Endometrium preparation in frozen embryo transfer :

Nature or Artificial

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台灣的冷凍植入週期佔 83.3% (111年)

圖 22　97 年至 111 年本國籍人工生殖治療週期數、活產週期數與活產嬰兒數

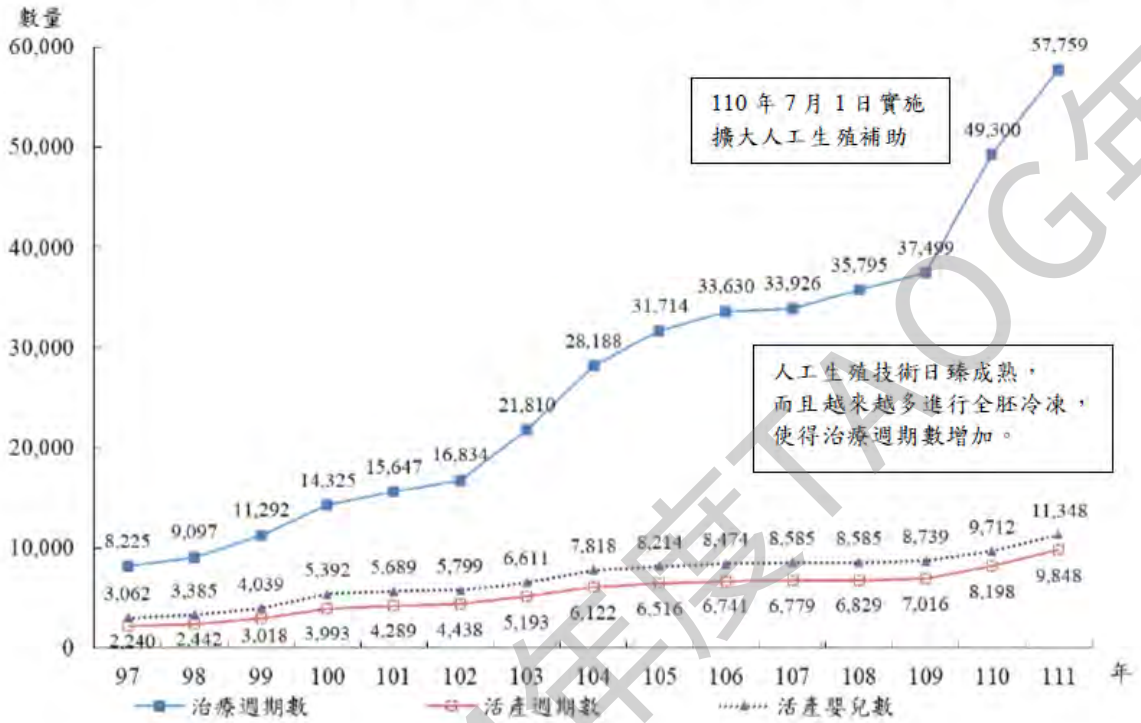


表 5　110 年人工生殖植入類型百分比

單位：週期/%

植入類型		植入週期數	百分比
配偶間		24,211	95.1
	新鮮	5,714	22.4
	冷凍	18,497	72.7
捐贈精卵		1,245	4.9
	新鮮	128	0.5
	冷凍	1,117	4.4
全部植入週期		**25,456**	**100.0**

110年 FET 佔 77.1%

表 5　111 年人工生殖植入類型百分比

單位：週期/%

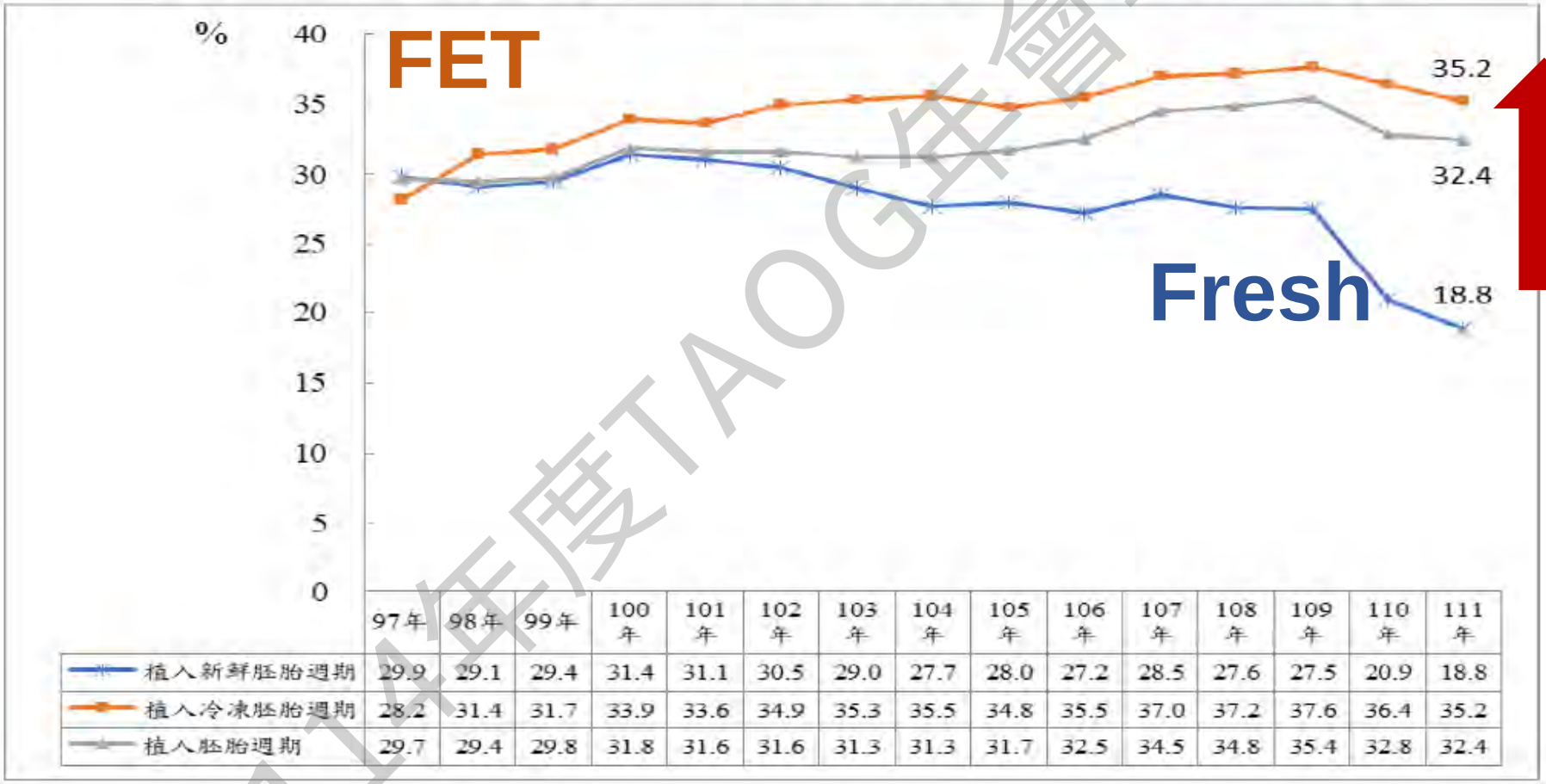
植入類型		植入週期數	百分比
配偶間精卵		29,430	94.8
	新鮮	5,061	16.3
	冷凍	24,369	78.5
捐贈精卵		1,604	5.2
	新鮮	146	0.5
	冷凍	1,458	4.7
全部植入週期		31,034	100.0

111年 FET 佔 83.3%

美國 70-80%　歐洲 40-60%

98年以後 植入週期活產率 冷凍>新鮮

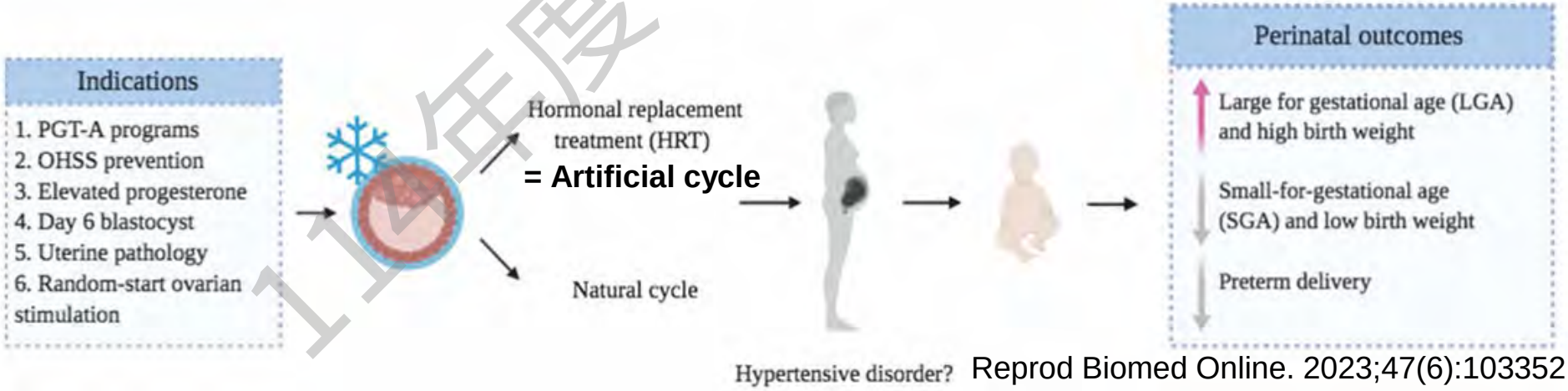
圖 27　97 年至 111 年本國籍植入新鮮胚胎與冷凍胚胎之植入週期活產率



	97年	98年	99年	100年	101年	102年	103年	104年	105年	106年	107年	108年	109年	110年	111年
植入新鮮胚胎週期	29.9	29.1	29.4	31.4	31.1	30.5	29.0	27.7	28.0	27.2	28.5	27.6	27.5	20.9	18.8
植入冷凍胚胎週期	28.2	31.4	31.7	33.9	33.6	34.9	35.3	35.5	34.8	35.5	37.0	37.2	37.6	36.4	35.2
植入胚胎週期	29.7	29.4	29.8	31.8	31.6	31.6	31.3	31.3	31.7	32.5	34.5	34.8	35.4	32.8	32.4

Freeze all strategy 增加

1. 植入前基因檢測
2. 減少 OHSS risk, 黃體素上升, D6 blastocysts
3. 子宮內膜容受性:減少卵巢刺激對內膜容受性的影響
4. Uterine pathology (polyp, adenomyosis)
5. Random start ovarian stimulation
6. 胚胎冷凍保存的進步



Reprod Biomed Online. 2023;47(6):103352.
Ups J Med Sci. 2020;125(2):104-11.

LGA、HDP、PPH 的風險　冷凍>新鮮

Human Reproduction, Vol.34, No.11, pp. 2282–2289, 2019
Advance Access Publication on November 4, 2019 doi:10.1093/humrep/dez212

human reproduction　ORIGINAL ARTICLE *Reproductive epidemiology*

Perinatal and maternal outcome after vitrification of blastocysts: a Nordic study in singletons from the CoNARTaS group

Erica Ginström Ernstad[1,*], Anne Lærke Spangmose[2], Signe Opdahl[3], Anna-Karina Aaris Henningsen[2], Liv Bente Romundstad[3], Aila Tiitinen[4], Mika Gissler[5,6], Ulla-Britt Wennerholm[1], Anja Pinborg[2], Christina Bergh[7,†], and Sara Sofia Malchau[1,†]

Sweden and Denmark
registry-based cohort study , 2002 - 2015
singletons born after FET and fresh ET
3650 children born after transfer of **vitrified blastocysts**,
8123 children born after transfer of slow-frozen cleavage stage embryos
4469 children born after transfer of **fresh blastocysts**

Table III Crude and adjusted odds ratios of perinatal and maternal outcome in singleton deliveries after vitrified blastocyst transfer (BT) compared with slow-frozen cleavage stage transfer (CT) and fresh BT, 2002–2015.

	Vitrified BT vs. slow-frozen CT		Vitrified BT vs. fresh BT	
	Crude OR (95% CI)	aOR * (95% CI)	Crude OR (95% CI)	aOR * (95% CI)
Male sex	1.15 [1.07—1.25]	**1.16 [1.05—1.27]**	1.00 [0.92—1.09]	**1.03 [0.93—1.13]**
<37 weeks	1.20 [1.03—1.40]	**1.33 [1.09—1.62]**	0.82 [0.70—0.97]	0.86 [0.71—1.04]
<32 weeks	0.93 [0.64—1.35]	0.98 [0.60—1.62]	0.78 [0.53—1.16]	0.84 [0.81—1.39]
≥42 weeks	1.01 [0.87—1.17]	1.01 [0.85—1.20]	1.87 [1.54—2.26]	**1.61 [1.31—1.98]**
<1500 g	0.92 [0.74—1.13]	1.17 [0.65—2.11]	0.82 [0.51—1.32]	0.92 [0.50—1.70]
<2500 g	0.92 [0.60—1.42]	0.91 [0.70—1.19]	0.59 [0.47—0.73]	**0.57 [0.44—0.74]**
≥4000 g	1.02 [0.93—1.12]	1.06 [0.95—1.18]	1.81 [1.62—2.03]	**1.68 [1.48—1.92]**
≥4500 g	0.99 [0.83—1.18]	0.93 [0.76—1.15]	1.96 [1.55—2.48]	**1.77 [1.35—2.31]**
SGA < −2 SD	0.87 [0.68—1.12]	0.85 [0.63—1.13]	0.56 [0.43—0.72]	**0.58 [0.44—0.78]**
LGA > +2 SD	1.07 [0.92—1.26]	1.10 [0.91—1.32]	1.72 [1.41—2.10]	**1.48 [1.18—1.84]**
Apgar <7 at 5 min	1.20 [0.90—1.61]	1.19 [0.84—1.68]	1.74 [1.20—2.52]	**1.79 [1.19—2.70]**
Apgar <4 at 5 min	1.70 [0.93—3.10]	**2.42 [1.07—5.48]**	1.77 [0.86—3.62]	1.56 [0.72—3.38]
Birth defects, any	0.99 [0.82—1.21]	1.16 [0.91—1.47]	0.85 [0.69—1.05]	0.99 [0.77—1.27]
Perinatal death	0.52 [0.18—1.50]	0.97 [0.17—5.73]	0.70 [0.20—2.39]	0.40 [0.07—2.16]
Neonatal death	0.58 [0.22—1.56]	0.93 [0.26—3.38]	0.68 [0.23—2.03]	0.67 [0.18—2.44]
HDP	1.08 [0.92—1.26]	0.97 [0.81—1.17]	1.39 [1.16—1.67]	**1.47 [1.19—1.81]**
Placental abruption	1.06 [0.62—1.80]	1.78 [0.93—3.40]	0.50 [0.29—0.84]	0.65 [0.37—1.16]
Placenta previa	1.58 [1.13—2.22]	1.48 [0.98—2.24]	0.38 [0.28—0.51]	**0.35 [0.25—0.48]**
PPH**	1.09 [0.95—1.25]	1.03 [0.88—1.25]	1.59 [1.34—1.89]	**1.68 [1.39—2.03]**
Induction of labour	1.10 [1.01—1.20]	**1.14 [1.03—1.27]**	1.46 [1.31—1.62]	**1.67 [1.48—1.88]**
Cesarean section	1.12[1.03—1.22]	**1.17 [1.05–1.30]**	1.13 [1.03—1.25]	**1.15 [1.03–1.29]**

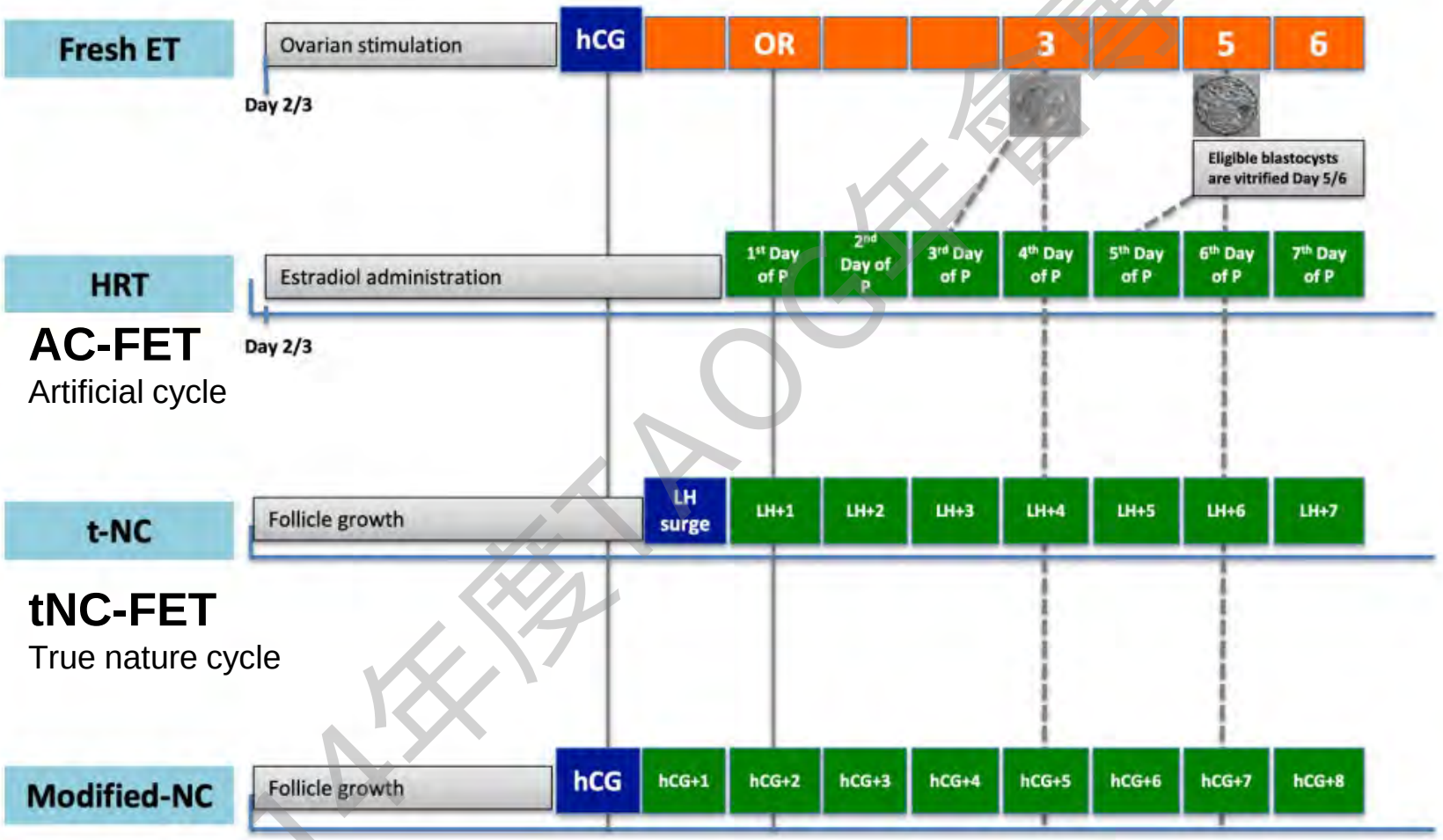
BT: blastocyst transfer, CT: cleavage stage transfer, OR: odds ratio, CI: confidence interval, SGA/LGA: small/large for gestational age, HDP: hypertensive disorders in pregnancy, PPH: postpartum hemorrhage.
*Adjusted for country of birth of child, year of birth of child, maternal age, BMI, parity, smoking, parental educational level, fertilisation method (IVF/ICSI), single embryo transfer, number of gestational sacs and child's sex.
**Only Swedish data.
Bold indicates statistical significance.

