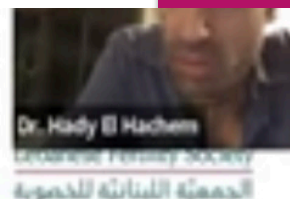


**Frozen Embryo Transfer:
What is the optimal
endometrial
preparation ?**

Background



- Oral
- Sub-cutaneous
- Vaginal
- Transdermal

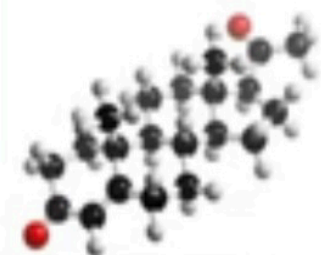


- GnRH suppression
- No GnRH suppression

Hormone Replacement Cycle

- CC / Letrozole
- Gonadotropins

Mildly Stimulated Cycle



- Oral
- Sub-cutaneous
- Vaginal
- Intra-muscular

True Natural Cycle

- With Luteal Phase Support
- Without Luteal Phase Support

Modified Natural Cycle

- With Luteal Phase Support
- Without Luteal Phase Support



Artificial Cycle

Estradiol

Day 1



Prime the endometrium

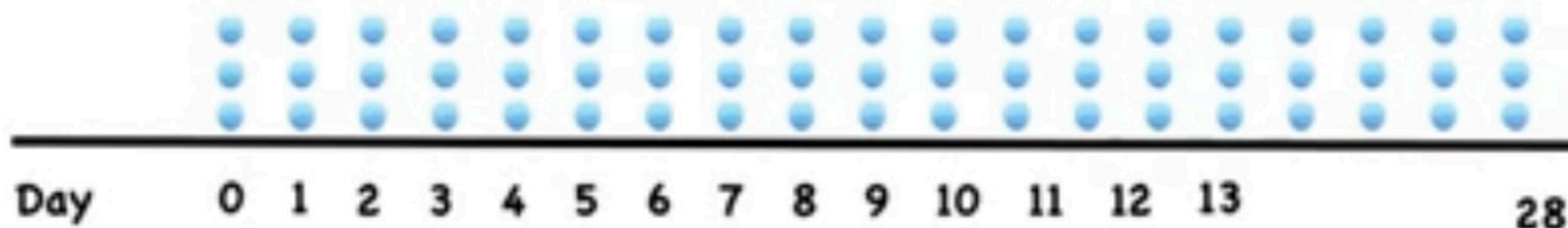
Day 2



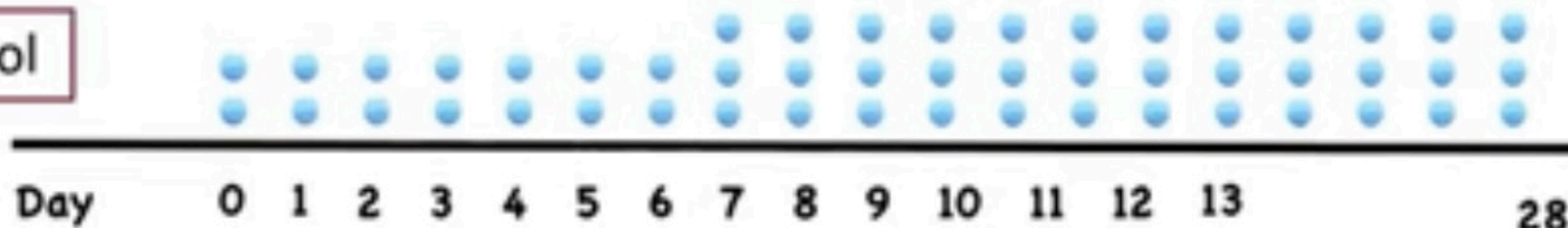
Suppress spontaneous follicle growth

Day 3

Fixed protocol



Incremental protocol



Route of E₂ administration

Oral Micronized
0.75 mg

Oral E₂ valerate
1 mg

Transdermal gel
1.25 mg

Vaginal E₂ valerate
1 mg

84%

9%

3%

SCIENTIFIC
REPORTS
nature research

Endometrial preparation for frozen-thawed embryo transfer in an artificial cycle: transdermal versus vaginal estrogen

Romain Corvoisier¹, Hady El Hachem¹, Caroline Verhaeghe¹, Guillaume Legendre¹, Cecile Dreux¹, Pauline Jeanneteau², Philippe Descamps², Pascale May-Panloup³ & Pierre-Emmanuel Bouet¹

- ➔ 318 FET: 119 Transdermal Vs 199 Vaginal Estrogen
- ➔ Significantly higher ET, Shorter duration of treatment
- ➔ Significantly higher ovulation rate
- ➔ Significantly higher satisfaction score / fewer side effects
- ➔ Comparable CP, PL and LBR

GNRH agonist pre-treatment

Human Reproduction Vol. 29, No. 3, pp. 476-479, 2014
Advance Access publication March 11, 2014

DOI: 10.1093/hrop/14.3

Pituitary suppression in ultrasound-monitored frozen embryo replacement cycles. A randomised study

LBR: 20% vs 8.5%

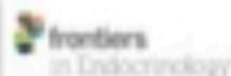
T.El-Toukhy¹, A.Taylor^{1,2}, Y.Khalaf¹, K.Al-Darazi¹, P.Rowell¹, P.Seed^{1,2} and P.Brade^{1,2}



