Fresh, Frozen or Personalized Day5 Transfer: How to Decide ?

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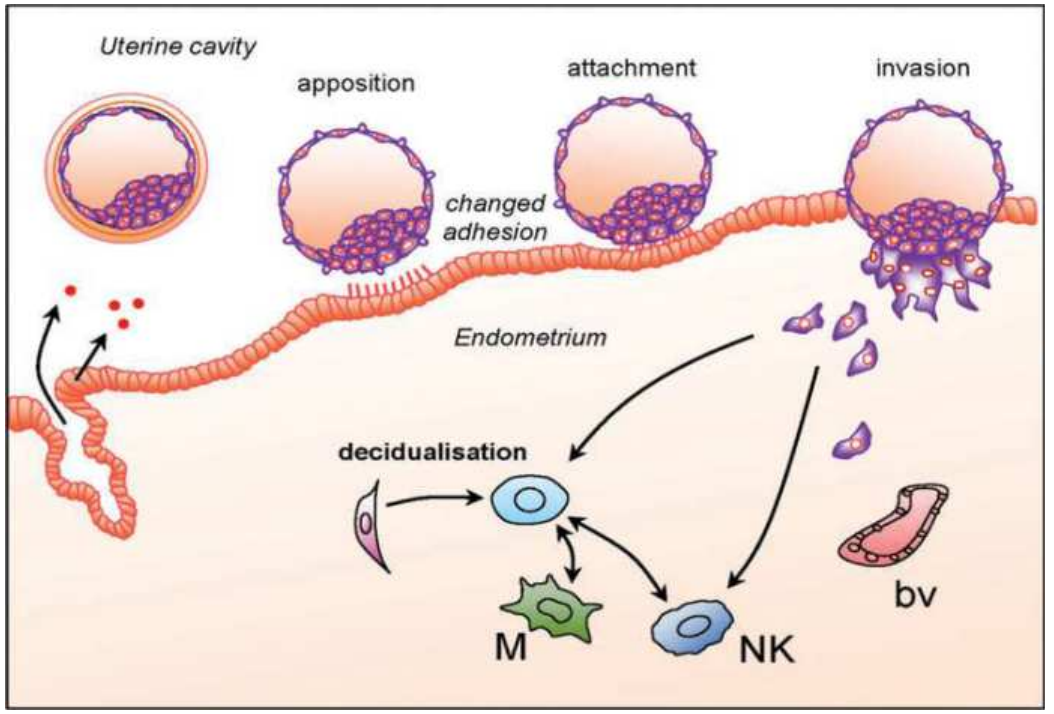
outlines

- COS and endometrial receptivity
- COS and uterine contractility
- IVF and OHSS – the OHSS-free clinic concept
- embryo cryopreservation
- IVF/ICSI outcomes of fresh versus frozen–thawed ET
- Obstetric and perinatal outcomes from fresh ET compared to frozen–thawed ET
- Role of Pre-implantation genetic screening (PGS)
- Costs

COS and endometrial receptivity

- WOI is a self-limited period marked by structural and functional maturation of the endometrium, which is necessary for blastocyst attachment.

- endometrium undergoes transformations mediated by a large number of genes and gene products, which are differentially expressed during the receptive phase of the menstrual cycle



COS and endometrial receptivity

- many genes related to endometrial receptivity are regulated by hormones and the COS may alter the gene expression of more than 200 genes related to implantation

- modifications may occur both under GnRHa and GnRH antagonist protocols for ovarian stimulation