FET 比 fresh ET
LGA、HDP、PPH的風險高

Large gestational age(LGA),
Hypertensive disorders in pregnancy (HDPs)
Postpartum hemorrhage (PPH)

Hum Reprod. 2019;34(11):2282-9.

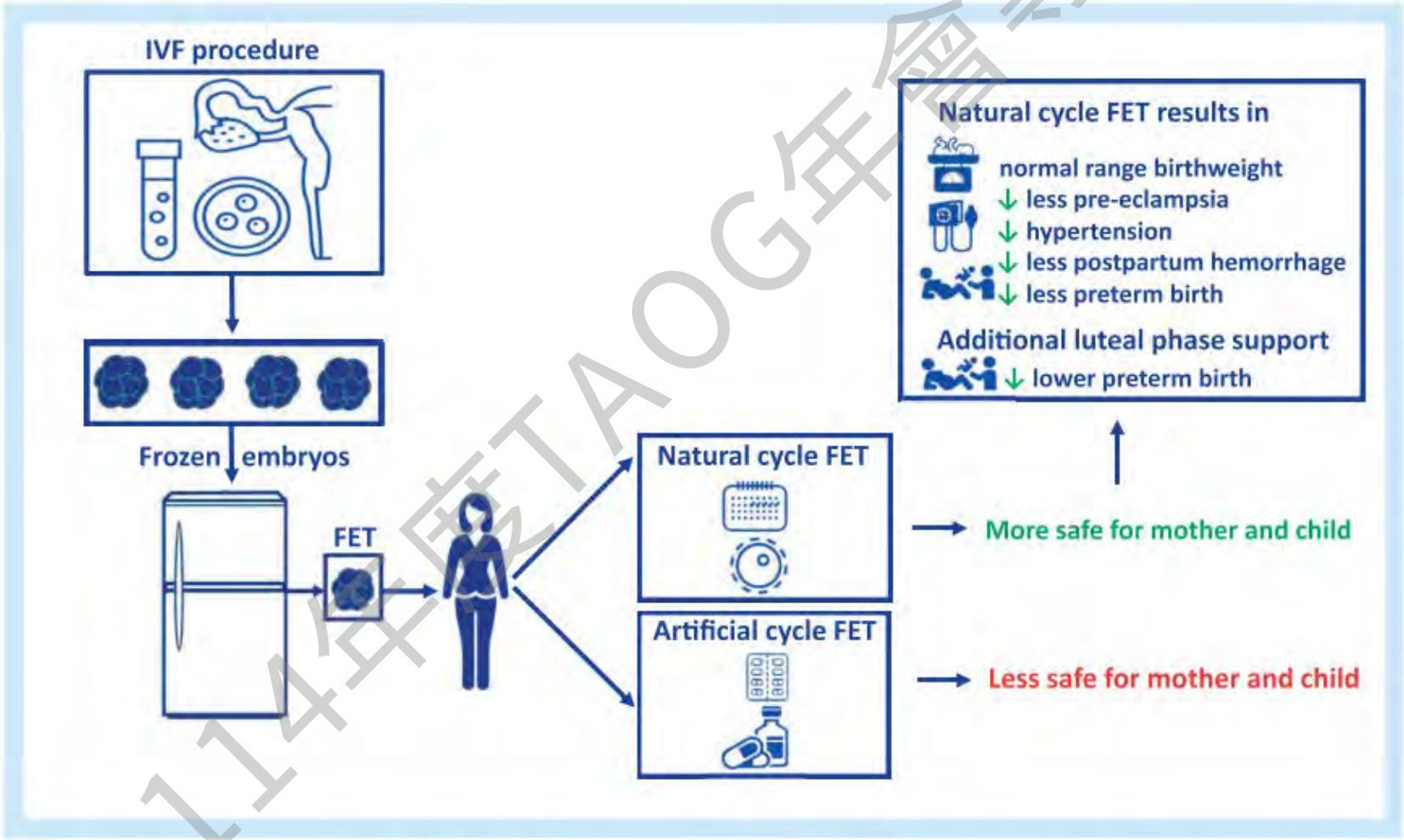
EM preparation of FET



Front Endocrinol (Lausanne). 2021;12:688237.

自然週期FET可降低產婦/新生兒併發症

GRAPHICAL ABSTRACT



Natural cycle FET decreases the risk of adverse obstetric and neonatal outcomes compared with artificial cycle FET. FET: frozen embryo transfer.

Hum Reprod Update. 2023;29(5):634-54.

OBS complications: (systematic review and meta-analysis)

AC-FET : NC-FET : fresh ET

Aust N Z J Obstet Gynaecol 2024; 64: 104–113

ANZJOG

DOI: 10.1111/ajo.13750

SYSTEMATIC REVIEW

Assessing obstetric outcomes: A systematic review and meta-analysis comparing fresh, artificial, and natural thaw embryo transfer cycles

Amy Field[1], Genia Rozen[2,3,4], Joscelyn Gan[5] and Alex Polyakov[3,4,6]

Australia **systematic review and meta-analysis**

1947-2022 23 studies, 279798 ET

- **26573 fresh ET**
- **115182 NC-FET (tNC-FET, mNC-FET)**
- **138043 AC-FET**

Outcomes :

hypertensive disorders of pregnancy (HDP), gestational diabetes (GDM), preterm birth (PTB), post-partum hemorrhage (PPH) large for gestational age (LGA).

比較

1. **AC-FET vs NC-FET**
2. **AC-FET vs Fresh ET**
3. **NC-FET vs Fresh ET.**

Aust N Z J Obstet Gynaecol. 2024;64(2):104-13.

OBS complications: (systematic review and meta-analysis)

AC-FET > NC-FET > fresh ET

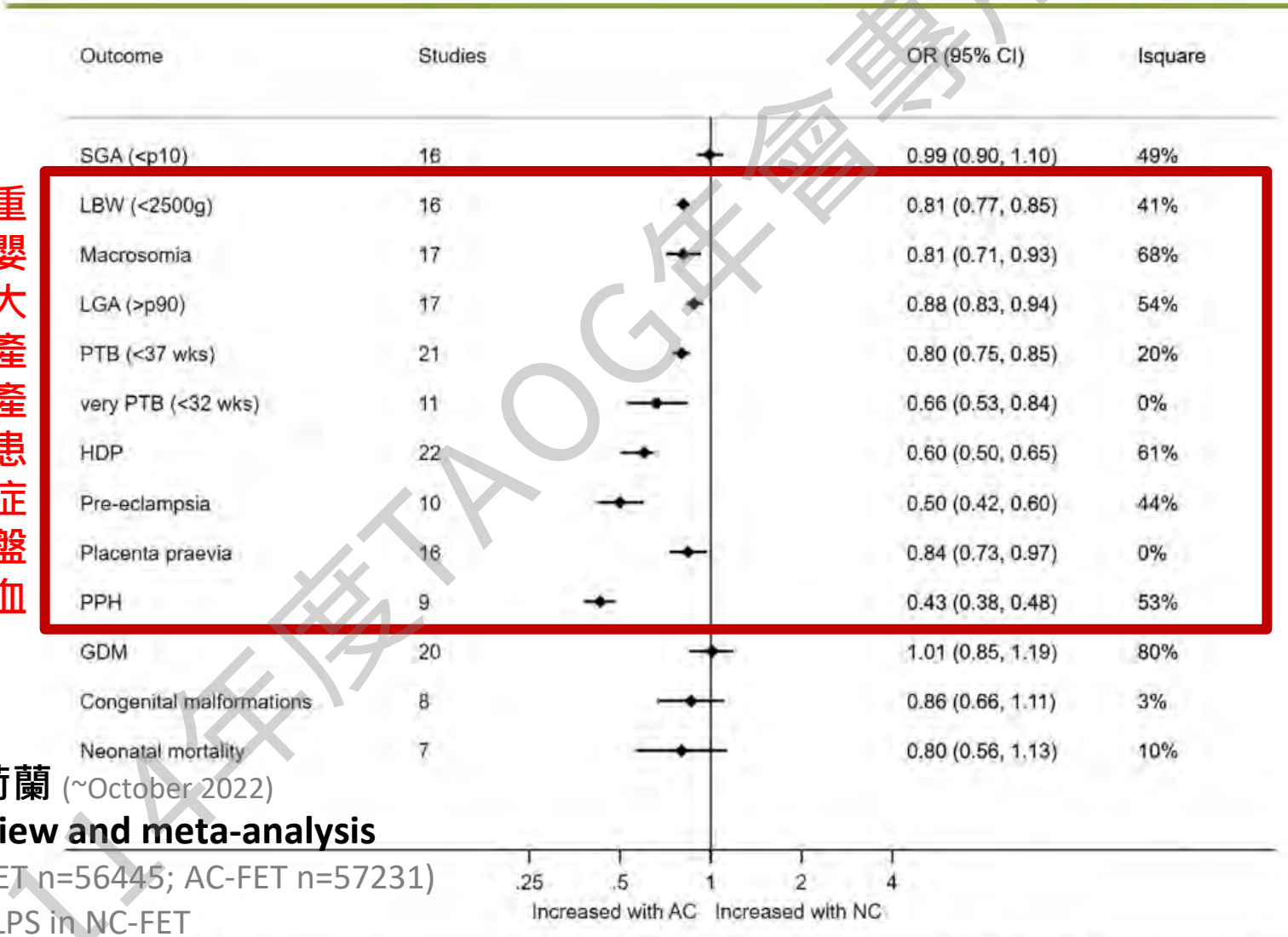
NC-FET (tNC+mNC)

	AC-FET vs NC-FET	AC-FET vs Fresh ET	NC-FET vs Fresh ET	
Outcome Measure	**ArtThawET vs NatThawET**	**ArtThawET vs Fresh ET**	**NatThawET vs Fresh ET**	
Hypertensive Disorders of Pregnancy (HDP)	No. of studies: 17/21 **OR = 1.76** **CI = 1.66-1.86**	No. of studies: 5/21 **OR = 2.13** **CI = 1.89-2.40**	No. of studies: 3/21 **OR = 1.20** **CI = 1.11-1.29**	**AC-FET > NC-FET > fresh ET**
Pre-Term Birth (PTB)	No. of studies: 13/15 **OR = 1.18** **CI = 1.13-1.23**	No. of studies:1/15 OR = 1.21 CI = 0.85-1.73	No. of studies: 1/15 OR = 0.07 CI = 0.00-1.21	**AC-FET > NC-FET**
Post-Partum Haemorrhage (PPH)	No. of studies: 6/8 **OR = 2.61** **CI = 2.30-2.97**	No. of studies: 2/8 **OR = 3.52** **CI = 3.06-4.04**	No. of studies: 2/8 **OR = 1.25** **CI = 1.14-1.38**	**AC-FET > NC-FET > fresh ET**
Gestational Diabetes (GD)	No. of studies: 14/17 **OR = 0.94** **CI = 0.88-0.99**	No. of studies: 2/17 OR = 1.20 CI = 0.78-1.83	No. of studies: 1/17 OR = 2.95 CI = 0.12-73.90	**AC-FET < NC-FET**
Large for Gestational Age (LGA)	No. of studies: 14/17 **OR = 1.11** **CI = 1.07-1.15**	No. of studies: 3/17 **OR = 2.12** **CI = 1.77-2.56**	No. of studies: 2/17 **OR = 1.85** **CI = 1.66-2.07**	**AC-FET > NC-FET > fresh ET**

Aust N Z J Obstet Gynaecol. 2024;64(2):104-13.

Neonatal , OBS outcomes:
AC-FET > NC-FET (systematic review and meta-analysis)

胎兒低體重
巨嬰
胎兒過大
早產
極低體重早產
妊娠高血壓疾患
子癲前症
前置胎盤
產後大出血



Netherlands 荷蘭 (~October 2022)
systematic review and meta-analysis
30 studies (NC-FET n=56445; AC-FET n=57231)
19 studies used LPS in NC-FET

Figure 3. **Summary of all averaged secondary outcomes for NC-FET versus AC-FET, expressed as odds ratio with 95% CI.** NC: natural cycle; AC: artificial cycle; OR: odds ratio.

Hum Reprod Update. 2023;29(5):634-54.

NC-FET (vs. AC-FET)
改善Obstetric and neonatal outcomes

OXFORD human reproduction update

Human Reproduction Update, 2023, 29(5), 634–654
https://doi.org/10.1093/humupd/dmad011
Advance Access Publication Date: May 12, 2023

Obstetric and neonatal outcomes after natural versus artificial cycle frozen embryo transfer and the role of luteal phase support: a systematic review and meta-analysis

T.R. Zaat[1,2,*], E.B. Kostova[1,2], P. Korsen[3], M.G. Showell[4], F. Mol[1,2], and M. van Wely[1,2]
[1]Department of Obstetrics and Gynecology, Amsterdam UMC Location University of Amsterdam, Amsterdam, The Netherlands
[2]Amsterdam Reproduction and Development Research Institute, Amsterdam, The Netherlands
[3]University Medical Center Groningen, Groningen, The Netherlands
[4]Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand

Netherlands 荷蘭
(~October 2022)

30 studies
56445 NC-FET
57231 AC-FET
19 studies NC-FET+ LPS

Outcomes	Present analysis	
	NC-FET	AC-FET
Birthweight	↓	↑
LGA	↓	↑
Macrosomia	↓	↑
SGA	=	=
LBW	↓	↑
Early pregnancy loss	↓	↑
GDM	=	=
HDP	↓	↑
PE	↓	↑
PPH	↓	↑
Placenta previa	↓	↑
PTB	↓	↑
Very PTB	↓	↑
Cong malformations	=	=
Neonatal mortality	=	=
Stratification PCOS	↑ LGA, EPS, very PTB in AC-FET	
Stratification LPS	↓ PTB and placenta previa	

=: no difference; ↑: increased risk; ↓: reduced risk. LGA: large for gest

Hum Reprod Update. 2023;29(5):634-54.

AC-FET會增加子癲前症風險
NC-FET、Fresh IVF子癲前症風險同自然懷孕

Table 4. Hypertensive Disorders of Pregnancy as a Function of Method of Conception for the Prospective Cohort Study of Obstetric Outcomes

	Method of Conception				
Hypertensive Disorder of Pregnancy	**AC-FET** Prog FET (n=94)	**NC-FET** Nat FET (n=127)	**Fresh** Fresh IVF (n=146)	**自然懷孕** Spont (n=143)	*P* Value
Gestational hypertension	3 (3.2)	4 (3.2)	0	3 (2.1)	0.11
Preeclampsia	12 (12.8)	5 (3.9)	7 (4.7)	7 (4.9)	0.05
sPE	9 (9.6)	1 (0.8)	4 (2.7)	3 (2.1)	0.005
Early-onset preeclampsia	0	1 (0.8)	1 (0.7)	0	0.84
HELLP syndrome	0	0	2 (1.4)	0	0.26
Chronic hypertension with superimposed preeclampsia	1 (1.1)	2 (1.6)	1 (0.7)	3 (2.1)	0.78
Eclampsia	0	0	0	0	

NC-FET, Fresh IVF 子癲前症風險與**自然懷孕**相似

Hypertension. 2019;73(3):640-9.

