in assisted reproduction

Patient or population: women undergoing assisted reproduction
Setting: assisted reproduction clinic
Intervention: frozen embryo transfers only
Comparison: fresh and frozen embryo transfers (conventional IVF)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with fresh and frozen embryo transfers	Risk with frozen embryo transfer only				
Live birth rate: cumulatively	579 per 1000	589 per 1000 (567 to 627)	OR 1.08 (0.95 to 1.22)	4712 (8 RCTs)	⊕⊕⊕⊖ Moderate[a]	
OHSS: per cycle with ovarian hyperstimulation	33 per 1000	9 per 1000 (6 to 13)	OR 0.26 (0.17 to 0.39)	4478 (6 RCTs)	⊕⊕⊖⊖ Low[a,b]	
Ongoing pregnancy rate: cumulatively	508 per 1000	495 per 1000 (436 to 551)	OR 0.95 (0.75 to 1.19)	1245 (4 RCTs)	⊕⊕⊕⊖ Moderate[a]	
Miscarriage rate: cumulatively	118 per 1000	124 per 1000 (88 to 171)	OR 1.06 (0.72 to 1.55)	986 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]	
Multiple pregnancy rate: cumulatively	156 per 1000	140 per 1000 (101 to 188)	OR 0.88 (0.61 to 1.25)	986 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]	
Time to pregnancy	Outcome could not be analysed. By design, time to pregnancy is shorter in the conventional strategy compared to the 'freeze all' strategy when the cumulative live birth rate is comparable, as embryo transfer is delayed in a 'freeze all' strategy.					

Recommendation

The available evidence shows that the cumulative LBR and LBR with the freeze-all strategy are not superior to fresh ET, while the time to achieve pregnancy is likely to be longer. Moreover, elective freeze-all carries obstetric and perinatal risks such as hypertensive disorders in pregnancy, large for gestational age, and macrosomia. The freeze-all strategy should only be considered when there is a clear clinical indication, such as a higher risk of OHSS or endometrial pathology, and in cases involving PGT. Adopting the freeze-all strategy should be done judiciously, considering individual patient factors and the potential risks involved. For the aim of this article, freeze-all in the context of women with PCOS or preventing OHSS was not evaluated as this is not considered an add-on.

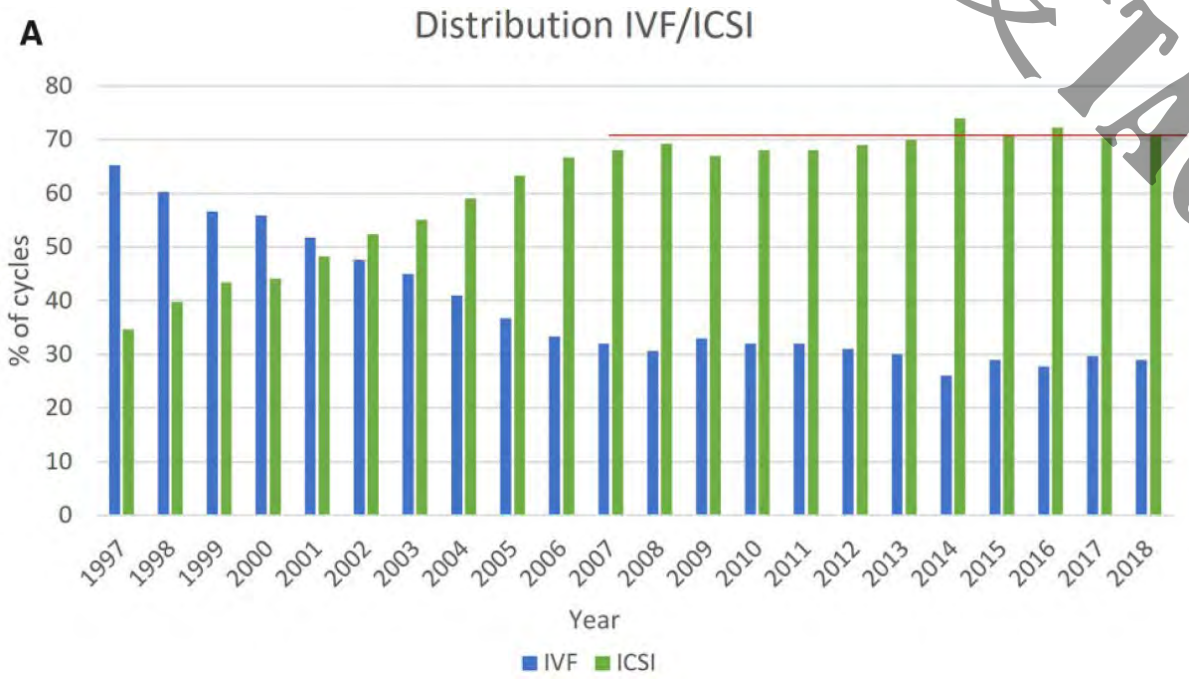
Elective freeze-all is currently not recommended for routine clinical use.

Cochrane Database Syst Rev. 2021 Feb 4;2(2):CD011184.

human reproduction open
ESHRE PAGES

ART in Europe, 2018: results generated from European registries by ESHRE†

The European IVF Monitoring Consortium (EIM)‡, for the European Society of Human Reproduction and Embryology (ESHRE)



人工生殖 49,652 治療週期中，80.1%週期有使用顯微操作技術(表 4)。

表 4　110 年人工生殖個案治療週期之使用顯微操作技術情形

單位：週期/%

顯微操作使用情形	治療週期數	百分比
使用	39,795	80.1
卵質內精子注射(ICSI)	19,254	38.8
協助孵化(Assisted Hatching)	15,406	31.0
胚胎著床前染色體篩檢(PGT-A)	1,199	2.4
胚胎著床前基因診斷(PGT-M)	55	0.1
其他(含合併多種技術)	3,881	7.8
未使用	9,857	19.9
全部治療週期	**49,652**	**100.0**

Hum Reprod Open. 2022 Jul 5;2022(3):hoac022.

Intracytoplasmic sperm injection versus conventional in-vitro fertilisation in couples with infertility in whom the male partner has normal total sperm count and motility: an open-label, randomised controlled trial

Vinh Q Dang, Lan N Vuong, Tam M Luu, Toan D Pham, Tuong M Ho, Anh N Ha, Binh T Truong, Anh K Phan, Dung P Nguyen, Thanh N Pham, Quan T Pham, Rui Wang, Robert J Norman, Ben W Mol

Multicenter, open-label, RCT, Vietnam, 2016-2018; normal S/A (WHO 2010);
532 IVF vs **532 ICSI**, 1st outcome: LBR /p 1st D3 ET;
2nd: cOPR at 12 mo (from initiated cycle), etc.

