TO BLAST

OR

NOT TO BLAST?

BY PRINCE OWUSU-MENSAH

TEMA WOMENS HOSPITAL

Introduction

- Since the early days after the first successful IVF cycle in 1978 (Steptoe and Edwards, 1978), various attempts including improvement in culture media and transfer high quality embryos at different developmental stages have been made to increase success.

- Laboratories made their own culture media, but now it is commercially produced, resulting in improved consistency and quality control between different laboratories and practices.

- It's been over 4 decades and optimal developmental stage of ET is still a subject of debate.

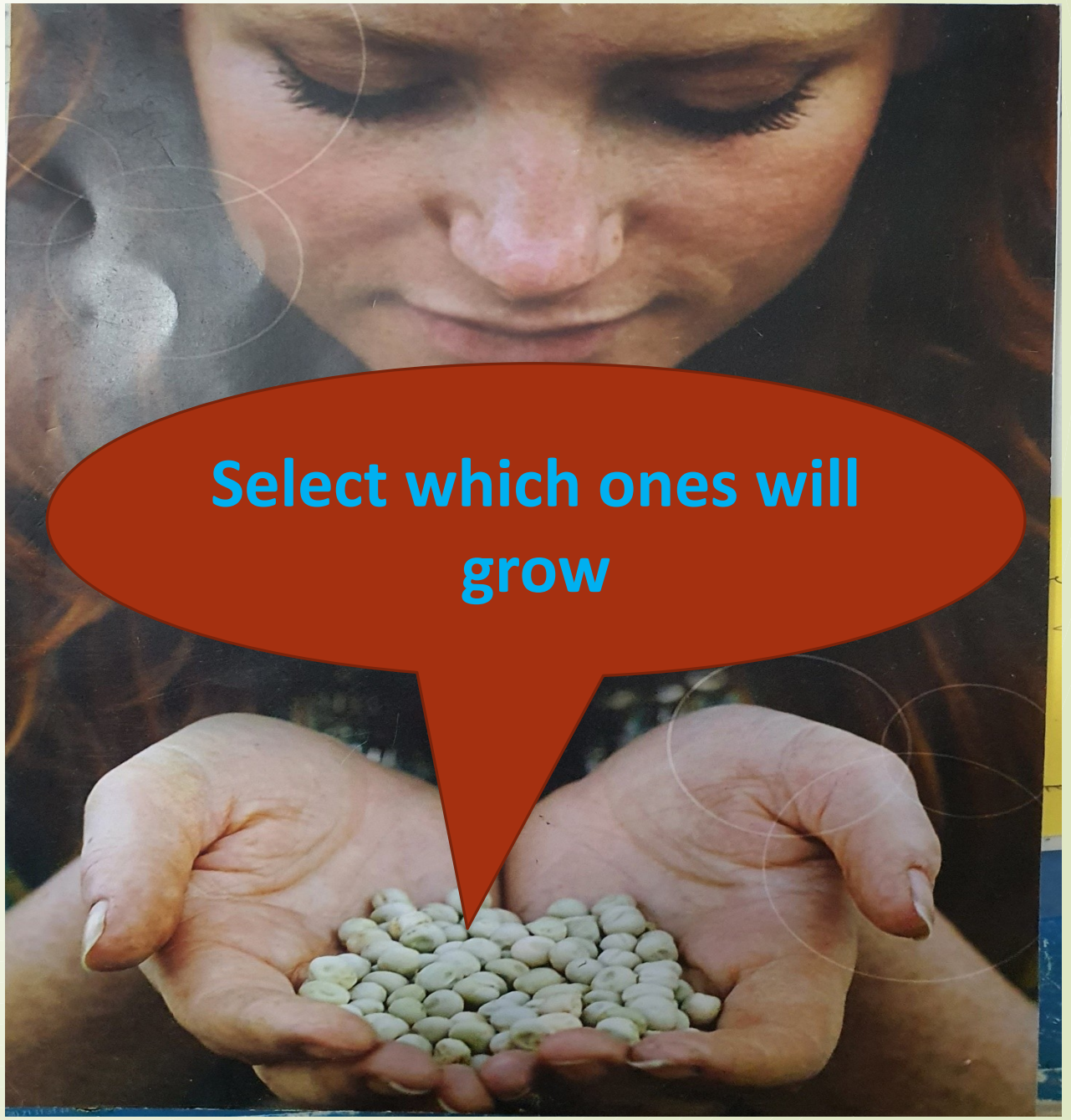
- Improvement in culture media (Racowsky et al 2015; Nastri et al, 2016; Sfontouris et al., 2016) and eSET have increased the popularity of blastocyst transfer.

