





Optimizing Human Gamete and Embryo Freezing

> GENOVA 13 GIUGNO 2014

PREPARAZIONE ENDOMETRIALE IN CICLO DI SCONGELAMENTO: SPONTANEO O INDOTTO? Silvia Colamaria

g.en.e.r.a. ROMA Clinica Valle Giulia



Oocyte and embryo cryopreservation

Cryopreservation of oocytes, embryos and blastocysts is an essential component of modern ART

Successful cryopreservation program:

- allows to reduce the number of embryos transferred, thereby reducing multiple pregnancies and maximizing cumulative pregnancy rates per oocyte retrieval
- 2. allows delayed embryo transfer during a natural menstrual cycle reducing OHSS risks (cycle segmentation)
- **3.** allows to preserve female fertility for medical or social reason



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human reproduction

ORIGINAL ARTICLE Infertility

Factors affecting the outcome of frozen-thawed embryo transfer

Zdravka Veleva^{1,*}, Mauri Orava¹, Sinikka Nuojua-Huttunen², Juha S. Tapanainen^{1,3}, and Hannu Martikainen¹
 Table IV
 Multivariate logistic regression analysis for live

 birth using the final adjusted model.

	P-value	OR (95.0% CI)
Embryo quality		
No top quality embryos frozen		Reference group
Top quality embryo(s)		
Frozen	0.02	1.85 (1.10-3.14)
Thawed	0.007	1.93 (1.20-3.11)
Transferred	< 0.0001	3.41 (2.12-5.49)
Type of FET cycle		
Spontaneous, luteal support		Reference group
Spontaneous	0.003	0.58 (0.40-0.83)
Hormonal substitution	< 0.0001	0.46 (0.31-0.69)
BMI	0.02	0.96 (0.92-0.99)
Two embryos versus one transferred	0.01	I.45 (I.08–I.94)
Overnight culture	0.07	I.37 (0.98–1.93)

LBRs after the transfer of a top quality embryo were similar in the FET (24.9%) and fresh cycles

of the same period (21.9%). The chance of live birth increased significantly if ≥ 1 top quality embryo was present at freezing (odds ratio (OR) 1.85, 95% confidence interval (CI) 1.10-3.14), at thawing (OR 1.93, CI 1.20-3.11) or at transfer (OR 3.41, CI 2.12-5.48). Compared with spontaneous cycles with luteal support, purely spontaneous cycles (OR 0.58, CI 0.40-0.84) and hormonally substituted FET (OR 0.47, CI 0.32-0.69) diminished the odds of pregnancy. BMI (OR 0.96, CI 0.92-0.99) and transfer of two embryos versus one (OR 1.45, CI 1.08-1.94) were other factors that improved LBR after FET.



The development of embryo and endometrium should be synchronized

Natural cyclespontaneous LH surge (NC FET)NCG administration (modified-NC FET)

Artificial cycle

exogenous estradiol and progesterone (AC FET) with or without GnRH-agonist co-treatment



NC-FET

Pregnancy rates are closely dependent on timely identification of ovulation and calculation of endometrial receptivity (Harper, 1992; Tabibzadeh 1998)

LH monitoring in either blood or urine

Urine: LH surge lag up to 20-21 h behind the surge in blood (Hoff, 1983; Frydman, 1984; Miller and Soules, 1996)



NC-FET

Problems associated with detection of spontaneous LH surge:

- a. variation in time of its occurence between cycles and between patients (*Park, 2007*)
- b. at least daily determination, better twice a day (*Miller and Soules 1996*)
- **c.** Large variation in thresholds of LH in urine kits and risk of up to 30% of false negative testing

(Guermandi, 2001; O'Connor, 2006)



Modified NC-FET

HCG triggering of ovulation to overcome LH monitoring:

- a. no LH monitoring
- b. 2-3 ultrasound evaluations of the dominant follicle
- **c.** HCG administered when follicle is 17-18 mm
- d. final oocyte maturation and ovulation will take place
 36-38 h later (Andersen, 1995)



NC-FET vs modified NC-FET

There are no published studies comparing patient preference or cost-efficiency with regard to the different methods of monitoring in NC-FET. A properly conducted cost-efficiency calculation, also including patient preference, should be performed as part of a future RCT.

(Groenewoud et al, 2013)



NC-FET and modified NC-FET

Thawing and transfer of the embryo should be performed 3-5 days after ovulation depending on the stage of the embryo when it was frozen

(Nawroth and Ludwig, 2005; Paulson, 2011)

NC-FET: risk of unexpected ovulation and difficulty in planning thawing and transfer of the embryo cycle cancellation







Modified NC and NC-FET: luteal phase supplementation? No luteal support Cryopreserved-thawed human embryo transfer: spontaneous natural cycle is superior to human chorionic gonadotropin-induced natural cycle

Human Mousavi Fatemi, M.D., Ph.D.,^a Dimitra Kyrou, M.D.,^a Claire Bourgain, M.D., Ph.D.,^b Etienne Van den Abbeel, Ph.D.,^c Georg Griesinger, M.D., Ph.D.,^d and Paul Devroey, M.D., Ph.D.^a

