



Nastal čas „Freeze all to all“

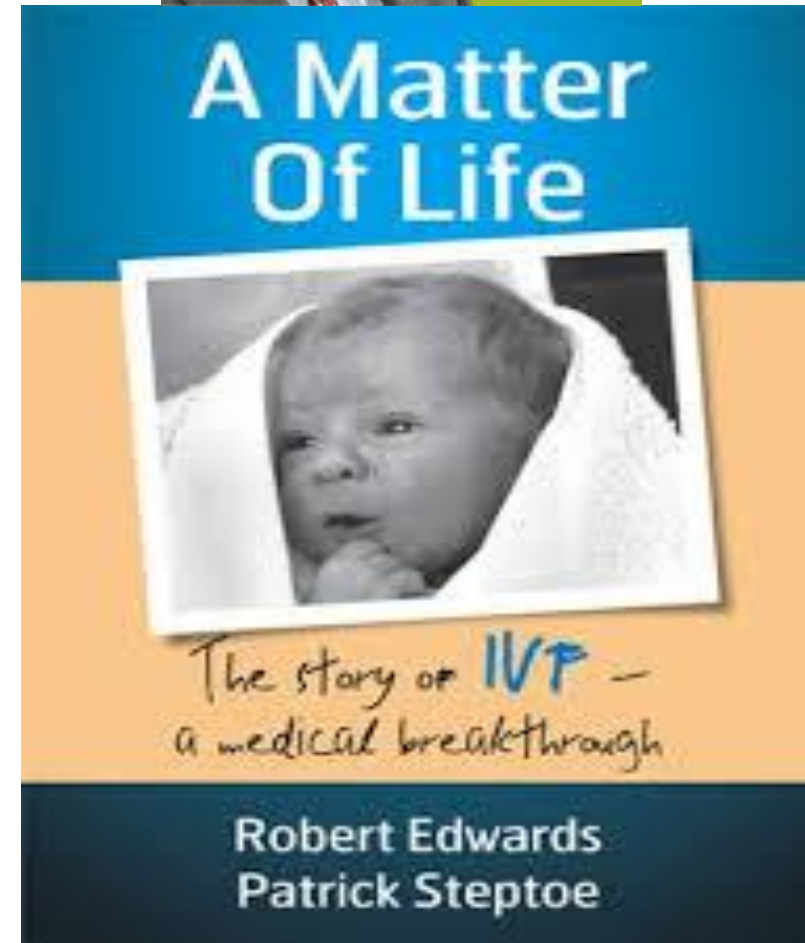
MUDr. Štěpán Machač, Ph.D.