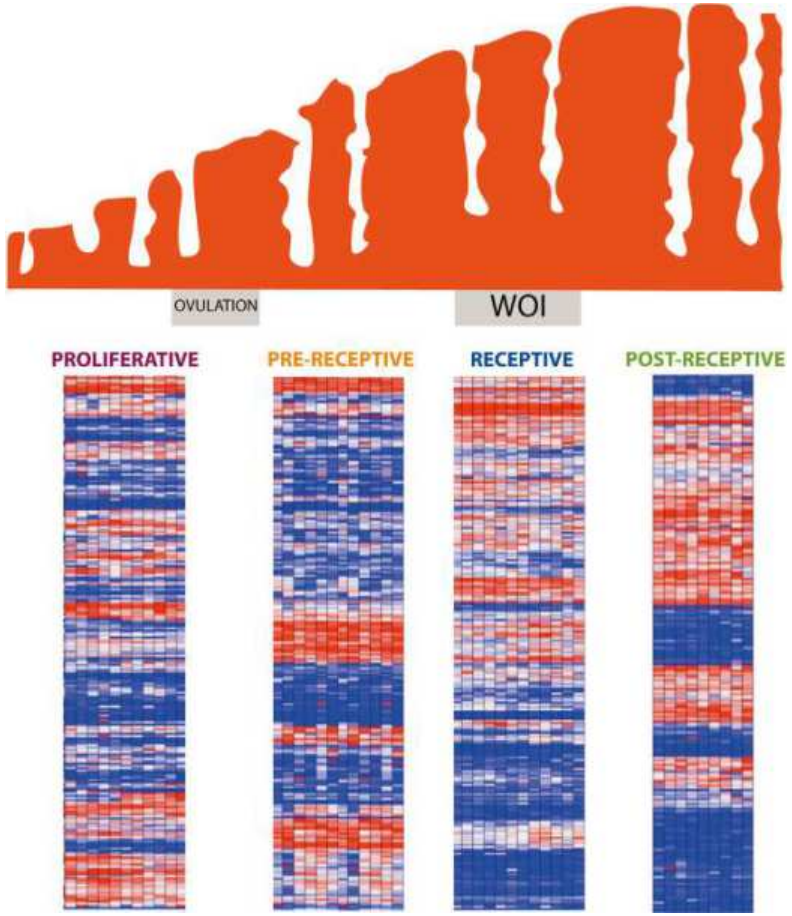


Fig. 1. Endometrial transcriptomics profile. *Evolution of endometrial tissue over time and the gene expression profile at each given stage. Heatmap showing the Endometrial Receptivity Array (ERA) gene expression profiles in each endometrial cycle stage (proliferative, pre-receptive, receptive, and post-receptive).*

COS and endometrial receptivity

- supraphysiologic levels of estradiol and progesterone during COS could lead to morphologic and biochemical modifications, and consequently impair endometrial receptivity -endometrium asynchrony

- higher levels of estradiol may lead to alterations in endometrial maturation and implantation

- in the final follicular phase, the subtle increases in progesterone levels are associated with advancements in the endometrium's ultrastructural morphology and echogenicity, and these levels seem to have a negative impact on embryo implantation

COS and endometrial receptivity

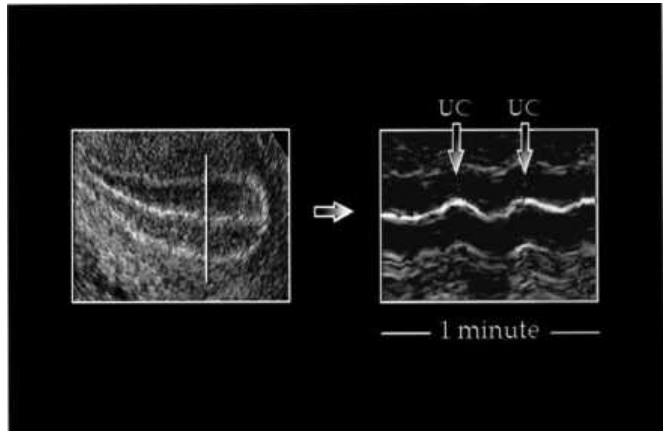
- there is no consensus regarding at what threshold a cycle becomes supraphysiologic and may lead to changes in endometrial receptivity

- hormonal changes do not seem to impact embryo quality !
- increases in progesterone levels in donors have no adverse effects on oocyte quality and in the implantation rates in recipients, corroborating the fact that progesterone levels do not impact embryo quality, but they probably influence the endometrium

- endometrial development and priming are controlled more precisely during frozen-thawed cycles when compared to COS with gonadotropins, and this could be related to better endometrial receptivity

