



Repercussões das TRA na Gestante e no Concepto

Edson Borges Jr.



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TRATAMENTOS

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CONTATO ▾

<http://fertility.com.br/producao-cientifica-2016/>

- ❖ USA: 1%
- ❖ Europa: 3%
- ❖ Dinamarca - Finlândia: 6%



- ❖ Brasil: 25 - 30.000 ciclos FIV/ICSI / ano
- ❖ ~ 6.000 cças nascidas

~ 0,2% % cças nascidas Brasil

Questionamentos das gestações e crianças nascidas por TRA

Morbidade da gestação múltipla

Desfechos pré / periconcepcionais

Malformações congênicas

Embriões frescos x criopreservados

Morbidade da gestação múltipla



Gravidez Múltipla risco relativo (RR)

- **Gêmeos:**

natimorto: RR 2

paralisia cerebral: RR 5

- **Trigêmeos**

natimorto: RR 7

paralisia cerebral: RR 18

Smith and Fretts. Lancet 2007, 370 (9600): 1715-1725
Pharoah PO. Clin Perinatol 2006, 33(2): 301-313

Gêmeos idênticos (monozigóticos)

- após gestação espontânea:
0,45%
- após TRA:
1,5 – 4,5%



Monozygotic twinning, cerebral palsy and congenital anomalies

P.O.D. Pharoah^{1,4} and Y. Dunder²

Paralisia Cerebral e Anomalias Congêntas
compartilham o mesmo mecanismo etiológico e estão diretamente relacionadas à gravidez monocoriônica)

- ➔ maior incidência de anomalias congêntas e paralisia cerebral em gêmeos
- ➔ “vanish twin”: aumento 40-50X paralisia cerebral no feto sobrevivente

**Risco relacionado com prematuridade / baixo peso
Risco aumentado para o feto sobrevivente (“vanish twim”)**

Desfechos pré/perinatais



TRA: desfechos obstétricos e perinatais

Desfecho	Efeito global: RR (IC-95%)
Hemorragia anteparto	2,49 (2,30 a 2,69)
Anomalias congênitas	1,67 (1,33 a 2,09)
Hipertensão	1,49 (1,39 a 1,59)
Ruptura prematura de membranas	1,16 (1,07 a 1,26)
Cesariana	1,56 (1,51 a 1,60)
Peso ao nascer < 2.500 g	1,65 (1,56 a 1,75)
Peso ao nascer < 1.500 g	1,93 (1,72 a 2,17)
Mortalidade perinatal	1,87 (1,49 a 2,37)
Nascimento antes de 37 semanas	1,54 (1,47 a 1,62)
Nascimento antes de 32 semanas	1,68 (1,48 a 1,91)
Transferência para UTI neonatal	1,58 (1,42 a 1,77)
Diabetes gestacional	1,48 (1,33 a 1,66)
Indução do parto	1,18 (1,10 a 1,28)
Pequeno para idade gestacional	1,39 (1,27 a 1,53)

Pandey S, et al. *Hum Reprod Update*. 2012 Sep-Oct;18(5):485-503.

Perinatal outcomes associated with assisted reproductive technology: the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART)

Fertility and Sterility® Vol. 103, No. 4, April 2015

Eugene Declercq, Ph.D.,^a Barbara Luke, Sc.D., M.P.H.,^b Candice Belanoff, Sc.D.,^a Howard Cabral, Ph.D.,^a Hafsatou Diop, M.D.,^c Daksha Gopal, M.P.H.,^a Lan Hoang, M.P.H.,^a Milton Kotelchuck, Ph.D.,^d Judy E. Stern, Ph.D.,^e and Mark D. Hornstein, M.D.^f

- 334.628 nascimentos e mortes fetais, 2004-2008
- 3 grupos:
- TRA: 11.271, subférteis: 6.609, férteis: 316.748

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- TRA gest única x subférteis: > pré-termo e baixo peso (AOR=1,23 – 1,26, respectivamente)
- TRA e subférteis x férteis: > pré-termo e baixo peso
- TRA gêmeos: < morte perinatal x subférteis e férteis (AOR= 0,55 – 0,15, respectivamente)

Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis

A. Pinborg^{1,*}, U.B. Wennerholm², L.B. Romundstad³, A. Loft¹,
K. Aittomaki⁴, V. Söderström-Anttila⁵, K.G. Nygren⁶, J. Hazekamp⁷,
and C. Bergh⁸


- ***Critérios de nascimentos pré-termo (PT)***
1982 – 2012, PUBMED, Cochrane, 65 trabalhos
- Fértéis x subfértéis (CE e TOG > 1 ano) (AOR= 1,35)
- FIV/ICSI x subfértéis (AOR= 1,55)
- IO/IIU x fértéis (AOR= 1,45)
- *Vanishing co-twin* x gestações únicas (AOR= 1,73)

Perinatal outcome of singleton siblings born after assisted reproductive technology and spontaneous conception: Danish national sibling-cohort study

Fertility and Sterility® Vol. 95, No. 3, March 1, 2011

959

*Anna-Karina Aaris Henningsen, M.D.,^a Anja Pinborg, M.D.Sc.,^a Øjvind Lidegaard, M.D.Sc.,^b
Christina Vestergaard, M.P.H.,^b Julie Lyng Forman, M.Sc., Ph.D.,^c and Anders Nyboe Andersen, M.D.Sc.^a*

Setting: Denmark, from 1994 to 2008. 

Patient(s): Pairs of siblings (13,692 pairs; n = 27,384 children) conceived after IVF, intracytoplasmic sperm injection (ICSI), frozen embryo replacement (FER), or spontaneous conception subcategorized into five groups according to succession: [1] IVF-ICSI vs. spontaneous conception (n = 7,758), [2] IVF-ICSI vs. FER (n = 716), [3] FER vs. FER (n = 34), [4] IVF-ICSI vs. IVF-ICSI (n = 2,876), and [5] spontaneous conception vs. spontaneous conception (n = 16,000).

- Ccas TRA (todos os tipos de tratamento) 65 g mais leves x pares Gestação Natural
- Ccas Embriões Descong 165 g mais pesadas x pares Embriões Frescos
- ICSI/FIV x Gestação Natural: maior risco de baixo peso (OR= 1,4) e pré-termo (OR= 1,3)

Assisted reproductive technology and perinatal outcomes: conventional versus discordant-sibling design

Nafeesa N. Dhalwani, Ph.D.,^{a,b,c} Sheree L. Boulet, Dr.P.H.,^a Dmitry M. Kissin, M.D.,^a Yujia Zhang, Ph.D.,^a Patricia McKane, M.P.H.,^d Marie A. Bailey, M.S.W.,^e Maria-Elena Hood, M.P.H.,^f and Laila J. Tata, Ph.D.^b

TABLE 4

Association among ART and low birth weight, preterm birth, low Apgar score, and SGA.

Type of analysis	ART group, n (%)	Non-ART group, n (%)	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Conventional analysis	n = 32,762	n = 3,863,480				
Low birth weight	2,762 (8.4)	230,048 (6.0)	1.46 (1.40, 1.51)	< .001	1.38 (1.32, 1.43)	< .001 ^a
Preterm birth	3,813 (11.6)	307,327 (8.0)	1.52 (1.47, 1.58)	< .001	1.51 (1.46, 1.56)	< .001 ^b
Low Apgar (<7)	424 (1.3)	45,599 (1.2)	1.09 (0.99, 1.21)	.059	0.99 (0.90, 1.09)	.888 ^c
SGA ^d	593 (1.8)	67,350 (1.7)	1.04 (0.96, 1.13)	.316	1.11 (1.03, 1.21)	.01 ^b
Discordant-sibling pair analysis^e	n = 6,458	n = 6,458				
Low birth weight	436 (6.8)	314 (4.9)	1.41 (1.24, 1.62)	< .001	1.33 (1.13, 1.56)	< .001 ^a
Preterm birth	627 (9.7)	516 (7.9)	1.24 (1.11, 1.38)	.001	1.20 (1.07, 1.34)	.002 ^b
Low Apgar (<7)	64 (1.0)	84 (1.3)	0.76 (0.55, 1.06)	.101	0.75 (0.54, 1.05)	.096 ^c
SGA ^d	94 (1.4)	75 (1.2)	1.25 (0.93, 1.69)	.132	1.22 (0.88, 1.68)	.237 ^b

^a Adjusted for maternal age, year of birth, parity, infant's sex, gestational age, and time since last recorded delivery.