IVF Clinic Olomouc



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Fresh or freeze all



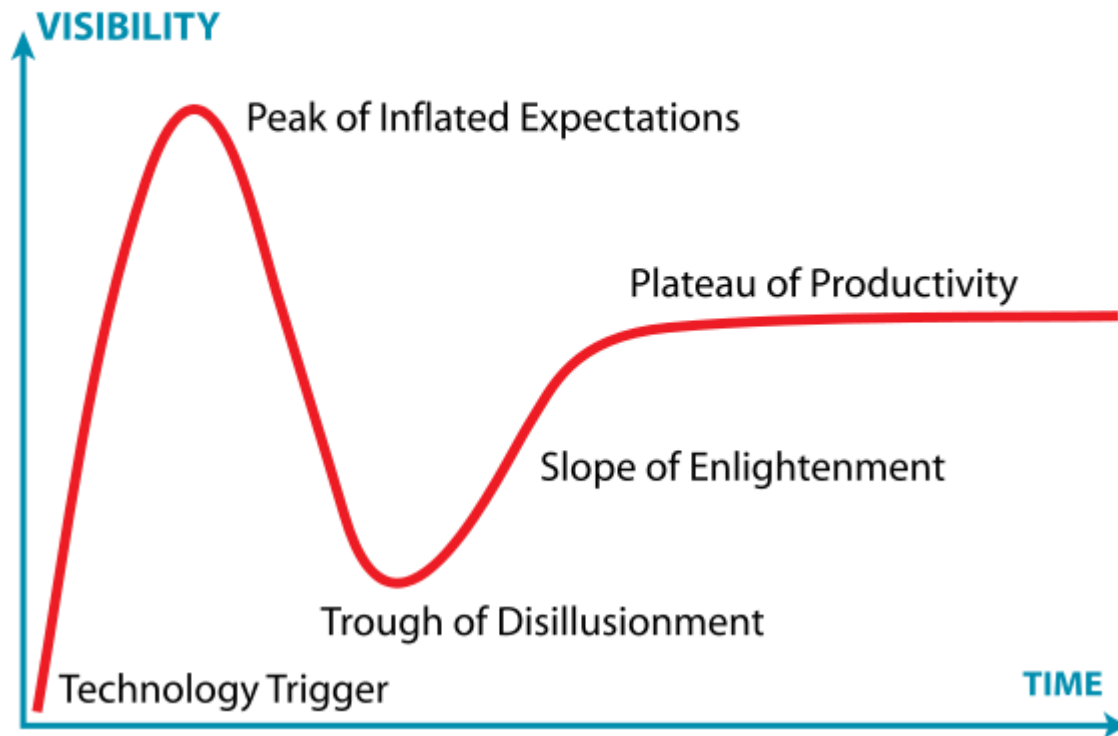
ICE
AGE



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FRESH versus FREEZE ALL

Gartner Hype Cycle



VITRIFIKACE

Freeze all nebo fresh

FREEZE ALL

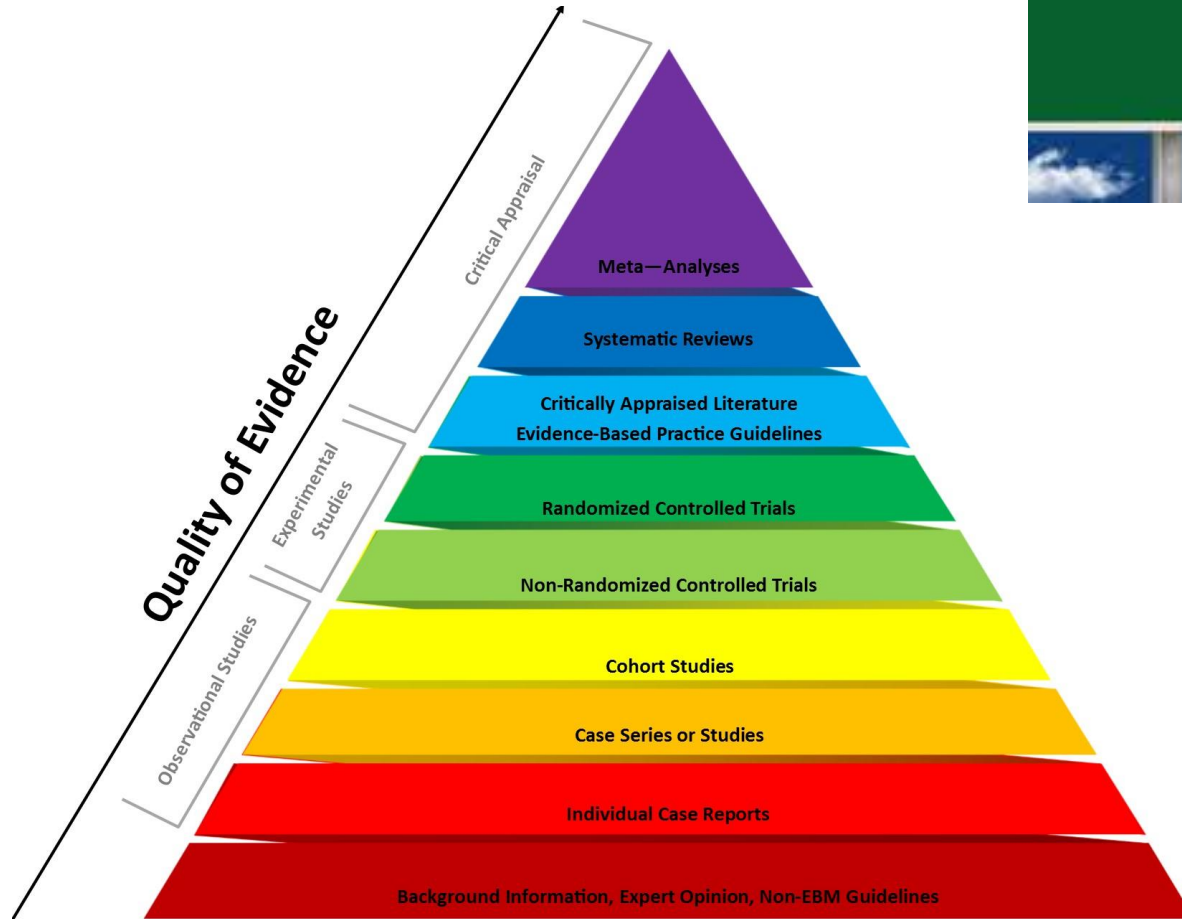
- Plánování léčby
- Vyšší úspěšnost
- Větší využití PGS
- Bez užívání vaginálního progesteronu
- OHSS free clinic
- **Řešení imunologického faktoru**