COS and uterine contractility

- UC at the time of ET adversely affect IVF outcomes,
- supraphysiologic hormonal levels may increase these UC
- UC is much higher in stimulated cycles than in natural cycles; however, there are no studies comparing COS cycles and cycles with endometrial priming for FET.
- during FET, due the lower hormonal levels, the UC would be lower than in the fresh ET, because high concentrations of circulating E2 in IVF patients may increase these UC
- these effects of UC seems to be more important for cleavage-stage embryo transfer because the contractility decreases progressively and reaches a nearly quiescent status at the time of blastocyst transfer



IVF and OHSS – the OHSS-free clinic concept

- iatrogenic, potentially lethal, and still one of the major complications encountered during COS in IVF
- 1–14 % of ART cycles
- increased vascular permeability (VP)

IVF and OHSS – the OHSS-free clinic concept

- Human chorionic gonadotropin (hCG), either exogenous or endogenous, is the most probable triggering factor of this syndrome

- following the administration of hCG, the expression of vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGFR-2) mRNA increases significantly, rising to a maximum level that coincides with peaked VP.

- trigger of final oocyte maturation in patients with an antagonist protocol should be performed with the use of a GnRHa and via cryopreservation of all embryos – not by performing fresh ET

embro cryopreservation

- embryo cryopreservation technique has evolved and become an established, safe, and effective procedure during IVF treatments

- embryo cryopreservation was previously performed with slow-freezing methods, and in the past few years, vitrification method has become increasingly more utilized, showing excellent results with up to a 95 % survival rate of vitrified blastocysts

- improvements in cryopreservation techniques leading to absence of detrimental effects to embryo, and no consequences to offspring when compared to fresh embryos, allowed reproductive practitioners to create freeze-all policy

IVF/ICSI outcomes of fresh versus frozen-thawed ET

- better IVF outcomes when performing elective FET
- increase of 32 % in the ongoing pregnancy rate when elective FET was performed

  Fertil Steril. 2015
- three RCTs that have compared IVF outcomes of fresh ET and elective FET.

  J Assist Reprod Genet. 2010;

  Fertil Steril. 2011

  Fertil.Steril. 2011

all showed better results in the elective FET cycles.
only evaluated patients with a good prognosis.

Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis

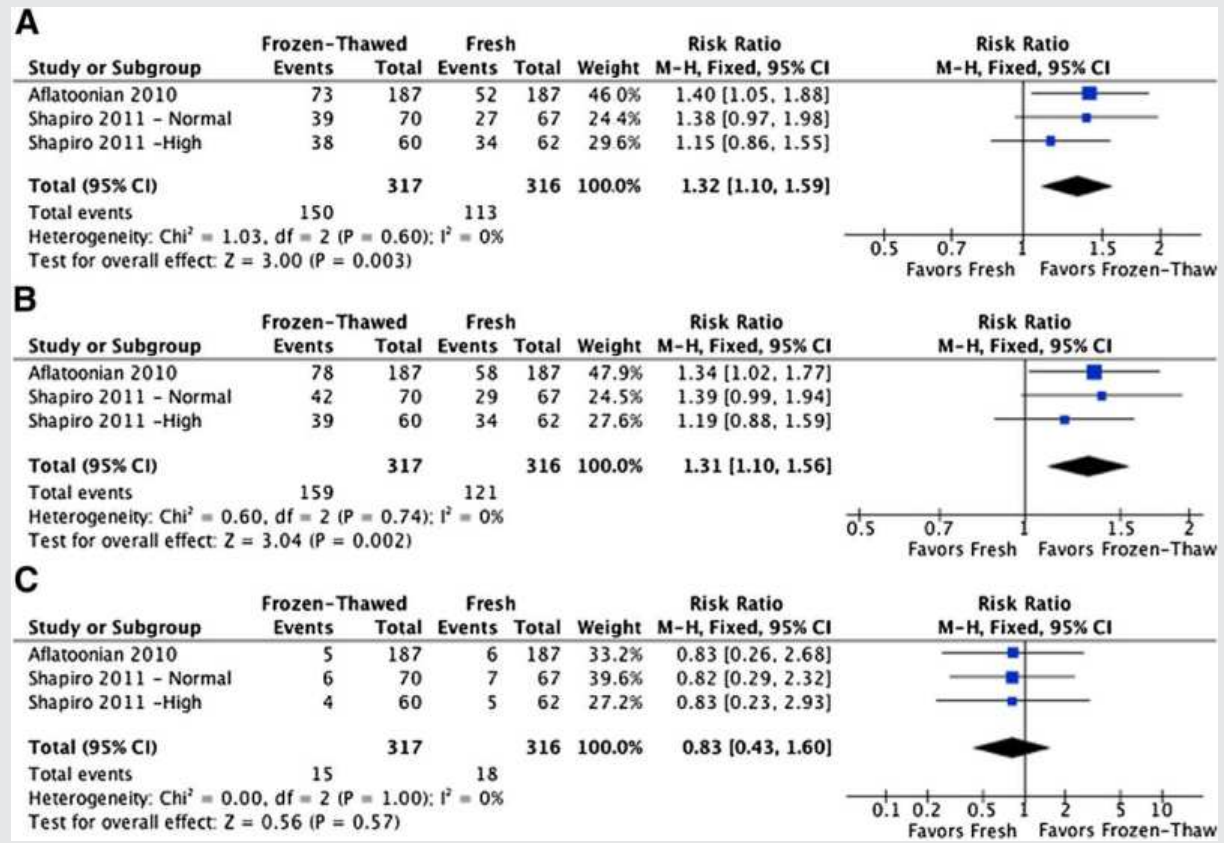
Matheus Roque, M.D.,[a,c] Karinna Lattes, M.D.,[a,d] Sandra Serra, M.Sc.,[a,d] Ivan Solà, B.Psych.,[e,f,g] Selmo Geber, Ph.D.,[c,h] Ramón Carreras, Ph.D.,[b] and Miguel Angel Checa, Ph.D.[b,d]