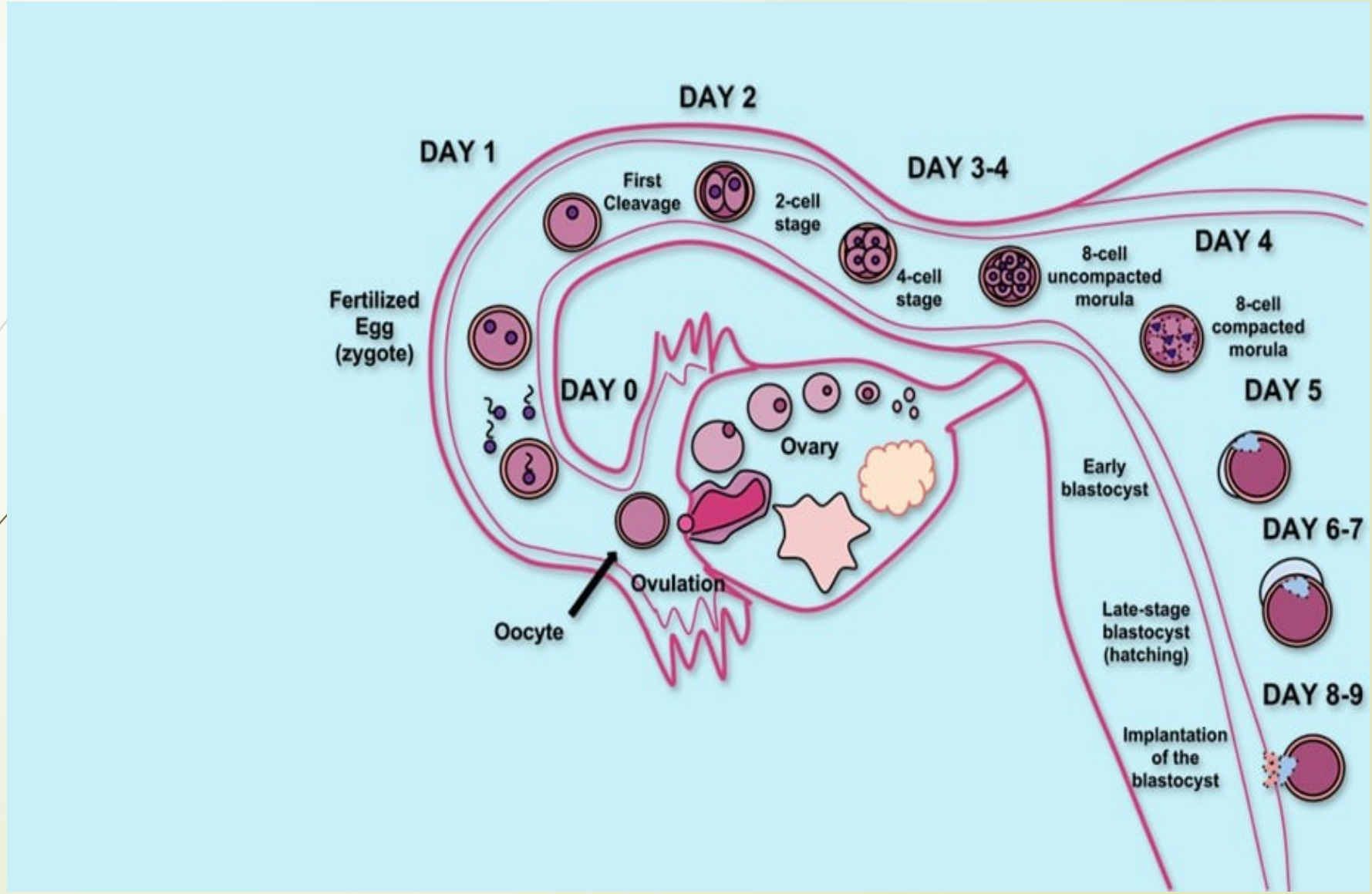
Introduction cont.