FRESH ET

- Časový faktor
- Co si přeje pacient
- Jak jsem zvyklí pracovat
- Finanční otázka, úhrada ZP
- Rozdíly mezi laboratořemi, lékaři



Evidence based





FRESH versus FREEZE ALL

Cochrane Database Syst Rev. 2017 Mar

Wong KM, Van Wely M, Mol F, et al (Center for Reproductive medicine, Univ of Amsterdam)

- METAANALYZA: Zahrnuty pouze RCT porovnávající freeze all a konvenční strategii /IVF+ICSI/
- Primary outcomes
 - Cumulative live birth – strategie fresh ET a zbytek freeze versus freeze all
 - OHSS
- 4 studie celkem **1892** žen

CUMULATIVE LIVE BIRTH AFTER FRESH 58% OR 1,09 95% CI 0,91-1,31

CUMULATIVE LIVE BIRTH AFTER FREEZE ALL 56-65%

OHSS 7% AFTER FRESH OR 0,67 95% CI 0,52-0,86

OHSS 1-3% AFTER FREEZE ALL

FRESH versus FREEZE ALL

Cochrane Database review conclusion:

Found moderate evidence showing that one strategy is not superior to the other in term of cumulative live birth rates.

Low quality evidence suggests that not performing a FRESH ET lowers the OHSS risk for women at risk of OHSS

FRESH versus FREEZE ALL

JBRA Assisted Reproduction 2017;21(3):260-272
doi: 10.5935/1518-0557.20170048

Review

Fresh embryos versus freeze-all embryos - transfer strategies: Nuances of a meta-analysis

Felipe C Dieamant^{1,2}, Claudia G Petersen^{1,2}, Ana L Mauri^{1,2}, V. Comar¹, Mariana Mattila¹, Laura D Vagnini², Adriana Renzi², Bruna Petersen², Andreia Nicoletti¹, João Batista A Oliveira^{1,2}, Ricardo LR Baruffi^{1,2}, Jose G Franco Jr^{1,2}

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This study was presented at the 33th annual meeting of ESHRE 2017, in Geneva, Switzerland

Ze 72 provedených studií POUZE 5 RCT bylo zahrnuto do meta analýzy
Pacientky rozděleny do skupin podle počtu získaných oocytů
Více než 12 a méně než 21
Více než 12 a méně než 15
Sledování CPR, OPR a LIVE BIRTH a Miscarriage rate – pro LB no difference

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Assumption: If immune response is key cause of repeated implantation failure

immune rejection?



.....then, no immune response must be best?





Low local immune activation

Strategies leading to the mobilisation and activation of immune cells

- **Endometrial scratching** in the mid-luteal phase of the cycle preceding the IVF/ICSI cycles (via Toll-like receptor signalling) stimulates expression of IL-15, chemokines and all the adhesion molecules¹
- **Decrease in ovarian stimulation** or transfer of frozen embryos during a natural cycle as endometrial exposure to high concentrations of oestrogens significantly decreases endometrial IL-18 expression²⁻⁴
- **Supplementation of the mid-luteal phase with low doses of hCG** following embryo transfer to stimulate local angiogenesis as well as recruitment and activation of uNK cells^{5,6}
- **Sexual intercourse after embryo transfer:** positive effect of the seminal plasma on the recruitment and activation of Treg⁷ and uNK^B cells

1. Gnainsky Y, et al. Fertil Steril 2010;94:2030–2036; 2. Murakami Y, et al. J Reprod Dev 2005;51:639–647; 3. Lédée N, et al. Am J Reprod Immunol 2006;56:119–123; 4. Ashworth MD, et al. Reprod Biol Endocrinol 2010;8:33; 5. Perrier d'Hauterive S, et al. Gynecol Obstet Invest 2007;64:156–160; 6. Kane N, et al. Endocrinology 2009;150:2882–2888; 7. Robertson SA. Cell Tissue Res 2005;322:43–52; 8. Blois SM, et al. J Mol Med (Berl) 2008;86:837–852.



