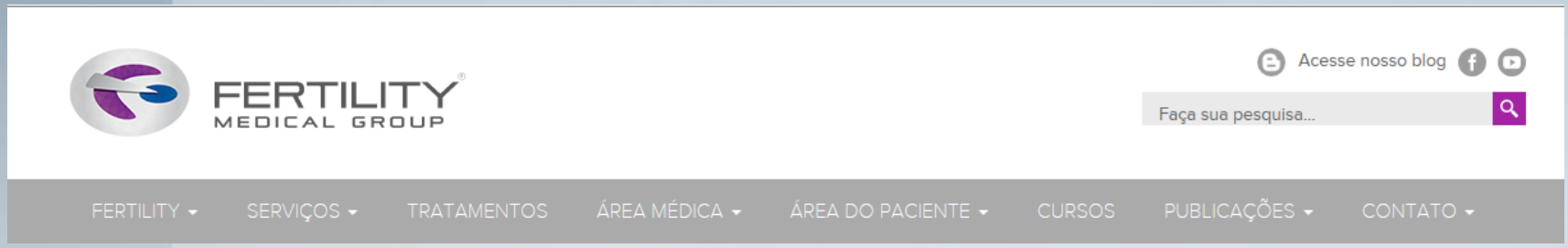
Severe seminal alteration: Consequences on embryo and offspring?

Edson Borges Jr.



http://fertility.com.br/producao-cientifica-2017/

Reproductive BioMedicine Online (2016) 32, 614–625

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ARTICLE

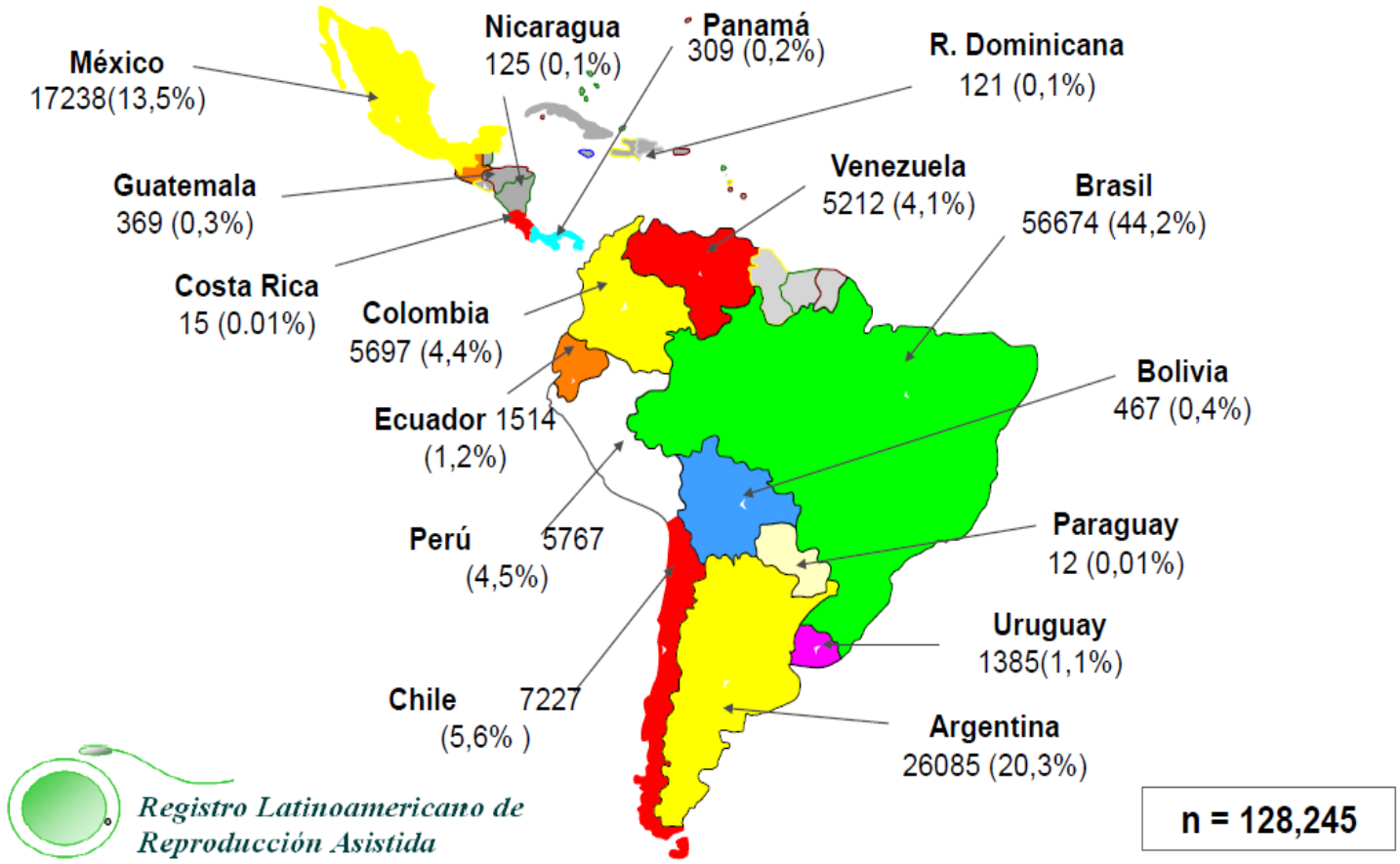
Assisted reproductive techniques in Latin America: the Latin American Registry, 2013

Fernando Zegers-Hochschild [a,b,c,*], Juan Enrique Schwarze [c,d], Javier A Crosby [a,c], Carolina Musri [a,c], Maria Teresa Urbina [c,e] on behalf of the Latin American Network of Assisted Reproduction (REDLARA)

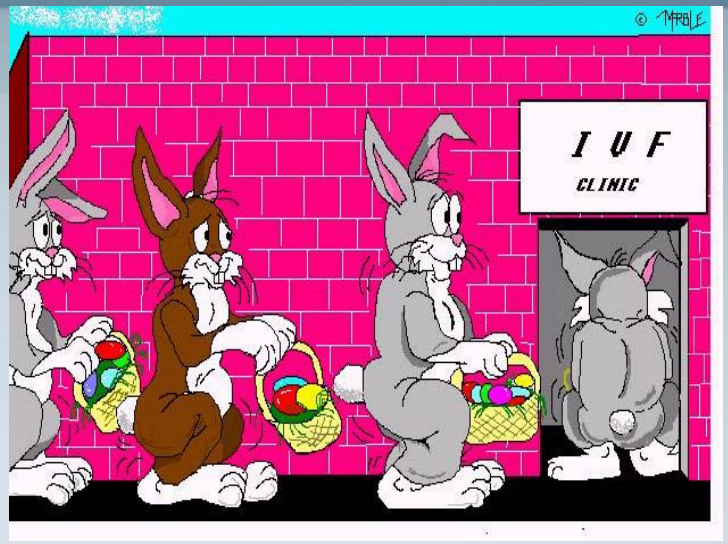
Table 1 Assisted reproduction technique procedures and access in 2013.

Country	Number of clinics	Assisted reproductive techniques							Total[d]	Access[e]
		IVF–ICSI[a]	IVF[b]	ICSI[b]	FET	Oocyte donation	Oocyte donation (FET)	Fertility preservation[c]		
Argentina	27	7769	749	6255	2481	1655	815	396	12,720	1368
Bolivia	2	280	195	71	17	46	3	840	346	141
Brazil	56	17,042	1060	14,974	5833	1159	579	0	24,613	512
Chile	8	1646	130	1405	543	170	84	61	2443	634
Colombia	9	967	288	613	182	209	95	5	1453	136
Ecuador	6	654	206	391	159	208	72	145	1093	297
Guatemala	1	99	52	47	16	20	1	9	136	39
Mexico	28	4476	1494	2648	929	1421	378	31	7204	251
Nicaragua	1	100	29	67	0	10	0	0	110	72
Panama	2	408	0	362	83	56	17	5	564	710
Paraguay	1	37	9	22	2	0	0	2	39	24
Peru	6	1404	470	837	390	587	306	98	2687	367
Dominican R.	1	49	18	30	6	36	2	0	93	40
Uruguay	2	340	35	239	52	56	19	5	467	652
Venezuela	8	1223	438	638	219	294	136	19	1872	274
Total	158	36,494	5173	28,599	10,912	5927	2507	1616	55,840	425

