Recurrent Implantation Failure

Controversy over

Definition, Diagnosis, and Treatment Efficacy

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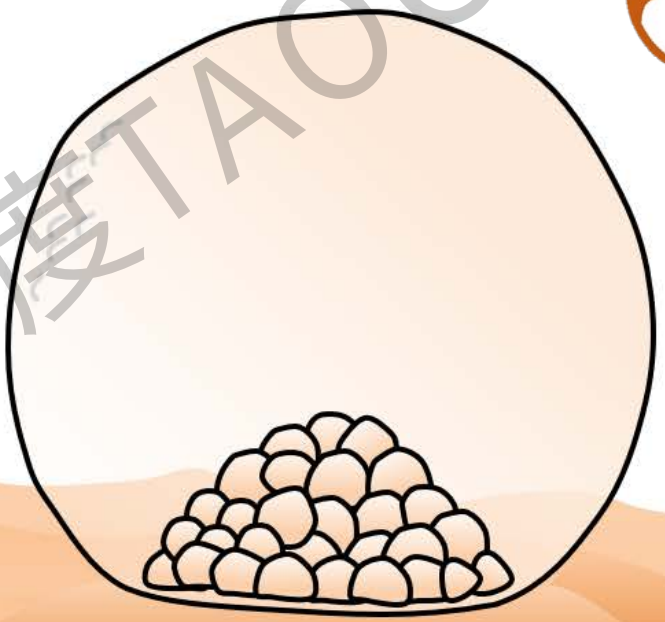


Controversy in RIF

Definition

定義反覆著床失敗

做了試管，植入幾次胚胎，結果都失敗

- **植入成功率非100%，受各種背景因素影響**
- 失敗尚可以機率解釋
- **不合理**的多次失敗，懷疑有未檢出的因素？
- 目的：**找出不會著床的族群，加以研究(或治療)**

What exactly do we mean by 'recurrent implantation failure'? A systematic review and opinion

最常見的定義：
≥2-3次失敗週期

Lukasz T Polanski [a,*], Miriam N Baumgarten [a], Siobhan Quenby [b], Jan Brosens [b], Bruce K Campbell [a], Nicholas J Raine-Fenning [a]

Table 1 Studies using a definition of RIF of three or more failed treatment cycles, alone or in combination with the number of embryos replaced.

Publication	Treatment modality in previous cycles	No. of embryos transferred	Embryo quality	Additional comments
De Placido et al. (1991)	Embryo transfers	–	–	–
Carp et al. (1994)	IVF	3 or more each time	–	–
Stein et al. (1995)	IVF	3 or 4 each time	Good	–
Creus et al. (1998)	IVF	2 or more each time	–	–
Rubio et al. (2001)	ICSI	–	Poor	–
Levran et al. (2002)	IVF, fresh cycles	–	–	–
Loutradis et al. (2004)	IVF or ICSI	–	Good	–
Rufas-Sapir et al. (2004)	IVF	–	–	Consecutive failed cycles
Pehlivan et al. (2003)	IVF	10 or more	Good	–
Ledee-Bataille et al. (2004b)	IVF	–	–	Good ovarian reserve (FSH <8 IU/l)
Ledee-Bataille et al. (2004a)	IVF	–	Good	Good ovarian reserve (FSH <8 IU/l) and good response in previous cycle
Primi et al. (2004)	Fresh cycles	2 or more each time	Good	–
Pantos et al. (2004)	IVF	–	–	–
Ledee-Bataille et al. (2005)	IVF	–	Good	–
Taranissi et al. (2005)	IVF	10 or more	–	–
Ghobara et al. (2006)	IVF or ICSI	–	–	–
Platteau et al. (2006)	IVF or ICSI	–	–	–
Qublan et al. (2006)	IVF	–	–	–
Mantzouratou et al. (2007)	IVF	–	–	–
Quenby et al. (2007)	IVF or ICSI	9 or more	Good	–
Matsubayashi et al. (2007)	IVF	–	–	–
Weissman et al. (2007)	IVF, fresh cycles	–	–	–
van den Heuvel et al. (2007)	IVF	–	–	Consecutive failed cycles
Matteo et al. (2007)	IVF, fresh cycles	2 or more each time	Good	Good ovarian reserve (FSH <8 IU/l) and good response in previous cycle
Kling et al. (2008b)	IVF, fresh cycles	–	–	–
Blockeel et al. (2008)	IVF	10 or more	Good	–
Prakash et al. (2008)	IVF, fresh or frozen	–	Good	–
Thum et al. (2008)	IVF	2 or 3 each time	Good	–
Yakin et al. (2008)	Fresh treatment cycles	–	–	–
Simur et al. (2009)	IVF	3 or more	Good	–
Kling et al. (2008a)	IVF	–	–	Consecutive failed cycles
Pagidas et al. (2008)	IVF	–	–	–
Jee et al. (2009)	IVF	–	–	Good number of oocytes, embryos and adequate transfer
Koler et al. (2009)	IVF	10 or more	High	–
Brosens et al. (2009)	IVF	–	Good	–

(continued on next page)

Table 1 (continued)

Publication	Treatment modality in previous cycles	No. of embryos transferred	Embryo quality	Additional comments
Debrock et al. (2009)	IVF, fresh cycles	–	–	–
Fragouli et al. (2010)	IVF	10 or more	Good	–
Germeyer et al. (2010)	Embryo transfers	–	Good	–
Achache et al. (2010b)	IVF, fresh cycles	–	–	–
Achache et al. (2010a)	IVF	–	Good	Good ovarian reserve and age under 40
Chernyshov et al. (2010)	IVF	2 or more each time	Good	–
Kim et al. (2011)	IVF or ICSI	–	Grade 1 or 2	–
Martínez-Zamora et al. (2011)	Fresh or frozen cycles	1 or more each time	Grade 1 or 2	–
Choi et al. (2011)	IVF	–	–	–
Tiboni et al. (2011)	Embryo transfers	–	–	–
Rajaei et al. (2011)	IVF or ICSI	10 or more	–	
Sudoma et al. (2011)	–	2 or more each time	Good	–
Sacks et al. (2012)	Fresh or frozen cycles	–	–	–
Scarpellini and Sbracia (2012)	IVF	7 or more	Good	Age <39, no systemic illness

Table 2 Studies using a definition of RIF of two or more failed treatment cycles, alone or in combination with the number of embryos replaced.

Publication	Treatment modality in previous cycles	No. of embryos transferred	Embryo quality	Additional comments
Gianaroli et al. (1997)	IVF	–	–	–
Kahraman et al. (2000)	–	–	–	–
Stephenson and Fluker (2000)	Fresh or frozen cycles	–	–	–
Matsubayashi et al. (2001)	IVF	–	Visually good	–
Spandorfer et al. (2002)	IVF	–	–	–
Kwak-Kim et al. (2003)	IVF	2 or more each time	–	–
Kahraman et al. (2004)	–	3 or more	Good	–
Martinuzzo et al. (2005)	IVF	–	Good	–
Petersen et al. (2005)	Fresh or frozen cycles	–	–	–
Fukui et al. (2006)	IVF	–	Good	–
Koscinski et al. (2006)	IVF	2 or more	Good	–
Vaquero et al. (2006)	IVF	–	–	–
Foulk et al. (2007)	–	–	Top	–
Arefi et al. (2008)	IVF or ICSI	3 or more	Good	–
Fukui et al. (2008)	IVF	4 or more	–	–
Hiraoka et al. (2008)	Fresh or frozen cycles	–	–	Cleavage–stage embryos
Kalu et al. (2008)	IVF	–	Good	–
Valojerdi et al. (2008)	–	–	–	–
Urman et al. (2009)	Fresh cycles	–	–	–
Aletebi (2010)	–	3 or more	Good	–
Berker et al. (2011)	ICSI	–	–	–
Eyheremendy et al. (2010)	IVF or ICSI, fresh or frozen cycles	–	–	–
Johnston-MacAnanny et al. (2010)	IVF	1 or more each time	Good	–
Schoolcraft et al. (2010)	–	–	–	–
Sharif and Ghunaim (2010)	IVF or ICSI, fresh cycles	6 or more	Good (G1 or G2)	–
Tsoumpou et al. (2010)	–	–	Good	–
Yang et al. (2010)	IVF	2 or more each time	–	–
Chou et al. (2011)	IVF	–	Good	–
Huang et al. (2011)	IVF	–	Good	–
Lodigiani et al. (2011)	IVF or ICSI	–	–	–
Oliveira et al. (2011)	ICSI	–	Morphologically good	–
Takahashi et al. (2011)	Fresh or frozen cycles	–	–	–
Ivanov et al. (2012)	IVF	–	–	–
Sermondade et al. (2012)	IVF	–	–	–

Table 3 Studies using less common inclusion criteria of RIF into study populations.

Publication	No. of previous failed cycles	Treatment modality in previous cycles	No. of embryos transferred	Embryo quality	Additional comments
Huang et al. (1999)	5 or more	IVF or ICSI	3 or more each time	–	–
Bashiri et al. (2002)	6 or more	–	15 or more	–	–
Vuillaire et al. (2002)	Multiple failed cycles	IVF	10 or more	–	–
Ekram et al. (2005)	7 or more	Fresh cycles	At least 2 each time	Good	–
Varia-Leftheriotí et al. (2007)	5 or more	IVF	More than 2 each time		<38 years
Ledee et al. (2008)	Several failed cycles	Fresh or frozen cycles	10 or more	Fragmentation <20% and at least 4-cell stage by day 2	Unexplained failure of treatment cycles
Brinsden et al. (2009)	2 or more or 3 or more	Assisted reproduction treatment cycles, fresh	2 or more or 1 or more each time, respectively	Grade A or B	–
Karimzadeh et al. (2009)	2–6 cycles	IVF	10 or more	Good	<40 years, good responders (>4 follicles at HCG), good ovarian reserve (FSH <10 IU/l), no uterine anomalies, endometriomas, hydrosalpinges or coagulation disorders
Tuckerman et al. (2010)	3 fresh or more or 2 fresh and 2 frozen cycles	IVF, fresh or frozen	–	Good	–
Dos Santos et al. (2012)	Several failed cycles	IVF, fresh or frozen	10 or more	Fragmentation <20% and at least 4-cell stage by day 2	Good hormonal reserve (FSH <10 IU/l) and good response to previous treatment

治療模式 × 胚胎品質 × 植入次數 × 週期次數 × 胚胎數量 × 個案條件

119個研究，計有數十種定義

Reprod Biomed Online. 2014 Apr;28(4):409-23.