	Intracytoplasmic sperm injection (n=532)	Conventional IVF (n=532)
Age (years)		
Women	32·7 (4·6)	32·6 (4·7)
Men	35·2 (5·2)	35·3 (5·6)
Body-mass index (kg/m²)		
Women	21·2 (2·5)	21·2 (2·4)
Female anti-Müllerian hormone (ng/mL)	2·5 (1·5–4·3)	2·6 (1·6–4·3)
Duration of infertility (years)	3·0 (2·0–5·0)	4·0 (2·0–6·0)
Number of previous IVF or intracytoplasmic sperm injection cycles		
0	480 (90%)	486 (91%)
1	52 (10%)	46 (9%)
2	0	0
Primary infertility	295 (55%)	299 (56%)
IVF indication		
Unexplained	199 (37%)	183 (34%)
Diminished ovarian reserve	121 (23%)	144 (27%)
Tubal factor	134 (25%)	120 (23%)
Ovulation disorder	58 (11%)	69 (13%)
Endometriosis	20 (4%)	16 (3%)
Duration of stimulation (days)	8·8 (1·3)	8·8 (1·3)
Total dose of follicle-stimulating hormone (IU)	2700 (2250–3075)	2700 (2100–3075)
Estradiol level on day of trigger (pg/mL)	3408·5 (1723·0–5866·3)	2943·0 (1738·0–5871·0)
Progesterone level on day of trigger (ng/mL)	0·8 (0·5–1·2)	0·8 (0·5–1·2)
Semen volume (mL)	2·0 (1·1–2·7)	2·0 (1·0–2·7)
Sperm concentration (million)	77·8 (46·8–123·4)	78·0 (51·0–143·2)
Total sperm count (million)	147·2 (91·0–230·8)	157·9 (93·0–258·5)
Sperm motility (%)	40·0 (32·0–50·3)	42·0 (34·0–51·0)
Total motile sperm count (million)	63·6 (36·5–103·5)	68·5 (38·9–117·3)
Sperm with normal morphology (%)*	3·0 (1·0–6·0)	3·0 (1·0–6·0)
Number of oocytes retrieved	11·0 (7·0–16·0)	11·0 (7·0–16·0)
Number of metaphase II oocytes	9·0 (5·0–13·0)	9·0 (5·0–14·0)

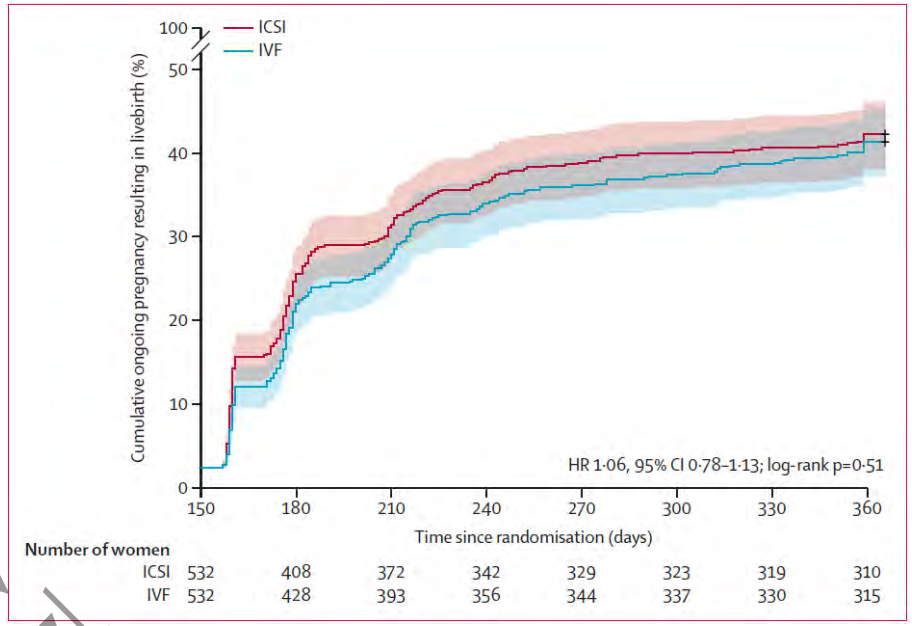
Data are mean (SD), median (IQR), or n (%). IVF=in-vitro fertilisation. *Data from samples obtained during the first consultation, before the IVF or intracytoplasmic sperm injection cycle.

Table 1: **Baseline characteristics**

	Intracytoplasmic sperm injection (n=532)	Conventional IVF (n=532)	Absolute difference (95% CI)	Risk ratio (95% CI)*	p value
Fertility outcomes					
Livebirths†	184 (35%)	166 (31%)	3·4% (−2·4 to 9·2)	1·11 (0·93 to 1·32)	0·27
Fertilisation per oocyte inseminated or injected‡	75·0% (56·9–88·9)	66·7% (50·0–83·3)	5·6% (2·2 to 8·6)	..	<0·0001
Fertilisation per oocyte retrieved	58·3% (40·0–72·7)	55·6% (38·8–70·0)	2·9% (0·0 to 5·7)	..	0·048
Abnormal fertilisation per oocyte inseminated or injected‡	1·3% (6·2)	7·4% (12·4)	−6·1% (−7·6 to −5·1)	..	<0·0001
Abnormal fertilisation per oocyte retrieved	1·1% (5·7)	6·3% (10·5)	−5·2% (−6·5 to −4·4)	..	<0·0001
Total fertilisation failure§	29 (5%)	34 (6%)	−0·9% (−4·0 to 2·1)	0·85 (0·53 to 1·38)	0·60
Couples without an embryo for transfer¶‖	8 (2%)	21 (4%)	−2·4% (−4·6 to −0·3)	0·38 (0·17 to 0·85)	0·024
Number of day 3 embryos	5 (3–8)	5 (2–8)	0 (0 to 1)	..	0·19
Number of good day 3 embryos**	4 (2–7)	3 (2–6)	0 (0 to 1)	..	0·25
Number of day 3 embryos frozen	4 (2–6)	4 (2–6)	0 (0 to 0)	..	0·37
Number of embryos transferred	1·9 (0·3)	1·9 (0·3)	..	..	..
Number of good embryos transferred	1·7 (0·6)	1·7 (0·6)	..	..	..
Type of transfer					
Fresh	213 (40%)	188 (35%)	..	..	..
Frozen-only	299 (56%)	314 (59%)	..	..	..
Positive pregnancy test	254 (48%)	236 (44%)	3·4% (−2·8 to 9·6)	1·08 (0·94 to 1·23)	0·29
Clinical pregnancy	227 (43%)	212 (40%)	2·8% (−3·3 to 8·9)	1·07 (0·93 to 1·24)	0·38
Ongoing pregnancy	190 (36%)	174 (33%)	3·0% (−2·9 to 8·9)	1·09 (0·92 to 1·29)	0·33
Implantation rate††	284/971 (29%)	278/953 (29%)	0·0% (−4·1 to 4·2)	1·00 (0·95 to 1·06)	..
Maternal safety outcomes					
Moderate or severe ovarian hyperstimulation syndrome	7 (1%)	6 (1%)	0·2% (−1·3 to 1·7)	1·17 (0·39 to 3·45)	0·99
Pregnancy complications					
Ectopic pregnancy	10 (2%)	10 (2%)	0·% (−1·6 to 1·6)	1·00 (0·42 to 2·38)	0·99
Miscarriage	27 (5%)	28 (5%)	−0·2% (−3·0 to 2·7)	0·96 (0·58 to 1·61)	0·99
Twin pregnancy	57 (11%)	66 (13%)	−1·7% (−5·9 to 2·5)	0·87 (0·62 to 1·21)	0·44
Twin delivery	50 (9%)	51 (10%)	−0·2% (−3·9 to 3·5)	0·98 (0·68 to 1·42)	0·99

