Zinnige zorg
wat kan het laboratorium hieraan bijdragen?

Madelon van Wely, PhD
Epidemiologist/Methodologist

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amc center for reproductive medicine

Conflict of interest

- I lead the Satellite of the Cochrane Gynecology and Fertility
- I am mother of identical healthy twins
- I have no commercial interests in assisted reproduction

amc enter for reproductive medicine

Zinnige zorg volgens ZN

de identificatie en het tegengaan van niet-effectieve en/of onnodige zorg, zodat de kwaliteit van de zorg voor de patiënt verbetert, de gezondheidswinst toeneemt en onnodige kosten worden vermeden

www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/zinnige-zorg---doorlichting-van-het-basispakket

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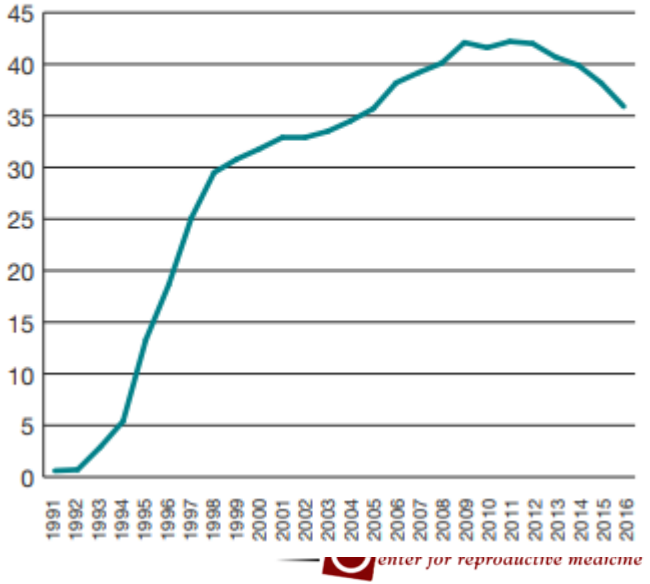
ICSI en IVF in Nederland

	2017				
	IVF		ICSI		
	Aantal	%	aantal	%	aantal
gestarte cycli	6417	100	7574	100	
follikelpuncties	5536	86,3	6500	85,8	
embryotransfers	5922	76,7	5793	76,5	13469
zwangerschappen	1636	25,5	2177	28,7	3166
doorgaande zwangersch.	1204	18,8	1676	22,1	2187
betrouwbaarheidsinterval		18-20		21-23	
eenling	1164	97,7	1608	95,9	2138
tweeling	40	3,3	67	4,0	48
drieling	0	0	1	0,1	1

IVF 2250 – 2650
ICSI 2600 – 3000

Figure 29: Proportion of IVF treatment cycles that used ICSI



To ICSI or not?

ICSI does not increase the cumulative live birth rate in non-male factor infertility

Z Li, A Y Wang, M Bowman, K Hammarberg, C Farquhar, L Johnson, N Safi, E A Sullivan ✉

Human Reproduction, Volume 33, Issue 7, July 2018, Pages 1322–1330,

8470 vrouwen ICSI | 4993 vrouwen IVF

HR kind 0.99 (95% CI 0.92–1.06)
HR cum kind 0.96 (95% CI 0.85–1.10)

Add-ons

Sperm DNA fragmentation tests
Hyaluron acid or MACS
Time-lapse imaging
Preimplantation genetic screening
Mitochondria DNA load measurement
Assisted hatching
Endometrial scratching

Asian Journal of Andrology

Asian J Androl. 2017 Jan-Feb; 19(1): 80–90.
Published online 2016 Jun 24. doi: 10.4103/1008-682X.182822

PMCID: PMC5227680
PMID: 27345006

A systematic review and meta-analysis to determine the effect of sperm DNA damage on *in vitro* fertilization and intracytoplasmic sperm injection outcome

Luke Simon,[1,*] Armand Zini,[2,*] Alina Dyachenko,[2] Antonio Ciampi,[2] and Douglas T Carrell[1,3,4]