Registro Latino Americano de Reproducción Asistida
bebés nacidos: 1990 - 2012

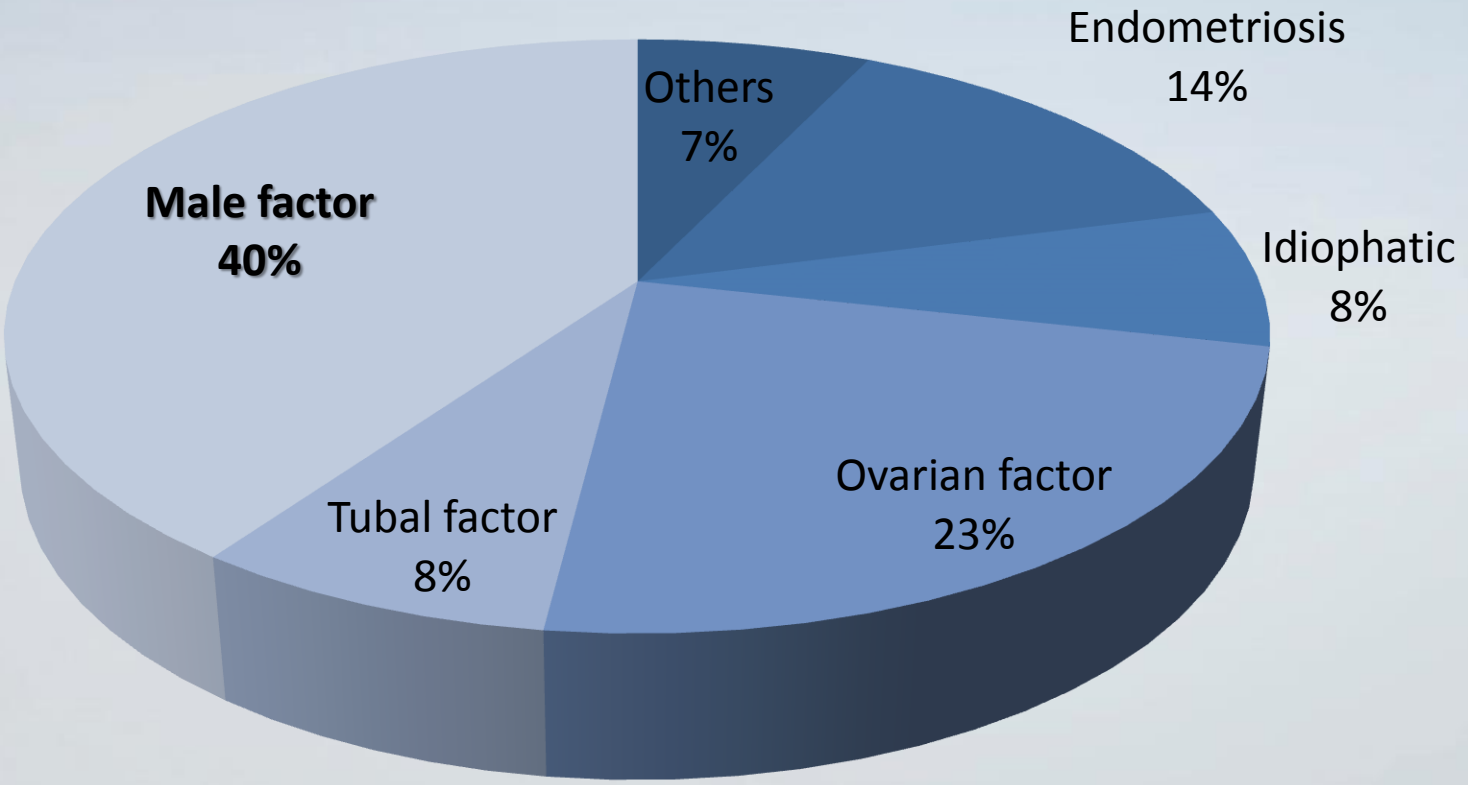


- USA: 1-2%
- Europe / Japan: 4%
- Denmark – Finland: 6-8%

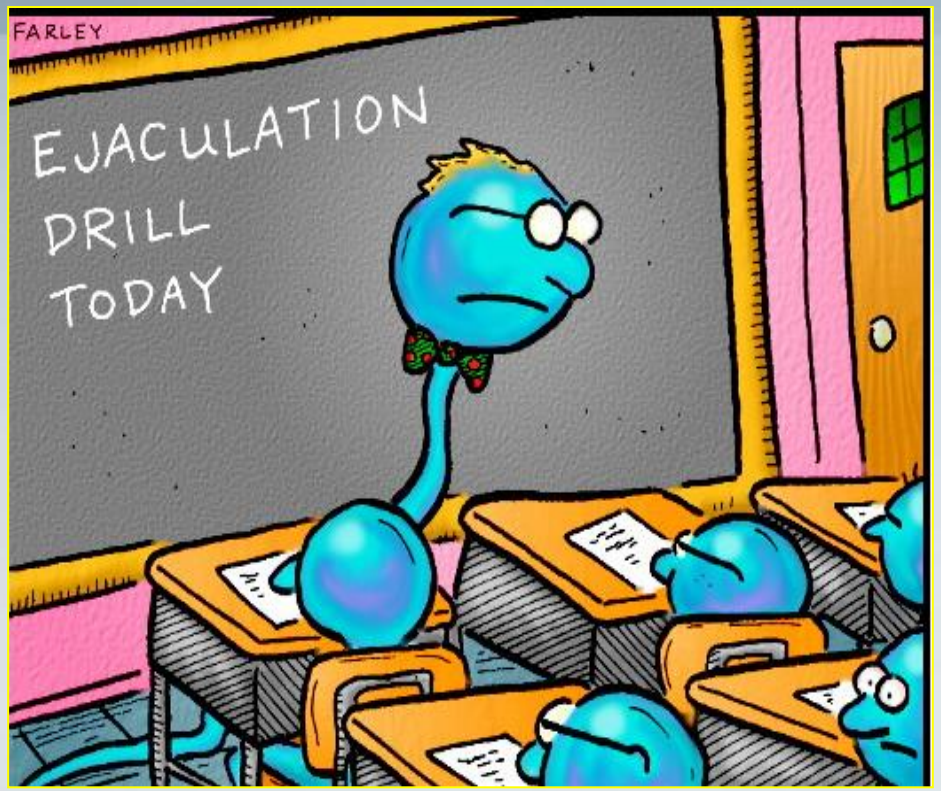


- Brasil: 30.000 IVF-ICSI cycles / year
- ~ 6,000 children born: ~ 0,2%

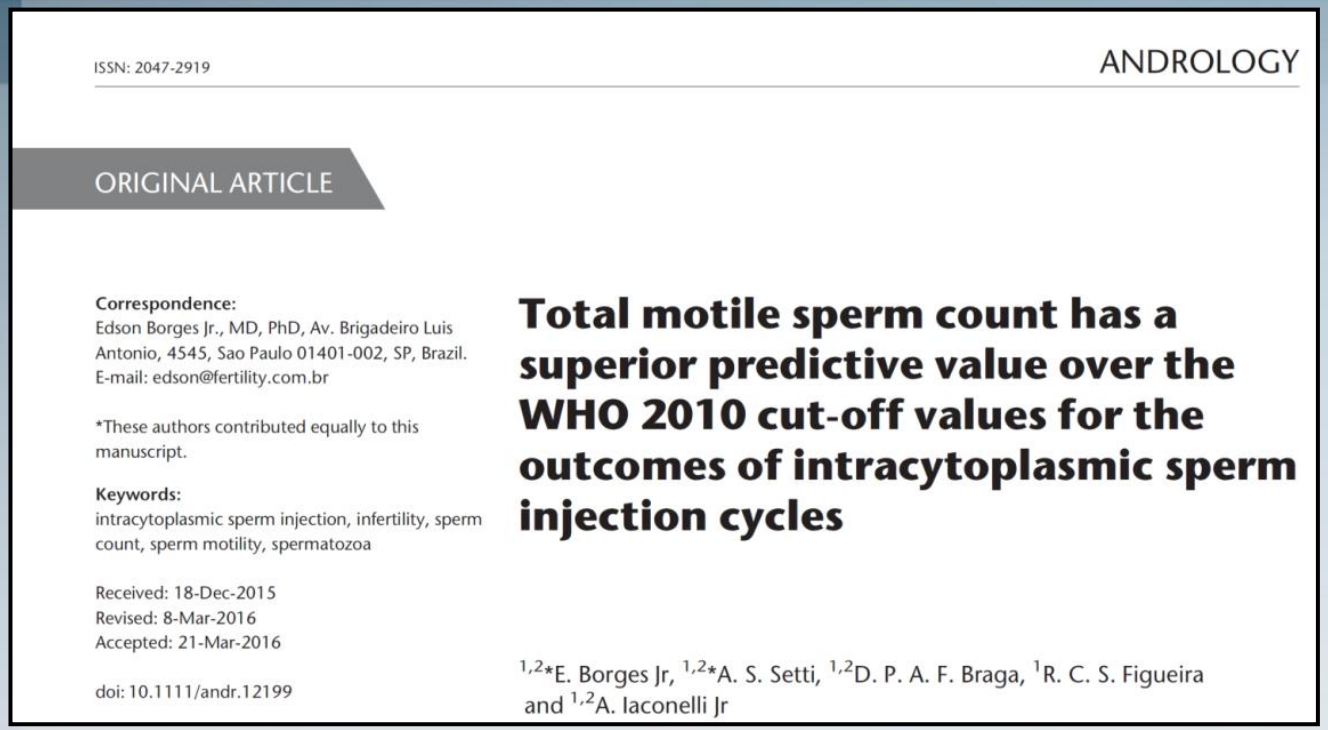
Distribution of ICSI procedures Fertility Medical Group 2005 - 2016



FERTILITY



Sperm quality
Consequences on embryo



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ANDROLOGY

ORIGINAL ARTICLE

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Total motile sperm count has a superior predictive value over the WHO 2010 cut-off values for the outcomes of intracytoplasmic sperm injection cycles

[1,2]*E. Borges Jr, [1,2]*A. S. Setti, [1,2]D. P. A. F. Braga, [1]R. C. S. Figueira and [1,2]A. Iaconelli Jr

- ***Definition: TMSC = volume x conc/ml x % A+B / 100%***

  - 518 ICSI cycles
  - TMSC: normal > 20 millions sptz

Table 4 Comparison of ICSI outcomes between normal and abnormal TMSC groups

Variables	Normal TMSC group (n = 328)	Abnormal TMSC group (n = 190)	p-value
Paternal age (year-old)	37.4 ± 4.8	38.1 ± 6.1	0.187
Maternal age (year-old)	35.4 ± 3.9	33.5 ± 4.0	<0.001
Number of aspirated follicles	17.8 ± 9.7	20.8 ± 11.2	0.002
Number of obtained oocytes	12.7 ± 7.2	15.1 ± 8.1	0.001
Number of mature oocytes	9.7 ± 5.5	11.2 ± 6.2	0.003
Number of injected oocytes	9.4 ± 4.3	10.2 ± 4.9	0.067
Fertilization rate (%)	84.9 ± 14.4	81.1 ± 15.8	0.016
Number of obtained embryos	8.2 ± 3.8	8.7 ± 4.4	0.204
Number of transferred embryos	2.2 ± 0.6	2.2 ± 0.5	0.469
Implantation rate (%)	25.1 ± 36.0	25.8 ± 35.2	0.832
Pregnancy rate (%)	134/328 (40.9)	94/190 (49.5)	0.060
Miscarriage rate (%)	29/162 (17.9)	23/78 (29.5)	0.041