TABLE 1

Characteristics of the clinical trial included in the review.

Study ID	Patients (Fresh/FET)	Age, y (Fresh/FET)	Duration of trial	Day of embryo transfer	Outcome
Aflatoonian et al. (24)	374 (187/187) High responders	28.1 ± 3.5/27.3 ± 4.4	February 2007–February 2009	Day 2	Ongoing pregnancy Implantation Clinical pregnancy Miscarriage rate
Shapiro et al. (13)	137 (67/70) Normal responders	32.9 ± 3.7/33.0 ± 3.8	October 2007–October 2010	Day 5 (blastocyst)	Ongoing pregnancy Implantation Clinical pregnancy Early pregnancy loss
Shapiro et al. (25)	122 (62/60) High responders	31.4 ± 3.7/30.6 ± 3.7	July 2007–July 2010	Day 5 (blastocyst)	Ongoing pregnancy Implantation Clinical pregnancy Early pregnancy loss

Roque. Elective frozen-thawed embryo transfer. Fertil Steril 2013.



(A–C) Meta-analysis results.

Roque. Elective frozen-thawed embryo transfer. Fertil Steril 2013.

IVF/ICSI outcomes of fresh versus frozen–thawed ET

- a recent cohort study that evaluated freeze-all strategy in patients with a previous failed blastocyst transfer ➔showing an odds ratio for live births of 3.8 when using freeze-all policy instead of fresh ET

Reprod Biomed Online. 2014

- lack of higher-quality RCTs regarding freeze-all policy and its relationship to IVF outcomes, the best developmental stage for embryo cryopreservation when applying this strategy, and the best endometrial priming to perform the FET

J Assist Reprod Genet (2011) 28:575–581
DOI 10.1007/s10815-011-9551-7

ASSISTED REPRODUCTION TECHNOLOGIES

Frozen-thawed embryo transfer cycles: clinical outcomes of single and double blastocyst transfers

Inna Berin · Sarah T. McLellan · Eric A. Macklin ·
Thomas L. Toth · Diane L. Wright

J Assist Reprod Genet (2010) 27:695–700
DOI 10.1007/s10815-010-9470-z

ASSISTED REPRODUCTION TECHNOLOGIES

Comparison of early pregnancy and neonatal outcomes after frozen and fresh embryo transfer in ART cycles

Abbas Aflatoonian · Fatemeh Mansoori Moghaddam ·
Mehri Mashayekhy · Farnaz Mohamadian