Data are n (%), median (IQR), mean (SD), or n/N (%), unless otherwise indicated. IVF=in-vitro fertilisation. *Risk ratios are for the intracytoplasmic sperm injection group compared with the conventional IVF group. †Natural conceptions were included (six in the intracytoplasmic sperm injection group and three in the conventional IVF group). ‡Denominator was the number of metaphase II oocytes, calculated as the number of oocytes retrieved−number of germinal vesicle oocytes−number of metaphase I oocytes. §Defined as the absence of any zygotes with two pronuclei at 16–18 h after injection or insemination. ¶Post-hoc analysis. ‖Defined by those with no embryo after failed fertilisation and those with no embryos due to embryo block on day 2. **Embryos were rated according to the Istanbul criteria, with good defined as grade I, cell number of 7–9, even cell size, less than 10% fragmentation, and no multinucleation. ††Denominator is the total number of embryos transferred.

Table 2: **Fertility outcomes and maternal safety after the first embryo transfer (intention-to-treat)**



ICSI於年輕族群的Non-male factor沒有幫助

Lancet. 2021 Apr 24;397(10284):1554-1563.

The role of ICSI vs. conventional IVF for patients with advanced maternal age—a randomized controlled trial

Jigal Haas[1,2] · Tal Elkan Miller[1,2] · Ravit Nahum[1,2] · Adva Aizer[1,2] · Michal Kirshenbaum[1,2] · Eran Zilberberg[1,2] · Oshrit Lebovitz[1,2] · Raoul Orvieto[1,2]

Prospective RCT, Israel, 2018-2020; **39-44 y**, normal S/A, exclude FR<50% prior cycle; randomize ICSI or IVF for **each ovary**, 60 pts.

Table 1 Demographic characteristics

Number of patients	60
Number of oocytes	509
Age (years)	41.1 ± 1.4
BMI (kg/m^2)	26.4 ± 5.6
Daily dose of gonadotropins (IU)	355 ± 100
Length of stimulation	9.3 ± 2.1
FSH levels	9.1 ± 3.4
LH levels	4.6 ± 1.9

Table 2 Number of oocytes retrieved, number of zygotes (2PN), and number of cleavage-stage embryos

*TFF: IVF 1 case, ICSI 1 case

60 patients	IVF	ICSI	*p* value
Total oocytes	258	257	
Oocytes per group (*n*)	4.3 ± 3.5	4.3 ± 3.3	0.92
2PN per group (*n*)	3.1 ± 2.5	2.7 ± 2.3	0.45
2PN/oocytes	72.4% ± 2.8	65.1% ± 2.9	0.38
Embryos at cleavage stage (*n*)	2.8 ± 2.4	2.4 ± 2.2	0.29
TQE at cleavage stage (*n*)	1.7 ± 2.1	1.6 ± 1.7	0.94
Embryos/oocytes (%)	65.7% ± 2.9	57.1% ± 3.2	0.17
Embryos/2PN (%)	90.4% ± 1.9	85.9% ± 2.7	0.17
TQE/oocytes (%)	41.2% ± 3.4	41% ± 3.5	0.8

高齡族群，受精率與高品質胚胎率相當

J Assist Reprod Genet. 2021 Jan;38(1):95-100.

Recommendation

There is no evidence regarding the advantages of ICSI for non-male factor infertility in terms of pregnancy outcomes, LBRs, and cumulative LBRs. In addition, ICSI is associated with higher costs compared to conventional IVF treatment. There may be specific treatments where ICSI is indicated, such as for PGT cycles.

ICSI is not recommended for non-male factor infertility.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

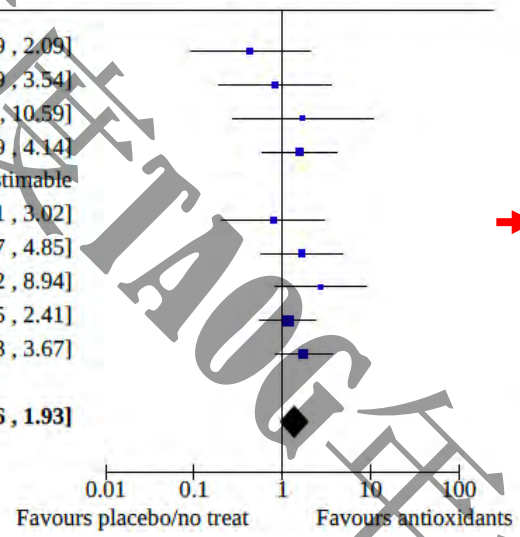
Antioxidants for female subfertility (Review)

Cochrane Library

Analysis 1.4. Comparison 1: Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 4: Live birth; IVF/ICSI