SD, standard deviation; TMSC: total motile sperm count.

Table 5 Linear and binary regression analysis results for the influences of TMSC and WHO cut-off values on ICSI outcome

Variables	Method	OR or RC	CI or R^2	*p*-value
Fertilization rate	Concentration	3.994	1.4%	0.015
	Motility	0.097	0.0%	0.957
	Progressive motility	2.299	0.5%	0.163
	Morphology	8.735	0.9%	0.047
	TMSC	3.784	1.5%	0.013
	Normal TMSC	−0.253	0.1%	0.592
Formation of high-quality zygotes on D1	Concentration	1.64	1.09–2.46	0.018
	Motility	1.34	0.85–2.12	0.208
	Progressive motility	1.22	0.80–1.85	0.355
	Morphology	0.89	0.65–1.22	0.461
	TMSC	1.13	1.01–1.28	0.049
	Normal TMSC	0.99	0.97–1.02	0.629
Formation of high-quality embryos on D2	Concentration	0.93	0.76–1.09	0.101
	Motility	0.91	0.79–1.06	0.222
	Progressive motility	1.06	0.92–1.22	0.420
	Morphology	0.84	0.60–1.18	0.314
	TMSC	1.18	1.03–1.35	0.013
	Normal TMSC	0.97	0.94–1.01	0.098
Formation of high-quality embryos on D3	Concentration	0.91	0.79–1.06	0.229
	Motility	0.93	0.79–1.09	0.379
	Progressive motility	1.00	0.85–1.17	0.969
	Morphology	1.18	0.83–1.67	0.354
	TMSC	1.12	1.07–1.29	0.037
	Normal TMSC	0.98	0.95–1.02	0.319
Formation of blastocyst on D5	Concentration	1.11	0.97–1.27	0.116
	Motility	1.03	0.90–1.19	0.660
	Progressive motility	0.91	0.70–1.23	0.303
	Morphology	1.13	0.83–1.55	0.427
	TMSC	1.16	1.04–1.26	0.011
	Normal TMSC	1.00	0.97–1.04	0.802
Blastocyst expansion grade on D5	Concentration	0.83	0.66–1.05	0.120
	Motility	1.01	0.79–1.29	0.948
	Progressive motility	1.08	0.85–1.38	0.533
	Morphology	0.99	0.57–1.71	0.962
	TMSC	1.27	1.01–1.60	0.042
	Normal TMSC	1.03	0.98–1.07	0.287

EJACULATED SPERMATOZOA

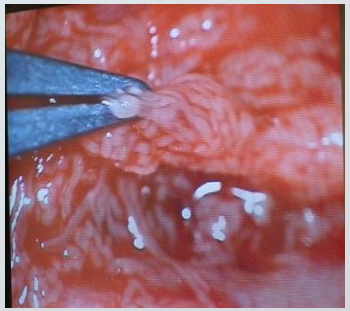
Epididimal spermatozoa

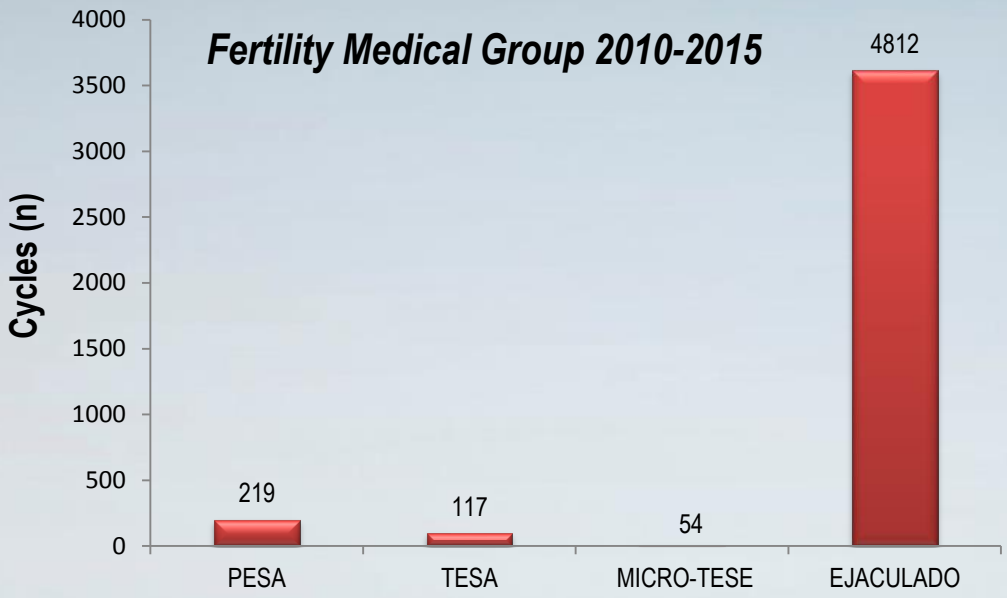
PERCUTANEOUS
EPIDYDIMAL
SPERM
ASPIRATION