缺乏黃體CL (嚴重)子癲前症增加

Table 3. Hypertensive Disorders of Pregnancy as a Function of CL Category for the Prospective Cohort Study of Obstetric Outcomes

	CL Category				
Hypertensive Disorder of Pregnancy	0 CL (n=94)	1 CL (n=290)	>1 CL (n=153)	Fresh IVF (n=146)	*P* Value
Gestational hypertension	3 (3.2)	8 (2.8)	3 (2.0)	0	0.14
Preeclampsia	12 (12.8)	14 (4.8)	9 (5.9)	7 (4.7)	0.06
sPE 嚴重子癲前症	9 (9.6)	4 (1.4)	6 (3.9)	4 (2.7)	0.004
Early-onset preeclampsia	0	1 (0.3)	1 (0.7)	1 (0.7)	1
HELLP syndrome	0	0	0	2 (1.4)	0.06
Chronic hypertension with superimposed preeclampsia	1 (1.1)	5 (1.7)	0	1 (0.7)	0.41
Eclampsia	0	0	0	0	

Table 5. Multivariable Model Results for the Prospective Cohort Study of Obstetric Outcomes

Variable	Level	AOR	95% CI	*P* Value
Preeclampsia				
CL number	0 vs 1 CL	2.73	1.14–6.49	0.02
FET	Programmed FET vs modified natural-cycle FET	3.55	1.20–11.94	0.03
sPE 嚴重子癲前症				
CL number	0 vs 1 CL	6.45	1.94–25.09	0.003
FET	Programmed FET vs modified natural-cycle FET	15.05	2.59–286.27	0.01

0 CL(嚴重)子癲前症發生率明顯較高

子癲前症:
0CL的是1CL的2.73倍
嚴重子癲:
0CL的是1CL的6.45倍

子癲前症:
AC的是mNC的3.55倍
嚴重子癲:
AC的是mNC的15.05倍

0 CL 是子癲前症的獨立預測因子

Hypertension. 2019;73(3):640-9.

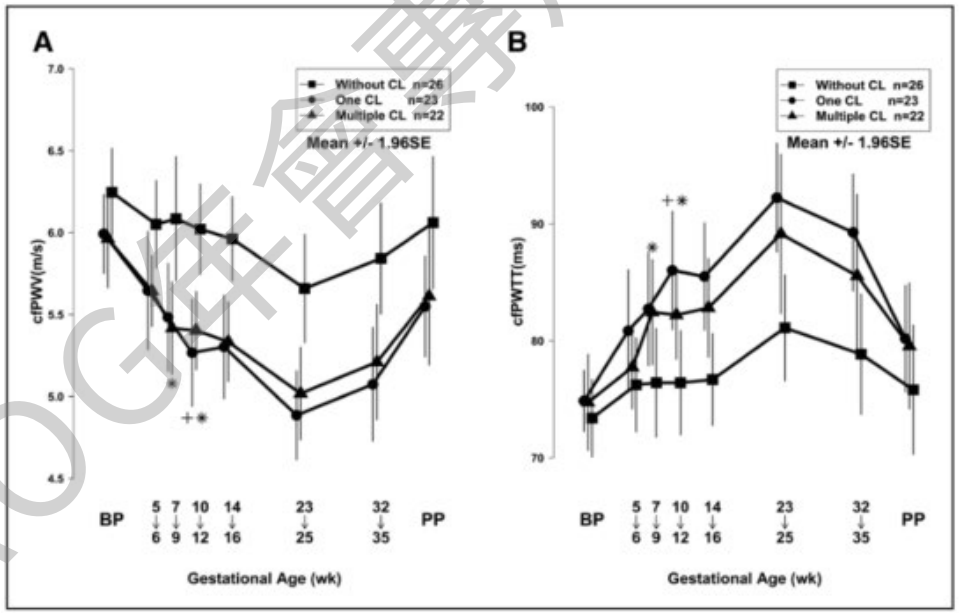
黃體可能影響孕期動脈適應

Preeclampsia

Increased Preeclampsia Risk and Reduced Aortic Compliance With In Vitro Fertilization Cycles in the Absence of a Corpus Luteum

頸動脈-股動脈脈波傳播速度 (cfPWV)
在 0 CL 群體**未顯著下降**
表示血管僵硬度未正常降低

頸動脈-股動脈脈波傳播時間 (cfPWTT)
在 0 CL 群體中**未正常增加**，
顯示**血管適應能力較差**。

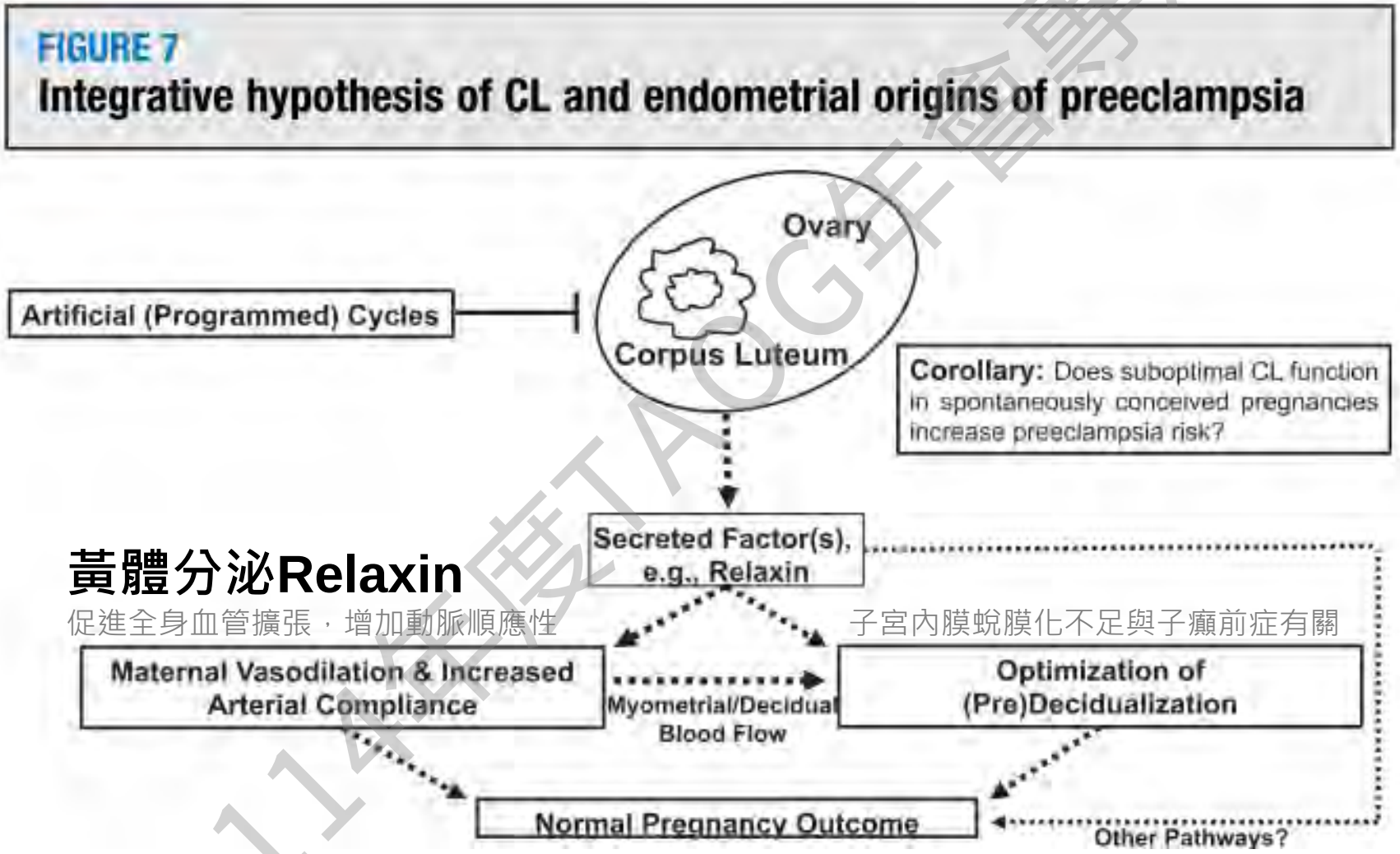


缺乏黃體的孕婦，主動脈順應性降低，
導致血管僵硬度增加，增加子癲前症風險

正常懷孕時動脈適應增加 pulse wave velocity (PWV) 下降
(cfPWV 下降1m/s 維持至22-25周，才回復未懷孕前)，與子癲前症相關
黃體分泌 **血管活性激素 (如 Relaxin)，影響母體血流動力學**。
這些異常在 **妊娠前 10-12 週最明顯**，對於子癎前症的發展很重要

Hypertension. 2019;73(3):640-9.

黃體corpus luteum與子癲前症關係



黃體分泌Relaxin

促進全身血管擴張，增加動脈順應性

子宮內膜蛻膜化不足與子癲前症有關

Am J Obstet Gynecol. 2022;226(5):683-99.

黃體CL不影響著床但影響持續懷孕

Open access Original research

BMJ Open

Treatment outcomes of blastocysts thaw cycles, comparing the presence and absence of a corpus luteum: a systematic review and meta-analysis

Joscelyn Gan ,[1] Genia Rozen,[2,3,4] Alex Polyakov[2,3,4]

Australia 2017-2020.

meta- analysis : 2 RCT,7 cohort studies.

比較有/無CL 對FET懷孕outcomes 的影響

positive hCG results (RR 1.0, 95% CI 0.95 to 1.05)

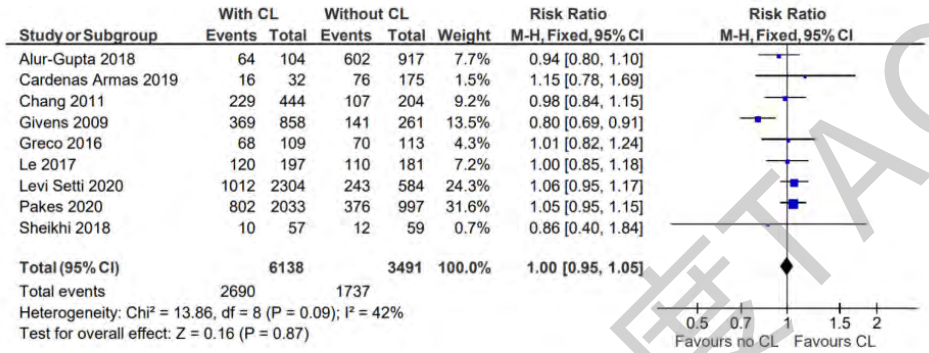
clinical pregnancies (RR 1.06, 95% CI 0.96 to 1.18)

兩組間沒有差異

live births: CL(+)(RR 1.14, 95% CI 1.06-1.22)

NC-FET明顯較高

Rate of hCG(+) CL(-)=CL(+)



Study or Subgroup	With CL Events	With CL Total	Without CL Events	Without CL Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alur-Gupta 2018	64	104	602	917	7.7%	0.94 [0.80, 1.10]
Cardenas Armas 2019	16	32	76	175	1.5%	1.15 [0.78, 1.69]
Chang 2011	229	444	107	204	9.2%	0.98 [0.84, 1.15]
Givens 2009	369	858	141	261	13.5%	0.80 [0.69, 0.91]
Greco 2016	68	109	70	113	4.3%	1.01 [0.82, 1.24]
Le 2017	120	197	110	181	7.2%	1.00 [0.85, 1.18]
Levi Setti 2020	1012	2304	243	584	24.3%	1.06 [0.95, 1.17]
Pakes 2020	802	2033	376	997	31.6%	1.05 [0.95, 1.15]
Sheikhi 2018	10	57	12	59	0.7%	0.86 [0.40, 1.84]
Total (95% CI)		**6138**		**3491**	**100.0%**	**1.00 [0.95, 1.05]**
Total events	2690		1737			

Heterogeneity: Chi² = 13.86, df = 8 (P = 0.09); I² = 42%

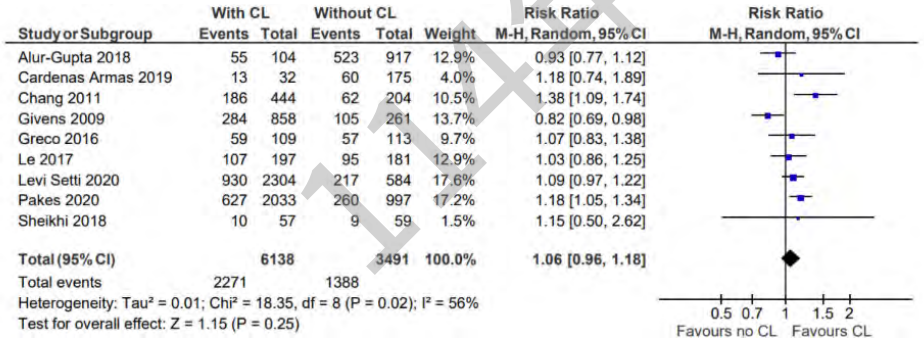
Test for overall effect: Z = 0.16 (P = 0.87)

Risk Ratio M-H, Fixed, 95% CI

0.5 0.7 1 1.5 2

Favours no CL Favours CL

Clinical pregnancy Rate CL(-)=CL(+)



Study or Subgroup	With CL Events	With CL Total	Without CL Events	Without CL Total	Weight	Risk Ratio M-H, Random, 95% CI
Alur-Gupta 2018	55	104	523	917	12.9%	0.93 [0.77, 1.12]
Cardenas Armas 2019	13	32	60	175	4.0%	1.18 [0.74, 1.89]
Chang 2011	186	444	62	204	10.5%	1.38 [1.09, 1.74]
Givens 2009	284	858	105	261	13.7%	0.82 [0.69, 0.98]
Greco 2016	59	109	57	113	9.7%	1.07 [0.83, 1.38]
Le 2017	107	197	95	181	12.9%	1.03 [0.86, 1.25]
Levi Setti 2020	930	2304	217	584	17.6%	1.09 [0.97, 1.22]
Pakes 2020	627	2033	260	997	17.2%	1.18 [1.05, 1.34]
Sheikhi 2018	10	57	9	59	1.5%	1.15 [0.50, 2.62]
Total (95% CI)		**6138**		**3491**	**100.0%**	**1.06 [0.96, 1.18]**
Total events	2271		1388			

Heterogeneity: Tau² = 0.01; Chi² = 18.35, df = 8 (P = 0.02); I² = 56%

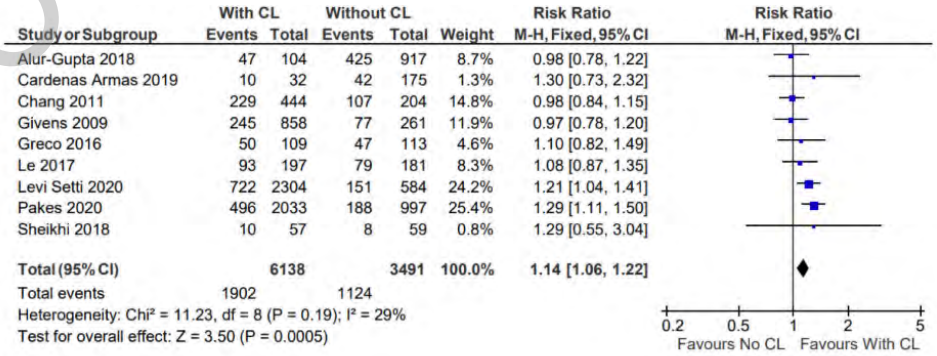
Test for overall effect: Z = 1.15 (P = 0.25)

Risk Ratio M-H, Random, 95% CI

0.5 0.7 1 1.5 2

Favours no CL Favours CL

Live Births and OPR CL(-)<CL(+)



Study or Subgroup	With CL Events	With CL Total	Without CL Events	Without CL Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alur-Gupta 2018	47	104	425	917	8.7%	0.98 [0.78, 1.22]
Cardenas Armas 2019	10	32	42	175	1.3%	1.30 [0.73, 2.32]
Chang 2011	229	444	107	204	14.8%	0.98 [0.84, 1.15]
Givens 2009	245	858	77	261	11.9%	0.97 [0.78, 1.20]
Greco 2016	50	109	47	113	4.6%	1.10 [0.82, 1.49]
Le 2017	93	197	79	181	8.3%	1.08 [0.87, 1.35]
Levi Setti 2020	722	2304	151	584	24.2%	1.21 [1.04, 1.41]
Pakes 2020	496	2033	188	997	25.4%	1.29 [1.11, 1.50]
Sheikhi 2018	10	57	8	59	0.8%	1.29 [0.55, 3.04]
Total (95% CI)		**6138**		**3491**	**100.0%**	**1.14 [1.06, 1.22]**
Total events	1902		1124			

Heterogeneity: Chi² = 11.23, df = 8 (P = 0.19); I² = 29%

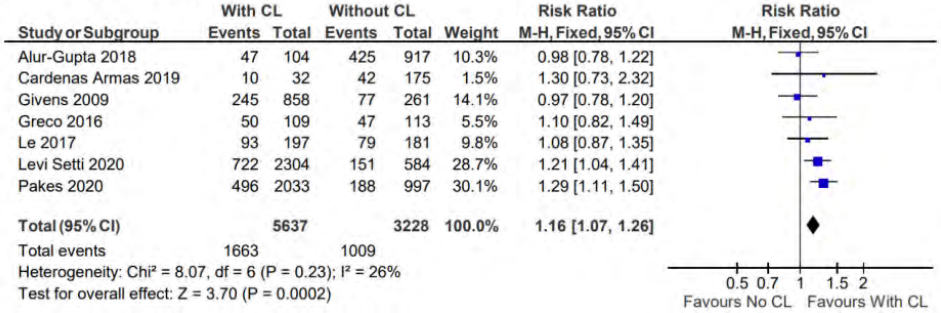
Test for overall effect: Z = 3.50 (P = 0.0005)

Risk Ratio M-H, Fixed, 95% CI

0.2 0.5 1 2 5

Favours No CL Favours With CL

Live Births Rates Only



Study or Subgroup	With CL Events	With CL Total	Without CL Events	Without CL Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alur-Gupta 2018	47	104	425	917	10.3%	0.98 [0.78, 1.22]
Cardenas Armas 2019	10	32	42	175	1.5%	1.30 [0.73, 2.32]
Givens 2009	245	858	77	261	14.1%	0.97 [0.78, 1.20]
Greco 2016	50	109	47	113	5.5%	1.10 [0.82, 1.49]
Le 2017	93	197	79	181	9.8%	1.08 [0.87, 1.35]
Levi Setti 2020	722	2304	151	584	28.7%	1.21 [1.04, 1.41]
Pakes 2020	496	2033	188	997	30.1%	1.29 [1.11, 1.50]
Total (95% CI)		**5637**		**3228**	**100.0%**	**1.16 [1.07, 1.26]**
Total events	1663		1009			

Heterogeneity: Chi² = 8.07, df = 6 (P = 0.23); I² = 26%

Test for overall effect: Z = 3.70 (P = 0.0002)

Risk Ratio M-H, Fixed, 95% CI

0.5 0.7 1 1.5 2

Favours No CL Favours With CL

BMJ Open. 2022;12(4):e051489.