^b Adjusted for maternal age, year of birth, parity, infant's sex, and time since last recorded delivery.

^c Adjusted for maternal age, year of birth, parity, infant's sex, gestational age, delivery type, and time since last recorded delivery.

^d 2 SD lower than the mean birth weight for gestational age and sex.

^e One sibling was conceived naturally, and the other one was conceived through ART.

Dhalwani. ART and perinatal outcomes. *Fertil Steril* 2016.

Rectangular Snip

Malformações Congênitas



Assisted reproductive technology and major structural birth defects in the United States[†]

J. Reefhuis^{1,3}, M.A. Honein¹, L.A. Schieve¹, A. Correa¹, C.A. Hobbs² and S.A. Rasmussen¹, and the National Birth Defects Prevention Study

¹National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 1600 Clifton Road N.E., MS E-86, Atlanta, GA 30033, USA ²University of Arkansas for Medical Sciences, Little Rock, AR 72202, USA

☞ *Gestações únicas:*

- ✓ defeitos septo cardíaco (aOR=3.1)
- ✓ lábio/palato / fenda (aOR=2.4)
- ✓ atresia esôfago (aOR=4.5)
- ✓ atresia ano-retal (aOR=3.7)

☞ *Gestações múltiplas:* ~ defeitos



Increased risk of blastogenesis birth defects, arising in the first 4 weeks of pregnancy, after assisted reproductive technologies

Jane L. Halliday^{1,2,7}, Obioha C. Ukoumunne^{1,2}, H.W. Gordon Baker^{3,4}, Sue Breheny⁵, Alice M. Jaques¹, Claire Garrett⁴, David Healy^{5,6}, and David Amor^{1,2,3}

aumento dos defeitos da blastogênese em cças nascidas por FIV/ICSI (embriões frescos): OR=3,65

☞ *defeitos do tubo neural, parede abdominal, atresia anal e esôfago, gêmeos monozigóticos*

Birth defects in children conceived by in vitro fertilization and intracytoplasmic sperm injection: a meta-analysis

Fertility and Sterility® Vol. 97, No. 6, June 2012

Juan Wen, B.S.,^{a,b} Jie Jiang, B.S.,^{a,b} Chenyue Ding, B.S.,^d Juncheng Dai, M.D.,^b Yao Liu, B.S.,^b Yankai Xia, M.D., Ph.D.,^{a,c} Jiayin Liu, M.D., Ph.D.,^{a,d} and Zhibin Hu, M.D., Ph.D.^{a,b}

- 925 estudos revisados; 56 elegíveis para comparação : 124.468 crianças FIV/ICSI comparadas com concepção natural
- RR para malformações: **1,37** (95%; CI: 1,26-1,48)
- 24 estudos comparando FIV (46.890) x ICSI (27.754): **sem diferença** (RR: 1,05, 95%; CI: 0,91-1,02)

Assisted reproductive technology and birth defects: a systematic review and meta-analysis

Michèle Hansen^{1,*}, Jennifer J. Kurinczuk², Elizabeth Milne¹,
 Nicholas de Klerk³, and Carol Bower^{1,4}

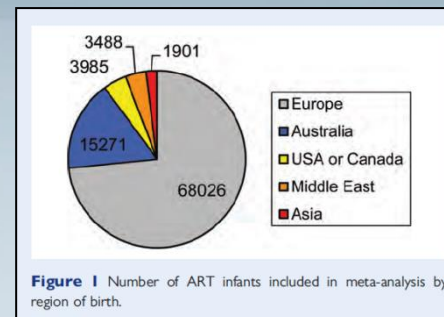


Figure 1 Number of ART infants included in meta-analysis by region of birth.