Testicular spermatozoa

TESTICULAR
SPERM
. ASPIRATION
. EXTRATION

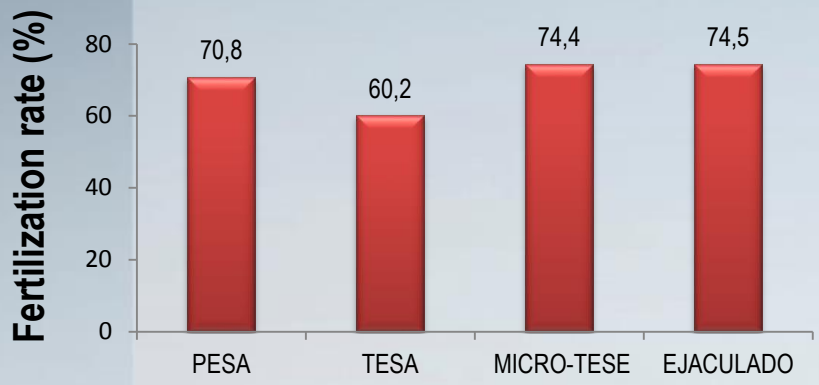
MICRO
TESTICULAR
SPERM
EXTRACTION





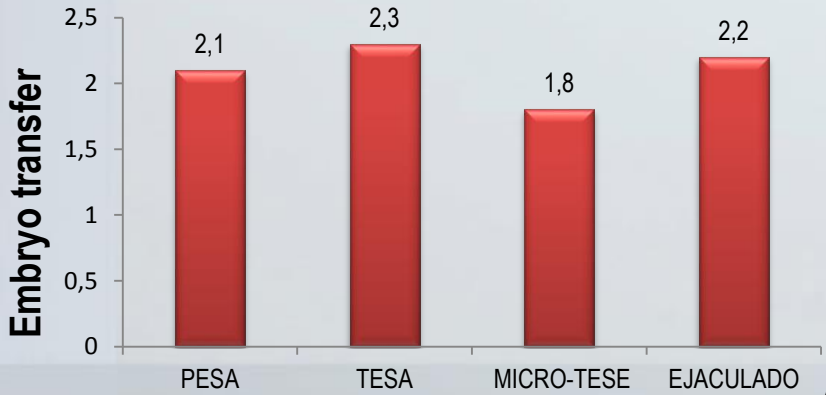
	PESA	TESA	MICRO-TESE	EJACULATE
Cycles (n)	219	117	54	4812
Age ± SD	34.9 ± 4.6	34.8 ± 5.4	32.2 ± 2.7	35.8 ± 4.7
Follicles ± SD	20.4 ± 15.4	18.1 ±11.3	15.9 ± 14.4	15.8 ± 12.4
Oocytes retrieved ± SD	14.2 ± 10.8	13.3 ± 9.3	11.0 ± 11.4	11.0 ± 9.0
Oocytes micromanipulated ± SD	9.8 ± 6.4	8.9 ± 5.1	8.0 ± 6.9	7.8 ± 5.8

Fertility Medical Group 2010-2015



	P
PESA *VS* TESA	**< 0.001**
PESA *VS* MICRO-TESE	> 0.05
PESA *VS* EJACULATE	> 0.05
TESA *VS* MICRO-TESE	> 0.05
TESA *VS* EJACULATE	**< 0.001**
MICRO-TESE *VS* EJACULAte	> 0.05

ANOVA

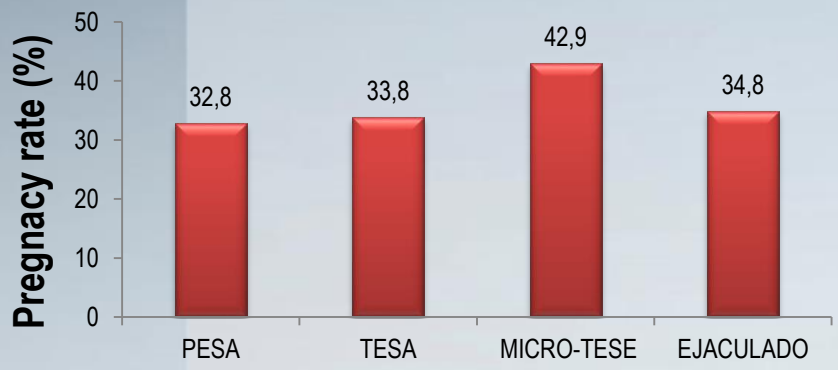


	P
PESA *VS* TESA	> 0.05
PESA *VS* MICRO-TESE	> 0.05
PESA *VS* EJACULATE	> 0.05
TESA *VS* MICRO-TESE	> 0.05
TESA *VS* EJACULATE	> 0.05
MICRO-TESE *VS* EJACULATE	> 0.05

ANOVA

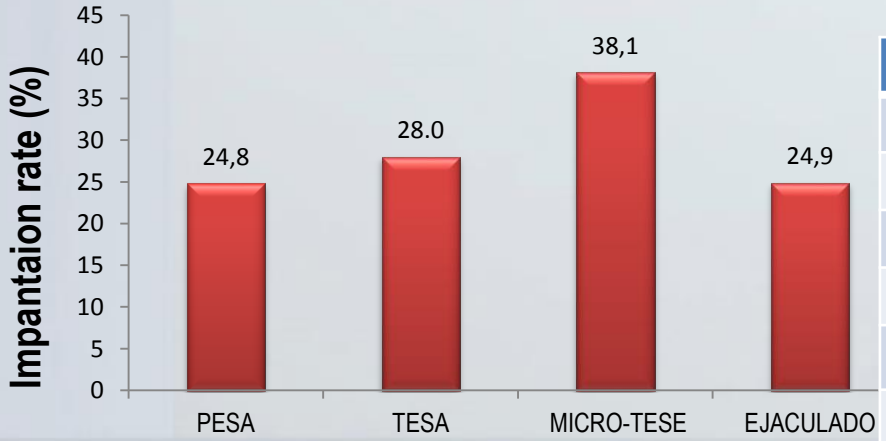
FERTILITY

Fertility Medical Group 2010-2015



	P
PESA *VS* TESA	> 0.05
PESA *VS* MICRO-TESE	> 0.05
PESA *VS* EJACULATE	> 0.05
TESA *VS* MICRO-TESE	> 0.05
TESA *VS* EJACUALTE	> 0.05
MICRO-TESE *VS* EJACULATE	> 0.05

QUI-QUADADRO



	P
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PESA *VS* MICRO-TESE	> 0.05
PESA *VS* EJACULATE	> 0.05
TESA *VS* MICRO-TESE	> 0.05
TESA *VS* EJACUALTE	> 0.05
MICRO-TESE *VS* EJACULATE	> 0.05

ANOVA

The Aging Male, 13(1):44-50, 2010

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[1]*Fertility – Assisted Fertilization Center, São Paulo, SP, Brazil,* [2]*Sapientiae Institute – Educational and Research Center in Assisted Reproduction, São Paulo, SP, Brazil, and* [3]*Institute of Biotechnology – Caxias do Sul University, Caxias do Sul, RS, Brazil*

ORIGINAL ARTICLE

Edson Borges Jr., *et al*

Assisted reproductive technology outcomes in azoospermic men: 10 years of experience with surgical sperm retrieval

Table II. ICSI outcomes from patients with obstructive azoospermia when the injected spem were retrieved from the testicle (TESA) or epididymis (PESA).

Variable	Study group		
	OA-TESA (n=103)	OA-PESA (n=171)	*p* value
Normal fertilization rate (%)	57.9 ± 9.5 (48.5–67.5)	65.2 ± 4.1 (54.7–69.3)	*0.0017*
Abnormal fertilization rate (%)	13.2 ± 6.3 (6.5–19.5)	12.7 ± 5.3 (7.9–18.0)	0.9437
Fertilization failure rate (%)	28.9 ± 8.9 (20.2–37.8)	22.1 ± 6.0 (15.8–28.1)	0.1081
Non-cleaved rate (%)	9.87 ± 5.9 (4.2–15.8)	7.46 ± 3.9 (3.5–11.4)	0.4406
Pregnancy rate (%)	31.9 ± 9.0 (23.0–41.0)	32.5 ± 7.5 (25.9–40.0)	0.8803
Abortion rate (%)	38.8 ± 9.6 (29.6–48.4)	18.0 ± 5.8 (12.2–23.8)	*0.0387*
Implantation rate (%)	9.4 ± 5.6 (3.8–15.0)	10.5 ± 4.0 (5.5–14.5)	0.6054

Values in percentage expressed as mean ± SD (confidence interval of the frequencies).