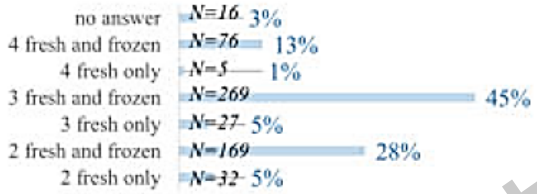
Definition, diagnostic and therapeutic options in recurrent implantation failure: an international survey of clinicians and embryologists

ESHRE special interest group on implantation and early pregnancy (**SIGIEP**), Online survey, 2020/May/4th-June/4th, ESHRE members (n=8579), 1061 responses (15%)

D. Cimadomo[1], L. Craciunas[2], N. Vermeulen[3], K. Vomstein[4,*], and B. Toth[4]

2.1 Do you define RIF based on the number of failed ETs? N=703

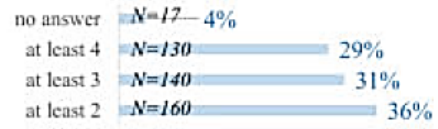
2.1.1 After at least how many failed ETs would you define RIF? N=594



2.1.2 Do you count ETs performed at other IVF centers? N=594

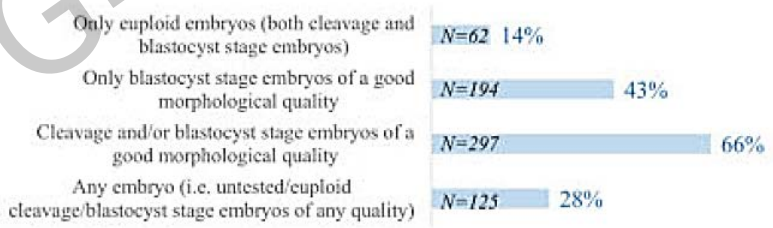
2.2 Do you define RIF based on the number of embryos that failed to implant? N=703

2.2.1 How many embryos should have been transferred unsuccessfully? N=447

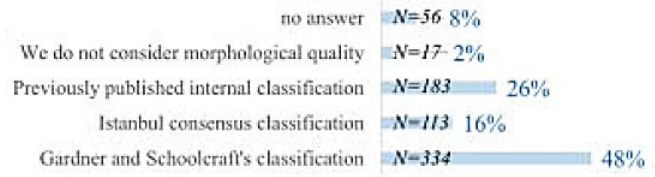


2.2.2 Do you count embryos transferred at other IVF centers? N=447

2.2.3 Which embryos do you consider in making a diagnosis of RIF? (multiple choice) N=447



2.3 How do you define a good morphological quality of the embryo? N=703



2.4 Do you take women's age into account in the definition of RIF? N=703

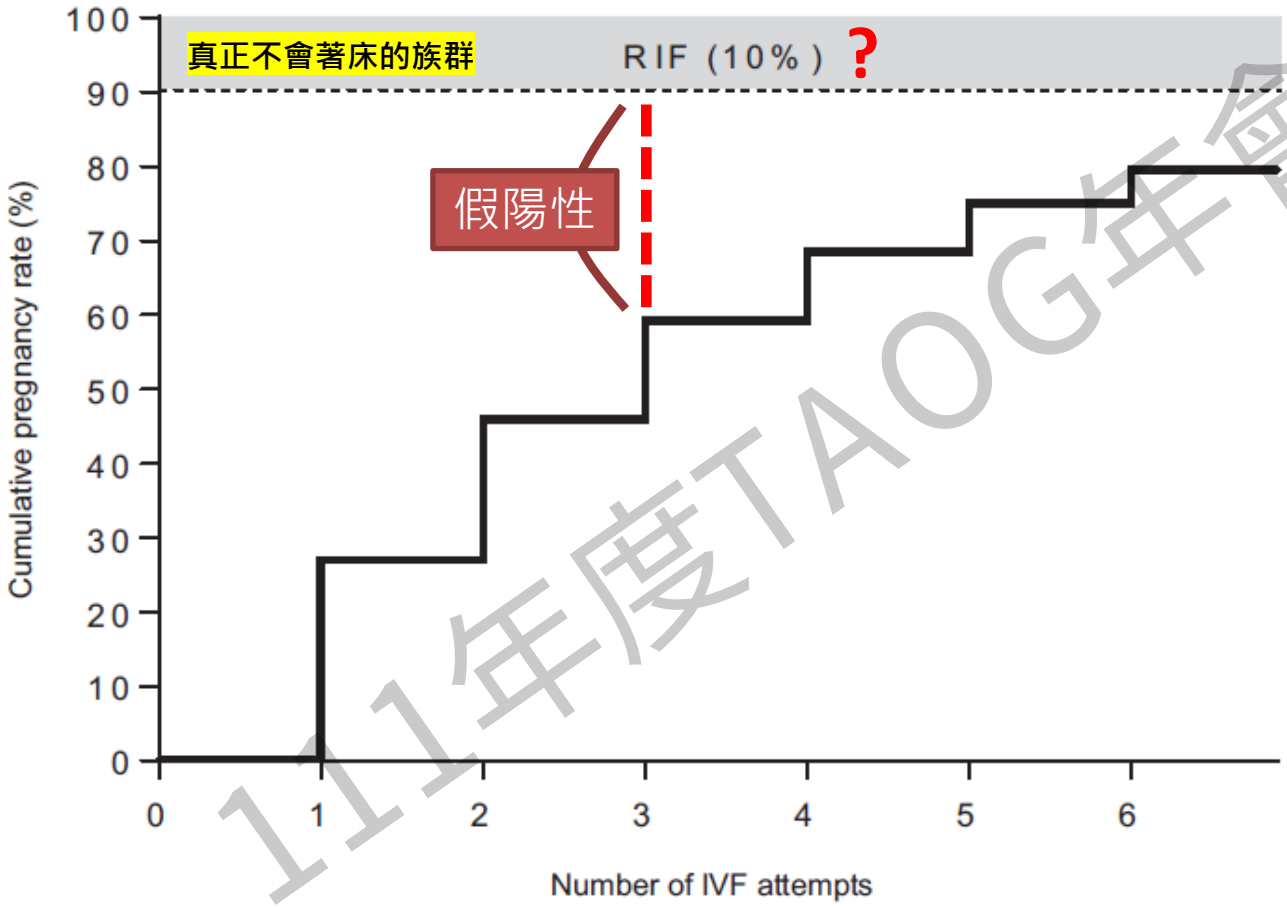
時至今日仍無共識

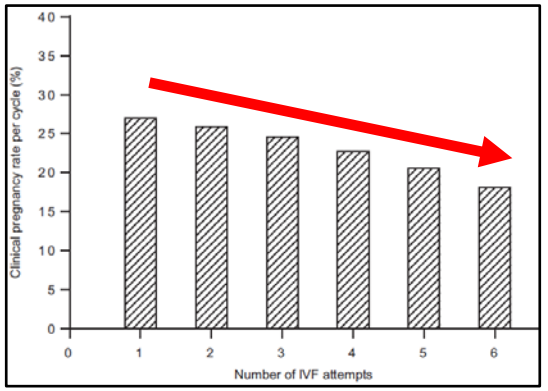
Hum Reprod. 2021 Jan 25;36(2):305-317.

量化 RIF

Repeated implantation failure at the crossroad between statistics, clinics and over-diagnosis

Edgardo Somigliana [a,b,], Paola Vigano [c], Andrea Busnelli [a,b], Alessio Paffoni [b], Walter Vegetti [b], Paolo Vercellini [a,b]*





成功者離開分母

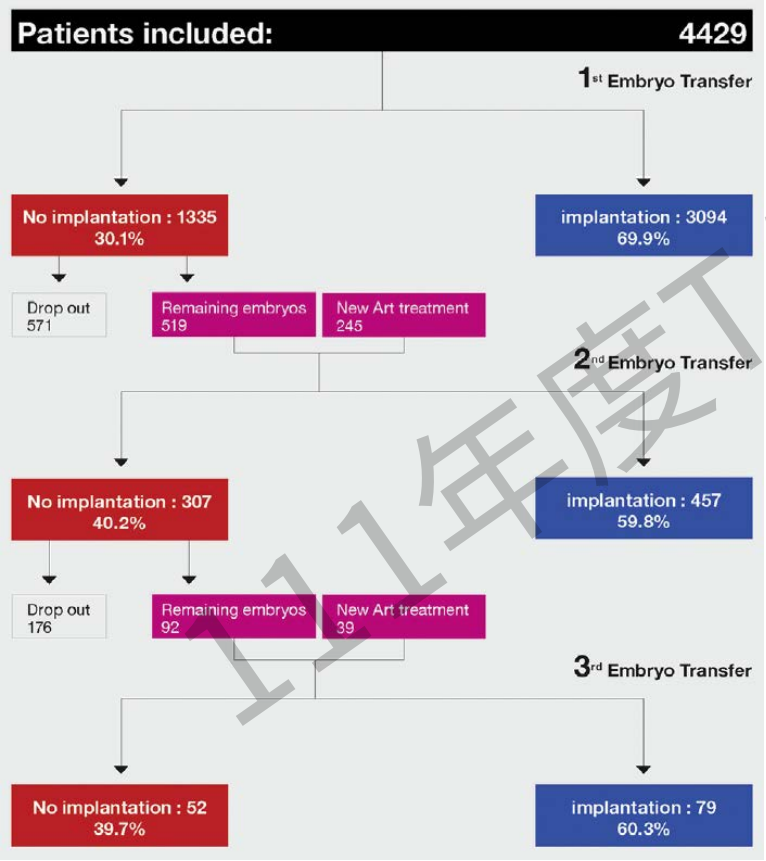
若RIF穩定存在(如10%)，三次失敗診斷RIF，仍有3/4為假陽性

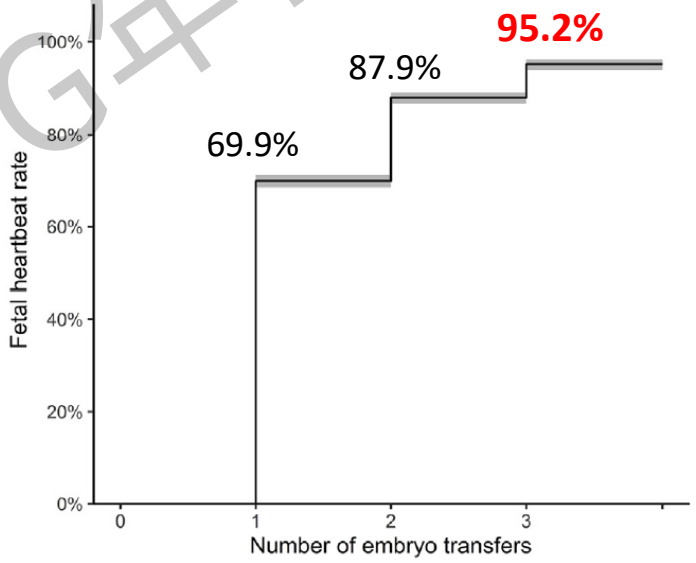
Reprod Biomed Online. 2018 Jan;36(1):32-38.