黃體CL不影響著床但影響持續懷孕

Open access Original research

BMJ Open

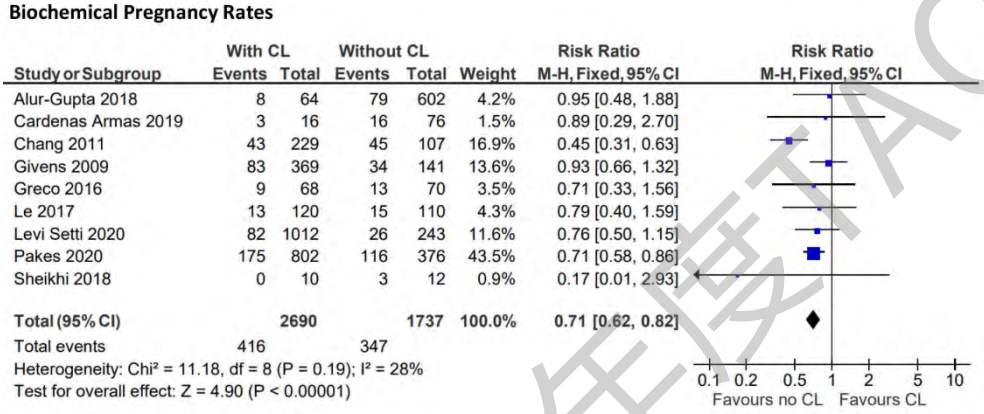
Treatment outcomes of blastocysts thaw cycles, comparing the presence and absence of a corpus luteum: a systematic review and meta-analysis

Australia 2017-2020.

meta- analysis : 2 RCT,7 cohort studies.

比較有/無CL 對FET懷孕outcomes 的影響

Biochemical pregnancy rates (early miscarriage) **CL(-)>CL(+)**



Biochemical Pregnancy Rates

Study or Subgroup	With CL Events	With CL Total	Without CL Events	Without CL Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alur-Gupta 2018	8	64	79	602	4.2%	0.95 [0.48, 1.88]
Cardenas Armas 2019	3	16	16	76	1.5%	0.89 [0.29, 2.70]
Chang 2011	43	229	45	107	16.9%	0.45 [0.31, 0.63]
Givens 2009	83	369	34	141	13.6%	0.93 [0.66, 1.32]
Greco 2016	9	68	13	70	3.5%	0.71 [0.33, 1.56]
Le 2017	13	120	15	110	4.3%	0.79 [0.40, 1.59]
Levi Setti 2020	82	1012	26	243	11.6%	0.76 [0.50, 1.15]
Pakes 2020	175	802	116	376	43.5%	0.71 [0.58, 0.86]
Sheikhi 2018	0	10	3	12	0.9%	0.17 [0.01, 2.93]
Total (95% CI)		**2690**		**1737**	**100.0%**	**0.71 [0.62, 0.82]**
Total events	416		347			

Heterogeneity: Chi² = 11.18, df = 8 (P = 0.19); I² = 28%

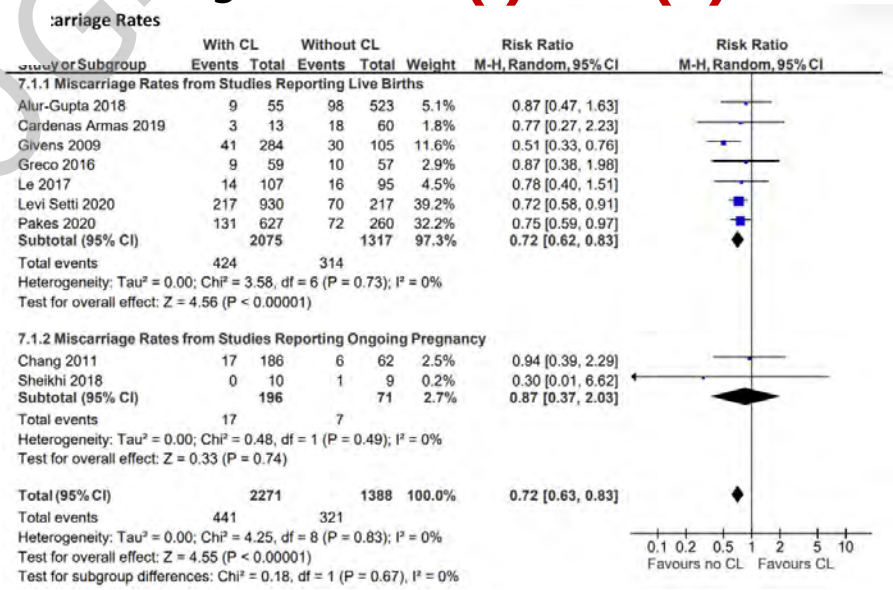
Test for overall effect: Z = 4.90 (P < 0.00001)

Risk Ratio M-H, Fixed, 95% CI

0.1 0.2 0.5 1 2 5 10

Favours no CL Favours CL

Miscarriage Rate **CL(-)>CL(+)**



arriage Rates

Study or Subgroup	With CL Events	With CL Total	Without CL Events	Without CL Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Miscarriage Rates from Studies Reporting Live Births						
Alur-Gupta 2018	9	55	98	523	5.1%	0.87 [0.47, 1.63]
Cardenas Armas 2019	3	13	18	60	1.8%	0.77 [0.27, 2.23]
Givens 2009	41	284	30	105	11.6%	0.51 [0.33, 0.76]
Greco 2016	9	59	10	57	2.9%	0.87 [0.38, 1.98]
Le 2017	14	107	16	95	4.5%	0.78 [0.40, 1.51]
Levi Setti 2020	217	930	70	217	39.2%	0.72 [0.58, 0.91]
Pakes 2020	131	627	72	260	32.2%	0.75 [0.59, 0.97]
Subtotal (95% CI)		**2075**		**1317**	**97.3%**	**0.72 [0.62, 0.83]**
Total events	424		314			
7.1.2 Miscarriage Rates from Studies Reporting Ongoing Pregnancy						
Chang 2011	17	186	6	62	2.5%	0.94 [0.39, 2.29]
Sheikhi 2018	0	10	1	9	0.2%	0.30 [0.01, 6.62]
Subtotal (95% CI)		**196**		**71**	**2.7%**	**0.87 [0.37, 2.03]**
Total events	17		7			
Total (95% CI)		**2271**		**1388**	**100.0%**	**0.72 [0.63, 0.83]**
Total events	441		321			

Heterogeneity: Tau² = 0.00; Chi² = 3.58, df = 6 (P = 0.73); I² = 0%

Test for overall effect: Z = 4.56 (P < 0.00001)

Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%

Test for overall effect: Z = 0.33 (P = 0.74)

Heterogeneity: Tau² = 0.00; Chi² = 4.25, df = 8 (P = 0.83); I² = 0%

Test for overall effect: Z = 4.55 (P < 0.00001)

Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%

Risk Ratio M-H, Random, 95% CI

0.1 0.2 0.5 1 2 5 10

Favours no CL Favours CL

<u>Pregnancy losses</u>

early miscarriage CL(+) RR 0.71 (0.62 - 0.82)

Miscarriages(<20wks) CL(+) RR 0.72 (0.62 - 0.83)

Pregnancy losses 在有黃體CL(+)明顯較低

BMJ Open. 2022;12(4):e051489.

Pregnancy rate AC=mNC=SC
Early Pregnancy loss rate AC>mNC>SC

Human Reproduction Open, pp. 1–10, 2022
https://doi.org/10.1093/hropen/hoac007

human reproduction open | ORIGINAL ARTICLE

Impact of endometrial preparation on early pregnancy loss and live birth rate after frozen embryo transfer: a large multicenter cohort study (14 421 frozen cycles)

France
multicenter retrospective cohort study
9 reproductive health units
2012 - 2016.
FET cycles : 14421 cycles
(**AC: n=8139; NC: n=3126; SC: n=3156**)
3844 pregnancies (hCG > 100 IU/l)
(AC: n=2214; NC: n=812; SC: n=818).
Primary outcome: pregnancy loss rate at 10 weeks of gestation.

AC:
E2: 4-6mg oral or vaginal
P4: micronized progesterone 400-800mg vaginal ~ 9wks
mNC: hCG+LPS
SC: menopure 50-75IU + hCG (DF>16mm) +LPS

黃體CL不影響著床但影響持續懷孕

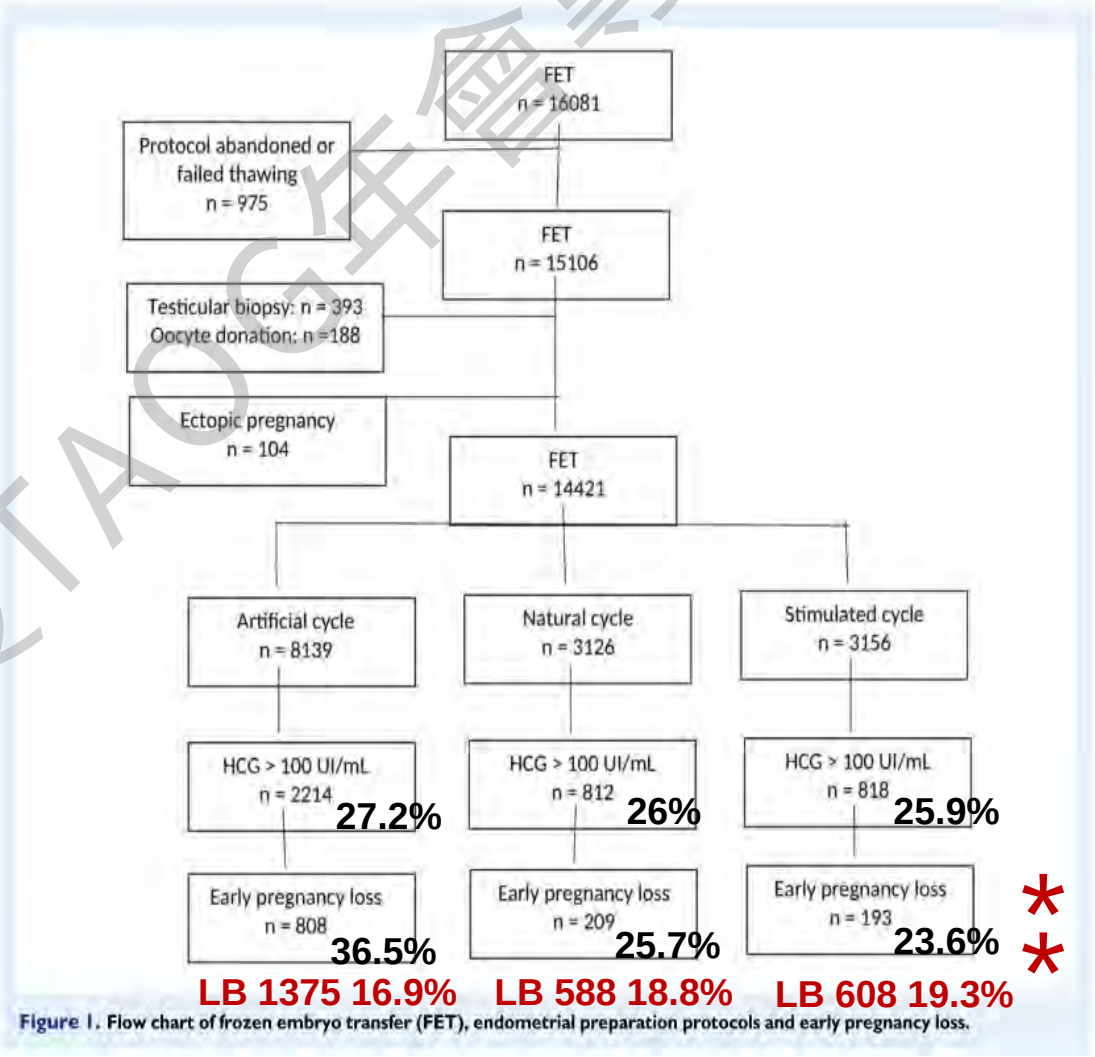


Figure 1. Flow chart of frozen embryo transfer (FET), endometrial preparation protocols and early pregnancy loss.

Hum Reprod Open. 2022;2022(2):hoac007.

Early pregnancy loss rate AC>NC>SC
LBR AC<NC<SC

Table I Patient characteristics and outcomes of frozen–thawed embryo transfer according to endometrial preparation protocol. 14421 cycles **(AC: n=8139; NC: n=3126; SC: n=3156)**

	Total population	Artificial cycle (AC)	Natural cycle (NC)	Stimulated cycle (SC)	P
Number of FET	14 421	8139	3126	3156	
Age (years), mean ± SD	34.2	34.1 ± 4.7	34.3 ± 4.5	34.2 ± 4.4	0.70
Primary infertility, n (%)	7326 (50.8)	4182 (51.4)	1513 (48.4)	1541 (48.8)	0.004
Length of infertility (days), mean ± SD	2042 ± 1054	2054 ± 1,059	2015 ± 1004	2035 ± 1088	0.92
History of early pregnancy loss, n (%)	2064 (14.3)	1134 (13.9)	476 (15.2)	454 (14.4)	0.21
BMI (kg/m^2), mean ± SD	23.4 ± 5.4	23.8 ± 5.2	22.7 ± 5.8	23.6 ± 5.2	0.07
Smoking, n (%)	3390 (23.5)	1923 (23.6)	736 (23.5)	731 (23.2)	0.87
ICSI, n (%)	8321 (57.7)	4638 (57.0)	2036 (65.1)	1647 (52.2)	<0.0001
Endometrial thickness (mm), mean ± SD	9.3 ± 2.5	9.1 ± 2.6	9.8 ± 2.3	9.1 ± 2.2	0.02
Number of embryos transferred, mean ± SD	1.4 ± 0.5	1.4 ± 0.5	1.3 ± 0.5	1.5 ± 0.5	0.09
Biochemical pregnancy (hCG 10–100 IU/ml) per pregnancy, n (%)	461 (10.7)	251 (10.2)	95 (10.5)	115 (12.2)	0.20
Pregnancy with HCG >100 IU/ml per FET, n (%)	3844 (26.7)	2214 (27.2)	812 (26.0)	818 (25.9)	0.20
Early pregnancy loss per pregnancy with HCG >100 IU/ml, n (%)	1210 (31.5)	808 (36.5)	209 (25.7)	193 (23.6)	<0.005
Live birth per FET, n (%)	2571 (17.8)	1375 (16.9)	588 (18.8)	608 (19.3)	<0.003

FET, frozen embryo transfer.

流產率AC>NC>SC→黃體CL不影響著床但影響持續懷孕

Pregnancy rate AC: 26.7%; NC: 27.2%; SC: 26% P 0.02 **AC=NC=SC**

Early pregnancy loss rate AC: 36.5%; NC: 25.6%; SC: 23.6% P<0.005 **AC>NC>SC**

LBR AC: 16.9%; NC: 18.8%; SC: 19.3% P<0.003 **AC<NC<SC**

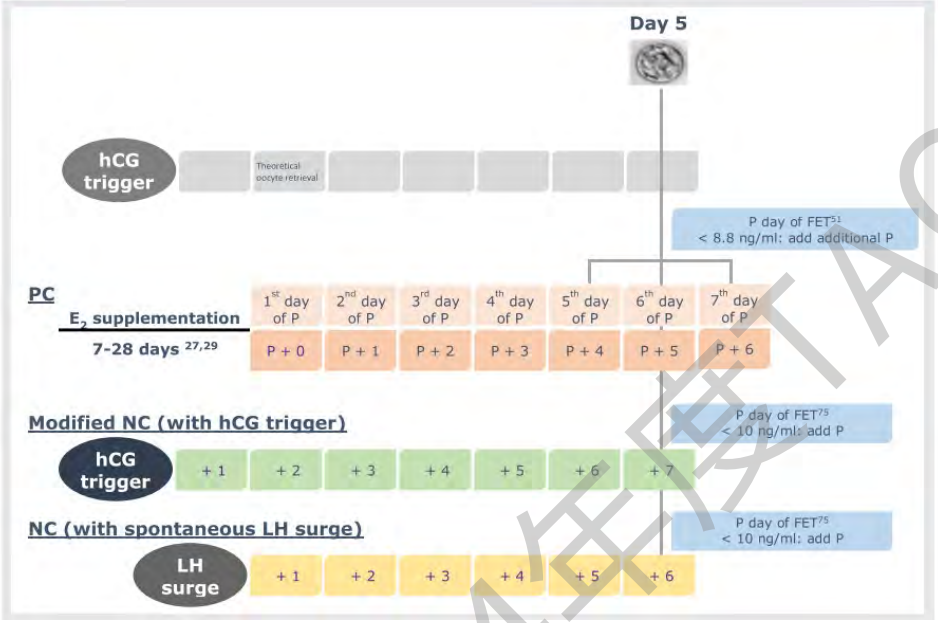
Hum Reprod Open. 2022;2022(2)

懷孕併發症及懷孕率及取消率 AC:mNC:NC

Livebirth rate after one frozen embryo transfer in ovulatory women starting with natural, modified natural, or artificial endometrial preparation in Viet Nam: an open-label randomised controlled trial