Cochrane Database of Systematic Reviews

Endometrial preparation for women with frozen embryos or embryos (Review)

Ghappinsky D, Ponce R, Swicks C, Quimero R



Endometrial Preparation for Frozen-Thawed Embryos With or Without Pretreatment with GnRH Agonist: A Randomised Controlled Trial at Two Centres

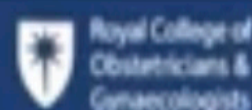
Jian Xu¹, Shu-Zhen Lu¹, Min-Na Yu¹, Pei-Ling Li¹, Lu Luo², Minghu

¹Center of Reproductive Medicine, Suning Hospital and Center of Reproductive Medicine, Suning Hospital, Guangzhou, China; ²Department of Obstetrics and Gynaecology, Suning Hospital, Guangzhou, China

Pregnancy outcome and cost-effectiveness comparisons of artificial

cycle-prepare
pretreatment

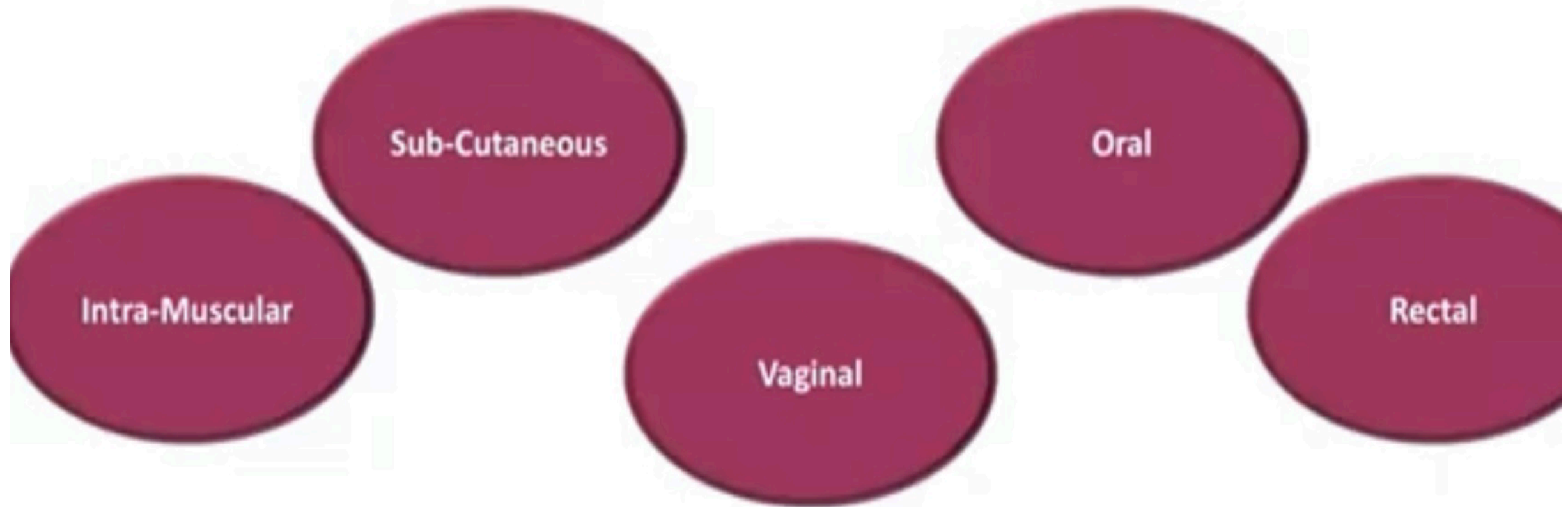
BJOG An International Journal of
Obstetrics and Gynaecology



Randomised controlled trial

Pregnancy outcome and cost-effectiveness comparisons of artificial cycle-prepared frozen embryo transfer with or without GnRH agonist pretreatment for polycystic ovary syndrome: a randomised controlled trial

Route of P₄ administration



Route of P₄ administration

Intramuscular progesterone optimizes live birth from programmed frozen embryo transfer: a randomized clinical trial

Kate Devine, M.D.,^{*} Kevin S. Richter, Ph.D.,[†] Samad Jahandideh, Ph.D.,^{*} Eric A. Widra, M.D.,^{*} and Jeffrey L. McKeeby, M.D.^{*}

^{*} Shady Grove Fertility; and [†] Fertility Science Consulting, Rockville, Maryland

3 armed, prospective, multicenter, noninferiority RCT

Vaginal
200 mg BID

Vaginal
+
IM (every 3rd day)

IM
50 mg
Daily

1,060 cycles in a ITT analysis

- ➔ 40% reduction in LBR with vaginal
 - ➔ Difference due to a high miscarriage and biochemical pregnancy loss (50%)
 - ➔ In groups receiving V progesterone, FET performed following a duration of one-half day shorter
 - ➔ Subjects preferred vaginal to IM
- ➔ Comparable outcomes between combination and IM

Fertility and Sterility




ASRM 2021
BALTIMORE ON-DEMAND
OCT 11-15, 2021

REPRODUCTION REIMAGINED



SEMINAL CONTRIBUTIONS

 Check for updates

Intramuscular progesterone optimizes live birth from programmed frozen embryo transfer: a randomized clinical trial