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

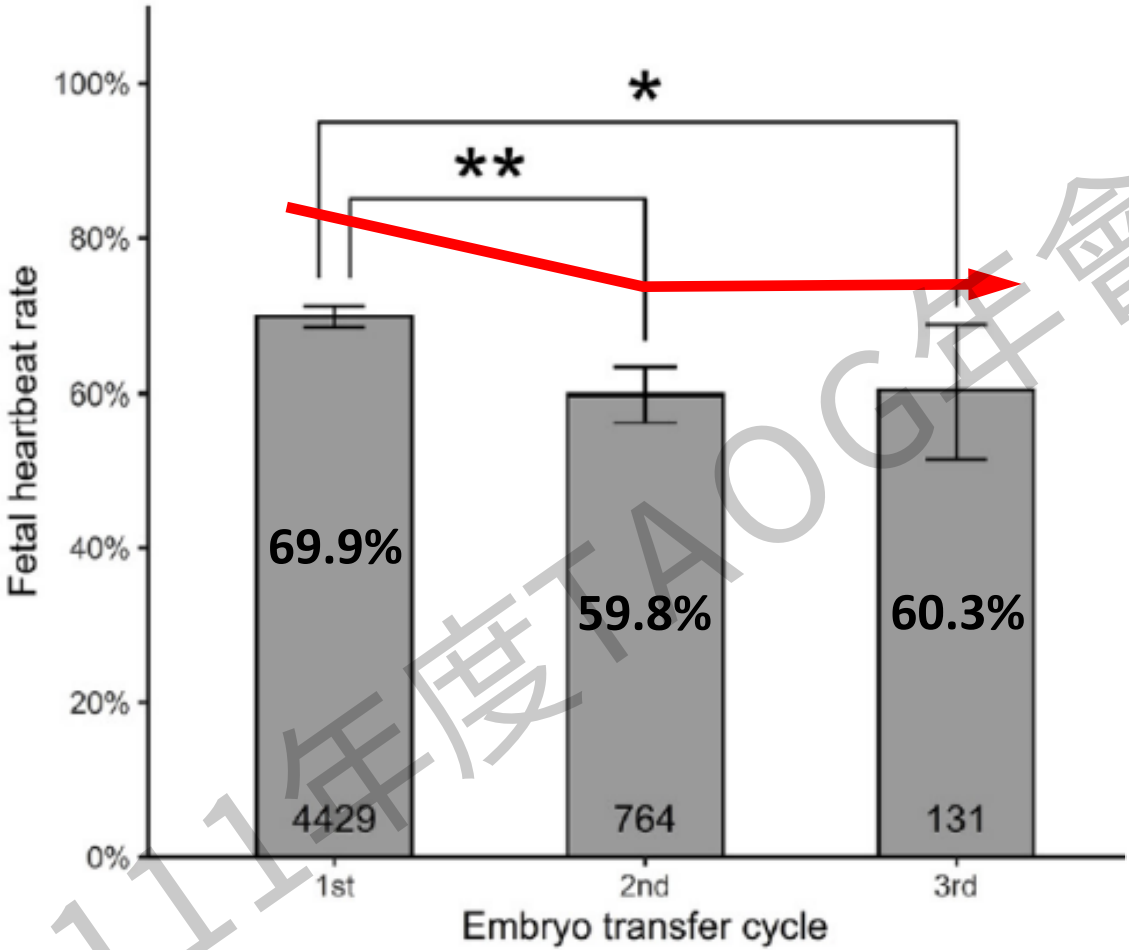


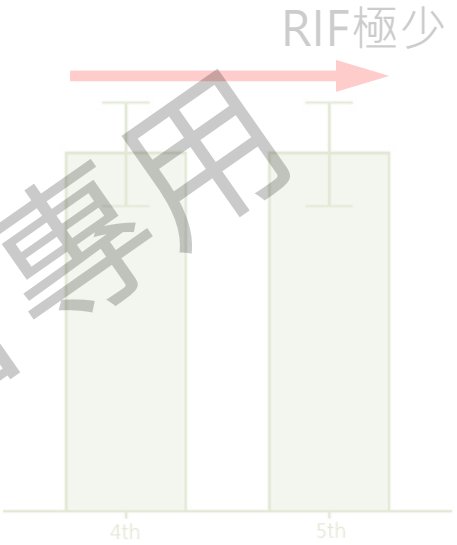


植入3次PGT-A正常胚胎，累積著床率可達95.2%

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

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





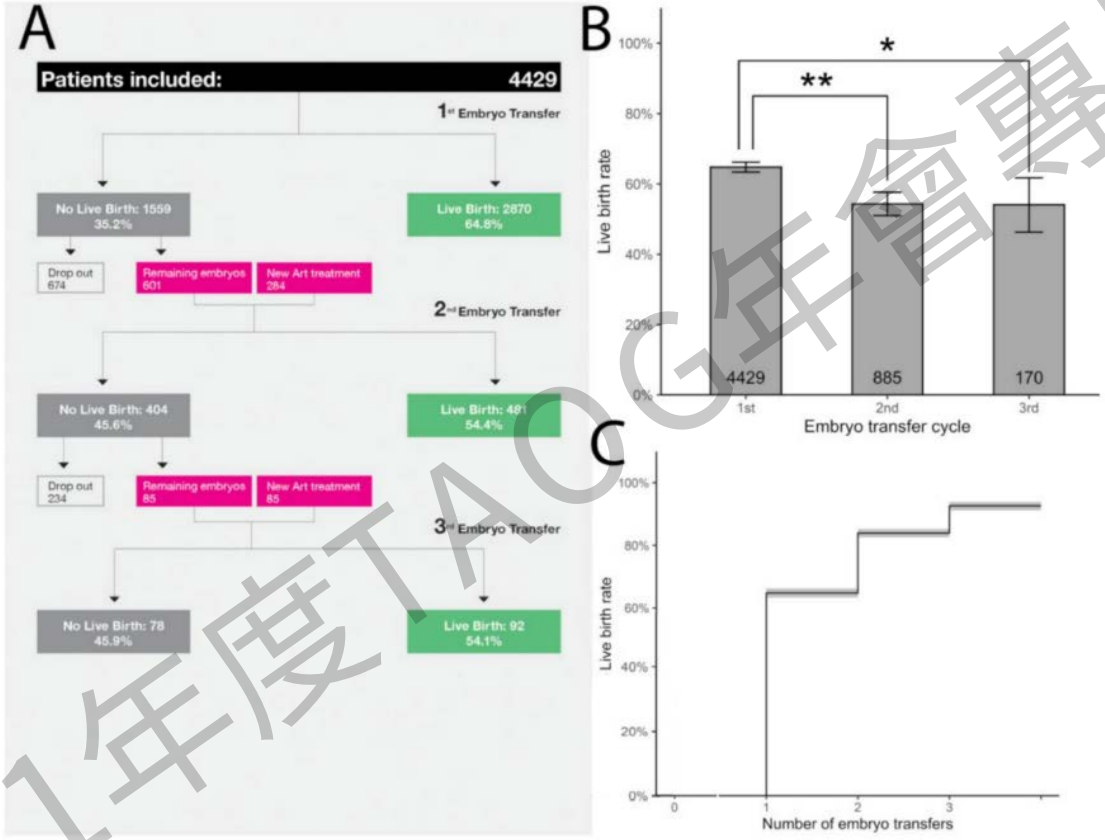
植入2次失敗後，著床率無持續下降趨勢

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

Review

Recurrent Implantation Failure—Is It the Egg or the Chicken?

Paul Pirtea *, Dominique de Ziegler and Jean Marc Ayoubi



On the contrary, our results suggest that the vast majority of RIFs are of embryonic origin, which can be considerably reduced by transferring embryos tested by PGT-A.

著床失敗主因為非整倍體胚胎！

Life (Basel). 2021 Dec 27;12(1):39.

未做
PGT-A

A new definition of recurrent implantation failure on the basis of anticipated blastocyst aneuploidy rates across female age

Baris Ata, M.D., M.Sc.,[a] Erkan Kalafat, M.D., M.Sc.,[a,b] and Edgardo Somigliana, M.D., Ph.D.[c,d]

$$p = p_{\text{aneuploid}} \times 0.01 + p_{\text{euploid}} \times p_{\text{i}}$$

(綜合著床機率)

(45%-65%)

植入N顆胚胎後的累積著床率

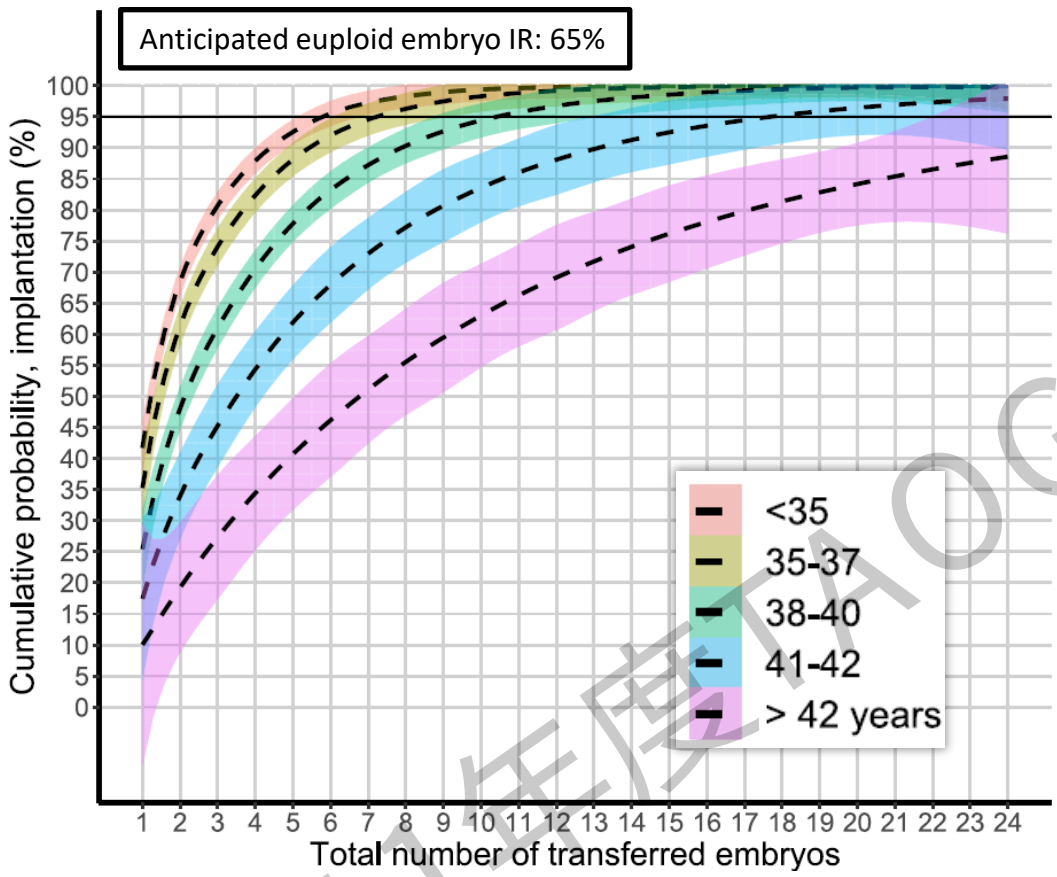
$$\Pr(X \geq k) = \sum_{i=k-1}^{n} \binom{n}{i} p^i (1-p)^{n-i},$$

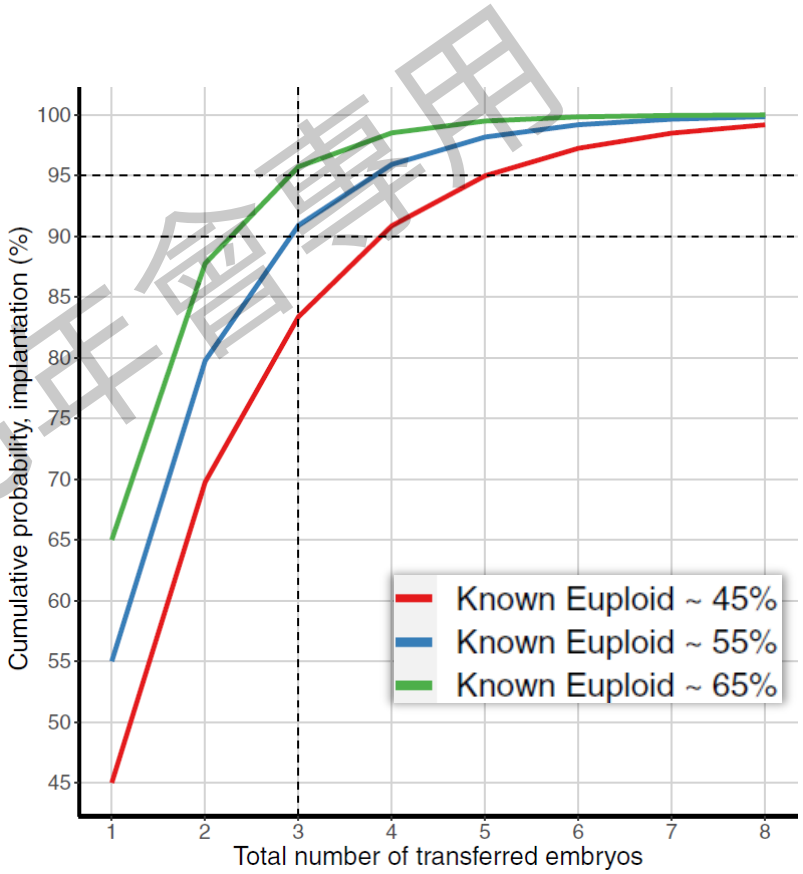
植入囊胚數

目標著床顆數 (≥1)

每個囊胎的綜合著床率

Fertil Steril. 2021 Nov;116(5):1320-1327.