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Assisted reproductive technology outcomes in azoospermic men: 10 years of experience with surgical sperm retrieval

Table IV. ICSI outcomes when the injected sperm were retrieved from the testicle (TESA) of patients with obstructive (OA) or non-obstructive (NOA) azoospermia.

Variable	Study group		*p* value
	OA-TESA (n=103)	NOA-TESA (n=102)	
Normal fertilization rate (%)	57.9 ± 9.5 (48.5–67.5)	50.4 ± 9.3 (40.3–59.7)	*0.0050*
Abnormal fertilization rate (%)	13.2 ± 6.3 (6.5–19.5)	13.98 ± 6.8 (7.3–20.7)	0.4421
Fertilization failure rate (%)	28.9 ± 8.9 (20.2–37.8)	35.65 ± 11.8 (27.6–47.4)	*0.0023*
Non cleaved rate (%)	9.87 ± 5.9 (4.2–15.8)	16.1 ± 17 (8.9–23.1)	*0.0034*
Pregnancy rate (%)	31.9 ± 9.0 (23.0–41.0)	29.7 ± 9.2 (21.1–38.9)	0.4166
Abortion rate (%)	38.8 ± 9.6 (29.6–48.4)	37.0 ± 9.4 (27.6–46.4)	0.9992
Implantation rate (%)	9.4 ± 5.6 (3.8–15.0)	9.65 ± 6.1 (4.2–15.8)	0.8519

Values in percentage expressed as mean ± SD (confidence interval of the frequencies).

The Aging Male, 13(1):44-50, 2010

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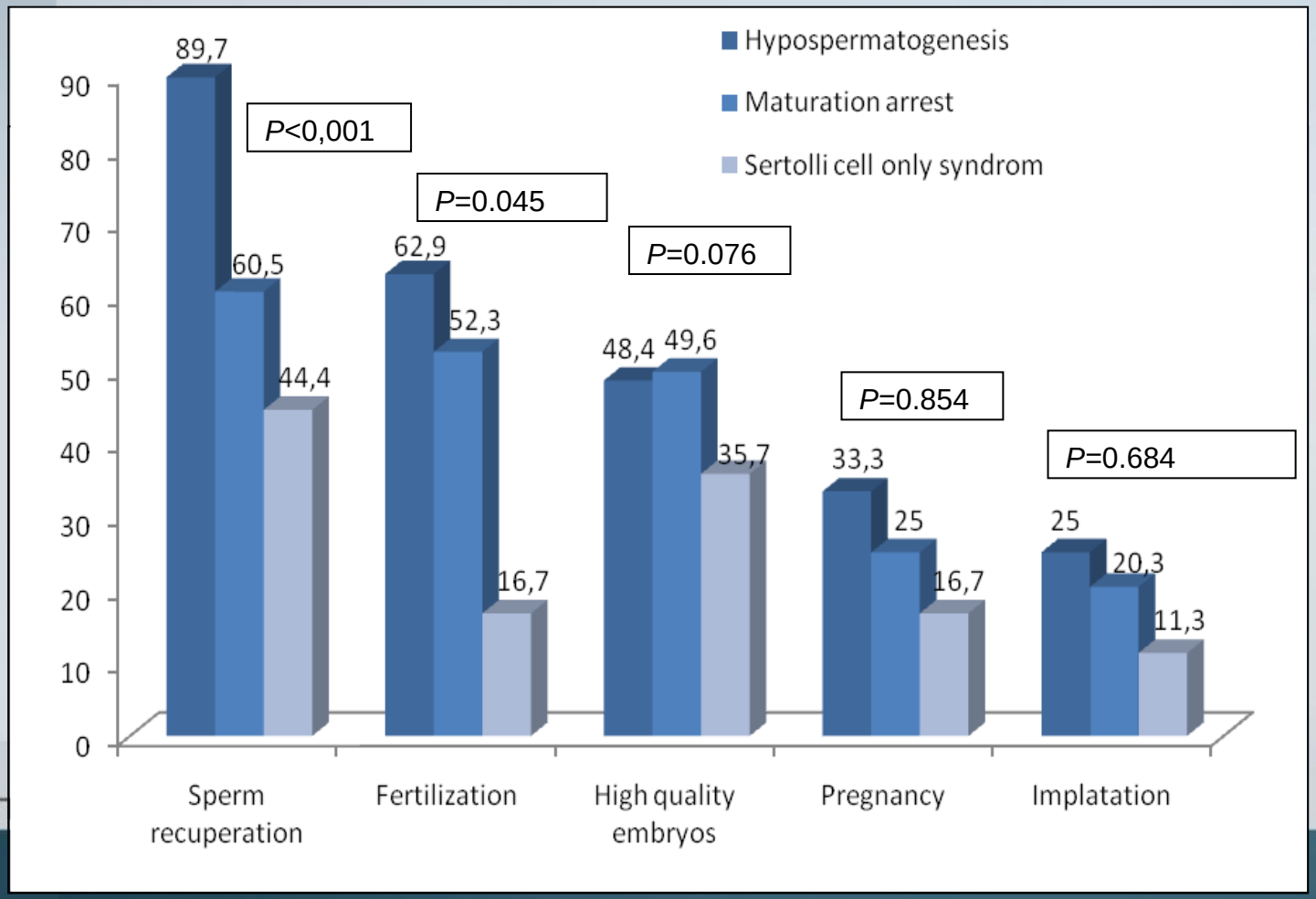
Artigo Original

JBRA Assist. Reprod. | V. 15 | nº5 | Sep-Oct / 2011

The prognostic value of the testicular histopathological pattern for sperm retrieval and intracytoplasmic sperm injection outcomes in non-obstructive azoospermic patients

O valor prognóstico do padrão histopatológico testicular na recuperação de espermatozóides e nos resultados da injeção intracitoplasmática de espermatozóides em pacientes com azoospermia não-obstrutiva

Edson Borges Jr. [a,b], Daniela Paes de Almeida Braga[a,b], Rita de Cássia Savio Figueira[a], Amanda Souza Setti[b], Assumpto Iaconelli Jr [a,b], Fabio Firmbach Pasqualotto[c]



European Journal of Obstetrics & Gynecology and Reproductive Biology 183 (2014) 96–103

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journal homepage: www.elsevier.com/locate/ejogrb

Review

Intracytoplasmic morphologically selected sperm injection results in improved clinical outcomes in couples with previous ICSI failures or male factor infertility: a meta-analysis

Amanda S. Setti [a,b,c], Daniela P.A.F. Braga [a,b], Rita C.S. Figueira [b,c], Assumpto Iaconelli Jr. [a,b], Dr.Edson Borges [a,b,*]

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Awarded by the Society for Assisted Reproductive Technology (SART) as best work presented at the 69th annual meeting of the American Society of Reproductive Medicine, 2013 (ASRM)

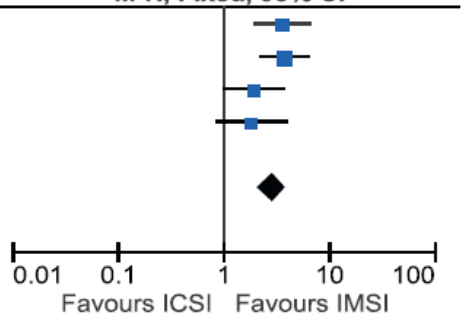
ICSI Failure (IF)

Implantation

Study or Subgroup	IMSI Events	IMSI Total	ICSI Events	ICSI Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Bartoov et al.	53	190	17	175	24.0%	3.60 [1.99, 6.50]	2003
Berkovitz et al.	69	248	23	248	31.2%	3.77 [2.26, 6.29]	2006
Gonzalez-Ortega et al.	35	78	25	84	25.0%	1.92 [1.01, 3.67]	2010
Oliveira et al.	24	164	11	128	19.8%	1.82 [0.86, 3.88]	2011
Total (95% CI)		**680**		**635**	**100.0%**	**2.88 [2.13, 3.89]**	
Total events	181		76				