High local immune activation



Updates
in Infertility
Treatment
Madrid 2018

Strategies able to control the activation of immune cells

- **No local injury, no scratching**
- Standard ovarian stimulation or replacement of frozen embryos in substituted cycle
- Adjunctive therapy of oestrogens and **high-dose progesterone** in the luteal phase to induce their well-known immunosuppressive properties¹
- Adjunctive therapy with **anti-inflammatory adjuvant** with anti-oxidant (Vitamin E)
- Corticoids (prednisone 20 mg daily): first line of treatment
- In case of resistance: slow perfusion of intralipids or LMHW
- No sexual intercourse

¹ Szekeres-Bartho J. Immunotherapy 2009;1:873–882.



FRESH versus FREEZE ALL

Co budeme studovat – intervention

1-2 nebo 3 intervence – FRESH, FREEZE, PGS, Imuno ?

Objectives – cíle

FRESH x FREEZE ALL

PCOS x NO PCOS

PGS x NO PGS

IMUNO Norma x aktivace

LIVE BIRTH RATE

RCT – nábor center a pacientek

Open Access

Protocol

BMJ Open Comparison of a ‘freeze-all’ strategy including GnRH agonist trigger versus a ‘fresh transfer’ strategy including hCG trigger in assisted reproductive technology (ART): a study protocol for a randomised controlled trial

Sacha Stormlund,¹ Kristine Løssl,¹ Anne Zedeler,¹ Jeanette Bogstad,¹ Lisbeth Prætorius,¹ Henriette Svarre Nielsen,² Mona Bungum,³ Sven O. Skouby,⁴ Anne Lis Mikkelsen,⁵ Anders Nyboe Andersen,² Christina Bergh,⁶ Peter Humaidan,⁷ Anja Pinborg¹

Accepted 24 May 2017



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Fresh or freeze all



Evidence on FRESH and FROZEN ET

FRESH versus FREEZE ALL in PCOS (8.2016)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fresh versus Frozen Embryos for Infertility in the Polycystic Ovary Syndrome

Z.-J. Chen, Y. Shi, Y. Sun, B. Zhang, X. Liang, Y. Cao, J. Yang, J. Liu, D. Wei,
N. Weng, L. Tian, C. Hao, D. Yang, F. Zhou, J. Shi, Y. Xu, J. Li, J. Yan, Y. Qin,
H. Zhao, H. Zhang, and R.S. Legro

ABSTRACT

Multicentrická RCT – 1508 pacientek PCOS
FRESH or FREEZE ALL

Results:

FROZEN: LBR 49,3% OR 1,17 95% CI 1,05-1,31 versus FRESH 42%

Conclusion: FET – higher LBR, lower risk OHSS and higher risk of PET

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FRESH versus FROZEN ET - GEU, FS 2015

ORIGINAL ARTICLE: EARLY PREGNANCY



Ectopic pregnancy after in vitro fertilization: differences between fresh and frozen-thawed cycles

Laura Londra, M.D.,^a Caroline Moreau, M.D., M.P.H., Ph.D.,^b Donna Strobino, Ph.D.,^b Jairo Garcia, M.D.,^a Howard Zacur, M.D., Ph.D.,^a and Yulian Zhao, M.D., Ph.D., M.B.A., H.C.L.D.^a

^a Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, Johns Hopkins University, Lutherville; and ^b Department of Population, Family, and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

103070 transferů – 1,38% GEU - celkem 1356 GEU
71906 fresh ET a 31164 KETů

Závěr:
transfery v cyklech bez ovariální stimulace mají signifikantně nižší riziko GEU



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Perinatal outcome in fresh versus frozen embryo transfer in ART cycles

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Received: 4 January 2016
Accepted: 14 February 2016

Abstract

Background: Despite of higher pregnancy rate after frozen embryo transfer (FET) which is accepted by the majority of researches, the safety of this method and its effect on neonatal outcome is still under debate.