若RIF發生率5%，<35歲者需要植入6顆才達診斷標準

Adapted from Fertil Steril. 2021 Nov;116(5):1320-1327.

A new definition of recurrent implantation failure on the basis of anticipated blastocyst aneuploidy rates across female age

Baris Ata, M.D., M.Sc.,[a] Erkan Kalafat, M.D., M.Sc.,[a,b] and Edgardo Somigliana, M.D., Ph.D.[c,d]

mmc1

Implantation and euploidy rates were derived from studies of PGT-A with comprehensive chromosome analysis published until 2021. The estimates are merely theoratical and actual cumulative implantation rate may differ for each patient.	
I want to use my own data for euploidy rate	No
Age of woman at the time of oocyte collection	Euploidy rate
<35	0.65
35-37	0.55
38-40	0.35
41-42	0.25
>42	0.15
Euploid blastocyst implantation rate	0.55
RIF calculator	
VARIABLES	VALUES
Age category	35-37
Were the blastocysts known to be euploid?	No, embryos were not screened for aneuploidy
Total number of blastocysts transferred	8
Threshold of expected cumulative implantation rate for diagnosing	90
Expected cumulative implantation rate (%)	89.59775404
Patient status	Cumulative implantation rate is within expected norms

Fertil Steril. 2021 Nov;116(5):1320-1327.

An algorithm to personalise the diagnosis of recurrent implantation failure based on theoretical cumulative implantation rate

Genia Rozen [1,2,3,*], Peter Rogers[2], Wan Tinn Teh[1,2,3], Catharyn J. Stern[1,2,3], and Alex Polyakov[1,2,3]

The concept of "**Theoretical Cumulative Implantation Rate**" (TCIR)

A 28 year old with tubal factor infertility has three ETs each with a good quality embryo. The assumption for this example is that every embryo has a 40% chance of producing a positive β-HCG. In this scenario the TCIR can be calculated in the following way:

The chance of not being pregnant after every transfer is multiplied by the chance of not being pregnant in the subsequent transfer:

$$0.6 \times 0.6 \times 0.6 = 0.22$$

The cumulative chance of being pregnant after three ETs with 40% chance of pregnancy per ET is therefore:

$$(1 - 0.22) \times 100 = 78\%$$

Number of ETs

$$TCIR = 1 - (1 - IC)^{ETN}$$

Chance of implantation per ET

Table 1 Calculation of the theoretical cumulative implantation rate.*

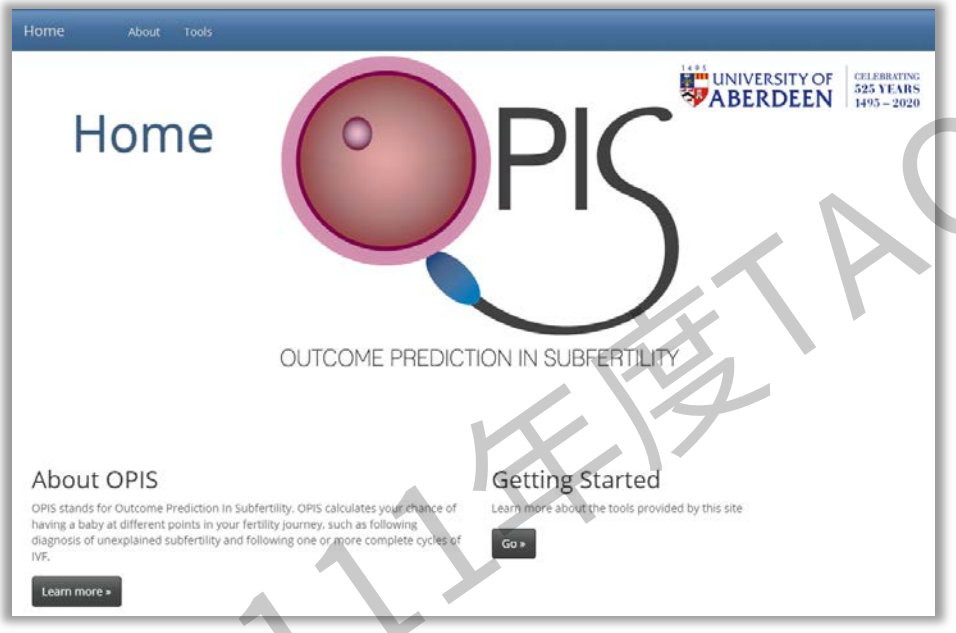
ET number	Theoretical cumulative implantation rate									
	50%	45%	40%	35%	30%	25%	20%	15%	10%	5%
1	0.500	0.450	0.400	0.350	0.300	0.250	0.200	0.150	0.100	0.050
2	0.750	0.698	0.640	0.578	0.510	0.438	0.360	0.278	0.190	0.098
3	0.875	0.834	0.784	0.725	0.657	0.578	0.488	0.386	0.271	0.143
4	0.938	0.908	0.870	0.821	0.760	0.684	0.590	0.478	0.344	0.185
5	0.969	0.950	0.922	0.884	0.832	0.763	0.672	0.556	0.410	0.226
6	0.984	0.972	0.953	0.925	0.882	0.822	0.738	0.623	0.469	0.265
7	0.992	0.985	0.972	0.951	0.918	0.867	0.790	0.679	0.522	0.302
8	0.996	0.992	0.983	0.968	0.942	0.900	0.832	0.728	0.570	0.337
9	0.998	0.995	0.990	0.979	0.960	0.925	0.866	0.768	0.613	0.370
10	0.999	0.997	0.994	0.987	0.972	0.944	0.893	0.803	0.651	0.401
11	1.000	0.999	0.996	0.991	0.980	0.958	0.914	0.833	0.686	0.431
12	1.000	0.999	0.998	0.994	0.986	0.968	0.931	0.858	0.718	0.460
13	1.000	1.000	0.999	0.996	0.990	0.976	0.945	0.879	0.746	0.487
14	1.000	1.000	0.999	0.998	0.993	0.982	0.956	0.897	0.771	0.512
15	1.000	1.000	1.000	0.998	0.995	0.987	0.965	0.913	0.794	0.537
16	1.000	1.000	1.000	0.999	0.997	0.990	0.972	0.926	0.815	0.560
17	1.000	1.000	1.000	0.999	0.998	0.992	0.977	0.937	0.833	0.582
18	1.000	1.000	1.000	1.000	0.998	0.994	0.982	0.946	0.850	0.603
19	1.000	1.000	1.000	1.000	0.999	0.996	0.986	0.954	0.865	0.623
20	1.000	1.000	1.000	1.000	0.999	0.997	0.988	0.961	0.878	0.642
21	1.000	1.000	1.000	1.000	0.999	0.998	0.991	0.967	0.891	0.659
22	1.000	1.000	1.000	1.000	1.000	0.998	0.993	0.972	0.902	0.676
23	1.000	1.000	1.000	1.000	1.000	0.999	0.994	0.976	0.911	0.693
24	1.000	1.000	1.000	1.000	1.000	0.999	0.995	0.980	0.920	0.708
25	1.000	1.000	1.000	1.000	1.000	0.999	0.996	0.983	0.928	0.723
26	1.000	1.000	1.000	1.000	1.000	0.999	0.997	0.985	0.935	0.736
27	1.000	1.000	1.000	1.000	1.000	1.000	0.998	0.988	0.942	0.750
28	1.000	1.000	1.000	1.000	1.000	1.000	0.998	0.989	0.948	0.762
29	1.000	1.000	1.000	1.000	1.000	1.000	0.998	0.991	0.953	0.774
30	1.000	1.000	1.000	1.000	1.000	1.000	0.999	0.992	0.958	0.785
31	1.000	1.000	1.000	1.000	1.000	1.000	0.999	0.994	0.962	0.796
32	1.000	1.000	1.000	1.000	1.000	1.000	0.999	0.994	0.966	0.806

Hum Reprod. 2021 May 17;36(6):1463-1468.

An algorithm to personalise the diagnosis of recurrent implantation failure based on theoretical cumulative implantation rate

Genia Rozen [1,2,3,*], Peter Rogers[2], Wan Tinn Teh[1,2,3], Catharyn J. Stern[1,2,3], and Alex Polyakov[1,2,3]

"Prognosis-based" predictive outcome model



BMJ. 2016 Nov 16;355:i5735.

Hum Reprod. 2021 May 17;36(6):1463-1468.

Views and Reviews

Defining recurrent implantation failure: a profusion of confusion or simply an illusion?

Audrey S. Garneau, M.D. and Steven L. Young, M.D., Ph.D.

UNC HEALTH CARE WOMEN'S CARE

We propose that large-scale data be applied to allow personalization of the diagnosis by modeling multiple factors. Until we have the ability to more fully personalize, definitions should, at a minimum, account for the risk of aneuploidy as a significant factor governing implantation.

個體化的RIF定義是趨勢；
目前應至少考慮非整倍體胚胎率

Fertil Steril. 2021 Dec;116(6):1432-1435.

現實層面

Repeated implantation failure at the crossroad between statistics, clinics and over-diagnosis

Edgardo Somigliana [a,b,*], *Paola Vigano* [c], *Andrea Busnelli* [a,b], *Alessio Paffoni* [b], *Walter Vegetti* [b], *Paolo Vercellini* [a,b]

- RIF若作為一個篩檢性的定義，可以接受**高敏感度**及**低特異性**
- 現行的定義(預後良好者2-3次植入失敗)仍可使用；但可能使個案暴露於**過度診斷**的風險！
- 需使個案了解試管嬰兒實際的成功率不高；多數個案無法接受失敗為常態

Reprod Biomed Online. 2018 Jan;36(1):32-38.