Kate Devine, M.D.,^a Kevin S. Richter, Ph.D.,^b Samad Jahandideh, Ph.D.,^a Eric A. Widra, M.D.,^a and Jeffrey L. McKeeby, M.D.^a

Fertility and Sterility® Vol. 116, No. 3, September 2021



ASRM 2021
BALTIMORE ON-DEMAND
ON-SITE OCT 17-20, 2021 OCT 18 - DEC 31, 2021

REPRODUCTION REIMAGINED



ASRM 2021
 BALTIMORE ON-DEMAND
 ON-SITE OCT 17-20, 2021 OCT 18 - DEC 31, 2021

TABLE 2

Pregnancy and birth outcomes compared among the three treatment groups

	Intention-to-treat analysis			Statistical comparisons			
	IMP	VP + IMP	VP	Overall chi-square	IMP vs. VP + IMP	IMP vs. VP	VP + IMP vs. VP
Embryo transfers	421	408	231				
Positive hCG (per transfer)	279 (66%)	254 (62%)	127 (55%)	$P = .02$	$P = .23$	$P = .004$	$P = .07$
Biochemical loss (per positive hCG)	50 (18%)	33 (13%)	41 (32%)	$P < .0001$	$P = .12$	$P = .001$	$P < .0001$
Clinical pregnancy (per transfer)	229 (54%)	221 (54%)	86 (37%)	$P < .0001$	$P = .95$	$P < .0001$	$P < .0001$
Clinical loss (per clinical pregnancy)	43 (19%)	33 (15%)	23 (27%)	$P = .038$	$P = .28$	$P = .12$	$P = .016$
Total pregnancy loss (per positive hCG)	93 (33%)	66 (26%)	64 (50%)	$P < .0001$	$P = .07$	$P < .0001$	$P < .0001$
Live birth (per transfer)	186 (44%)	188 (46%)	63 (27%)	$P < .0001$	$P = .58$	$P < .0001$	$P < .0001$

REPRODUCTION REIMAGINED

Route of P₄ administration

Human Reproduction, Vol.00, No.0, pp. 1-11, 2021
doi:10.1093/hrop/raab071

Human
reproduction

ORIGINAL ARTICLE Infertility

Micronized progesterone plus dydrogesterone versus micronized progesterone alone for luteal phase support in frozen-thawed cycles (MIDRONE): a prospective cohort study

Cyclogest
400 mg BID
+
Duphaston
(10 mg BID)

n = 732

Cyclogest
400 mg BID)

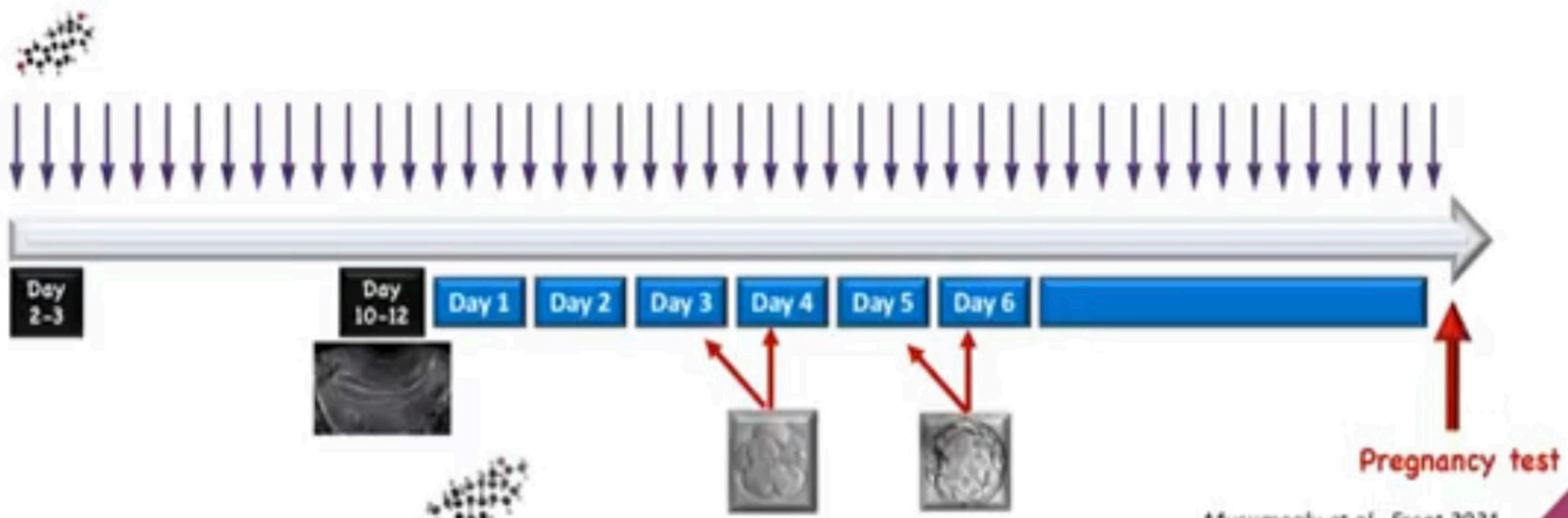
n = 632

LBR: 46.3% versus 41.3%, p=0.06

- ➔ Multivariate analysis: RR: 1.30 (95% CI 1.01–1.68; p=0.042)
- ➔ Miscarriage rate: 3.4% versus 6.6%, p=0.009
- ➔ Birthweights significantly lower in the combination groups