- Embryo transfer in IVF is typically performed either at the cleavage stage (days 2/3) after fertilization, or at blastocyst stage (days 5/6).

- Improvements in embryo culture over the years have allowed us to extend *in vitro* culture of embryos to the blastocyst stage, permitting detailed morphologic assessment of embryos and better selection of embryos for transfer.

- Extended culture has also allowed us to perform genetic testing of embryos, a process that is best applied when the embryos are far enough developed in culture to sustain removal of several cells for genetic testing.


Select which ones will grow


DAY 2
DAY 1
First Cleavage
2-cell stage
DAY 3-4
4-cell stage
8-cell uncompacted morula
DAY 4
8-cell compacted morula
Fertilized Egg (zygote)
DAY 0
Ovary
DAY 5
Early blastocyst
DAY 6-7
Ovulation
Oocyte
Late-stage blastocyst (hatching)
DAY 8-9
Implantation of the blastocyst

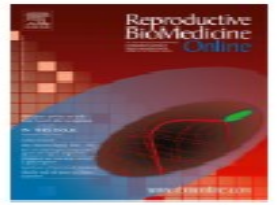
TO BLAST ?
WHY NOT?

ARTICLE IN PRESS

Reproductive BioMedicine Online (2015) ■■, ■■–■■

ELSEVIER

www.sciencedirect.com
www.rbmonline.com



COMMENTARY

Should we be promoting embryo transfer at blastocyst stage?

Abha Maheshwari [a,*], Mark Hamilton [a], Siladitya Bhattacharya [b]

Improved laboratory standards and advancement in culture media have made extended culture to blastocyst a reality.(Gardner et al., 1998)

Benefits/Reasons of blastocyst transfer

First pregnancy and live birth from blastocyst (day 5, Cohen et al., 1985) and day 6(Bolton et al., 1991)

- The rationale for blastocyst culture is to improve both uterine and embryonic synchronicity and thus resulting in higher implantation rates.
- It is more physiological as embryos are placed in the uterine cavity at the stage similar to that in nature.
- Extended culture to blastocyst allows improved embryo selection (natural selection) for transfer, hence increase in implantation and pregnancy rate.

To Blast cont.

- PGD/PGS
- Replacement of fewer embryos
- Reduced high order multiple gestation
- Day 3 embryos may experience stress in its environment (Glujovsky & Farquhar, 2016).
- Day 3 embryos have a higher aneuploidy rate and get arrested.
- Uterine env’t likely to favour blastocyst transfer (fanchin et al 2012)