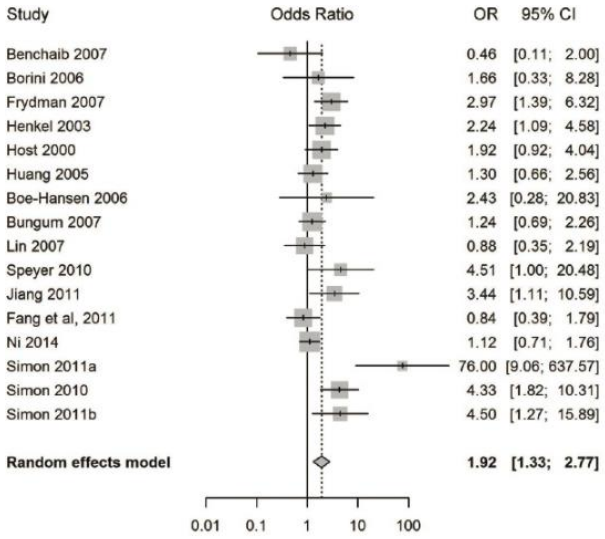
Study characteristics

Sperm DNA damage test	Nr of studies	Number of cycles	Cut-off value (range %)
SCSA	23	2813	10-30
SCD	8	2358	17-30
TUNEL	18	2098	4-48
COMET	7	798	52-82

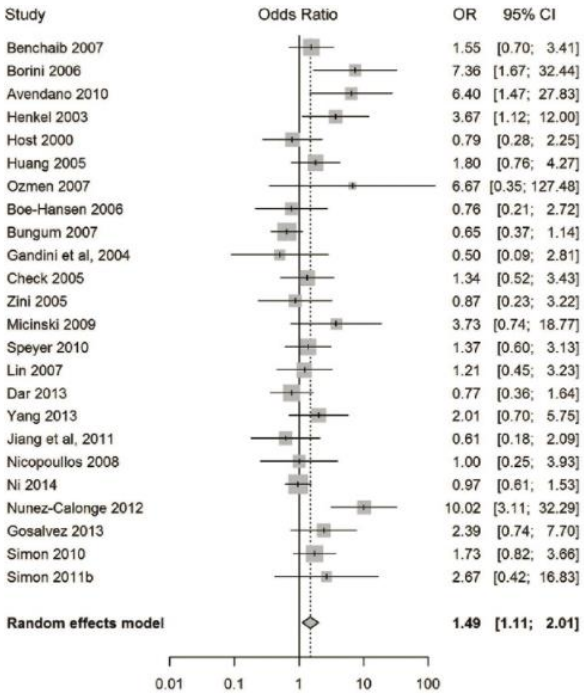
Simon et al., 2017

Effect		Number of studies	Fixed effects model		Random effects model		Percentage of variation across studies I^2 (%)
			OR (95% CI)	P	OR (95% CI)	P	
Overall effect		56	1.68 (1.49–1.89)	0.0000*	1.84 (1.5–2.27)	<0.0001*	60.9
Sperm DNA damage assays							
SCSA		23	1.18 (0.96–1.44)	0.1115	1.22 (0.93–1.61)	0.1522	38.1
TUNEL		18	2.18 (1.75–2.72)	0.0000*	2.22 (1.61–3.05)	<0.0001*	43.8
Comet		7	3.34 (2.32–4.82)	0.0000*	3.56 (1.78–7.09)	0.0003*	65.5
SCD		8	1.51 (1.18–1.92)	0.0011*	1.98 (1.19–3.3)	0.0086*	72.9
Types of assisted treatment							
IVF		16	1.65 (1.34–2.04)	0.0000*	1.92 (1.33–2.77)	0.0005*	60.7
ICSI		24	1.31 (1.08–1.59)	0.0068*	1.49 (1.11–2.01)	0.0075*	48.7
Mixed		16	2.37 (1.89–2.97)	0.0000*	2.32 (1.54–3.5)	0.0001*	64.4
Assays	*Types*						
SCSA	IVF	6	1.32 (0.91–1.91)	0.1471	1.43 (0.86–2.37)	0.1670	35.9
SCSA	ICSI	12	0.96 (0.72–1.27)	0.7800	0.96 (0.72–1.27)	0.7800	0.0
SCSA	Mixed	5	1.69 (1.07–2.66)	0.0234*	1.93 (0.68–5.42)	0.2147	70.5
TUNEL	IVF	6	1.81 (1.29–2.55)	0.0007*	1.78 (1.2–2.65)	0.0039*	20.1
TUNEL	ICSI	7	2.11 (1.38–3.23)	0.0005*	2.38 (1.31–4.31)	0.0042*	42.4
TUNEL	Mixed	5	2.92 (1.95–4.38)	0.0000*	3.17 (1.45–6.94)	0.0038*	61.5
Comet	IVF	3	5.86 (2.97–11.53)	0.0000*	8.39 (2.16–32.55)	0.0021*	67.8
Comet	ICSI	2	1.84 (0.92–3.68)	0.0859	1.84 (0.92–3.68)	0.0859	0.0
Comet	Mixed	2	3.36 (1.92–5.86)	0.0000*	2.27 (0.46–11.26)	0.3150	81.9
SCD	IVF	1	1.12 (0.71–1.76)	0.6405	1.12 (0.71–1.76)	0.6405	N/A
SCD	ICSI	3	1.42 (0.95–2.12)	0.0896	2.65 (0.64–10.86)	0.1770	85.9
SCD	Mixed	4	2.07 (1.36–3.16)	0.0007*	2.14 (1.09–4.19)	0.0272*	60.9