TABLE 3				
Treatment outcomes in spo	ontaneous LH and hCG group.			
	Spontaneous LH (n = 61)	hCG group (n = 63)	Difference, % (95% CI)	P value
Ongoing pregnancy rate-ET (%)	31.1 (19)	14.3 (9)	16.9 (2.1–30.9)	.025
Miscarriage rate-ET (%)	0 (0)	3.2 (2)	-3.2 (-10.9 to 3.2)	NS
Biochemical rate-ET (%)	3.3 (2)	3.2 (2)	0.1 (-7.9 to 8.3)	NS
Positive hCG-ET(%)	34.4 (21)	20.6 (13)	13.8 (-1.9 to 28.7)	NS
Note: CI = confidence interval; N	S = not significant.			
Fatemi. Natural cycle vs. hCG induce	ed for frozen ET. Fertil Steril 2010.			

Conclusion(s): The results suggest the superiority of the natural cycle as compared with the natural cycle controlled by hCG administration in cryothawed ET cycles. (Fertil Steril® 2010;94:2054–8. ©2010 by American Society for Reproductive Medicine.)



Modified NC and NC-FET: luteal phase supplementation?

Reproductive BioMedicine Online (2011) 23, 484-489



ARTICLE

Spontaneous ovulation versus HCG triggering for timing natural-cycle frozen—thawed embryo transfer: a randomized study

Ariel Weissman *, Eran Horowitz, Amir Ravhon, Zohar Steinfeld, Ravit Mutzafi, Avraham Golan, David Levran

Clinical and laboratory characteristics of fresh and frozen cycles and pregnancy and deliv-

Luteal support

ery rates were comparable for both groups. The number of monitoring visits in group A (3.2 ± 1.4) was significantly lower than in group B (4.7 ± 1.6) (P = 0.002). In patients undergoing NC-FET, triggering ovulation by HCG can significantly reduce the number of visits necessary for cycle monitoring without an adverse effect on cycle outcome. Ovulation triggering can increase both patient convenience and cycle cost effectiveness.



Modified NC and NC-FET: luteal phase supplementation? Luteal phase progesterone increases live birth rate after frozen embryo transfer

Luteal support

Kerstin Bjuresten, B.S.,^a Britt-Marie Landgren, M.D., Ph.D.,^a Outi Hovatta, M.D., Ph.D.,^a and Anneli Stavreus-Evers. Ph.D.^b

	Progesterone	No progesterone	P value
No. of transfers	n = 219	n = 216	.8921
No. of embryos transferred	n = 290	n = 293	.9067
No. of embryos transferred (mean)	n = 1.32	n = 1.36	_
No. of single embryo transfers	n = 148	n = 139	.5423
No. of transfers with good-quality embryos	n = 164	n = 178	.3706
No. of transfers with lower-quality embryos	n = 126	n = 116	.3706
No. of blastocyst transfers	n = 3	n = 9	.1497
No. of IVF transfers	n = 110	n = 105	.7728
No. of ICSI embryos	n = 109	n = 112	.7728
Positive hCG rate	0.35 (76 of 219)	0.28 (60 of 216)	.1458
Miscarriage rate	0.03 (7 of 219)	0.03 (6 of 216)	.7977
Clinical pregnancy rate	0.32 (69 of 219)	0.25 (54 of 216)	.1614
Clinical abortion rate	0.02 (4 of 219)	0.05 (10 of 216)	.1105
Live birth rate (at least one live infant)	0.30 (65 of 219)	0.20 (44 of 216)	.0272*

Result(s): Live birth rate were significantly greater in women receiving vaginal progesterone as luteal phase support after frozen-thawed embryo transfer in natural cycles compared with those who did not take progesterone. There were no differences in biochemical pregnancy rate, pregnancy rate, or spontaneous abortion rate. **Conclusion(s)**: Progesterone supplementation improves live birth rate after embryo transfer in natural cycles. (Fertil Steril® 2011;95:534-7. ©2011 by American Society for Reproductive Medicine.)



Modified NC and NC-FET: luteal phase supplementation

Luteal support (retrospective study)

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human reproduction **ORIGINAL ARTICLE Infertility**

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Two embryos versus one transferred	0.01	1.45 (1.08–1.94)
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Compared with spontan-

eous cycles with luteal support, purely spontaneous cycles (OR 0.58, Cl 0.40-0.84) and hormonally substituted FET (OR 0.47, Cl 0.32-0.69) diminished the odds of pregnancy.



Modified NC and NC-FET: luteal phase supplementation?

Pregnancy loss after frozen-embryo transfer—a comparison of three protocols Luteal support (retrospective study)

Candido Tomás, M.D., Ph.D.,^a Birgit Alsbjerg, M.D.,^b Hannu Martikainen, M.D., Ph.D.,^c and Peter Humaidan, M.D., D.M.Sc.^d

NC-FET + luteal support vs modified NC no luteal support vs Artificial Cycle

Conclusion(s): A higher positive pregnancy test rate was obtained in E + P frozen ET cycles in comparison with other protocols; however, due to an increased preclinical and clinical pregnancy loss, comparable clinical pregnancy, and delivery rates are reported for the three protocols. (Fertil Steril® 2012;98:1165–9. ©2012 by American Society for Reproductive Medicine.) Key Words: FET, frozen embryo transfer, substituted cycles, pregnancy loss, luteal support



Modified NC and NC-FET: luteal phase supplementation?