MORPHOLOGICAL PARAMETERS OF EARLY CLEAVAGE EMBRYO

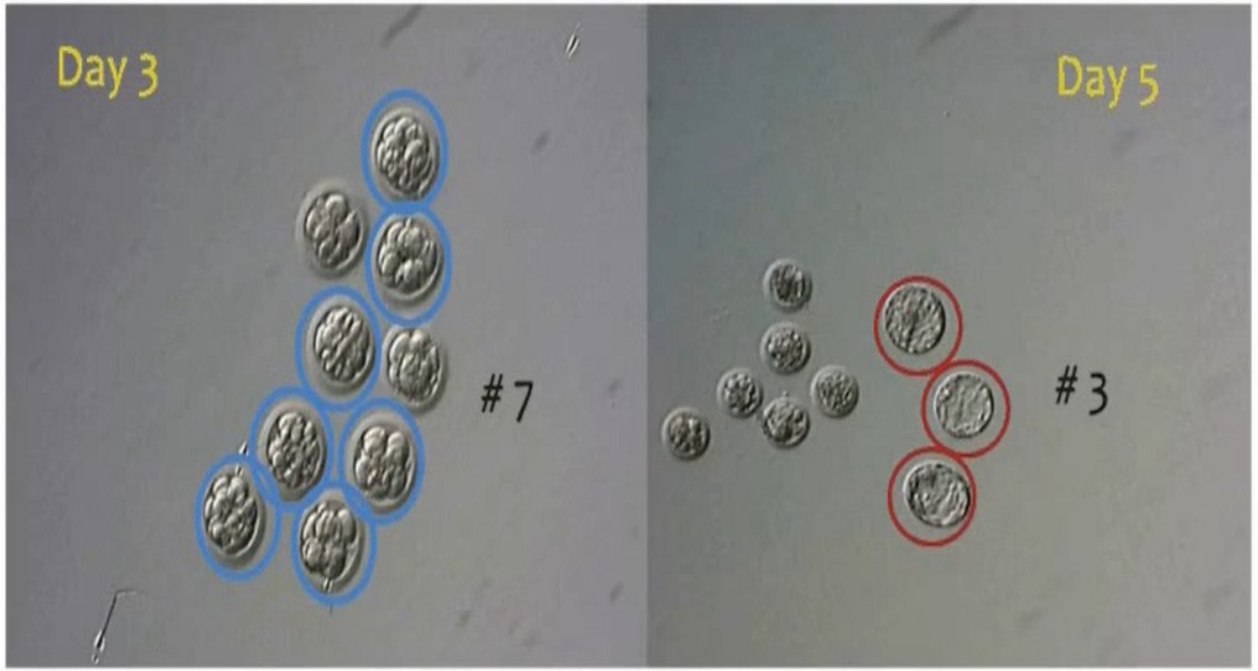
- Pronucler(PN) scoring
- Degree of fragmentation
- Symmetry
- Cell size/ number
- Multinucleation etc
- Morphology score of cleavage embryo cannot predictive accurately the developmental potential(Graham et al., 2000, Guerif et al., 2007, Rijnders &Jansen, 1998; Skiadas &Racowsky, 2007 and cannot predict pregnancy rates (Lemmen et al., 2008).

- Morphology is not a good predictor of blastocyst formation—50% of good quality day 3 embryos will become blastocysts but so will 20% of poor quality embryos (Rijnders and Jansen, 1998)

Studies have demonstrated:

Limited predictive value of day 3 embryo morphology for blastocyst

(Rijnders & Jansen, 1998; Graham et al., 2000; Racowsky et al., 2000; Milki et al., 2002; Zech et al., 2006



50% of morphologically **top quality** embryos at cleavage stage **did not reach** the blastocyst stage

Important to remember if we want to transfer ONE embryo

«**Blastocyst transfer represent the strictest form of embryo selection**» (Boiso et al., 2002)

Reproductive BioMedicine Online (2014) 28, 424–435

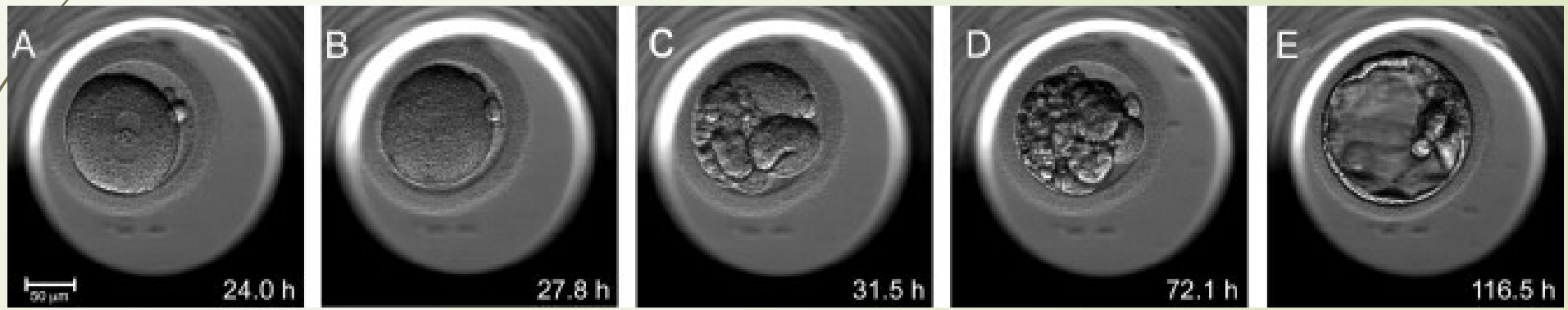
www.sciencedirect.com
www.rbmonline.com

ARTICLE

Transfer of blastocysts with deviant morphological and morphokinetic parameters at early stages of in-vitro development: a case series