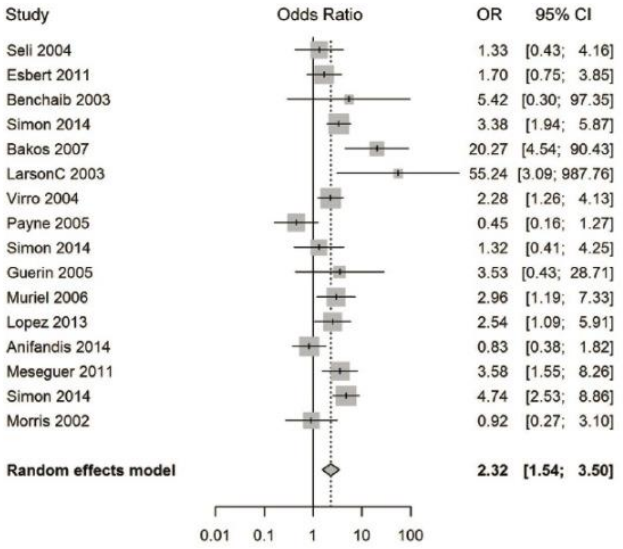
IVF



ICSI



IVF/ICSI



Reproductive BioMedicine Online (2015) 30, 120–127

www.sciencedirect.com
www.rbmonline.com

REVIEW

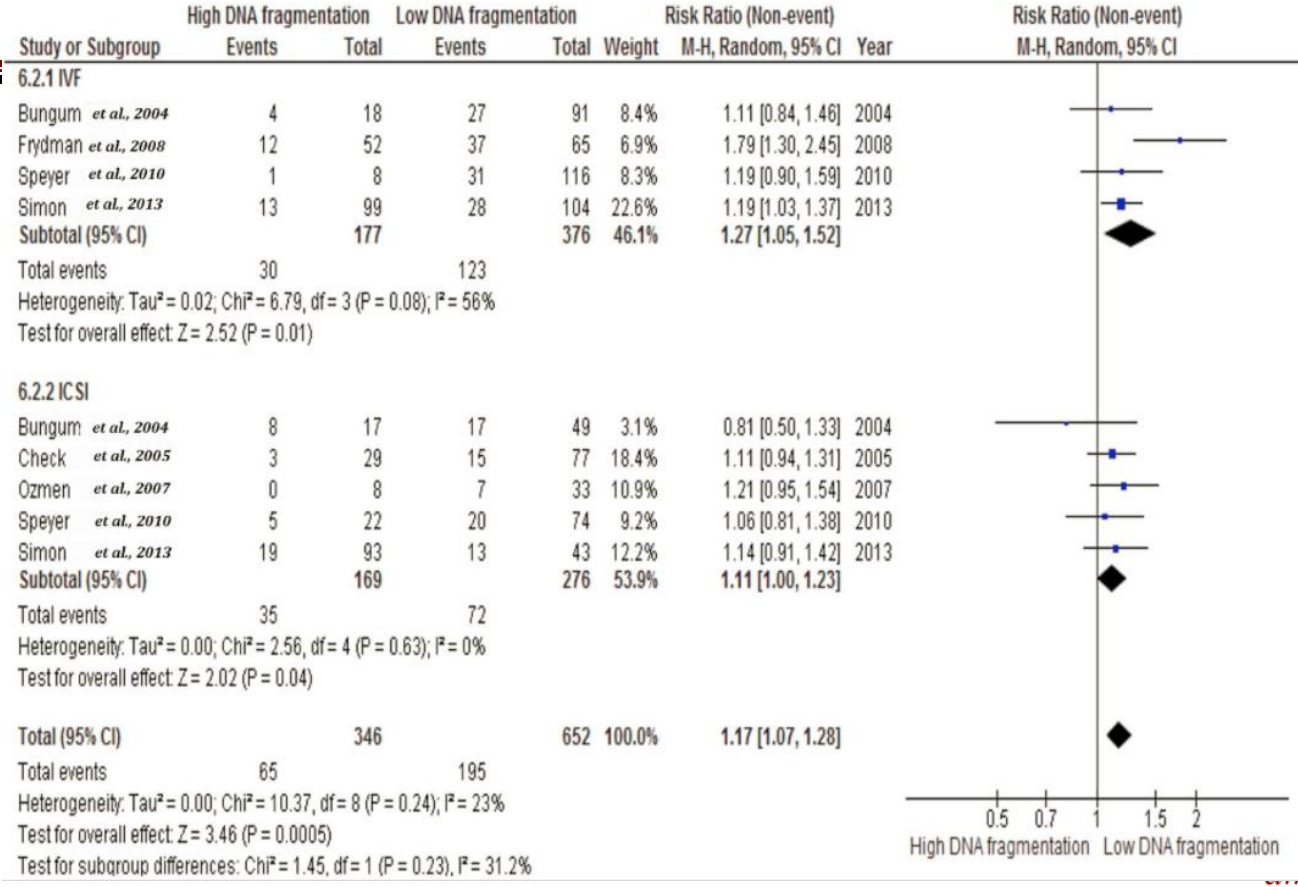
The effect of sperm DNA fragmentation on live birth rate after IVF or ICSI: a systematic review and meta-analysis