Human Reproduction Update, Vol.19, No.5 pp. 458–470, 2013 Advanced Access publication on July 2, 2013 doi:10.1093/humupd/dmt030

human reproduction update

> What is the optimal means of preparing the endometrium in frozen-thawed embryo transfer cycles? A systematic review and meta-analysis

Eva R. Groenewoud^{1,*}, Astrid E.P. Cantineau¹, Boudewijn J. Kollen², Nick S. Macklon³, and Ben J. Cohlen⁴

"Based on the conflicting results of the previously mentioned

studies we

conclude that currently there is too little evidence supporting a positive



Artificial cycle (AC-FET)

Estrogen (E2) and progesterone (P) in sequential regimen:

- a. E2 causes endometrial proliferation and suppression of the development of the dominant follicle
- b. when endometrial thickness is 7-9 mm on US, P is added to initiate secretory changes (Dor, 1991; El-Toukhy, 2008)
- c. embryo thawing and transfer is planned according to the moment of P supplementation (Dor, 1991; Jaroudi 1991)



AC-FET with GnRH-FET

E2 and P in sequential regimen after GnRH-a desensitization

- a. E2 administration does not guaratee complete pituitary suppression and dominant follicle may occur
 - b. should spontaneous ovulation occur, the endometrium is maybe exposed to P earlier incorrect timing of thawing and transferring



GnRH-agonist co-treatment









AC-FET with or without GnRH-FET vs NC-FET

Pros

- cycles easier to plan making it popular among many doctors
- patients with anovulatory cycles

Cons

Is any one of these approaches superior to another



Cycle regimens for frozen-thawed embryo transfer (Review)

Ghobara T, Vanderkerchove P

Ghobara T, Vanderkerchove P. Cycle regimens for frozen-thawed embryo transfer. Cochrane Database of Systematic Reviews 2008, Issue 1 Art. No.: CD003414. DOI: 10.1002/14651858.CD003414.pub2.

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Main results

Seven randomised controlled studies assessing six comparisons and including 1120 women in total were included in this review.

 O + P FET versus natural cycle FET: this comparison demonstrated no significant differences in outcomes but confidence intervals remain wide, and therefore moderate differences in either direction remain possible (OR 1.06, 95% CI 0.40 to 2.80, P 0.91).

2) GnRHa plus day O plus day P FET versus O plus day P FET: this comparison showed that the live birth rate per woman was significantly higher in the former group (OR 0.38, 95% CI 0.17 to 0.84, P 0.02). The clinical pregnancy rate was also higher but not significantly so (OR 0.76, 95% CI 0.52 to 1.10, P 0.14).

3) O plus day P FET versus follicle stimulating hormone (FSH) FET, 4) O plus day P FET versus clomiphene FET and 5) GnRHa plus day O plus day P FET versus clomiphene FET: there were no differences in the outcomes in the comparison of these cycle regimens.

6) Clomiphene plus day human menopausal gonadotrophin (HMG) FET versus HMG FET: in a comparison of two ovulation induction regimes the pregnancy rate was found to be significantly higher in the HMG group (OR 0.46, 95% CI 0.23 to 0.92). There were also fewer cycle cancellations and a lower multiple pregnancy rate when HMG was used without clomiphene but these did not reach statistical significance.

Authors' conclusions

At the present time there is insufficient evidence to support the use of one intervention in preference to another.





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human reproduction update

What is the optimal means of preparing the endometrium in frozen-thawed embryo transfer cycles? A systematic review and meta-analysis

Eva R. Groenewoud^{1,*}, Astrid E.P. Cantineau¹, Boudewijn J. Kollen², Nick S. Macklon³, and Ben J. Cohlen⁴





 Table I
 Overview of studies included in a meta-analysis to determine the optimal means of preparing the endometrium in

 FET cycles in patients undergoing IVF.