Astrid Stecher [a,*], Pierre Vanderzwalmen [a,b], Martin Zintz [a], Barbara Wirleitner [a], Maximilian Schuff [a], Dietmar Spitzer [c], Nicolas H Zech [a]

[a] IVF Centers Prof. Zech-Bregenz, Austria; [b] Centre Hospitalier Inter Régional Edith Cavell (CHIREC), Braine-l'Alleud, Brussels, Belgium; [c] IVF Centers Prof. Zech-Salzburg, Austria
* Corresponding author. E-mail address: a.stecher@ivf.at (A Stecher).



Direct cleavage from 1 to 3 cells (A–C), high degree of fragmentation on day 3 (D) and outcome on day 5 (E).Transfer and outcome of healthy baby.(Stecher et al., 2008)

Springer | JARG | Journal of Assisted Reproduction and Genetics
springer.com | This journal | Toc Alerts | Submit Online | Open Choice

J Assist Reprod Genet. 2013 Aug; 30(8): 1035–1042.
Published online 2013 Jul 10. doi: 10.1007/s10815-013-0037-7
PMCID: PMC3790109
PMID: 23838796

Vitrification of blastocysts derived from fair to poor quality cleavage stage embryos can produce high pregnancy rates after warming

Chloë Shaw-Jackson,✉ Evelyne Bertrand, Bénédicte Becker, Jérôme Colin, Caroline Beaudoin-Chabot, Serge Rozenberg, and Candice Autin

>20% fragmentation

Slow cleaving embryos(3-6 cells)

Fast cleaving day 2 embryos(> 6 cells)

Embryos with strong granularity

Vacuoles

Zona anomalies

Uneven blastomeres

Clinical outcome after transfer of vitrified day 3 or day 5 embryos

Shaw-Jackson et al., 2013

Blastocysts derived from day 3

	low quality: Blastocyst (D5/6)		top quality: Cleavage stage (D3)	
	n	%	n	%
Warming cycles:	50		213	
Patients:	46		151	
Mean patients age±SD (years):	33.7±4.0		33.2±5.0	
Warmed embryos:	63		373	
Transferred embryos	46		336	
Mean embryos TF/cycle±SD:	1.2±0.4		1.6±0.6	
Lost embryos:	1	1.6 %	16	4.3 %
Survival:	47	75.8 %	345	96.6 %
Transfers:	39	78.0 %	204	96.0 %
Positive βHCG/Transfer:	22	56.0 %	62	30.4 %
CP/Transfer:	17	43.6 %	47	23.0 %
IR:	18	39.1 %	52	15.5 %
TFs with live births:	10	25.6 %	30	13.7 %
Cycles with live births:	10	20.0 %		
Babies born:	10		30[a]	
Ongoing pregnancies:	1		2	

Reduced Ectopic Pregnancy Rate on Day 5 Embryo Transfer Compared with Day 3: A Meta-Analysis

Bingqian Zhang, Linlin Cui, Rong Tang, Lingling Ding, Lei Yan, Zi-Jiang Chen

Published: January 25, 2017 • https://doi.org/10.1371/journal.pone.0169837

The present study suggested that D5-ET can reduce the EP rate compared with D3-ET in IVF/ICSI cycles, no matter fresh or frozen-thawed embryo transfer was performed. D5-ET may be a better choice for decreased EP risk in ART treatment.

Human Reproduction, Vol.30, No.9 pp. 2048–2054, 2015
Advanced Access publication on July 22, 2015 doi:10.1093/humrep/dev168

human reproduction

ORIGINAL ARTICLE *Early pregnancy*

Risk of ectopic pregnancy lowest with transfer of single frozen blastocyst

Z. Li[1,2,3], E.A. Sullivan[1,2], M. Chapman[2], C. Farquhar[4], and Y.A. Wang[1,2,*]

[1]Faculty of Health, University of Technology Sydney, Sydney 2007, Australia [2]School of Women's and Children's Health, The University of New South Wales, Sydney 2031, Australia [3]Sydney Medical School, The University of Sydney, Sydney 2006, Australia [4]Department of Obstetrics and Gynaecology, University of Auckland, Auckland 1142, New Zealand