Start of P₄ administration

- ➔ Day 3 embryos: 2 RCT's → Transfer on 3rd or 4th day of P₄ administration
- ➔ Day 5/6 embryos: 2 RCT's → Transfer on 5th or 6th day of P₄ administration



Start of P₄ administration

Frozen-warmed blastocyst transfer after 6 or 7 days of progesterone administration: impact on live birth rate in hormone replacement therapy cycles

Transfer on 6th day of P₄

n = 346

Transfer on 7th of P₄

n = 273

Comparable LBR (36.6%)

- ➔ Subgroup Analysis of Day 6 blastocysts
- ➔ Miscarriage rates: 50.0% versus 21.4%, $p=0.02$
- ➔ LBR: 21.5% versus 35.5%, $p=0.06$

One more P₄ day for Day 6 blastocysts ??

Endocrine Monitoring

- ➔ Standard LPS for all patients
- ➔ Marked inter-personal variation in serum P_4 levels
- ➔ Impact on reproductive outcomes
- ➔ Endometrial P_4 measurements: Ideal but not feasible
- ➔ Serum P_4 level best marker of endometrial P_4 level

Endocrine Monitoring

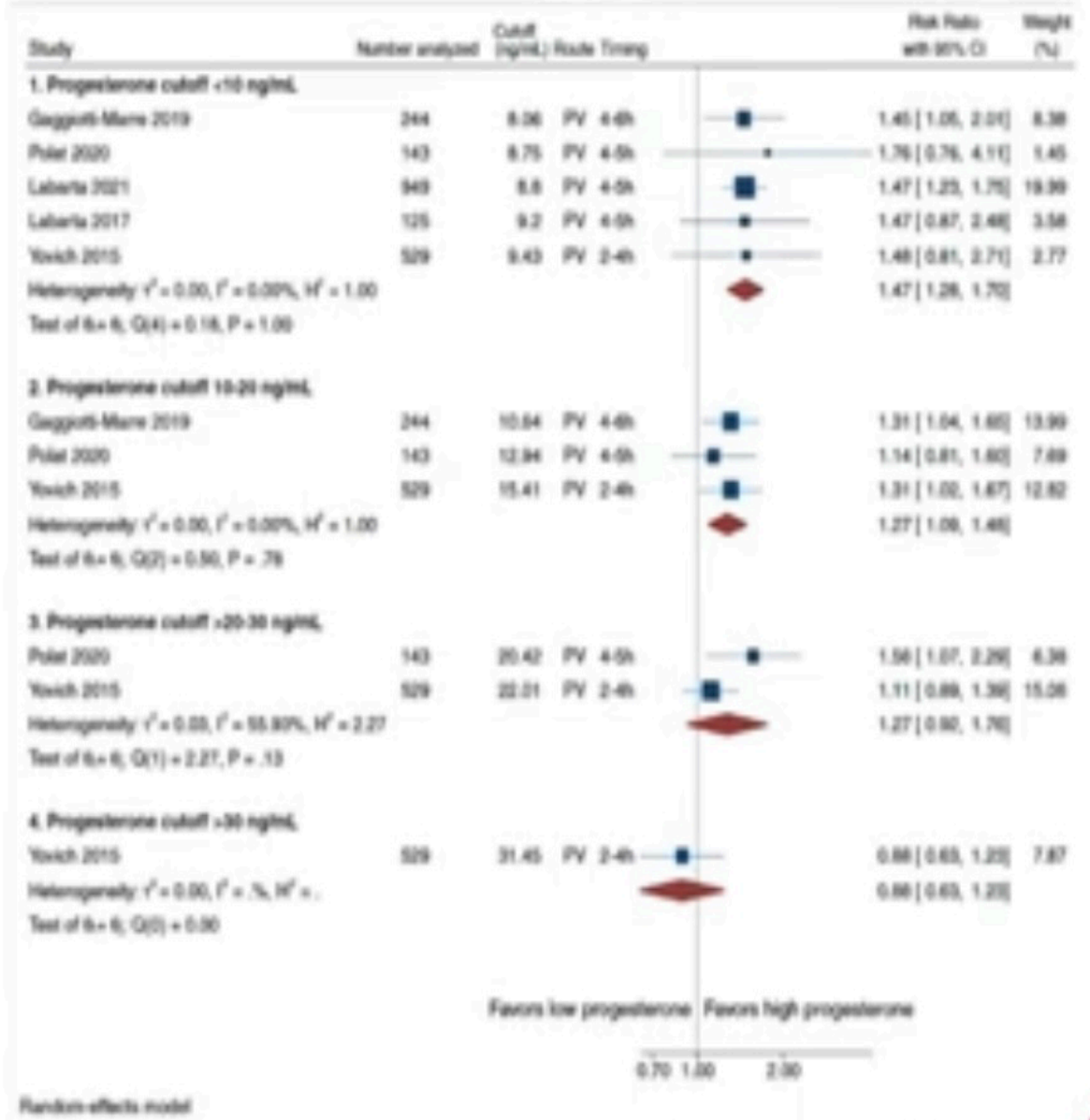
ARTICLE IN PRESS

ORIGINAL ARTICLE, ASSISTED REPRODUCTION

Serum luteal phase progesterone in women undergoing frozen embryo transfer in assisted conception: a systematic review and meta-analysis