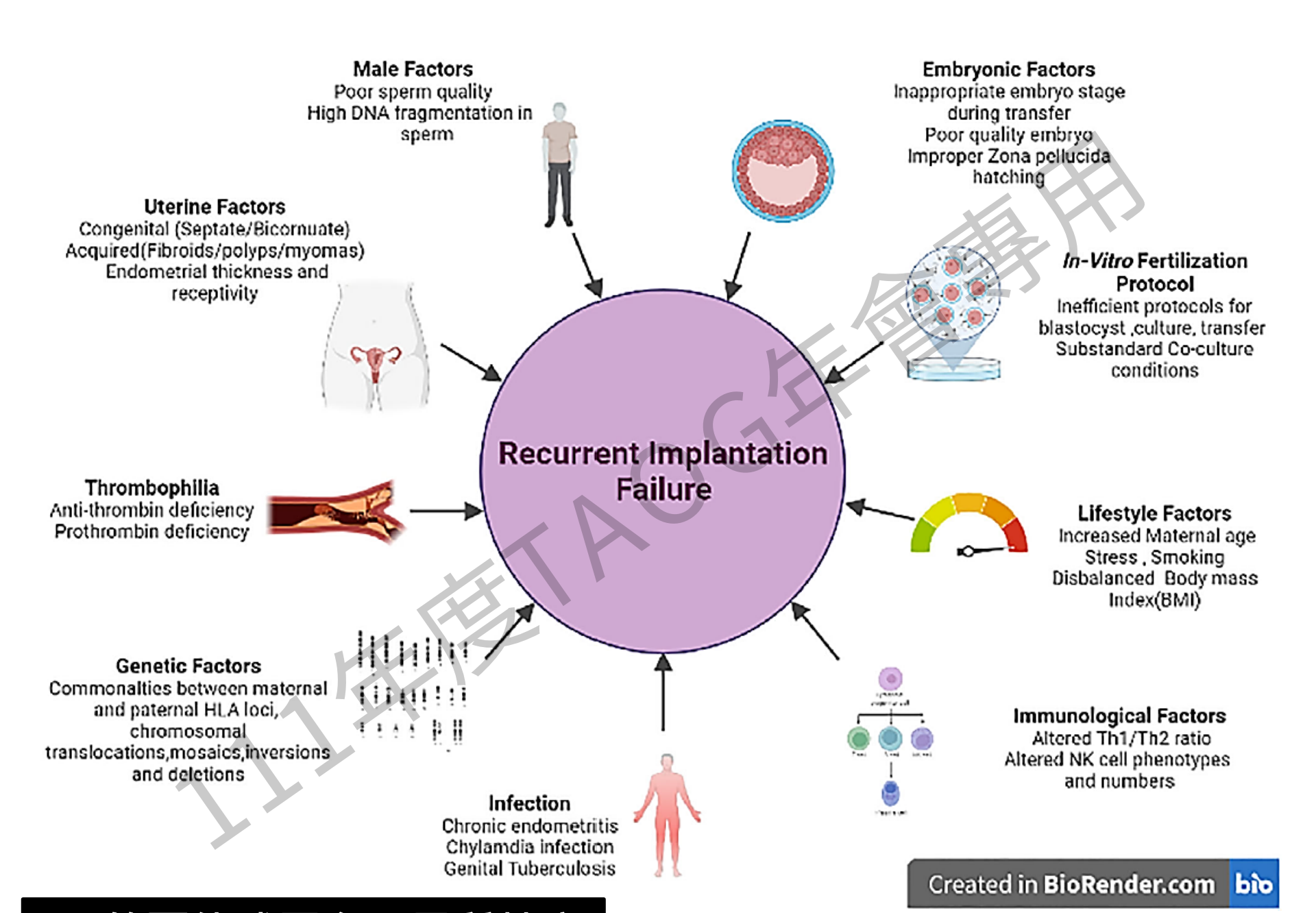
關於定義的Take Home Messages

1. 「非整倍體」胚胎是著床失敗的已知主因；95%的累積著床率是可達成的
   - 真正無法著床的族群可能<5%

2. 未施作PGT-A，仍可估算LBR找出非預期的失敗族群
   - 以固定次數定義RIF，極可能過度診斷

Controversy in RIF

Management



RIF的可能成因多 - 異質性高

Am J Reprod Immunol. 2022 May 19;e13563.

Repeated implantation failure: clinical approach

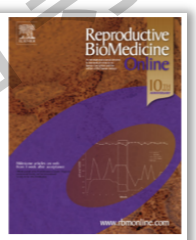
Alex Simon, M.D., and Neri Laufer, M.D.

In Vitro Fertilization Unit, Department of Obstetrics and Gynecology, Ein Kerem, Hebrew University, Hadassah Medical Center, Jerusalem, Israel

Fertil Steril. 2012 May;97(5):1039-43.

ELSEVIER

www.sciencedirect.com
www.rbmonline.com



REVIEW

Reprod Biomed Online. 2014 Jan;28(1):14-38.

Recurrent implantation failure: definition and management

C Coughlan [a], W Ledger [b], Q Wang [c], Fenghua Liu [d], Aygul Demirol [e], Timur Gurgan [e], R Cutting [a], K Ong [f], H Sallam [g], TC Li [a,*]

REVIEW Open Access

Recurrent Implantation Failure-update overview on etiology, diagnosis, treatment and future directions

Reprod Biol Endocrinol. 2018 Dec 5;16(1):121.

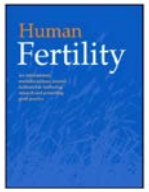
Asher Bashiri[1,2], Katherine Ida Halper[2*] and Raoul Orvieto[3,4]

RBMO

REVIEW

Recurrent implantation failure in IVF: A Canadian Fertility and Andrology Society Clinical Practice Guideline

Talya Shaulov[1,2], Sony Sierra[3,4], Camille Sylvestre[2,5,*]



Management of recurrent implantation failure: British Fertility Society policy and practice guideline

Mariano Mascarenhas, Yadava Jeve, Lukasz Polanski, Abigail Sharpe, Ephia Yasmin & Harish M. Bhandarion behalf of the British Fertility Society

Reprod Biomed Online. 2020 Nov;41(5):819-833.

Hum Fertil (Camb). 2021 Apr 5;1-25.

Recurrent implantation failure in IVF: A Canadian Fertility and Andrology Society Clinical Practice Guideline

TABLE 6 SUMMARY OF RECOMMENDATIONS

May be offered	Limited to research settings only
Karyotype testing	Serological and endometrial immune testing
Preimplantation genetic testing for aneuploidies	Endometrial receptivity assays
	Empirical low molecular weight heparin
	Immunotherapy, Intralipid, glucocorticoids, granulocyte colony-stimulating factor

Not recommended
Hysteroscopy if baseline ultrasound is normal
Acquired and congenital thrombophilia workup
Sperm DNA fragmentation index
Screening for chronic endometritis
Endometrial injury in the preceding menstrual cycle
Aspirin

Reprod Biomed Online. 2020 Nov;41(5):819-833.

Management of recurrent implantation failure: British Fertility Society policy and practice guideline

Table 2. Summary of evidence for investigations into RIF.

Sperm	Sperm aneuploidy	Yellow
	Sperm epigenetics	Red
	Computer assisted sperm analysis	Red
	DNA fragmentation	Yellow
Oocyte	AMH	Yellow
Parental karyotype	Blanket testing	Red
	Higher order RIF or additional risk factors such as recurrent miscarriages	Yellow
Uterine and adnexal factors	Ultrasound (including 3D ultrasound)	Green
	Screening hysteroscopy	Red
	Endometrial receptivity array	Red
Immunological disorders and thrombophilia	Uterine natural killer cells	Yellow
	Peripheral natural killer cells	Red
	Endometrial cytokines	Red
	Genital microbiome	Red
	Peripheral blood cytokines	Red
	HLA incompatibility	Red
	Inherited thrombophilia	Red
	Antiphospholipid antibody syndrome	Yellow
Endocrine factors	Thyroid function test	Green
	Thyroid antibody testing	Yellow
	Prolactin	Red
	Free androgen index	Red
	HbA1c	Red

Green: There is evidence to support the investigation or management modality in RIF.
Yellow: Need additional data to make a firm recommendation.
Red: Lack of evidence to support the investigation or management modality.

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Hum Fertil (Camb). 2021 Apr 5;1-25.

Recommendations

May be offered

- Karyotype testing
- PGT-A

- Ultrasound (including 3D US)
- Thyroid function test
- Smoking cessation, Optimising weight, Vitamin D supplementation
- Counseling
- US-guided ET, full bladder at ET
- Endometrial polypectomy, Surgery for submucous fibroid, Salpingectomy for hydrosalpinx
- Rx for subclinical hypothyroidism

兩份指引的共識：無實證支持之有效檢查或治療！

Reprod Biomed Online. 2020 Nov;41(5):819-833.

Hum Fertil (Camb). 2021 Apr 5;1-25.

Controversy in RIF

Management

- PGT-A
- ERA
- Immune
- Others (HSC)

Pregestational Genetic Testing for Aneuploidy (PGT-A)

PGT-A	**May be offered**	**Grade C evidence**

Lack of evidence to support the modality

The status of preimplantation genetic testing in the UK and USA

Rachel Theobald[1], Sioban SenGupta[1], and Joyce Harper[1,2,*]

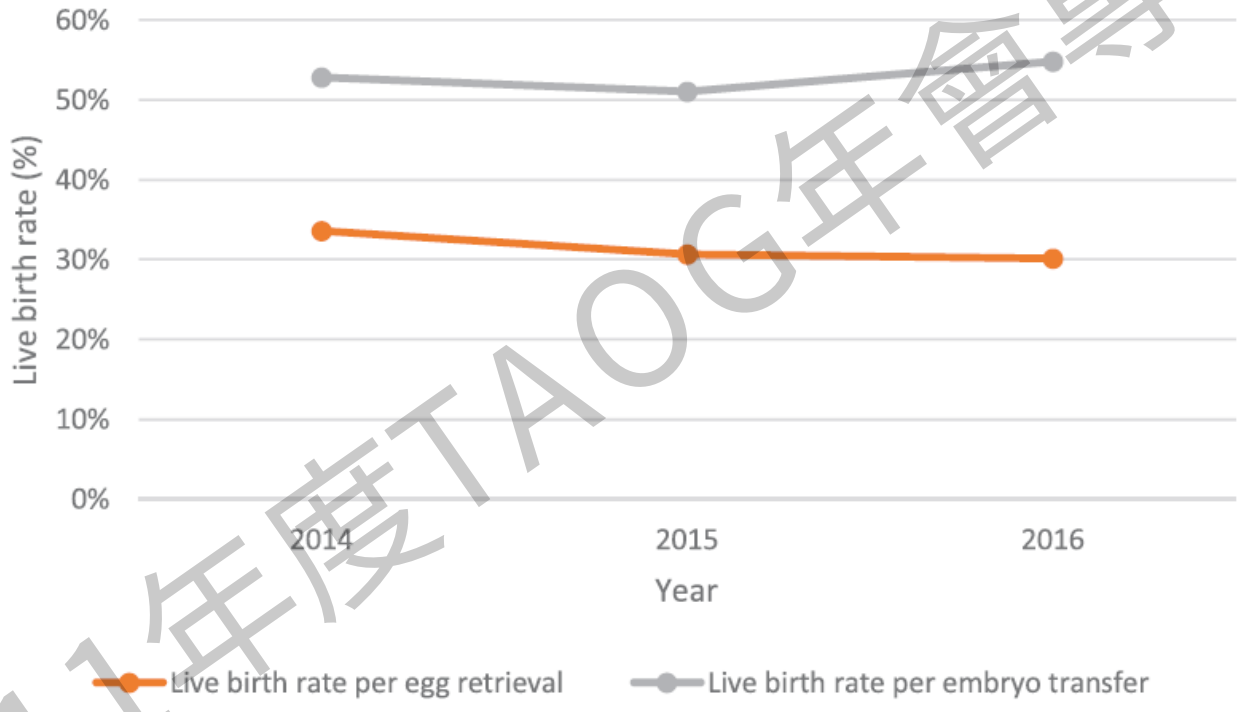


Figure 4 SART data—PGT LBRs per year (fresh and frozen cycles). The LBR per egg collection for the years 2014, 2015 and 2016 was

PGT-A不會增加LBR per retrieval

Hum Reprod. 2020 Apr 28;35(4):986-998.

Comparative Genomic Hybridization Selection of Blastocysts for Repeated Implantation Failure Treatment: A Pilot Study

Ermanno Greco,[1] Sara Bono,[2] Alessandra Ruberti,[1] Anna Maria Lobascio,[1] Pierfrancesco Greco,[1] Anil Biricik,[2] Letizia Spizzichino,[2] Alessia Greco,[1] Jan Tesarik,[3] Maria Giulia Minasi,[1] and Francesco Fiorentino[2]

Prospective cohort, 2012/Mar-2013/Mar, 76 RIF (3-9 IF) vs 45 good prognosis group (1st IVF)

	Group RIF PGS (n = 43)	Group RIF NO PGS (n = 33)	Group NO RIF PGS (n = 45)	P
Mean female age ± SD	32.8 ± 3.1	31.5 ± 2.9	31.7 ± 2.9	NS
Blastocysts with amplification (efficiency %)	182/190 (95.8%)	Not applicable	245/257 (95.3%)	0.817
Euploidy	84/182 (46.2%)	Not determined	127/245 (51.8%)	0.245
Aneuploidy	98/182 (53.8%)	Not determined	118/245 (48.2%)	

	Group RIF PGS (n = 43)	Group RIF NO PGS (n = 33)	Group NO RIF PGS (n = 45)	P
Total single embryo transfer	41	25	44	
Total double embryo transfer	0	8	0	
Total embryos transferred	41	41	44	<0.001
bHCG positive	34 (82.9%)	9 (27.3%)	37 (84.1%)	A versus B 0.001* A versus C 1.00*
Implantation (IR)	28 (68.3%)	9 (22.0)	31 (70.5%)	<0.001 A versus B 0.001* A versus C 1.00*
Clinical pregnancy (CPR)	28 (68.3%)	7 (21.2%)	31 (70.5%)	

診斷RIF後使用PGT-A，CPR per transfer顯著較佳

Biomed Res Int. 2014;2014:457913.