A Osman *, H Alsomait, S Seshadri, T El-Toukhy, Y Khalaf

Study characteristics

Sperm DNA damage test	Nr of studies	Number of cycles	Cut-off value DFI (%))
SCSA	3	620	27-30
TUNEL	2	158	10-35
COMET	1	339	50

Osman et al., 2015



Osman et al., 2015

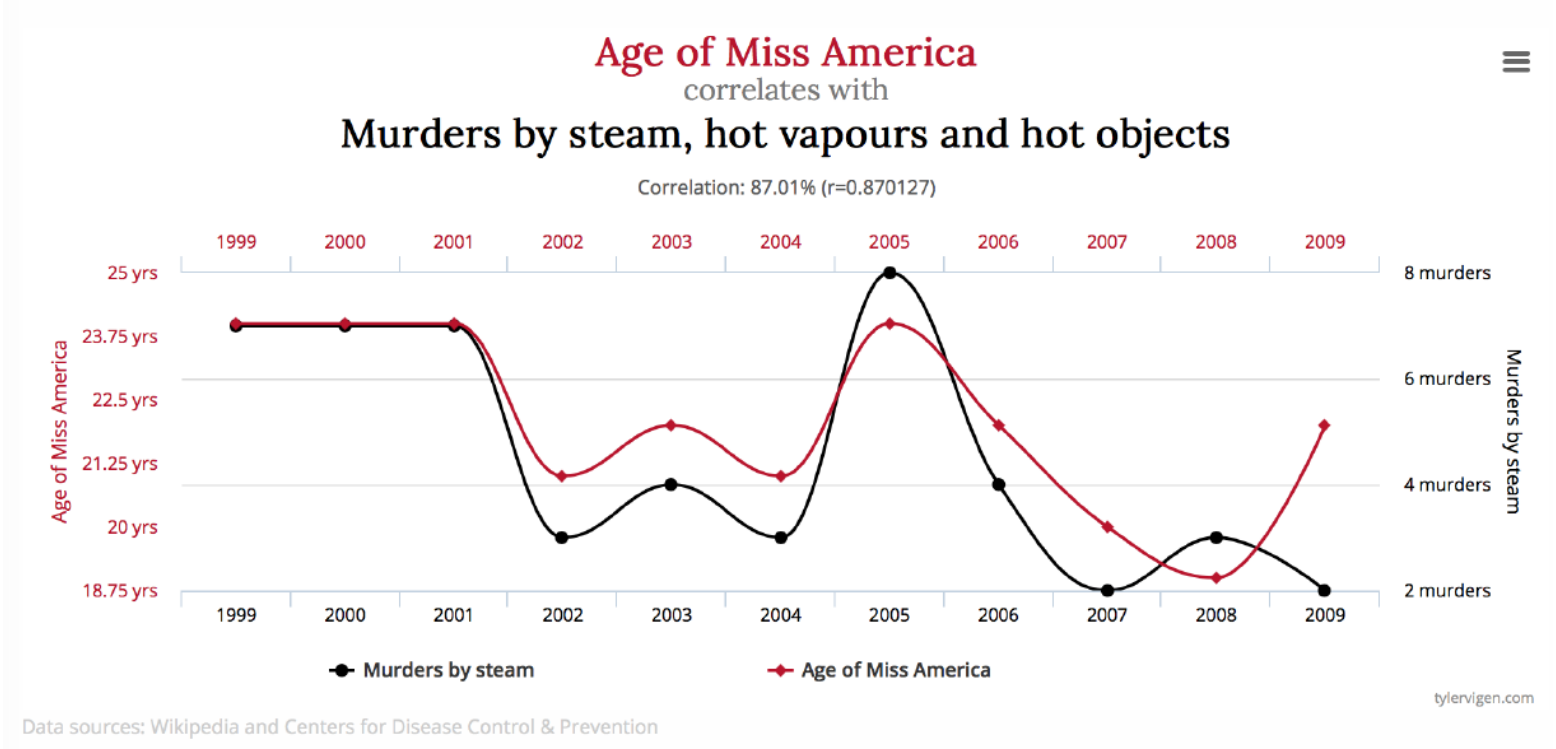
Pregnancy loss

- Miscarriage: Robinson 2011
  - Meta-analysis more miscarriage in high vs low SDF
  - Overall RR 2.16 (1.54, 3.03)
  - TUNEL assay RR 3.94 (2.45, 6.32)

Association is not causation

- Association
  - A relation was found between 2 variables
  - Is the relationship due to other factors?
  - Controlling for confounders helps
- Causation