Heterogeneity: Chi² = 4.52, df = 3 (P = 0.21); I² = 34%

Test for overall effect: Z = 6.88 (P < 0.00001)

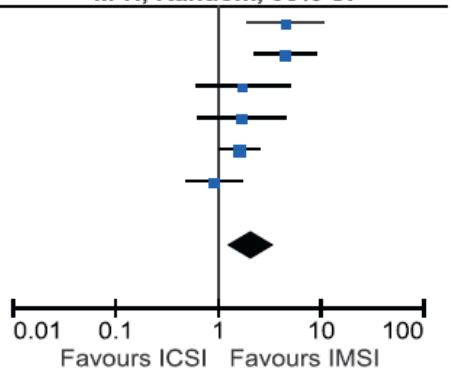


Pregnancy

Study or Subgroup	IMSI Events	IMSI Total	ICSI Events	ICSI Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Bartoov et al.	33	50	15	50	15.3%	4.53 [1.95, 10.51]	2003
Berkovitz et al.	48	80	20	80	17.8%	4.50 [2.29, 8.84]	2006
Gonzalez-Ortega et al.	19	30	15	30	12.8%	1.73 [0.62, 4.84]	2010
Oliveira et al.	14	63	8	55	13.8%	1.68 [0.65, 4.37]	2011
Klement et al.	52	127	97	322	21.6%	1.61 [1.05, 2.46]	2013
El Khattabi et al.	22	90	34	130	18.7%	0.91 [0.49, 1.70]	2013
Total (95% CI)		**440**		**667**	**100.0%**	**2.07 [1.22, 3.50]**	
Total events	188		189				

Heterogeneity: Tau² = 0.29; Chi² = 16.40, df = 5 (P = 0.006); I² = 70%

Test for overall effect: Z = 2.71 (P = 0.007)



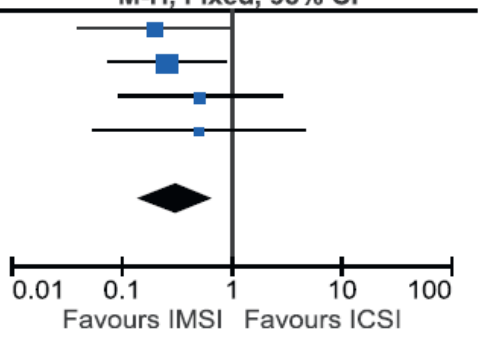
ICSI Failure (IF)

Micarriage

Study or Subgroup	IMSI Events	IMSI Total	ICSI Events	ICSI Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Bartoov et al.	3	33	5	15	28.6%	0.20 [0.04, 0.99]	2003
Berkovitz et al.	7	48	8	20	44.2%	0.26 [0.08, 0.85]	2006
Gonzalez-Ortega et al.	3	19	4	15	17.2%	0.52 [0.10, 2.77]	2010
Oliveira et al.	2	14	2	8	10.0%	0.50 [0.06, 4.47]	2011
Total (95% CI)		**114**		**58**	**100.0%**	**0.31 [0.14, 0.67]**	
Total events	15		19				

Heterogeneity: $Chi^2 = 0.92$, $df = 3$ ($P = 0.82$); $I^2 = 0\%$

Test for overall effect: $Z = 2.96$ ($P = 0.003$)

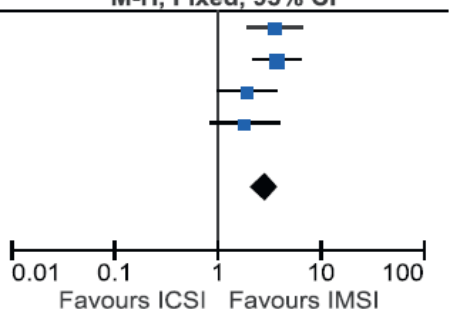


Male Factor

Implantaion

Study or Subgroup	IMSI Events	IMSI Total	ICSI Events	ICSI Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Bartoov et al.	53	190	17	175	24.0%	3.60 [1.99, 6.50]	2003
Berkovitz et al.	69	248	23	248	31.2%	3.77 [2.26, 6.29]	2006
Gonzalez-Ortega et al.	35	78	25	84	25.0%	1.92 [1.01, 3.67]	2010
Oliveira et al.	24	164	11	128	19.8%	1.82 [0.86, 3.88]	2011
Total (95% CI)		**680**		**635**	**100.0%**	**2.88 [2.13, 3.89]**	
Total events	181		76				

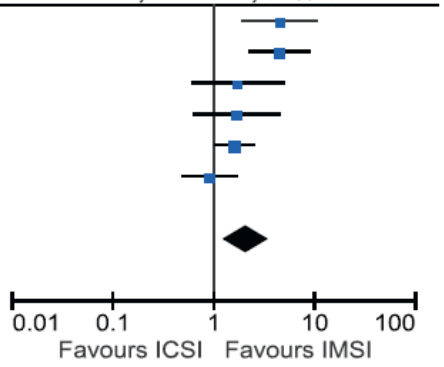
Heterogeneity: Chi² = 4.52, df = 3 (P = 0.21); I² = 34%
Test for overall effect: Z = 6.88 (P < 0.00001)



Pregnancy

Study or Subgroup	IMSI Events	IMSI Total	ICSI Events	ICSI Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Bartoov et al.	33	50	15	50	15.3%	4.53 [1.95, 10.51]	2003
Berkovitz et al.	48	80	20	80	17.8%	4.50 [2.29, 8.84]	2006
Gonzalez-Ortega et al.	19	30	15	30	12.8%	1.73 [0.62, 4.84]	2010
Oliveira et al.	14	63	8	55	13.8%	1.68 [0.65, 4.37]	2011
Klement et al.	52	127	97	322	21.6%	1.61 [1.05, 2.46]	2013
El Khattabi et al.	22	90	34	130	18.7%	0.91 [0.49, 1.70]	2013
Total (95% CI)		**440**		**667**	**100.0%**	**2.07 [1.22, 3.50]**	
Total events	188		189				

Heterogeneity: Tau² = 0.29; Chi² = 16.40, df = 5 (P = 0.006); I² = 70%
Test for overall effect: Z = 2.71 (P = 0.007)



MALE FACTOR

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

Morphological nuclear integrity of sperm cells is associated with preimplantation genetic aneuploidy screening cycle outcomes

Rita de Cássia S. Figueira, M.Sc.,[a] *Daniela P. A. F. Braga, M.Sc.,*[a,b] *Amanda S. Setti, B.Sc.,*[b] *Assumpto Iaconelli, Jr., M.D.,*[a] *and Edson Borges, Jr., M.D., Ph.D.*[a,b]

[a] Fertility-Assisted Fertilization Centre; and [b] Sapientiae Institute-Educational and Research Centre in Assisted Reproduction, São Paulo, Brazil

Patient(s): Couples who underwent IVF-PGS cycle, as a result of advanced maternal age, were randomly allocated into two groups: intracytoplasmic sperm injection (ICSI; n = 60) or intracytoplasmic morphologically selected sperm injection (IMSI; n = 60).

MALE FACTOR

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

Morphological nuclear integrity of sperm cells is associated with preimplantation genetic aneuploidy screening cycle outcomes

Edson Borges Jr., *et al*

IMSI:

- Lower incidence of sexual chromosomes aneuploidy (23,5% x 15,0%) OR= 0,57 (0,37-0,90; p= 0,015)
- Lower incidence of chaotic embryos (27,5% x 18,8%) OR=0,64 (0,43-0,96; p=0,032)
- Lower chance of cycle cancellation (11,8 % x 2,5%) OR=0,26 (0,11-0,62; p=0,001)

Conclusion(s): Spermatozoa free of nuclear morphological malformations were found to be significantly associated with the lower incidence of aneuploidy in derived embryos, resulting in lower rates of cycle cancellation.