Study or Subgroup	Antioxidant(s) Events	Total	Placebo/No treatment Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Battaglia 2002	3	18	6	19	8.8%	0.43 [0.09 , 2.09]
Bentov 2014	4	17	6	22	7.3%	0.82 [0.19 , 3.54]
Espino 2019 (1)	6	20	2	10	3.4%	1.71 [0.28 , 10.59]
Fernando 2018 (2)	26	120	6	40	12.8%	1.57 [0.59 , 4.14]
Jahromi 2017	0	40	0	40		Not estimable
Polak de Fried 2013	5	26	6	26	8.8%	0.79 [0.21 , 3.02]
Schachter 2007	14	27	11	28	9.5%	1.66 [0.57 , 4.85]
Schachter 2007	13	24	7	23	6.0%	2.70 [0.82 , 8.94]
Tunon 2017	24	60	22	60	24.0%	1.15 [0.55 , 2.41]
Xu 2018	22	93	14	93	19.4%	1.75 [0.83 , 3.67]
Total (95% CI)		**445**		**361**	**100.0%**	**1.36 [0.96 , 1.93]**
Total events:	117		80			

Heterogeneity: Chi² = 5.29, df = 8 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)
Test for subgroup differences: Not applicable



Comparison 1. Antioxidant(s) versus placebo or no treatment/standard treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Live birth; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)	13	1227	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [1.36, 2.43]
1.1.1 Placebo	7	628	Odds Ratio (M-H, Fixed, 95% CI)	1.89 [1.18, 3.03]
1.1.2 No treatment	6	599	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [1.22, 2.56]
1.2 Live birth; type of antioxidant	13	1227	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [1.36, 2.43]
1.2.1 N-acetyl-cysteine	1	60	Odds Ratio (M-H, Fixed, 95% CI)	3.00 [1.05, 8.60]
1.2.2 L-arginine	1	37	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.09, 2.09]
1.2.3 CoQ10	2	225	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.78, 2.88]
1.2.4 Vitamin D	1	52	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.21, 3.02]
1.2.5 Vitamin B complex	1	102	Odds Ratio (M-H, Fixed, 95% CI)	2.07 [0.93, 4.57]
1.2.6 Combined antioxidants	3	378	Odds Ratio (M-H, Fixed, 95% CI)	2.59 [1.52, 4.40]
1.2.7 Vitamin E	1	103	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.50, 4.10]
1.2.8 Melatonin	3	270	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.68, 3.76]

作者結論：

- Low- to very low-quality evidence to show that taking an antioxidant may provide benefit for subfertile women
- Insufficient evidence to draw any conclusions about adverse events

Cochrane Database Syst Rev. 2020 Aug 27;8(8):CD007807.

Antioxidants for male subfertility (Review)

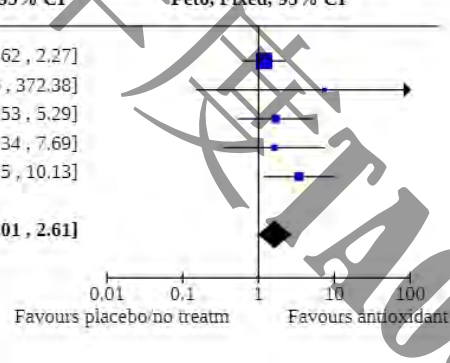
de Ligny W, Smits RM, Mackenzie-Proctor R, Jordan V, Fleischer K, de Bruin JP, Showell MG

Cochrane Library

Analysis 1.2. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 2: Live birth; IVF/ICSI

Study or Subgroup	Antioxidant Events	Antioxidant Total	Placebo/no treatm Events	Placebo/no treatm Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Joseph 2020 (1)	25	100	22	100	53.0%	1.18 [0.62 , 2.27]
Kessopoulou 1995 (2)	1	15	0	15	1.5%	7.39 [0.15 , 372.38]
Korshunov 2018 (3)	13	24	9	22	17.2%	1.68 [0.53 , 5.29]
Kumalic 2020 (4)	5	19	3	17	9.3%	1.63 [0.34 , 7.69]
Tremellen 2007 (5)	20	40	4	20	19.1%	3.42 [1.15 , 10.13]
Total (95% CI)		**198**		**174**	**100.0%**	**1.63 [1.01 , 2.61]**
Total events:	64		38			

Heterogeneity: Chi² = 3.30, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)
Test for subgroup differences: Not applicable



Summary of findings 1. Antioxidants compared to placebo or no treatment for patients with male subfertility

Antioxidants compared to placebo or no treatment for patients with male subfertility

Patient or population: patients with male subfertility
Setting: clinic
Intervention: antioxidants
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with antioxidants				
Live birth rate per couple randomised	162 per 1000	216 per 1000 (171 to 269)	OR 1.43 (1.07 to 1.91)	1283 (12 RCTs)	⊕⊝⊝⊝ VERY LOW [1 2 3]	
Clinical pregnancy rate per couple randomised	146 per 1000	245 per 1000 (199 to 297)	OR 1.89 (1.45 to 2.47)	1706 (20 RCTs)	⊕⊕⊝⊝ LOW [1 3]	
Adverse events - Miscarriage	48 per 1000	68 per 1000 (36 to 125)	OR 1.46 (0.75 to 2.83)	664 (6 RCTs)	⊕⊝⊝⊝ VERY LOW [1 3 4]	
Adverse events - Gastrointestinal	15 per 1000	39 per 1000 (22 to 71)	OR 2.70 (1.46 to 4.99)	1355 (16 RCTs)	⊕⊕⊝⊝ LOW [1 3]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

作者結論：

- Very low-certainty evidence suggesting that antioxidant supplementation in subfertile males may improve live birth rates
- Subfertile couples should be advised that the current evidence is inconclusive based on serious risk of bias.

Cochrane Database Syst Rev. 2022 May 4;5(5):CD007411.

Recommendation

Antioxidant therapy lacks substantial and reliable evidence demonstrating a significant enhancement in LBRs.

Antioxidant therapy is not recommended in ART.

Hum Reprod. 2023 Nov 2;38(11):2062-2104.