Yoon Huh, M.D.,^{1,2} Yeonjung Chung, M.B.B.S.,^{3,4} George Parkin, B.Sc.,⁵ Marwan J. Pasha, Ph.D.,^{1,6} Simon Taheri, Ph.D.,^{7,8} Mohammed Khairy, M.D.,⁹ Charles Kingland, M.D.,¹⁰ Philip Lown, M.B.Ch.B.,¹¹ George Parnis, M.D., Ph.D.,¹² Madhurima Rajkhowa, M.D.,¹³ Victoria Spathis, M.B.Ch.B.,¹⁴ Amanda Toner, M.B.Ch.B.,¹⁵ Simon Wood, M.D.,¹⁶ Elena Labarta, M.D., Ph.D.,¹⁷ Mark Wilson, D.M.,¹⁸ Adam Dawood, Ph.D.,¹⁹ Susan Collins, M.D.,²⁰ and Art Loomis, M.D.²¹

- ➔ 16 heterogeneous studies
- ➔ 8.75 to 32.50 ng/ml
- ➔ 10 ng/mL
- ➔ Ceiling effect ? > 20 > 30 ng/ml ?



Rescue Protocols

➔ Studies showing no improvement in LBR after rescue dose

Brady PC et al. JARG 2014

Cedrin-Dunerin I et al. RBMO 2019



- ➔ 574 Frozen euploid blastocyst transfer
- ➔ Cut-off point of 10.6 ng/ml, one day before ET
- ➔ Rescue with 25 mg S/C daily

➔ 226 cycles (39.4%) required rescue

➔ LBR: 49.1% vs 52.3%

➔ 98% had P₄ > 10.6 ng/ml the day of ET

➔ Miscarriage rate: 12.4% vs 9.2%



Natural Cycle

PubMed.gov

natural cycle frozen embryo transfer

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470 results

Page 1 of 47

RESULTS



TEXT AVAILABILITY

- Abstract
- Free full text
- Full text

ARTICLE ATTRIBUTE

- Associated data

ARTICLE TYPE

Cycle regimens for frozen-thawed embryo transfer.

1 Ghobara T, Gelbaya TA, Ayeleke RO.

Cochrane Database Syst Rev. 2017 Jul 5;7(7):CD003414. doi: 10.1002/14651858.CD003414.pub3.

PMID: 28575921 [Free PMC article.](#) [Review.](#)

Share

BACKGROUND: Among subfertile couples undergoing assisted reproductive technology (ART), pregnancy rates following frozen-thawed embryo transfer (FET) treatment cycles have historically been found to be lower than following embryo transfer ...

The ART of frozen embryo transfer: back to nature!

2 Lorenz B, Coughlan C, Melado L, Fatemi HM.

Gynecol Endocrinol. 2020 Jun;36(6):479-483. doi: 10.1080/09513590.2020.1740918. Epub 2020

Mar 18.

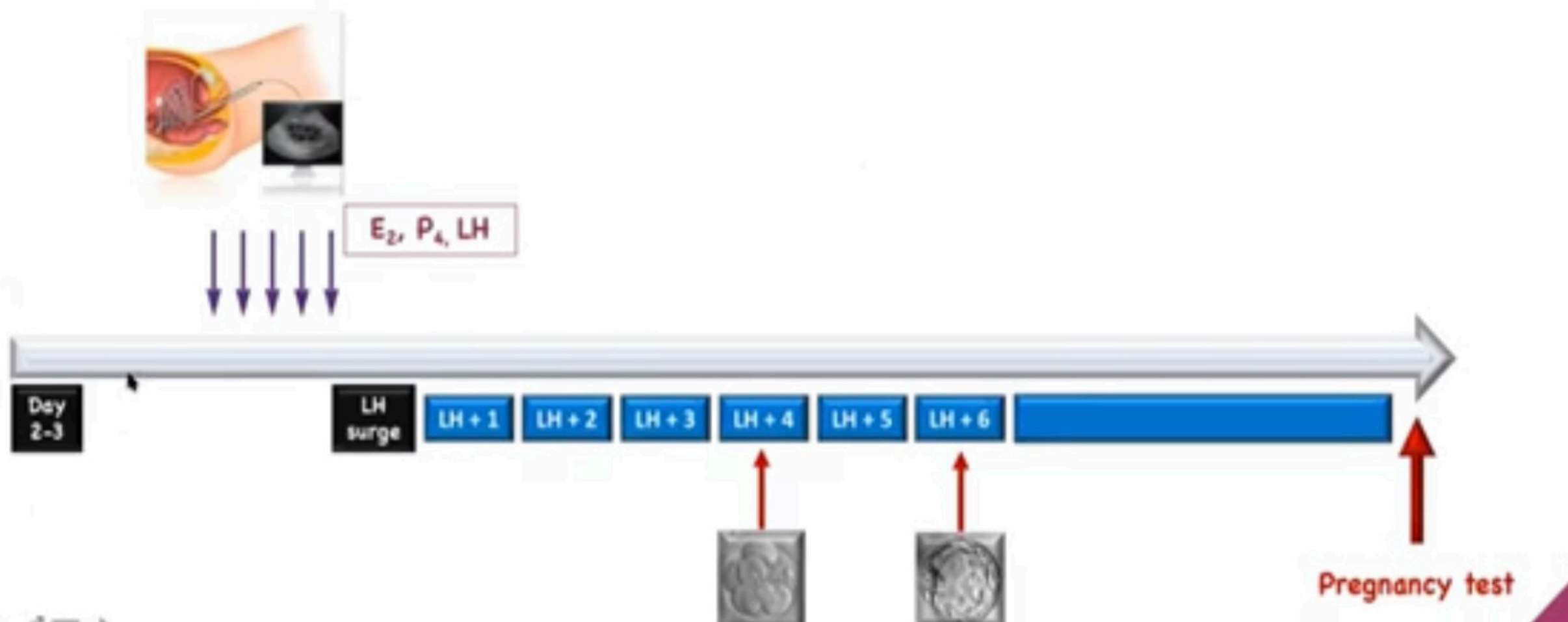
Share

PMID: 32188299 [Review.](#)