Study and year	Design	Population	Allocation	Outcome
True NC versus modifie	dNC			
Chang et al. (2011)	Retrospective cohort	644 cycles (tNC 310, mNC 130, AC 204), ovulatory patients	Preference, costs	CP/OP
Fatemi et al. (2010)	RCT	124 cycles (tNC 61, mNC 63), ovulatory patients	Concealed allocation, non-blinded	OP
Tomax et al. (2012)	Retrospective cohort	4470 cycles (tNC 1019, mNC 444, AC 2858), ovulatory and anovulatory patients	Preference, cycle characteristics	CP/LB
Weissman et al. (2009)	Retrospective cohort	132 cycles (tNC 71, mNC 61), ovulatory patients	Preference	CP/LB
Weissman et al. (2011)	RCT	55 cycles (tNC 30, mNC 25), ovulatory patients	Concealed allocation non-blinded	CP/OP/LB
NC versus AC				
Cattoli (1994)	RCT	100 cycles (AC 56, NC 44), ovulatory patients	Not stated	CP
Chang et al. (2011)	Retrospective cohort	644 cycles (tNC 310, mNC 130, AC 204), ovulatory patients	Preference, costs	CP/OP
Givens et al. (2009)	Retrospective cohort	807 cycles (NC 602, AC 205), ovulatory and anovulatory patients	Preference, cycle characteristics	CP/LB
Hancke et al. (2012)	Retrospective cohort	203 cycles (NC 148, AC 55), ovulatory and anovulatory patients	Not stated	CP
Kawamura (2007)	Retrospective cohort	856 cycles (NC 720, AC 136), ovulatory patients	Preference	ChP/CP/LE
Loh and Leong (1999)	Retrospective cohort	212 cycles (NC 51, AC 161), ovulatory patients	Preference	CP/LB
Morozov et al. (2007)	Retrospective cohort	242 cycles (AC 174, NC 68), ovulatory patients	Not stated	CP
Tomax et al. (2012)	Retrospective cohort	4470 cycles (tNC 1019, mNC 444, AC 2858), ovulatory and anovulatory patients	Preference, cycle characteristics	CP/LB
Xiao et <i>al.</i> (2011)	Retrospective cohort	1020 cycles (NC 380, AC 640), ovulatory and anovulatory patients	Preference, cycle characteristics	CP/OP
NC versus AC with GnR	н			
al Shawaf et al. (1993)	Retrospective cohort	149 cycles (AC 72, NC 77), ovulatory and anovulatory patients	Age, cycle characteristics	CP
Gelbaya et al. (2006)	Retrospective cohort	417 cycles (NC 212, AC + GnRH 205), ovualtory patients	Changed protocol	CP/LB
Hill et al. (2010)	Retrospective cohort	1391 cycles (NC 240, AC + GnRH 1151), ovulatory and anovulatory patients	Preference, cycle characteristics	ChP/CP/LB
Queenan et al. (1994)	Retrospective cohort	528 cycles (NC 398, AC + GnRH 230), ovulatory and anovulatory patients	Cyde characteristics	CP/OP
Tanos et al. (1996)	Quasi-randomized	304 cycles (NC 219, AC + GnRH 85), ovulatory and anovulatory patients	Preference, cycle characteristics	CP
AC versus AC with GnR	н			
Dal Prato et al. (2002)	RCT	296 cycles (AC 150, AC + GnRH 145), ovulatory patients	Concealed allocation, non-blinded	CP
El Toukhy et al. (2004)	RCT	234 cycles (AC 117, AC + GnRH 117), ovulatory patients	Concealed allocation, non-blinded	CP/LB
Simon et al. (1998)	RCT	106 cycles (AC 53, AC + GnRH 53), ovulatory and anovulatory patients	Not stated	CP/OP



NC-FET vs modified NC-FET

1965 cycles

	true natura	cycle	modified natural	l cycle		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chang 2011	56	134	130	310	25.2%	0.99 [0.66, 1.50]	+
Faterni 2010	19	61	11	63	4.1%	2.14 [0.92, 4.99]	
Tomas 2012	248	1019	95	327	60.1%	0.79 [0.59, 1.04]	-
Weismann 2009	21	62	20	54	7.8%	0.87 [0.41, 1.87]	_
Weismann 2011	8	24	8	27	2.8%	1.19 [0.36, 3.88]	
Total (95% CI)		1300		781	100.0%	0.91 [0.74, 1.12]	•
Total events	352		264				
Heterogeneity: Chi2 = 5	5.37, df = 4 (P	= 0.25); 1	² = 26%			H	
Test for overall effect:	Z = 0.86 (P =	0.39)				U U	Favours mNC Favours tNC
Ingoing pregn	ancy						
	true natural	cycle	modified natural	cycle		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
Chang 2011	118	310	51	134	34.0%	1.00 [0.66, 1.52]	+
Fatemi 2010	19	61	9	63	16.5%	2.71 [1.11, 6.61]	
Tomas 2012	211	1019	77	327	39.9%	0.85 [0.63, 1.14]	*
Weismann 2011	5	27	8	24	9.6%	0.45 [0.13, 1.65]	
Total (95% CI)		1417		548	100.0%	1.02 [0.66, 1.60]	•
Total events	353		145				
Heterogeneity: Tau ² = Test for overall effect: 2	0.11; ChP = 7 Z = 0.1 (P =	23. df = 3 0.92)	s (P = 0.07); I ^z = 58	8%			0.01 0.1 1 10 10 Favours mNC Favours tNC
Live birth							
	true natura	cycle	modified natural	l cycle		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI
Tomas 2012	211	1019	77	444	64.6%	1.24 [0.93, 1.66]	=
Weismann 2009	17	62	17	54	24.2%	0.82 [0.37, 1.83]	
Weismann 2011	5	27	8	24	11.2%	0.45 [0.13, 1.65]	
Total (95% CI)		1108		522	100.0%	1.01 [0.63, 1.60]	+
Total events	233		102				
Heterogeneity: Tau ² = Test for overall effect:	0.07; Chi ² = 2 Z = 0.00 (P =	.95. df = 2 0.98)	? (P = 0.23); I ² = 32	2%			0.01 0.1 1 10