J Assist Reprod Genet (2016) 33:401–412
DOI 10.1007/s10815-016-0647-y

ASSISTED REPRODUCTION TECHNOLOGIES

Reproductive outcome is optimized by genomic embryo screening, vitrification, and subsequent transfer into a prepared synchronous endometrium

Jorge Rodriguez-Purata[1] · Joseph Lee[1] · Michael Whitehouse[1] · Marlena Duke[1] ·
Lawrence Grunfeld[1,2] · Benjamin Sandler[1,2] · Alan Copperman[1,2] ·
Tanmoy Mukherjee[1,2]

human reproduction

ORIGINAL ARTICLE *Infertility*

Reproductive outcome of fresh or frozen–thawed embryo transfer is similar in high-risk patients for ovarian hyperstimulation syndrome using GnRH agonist for final oocyte maturation and intensive luteal

obstetric and perinatal outcomes from fresh ET compared to frozen–thawed ET

- no adverse neonatal outcomes were observed in children born after transfer of vitrified, as compared with fresh blastocysts

  Human Reprod 2010

- ectopic pregnancy is more frequent in pregnancies that result from IVF treatments when compared to natural pregnancies. This higher risk would be related to increased UC and supraphysiologic hormonal levels during COS

  Fertil Sterility, Shapiro2012

- COS and the supraphysiologic hormonal levels may be related to altered placentation, leading to an increased risk of pre-eclampsia, low birth weight, prematurity, small size for gestational age, antepartum hemorrhage, and perinatal death

  Fertil Sterility, Ishihara 2014,

  Human Reprod Wennerholm 2013

obstetric and perinatal outcomes from fresh ET compared to frozen–thawed ET

- risk of major congenital anomalies between children conceived after fresh ET and FET, no difference between the techniques was shown

Human Reprod Pelkonen 2014

- increased risk of macrosomia in singletons born after FET when comparing to fresh embryo transfer

Human Reprod Pinborg 2014

Human Reproduction, Vol.25, No.7 pp. 1699–1707, 2010
Advanced Access publication on May 15, 2010 doi:10.1093/humrep/deq117

human reproduction

ORIGINAL ARTICLE *Infertility*

Obstetric outcomes after transfer of vitrified blastocysts

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Perinatal outcomes after fresh versus vitrified-warmed blastocyst transfer: retrospective analysis

Kemal Ozgur, M.D.,[a] Murat Berkkanoglu, M.D.,[a] Hasan Bulut, M.D.,[a] Peter Humaidan, M.D., D.M.Sc.,[b] and Kevin Coetzee, Ph.D.[a]

[a] Antalya IVF, Özel Antalya Tüp Bebek Merkezi, Antalya, Turkey; and [b] The Fertility Clinic, Skive Regional Hospital and Faculty of Health, Aarhus University, Aarhus, Denmark

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?

A. Pinborg[1,*], A.A. Henningsen[2], A. Loft[2], S.S. Malchau[2], J. Forman[3], and A. Nyboe Andersen[2]

Slightly lower incidence of ectopic pregnancies in frozen embryo transfer cycles versus fresh in vitro fertilization-embryo transfer cycles: a retrospective cohort study

Wim Decleer, M.D.,[a] Kaan Osmanagaoglu, Ph.D.,[a] Geertrui Meganck, M.D.,[b] and Paul Devroey, Ph.D.[c]

[a] IVF Centrum, AZ Jan Palfijn Hospital, Gent; [b] Onze-Lieve-Vrouwziekenhuis, Aalst; and [c] Center for Reproductive Medicine, Dutch-speaking Free University Brussels, Brussels and AZ Jan Palfijn Hospital, Gent, Belgium

role of pre-implantation genetic screening

- PGS in the blastocyst stage with 24-chromosome screening

- higher implantation and delivery rates following the 24-chromosome screening when compared to fluorescent in-situ hybridization (FISH) PGS

Fertil Sterility Scott 2014

- use of CCS in blastocyst stage with elective single embryo transfer (eSET) is as effective as double-embryo transfer of unscreened embryos and dramatically reduce the risk of twins

Fertil Sterility Forman 2013

role of pre-implantation genetic screening

- unclear if the screened embryo transfer results in better outcomes when performed in fresh or FET cycles ??