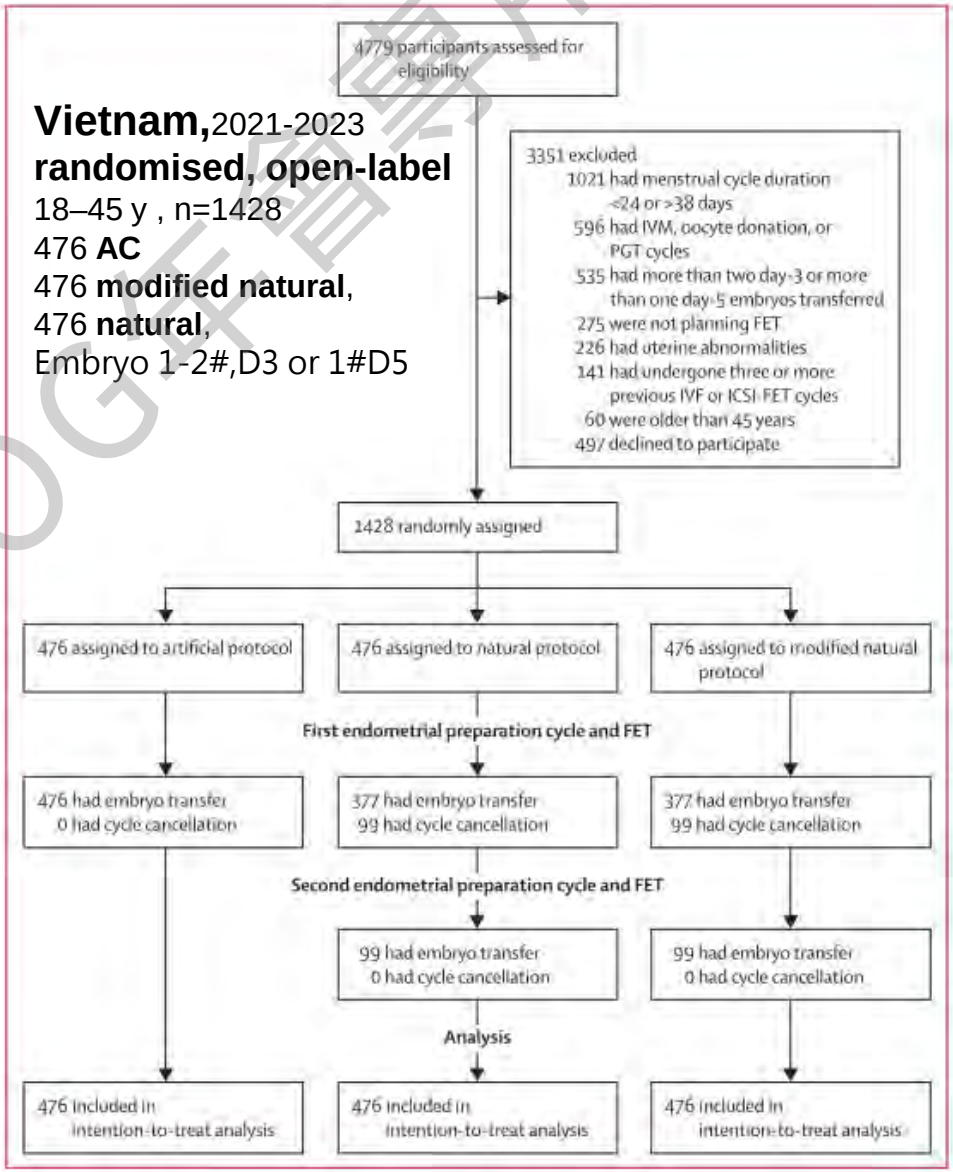
Vu N A Ha, Toan D Pham, Nam T Nguyen, Rui Wang, Robert J Norman, Ben W Mol, Trung M Ho, Lan N Vuong

FIGURE 1



476 AC: E2 8mg- EM≧7mm +Vag P4 800mg/d
476 mNC:DF>16mm→ +hCG(Ovitrelle 250 µg)
Cancel :no follicle >16mm after D21
476 NC: TVS since DF>14mm, LH>180%,
Cancel: no LH surge till D21

Vietnam,2021-2023
randomised, open-label
18–45 y , n=1428
476 **AC**
476 **modified natural**,
476 **natural**,
Embryo 1-2#,D3 or 1#D5



Lancet. 2024;404(10449):266-75.

NC , mNC 取消率高

	Natural cycle strategy (n=476)	Modified natural cycle strategy (n=476)	Artificial cycle strategy (n=476)	p value	
				Natural vs artificial cycle strategy	Modified natural vs artificial cycle strategy
Completed first endometrial preparation as randomly assigned	377 (79%)	377 (79%)	476 (100%)	..	..
Endometrial preparation cycle cancellation	99 (21%)	99 (21%)	0	..	..
Second artificial endometrial preparation	99 (21%)	99 (21%)	0	..	..

取消1st FET 週期

NC 99 位(21%)

66.7% 沒有濾泡產生

32% 沒有LH surge

mNC 99 位(21%)

66.7% 沒有濾泡產生

18.2% 沒有長大的濾泡

15.1% 非預期排卵

AC 沒有取消

Table S1: **Reasons for cancellation in the first frozen embryo transfer cycle of the natural and modified natural cycle protocol groups**

Reasons	Natural cycle (n=99)	Modified natural cycle (n=99)
No development of follicles	67 (67·7)	66 (66·7)
No developing follicles (≥16 mm)	-	18 (18·2)
No onset of luteinising hormone surge	32 (32·3)	-
Unexpected spontaneous ovulation	-	15 (15·1)

Lancet. 2024;404(10449):266-75.

CPR.OPR.LBR.miscarriage
AC = NC/mNC

Table S2: **Fertility outcomes after first endometrial preparation**

	Natural cycle	Modified natural cycle	Artificial cycle	Relative risk (95% confidence interval)	
				Natural vs. artificial cycle	Modified natural vs. artificial cycle
PER PROTOCOL	**(n=377)**	**(n=377)**	**(n=476)**		
Live birth, n (%)	127 (33·7)	117 (31·0)	162 (34·0)	0·99 (0·78; 1·25)	0·91 (0·72; 1·16)
After day-3 embryo transfer	44/181 (24·3)	42/182 (23·1)	43/214 (20·1)	1·21 (0·79; 1·85)	1·15 (0·75; 1·76)
After day-5 embryo transfer	83/196 (42·4)	75/195 (38·5)	119/262 (45·4)	0·93 (0·70; 1·23)	0·85 (0·63; 1·13)
Positive pregnancy test, n (%)	171 (45·4)	160 (42·4)	232 (48·7)	0·93 (0·76; 1·13)	0·87 (0·71; 1·06)
Clinical pregnancy, n (%)	157 (41·6)	144 (38·2)	205 (43·1)	0·97 (0·79; 1·19)	0·89 (0·72; 1·10)
Ongoing pregnancy, n (%)	130 (34·5)	122 (32·4)	165 (34·7)	0·99 (0·79; 1·25)	0·93 (0·74; 1·18)
Implantation, n (%)	172/516 (33·3)	155/529 (29·3)	216/633 (34·1)	0·98 (0·83; 1·15)	0·86 (0·72; 1·02)
Ectopic pregnancy, n (%)	3 (0·8)	8 (2·1)	4 (0·8)	0·95 (0·19; 4·30)	2·53 (0·80; 9·46)
Miscarriage <12 weeks, n (%)	24 (6·4)	14 (3·7)	36 (7·6)	0·84 (0·50; 1·40)	0·49 (0·26; 0·89)
Miscarriage 12 to <20 weeks, n (%)	3 (0·8)	5 (1·3)	3 (0·6)	1·26 (0·23; 6·82)	2·10 (0·52; 10·3)
Multiple pregnancy, n (%)	7 (1·9)	8 (2·1)	8 (1·7)	1·10 (0·39; 3·08)	1·26 (0·47; 3·43)
Multiple delivery, n (%)	7 (1·9)	8 (2·1)	7 (1·5)	1·26 (0·43; 3·69)	1·44 (0·52; 4·12)

1st FET: NC/mNC/AC
LBR : 33.7% 31% 34% 無差異
CPR: 41.6% 38.2% 43.1% 無差異
OPR: 34.5% 32.4% 34.7% 無差異
Miscarriage(<12Wks): 6.4% 3.7% 7.6%無差異

Lancet. 2024;404(10449):266-75.

OBS outcomes (GDM/HDP),perinatal outcomes

NC=mNC=AC , Preeclampsia ??

	Natural cycle strategy* (n=476)	Modified natural cycle strategy* (n=476)	Artificial cycle strategy* (n=476)	RR	
				Natural then artificial cycle vs artificial cycle	Modified natural vs artificial cycle
Obstetric outcomes					
Preterm delivery 20 to <28 weeks' gestation, singletons	0	0	1 (<1%)	..	..
Preterm delivery 28 to <32 weeks' gestation, singletons	0	2 (<1%)	0	..	..
Preterm delivery 32 to <37 weeks' gestation, singletons	15 (3%)	11 (2%)	7 (1%)	2·14 (0·90 to 5·61)	1·57 (0·62 to 4·27)
Preterm delivery 20 to <28 weeks' gestation, twins	1 (<1%)	0	0	..	..
Preterm delivery 28 to <32 weeks' gestation, twins	1 (<1%)	0	0	..	..
Preterm delivery 32 to <37 weeks' gestation, twins	4 (<1%)	4 (<1%)	2 (<1%)	2·00 (0·39 to 14·40)	2·00 (0·39 to 14·40)
Gestational diabetes **GDM**	44 (9%)	37 (8%)	32 (7%)	1·37 (0·88 to 2·18)	1·16 (0·72 to 1·87)
Hypertensive disorders in pregnancy	10 (2%)	8 (2%)	12 (3%)	0·83 (0·35 to 1·93)	0·67 (0·26 to 1·61)
Hypertensive disorders in pregnancy per ongoing pregnancy **HDP**	10/177 (6%)	8/164 (5%)	12/165 (7%)	0·78 (0·33 to 1·80)	0·67 (0·26 to 1·62)
Perinatal outcomes					
Singleton birthweight, g (469 babies)	3178·4 (463·2)	3147·1 (515·2)	3245·9 (450·3)	−67·5 (−170·1 to 35·1)†	−98·8 (−210·3 to 12·7)†
Twin birthweight, g (52 babies‡)	2370·0 (444·7)	2598·9 (342·2)	2300·0 (434·8)	70·0 (−260·7 to 400·7)†	298·9 (−24·2 to 622·1)†
Singleton birthweight, very low	0	1 (<1%)	1 (<1%)	..	1·00 (0·04 to 25·30)
Singleton birthweight, low	6 (1%)	8 (2%)	5 (1%)	1·20 (0·36 to 4·16)	1·60 (0·53 to 5·30)
Singleton birthweight, high	5 (1%)	5 (1%)	4 (<1%)	1·25 (0·33 to 5·05)	1·25 (0·33 to 5·05)
Singleton birthweight, very high	1 (<1%)	0	0	..	..
Major congenital abnormalities§	1 (<1%)	2 (<1%)	1 (<1%)	1·00 (0·04 to 25·3)	2·00 (0·19 to 43·00)
Admission to NICU	15 (3%)	8 (2%)	18 (4%)	0·83 (0·41 to 1·65)	0·44 (0·18 to 0·99)
Stillbirth	0	0	0	..	..
Neonatal mortality	1 (<1%)	0	1 (<1%)	1·00 (0·04 to 25·30)	..

NC/mNC/AC
OBS outcomes (GDM/HDP),perinatal outcomes 無差異

Lancet. 2024;404(10449):266-75.

Endometrium preparation protocols for FET

Hormone replacement treatment (HRT)(AC)

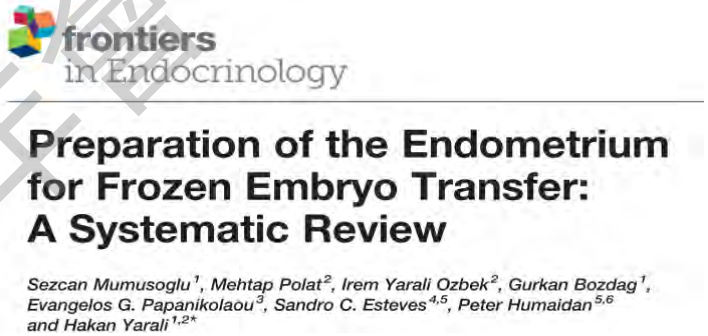
HRT with/without GnRH-a suppression

True natural (t-NC) cycle

t-NC with/without luteal phase support

Modified natural (modified-NC) cycle

Modified-NC with/without luteal phase support



Mild ovarian stimulation (Mild-OS)

- Clomiphene Citrate (CC)
- Aromatase Inhibitor(Letrozole)
- Follicle Stimulating Hormone (FSH)

Front Endocrinol (Lausanne). 2021;12:688237.

HRT-FET , AC-FET protocol

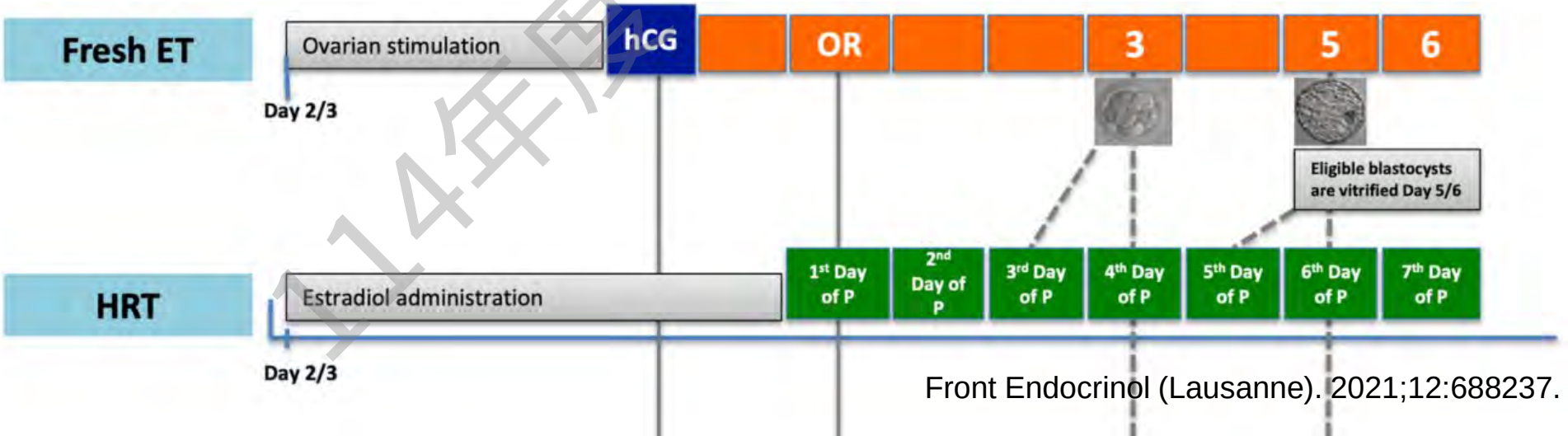
Estrogen Start on D1-3 (7 – 36 days)

- Fixed regimen (6mg daily)
- Step-up regimen (D1-7 2mg/d, D7-12 4mg, D13~ 6mg)

D12 -14 → TVS : **EM >7mm** and **leading follicle (N)**

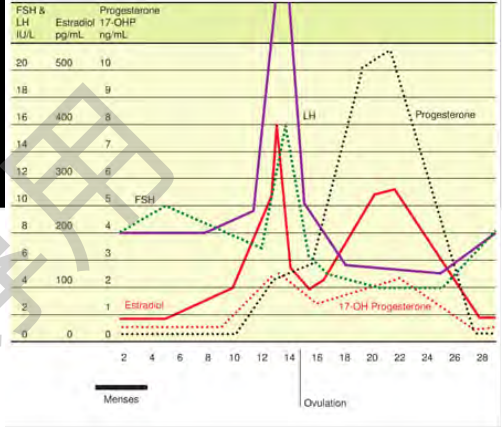
Progesterone

- Day3 embryos FET on the 3rd/4th day of P administration
- Day5/6 blastocysts FET on the 5th/6th day of P administration



Front Endocrinol (Lausanne). 2021;12:688237.