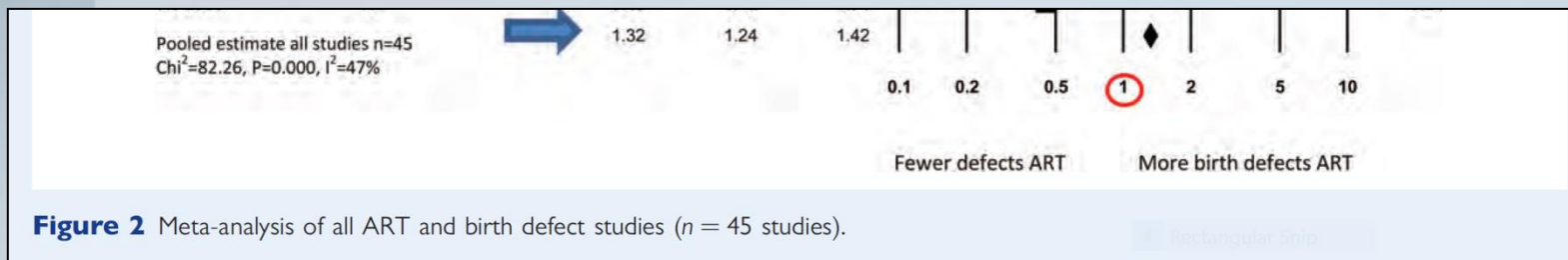


Figure 2 Meta-analysis of all ART and birth defect studies ($n = 45$ studies).

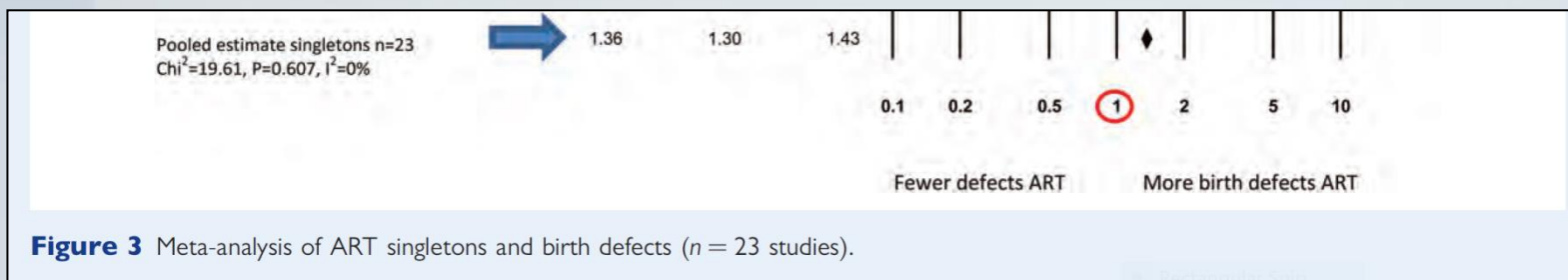


Figure 3 Meta-analysis of ART singletons and birth defects ($n = 23$ studies).

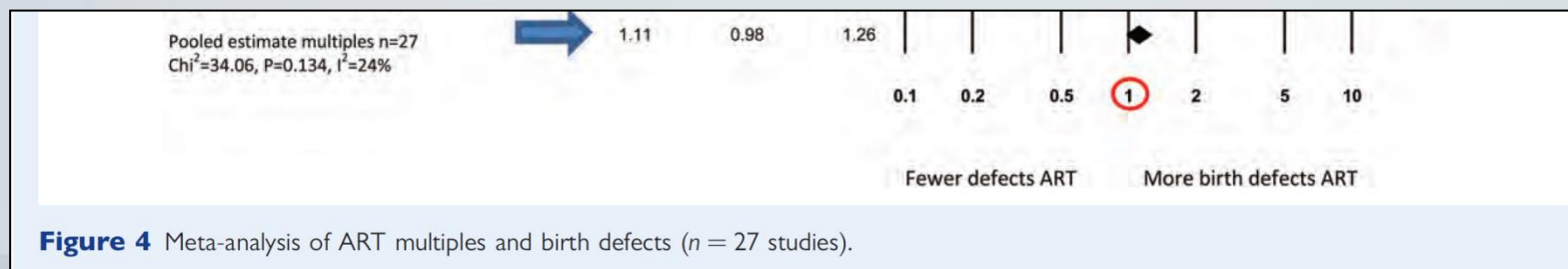


Figure 4 Meta-analysis of ART multiples and birth defects ($n = 27$ studies).