Diagnosis and treatment of infertility in men: AUA/ASRM guideline part II

Peter N. Schlegel, M.D.,[a] Mark Sigman, M.D.,[b] Barbara Collura,[c] Christopher J. De Jonge, Ph.D, H.C.L.D.(A.B.B.),[d] Michael L. Eisenberg, M.D.,[e] Dolores J. Lamb, Ph.D., H.C.L.D.(A.B.B.),[f] John P. Mulhall, M.D.,[g] Craig Niederberger, M.D., F.A.C.S.,[h] Jay I. Sandlow, M.D.,[i] Rebecca Z. Sokol, M.D., M.P.H.,[j] Steven D. Spandorfer, M.D.,[f] Cigdem Tanrikut, M.D., F.A.C.S.,[k] Jonathan R. Treadwell, Ph.D.,[l] Jeffrey T. Oristaglio, Ph.D.,[l] and Armand Zini, M.D.[m]

43. Clinicians should counsel patients that the benefits of supplements (e.g., antioxidants, vitamins) are of questionable clinical utility in treating male infertility. Existing data are inadequate to provide recommendation for specific agents to use for this purpose. (Conditional Recommendation; Evidence Level: Grade B)

There are no clear, reliable data to support use of the variety of supplements (vitamins, antioxidants, nutritional supplement formulations) that have been offered to men attempting conception. Current data suggest that they are likely not harmful, but they are of questionable value in improving fertility outcomes.

指引未建議(或反對)使用抗氧化劑或維生素補充，需適當SDM

Fertil Steril. 2021 Jan;115(1):62-69.

CAM常包含：Acupuncture, reflexology, nutritionist services, Chinese herbal medicine (CHM), mindfulness, hypnotherapy, massage, yoga, reiki healing, meditation, neuro-linguistic programming therapy, kinesiology, and detoxing

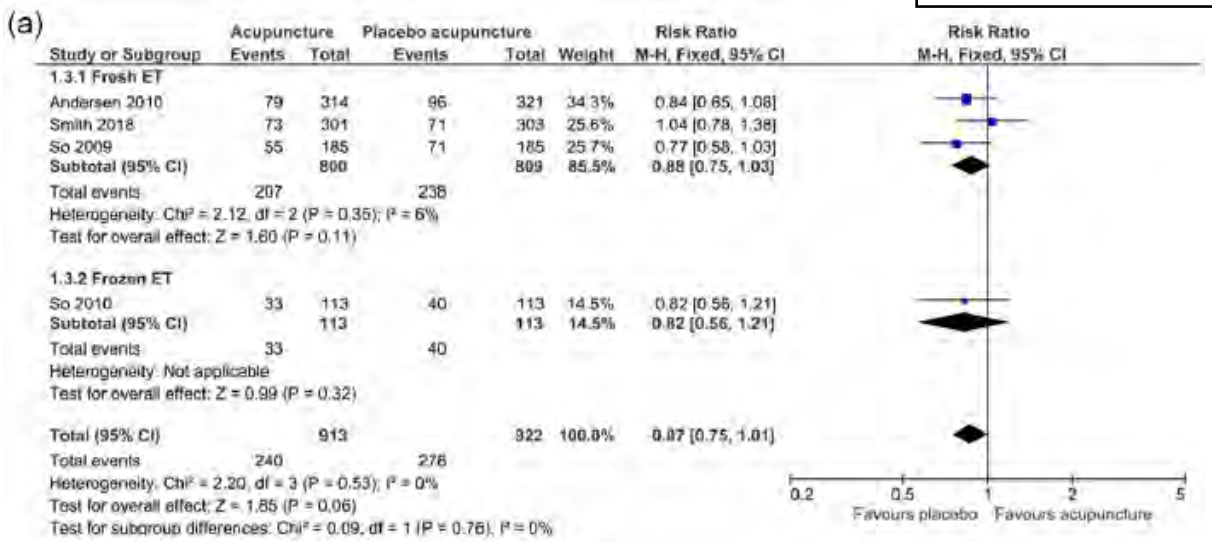
Acupuncture: 34 RCTs, 25 Systemic reviews ➔ Reported methods very heterogenous

Four meta-analyses from the last 2 years

Acupuncture versus placebo acupuncture for in vitro fertilisation: a systematic review and meta-analysis

Meaghan E Coyle[1], Ieva Stupans[2], Katherine Abdel-Nour[2], Hiba Ali[2], Michelle Kotlyarsky[2], Phillip Lie[2], Sinan Tekin[2] and Thilini Thrimawithana[2]

Till Apr 2019, 8 studies



Acupunct Med. 2021 Feb;39(1):20-29.

Herbal medicine in women undergoing in vitro fertilization/ intracytoplasmic sperm injection: A systematic review and meta-analysis

Chan-Young Kwon[a], Boram Lee[b], Sun Haeng Lee[a,c,**], Junyoung Jo[d,*]

Till Sep 2019, 43 trials, 61 HM prescriptions, 92 herbs

Table 2
Summary of Meta-Analysis: HM versus no treatment or placebo.

Outcomes		RCT	Sample size	RR	Effects model	95 % CI	I^2 value	Z value	P value
vs. no treatment									
Live birth rate	Total	5	837	1.34	Random	1.05, 1.72	35	2.31	0.02
Subgroup1 (Timing of HM)	Before IVF	2	201	1.16	Random	0.83, 1.63	0	0.88	0.38
	During IVF	1	112	1.59	Random	0.99, 2.56	NA	1.91	0.06
	During&After IVF	2	524	1.43	Random	0.78, 2.62	77	1.15	0.25
vs. placebo									
Clinical pregnancy rate	Total	5	330	1.85	Random	1.42, 2.42	0	4.57	< 0.00001
Subgroup1 (Timing of HM)	Before IVF	2	140	1.83	Random	1.26, 2.65	0	3.20	0.001
	During IVF	2	124	1.94	Random	1.19, 3.15	0	2.66	0.008
	Before&During IVF	1	66	1.80	Random	0.98, 3.29	NA	1.91	0.06

- 針灸並未增加活產率
- 中草藥可能對活產有幫助 (low-quality evidence)

Complement Ther Med. 2020 Sep:53:102528.

Recommendation

For acupuncture, the existing evidence is contradictory regarding its potential to enhance the LBR. As for Chinese and herbal medicine, it is essential to conduct RCTs with rigorous methodologies and long-term follow-up to ascertain the treatments' efficacy and safety. For the other complementary therapies and alternative medicine included, there are insufficient clinical studies on their efficacy and safety to draw any conclusions.

Acupuncture, Chinese and herbal medicine and other complementary therapies are not recommended.

Fertil Steril. 2022 Apr;117(4):747-755.