Nature cycle protocol



超音波：since D10

EM >7mm , follicle collapse D0(FC+5)

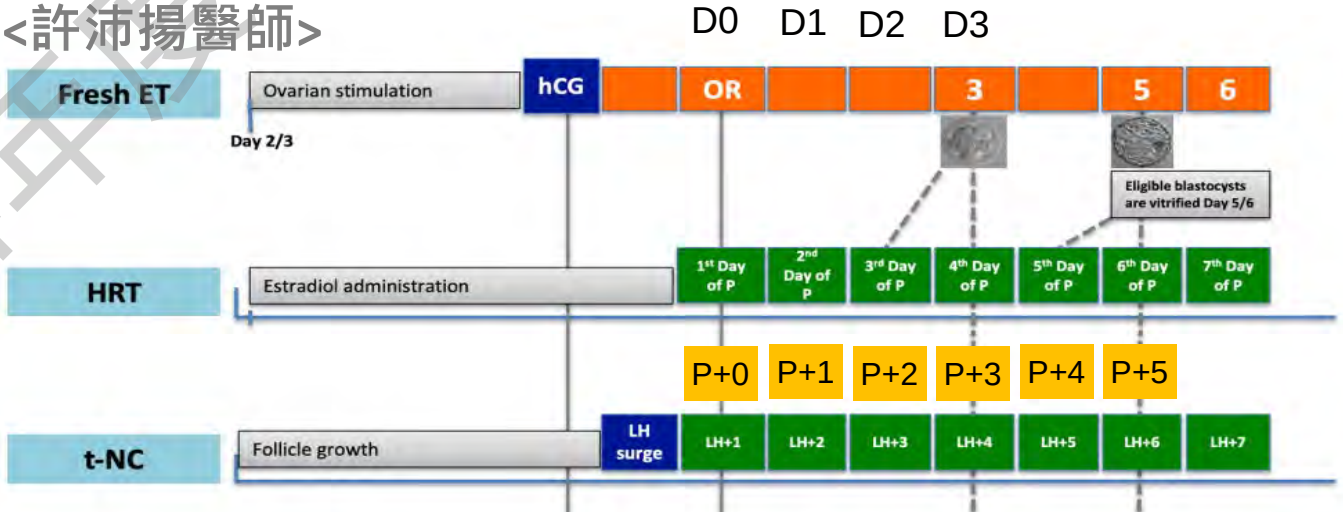
LH surge daily check (LH surge +6/+7/+8/+9) <黃斑琦醫師>

Dominant follicle >14mm, LH >17IU/ml,
followed by E2 drop >30% in the next day (Irani et al., 2017)

LH ≥10 IU/l (Groenewoud et al., 2012) LH ≥15 IU/l (Ursillo et al., 2021)
LH>20 IU/l (Chantal et al.,2019)
LH ≥180% of the mean of the preceding values (Testart *et al.*, 1981)

P上升 (P+5) <許沛揚醫師>

D0: 1< P≦3 ng/mL
D1: 3<P≦6
D2: 6<P≦8
D3: 8<P ≦10



改善自然週期靈活性策略

Modified natural (modified-NC) cycle

- **HCG → Flexibly HCG**
- **NPP (natural proliferative-phase protocol)**

= Progesterone-modified natural cycle (P4mNC)

Mild ovarian stimulation (Mild-OS)

- Clomiphene Citrate (CC)
- Aromatase Inhibitor(Letrozole)
- Follicle Stimulating Hormone (FSH)

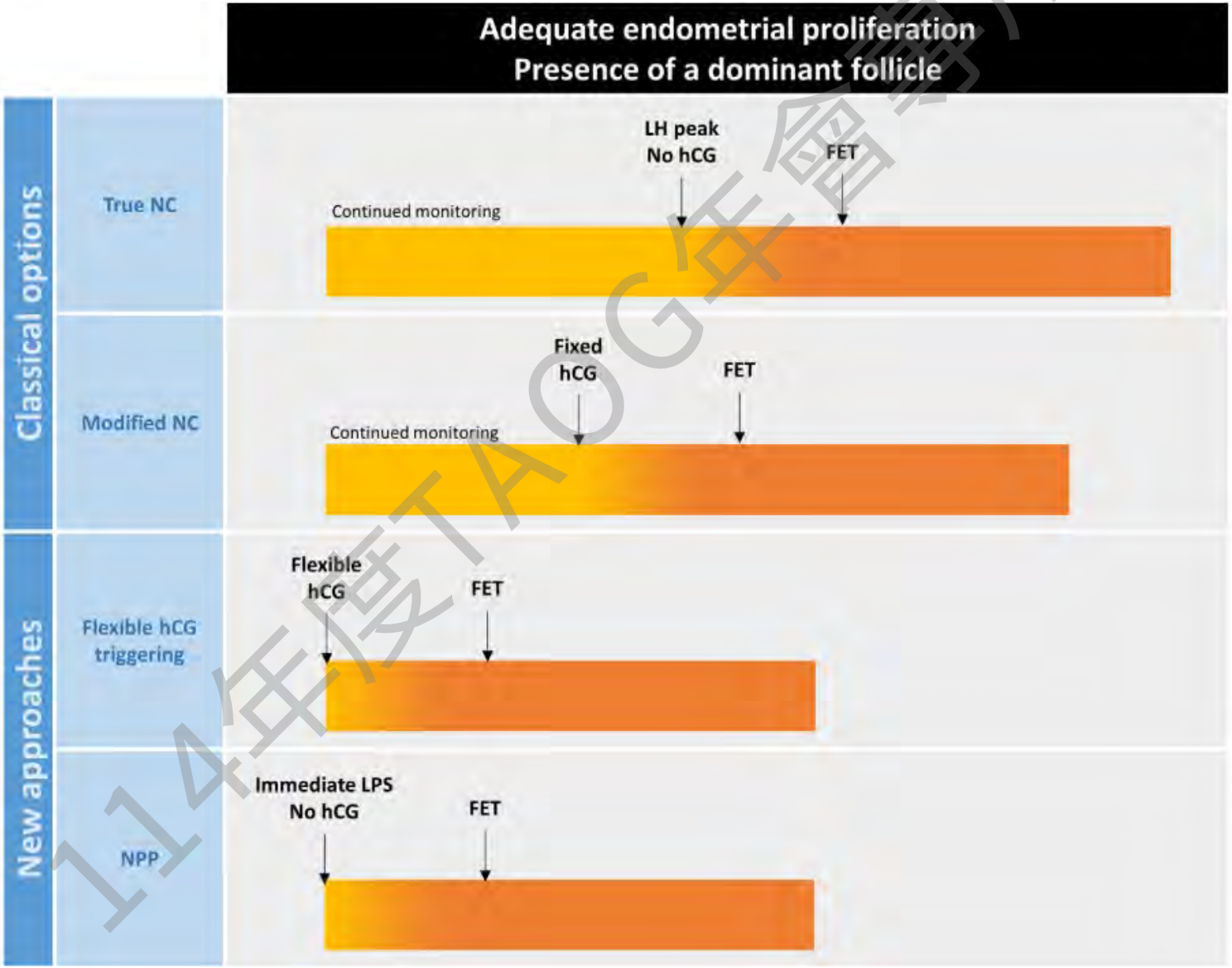
解決無排卵問題 → **SC (Mild-OS)**

減少週期監測 → **hCG,NPP**

降低週期取消率,提高NC-FET 靈活性 → **hCG,NPP**

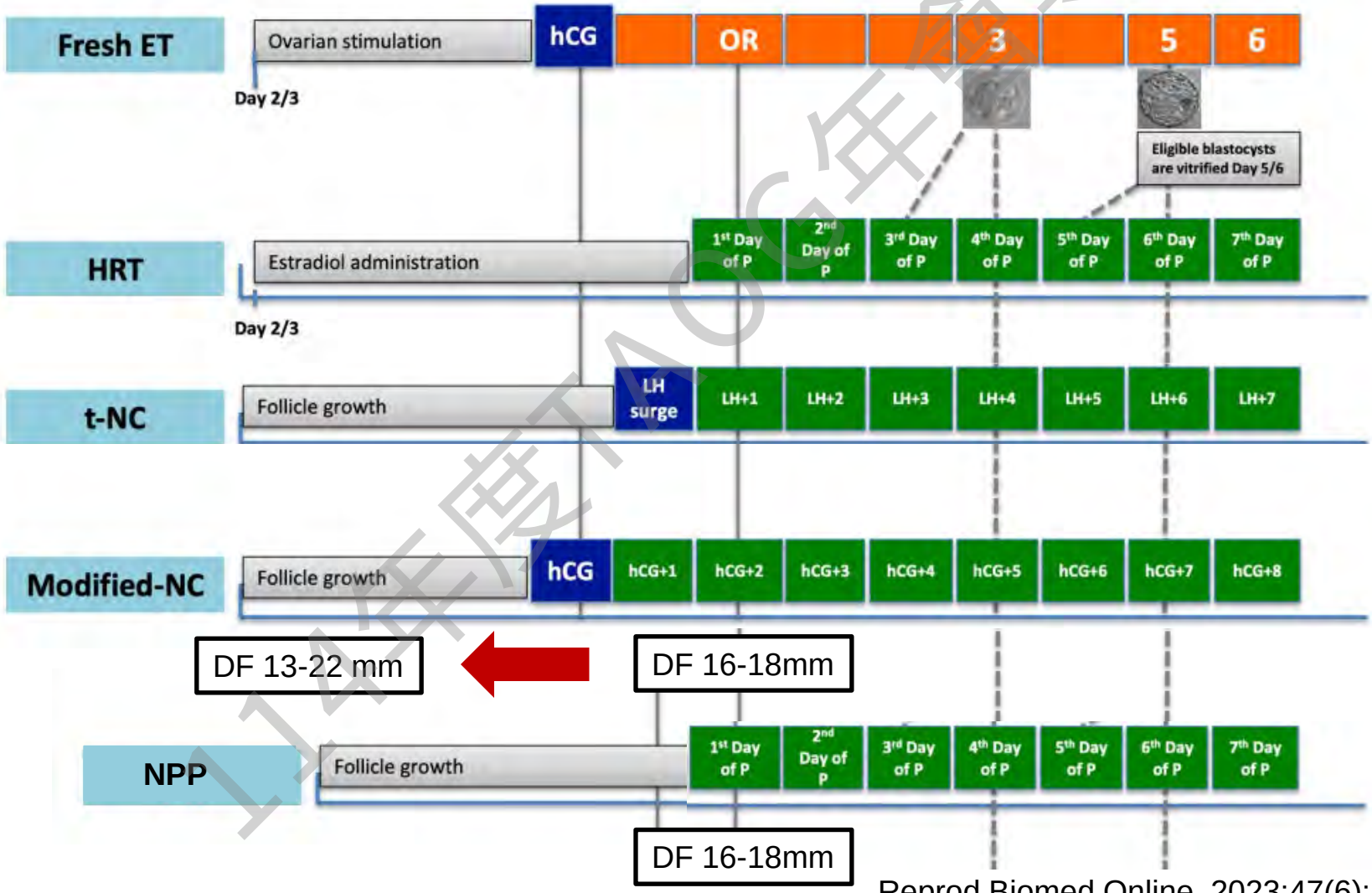
Reprod Biomed Online. 2023;47(6):103352.

Nature cycle- 傳統 及 創新



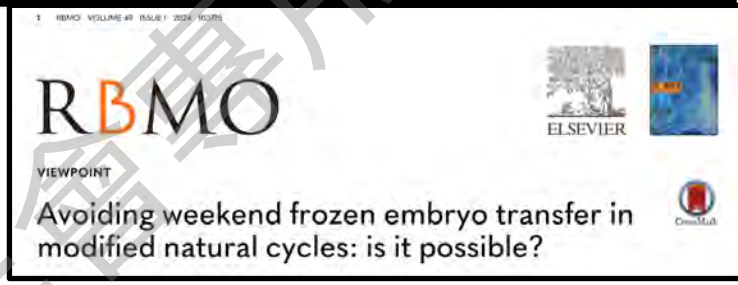
Reprod Biomed Online. 2023;47(6):103352

Nature cycle- 傳統 及 創新



Reprod Biomed Online. 2023;47(6):103352

hCG - Modified natural cycle protocol



HCG trigger

過去

Follicle 17(16-20) mm ,EM ≧7mm→ +HCG

新法 **Flexibly HCG**

Follicle 13 -22 mm (1-1.5mm/d) ,EM ≧7mm, P4<1.5 ng/ml → +HCG

Flexible range of 5-7 days for FET

優勢: 可以有彈性.用藥少.有黃體保護

Reprod Biomed Online. 2024;49(1):103775.

CPR,OPR,流產率 NC = mNC

Human Reproduction, Vol.35, No.5, pp. 1073–1081, 2020
Advance Access Publication on May 12, 2020 doi:10.1093/humrep/deaa026

human reproduction ORIGINAL ARTICLE Infertility

To trigger or not to trigger ovulation in a natural cycle for frozen embryo transfer: a randomized controlled trial

比利時 n=260 ,26-35 y/o , **No LPS**
130 **tNC group**: TVS+ FSH/LH/E2/P D9-11 , LH surge "180% above last value", confirmed the next day "drop in E2+ P rise >1.5ng/ml" → LH+5 ET(D4 embryo)
130 mNC group: (37 spontenous LH surge)
DF≧17mm+ EM ≧6mm → uhCG 5000IU (pregnyl®) hCG+6 ET(D4 embryo)

Table III Outcome parameters of the NC-FET versus the modified NC-FET group according to the intention-to-treat analysis.

	NC-FET (group A) N = 125	Modified NC-FET (group B) N = 123	P-value	Relative Risk (95% CI)	Risk difference (95% CI)
Biochemical pregnancy rate	46 (36.8%)	40 (32.5%)	0.48	0.88 (0.63;1.24)	−0.04 (−0.16;0.07)
Biochemical pregnancy losses	4 (3.2%)	4 (3.2%)	0.98	1.01 (0.26;3.97)	0.00 (−0.04;0.04)
Clinical pregnancy rate	**42 (33.6%)**	**36 (29.3%)**	**0.46**	**0.87 (0.60;1.26)**	**−0.04 (−0.16;0.07)**
Extra-uterine pregnancies	2 (1.6%)	0 (0.0%)	0.16	0 -	−0.02 (−0.04;0.01)
Early miscarriages	6 (4.8%)	6 (4.9%)	0.98	1.01 (0.34;3.06)	0.00 (−0.05;0.05)
Ongoing pregnancy rate	34 (27.2%)	30 (24.4%)	0.61	0.90 (0.59;1.37)	−0.03 (−0.14;0.08)

CPR, OPR 兩者無差異 ,

Biochemical pregnancy rate , pregnancy loss ,miscarriage 沒有差異

NC-FET組回診頻率較高 NC-FET group (4.05±1.39) mNC-FET group (3.03±1.16, P =<0.001)

Hum Reprod. 2020;35(5):1073-81.

Flexible hCG-mNC 是否可行?

RBMO

ELSEVIER

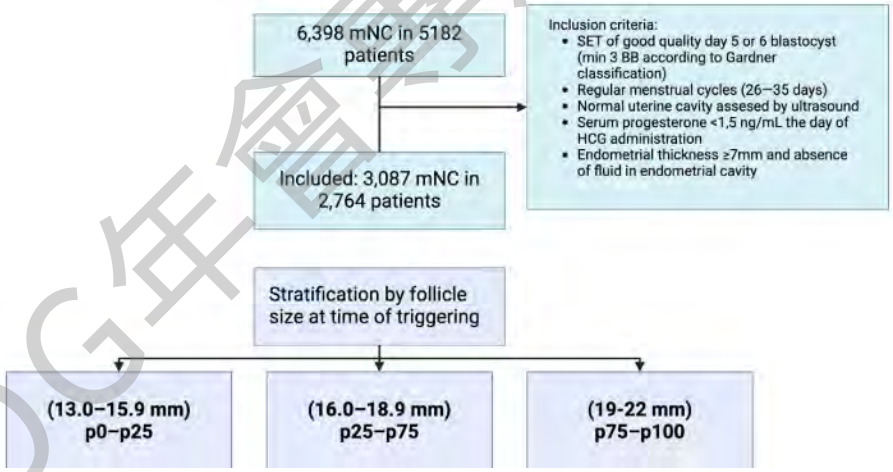
ARTICLE

Modified natural cycle allows a window of 7 days for frozen embryo transfer planning

BIOGRAPHY

Carlos Alonso is a Reproductive Medicine Specialist at IVIRMA, Spain. He obtained his medical degree from the University of Barcelona, completed his obstetrics and gynaecology residency at Hospital General Universitario Gregorio Marañón and pursued a Master's Degree in Reproductive Medicine at Complutense University. His primary areas of interest encompass gynaecological endocrinology and reproductive surgery.

Carlos Alonso-Mayo[1,*], Graciela Kohls[1], Samuel Santos-Ribeiro[2], Sergio Reis Soares[2], Juan A. Garcia-Velasco[1,3,4]



84%

Spain, 2020-2022. multicentre,
retrospective observational study
3087 single FET in mNC , +- PGT-A
good-quality D5/6 blastocyst (> 3BB)
TVS D1-3 confirm ovarian quiescence
DF:13-15.9mm,16-18.9mm,19-22mm
+ rHCG: serum P4 <1.5 ng/ml, EM≧7mm
LPS: mP4 200 mg bid (2 days after rHCG)
FET: rHCG+7

TABLE 3 AOR FOR ONGOING PREGNANCY RATE AFTER ADJUSTING FOR POSSIBLE CONFOUNDERS

Follicle grouping comparisons	aOR	95% CI	*P*-value
13–15.9 mm (*n* = 124) vs 16–18.9 mm (*n* = 2014)	2.4	0.7–7.6	0.15
19–22 mm (*n* = 949) vs 16–18.9 mm (*n* = 2014)	0.8	0.5–1.1	0.1

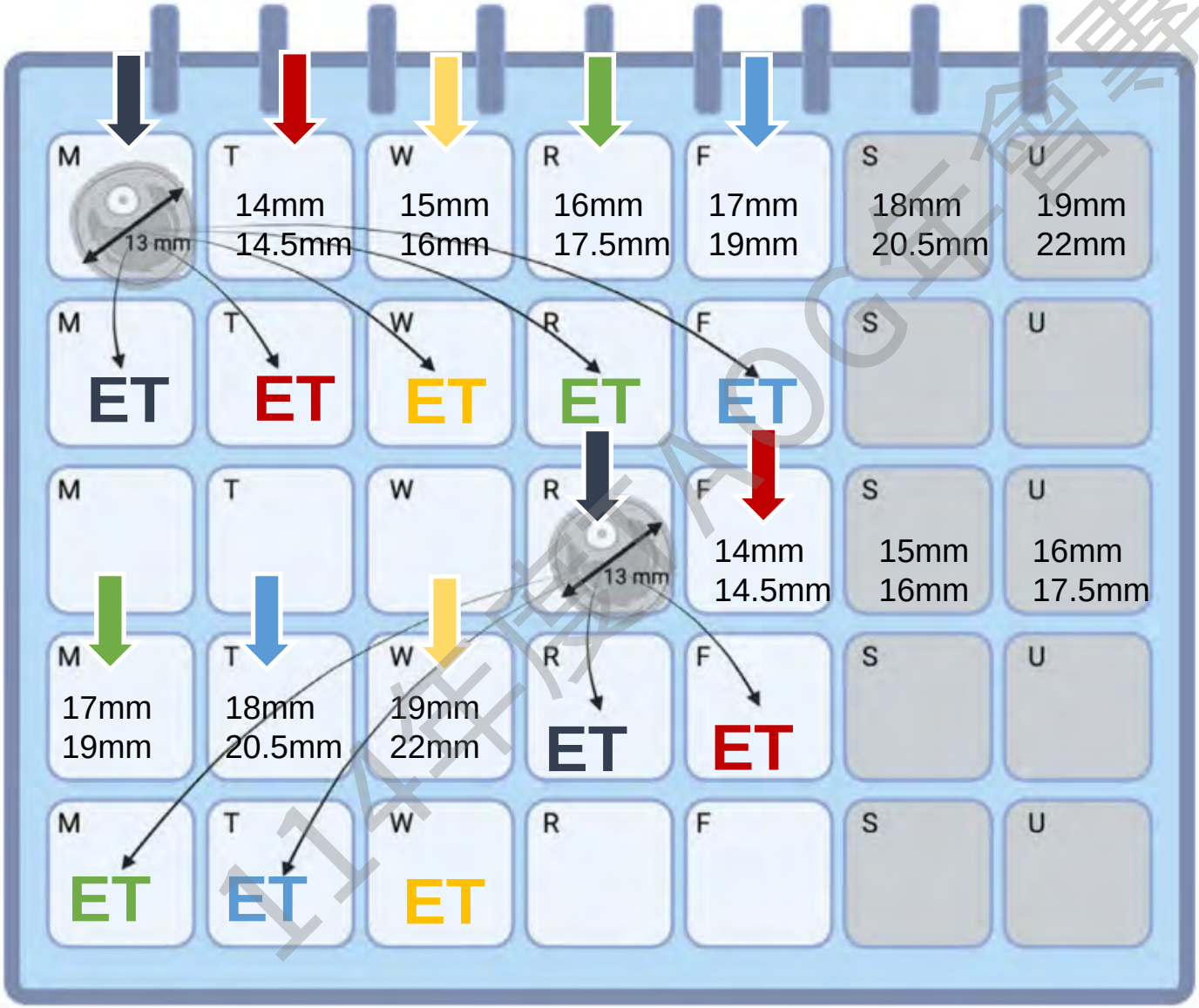
Confounders controlled for were the use of preimplantation genetic testing for aneuploidies and egg donation.

aOR, adjusted odds ratio.