NC-FET vs modified NC-FET: luteal phase support

	true N	С	modified	INC		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
5.3.1 without luteal p	hase supp	oort					
Chang 2011	56	134	130	310	67.9%	0.99 [0.66, 1.50]	
Fatemi 2010	19	61	11	63	11.1%	2.14 [0.92, 4.99]	
Weismann 2009 Subtotal (95% CI)	21	62 257	20	54 427	21.0% 100.0%	0.87 [0.41, 1.87] 1.09 [0. 79, 1.52]	•
Total events	96		161				
5.3.2 with luteal phas	se support		-				
5.3.2 with luteal phas Tomas 2012	se support 248	1019	95	327	95.6%	0.79 [0.59, 1.04]	
5.3.2 with luteal phas Tomas 2012 Weismann 2011 Subtotal (95% Cl)	se support 248 8	1019 24 1043	95 8	327 27 354	95.6% 4.4% 100.0%	0.79 [0.59, 1.04] 1.19 [0.36, 3.88] 0.80 [0.61, 1.05]	•
5.3.2 with luteal phas Tomas 2012 Weismann 2011 Subtotal (95% CI) Total events	se support 248 8 256	1019 24 1043	95 8 103	327 27 354	95.6% 4.4% 100.0%	0.79 [0.59, 1.04] 1.19 [0.36, 3.88] 0.80 [0.61, 1.05]	•
5.3.2 with luteal phas Tomas 2012 Weismann 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² =	248 248 8 256 0.44, df = 1	1019 24 1043 I (P = 0	95 8 103 . <u>5</u> 1); I ² = 0	327 27 354 %	95.6% 4.4% 100.0%	0.79 [0.59, 1.04] 1.19 [0.36, 3.88] 0.80 [0.61, 1.05]	•
5.3.2 with luteal phas Tomas 2012 Weismann 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	248 248 256 0.44, df = 1 Z = 1.58 (F	1019 24 1043 1 (P = 0 P = 0.11	95 8 103 .51); I ² = (327 27 354 %	95.6% 4.4% 100.0%	0.79 [0.59, 1.04] 1.19 [0.36, 3.88] 0. 80 [0.61, 1.05]	•
5.3.2 with luteal phas Tomas 2012 Weismann 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	248 248 256 0.44, df = 1 Z = 1.58 (F	1019 24 1043 1 (P = 0 P = 0.11	95 8 103 .51); I² = 0	327 27 354 %	95.6% 4.4% 100.0%	0.79 [0.59, 1.04] 1.19 [0.36, 3.88] 0.80 [0.61, 1.05]	

Figure 3 True versus modified NC: subgroup analysis based on luteal phase support.



NC-FET vs modified NC-FET: luteal phase support

Ongoing pregnancy



Figure 3 True versus modified NC: subgroup analysis based on luteal phase support.



8152 cycles

NC-FET vs AC-FET

Clinical pregnancy

	NC		AC			Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	È	M-H, Random, 95% CI	
Catolli 1994	9	50	12	64	6.2%	0.95 [0.37, 2.48]			
Chang	186	444	62	204	13.0%	1.65 [1.16, 2.35]			
Givens 2009	288	862	106	262	13.9%	0.74 [0.56, 0.98]			
Hancke 2012	51	148	12	55	8.4%	1.88 [0.91, 3.89]			
Kawamura 2007	310	720	55	136	12.8%	1.11 [0.77, 1.62]		-	
Loh 1999	9	51	14	161	6.6%	2.25 [0.91, 5.56]			
Morozov 2007	25	68	41	174	9.8%	1.89 [1.03, 3.45]			
tomas 2012	343	1346	854	2492	15.2%	0.66 [0.57, 0.76]		-	
Xiao 2011	144	380	228	646	14.1%	1.12 [0.86, 1.45]		-	
Total (95% CI)		4069		4194	100.0%	1.17 [0.86, 1.58]		•	
Total events	1365		1384					12	
Heterogeneity: Tau ² =	0.15; Chi2	= 48 0	8 df = 8 (P < 0.0	00001); F =	= 83%	1	<u>t.</u> t. t.	
Test for overall effect:	Z = 0.99 (P = 0.3	2)				0.01	0.1 1 10 Favours AC Favours NC	100

Ongoing pregnancy

	NC		AC			Odds Ratio			Odd	is Ratio)		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	1		M-H, Rar	ndom, 9	5% CI		
Chang	169	444	56	204	22.8%	1.62 [1.13, 2.33]				-	_		
tomas 2012	288	1346	500	2492	46.5%	1.08 [0.92, 1.28]				+			
Xiao 2011	112	380	181	646	30.7%	1.07 [0.81, 1.42]				-			
Total (95% CI)		2170		3342	100.0%	1.19 [0.95, 1.47]				٠			
Total events	569		737										
Heterogeneity: Tau ² =	0.02; Chi2	= 4 20	df = 2 (F	9 = 0.12); l ² = 52%	6	1	10	0.5	+	1	+	
Test for overall effect:	Z = 1.54 (P = 0.1	2)				0.1	0.2 F	avours A	C Favo	urs NC	5	10