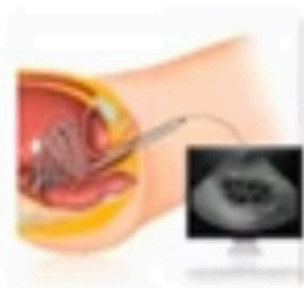
The implementation of cryopreservation-techniques in the IVF laboratory and the improved survival rates of oocytes, cleavage and blastocyst stage embryos have led to a significant increase in the number of frozen-thawed embryo transfer cycles (FET). FE ...

Frozen embryo transfer: a review on the optimal endometrial preparation and

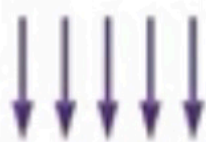
True Natural cycle



True Natural cycle



E_2 , P_4 , LH



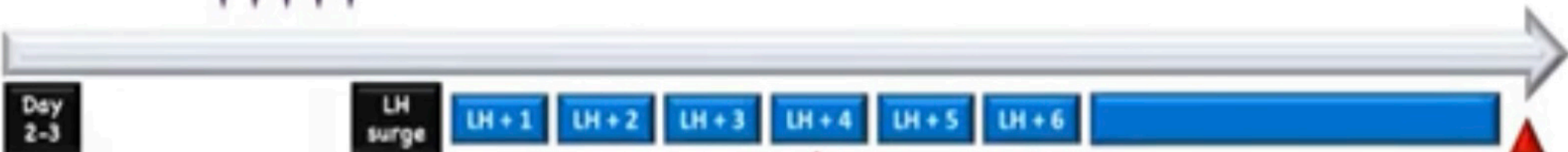
Serum Vs Urinary

Definition of LH Surge

Cut-off point

80% rise
>17 IU/L - 30% drop E_2
> 10 IU/L

$P_4 > 1.5$ ng/mL



Pregnancy test

Luteal phase support in t-NC

Luteal phase progesterone increases live birth rate after frozen embryo transfer

Kerstin Björnstam, B.S.,^{*} Britt-Marie Landgren, M.D., Ph.D.,^{*} Ossi Hovatta, M.D., Ph.D.,^{*} and Anneli Stavreus-Evers, Ph.D.^{*}

- ➔ Vaginal (400 mg BID) Vs No LPS
- ➔ FET performed on LH + 3
- ➔ P₄ started evening of FET
- ➔ LBR: 30% versus 20%, p=0.027

Human reproduction

ORIGINAL ARTICLE *Infertility*

Low progesterone levels on the day before natural cycle frozen embryo transfer are negatively associated with live birth rates

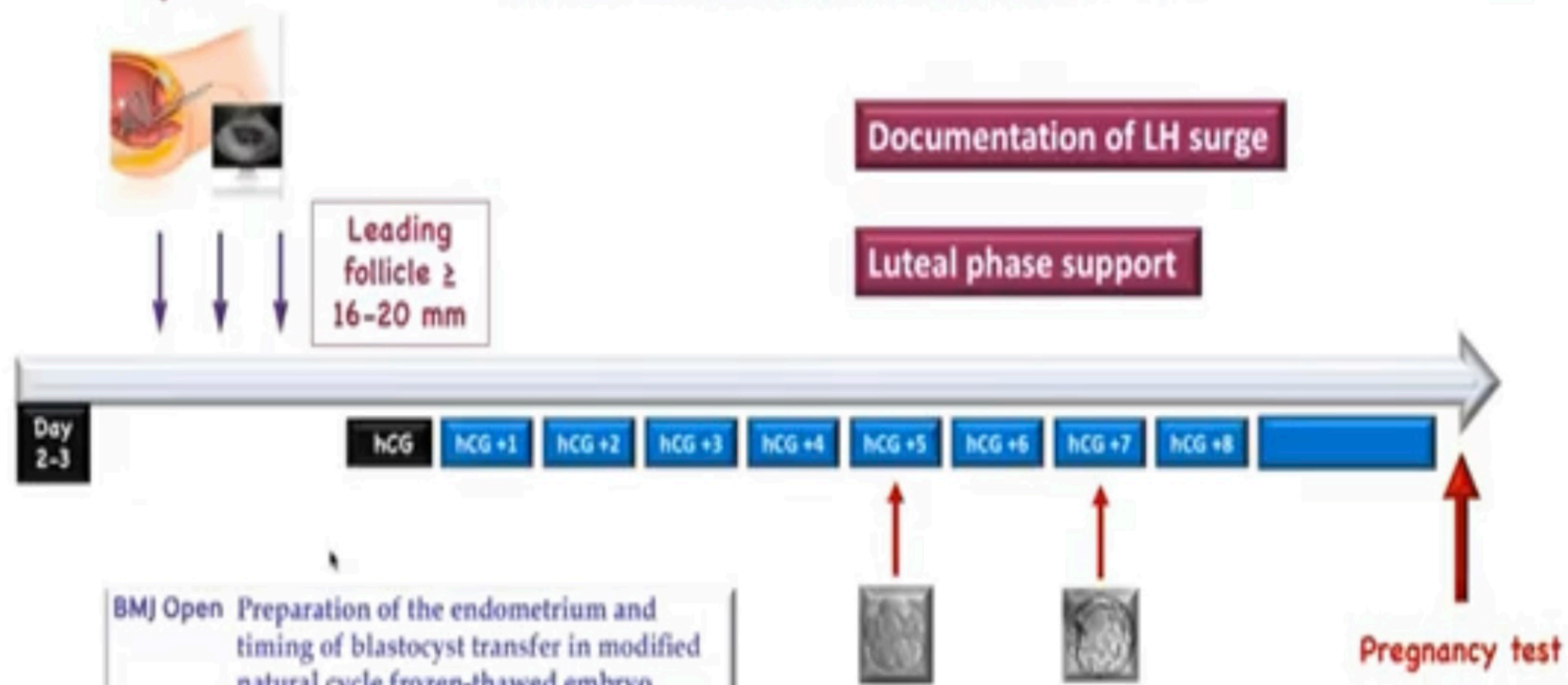
Sofia Gaggiotti-Marre^{*}, Manuel Álvarez, Inaki González-Foruria, Mónica Parriego, Sandra García, Francisca Martínez, Pedro N. Barri, Nikolaos P. Polyzos, and Buenaventura Coroleu