Messages

- The worse is the seminal analysis (TMSC), the worse is the sperm behavior on ART cycles
- The non-ejaculated sperm is worse in comparing with the ejaculated in terms of fertilization. But once the oocyte is fertilized, they are as good as the first one
- The worse is the testicle histology, the worse is the sperm retrieved
- The selection techniques, to obtain the best sperm, promote better results on ART cycles (the better sperm, the better outcome)

Sperm quality
Consequences on offspring

Human Reproduction Update, Vol.18, No.5 pp. 485–503, 2012
Advanced Access publication on May 19, 2012 doi:10.1093/humupd/dms018

human reproduction update

Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis

Shilpi Pandey[1], Ashalatha Shetty[2], Mark Hamilton[1], Siladitya Bhattacharya[3], and Abha Maheshwari[3,*]

[1]Assisted Reproduction Unit, Aberdeen Maternity Hospital, Aberdeen AB25 2ZL, UK [2]Aberdeen Maternity Hospital, Aberdeen AB25 2ZL, UK [3]Division of Applied Health Sciences, University of Aberdeen, Aberdeen Maternity Hospital, Aberdeen AB25 2ZL, UK

ART: obstetric and perinatal outcomes

Outcome	Overal effect: RR (IC-95%)
Antipartum hemorrhage	2,49 (2,30 a 2,69)
Congenital anomalies	1,67 (1,33 a 2,09)
Hypertension	1,49 (1,39 a 1,59)
Premature rupture of membranes	1,16 (1,07 a 1,26)
Caesarean Section	1,56 (1,51 a 1,60)
Birth weight< 2.500 g	1,65 (1,56 a 1,75)
Birth weight < 1.500 g	1,93 (1,72 a 2,17)
Perinatal mortality	1,87 (1,49 a 2,37)
Delivery at 37 weeks	1,54 (1,47 a 1,62)
Delivery at 32 weeks	1,68 (1,48 a 1,91)
Transfer to NICU	1,58 (1,42 a 1,77)
Gestacional diabetes	1,48 (1,33 a 1,66)
Induction of labour	1,18 (1,10 a 1,28)
Small for gstacional age	1,39 (1,27 a 1,53)

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

Human Reproduction Update, Vol.19, No.2 pp. 87–104, 2013
Advanced Access publication on November 14, 2012 doi:10.1093/humupd/dms044

human reproduction update

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

A. Pinborg[1,*], U.B. Wennerholm[2], L.B. Romundstad[3], A. Loft[1], K. Aittomaki[4], V. Söderström-Anttila[5], K.G. Nygren[6], J. Hazekamp[7], and C. Bergh[8]

Birth criteria – Preterm (PT)

1982 – 2012, PUBMED, Cochrane, 65 studies

- Fertile x Subfertile *(AOR= 1,35)*
- FIV/ICSI x subfertile *(AOR= 1,55)*

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 birth and fetal death, 2004-2008*
- 3 groups:
  - *ART: 11.271, subfertile: 6.609, fertile: 316.748*

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]

- ART singleton x subfertile: > preterm and low birth weight

  (AOR=1,23 – 1,26, respectively)

- ART and subferile x fertile: > preterm and low birth weight

  (OR= 1,3)

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, intracytoplasmatic 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).

- ART children (all treatments) 65 g lighter *x* Natural conceived pars
- ICSI/FIV *x* Natural conceive: > risk lower birth weight (OR= 1,4) and preterm delivery (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

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

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, nd 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.

Human Reproduction, Vol.26, No.7 pp. 1752–1758, 2011
Advanced Access publication on April 21, 2011 doi:10.1093/humrep/der121

human reproduction

ORIGINAL ARTICLE *Infertility*

Neonatal outcome of 724 children born after ICSI using non-ejaculated sperm

F. Belva [1,*], F. De Schrijver [1], H. Tournaye [2], I. Liebaers [1,2], P. Devroey [2], P. Haentjens [3], and M. Bonduelle [1]

[1]Center for Medical Genetics, UZ Brussel, Brussels 1090, Belgium [2]Center for Reproductive Medicine, UZ Brussel, Brussels, Belgium
[3]Center for Outcomes Research and Laboratory for Experimental Surgery, UZ Brussel, Brussels, Belgium

Overall ***neonatal health in terms of birth parameters, major anomalies and chromosomal aberrations*** of children born by the use of non-ejaculated sperm ***seems reassuring*** in comparison to the outcome of children born after the use of ejaculated sperm.

Birth Defects

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]

- 124.468 children: FIV/ICSI compared with Natural conceived

- RR Congenital anomalies: ***1,37*** (95%; CI: 1,26-1,48)

- FIV (46.890) x ICSI (27.754): ***no difference***
  (RR: 1,05, 95%; CI: 0,91-1,02)

Human Reproduction Update, Vol.19, No.4 pp. 330–353, 2013
Advanced Access publication on February 28, 2013 doi:10.1093/humupd/dmt006

human reproduction update

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

Michèle Hansen[1,*], Jennifer J. Kurinczuk[2], Elizabeth Milne[1], Nicholas de Klerk[3], and Carol Bower[1,4]

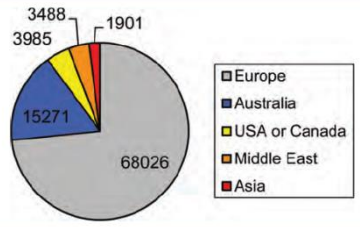


Figure 1 Number of ART infants included in meta-analysis by region of birth.

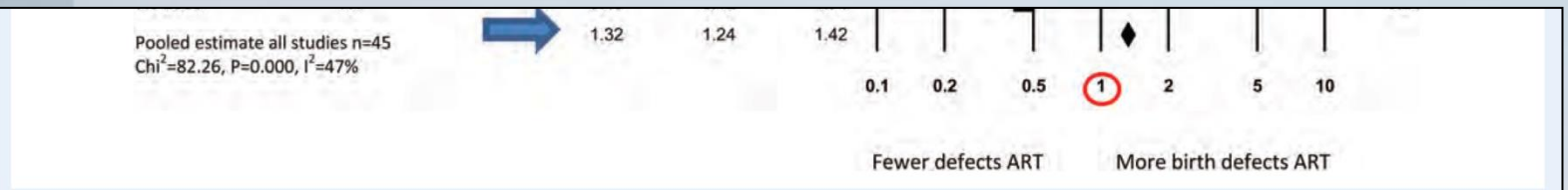


Figure 2 Meta-analysis of all ART and birth defect studies ($n = 45$ studies).

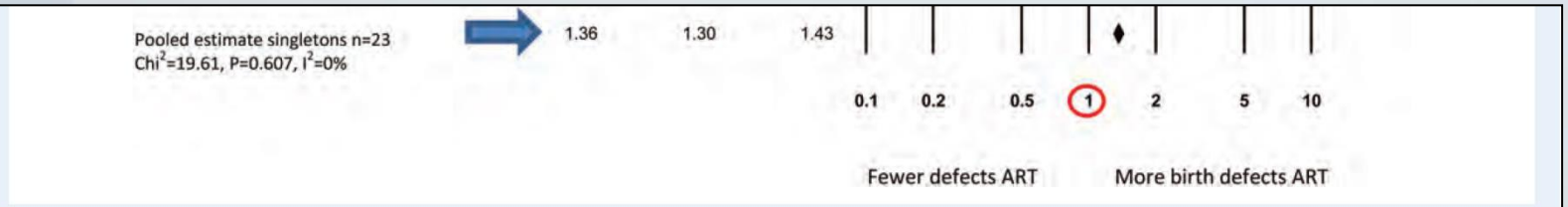


Figure 3 Meta-analysis of ART singletons and birth defects ($n = 23$ studies).

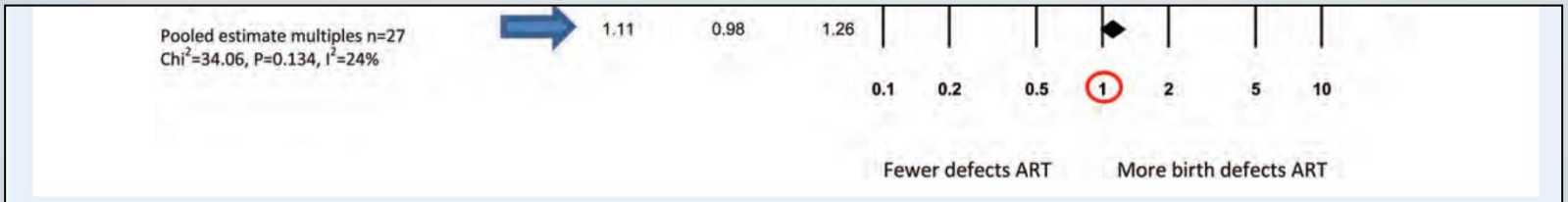


Figure 4 Meta-analysis of ART multiples and birth defects ($n = 27$ studies).