Preimplantation genetic testing for aneuploidy: a comparison of live birth rates in patients with recurrent pregnancy loss due to embryonic aneuploidy or recurrent implantation failure

Takeshi Sato[1], Mayumi Sugiura-Ogasawara[1,*], Fumiko Ozawa[1], Toshiyuki Yamamoto[2], Takema Kato[3], Hiroki Kurahashi[3], Tomoko Kuroda[4], Naoki Aoyama[4], Keiichi Kato[4], Ryota Kobayashi[5], Aisaku Fukuda[5], Takafumi Utsunomiya[6], Akira Kuwahara[7], Hidekazu Saito[8], Toshiyuki Takeshita[9], and Minoru Irahara[7]

JOSG, **multi-center, prospective pilot study** (for future RCT originally), **2017-2018, 92 RIF (≥3 good quality BC transfer), aCGH PGT-A**

Table IV Comparison of clinical outcomes between PGT-A and non-PGT-A patients with recurrent implantation failure.

	PGT-A (n = 42)[a]	Non-PGT-A (n = 50)[b]	Adjusted ORs (95% CI)*, *p*-value
Number of patients with at least one good quality blastocyst	24	42	
Diagnosed blastocysts/total number of blastocysts	199/208 (95.7%)	-	
Euploid blastocysts/diagnosed blastocysts	42/199 (21.1%)	-	
Embryo transfers/patients	24/42 (57.1%)	41/50 (82.0%)	**0.29 (0.11–0.75), 0.01**
Biochemical pregnancies/embryo transfers	19/24 (79.2%)	22/41 (53.7%)	**3.28 (1.03–10.5), 0.05**
Biochemical pregnancy losses/biochemical pregnancies	2/19 (10.5%)	9/22 (40.9%)	**0.17 (0.03–0.92), 0.04**
Clinical pregnancies/embryo transfers	17/24 (70.8%)	13/41 (31.7%)	**5.62 (1.82–17.3) 0.003**
Miscarriages/clinical pregnancies	2/17 (11.8%) 46,XY not tested	0/13 (0%)	-, 0.999
Ectopic pregnancies/clinical pregnancies	0/17 (0%)	0/13 (0%)	-
Live births/embryo transfers	15/24 (62.5%)	13/41 (31.7%)	**3.75 (1.28–10.95) 0.016**
Live births/patients	15/42 (35.7%)	13/50 (26.0%)	1.69 (0.68–4.20) 0.26

LBR per transfer : PGT-A > Non-PGT-A

Hum Reprod. 2019 Dec 1;34(12):2340-2348.

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

ESHRE PGT Consortium good practice recommendations for the organisation of PGT†

ESHRE PGT Consortium Steering Committee, Filipa Carvalho[1], Edith Coonen[2,3], Veerle Goossens[4], Georgia Kokkali[5], Carmen Rubio[6], Madelon Meijer-Hoogeveen[7], Céline Moutou[8], Nathalie Vermeulen[4], and Martine De Rycke[9,10,*]

PGT-A: inclusion/exclusion

Although PGT-A remains heavily debated in clinical practice, the following indications for its use have been reported:

- AMA;
- RIF;
- RM. It should be noted that couples with a history of RM have a high chance of successfully conceiving naturally and that PGT-A for RM without a genetic cause is not recommended in a recent evidence-based guideline (The ESHRE Guideline Group on RPL *et al.*, 2018);
- SMF.

Hum Reprod Open. 2020 May 29;2020(3):hoaa021.

asrm
American Society for Reproductive Medicine

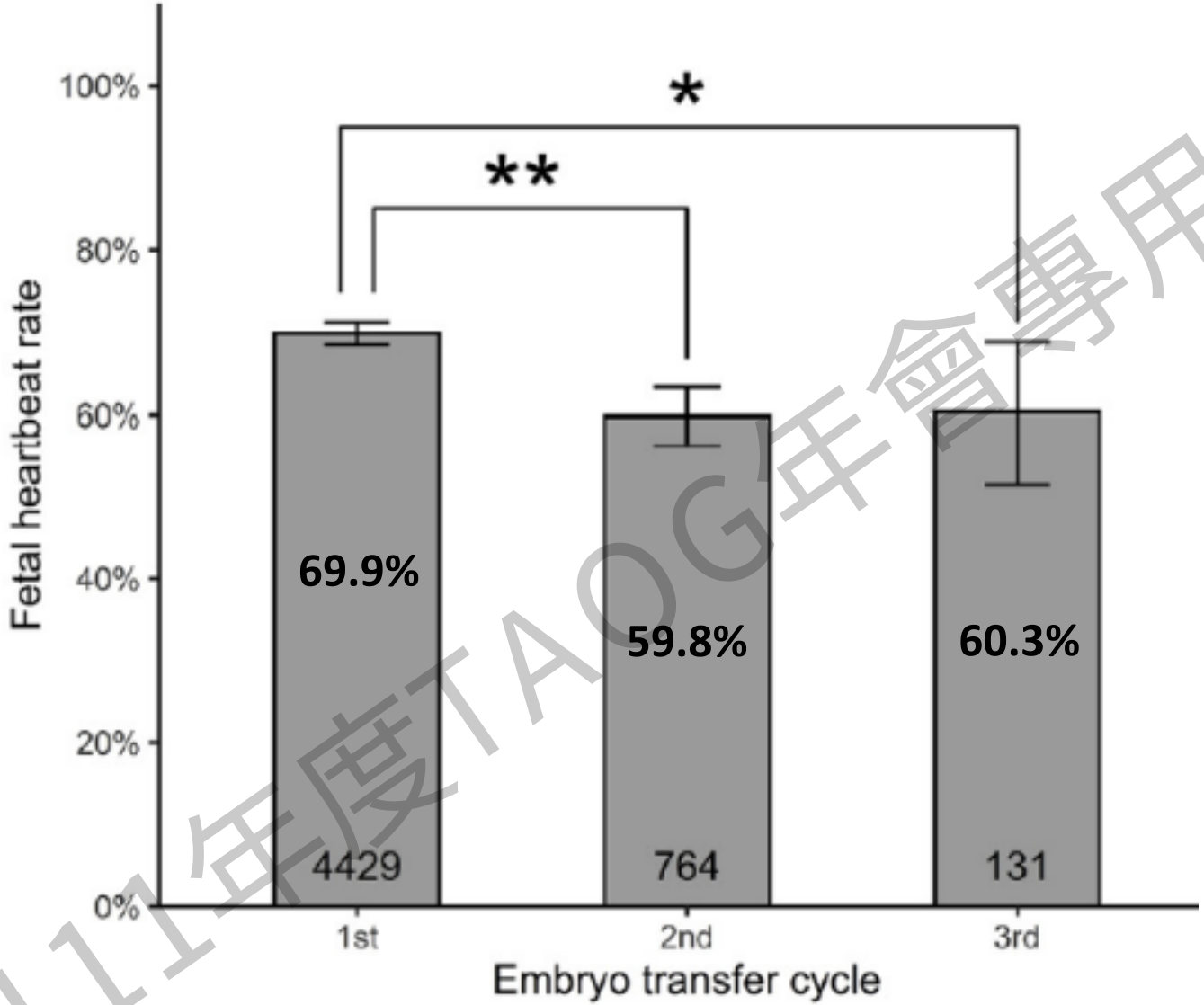
The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion

Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

- Other important considerations about PGT-A that must be addressed by further research include: cost-effectiveness; the role and effect of cryopreservation, time to pregnancy, utility in specific subgroups (such as recurrent loss, prior implantation failure, advanced maternal age, etc.); cumulative success rates over time; and total reproductive potential per intervention. Unfortunately, at the time of this publication, there are currently very few randomized trials registered to elucidate these answers.

Fertil Steril. 2018 Mar;109(3):429-436.

ESHRE PGT Consortium仍將RIF列為PGT-A可能的適應症



PGT-A或許可作為減少RIF假陽性的手段

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

Endometrial receptivity arrays (ERA)

ERA	**Limited to research settings only**	**Grade B evidence**

Lack of evidence to support the modality

ERA/pET in RIF

- NO RCT
- 4 OBS studies

	RIF Definition	N	Non-receptive rate	Outcomes
Ruiz-Alonso et al., 2013	38.4±4.7 y/o, ≥3 failed cycles (total ≥4 high-grade embryo transfers)	85 RIF vs 25 No RIF	25.9%	RIF接受pET，與控制組懷孕率相當
Mahajan, 2015	34.8±4.8 y/o, ≥2 consecutive cycles	80 RIF vs 93 one IVF failure	27.5%	RIF組經pET，懷孕率仍低於控制組(未顯著)
Hashimoto et al., 2017	38.4±3 & 40±5 y/o, ≥3 good-quality embryo transfers	38 R vs 12 NR	24%	比較R與NR組，無差異
Patel et al., 2019	33.7±5.1 y/o, ≥3 unsuccessful fresh/frozen ET cycles (1-2 high-grade embryos per cycle)	204 R vs 44 NR	17.7%	比較R與NR組，無差異

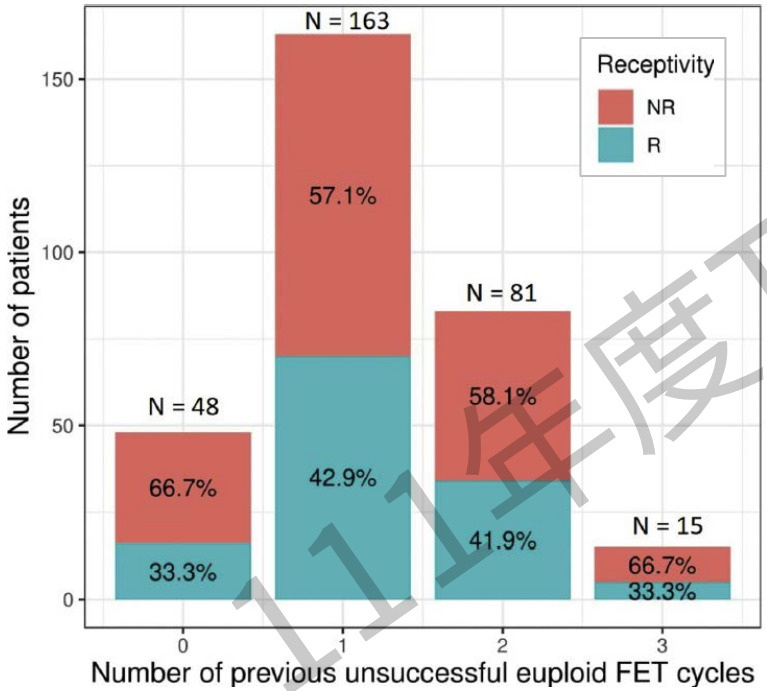
均無RIF未使用ERA之對照組

Reprod Biomed Online. 2020 Nov;41(5):819-833.

Live birth after transfer of a single euploid vitrified-warmed blastocyst according to standard timing vs. timing as recommended by endometrial receptivity analysis

Retrospective cohort, **2018-2019**, Shady Grove, NGS PGT-A, Avg age 36.7 ys. Single euploid frozen embryo transfer, ERA timing (N=307) vs. routine (N=2284).