- ➔ 294 Blastocysts transfers in natural cycles
- ➔ P₄ measured morning of day before FET
- ➔ P₄ < 10 ng/mL (37%) Vs P₄ > 10 ng/mL
- ➔ LBR: 25.7% Vs 41.1%

Björnstam et al. *Fertil Steril* 2011

Gaggiotti-Marre et al. *Hum Reprod* 2020

Modified Natural Cycle



BMJ Open Preparation of the endometrium and timing of blastocyst transfer in modified natural cycle frozen-thawed embryo transfers (mNC-FET): a study protocol for a randomised controlled multicentre trial

Marie Saupeard,¹ Nina La Cour Fresselien,¹ Sven Olof Skouby,¹ Lars Franch Andersen,¹ Lilla Beeth Knudsen,¹ Kathrine Birch Petersen,¹ Mette Huuth,¹ Anne Egeberg,¹ Morten Ravn Petersen,¹ Søren Ziebe,¹ Anders Nyboe Andersen,¹ Kristine Lavel,¹ Arja Priborg²

True Versus Modified NC

➔ 2 RCT's: 1 showed no difference and 1 favoured t-NC

Fatemi H et al. Fert Ster 2010

Weissman et al RBMO 2011

Human reproduction ORIGINAL ARTICLE **Infertility**

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

S. Mackens^{1,2*}, A. Stubbe¹, S. Santos-Ribeiro³, L. Van Landuyt¹, A. Racca¹, C. Roelens¹, M. Carnus¹, M. De Vos¹, A. van de Vijver⁴, H. Tournaye¹, and C. Blockeel¹

- ➔ 130 t-NC vs 130 m-NC
- ➔ LH +5 Vs hCG+6
- ➔ CPR: 27.2% vs 24.4%
- ➔ Fewer visits with m-NC

Journal of Assisted Reproduction and Genetics
<https://doi.org/10.1007/s10815-021-02125-8>

REVIEW

Endometrial preparation for frozen-thawed embryo transfer cycles: a systematic review and network meta-analysis

- ➔ 26 RCTs and 113 cohorts studies
- ➔ No significant difference between the two

Mild Ovarian Stimulation

Clomiphene 50-100 mg

Letrozole 2.5 – 5 mg

Gn \leq 150 IU/day



Leading follicle \geq 16 mm
Endometrium \geq 7 mm
E₂ \geq 150 pg/mL

Luteal Phase Support



Pregnancy test

- ➔ Improve Subtle Follicular / Luteal Phase defects
- ➔ Better Endometrial Milieu
- ➔ Lower Risk of Thromboembolism

Is there a "best" protocol ?



Cochrane Library
Cochrane Database of Systematic Reviews

Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes (Review)

Glujovsky D, Perce R, Suedo C, Quinteiro Retamar AM, Hart RJ, Clapponi A

➔ 31 RCTs including 5426 women

➔ Evidence moderate to very low-quality

Natural Vs HRT: Uncertain, but with less cycle cancelation in Natural

Stimulated Vs HRT: Significantly improved CPR with stimulated (Letrozole)

Although HRT and NC (t-NC/modified-NC) are the most commonly used protocols, recent emerging evidence suggests that mild-OS may be a viable option for FET.

Is there a "best" protocol ?