Objective: The aim of this study was to evaluate pregnancy and neonatal outcome of FET compare to fresh cycles.

Materials and Methods: In this study, 1134 patients using fresh ET and 285 women underwent FET were investigated regarding live birth as primary outcome and gestational age, birth weight, gender, multiple status, ectopic pregnancy, still birth and pregnancy loss as secondary outcomes.

Results: Our results showed that there is no difference between FET and fresh cycles regarding live birth (65.6% vs. 70.4% respectively). Ectopic pregnancy, still birth and abortion were similar in both groups. The mean gestational age was significantly lower among singletons in FET group compared to fresh cycles ($p=0.047$). Prematurity was significantly elevated among singleton infants in FET group (19.6%) in comparison to neonates born after fresh ET (12.8%) ($p=0.037$).

Conclusion: It seems that there is no major difference regarding perinatal outcome between fresh and frozen embryo transfer. Although, live birth is slightly increased in fresh cycles and prematurity was significantly increased among singleton infants in FET group.

Keywords: Frozen-thawed embryo transfer, Fresh embryo transfer, Perinatal outcome, Pregnancy outcome.

1134 pacientek FRESH
285 pacientek FET

Conclusion: no difference



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FRESH versus FROZEN ET

First trimester pregnancy loss after fresh and frozen in vitro fertilization cycles

Hipp H, Crawford S, Kawwass JF et al.: Fertil Steril 2016, Mar; 105 (3): 722-728

- Objective: to characterise risk for early pregnancy loss after fresh and frozen IVF cycles
- Počet těhotenství: **249 630**
- Conclusion:
 - uterine factor had the largest increased risk of loss among diagnosis
 - When transferring embryos of similar quality the risks of loss were similar between FRESH and FROZEN

FRESH or FROZEN

Human Reproduction, Vol.29, No.3 pp. 618–627, 2014

Advanced Access publication on January 9, 2014 doi:10.1093/humrep/det440

human
reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Large baby syndrome in singletons born after frozen embryo transfer (FET): is it due to maternal factors or the cryotechnique?

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and A. Nyboe Andersen²**

¹Department of Obstetrics and Gynaecology, Hvidovre Hospital, University of Copenhagen, Kettegaard Allé 30, Hvidovre DK-2650, Denmark

²Fertility Clinic, Rigshospitalet, University of Copenhagen, Copenhagen DK-2100, Denmark ³Department of Biostatistics, University of Copenhagen, Copenhagen DK-1014, Denmark

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Submitted on July 15, 2013; resubmitted on October 28, 2013; accepted on November 14, 2013