Human Reproduction, Vol.32, No.1 pp. 239–247, 2017
Advanced Access publication on December 6, 2016 doi:10.1093/humrep/dew289

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Risk of childhood mortality in family members of men with poor semen quality

Heidi A. Hanson[1,2,*], Erik N. Mayer[3], Ross E. Anderson[3], Kenneth I. Aston[3,4,5], Douglas T. Carrell[3,5], Justin Berger[2], William T. Lowrance[3], Ken R. Smith[2,6], and James M. Hotaling[3,4]

- Relationship between Fertility and Congenital Malformations
- The increased risk of congenital birth defects may not be due to the ART, but rather genetic or environmental factors that link the two outcomes
- ***An increased risk of death due to Congenital Malformations (CM) in First Degree Relatives (FDR), but not Second DR, of men with lower semen parameters***

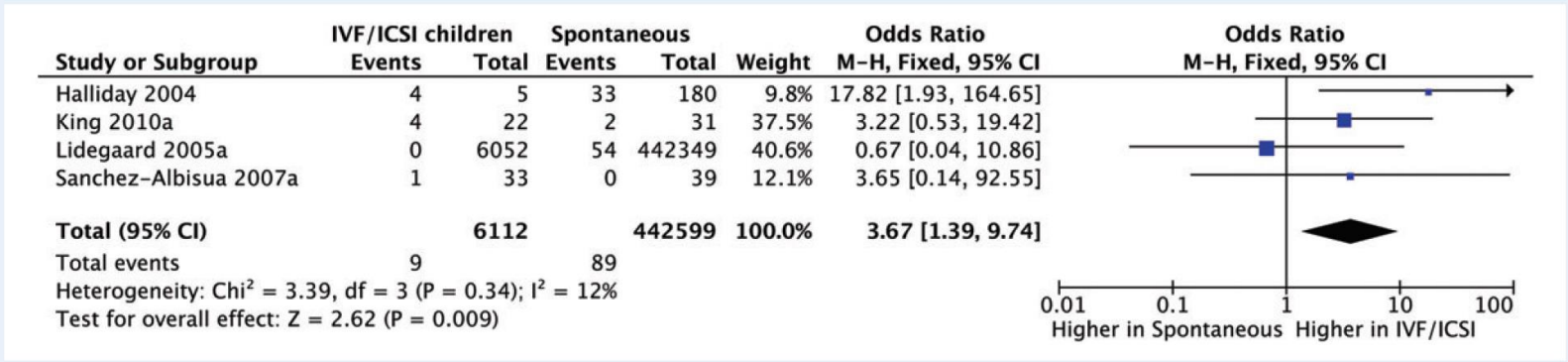
Human Reproduction Update, Vol.20, No.6 pp. 840–852, 2014
Advanced Access publication on June 24, 2014 doi:10.1093/humupd/dmu033

human reproduction update

A systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously

Gabija Lazaraviciute[1], Miriam Kauser[1], Sohinee Bhattacharya[1], Paul Haggarty[2], and Siladitya Bhattacharya[1,*]

[1]Division of Applied Health Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK [2]Division of Lifelong Health, Rowett Institute of Nutrition and Health, University of Aberdeen, Greenburn Road, Bucksburn, Aberdeen AB21 9SB, UK

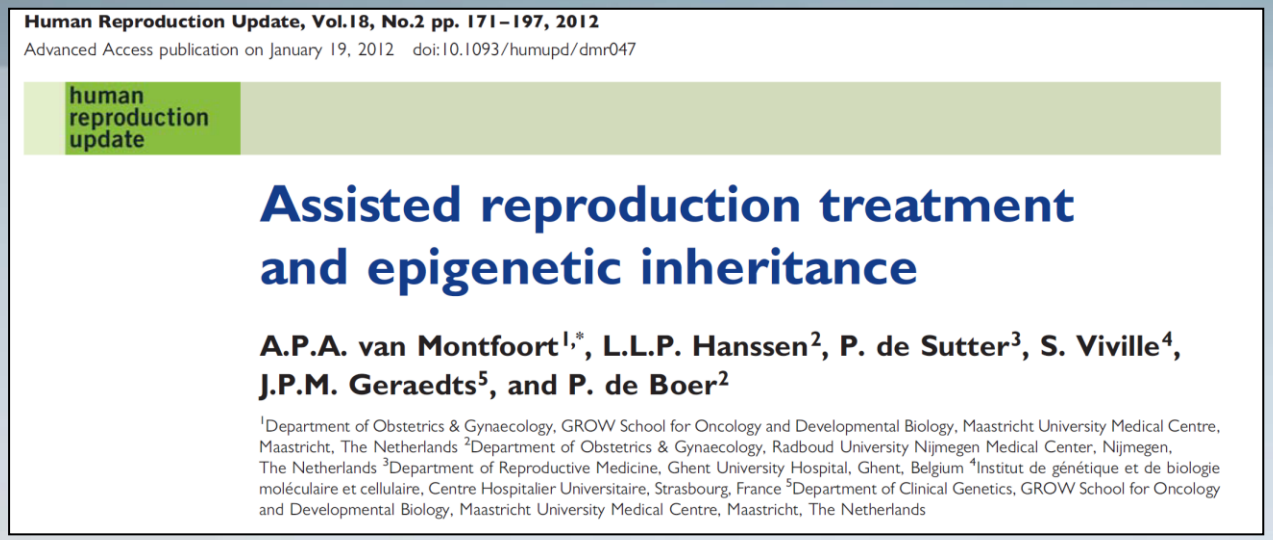


Study or Subgroup	IVF/ICSI children Events	Total	Spontaneous Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Halliday 2004	4	5	33	180	9.8%	17.82 [1.93, 164.65]
King 2010a	4	22	2	31	37.5%	3.22 [0.53, 19.42]
Lidegaard 2005a	0	6052	54	442349	40.6%	0.67 [0.04, 10.86]
Sanchez-Albisua 2007a	1	33	0	39	12.1%	3.65 [0.14, 92.55]
Total (95% CI)		**6112**		**442599**	**100.0%**	**3.67 [1.39, 9.74]**
Total events	9		89			

Heterogeneity: $Chi^2 = 3.39$, df = 3 (P = 0.34); $I^2 = 12\%$
Test for overall effect: Z = 2.62 (P = 0.009)

Figure 4 Forest plot analyses for risk of any imprinting disorder between IVF/ICSI versus spontaneously conceived children.

- ***Conclusions:*** There was an increase in imprinting disorders in children conceived though IVF and ICSI



Human Reproduction Update, Vol.18, No.2 pp. 171–197, 2012
Advanced Access publication on January 19, 2012 doi:10.1093/humupd/dmr047

human reproduction update

Assisted reproduction treatment and epigenetic inheritance

A.P.A. van Montfoort[1,*], L.L.P. Hanssen[2], P. de Sutter[3], S. Viville[4], J.P.M. Geraedts[5], and P. de Boer[2]

[1]Department of Obstetrics & Gynaecology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands [2]Department of Obstetrics & Gynaecology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands [3]Department of Reproductive Medicine, Ghent University Hospital, Ghent, Belgium [4]Institut de génétique et de biologie moléculaire et cellulaire, Centre Hospitalier Universitaire, Strasbourg, France [5]Department of Clinical Genetics, GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands

- In human sperm from compromised spermatogenesis, sequence-specific DNA hypomethylation is observed repeatedly.
- Transmittance of sperm and oocyte DNA methylation defects is possible.
- ***ART can induce epigenetic variation that might be transmitted to the next generation.***

Messages

- Worse obstetric and perinatal outcomes in children conceived after ART
- Increase preterm delivery and low birth weight comparing ART x subfertile x fertile children
- Neonatal outcome ejaculated x non-ejaculate sperm: no difference
- Increase birth defects in ART children
- Increased risk of death due to Congenital Malformations (CM) in First Degree Relatives (FDR) of men with lower semen parameters
- Increased risk of Imprinting Disorders in ICSI/IVF children related to compromised spermatogenesis