*Correspondence address. Faculty of Health, University of Technology Sydney, PO Box 123, Broadway, NSW 2007, Australia. Tel: +61-2-9514-4578; Fax: +61-2-9514-4917; E-mail: alex.wang@uts.edu.au

Submitted on March 17, 2015; resubmitted on May 18, 2015; accepted on June 12, 2015

" the highest ectopic pregnancy rate was for pregnanciesfrom transfers of freash cleavage embryos followed by transfers of frozen cleavage embryo, transfers of fresh blastocyst and transfers of frozen blastocyst". (Sullivan et al., 2015)

AJOG American Journal of Obstetrics & Gynecology

RESEARCH REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY | VOLUME 211, ISSUE 2, P165.E1-165.E7, AUGUST 01, 2014

Extended embryo culture is not associated with increased adverse obstetric or perinatal outcome

Galia Oron, MD • Tamar Sokal-Arnon, MD • Weon-Young Son, PhD • ... Atef Zeadna, MD • Hananel Holzer, MD • Togas Tulandi, MD, MHCM • Show all authors

Published: March 13, 2014 • DOI: https://doi.org/10.1016/j.ajog.2014.03.018

Live births resulting from extended embryo culture and a single blastocyst transfer are not associated with increased adverse obstetric and perinatal outcome compared to live births from a single cleavage embryo transfer in women ≤40 years old.

Publication of Indian Society of Assisted Reproduction
Journal of Human Reproductive Sciences
Home
Current issue
Instructions
Submit article

J Hum Reprod Sci. 2017 Jul-Sep; 10(3): 201–207.
doi: 10.4103/jhrs.JHRS_130_16
PMCID: PMC5672726
PMID: 29142449

Single Blastocyst Transfer: The Key to Reduce Multiple Pregnancy Rates Without Compromising the Live Birth Rate

Uma M. Sundhararaj, Monali V. Madne, Reeta Biliangady, Sumana Gurunath, Ambika G. Swamy, and Indu S.T. Gopal

Single blastocyst transfer is an effective method to reduce the risk of multiple births without compromising the pregnancy outcomes. Given the promising potential of vitrification; the remaining blastocyst can be cryopreserved.

Sundhararai et al 2017

Extended embryo culture can be used both poor and good prognosis .

Poor or absent embryo development after 3 days of culture provides information about embryo quality that may prove useful in planning future treatment cycles.

Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology

Demián Glujovsky, Cindy Farquhar, Andrea Marta Quinteiro Retamar, Cristian Roberto Alvarez Sedo, Deborah Blake

Authors' declarations of interest

Version published: 30 June 2016 Version history

https://doi.org/10.1002/14651858.CD002118.pub5

There is low quality evidence that blastocyst stage transfer is associated with higher rates of live birth and clinical pregnancy than cleavage stage transfer.(Glujovsky et al 2016)

Live birth rates after transfer of equal number of blastocysts or cleavage-stage embryos in IVF. A systematic review and meta-analysis

FREE

Evangelos G. Papanikolaou ✉, Efstratios M. Kolibianakis, Herman Tournaye, Christos A Venetis, Human Fatemi, Basil Tarlatzis, Paul Devroey

Human Reproduction, Volume 23, Issue 1, January 2008, Pages 91–99, https://doi.org/10.1093/humrep/dem339

A systemic review and meta-analysis that reviewed 1654 patient showed a significantly higher CPR and LBR after blastocyst transfer compared to cleavage-stage transfer when equal number of embryos are transferred. Papanikolaou et al., 2008

Similar results were confirmed by Martin et al., 2017

NOT TO BLAST?
WHY NOT?

Benefits/Reasons of cleavage stage embryo transfer

The first IVF pregnancy was achieved after transfer of day 2 embryos (Steptoe and Edwards 1978)

- **Extended culture decreases the number of usable embryos(ET/frozen) and concerns of safety whether any harm is caused with extended culture beyond embryo genomic activation (Glujovsky et al., 2016)**

- **Longer duration of embryo culture regarding fetal safety such as increased preterm birth(PTB) and birth defects has also been raised (Maheshwari et al., 2013; Dar et al.,2014).**

Cleavage stage cont.