FET singletons: 896
FRESH singletons: 9480
Natural conception singletons: 4510

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Velké plody po KETech

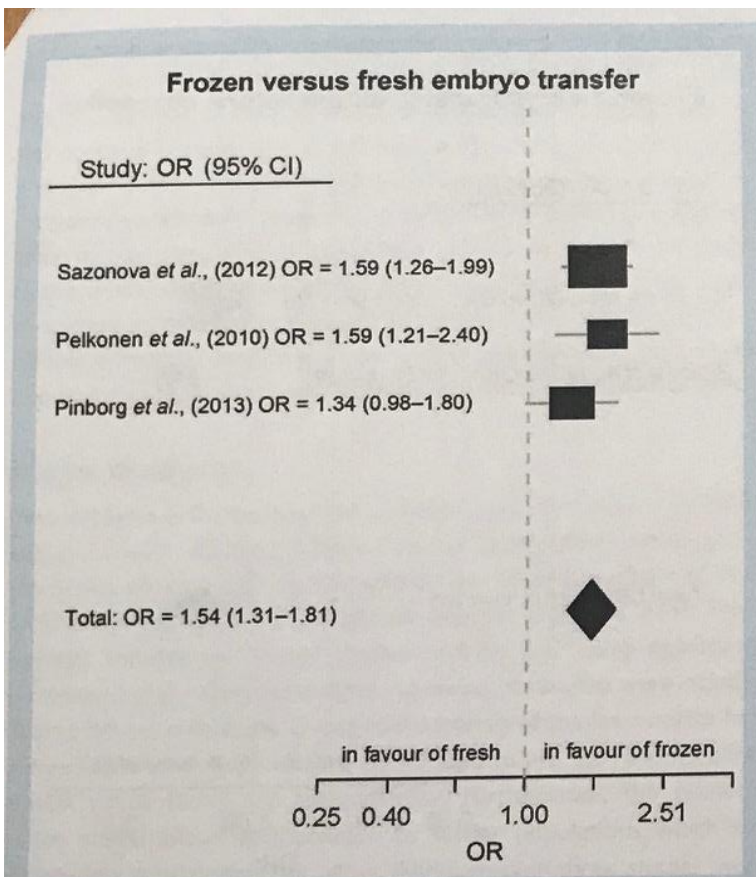


Figure 1 Forest plot of pooled estimate of being born LGA (z-score >2 SD) in singletons conceived after frozen embryo transfer (FET)

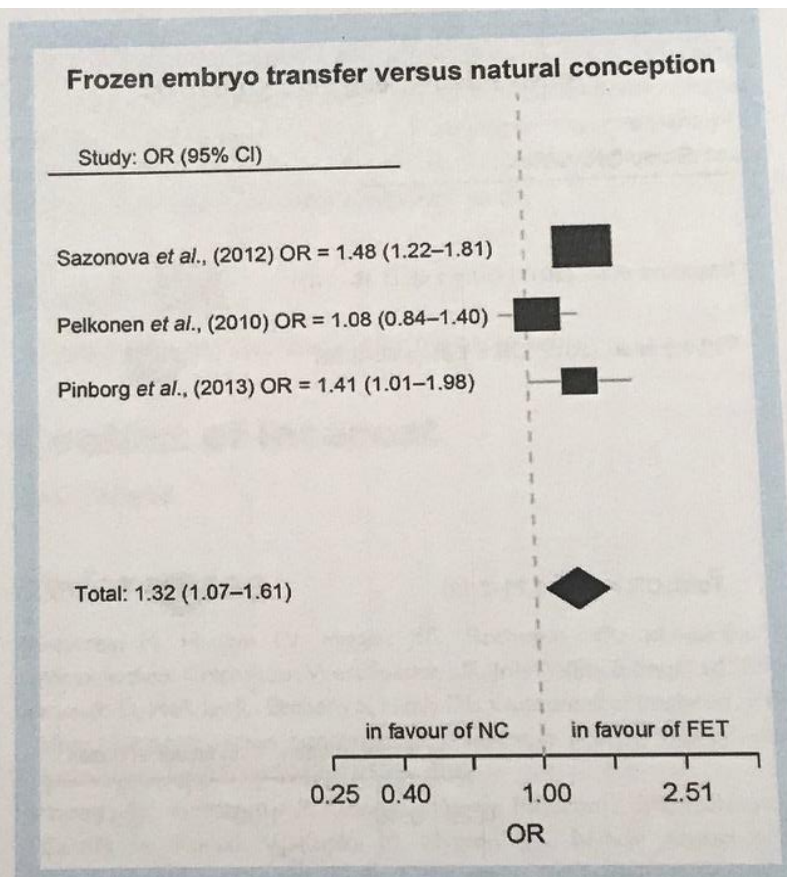


Figure 2 Forest plot of pooled estimate of being born LGA (z-score >2 SD) in singletons conceived after frozen embryo transfer (FET) versus naturally conceived singletons. OR, odds ratio; CI, confidence

FRESH ET

IN VITRO FERTILIZATION

FERTILITY AND STERILITY®

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Pregnancy rates after embryo transfer depend on the provider at embryo transfer