  - A change in the variable under study directly caused a change in the outcome

Biological plausibility…



Fertility and Sterility

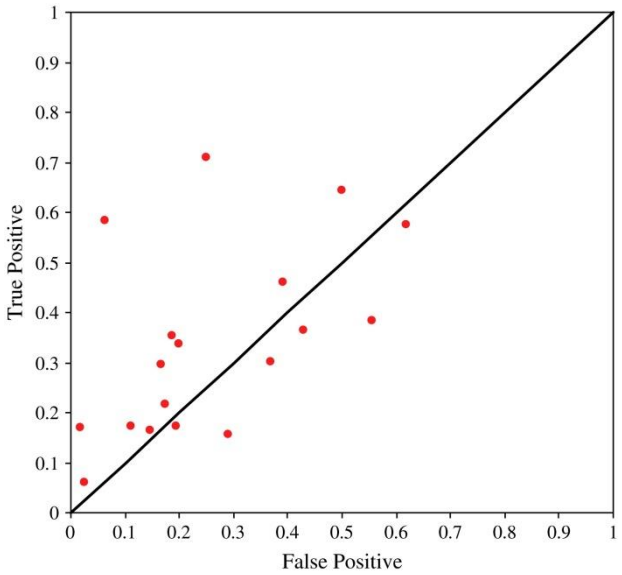
asrm American Society for Reproductive Medicine

Do sperm DNA integrity tests predict pregnancy with in vitro fertilization?

John A. Collins, M.D., Kurt T. Barnhart, M.D., Peter N. Schlegel, M.D.

DNA damage to predict pregnancy

- 22 studies
- 13 studies involving 2162 cycles



Collins et al., 2008

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COLLECTION REVIEW

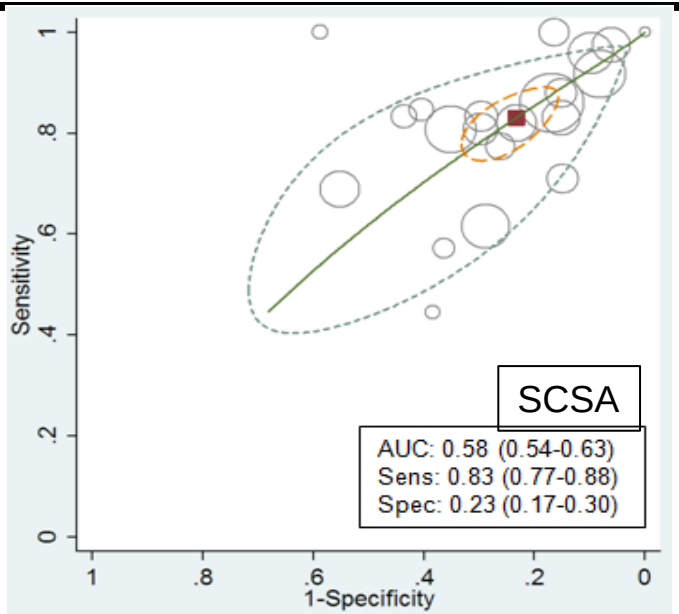
Measuring Sperm DNA Fragmentation and Clinical Outcomes of Medically Assisted Reproduction: A Systematic Review and Meta-Analysis