Journal of Assisted Reproduction and Genetics
<https://doi.org/10.1007/s10883-021-02123-0>

REVIEW



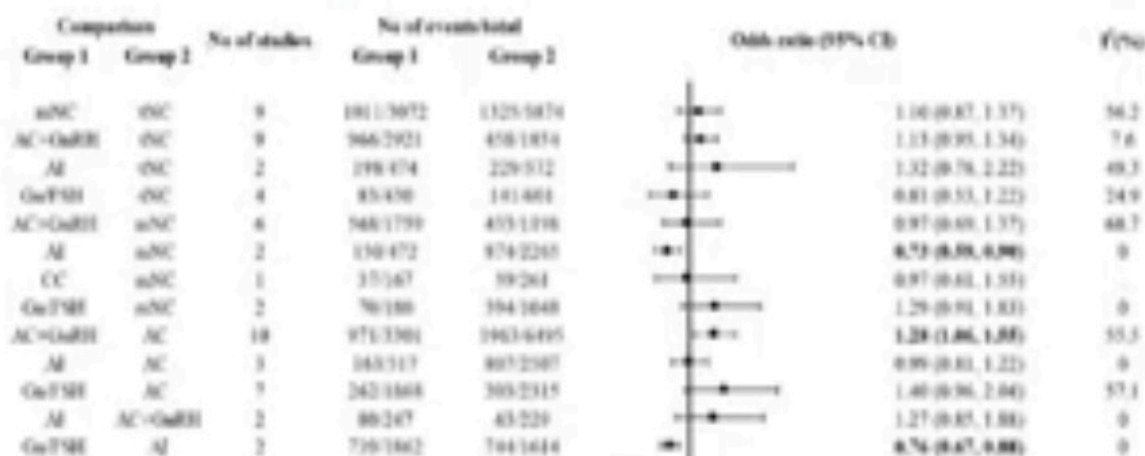
Endometrial preparation for frozen-thawed embryo transfer cycles:
 a systematic review and network meta-analysis

➔ 26 RCTs

GnFSH	NA	0.97 (0.43, 2.19)	NA	NA	NA
1.06 (0.58, 1.94)	AI	NA	NA	NA	0.60 (0.44, 0.81)
1.39 (0.90, 2.14)	1.31 (0.85, 2.02)	mNC	0.92 (0.66, 1.28)	0.94 (0.57, 1.56)	0.79 (0.56, 1.11)
1.55 (0.92, 2.63)	1.46 (0.95, 2.27)	1.12 (0.84, 1.49)	AC+GnRH	0.89 (0.58, 1.36)	0.78 (0.43, 1.41)
1.68 (0.93, 3.03)	1.59 (0.94, 2.66)	1.21 (0.81, 1.82)	1.08 (0.73, 1.60)	tNC	0.85 (0.48, 1.49)
1.77 (1.06, 2.98)	1.67 (1.22, 2.28)	1.28 (0.95, 1.72)	1.14 (0.84, 1.55)	1.05 (0.70, 1.60)	AC

➔ 113 cohort studies

AC < t-NC and m-NC



Neonatal Outcomes

H
R
T

Abnormal implantation / placentation in HRT cycles

Hypertensive disorders in pregnancy

Premature Rupture of Membranes

Postpartum hemorrhage

LGA / Cesarean sections

Adverse obstetric and perinatal outcomes in 1,136 singleton pregnancies conceived after programmed frozen embryo transfer (FET) compared with natural cycle FET

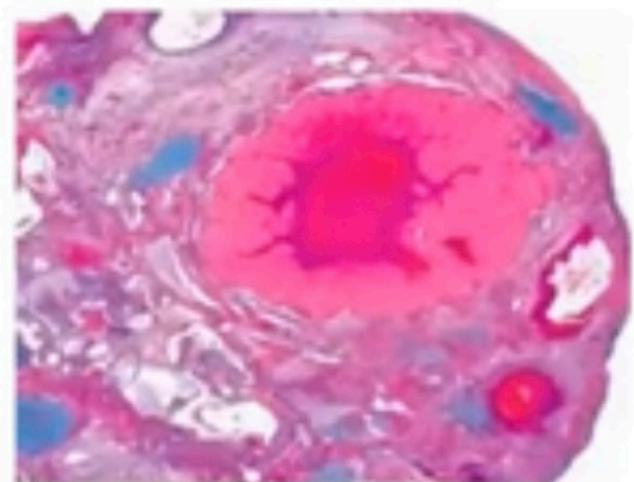
Lucas Leckie, Richard, M.D.,¹ Anne Lurie, Neerajkumar, M.D.,² Anne Karim, Aron Henningsen, M.D.,³ Tom D'Alagni, Christy, M.D., Ph.D.,⁴ Brian 2006, D.M.Sc.,⁵ Mike Beck, aron, M.D., Ph.D.,⁶ and Alan Pritsky, D.M.Sc.⁷

¹ Lucile Packard Children's Hospital, Stanford University School of Medicine, Stanford, CA, USA; ² Department of Obstetrics and Gynecology, University of California, San Francisco, San Francisco, CA, USA; ³ Department of Obstetrics and Gynecology, University of California, San Francisco, San Francisco, CA, USA; ⁴ Department of Obstetrics and Gynecology, University of California, San Francisco, San Francisco, CA, USA; ⁵ Department of Obstetrics and Gynecology, University of California, San Francisco, San Francisco, CA, USA; ⁶ Department of Obstetrics and Gynecology, University of California, San Francisco, San Francisco, CA, USA; ⁷ Department of Obstetrics and Gynecology, University of California, San Francisco, San Francisco, CA, USA

Relaxin

VEGF

Other vasoactive substances



Asserhøj et al., Fertil Steril 2020

Mumusoglu et al., Front 2021

Wu H et al. IJRG 2021