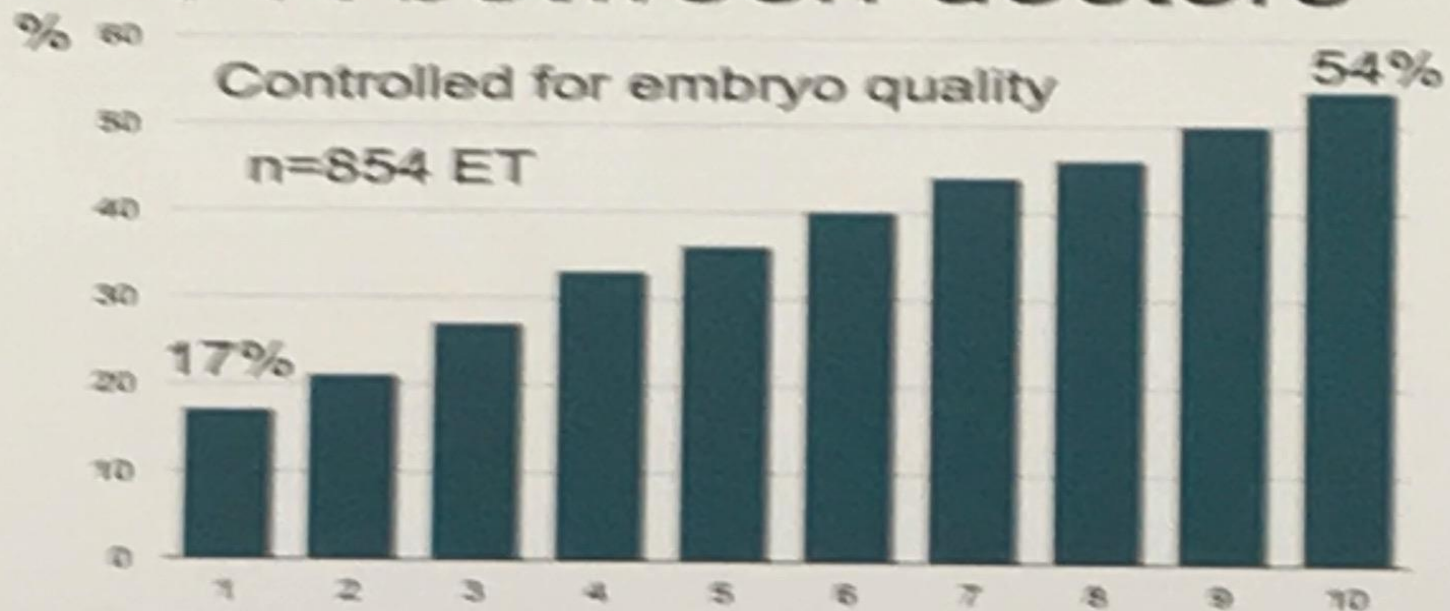
Rhonda M. Hearn-Stokes, M.D.,^{a,b} Bradley T. Miller, M.D.,^{a,c} Lynette Scott, Ph.D.,^a David Creuss, Ph.D.,^c Prabir K. Chakraborty, Ph.D.,^c and James H. Segars, M.D.^b

Walter Reed Army Medical Center and National Institute of Child Health and Human Development, National Institutes of Health, Washington, D.C.; and Uniformed Services University of the Health Sciences, Bethesda, Maryland

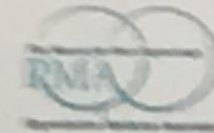
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PR between doctors



Hearty-Stokes, Fertl Steril 2000



Future life – IVF + ICSI s vlastními oocyty

text

FutureLife 2016

FutureLife 2015

FRESH ET (bez TimeLaps)		průměr	MAX	MIN		průměr	MAX	MIN
Počet všech fresh ET	3623	329	840	96	3347	293	910	169
Clinical Pregnancy rate (cPR) [%]	-	37,1%	43,8%	29,2%	-	37,9%	45,8%	30,4%
Kompletních výsledků [%]	-	93,0%	100,0%	74,4%	-	73,7%	100,0%	30,1%
FROZEN KET bez PGT (vitrifikace)								
Počet frozen ET	2546	231	380	159	2108	162	382	96
Clinical Pregnancy rate (cPR) [%]		34,5%	46,4%	26,9%		+	44,9%	19,0%
Kompletních výsledků [%]	-	93,7%	100,0%	70,8%	-	68,0%	100,0%	33,5%
FROZEN KET po PGT (vitrifikace)								
Počet frozen ET	543	54	185	3	365	33	110	1
Clinical Pregnancy rate (cPR) [%]	-	41,6%	51,8%	28,7%	-	34,1%	46,6%	9,0%
Kompletních výsledků [%]	-	93,4%	100,0%	69,3%	-	63,1%	100,0%	72,7%



FRESH VS FROZEN

ZÁVĚR



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Take home messages

A paradigm shift is occurring as FETs show increasing benefits

It is too soon for freeze-for-all, but more than enough time for freeze-for-more in case of:

Excessive ovarian response

Abnormal progesterone

RIF/RM

More (and better) research is needed before we jump to a future of freeze-for-all