1. 生殖中心應僅於下列狀況提供“附加措施”：
   a. 有≥1個高品質研究(隨機臨床分派試驗)顯示該附加措施能安全且有效的改善預後
   b. 生殖中心應持續監測其成功率及有長期追蹤資料，並報告不良反應
   c. 當附加措施的證據有限或不確定時，生殖中心應能提供該附加措施的統計資料
   d. 當沒有證據支持該附加措施時，應僅提供該措施給加入臨床試驗的個案，且經過倫理委員會審核
2. 生殖中心應提供個案附加措施的最新實證資料；提供的資訊需與HFEA的臨床指引相符
3. 當使用實驗性質的附加措施時，病人應被清楚的被告知，且不應向病人收取額外費用
4. 當與病人或公開場合討論附加措施時，應正確且透明的澄清使用該附加措施的利益關係
5. 生殖中心應持續精進專業，提升標準照護

https://www.hfea.gov.uk/treatments/treatment-add-ons

Moving innovation to practice: an Ethics Committee opinion

The Ethics Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

倫理委員會建議在使用新治療(或附加措施)前，須先檢討的幾個問題

是否有適當證據支持新治療的有效性？

採用新治療的動機因素為何？

研究結果是否適用於個別臨床環境，且能否有效提供該新治療？

是否有足夠追蹤及預後資料支持新治療的使用？

臨床醫師如何與其病患溝通新治療？
(決策共享與知情同意書)

Fertil Steril. 2021 Aug;116(2):331-336.

Applying a simplified economic evaluation approach to evaluate infertility treatments in clinical practice

Qian Feng [1,*], Wentao Li [1], Emily J. Callander[2], Rui Wang [1], and Ben W. Mol[1,3]

"The cost of add-ons should be weighed against the **cost of a new subsequent IVF cycle**, …to ensure cost-effective use of funds"

The formula for how the benchmark cost per baby is calculated is as follows:

$$\text{Benchmark cost per baby} = \text{ICER} = \frac{\Delta C}{\Delta E} = \frac{C1 - C0}{E1 - E0}$$

$$= \frac{\$12\ 000 - \$0}{44.6\% - 0} = \$26\ 905$$

For a woman aged 30 years,

- C1 = cost for one complete IVF cycle is $12 000.
- C0 = cost for not performing IVF is 0.
- E1 = effectiveness denotes the cumulative live birth of performing one complete IVF cycle, which is 44.6%, according to the data from SART (2020).
- E0 = effectiveness of not performing IVF is 0.

Abbreviations: ICER: incremental cost-effectiveness ratio.

Table 1. The benchmark for cost-effectiveness based on the cost of a conventional complete IVF in relation to the success rates per age stratum (SART, 2020).

Age of women at oocyte retrieval, years	CLBR per started cycle (%)	Estimated cost per conventional complete IVF cycle	The cost to achieve a live-born baby	The maximal acceptable cost for achieving a 2% increase in CLBR
Under 35 years old	44.6	$12 000	$26 905	$538
35–37	31.5	$12 000	$38 095	$762
38–40	19.9	$12 000	$60 301	$1206
40–41	9.7	$12 000	$123 711	$2474
42 and above	2.9	$12 000	$413 793	$8276

選用Add-ons時，應(替病人)考慮成本效益

Human Reproduction 2024;39(3):448–453.

Table 2. The improvements in live birth rates (effectiveness) of add-ons and their costs.

Interventions (A)	Comparators (B)	Absolute CLBR differences between A and B	95% CI of the CLBR difference	Additional cost of adopting the intervention	Mean age, years (SD)	References
Add-ons in IVF						
PICSI	Standard ICSI	2.2%	−1.1%, 5.5%	$395	33.6 (4.4)	Hert & Essex Fertility Center (n.d.) and Miller *et al.* (2019)
Assisted hatching	No assisted hatching	1.0%	−13.2%, 15.0%	$700	34.0 (3.3)	Assisted Fertility Program (2023) and Sagoskin *et al.* (2007), and van de Wiel *et al.* (2020)
Endometrial scratching	No endometrial scratching	5.1%	−1.2%, 11.4%	$303	35.5 (range: 31.8–39.0)	van Hoogenhuijze *et al.* (2021) and van Hoogenhuijze *et al.* (2022)
Hyaluronate enriched medium	Low hyaluronate medium	8.8%	5.7%, 12.0%	$215	Median: under 35[a]	Adeniyi *et al.* (2021) and CareFertility (2023)
Other infertility treatments						
HSG with oil-based contrast	HSG with water contrast	10.7%	5.2%, 16.2%	$900	32.8 (IQR: 30.1–35.7)	Dreyer *et al.* (2017) and VARTA (2017)

[a] The exact median or mean age was not given in the original article, nor was the standard deviation.
CLBR: cumulative live birth rate; HSG: hysterosalpingography; IQR: interquartile range; PICSI: physiological ICSI.

***Safety issues should be heeded**

Human Reproduction 2023 Dec; dead265.