Reprod Biomed Online. 2024;49(1):103774.

在DF不同大小時打hCG → OPR沒有差異

hCG-mNC 可以較有彈性



Progesterone-modified natural cycle (P4mNC), Natural proliferative phase (NPP) protocol

Natural proliferative phase (NPP)

Reprod Biomed Online. 2024;49(1):103775.

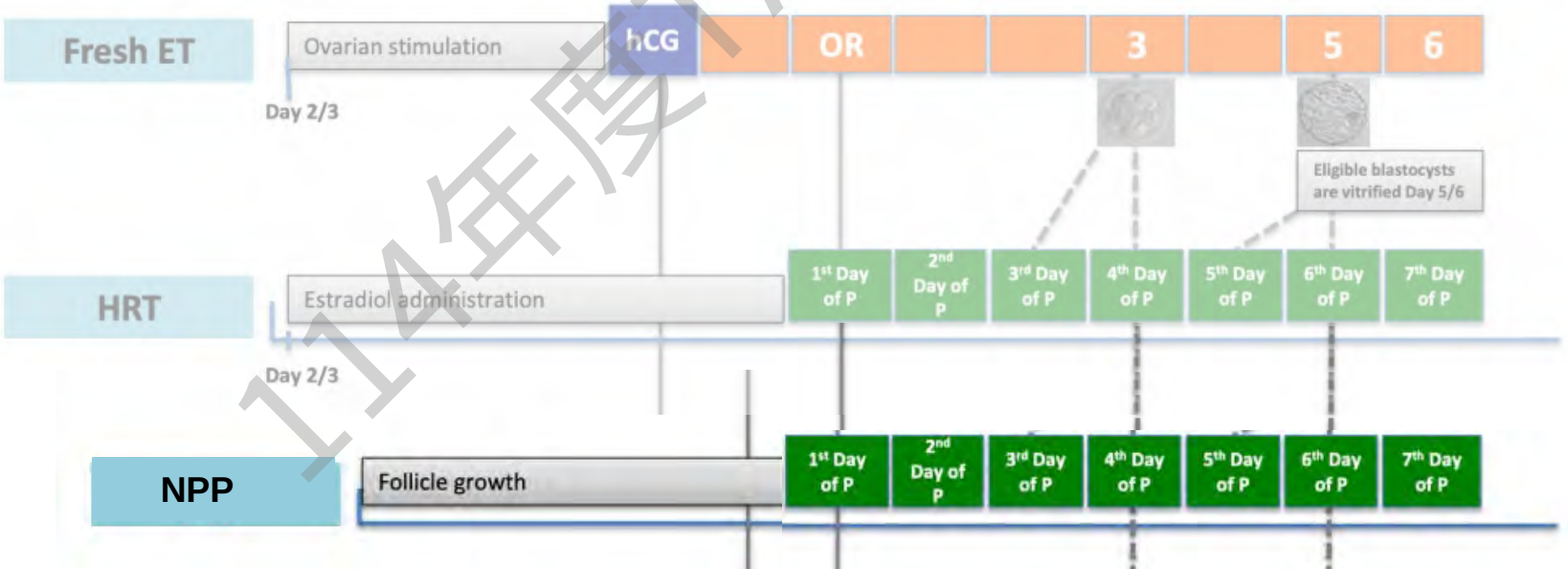
D10-12(Interval 28days) + P

D8-10 (interval <28 days) +P (low ovarian reserve)

EM>7mm, Follicle 16-18 (14) mm, LH surge (N)

→ **Start Exogeneous progesterone**

優勢: 方便追蹤.用藥減少.有黃體保護



P4mNC使用黃體素P4卻不會抑制排卵?

黃體素加入時機: DF 16-18mm, EM >7mm

Late follicular phase

內生性LH surge快要發生

此時給予P4不會阻止排卵

Corpus luteum還是會產生

黃體素可能會抑制排卵，因黃體素會抑制腦下垂體分泌LH,

黃體素需要 6 天以上的持續使用才能完全抑制 LH surge

P4mNC在接近濾泡成熟時使用，不會干擾LH surge 及排卵

Nikolay Kornilov

Reprod Biomed Online. 2024;49(5):104350.

懷孕結果 NPP(P4mNC) = AC

RBMO VOLUME 49 ISSUE 5 2024 104350

RBMO

ELSEVIER

ARTICLE

Progesterone-modified natural cycle preparation for frozen embryo transfer

BIOGRAPHY

Nikolay Kornilov is a fertility specialist with over 30 years of expertise in clinical practice and leadership roles. He earned his MD from the Pavlov First Saint Petersburg Medical University and completed his residency at the St Petersburg Medical Postgraduate Academy, Russia. He is the founder of the network Next Generation Clinic.

Nikolay Kornilov[1,2], Alex Polyakov[3,4], Anastasiya Mungalova[1], Lubov Yakovleva[5], Pavel Yakovlev[2,*]

Russia , 2017-2019

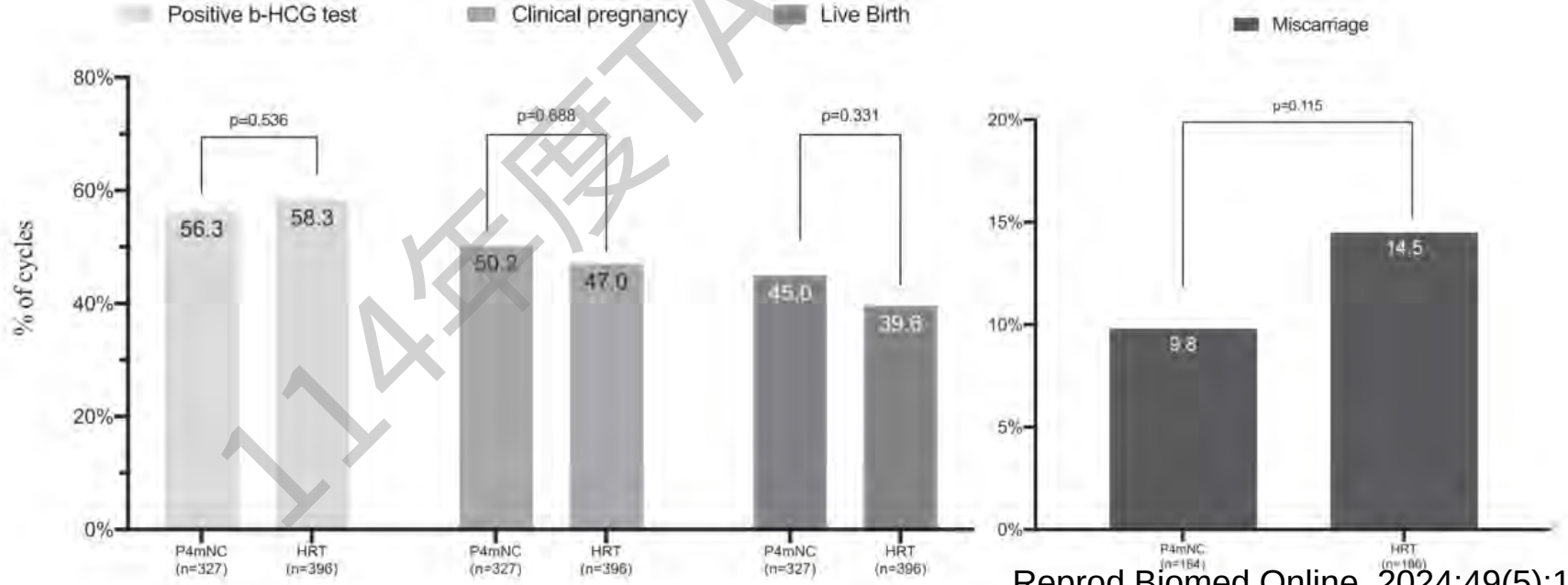
retrospective cohort study,

723 FET (PGT-A)- single euploid blastocyst

327 **P4mNC-FET** : EM>7mm,DF>16mm +mP4 200mg P4 bid~ stop on 9th days B-hCG test

396 **HRT-FET**: E(oral or transdermal) EM>7mm +mP4 600mg mP4 qd micronized vaginal progesterone (Utrogestan)

P4mNC 的CPR,LBR較高，miscarriage rate較低 但無統計意義



Reprod Biomed Online. 2024;49(5):104350.

AC:NC(±hCG):NPP(P4mNC)

OXFORD human reproduction

Human Reproduction, 2024, **39(5)**, 1089–1097
https://doi.org/10.1093/humrep/deae061
Advance Access Publication Date: March 26, 2024
Original Article

Reproductive endocrinology

Natural proliferative phase frozen embryo transfer—a new approach which may facilitate scheduling without hindering pregnancy outcomes

Catarina Mendes Godinho [1,*], Sérgio Reis Soares [1], Sofia Gouveia Nunes[1], Juan M Mascarós Martínez[2], and Samuel Santos-Ribeiro [1,3]

Portugal, 2010-2022

single center retrospective cohort study

5791 FET cycles

2226 AC: E2 6mg-EM≧7mm,P4≦1.5ng/mL-+P4 400mg BID~11wks

3216 NC(tNC/mNC):EM≧7mm,DF ≧ 16mm, P4≦1.5ng/mL, LH ≦18UI/mL(+hCG 44%); LH>18UI/mL (-hCG) +P4 400mg BID~8wks

349 NPP: EM≧7mm, DF ≧ 14mm, P4≦1.5ng/mL-+P4 200mg BID~11wks

Rescue im P4 100mg QOD, if P4<8.5ng/mL on FET day

AC:26%,NC:1.3%, NPP:2.9% P<0.01

AC/NPP~11wks , NC~8wks

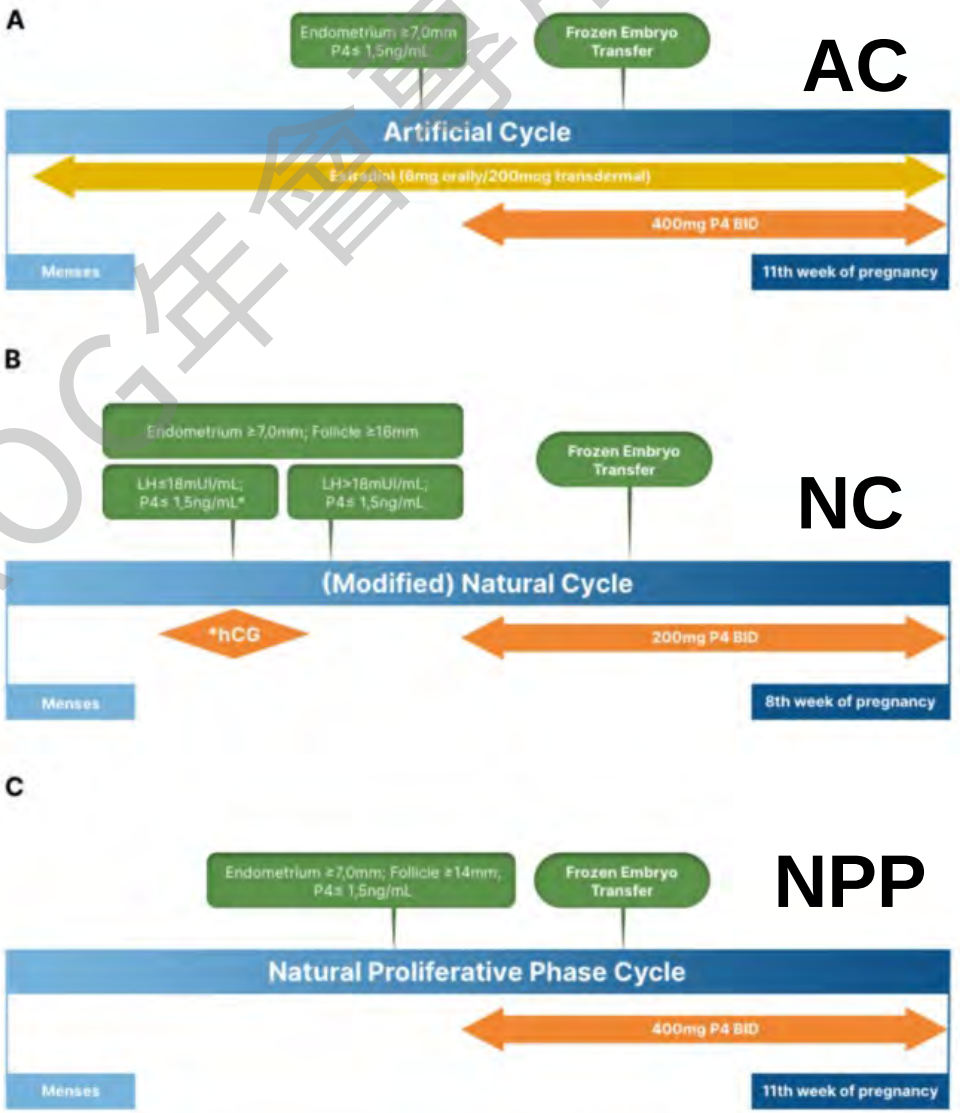


Figure 1. Summary of the different endometrial preparations for frozen embryo transfer included in the study. (**A**) Artificial cycle, (**B**) natural cycle, and (**C**) natural proliferative phase cycle. P4, progesterone; BID, twice per day.

Human Reproduction. 2024;39(5): 1089–97

CPR,LBR AC<NPP=NC GDM AC=NPP=NC HDP, miscarriage, 1st 孕期出血 AC>NPP=NC

Table 2. Comparison of pregnancy outcomes after frozen embryo transfer considering each subgroup with confounder adjustment.

	AC (n = 2226)	NPP (n = 349)	NC (n = 3216)	P-value
hCG-positive pregnancy	1343 (60.4%) **0.96 (0.93–0.99)**	219 (62.8%) 1.01 (0.96–1.07)	1978 (61.6%) Reference	0.56
Clinical pregnancy **AC<NPP=NC**	1122 (50.5%) **0.94 (0.91–0.96)**	199 (57.0%) 1.01 (0.95–1.07)	1748 (54.4%) Reference	<0.01†
Miscarriage **AC>NPP=NC**	466/1335 (34.9%) **1.11 (1.07–1.15)**	43/218 (19.7%) 0.98 (0.92–1.04)	491/1962 (25.0%) Reference	<0.01*,†
Live birth **AC<NPP=NC**	848/2206 (38.4%) **0.91 (0.88–0.94)**	168/342 (49.1%) 1.02 (0.96–1.09)	1437/3182 (45.2%) Reference	<0.01*,†

Pairwise P < 0.05 for the following comparisons:
* AC versus NPP.
† AC versus NC.

NPP 的CPR,LBR較高，miscarriage rate較低

Table 3. Perinatal outcome after frozen embryo transfer from different subgroups. **AC第一孕期出血比例較高 . HDP 較高**

	AC (n = 804)	NPP (n = 160)	NC (n = 1348)	P-value
First trimester bleeding **AC>NPP=NC**	246/655 (37.6%)	25/144 (17.4%)	163/1110 (14.7%)	<0.01*,†
Second/third trimester bleeding	39/653 (3.7%)	8/144 (5.6%)	41/1110 (3.7%)	0.08
Preterm rupture of membranes	41/655 (6.3%)	7/144 (4.9%)	44/1101 (4.0%)	0.10
Gestational diabetes **AC=NPP=NC**	113/653 (17.3%)	22/144 (15.3%)	159/1113 (14.3%)	0.24
Gestational hypertensive disorders **AC>NPP=NC**	92/636 (14.5%)	13/138 (9.4%)	95/1099 (8.6%)	<0.01†
Gestational age at delivery (weeks)	38.5 (2.8)	39.1 (4.7)	38.8 (2.6)	0.02†

Pairwise P < 0.05 for the following comparisons:
* AC versus NPP.
† AC versus NC.