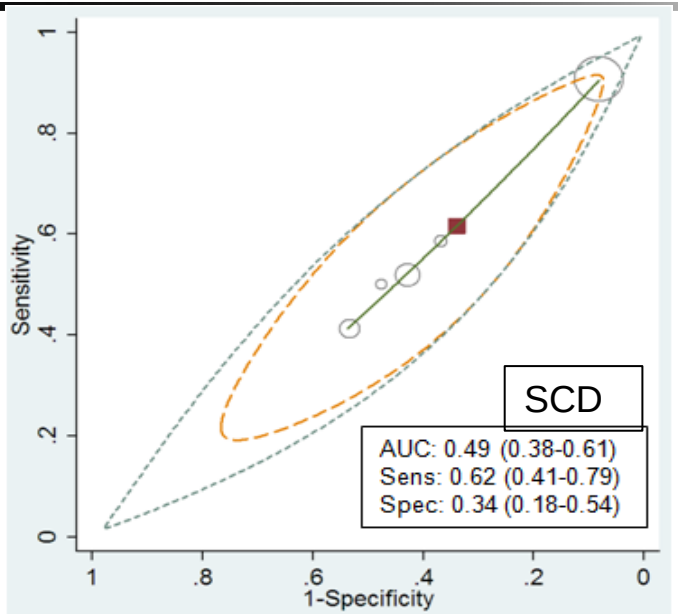
Maartje Cissen, Madelon van Wely, Irma Scholten, Steven Mansell, Jan Peter de Bruin, Ben Willem Mol, Didi Braat, Sjoerd Repping, Geert Hamer

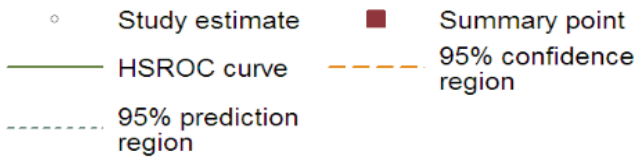
Published: November 10, 2016 • https://doi.org/10.1371/journal.pone.0165125