Nicole Doyle, M.D., Ph.D.,[a] Joshua C. Combs, M.D.,[b] Samad Jahandideh, Ph.D.,[a] Victoria Wilkinson, B.A.,[a] Kate Devine, M.D.,[a] and Jeanne E. O'Brien, M.D., M.S.[a]



RIF個案NR比率無差異

TABLE 3

ERA-timed FET outcomes within the exposed group and ERA-timed FET outcomes for exposed vs. unexposed groups.

	ERA receptive n (%)	ERA nonreceptive n (%)	aOR (95% CI)	*P* value
Total patients	125	182		
Positive hCG	94 (75.2)	122 (67.0)	1.12 (0.92-1.34)	.16
Clinical pregnancy[a]	74(59.2)	94 (51.6)	1.15 (0.95-1.38)	.23
Live birth[b]	61 (48.8)	76 (41.7)	1.17 (0.97-1.40)	.27
	Exposed group (ERA-timed FET) n (%)	**Unexposed group (Standard FET) n (%)**	**aOR (95% CI)**	***P* value**
Total patients	307	2,284		
Positive hCG	215 (70.0%)	1,585 (69.4%)	1.01 (0.84-1.16)	.74
Clinical pregnancy[a]	166 (54.1%)	1,346 (58.9%)	0.92 (0.79-1.2)	.25
Live birth[b]	137 (44.6%)	1,173 (51.3%)	0.87 (0.73-1.04)	.08

Note: aOR = adjusted odds ratio; CI = confidence interval; ERA = endo[illegible]rial receptivity analysis; FET = frozen embry[illegible]nsfer; hCG = human chorionic gonadotropin.
[a] Clinical pregnancy = presence of gestational sac at 5 to 7 weeks of esta[illegible]d gestational age.
[b] Live birth = live birth at 23 weeks gestation or beyond.

Doyle. Endometrial receptivity analysis. Fertil Steril 2022.

ERA/pET組活產率稍低(無顯著差異)

Fertil Steril. 2022 Aug;118(2):314-321.

	ERA receptive N (%)				ERA non-receptive N (%)			
Total patients	125 (40.7%)				182 (59.3%)			
Number of previous unsuccessful euploid FET cycles	0 (N=16)	1 (N=70)	2 (N=34)	3 (N=5)	0 (N=32)	1 (N=93)	2 (N=47)	3 (N=10)
Positive hCG	11 (68.8)	50 (71.4)	31 (91.2)	2 (40.0)	21 (65.6)	68 (73.1)	32 (68.1)	1 (10.0)
Biochemical loss (per positive hCG)	3 (27.3)	11 (22.0)	6 (19.4)	0 (0.0)	4 (19.0)	14 (20.6)	10 (31.3)	0 (0.0)
Clinical pregnancy	8 (50.0)	39 (55.7)	25 (73.5)	2 (40.0)	17 (53.1)	54 (58.1)	22 (46.8)	1 (10.0)
Clinical loss (per clinical pregnancy)	1 (12.5)	8 (16.0)	2 (8.0)	0 (0.0)	3 (17.6)	11 (22.4)	8 (25)	0 (0.0)
Total pregnancy loss (per positive hCG)	4 (36.4)	19 (38.0)	8 (25.8)	0 (0.0)	7 (33.3)	25 (36.8)	18 (56.3)	0 (0.0)
Live birth	7 (43.8)	29 (41.4)	23 (67.6)	2 (40.0)	14 (43.8)	43 (46.2)	18 (38.3)	1 (10.0)

P=0.01, OR 3.37; 95% CI: 1.33–8.53

2次Euploid胚胎植入失敗者，若ERA NR，活產率顯著較低(pET也未能改善)

pET無效，有無其他治療？

ERA NR作為內膜疾患之替代指標？

Fertil Steril. 2022 Aug;118(2):314-321.

Serological and endometrial immune testing

Immune testing	Limited to research settings only	Need addition data to make a firm recom
Uterine natural killer cells		Grade B evidence
Peripheral NK cells		Grade C evidence
Endometrial cytokines		Grade C evidence
Genital microbiome		Grade D evidence
Peripheral blood cytokines		Grade C evidence
HLA incompatibility		Grade C evidence

Lack of evidence to support the modality

Immunotherapy

IVIG	**Limited to research settings only**	**Grade C evidence**
PBMC		-
Intralipid		-
Glucocorticoid		**Grade C evidence**
G-CSF		**Grade C evidence**

Thrombophilia workup	**NOT recommended**	
Inherited thrombophilia		**Grade B evidence**
Antiphospholipid antibody syndrome		**Grade C evidence**
Empirical LMWH	**Limited to research settings only**	

Efficacy of therapies and interventions for repeated embryo implantation failure: a systematic review and meta-analysis

Andrea Busnelli[1,2]✉, Edgardo Somigliana[3,4], Federico Cirillo[1], Annamaria Baggiani[1] & Paolo Emanuele Levi-Setti[1]

Search till **2020/May**, 746 records identified, **42 studies** included: 7 case-control, 13 prospective cohort, **22 RCTs**.

Therapy/intervention	Outcome	RCTs/Observational studies	Number of studies	Number of participants	Effect (95% CI)	GRADE score (RCTs = + 4; Observational studies = + 2)							GRADE quality of the evidence
						Quality	Consistency	Directness	Precision	Publication bias	Upgrading	Total score	
Intrauterine G-CSF	LBR	RCTs	1	157	RR 0.84 (0.41–1.73)	− 1	0	0	− 1	0	0	2	Low
	CPR	RCTs	2	257	RR 1.53 (1.00–2.33)	− 1	0	0	− 1	0	0	2	Low
	IR	RCTs	1	100	RR 2.28 (0.90–5.74)	− 1	0	0	− 1	0	0	2	Low
	MR	RCTs	1	157	RR 3.20 (0.69–14.93)	− 1	0	0	− 1	0	0	2	Low
Subcutaneous G-CSF	CPR	RCTs	4	333	RR 2.29 (1.58–3.31)	− 1	0	0	− 1	0	+ 1 (magnitude)	3	Moderate
	IR	RCTs	1	112	RR 2.94 (1.24–5.01)	− 1	0	0	− 1	0	0	2	Low
Sequential ET	CPR	RCTs	1	120	RR 1.04 (0.67–1.63)	− 2	0	0	− 1	0	0	1	Very low
	CPR	Observational studies	2	282	OR 2.44 (1.56–4.47)	− 1	0	0	0	0	0	1	Very low
	IR	Observational studies	1	151	OR 2.95 (1.65–5.27)	− 1	0	0	0	0	0	1	Very low
Intralipid	LBR	RCTs	1	142	RR 1.30 (0.61–2.77)	− 1	0	0	− 1	0	0	2	Low
	CPR	RCTs	1	142	RR 1.30 (0.80–2.10)	− 1	0	0	− 1	0	0	2	Low
Endometrial injury	LBR	RCTs	3	376	RR 1.55 (0.81–2.94)	− 1	0	0	− 1	0	0	2	Low
	CPR	RCTs	3	376	RR 1.43 (0.79–2.61)	− 1	0	0	− 1	0	0	2	Low
	IR	RCTs	1	101	RR 1.70 (1.01–2.84)	− 1	0	0	− 1	0	0	2	Low
	MR	RCTs	3	376	RR 1.39 (0.55–3.53)	− 1	0	0	− 1	0	0	2	Low
	CPR	Observational studies	2	200	OR 3.03 (1.48–6.18)	− 1	0	0	− 1	0	+ 1 (magnitude)	1	Very low
LMWH	LBR	RCTs	1	71	RR 1.38 (0.64–2.96)	− 2	0	0	− 1	0	0	1	Very low
	CPR	RCTs	2	218	RR 1.39 (0.87–2.23)	− 2	0	0	− 1	0	0	1	Very low
	LBR	Observational studies	1	91	OR 1.50 (0.58–3.82)	− 1	0	0	0	0	0	1	Very low
	CPR	Observational studies	1	91	OR 1.42 (0.58–3.45)	− 1	0	0	0	0	0	1	Very low
Hysteroscopy	LBR	RCTs	1	230	RR 0.96 (0.69–1.32)	0	0	0	− 1	0	0	3	Moderate

Continued

Therapy/intervention	Outcome	RCTs/Observational studies	Number of studies	Number of participants	Effect (95% CI)	GRADE score (RCTs = + 4; Observational studies = + 2)							GRADE quality of the evidence
						Quality	Consistency	Directness	Precision	Publication bias	Upgrading	Total score	
PGT-A	LBR	RCTs	1	91	RR 1.72 (0.98–3.02)	− 1	0	0	− 1	0	0	2	Low
	CPR	RCTs	1	91	RR 1.86 (1.11–3.12)	− 1	0	0	− 1	0	0	2	Low
	IR	RCTs	1	91	RR 1.71 (0.99–2.94)	− 1	0	0	− 1	0	0	2	Low
	MR	RCTs	1	91	RR 3.58 (0.42–30.83)	− 1	0	0	− 1	0	0	2	Low
	LBR	Observational studies	2	219	OR 0.83 (0.33–2.07)	0	0	0	0	0	0	1	Low
	CPR	Observational studies	3	295	OR 1.58 (0.35–7.12)	− 1	0	0	0	0	0	1	Very low
Atosiban	CPR	Observational studies	1	88	OR 2.63 (1.08–6.40)	− 1	0	0	0	0	0	1	Very low
	IR	Observational studies	1	88	OR 3.12 (1.54–6.28)	− 1	0	0	0	0	0	1	Very low
	MR	Observational studies	1	88	OR 1.66 (0.43–6.35)	− 1	0	0	0	0	0	1	Very low
IVIG	LBR	Observational studies	1	283	OR 1.76 (1.08–2.89)	− 1	0	0	0	0	0	1	Very low
	CPR	Observational studies	1	283	OR 2.08 (1.28–3.36)	− 1	0	0	0	0	0	1	Very low
	IR	Observational studies	1	283	OR 1.43 (1.06–1.94)	− 1	0	0	0	0	0	1	Very low
hCG	LBR	Observational studies	1	67	OR 1.78 (1.02–3.09)	− 1	0	0	0	0	0	1	Very low
	CPR	Observational studies	2	166	OR 1.81 (1.23–2.65)	− 1	0	0	0	0	0	1	Very low
Blastocyst-stage ET	LBR	RCTs	1	54	RR 1.35 (0.30–6.09)	− 1	0	0	− 1	0	0	2	Low
	CPR	RCTs	1	54	RR 1.68 (0.51–5.59)	− 1	0	0	− 1	0	0	2	Low
	IR	RCTs	1	54	RR 3.54 (1.28–9.77)	− 1	0	0	− 1	0	0	2	Low
	MPR	RCTs	1	54	RR 0.90 (0.16–4.95)	− 1	0	0	− 1	0	0	2	Low

Continued

Therapy/intervention	Outcome	RCTs/Observational studies	Number of studies	Number of participants	Effect (95% CI)	GRADE score (RCTs = + 4; Observational studies = + 2)							GRADE quality of the evidence
						Quality	Consistency	Directness	Precision	Publication bias	Upgrading	Total score	
ZIFT	LBR	Observational studies	2	314	OR 3.43 (0.03–43.80)	− 1	0	0	0	0	0	1	Very low
	CPR	Observational studies	4	454	OR 2.40 (0.52–11.05)	− 1	0	0	0	0	0	1	Very low
	IR	Observational studies	2		OR 3.73 (0.69–20.27)	− 1	0	0	0	0	0	1	Very low
	MR	Observational studies	1	250	OR 2.09 (0.70–6.21)	− 1	0	0	0	0	0	1	Very low
	MPR	Observational studies	1	250	OR 0.26 (0.07–0.91)	− 1	0	0	0	0	0	1	Very low
PBMC	LBR	RCTs	1	198	RR 2.41 (1.40–4.16)	− 1	0	0	− 1	0	+ 1 (magnitude)	3	Moderate
	CPR	RCTs	3	363	RR 2.18 (1.58–3.00)	− 1	0	0	− 1	0	+ 1 (magnitude)	3	Moderate
	LBR	Observational studies	2	90	OR 3.73 (1.13–12.29)	− 1	0	0	− 1	0	+ 1 (magnitude)	1	Very low
	CPR	Observational studies	3	306	OR 2.03 (1.22–3.36)	− 1	0	0	− 1	0	+ 1 (magnitude)	1	Very low
	IR	Observational studies	2	90	OR 4.54 (1.82–11.35)	− 1	0	0	− 1	0	+ 1 (magnitude)	1	Very low
AH	CPR	RCTs	1	207	RR 0.78 (0.48–1.27)	− 1	0	0	− 1	0	0	2	Low
	LBR	Observational studies	1	109	OR 0.52 (0.13–2.09)	− 1	0	0	0	0	0	1	Very low
	CPR	Observational studies	1	109	OR 1.42 (0.45–4.48)	− 1	0	0	0	0	0	1	Very low
	MPR	Observational studies	1	109	OR, 1.49 (0.09–24.44)	− 1	0	0	0	0	0	1	Very low
PRP	CPR	RCTs	2	195	RR 2.45 (1.55–3.86)	− 1	0	0	− 1	0	0	2	Low

各種治療方式多無效且證據力低

Sci Rep. 2021 Jan 18;11(1):1747.