Original Investigation

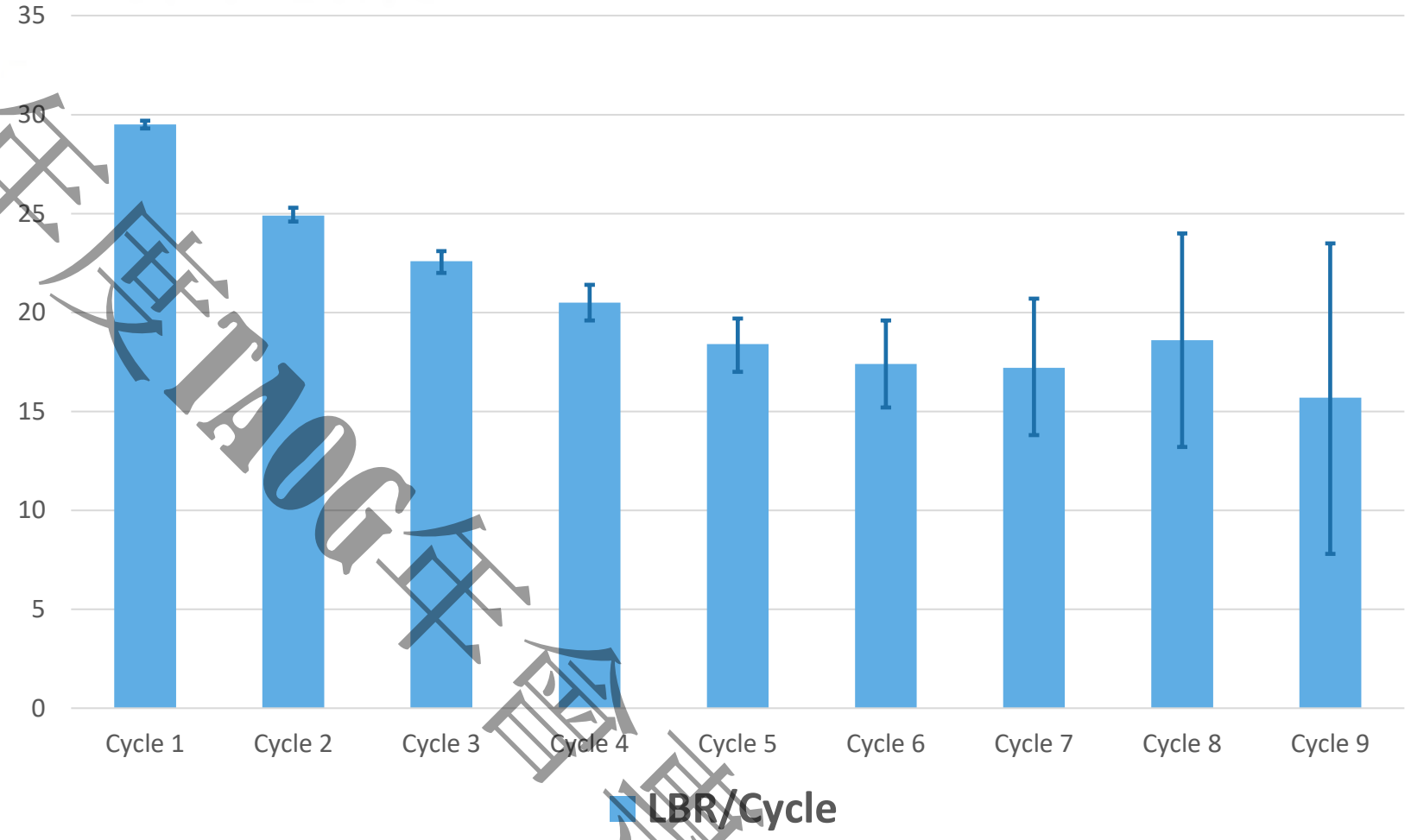
Live-Birth Rate Associated With Repeat In Vitro Fertilization Treatment Cycles

Andrew D. A. C. Smith, PhD; Kate Tilling, PhD; Scott M. Nelson, PhD; Debbie A. Lawlor, PhD

HFEA data, 2003/Jan-2012/Jun

Woman's age, median (IQR), y	35 (32-38)

Cycle No.	No. of Cycles	No. of Live Births	Live-Birth Rate Within Each Cycle, % (95% CI)
1	156 947	46 333	29.5 (29.3-29.7)
2	63 453	15 825	24.9 (24.6-25.3)
3	23 746	5358	22.6 (22.0-23.1)
4	8239	1690	20.5 (19.6-21.4)
5	3012	553	18.4 (17.0-19.7)
6	1162	202	17.4 (15.2-19.6)
7	458	79	17.2 (13.8-20.7)
8	199	37	18.6 (13.2-24.0)
9	83	13	15.7 (7.8-23.5)