Rescue im P4, if P4<8.5ng/mL **AC:26%, NC:1.3%, NPP:2.9% P<0.01**

AC需要Rescue P4的比例較高

Human Reproduction. 2024;39(5): 1089–97

CPR.OPR.LBR AC<SC(Letrozole) miscarriage AC>SC(Letrozole)

Full length article

What is the optimal means of preparing the endometrium in frozen-thawed embryo transfer cycles among anovulatory women? A retrospective cohort study

Wen Wen, Juanzi Shi, Xitong Liu

China ,2020-2021,

retrospective cohort study

5,322 anovulatory women

694 **Letrozole stimulated cycles**

oral letrozole (Femara) 5 mg daily MC day 5–9

(If DF<12mm+hMG 75IU/d)

DF>17 mm, EM ≥ 7 mm, → 10,000 IU hCG

600 mg of vag mP4 (Utrogestan) 2 days later

4628 **AC-FET**

Oral estradiol valerate (Progynova) 10-12 days

→ TVS : no DF. EM ≥ 7 mm , P4 level < 1.5 ng/ml,

→vag mP4

Table 2
Clinical outcomes between artificial cycle and letrozole.

Characteristic	AC (n = 4628)	Letrozole (n = 694)	*P*-value
Biochemical pregnancy	2927/4628 (63.25 %)	456/694 (65.71 %)	0.209
Clinical pregnancy	2721/4628 (58.79 %)	427/694 (61.53 %)	0.172
Ongoing pregnancy	2113/4628 (45.66 %)	348/694 (50.14 %)	0.027
Miscarriage	516/2721 (18.96 %)	53/427 (12.41 %)	0.001
Ectopic pregnancy	32/4628 (0.69 %)	6 (0.86 %)	0.614
Live birth	2093/4628 (45.22 %)	344/694 (49.57 %)	0.032
Singletons	1947/4628 (42.07 %)	316/694 (45.53 %)	0.085
Twins	146/4628 (3.15 %)	28/694 (4.04 %)	0.224

AC, artificial cycle.

Table 3
Crude and adjusted odds ratios of clinical outcomes comparing artificial cycle versus letrozole frozen-thawed embryo transfer protocol.

Characteristic	Crude OR (95 %CI)	Adjusted OR (95 %CI)
Biochemical pregnancy	1.11 (0.94, 1.32)	1.20 (1.01, 1.43)
Clinical pregnancy	1.12 (0.95, 1.32)	1.20 (1.02, 1.43)
Ongoing pregnancy	1.20 (1.02, 1.40)	1.28 (1.08, 1.51)
Miscarriage	0.61 (0.45, 0.82)	0.59 (0.43, 0.80)
Ectopic pregnancy	1.25 (0.52, 3.01)	1.06 (0.41, 2.72)
Live birth	1.19 (1.01, 1.40)	1.27 (1.08, 1.50)

Analyses were adjusted for female age at embryo transfer, AFC, BMI, and number of oocytes retrieved. CI, confidence interval; OR, odds ratio.

Eur J Obstet Gynecol Reprod Biol. 2024;294:79-83

	NC-FET 自然週期	AC-FET 人工週期
Miscarriage PTB CPR,OPR,LBR	著床率相同，流產率低或相同 **低** **高**或相近	高或相同 **高** **低**或相近
GDM	相同	相同或低
子癲前症	**低** (因為有黃體生成)	**高**
HDP,PPH,前置胎盤	**低**或相同	**高**或相同
LGA, macrosomia	**低** (BW較低.SGA相同)	**高**
內膜準備 荷爾蒙使用	無需外源性E2與P4 有黃體 可加LPS	需長時間服用E2與P4 無黃體 + LPS(單用Vag較差)
回診及監測	密切監測 LH/E2/P4與超音波	回診及抽血次數少
靈活性	**難掌控時間 取消率較高 (21%)**	取消率較低 較易掌控時間
適用族群	排卵正常的女性 有子癲風險因子女性	排卵異常或無排卵者 卵巢衰竭或切除.較無限制
改善方案	**Flexible hCG** **NPP(P4mNC)** **SC**	**懷孕後考慮加Aspirin** **LPS補充** **莊蕙瑜醫師 製表 2025**

不建議會排卵的病人使用AC-FET

排卵女性應優先採用**自然週期**，個人化監測與LPS

無排卵女性應考慮**誘導排卵SC**與LPS。

POI, 無卵巢女性使用**人工週期**，應設法改善缺乏CL問題


Human Reproduction, Vol.37, No.8, pp. 1697–1703, 2022

human reproduction OPINION

Should any use of artificial cycle regimen for frozen-thawed embryo transfer in women capable of ovulation be abandoned: yes, but what's next for FET cycle practice and research?

Frauke von Versen-Höynck [1] and Georg Griesinger [2,*]

[1]Department of Obstetrics and Gynecology, Hannover Medical School, Hannover, Germany [2]Department of Gynecological Endocrinology and Reproductive Medicine, University Hospital of Schleswig-Holstein, Lübeck, Germany

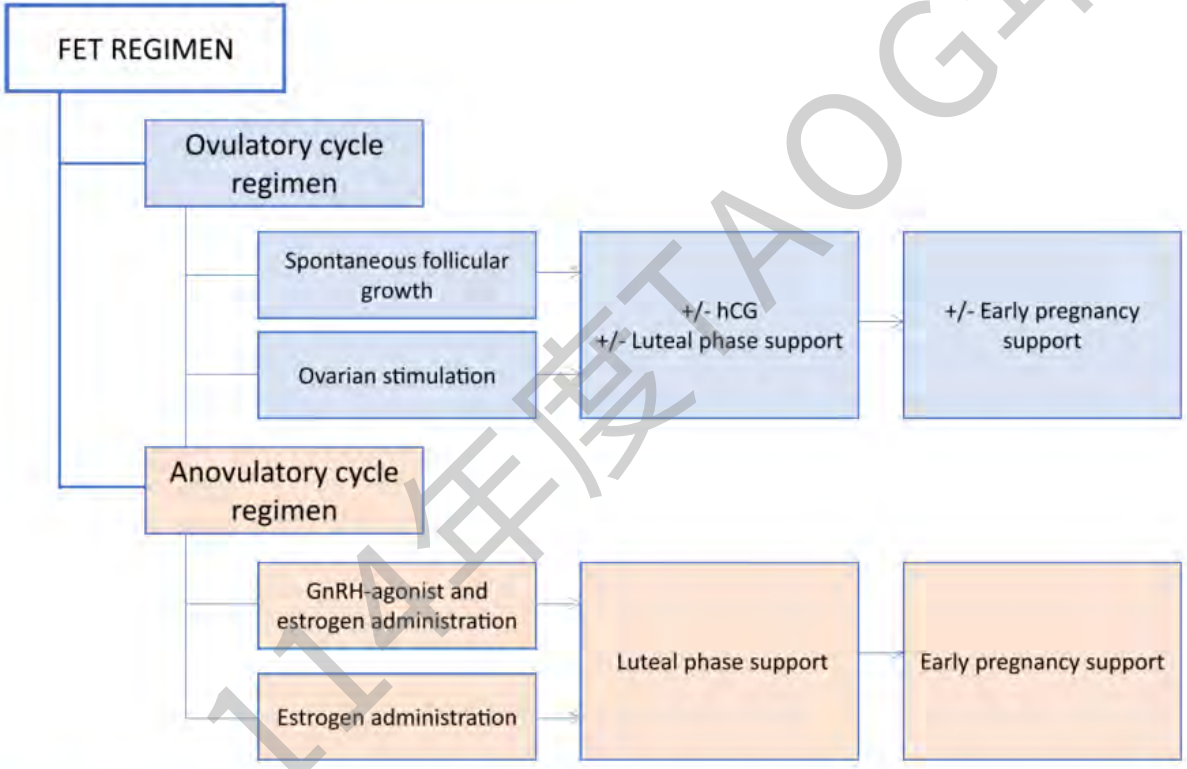


Figure 1. FET regimens can, in principle, be distinguished as ovulatory versus anovulatory cycles. For both cycle types, a variety of different medication regimens and monitoring regimens have been described in the literature. FET, frozen-thawed embryo transfer.

Hum Reprod. 2022;37(8):1697-703

建議不排卵女性採用SC取代AC

Table 3. Meta-analyses presenting risk estimates of obstetric outcomes in pregnancies resulting from different FET protocols

	Moreno-Sepulveda *et al.*, 2021	Wu *et al.*, 2021		Busnelli *et al.*, 2022
Comparison vs. reference group	*HRT FET vs. NC-FET*	*HRT FET vs. iNC-FET*	*HRT FET vs. mNC-FET*	*HRT FET vs. NC-FET*
Risk estimate	*RR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*
Hypertensive disorders in pregnancy (HDP)	*10 studies* *50 219 participants* RR 1.64 (1.37–2.00)*			*12 studies* *139 182 participants* OR 1.90 (1.64–2.20)
Preeclampsia	*4 studies* *22 856 participants* RR 2.13 (1.89–2.38)*			*8 studies* *31 697 participants* OR 2.11 (1.87–2.39)
Pregnancy induced hypertension (PIH)	*3 studies* *8 483 participants* RR 1.39 (0.98–1.96)*	*2 studies* *4 927 participants* OR 1.82 (1.37–2.38)*	*3 studies* *7 347 participants* OR 1.85 (1.15–3.03)*	*5 studies* *11 220 participants* OR 1.46 (1.03–2.07)
Placenta previa	*7 studies* *57 356 participants* RR 1.18 (0.81–1.69)*	*2 studies* *4 089 participants* OR 1.20 (0.43–3.45)*	*1 study* *6 369 participants* OR 1.47 (0.90–2.44)	*10 studies* *147 997 participants* OR 1.27 (1.05–1.54)
Placenta abruption	*4 studies* *46 986 participants* RR 1.64 (1.02–2.63)*			
Placenta accreta	*2 studies* *35 755 participants* RR 5.56 (3.03–10.0)*			*2 studies* *106 009 participants* OR 6.29 (2.75–14.40)
Postpartum haemorrhage	*4 studies* *23 343 participants* RR 2.56 (2.22–2.86)*	*1 study* *2 503 participants* OR 2.08 (1.61–2.78)*		*6 studies* *24 558 participants* OR 2.53 (2.19–2.93)
Caesarean section	*7 studies* *70 020 participants* RR 1.19 (1.10–1.30)*			*12 studies* *167 632 participants* OR 1.62 to (1.53–1.71)
Gestational diabetes mellitus	*9 studies* *56 628 participants* RR 0.93 (0.68–1.25)*	*1 study* *4 897 participants* OR 1.01 (0.79–1.30)*	*3 studies* *7 347 participants* OR 1.20 (0.96–1.52)*	

CI, confidence interval; FET, denotes frozen embryo transfer; mNC-FET, modified natural cycle-FET; NC-FET, natural cycle-FET; OR, odds ratio; RR, risk ratio; tNC-FET, true natural cycle-FET.
*Reciprocal value of the original.

The future of frozen-thawed embryo transfer in hormone replacement therapy cycles

Kristine Lassen[a], Anne Lærke Spangmose[a], Louise Laub Asserhøj[a], Tine Vrist Dam[a] and Anja Pinborg[a,b]

oligo-ovulation
Anovulation
PCOS
→ **建議使用SC**
Letrozole±hMG
~25-30% 對letrozole沒反應

AC:NC

PIH	**RR1.39**
HDP	**RR 1.64**
Preeclampsia	**RR 2.13**
Pl. abruption	**RR 1.64**
Pl. accreta	**RR 5.56**
PPH	**RR 2.56**

Curr Opin Obstet Gynecol. 2023;35(3):200-9.

高風險孕婦給予Aspirin可降低子癲前症發生率

Table 1. Clinical Risk Assessment for Preeclampsia[a]

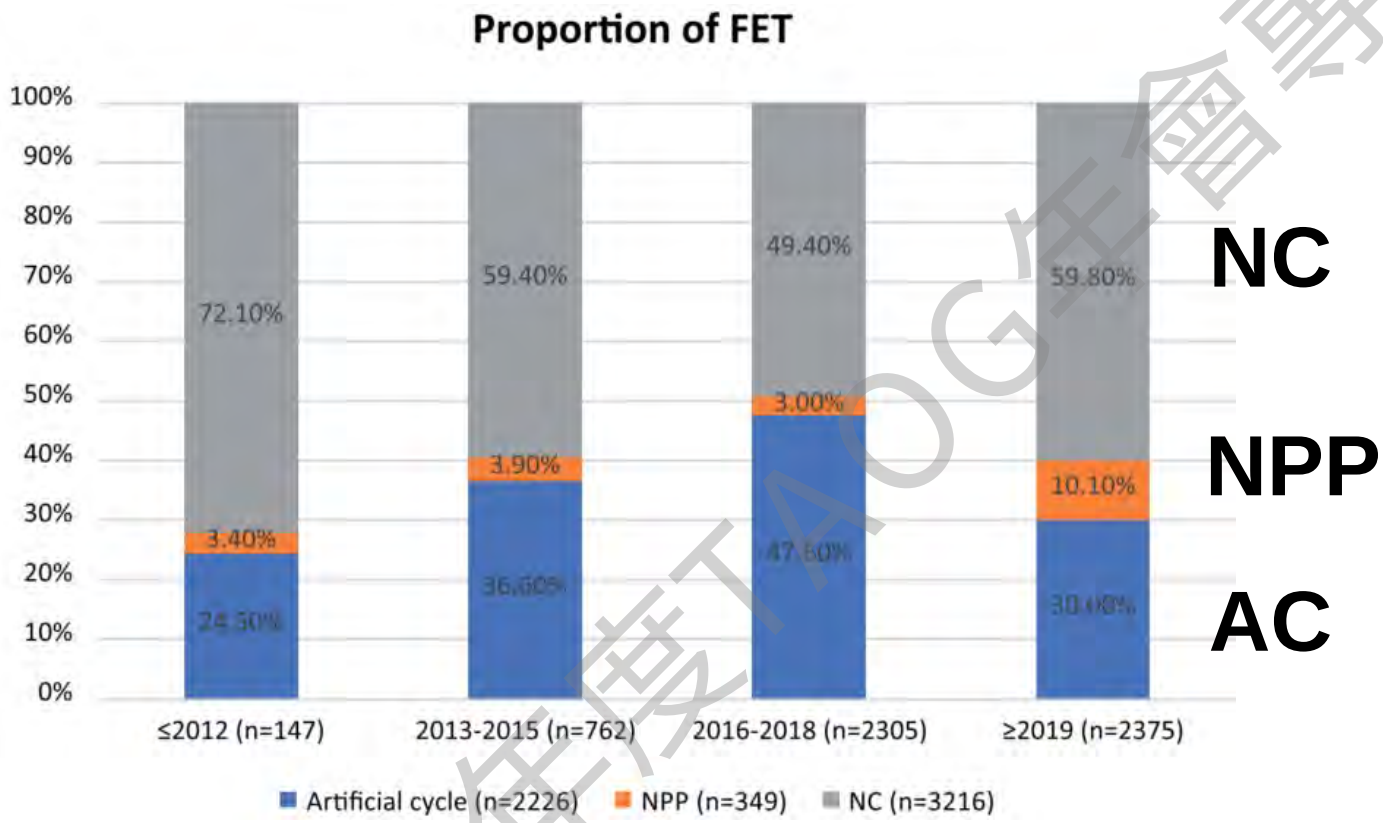
Risk level	Risk factors	Recommendation
High[b]	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Pregestational type 1 or 2 diabetes • Kidney disease • Autoimmune disease (ie, systemic lupus erythematous, antiphospholipid syndrome) • Combinations of multiple moderate-risk factors	Recommend low-dose aspirin if the patient has ≥1 of these high-risk factors
Moderate[c]	• Nulliparity • Obesity (ie, body mass index >30) • Family history of preeclampsia (ie, mother or sister) • Black persons (due to social, rather than biological, factors)[d] • Lower income[d] • Age 35 years or older • Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval) • In vitro conception	Recommend low-dose aspirin if the patient has ≥2 moderate-risk factors Consider low-dose aspirin if the patient has 1 of these moderate-risk factors
Low	Prior uncomplicated term delivery and absence of risk factors	Do not recommend low-dose aspirin

Aspirin reductions severe preeclampsia RR 0.47 (0.26–0.83)

Aspirin使用明顯降低子癲前症早產 OR 0.38 (0.2-0.74)

Jama. 2021;326(12).
New England Journal of Medicine. 2017;377(7):613-22.
OBSTETRICS & GYNECOLOGY. 2018;VOL. 132, NO. 1, JULY 2018

單一中心使用比例 (IVI Lisboa)



Portugal, 2010-2022 **即使推崇NC 還是使用許多AC**

single center retrospective cohort study (IVI Lisboa)

5791 FET cycles (2226 AC, 349 NPP, and 3216 NC)

Human Reproduction. 2024;39(5): 1089–97

NC-FET美國臨床實踐中的應用調查

匿名問卷調查，發送至 441 家美國 ART 診所，回應率 49%（216 份回覆）

83% 179診所提供 NC-FET , 52% 93 診所有施行限制

NC≧25% 24% 24% 50% 76%

NC<25% **76 %**

Natural cycle frozen embryo transfer: a survey of current assisted reproductive technology practices in the U.S

Jacqueline C. Lee[1] · Natalia S. Calzada-Jorge[2] · Heather S. Hipp[1] · Jennifer F. Kawwass[1]

J Assist Reprod Genet. 2023;40(4):891-9

NC-FET美國臨床實踐中的應用調查

美國ART診所對 NC-FET 的未來展望

45% 因新研究對NC-FET改觀

41% 對新研究持保留態度

21% 感受患者要求 NC-FET 增加

65% 診所對 NC-FET 持正面態度

56% 預期未來 NC-FET 使用率會增加

J Assist Reprod Genet. 2023;40(4):891-9

NC

安全
藥少

Flexibly

hCG

NPP

簡單
方便

AC