Embriões criopreservados



Transferência de embriões congelados

Transferência de embriões a fresco x congelados em ciclos de FIV:
revisão sistemática e meta-análise

Estudo ou subgrupo	Congelados/desc.		A fresco		Peso	Razão de Risco M-H, fixos, IC-95%	Razão de Risco M-H, fixos, IC-95%
	Eventos	Total	Eventos	Total			
Aflattonian 2010	73	187	52	187	46,0%	1,40 (1,05 a 1,88)	
Shapiro 2011 (normal)	39	70	27	67	24,4%	1,38 (0,97 a 1,98)	
Shapiro 2011 (alta)	38	60	34	62	29,6%	1,15 (0,86 a 1,55)	
Total (IC-95%)		317		316	100,0%	1,32 (1,10 a 1,59)	
Total de eventos	150		113				
Heterogeneidade: $\chi^2 = 1,03$, $df = 2$ ($P = 0,60$), $I^2 = 0\%$							
Teste do efeito global: $Z = 3,00$ ($P = 0,003$)							

Melhores resultados para gestação clínica, gestação continuada e implantação

Roque M, et al. *Fertil Steril* 2013;99:156–62

Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis

Fertility and Sterility® Vol. 98, No. 2, August 2012

Abha Maheshwari, M.D.,^a Shilpi Pandey, M.R.C.O.G.,^b Ashalatha Shetty, M.D.,^b Mark Hamilton, M.D.,^b and Siladitya Bhattacharya, M.D.^a

	RR	CI
Hemorragia	0,67	0,55 – 0,81
Prematuridade	0,84	0,78 – 0,90
Pequeno idade gestacional	0,45	0,30 – 0,66
Baixo peso	0,69	0,62 – 0,76
Mortalidade peri-natal	0,68	0,48 – 0,96

Neonatal health including congenital malformation risk of 1072 children born after vitrified embryo transfer

F. Belva^{1,*}, M. Bonduelle¹, M. Roelants², G. Verheyen³,
and L. Van Landuyt³

Table V Unadjusted and adjusted ORs for neonatal characteristics in singletons and twins following vitrified embryo transfer compared with fresh embryo transfer.

Neonatal outcome	Singletons		Twins	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Low birthweight	0.83 (0.59–1.1)	0.76 (0.457–1.28)	0.44 (0.24–0.79)	0.53 (0.20–1.44)
Small-for-gestational age	0.62 (0.45–0.87)	0.55 (0.34–0.90)	0.62 (0.40–0.96)	0.46 (0.20–1.04)
Large-for-gestational age	2.22 (0.77–6.44)	1.85 (0.42–8.06)	/	/
Preterm delivery	1.08 (0.80–1.43)	0.91 (0.57–1.43)	1.02 (0.74–1.41)	1.40 (0.74–2.66)
Perinatal death	0.94 (0.39–2.26)	0.97 (0.40–2.36)	0.35 (0.12–1.04)	0.37 (0.12–1.10)
Major congenital malformations	0.93 (0.53–1.63)	0.91 (0.47–1.78)	0.87 (0.04–19.6)	0.88 (0.15–4.96)

Adjusted for treatment variables (number of embryos transferred and embryo stage at vitrification/transfer: cleavage-stage or blastocyst) and maternal characteristics (age, BMI, parity, smoking and pregnancy-induced hypertensive disorder).

Parâmetros da saúde neonatal, incluindo malformações congênitas em únicos ou gêmeos nascido após vitrificação embrionária, são similares ou um pouco melhores que aqueles nascidos por tranfeência de embriões frescos