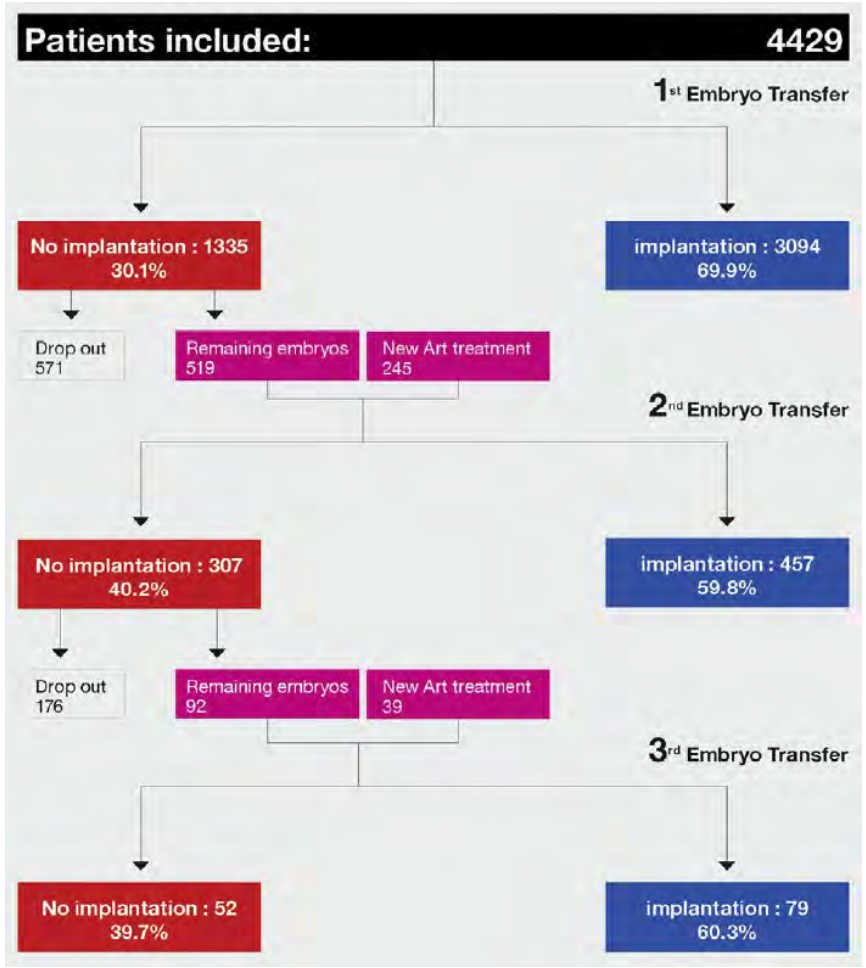
持續接受試管嬰兒治療，仍能維持一定每週期活產率

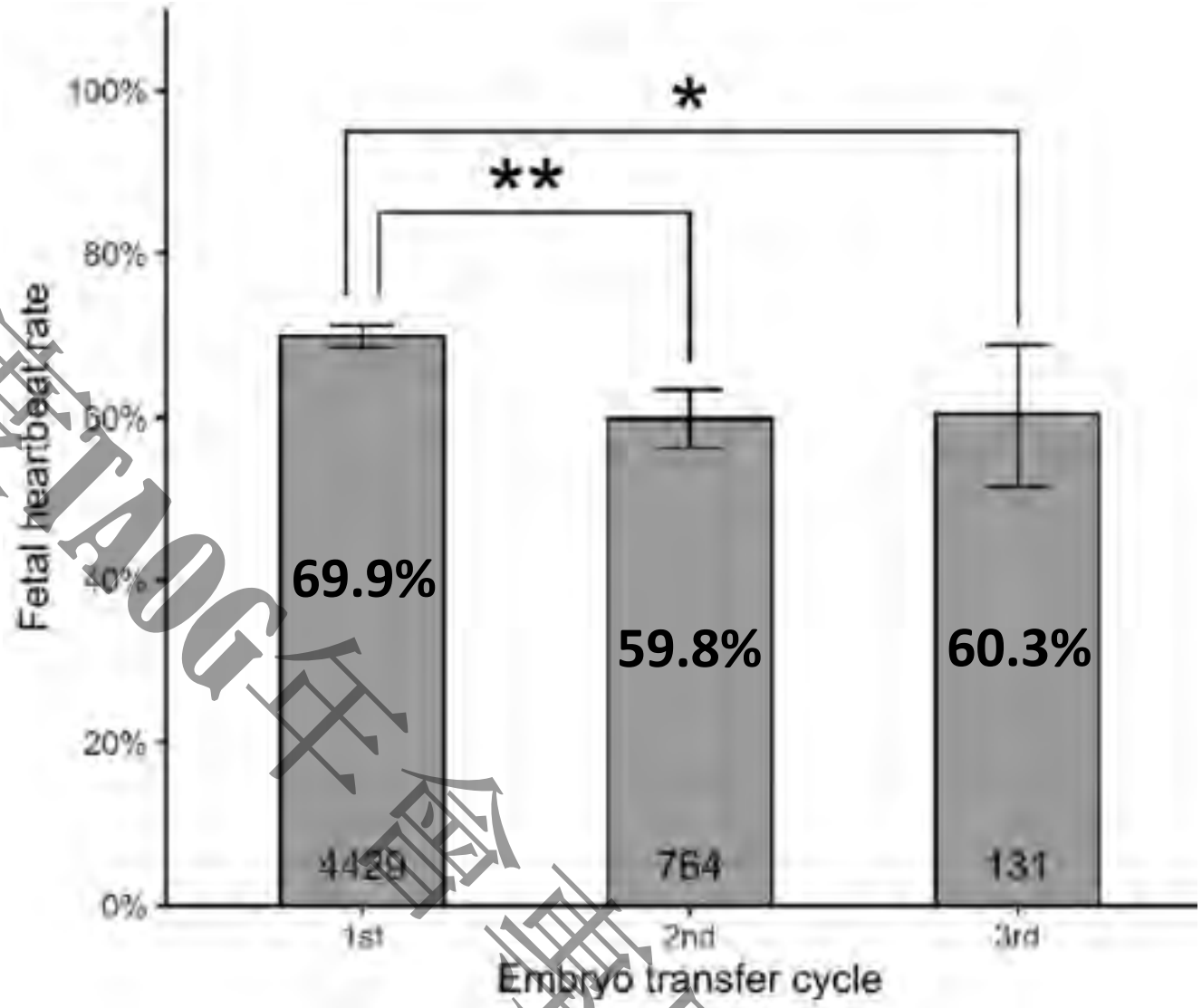
JAMA. 2015 Dec 22-29;314(24):2654-2662.

Rate of true recurrent implantation failure is low: results of three successive frozen euploid single embryo transfers

Paul Pirtea, M.D.,[a,b] Dominique De Ziegler, M.D.,[b] Xin Tao, Ph.D.,[c] Li Sun, Ph.D.,[c] Yiping Zhan, Ph.D.,[c] Jean Marc Ayoubi, M.D.,[b] Emre Seli, M.D.,[a,d] Jason M. Franasiak, M.D., H.C.L.D.,[a] and Richard T. Scott Jr., M.D., H.C.L.D.[a]

[a] IVIRMA New Jersey, Basking Ridge, New Jersey; [b] Hospital Foch, Paris, France; [c] Foundation for Embryonic Competence, Basking Ridge, New Jersey; and [d] Yale School of Medicine, New Haven, Connecticut





持續植入PGT-A正常胚胎仍能維持一定著床率

Fertil Steril. 2021 Jan;115(1):45-53.

Common practices among consistently high-performing in vitro fertilization programs in the United States: 10-year update

SART database

Jennifer F. Knudtson, M.D.,[a] Randal D. Robinson, M.D.,[a] Amy E. Sparks, Ph.D.,[b] Micah J. Hill, M.D.,[c] T. Arthur Chang, Ph.D.,[a] and Bradley J. Van Voorhis, M.D.[b]

TABLE 1

Clinical outcomes of in vitro fertilization in high-performing clinics and all programs in 2016 and 2017.

	2016		2017	
Outcome	**High-performing clinics (N = 13)**	**All programs**	**High-performing clinics (N = 13)**	**All programs**
Singleton birth cumulative outcome per egg retrieval				
Women <35 y	59% (53%–65%)	45%	61% (52%–66%)	48%
Women 35–37 y	47% (38%–55%)	34%	50% (36%–60%)	36%
% eSET rate in first transfer per clinic				
Women <35 y	78% (56%–100%)	56%	85% (43%–100%)	68%
Women 35–37 y	71% (61%–100%)	46%	74% (37%–100%)	59%
Singleton delivery per eSET: first transfer				
Women <35 y	62% (46%–72%)	51%	61% (51%–77%)	51%
Women 35–37 y	57% (47%–68%)	48%	56% (51%–70%)	49%

Note: eSET = elective single embryo transfer.

應致力於提高基礎成功率，從而減少非必要附加措施的使用

Fertil Steril. 2022 Jan;117(1):42-50.

總結—

1. Add-ons附加措施的使用在現今環境已相當普及，專業建議仍是重要決定因子
2. Add-ons附加措施的使用仍應本於實證醫學，ESHRE的Good practice recommendations及英國HFEA的建議可以做為參考
3. 在考慮使用Add-ons之前，應持續精進專業，提升標準照護成功率

總結二

4. 依據ESHRE的優良臨床建議:

建議使用：Additions to transfer media (HA), AOA (於特殊情況下)

可以考慮：Screening hysteroscopy (RIF), Microfluidics sperm selection

不建議(常規)使用：其他

與HFEA共同不建議：ERA, IVIG, Steroids

Thank You for Your Attention!

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