amc enter for reproductive medicine

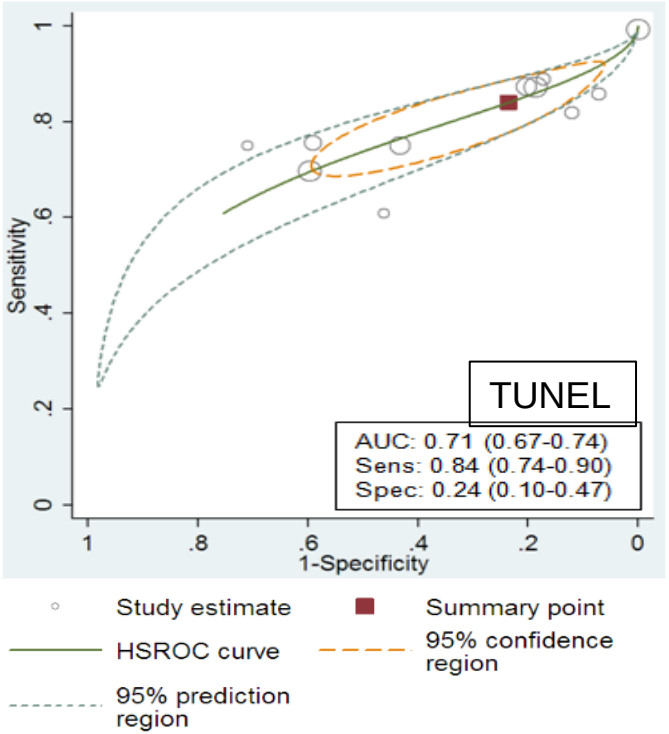
Results: HSROC curve

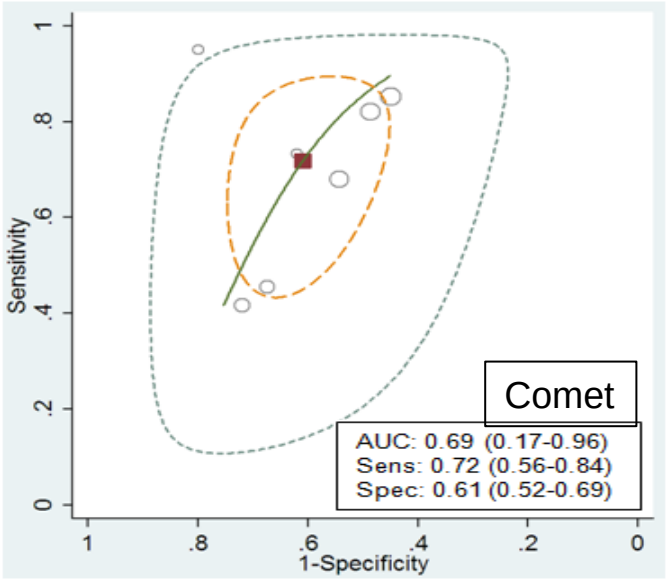






Results: HSROC curve

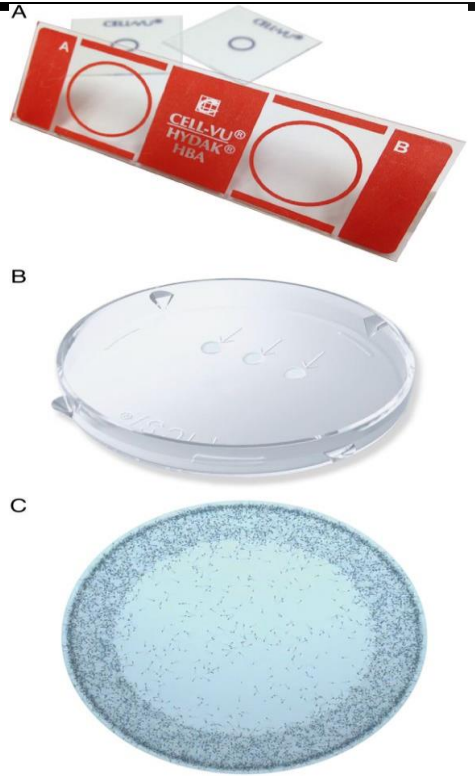




Add-ons

Adjunct	Evidence
Sperm DNA fragmentation tests	Limited - no clinical value
Hyaluron acid for PICSI	
Time-lapse imaging	
Preimplantation genetic screening	
Mitochondria DNA load measurement	
Assisted hatching	
Endometrial scratching	

Hyaluronic acid selected sperm for PICSI



(A) Hydak slide showing twin chambers

(B) PICSI plate showing channels (arrows) into which sperm suspensions are introduced.

(C) Photomicrograph from time-lapse recording showing a single PICSI hyaluronan dot.

K D Witt et al. BMJ Open 2016;6:e012609

Physiological, hyaluronan-selected intracytoplasmic sperm injection for infertility treatment (HABSelect): a parallel, two-group, randomised trial

David Miller, Susan Pavitt, Vinay Sharma, Gordon Forbes, Richard Hooper, Siladitya Bhattacharya, Jackson Kirkman-Brown, Arri Coomarasamy, Sheena Lewis, Rachel Cutting, Daniel Brison, Allan Pacey, Robert West, Kate Brian, Darren Griffin, Yakoub Khalaf

Lancet 2019; 393: 416–22

See Comment page 380

Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds Laboratories (D Miller PhD), Dental Translational and Clinical Research Unit, Leeds National Institute for Health Research Clinical Research Facility (Prof S Pavitt PhD), and Leeds Institute of Health Sciences (Prof R West PhD), University of Leeds, Leeds, UK; The Leeds Centre for Reproductive Medicine, Seacroft Hospital, Leeds, UK (Prof V Sharma PhD); Pragmatic Clinical Trials Unit, Centre for Primary Care and Public Health, Queen Mary University of London, London, UK (G Forbes MSc, R Hooper PhD); School of Medicine, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK (Prof S Bhattacharya MD); Institute of Metabolism and Systems Research, College of Medical & Dental Sciences, University of Birmingham, Birmingham, UK

Summary

Background Sperm selection strategies aimed at improving success rates of intracytoplasmic sperm injection (ICSI) include binding to hyaluronic acid (herein termed hyaluronan). Hyaluronan-selected sperm have reduced levels of DNA damage and aneuploidy. Use of hyaluronan-based sperm selection for ICSI (so-called physiological ICSI [PICSI]) is reported to reduce the proportion of pregnancies that end in miscarriage. However, the effect of PICSI on livebirth rates is uncertain. We aimed to investigate the efficacy of PICSI versus standard ICSI for improving livebirth rates among couples undergoing fertility treatment.