Live birth

	NC		AC			Odds Ratio		Odd	s Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	1	M-H, Ran	dom, 95% Cl	
Givens 2009	245	862	77	262	27.7%	0.95 [0.70, 1.29]			+	
Hancke 2012	31	148	7	55	7.9%	1.82 [0.75, 4.41]				
Kawamura 2007	263	720	42	136	22.6%	1.29 [0.87, 1.91]				
Loh 1999	8	51	6	161	5.4%	4.81 [1.58, 14.60]				
Tomas 2012	288	1346	500	2492	36.3%	1.08 [0.92, 1.28]			†	
Total (95% CI)		3127		3106	100.0%	1.23 [0.93, 1.62]			•	
Total events	835		632							
Heterogeneity: Tau ² =	0.05; Chi2	= 9.44	df = 4 (F	P = 0.05	5); I ^z = 58%	6				100
Test for overall effect:	Z = 1.48 (P = 0.1	5)				0.01	Eavours AC	Favours NC	100

Figure 4 NC versus AC.



NC-FET vs AC-FET: true NC or modified NC

	NC		AC			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
6.1.1 true natural cyc	cle						
Catolli 1994	9	50	12	64	8.0%	0.95 [0.37, 2.48]	
Chang 2011	130	310	62	204	20.2%	1.65 [1.14, 2.40]	-
Loh 1999	9	51	14	161	8.7%	2.25 [0.91, 5.56]	
Morozov 2007	25	68	41	174	14.0%	1.89 [1.03, 3.45]	
Tomas 2012	248	1019	691	2492	25.7%	0.84 [0.71, 0.99]	-
Xiao 2011 Subtotal (95% CI)	144	380 1878	228	646 3741	23.4% 100.0%	1.12 [0.86, 1.45] 1.27 [0.92, 1.75]	•
Test for overall effect: 6.1.2 modified nature	Z = 1.4. (P = 0.1	5) 5)	F - 0.0	uz), r - n	470	
Chang 2011	56	134	62	204	40.1%	1.64 [1.04, 2.59]	-
Tomas 2012 Subtotal (95% CI)	95	327 461	691	2492 2696	59.9% 100.0%	1.07 [0.83, 1.38] 1.27 [0.84, 1.92]	t
Total events	151		753				
Heterogeneity: Tau ² =	0.06; Chi ² Z = 1.1 (= 2.64 P = 0.2	df = 1 (F 6)	9 = 0.10); I² = 62%		

Figure 5 NC versus AC: subgroup analyses based on modified or NC.



NC-FET vs AC-FET: true NC or modified NC





NC-FET vs AC-FET: NC-luteal support or no support

	NC		AC			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H. Random, 95% CI
2.1.1 NC with luteal p	hase sup	port					
Givens 2009	288	862	106	262	17.5%	0.74 [0.56, 0.98]	-
Hancke 2012	51	148	12	55	9.9%	1.88 [0.91, 3.89]	-
Kawamura 2007	310	720	55	136	15.9%	1.11 [0.77, 1.62]	+
Loh 1999	9	51	14	161	7.7%	2.25 [0.91, 5.56]	
Morozov 2007	25	68	41	174	11.7%	1.89 [1.03, 3.45]	-
Tomas 2012	343	1346	854	2492	19.4%	0.66 [0.57, 0.76]	
Xiao 2011	144	380	228	646	17.8%	1.12 [0.86, 1.45]	+
Subtotal (95% CI)		3575		3926	100.0%	1.11 [0.80, 1.53]	•
Heterogeneity: Tau ² = Test for overall effect:	0.13; Chi ² Z = 0.6; (F	= 34.37 P = 0.53	7, df = 6 (P < 0.0	0001); l² =	83%	
Heterogeneity: Tau ² = Test for overall effect: 2.1.2 NC without lute	0.13; Chi ² Z = 0.63 (F	= 34.37 P = 0.57	7, df = 6 (3)	P < 0.0	0001); l² =	83%	
Heterogeneity: Tau ² = Test for overall effect: 2.1.2 NC without lute Catolli 1994	0.13; Chi ² Z = 0.63 (F al phase s 9	= 34.3 = 0.5 support 50	1310 7, df = 6 (3) t 12	P < 0.0	0001); l² = 16.2%	83%	
Heterogeneity: Tau ² = Test for overall effect: 2.1.2 NC without lute Catolli 1994 Chang 2011 Subtotal (95% CI)	0.13; Chi ² Z = 0.65 (F al phase s 9 186	= 34.3 = 0.5 support 50 444 494	1010 7, df = 6 (3) t 12 62	P < 0.0 64 204 268	16.2% 83.8% 100.0%	83% 0.95 [0.37, 2.48] 1.65 [1.16, 2.35] 1.51 [1.01, 2.25]	
Heterogeneity: Tau ² = Test for overall effect: 2.1.2 NC without lute Catolli 1994 Chang 2011 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	0.13; Chi ² Z = 0.63 (f al phase s 9 186 195 0.02; Chi ² Z = 2.03 (f	= 34.3 = 0.5 support 50 444 494 = 1.12, = 0.04	t 12 62 74 df = 1 (P	P < 0.0 64 204 268 9 = 0.29	16.2% 83.8% 100.0%); l ² = 11%	83% 0.95 [0.37, 2.48] 1.65 [1.16, 2.35] 1.51 [1.01, 2.25]	•

Figure 6 NC versus AC: subgroup analyses based on luteal phase support.