- sometimes it is not possible to obtain the screening result within the implantation window !

- embryos that the biopsy needs to be performed on day 6 are not eligible for fresh embryo transfer due to an asynchrony between embryo and endometrium.

it is necessary to perform the cryopreservation of all embryos and a posterior frozen-thawed embryo transfer

Fertil Steriliy Rubio 2013

costs

- studies concerning cost-effectiveness of elective FET when compared to fresh ET ???

Human Reproduction, Vol.24, No.7 pp. 1632–1639, 2009
Advanced Access publication on March 24, 2009 doi:10.1093/humrep/dep042

human reproduction ORIGINAL ARTICLE *Infertility*

Elective single embryo transfer with cryopreservation improves the outcome and diminishes the costs of IVF/ICSI

Zdravka Veleva[1], Petri Karinen[2], Candido Tomás[3], Juha S. Tapanainen[1], and Hannu Martikainen[1,4]

BACKGROUND: Although elective single embryo transfer (eSET) minimizes the multiple birth rate after *in vitro* fertilization (IVF)/intra cytoplasmic sperm injection (ICSI), there remain concerns in many countries that it is less effective and more expensive than conventional double embryo transfer (DET).

METHODS: We compared the clinical outcome achieved in the years 1995–1999, in which eSET was rarely used (4.2% of women, DET period) with that of the years 2000–2004, in which eSET was more widely used (46.2%, eSET period). In the DET period, 826 women had 1359 fresh embryo cycles followed by 589 frozen–thawed embryo transfer (FET) cycles. In the eSET period, 684 women had 1027 fresh and 683 FET cycles. The cumulative term live birth rate/woman was the primary clinical outcome measure. An incremental cost-effectiveness ratio of a term live birth was also calculated based on hospital charges and medication prices of IVF/ICSI treatment.

RESULTS: The cumulative pregnancy rate/oocytes pickup (38.2 versus 33.1%, $P = 0.01$), cumulative live birth rate/oocytes pickup (28.0 versus 22.5%, $P = 0.002$) and cumulative live birth rate/woman (41.7 versus 36.6%, $P = 0.04$) were all higher in the eSET period than in the DET period. The cumulative multiple birth rate was significantly lower in the eSET period than in the DET period (8.9 versus 19.6%, $P < 0.0001$). A term live birth in the eSET period was 19 889 euros less expensive than in the DET period.

CONCLUSIONS: This study shows that eSET with cryopreservation is more effective and less expensive than DET and should be adopted as a treatment of choice.

Key words: *in vitro* fertilization / multiple pregnancy / elective single embryo transfer / cost-effectiveness

Are we ready to eliminate the transfer of fresh embryos in in vitro fertilization?

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informa
healthcare

ORIGINAL ARTICLE

To freeze or not to freeze embryos: clarity, confusion and conflict

MOHAR GOSWAMI[1], ALISON P. MURDOCH[1] & ERICA HAIMES[2]

J Assist Reprod Genet (2015) 32:171–176
DOI 10.1007/s10815-014-0391-0

COMMENTARY

Freeze-all policy: is it time for that?

Matheus Roque

results

- Improvements in vitrification now make frozen embryo transfers (FETs) a viable alternative to fresh embryo transfer,

- with reports from observational studies and randomized controlled trials suggesting that:

(i) the endometrium in stimulated cycles is not optimally prepared for implantation;

(ii) pregnancy rates are increased following FET

(iii) perinatal outcomes are less affected after FET.

discussion

- better IVF outcomes when adopting the freeze-all policy instead of fresh ET (consequences associated with COS on endometrial receptivity)
- more important than the pregnancy and implantation rates is the safety of the ART procedures
- freeze-all policy may decrease the risks of OHSS development, as well as obstetric and perinatal morbidity and mortality
- **more research and RCTs are necessary to establish a change in the routine policy regarding embryo transfer**
- **personalized approach should be followed to decide on fresh or frozen embryo transfer as in the other stages of IVF treatment !**