- Cleavage-stage transfer is associated with greater numbers of embryos available for freezing.
- Blastocyst transfer is associated with increased number of cycles with no embryos to transfer
- Cumulative pregnancy rate may be high.
- To some researchers cleavage transfer is a pshychological one.

Ultrasound Obstet Gynecol 2017; **49**: 583–591
Published online 10 April 2017 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17327

Blastocyst *vs* cleavage-stage embryo transfer: systematic review and meta-analysis of reproductive outcomes

W. P. MARTINS[1,2], C. O. NASTRI[1], L. RIENZI[3], S. Z. VAN DER POEL[4,5], C. GRACIA[6] and C. RACOWSKY[7]

[1]*SEMEAR Fertilidade, Reproductive Medicine, Ribeirão Preto, Brazil;* [2]*Department of Obstetrics and Gynecology, Ribeirão Preto Medical School, University of Sao Paulo, Ribeirão Preto, Brazil;* [3]*GENERA Centre for Reproductive Medicine, Clinica Valle Giulia, Rome, Italy;* [4]*HRP (the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction), Geneva, Switzerland;* [5]*Population Council, Reproductive Health Program, New York, NY, USA;* [6]*Division of Reproductive Endocrinology, University of Pennsylvania, Philadelphia, PA, USA;* [7]*Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

No superiority of blastocyst transfer compared with cleavage-stage embryo transfer in clinical assisted reproductive techniques:(Martins et al .2017)

human reproduction ORIGINAL ARTICLE *Infertility*

Obstetrical and perinatal outcomes following blastocyst transfer compared to cleavage transfer: a systematic review and meta-analysis

W.P. Martins[1], C.O. Nastri[2], L. Rienzi[3], S.Z. van der Poel[4], C.R. Gracia[5], and C. Racowsky[6,*]

[1]Department of Obstetrics and Gynecology, Ribeirao Preto Medical School, University of Sao Paulo, Av. Bandeirantes, 3900 - Monte Alegre, Ribeirao Preto - SP, 14049-900, Brazil [2]SMEAR fertilidade, Reproductive Medicine, Av. Aurea Aparecida Bragheto Machado, 220 - City Ribeirao, Ribeirao Preto - SP, 14021-570, Brazil [3]GENERA Centre for Reproductive Medicine, Clinica Valle Giulia, via de Notaris 2b, Rome, Italy [4]HRP (UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction), Avenue Appia 20, 1211 Geneva, Switzerland (at the time of the study); Population Council, Reproductive Health Programme, Center for Biomedical Research, 1230 York Ave, New York, NY 10065, USA [5]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Pennsylvania, 3701 Market Street, Suite 800, Philadelphia, PA 19104, USA [6]Division of Reproductive Medicine, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

*Correspondence address. Division of Reproductive Medicine, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA. Tel: +1-617-732-5570; Fax: +1-617-975-0825. E-mail: cracowsky@partners.org

The results of this meta-analysis suggest no significant difference regarding the incidence of birth defects or LBW between blastocyst and cleavage stage transfers.(Martins et al., 2017)