Hysteroscopy

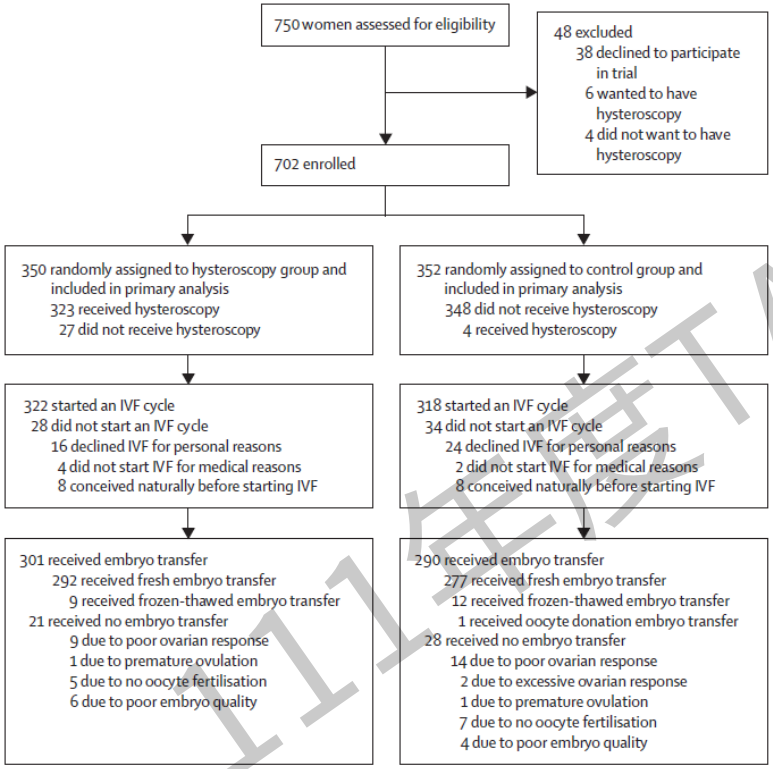
Diagnostic HSC	**NOT recommended**	**Grade A evidence**

Lack of evidence to support the modality

Hysteroscopy in recurrent in-vitro fertilisation failure (TROPHY): a multicentre, randomised controlled trial

Tarek El-Toukhy, Rudi Campo, Yacoub Khalaf, Carla Tabanelli, Luca Gianaroli, Sylvie S Gordts, Stephan Gordts, Greet Mestdagh, Tonko Mardesic, Jan Voboril, Gian L Marchino, Chiara Benedetto, Talha Al-Shawaf, Luca Sabatini, Paul T Seed, Marco Gergolet, Grigoris Grimbizis, Hoda Harb, Arri Coomarasamy

Multicenter RCT, 2010/Jan-2013/Dec, women <38 yrs, **2-4 IVF failure**



	Hysteroscopy group	Control group	Risk ratio (95% CI)
Rates per participant			
Pregnancy	38% (133/350)	39% (136/352)	0·97 (0·72–1·32); p=0·86
Clinical pregnancy	35% (121/350)	33% (116/352)	1·08 (0·79–1·47);p=0·65
Livebirth	29% (102/350)	29% (102/352)	1·0 (0·79–1·25); p=0·96
Rates per participant receiving embryo transfer			
Pregnancy	42% (125/301)	44% (128/290)	0·94 (0·78–1·13); p=0·52
Clinical pregnancy	38% (114/301)	38% (110/290)	0·99 (0·81–1·22); p=0·99
Livebirth	32% (95/301)	33% (96/290)	0·95 (0·76–1·20); p=0·69
Rates per participant receiving a top-quality embryo			
Pregnancy	45% (104/232)	46% (109/236)	0·97 (0·80–1·18); p=0·77
Clinical pregnancy	42% (97/232)	42% (98/236)	1·01 (0·84–1·21); p=0·99
Livebirth	35% (82/232)	36% (86/236)	0·98 (0·81–1·24); p=0·81

Outcome data are % (n/N).

Table 4: Pregnancy and livebirth outcomes

反覆試管失敗，施作檢查性子宮鏡，不影響懷孕率

Lancet. 2016 Jun 25;387(10038):2614-2621.

	Women (n=323)
Cervical abnormalities	
Stenosis of external os	3 (1%)
Stenosis of internal os	4 (1%)
Cervical canal adhesions	3 (1%)
Cervical canal deviation (retroversion)	2 (1%)
Cervical canal polyps	1 (<1%)
Shortened cervical canal	1 (<1%)
Uterine cavity abnormality	
Dysmorphic (arcuate) cavity	15 (6%)
Hemi-uterus	3 (1%)
Endometrial polyps	8 (2%)
Partial uterine septum	5 (2%)
Submucous fibroid	2 (1%)
T-shaped uterine cavity	1 (<1%)
Subtle endometrial abnormality	
Hypervascularisation	20*(6%)
Mucosal elevation	12 (4%)
Micropolyps	3 (1%)
Pale endometrium	3 (1%)
Endometrial defect	2 (1%)
Single adhesion band	1 (<1%)

*Four women also had dysmorphic (arcuate) uterus.

Table 2: Findings in women who received hysteroscopy in the hysteroscopy group

85/323 (26%)有子宮鏡發現

然而，67% (57/85)的個案並未對子宮鏡發現進行處置(不可治療或未知臨床重要性)

作者結論：針對特定子宮鏡發現的處置是否能改善預後，有待進一步研究！

Lancet. 2016 Jun 25;387(10038):2614-2621.

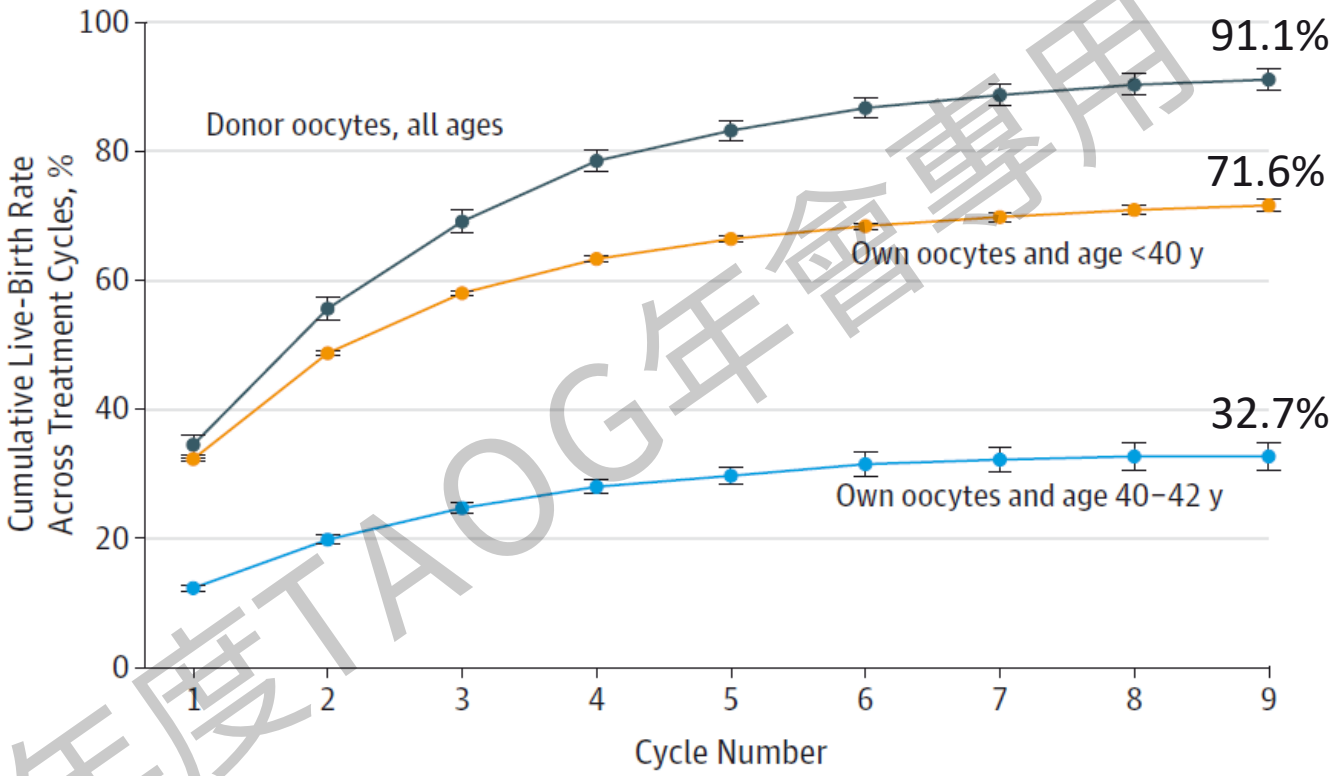
Original Investigation

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

HFEA data, 2003/Jan-2012/Jun

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

毅力



No. of women									
Donor oocytes, all ages	3587	1636	939	554	287	126	53	27	8
Own oocytes and age <40 y	133 379	53 568	19 719	6641	2357	882	335	131	51
Own oocytes and age 40–42 y	15 561	6671	2579	884	301	130	60	36	20
Own oocytes and age >42 y	4420	1578	509	160	67	24	10	5	4

失敗後繼續嘗試，累積活產率7-9成

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

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

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.

致力於提高基礎成功率，減少RIF假陽性的診斷

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

Aspire 2022

The 11th Virtual Congress of the Asia Pacific Initiative on Reproduction

Adding Adjuvant in Poor Responder

Against: Tin-Chiu Li (Hong Kong)

Recommendations

① 選擇副作用最少的輔助治療
(Choose one with the least adverse effects)

② 做一位負責任的臨床工作者
(Be a responsible practitioner)

③ 誠實面對你的病人
(Be honest with you patients)

④ 避免昂貴的輔助治療
(Avoid an expensive adjuvant)

⑤ 避免使用非適應症的用藥
(Take steps to minimize medico-legal liability)

關於處置的Take Home Messages

1. 在RIF成因不明下，目前無實證支持之有效處置
2. PGT-A僅改變per transfer的成功率；或許可作為減少RIF偽陽性的工具
3. ERA/pET 及 免疫療法，目前皆無足夠證據支持使用於RIF

關於處置的Take Home Messages

4. 若欲使用輔助治療，應提供個案正確實證資訊並考量病人自主，把握Do No Harm原則

5. 建議處置：
   - 致力於提高基礎成功率
   - 適當諮詢，以實證鼓勵個案堅持療程

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Thank You for Your Attention!