NC-FET vs AC-FET with GnRH agonist

2789 cycles

	NC	NC		GnRH		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
Al Shawaf 1993	20	77	18	72	6.5%	1.05 [0.50, 2.20]	+	
Gelbaya 2006	20	172	18	173	7.5%	1.13 [0.58, 2.23]	+	
Hill 2010	77	198	520	1049	47.8%	0.65 [0.47, 0.88]	=	
Queenan 1994	112	398	70	230	30.2%	0.90 [0.63, 1.28]	+	
Tanos 1996	37	219	14	85	7.9%	1.03 [0.53, 2.02]	+	
Total (95% CI)		1064		1609	100.0%	0.82 [0.67, 1.00]	٠	
· · · · · · · · · · · · · · · · · · ·								
Total events	266		640					
Total events Heterogeneity: Chi ² = - Test for overall effect.	266 4.23, df = Z = 1.99 (4 (P = (P = 0.0	640 0.38); I ² = 5)	5%		0.0 Favours	1 0.1 1 10 100 AC with GnRH Favours NC	
Total events Heterogeneity: Chi ² = - Test for overall effect.	266 4.23, df = Z = 1.99 (4 (P = (P = 0.0	640 0.38); I ² = 5)	5%		0.0 Favours	1 0.1 1 10 100 AC with GnRH Favours NC	
Total events Heterogeneity: Chi ² = - Test for overall effect ive birth rate	266 4.23, df = Z = 1.95 (NC	4 (P = (P = 0.0	640 0.38); P = 5) GnRt	5%		0.0 Favours	1 0.1 1 10 100 AC with GnRH Favours NC Odds Ratio	
Total events Heterogeneity: Chi ² = - Test for overall effect. Live birth rate Study or Subgroup	266 4.23, df = Z = 1.99 (NC Events	4 (P = (P = 0.0 Total	640 38); I ² = 5) GnRł Events	5% H Total	Weight	Odds Ratio M-H, Random, 95% CI	1 0.1 1 10 100 AC with GnRH Favours NC Odds Ratio M-H, Random, 95% CI	
Total events Heterogeneity: Chi ² = . Test for overall effect ive birth rate <u>Study or Subgroup</u> Al Shawaf 1993	266 4.23, df = Z = 1.99 NC Events 16	4 (P = (P = 0.0 Total 77	640 38); ² = 5) GnRł Events 15	5% H Total 72	Weight 21.1%	Odds Ratio M-H, Random, 95% Cl 1.00 [0.45, 2.20]	1 0.1 1 10 100 AC with GnRH Favours NC Odds Ratio M-H, Random, 95% Cl	
Total events Heterogeneity: Chi ² = . Test for overall effect: ive birth rate <u>Study or Subgroup</u> Al Shawaf 1993 Gelbaya 2006	266 4.23, df = Z = 1.98 NC Events 16 19	4 (P = (P = 0.0 Total 77 172	640 ().38); ² = 5) GnRł Events 15 17	5% H <u>Total</u> 72 173	Weight 21.1% 25.7%	0.0 Favours Odds Ratio <u>M-H, Random, 95% Cl</u> 1.00 [0.45, 2.20] 1.14 [0.57, 2.27]	1 0.1 1 10 100 AC with GnRH Favours NC Odds Ratio M-H, Random, 95% CI	
Total events Heterogeneity: Chi ² = - Test for overall effect. Live birth rate <u>Study or Subgroup</u> Al Shawaf 1993 Gelbaya 2006 Hill 2010	266 4.23, df = Z = 1.95 NC Events 16 19 46	4 (P = 0 P = 0.0 Total 77 172 198	640 0.38); ² = 5) 6 6 7 7 15 17 347	5% Total 72 173 1049	Weight 21.1% 25.7% 53.2%	Odds Ratio M-H, Random, 95% CI 1.00 [0.45, 2.20] 1.14 [0.57, 2.27] 0.61 [0.43, 0.87]	1 0.1 1 10 100 AC with GnRH Favours NC Odds Ratio M-H, Random, 95% Cl	
Total events Heterogeneity: Chi ² = - Test for overall effect ive birth rate <u>Study or Subgroup</u> Al Shawaf 1993 Gelbaya 2006 Hill 2010 Total (95% CI)	266 4.23, df = Z = 1.95 (Events 16 19 46	4 (P = 0 P = 0.0 Total 77 172 198 447	640 0.38); ² = 5) GnRH Events 15 17 347	5% Total 72 173 1049 1294	Weight 21.1% 25.7% 53.2% 100.0%	Odds Ratio M-H, Random, 95% Cl 1.00 [0.45, 2.20] 1.14 [0.57, 2.27] 0.61 [0.43, 0.87] 0.80 [0.52, 1.21]	1 0.1 1 10 100 AC with GnRH Favours NC Odds Ratio M-H, Random, 95% CI	
Total events Heterogeneity: Chi ² = - Test for overall effect. Live birth rate <u>Study or Subgroup</u> Al Shawaf 1993 Gelbaya 2006 Hill 2010 Total (95% CI) Total events	266 4.23, df = Z = 1.95 Events 16 19 46 81	4 (P = (P = 0.0 Total 77 172 198 447	640 0.38); ² = 5) GnR Events 15 17 347 379	5% 1 <u>Total</u> 72 173 1049 1294	Weight 21.1% 25.7% 53.2% 100.0%	Odds Ratio M-H, Random, 95% CI 1.00 [0.45, 2.20] 1.14 [0.57, 2.27] 0.61 [0.43, 0.87] 0.80 [0.52, 1.21]	1 0.1 1 10 100 AC with GnRH Favours NC Odds Ratio M-H, Random, 95% Cl	