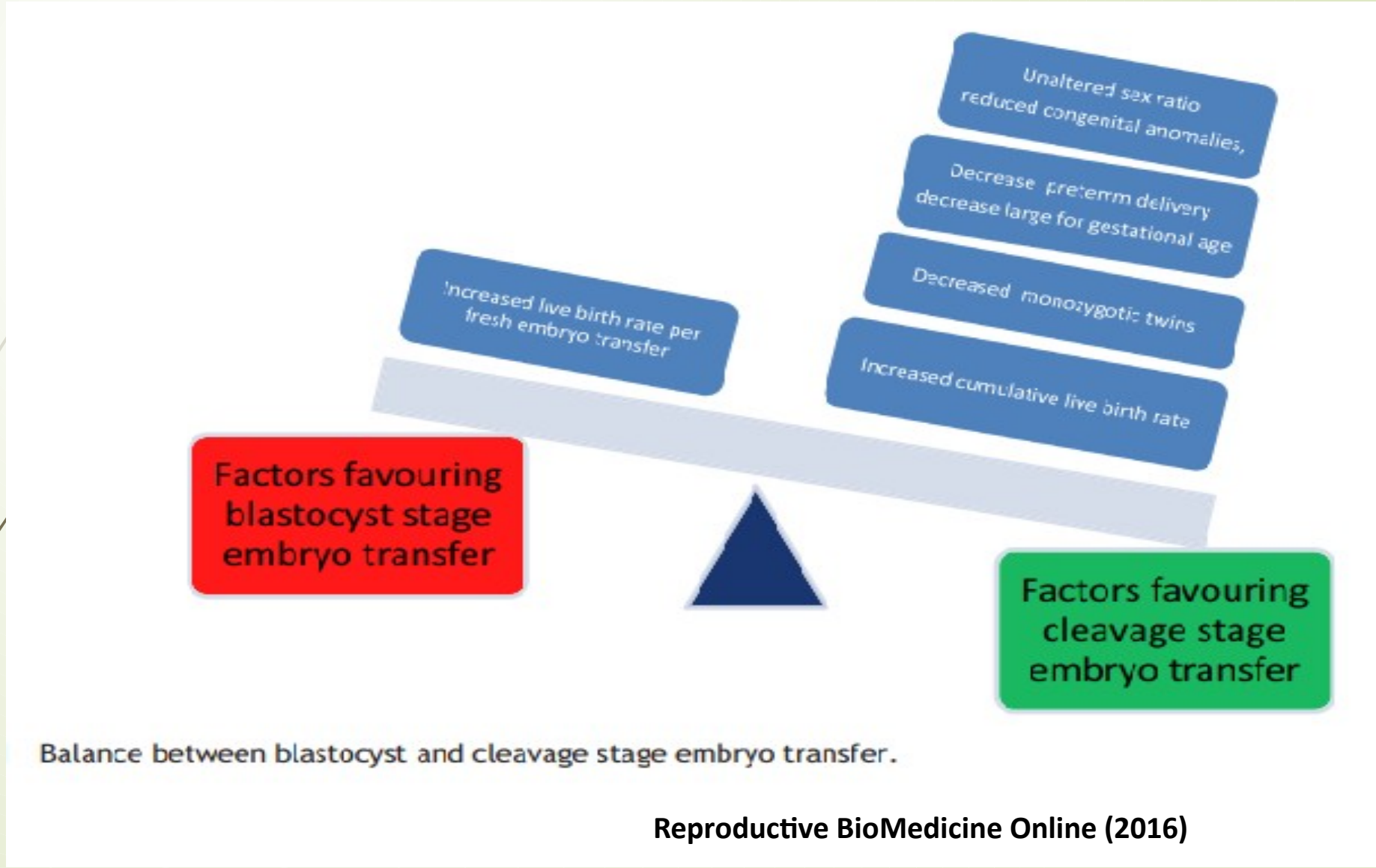
Extended culture is associated with preterm delivery, even in singletons. Blastocyst transfer is more likely to result in twins, the strongest determinant of perinatal morbidity, highlighting the importance of single embryo transfer in select patients. (Kansal kalra 2010)

Neonatal outcomes among singleton births after blastocyst versus cleavage stage embryo transfer: a systematic review and meta-analysis

S. Dar, T. Lazer, P.S. Shah, C.L. Librach

Human Reproduction Update, Volume 20, Issue 3, May/June 2014, Pages 439–448,
https://doi.org/10.1093/humupd/dmu001

Risk of PTB in IVF singleton pregnancies is significantly higher following blastocyst transfer compared with cleavage stage transfer.(Dar et al., 2014)



Balance between blastocyst and cleavage stage embryo transfer.

Reproductive BioMedicine Online (2016)

SUMMARY

- Performing blastocyst transfer have benefits associated with satisfactory pregnancy rates
- The assessment of embryo morphology at day 3 has limited predictive value for subsequent developmental process.
- The maintenance of embryo culture until day 5 may be a more sensible approach for the correct identification of best quality embryos with the highest probability of success for implantation.

CONCLUSION

- The debate is still ongoing , but whether blastocyst or cleavge embryo transfer , the aim of ART (i.e to achieve a healthy live baby with potential of developing a healthy adult) should be weighed against any potential outcome.

- Effectiveness and safety should be weighed to permit evidence-based decisions in clinical practice.

Thank you