Risco mais baixo de gestação ectópica

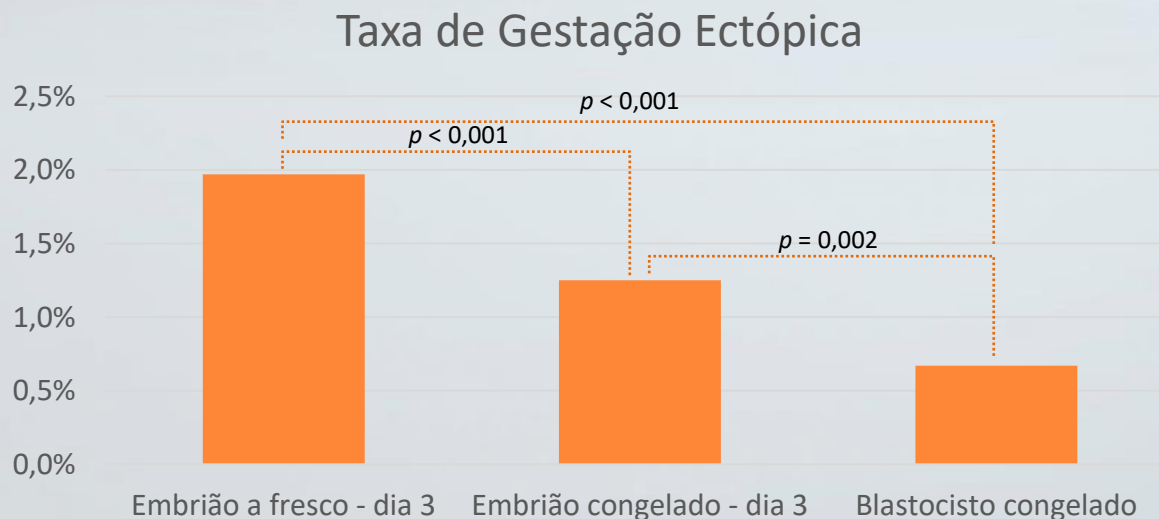
human
reproduction

ORIGINAL ARTICLE *Early pregnancy*

Hum Reprod. 2015 Sep;30(9):2048-54.

Risk of ectopic pregnancy lowest with transfer of single frozen blastocyst

Z. Li, E.A. Sullivan, M. Chapman, C. Farquhar and Y.A. Wang



FERTILITY

Freeze-all, oocyte vitrification, or fresh embryo transfer? Lessons from an egg-sharing donation program

Daniela Paes Almeida Ferreira Braga, D.V.M., Ph.D.,^{a,b,c} Amanda Souza Setti, M.Sc.,^{a,c}
 Rita Cássia Sávio Figueira, Ph.D.,^a Matheus de Castro Azevedo, B.Sc.,^a Assumpto Iaconelli Jr., M.D.,^a
 Edson Guimarães Lo Turco, D.V.M., Ph.D.,^b and Edson Borges Jr., M.D., Ph.D.,^{a,b,c}

^a Fertility–Medical Group; ^b Disciplina de Urologia, Área de Reprodução Humana, Departamento de Cirurgia, Universidade Federal de São Paulo; and ^c Instituto Sapientiae–Centro de Estudos e Pesquisa em Reprodução Humana Assistida, São Paulo, Brazil

TABLE 3

Fertility and Sterility® Vol. 106, No. 3, September 1, 2016

Comparison of oocyte/embryo survival rate, total usable embryos rate, and clinical outcomes considering the status of transferred embryos: [1] fresh oocytes and fresh embryos (Fresh Cycles Group), [2] fresh oocytes and vitrified embryos (Thaw Cycles Group), and [3] vitrified oocytes (Banked Donor Egg Group).

Variable	Group			P value
	Fresh cycles	Thaw cycles	Banked donor egg	
n	128	297	425	
Oocyte/embryo survival rate, % (n)	98.6 (3,165/3,209) ^a	95.1 (2,128/2,635) ^b	NA	< .001
Total usable embryos rate, % (n)	36.4 (501/1,376) ^c	NA	39.7 (846/2,128) ^d	.047
Pregnancy rate, % (n)	39.8 (51/128) ^e	71.4 (212/297) ^f	49.6 (211/425) ^g	< .001
Miscarriage rate, % (n)	9.4 (5/53)	10.8 (23/212)	12.8 (21/164)	.679
Implantation rate (%), mean ± SD	37.2 ± 41.1 ^h	67.3 ± 38.4 ⁱ	43.0 ± 41.0 ^j	< .001

Note: Regarding superscript letters, a ≠ b, c ≠ d, e ≠ f ≠ g, and h ≠ i ≠ j. NA = Not applicable.

Braga. Embryo or oocyte vitrification? *Fertil Steril* 2016.

Embriões Criopreservados

Melhores chances de implantação e gestação, menores taxas de gestação ectópica, melhor saúde pré/perinatal, iguais/menores chances de malformação.....

Criopreservação de todos os embriões

Estratégia de rotina ??...



Obrigado !

Edson Borges Jr.

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