Figure 7 NC versus AC with GnRH agonist.



AC-FET vs AC-FET with GnRH agonist

631 cycles

El Toukhy 2004 13 117 28 117 32.1% 0.46 [0.25, 0.85] Simon 1998 11 52 14 53 28.8% 0.80 [0.40, 1.60] Total (95% CI) 319 312 100.0% 0.77 [0.44, 1.35]	Dal Prato 2002	34	150	28	142	39.0%	1.15 [0.74, 1.79]	+
Simon 1998 11 52 14 53 28.8% 0.80 [0.40, 1.60] Total (95% Cl) 319 312 100.0% 0.77 [0.44, 1.35]	El Toukhy 2004	13	117	28	117	32.1%	0.46 [0.25, 0.85]	
Total (95% Cl) 319 312 100.0% 0.77 [0.44, 1.35]	Simon 1998	11	52	14	53	28.8%	0.80 [0.40, 1.60]	-
	Total (95% Cl)		319		312	100.0%	0.77 [0.44, 1.35]	•
Total events 58 70	Total events	58		70				
Heterogeneity: Tau ² = 0.15; Chi ² = 5.63, df = 2 (P = 0.06); l ² = 64%	Heterogeneity: Tau ² = Test for overall effect:	0.15; Chi ² = Z = 0.90 (P	= 5.63, d = 0.37)	= 2 (P = 0).06); P =	64%		0.01 0.1 1 10 100

Figure 8 AC versus AC with GnRH agonist.



human reproduction update

What is the optimal means of preparing the endometrium in frozen-thawed embryo transfer cycles?

We conclude that it is not possible, based on the current published literature, to recommend one endometrial preparation method in FET over another. The number of RCTs is limited and small numbers of patients are included. Future prospective RCTs should not only address pregnancy rates but also consider convenience and cost efficiency.

Therefore, there remains a need

for prospective randomized studies to clarify which approach, if any, may improve clinical pregnancy rate after FET, which is the most efficient and cost-effective, and which is associated with the lowest patient burden. Only then can the optimal approach be discerned.



FET cycles: endometrial preparation GENERA 2009-2012





Warmed cycles clinical outcomes: GENERA 2009-2012 (up

to	(12 v)		
10		Oocyte Warmed Cycle	Embryo Warmed Cycle
	N of cycles	503	919
	N of patients	373	715
	Female Age (mean±SD)	36.4±4.1	36.9±3.8
	Warmed Oocytes/Embryos	2064	1746
	Survival rate (%)	1828/2064 (88.5)	1696/1746 (97.1)
	N of ET (%)	437/503 (86.8)	900/919 (97.9)
	Transferred embryo (mean±SD)	2,10±0,8	1.86±0.9
	Clinical PR per Cycle (%)	131/503 (26.0)	267/919 (29.0)
	Clinical PR per ET (%)	131/437 (29.9)	267/900 (29.7)
	Implantation Rate	142/919 (15.4)	280/1680 (16.6)
	Delivery Rate per warmed cycle (%)	106/503 (21.0)	231/919 (25.1)
	Delivery Rate per Embryo transfer	100/407 (04.0)	



Thank you for your attention



CLINICAL DIRECTOR: Filippo Maria Ubaldi

Rienzi

Silvia Colamaria Maddalena Giuliani Enrica Gravotta Fabio Sapienza



LABORATORY DIRECTOR: Laura

Laura Albricci Antonio Capalbo Danilo Cimadomo Lisa Dovere Elena Ievoli Roberta Maggiulli Giovanna Orlando Stefania Romano Federica Sanges Catello Scarica Emiliano Scepi Marta Stoppa

Annalise Giallonardo Mauro Schimberni

Michele Ermini Beatrice Ermini

www.generaroma.it colamaria@generaroma.it