Methods This parallel, two-group, randomised trial included couples undergoing an ICSI procedure with fresh embryo transfer at 16 assisted conception units in the UK. Eligible women (aged 18–43 years) had a body-mass index of 19–35 kg/m² and a follicle-stimulating hormone (FSH) concentration of 3·0–20·0 mIU/mL or, if no FSH measurement was available, an anti-müllerian hormone concentration of at least 1·5 pmol/L. Eligible men (aged 18–55 years) had not had a vasovasostomy or been treated for cancer in the 24 months before recruitment and were able, after at least 3 days of sexual abstinence, to produce freshly ejaculated sperm for the treatment cycle. Couples were randomly assigned (1:1) with an online system to receive either PICSI or a standard ICSI procedure. The primary outcome was full-term (≥37 weeks' gestational age) livebirth, which was assessed in all eligible couples who completed follow-up. This trial is registered, number ISRCTN99214271.

Findings Between Feb 1, 2014, and Aug 31, 2016, 2772 couples were randomly assigned to receive PICSI (n=1387) or ICSI (n=1385), of whom 2752 (1381 in the PICSI group and 1371 in the ICSI group) were included in the primary analysis. The term livebirth rate did not differ significantly between PICSI (27·4% [379/1381]) and ICSI (25·2% [346/1371]) groups (odds ratio 1·12, 95% CI 0·95–1·34; p=0·18). There were 56 serious adverse events in total, including 31 in the PICSI group and 25 in the ICSI group; most were congenital abnormalities and none were attributed to treatment.

Interpretation Compared with ICSI, PICSI does not significantly improve term livebirth rates. The wider use of PICSI, therefore, is not recommended at present.

Add-ons

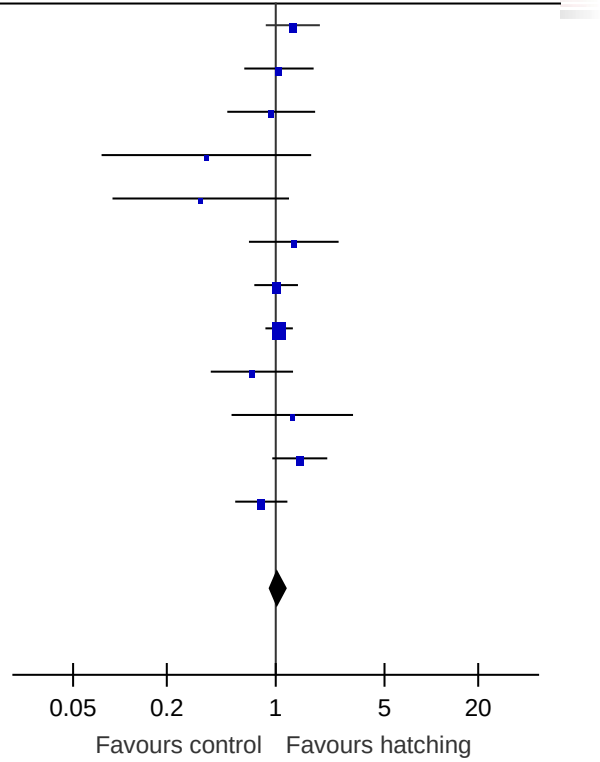
Adjunct	Evidence
Sperm DNA fragmentation tests	Moderate - no value for clinical practise
Hyaluron acid or MACS	Moderate - possible clinical value
Time-lapse imaging	
Preimplantation genetic screening	
Mitochondria DNA load measurement	
Assisted hatching	
Endometrial scratching	

Assisted hatching

Study or Subgroup	Assisted hatching Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Cohen 1992	34	69	26	68	10.6%	1.29 [0.88, 1.89]	1992
Hellebaut 1996	21	60	20	60	6.8%	1.05 [0.64, 1.73]	1996
Lanzendorf 1998	12	41	15	48	4.4%	0.94 [0.50, 1.77]	1998
Hurst 1998	2	13	3	7	0.8%	0.36 [0.08, 1.67]	1998
Germond 2004	3	84	8	74	1.1%	0.33 [0.09, 1.20]	2004
Petersen 2005	17	75	13	75	4.2%	1.31 [0.68, 2.50]	2005
Sagoskin 2007	55	121	37	82	15.0%	1.01 [0.74, 1.37]	2007
Ge 2008	156	487	144	473	28.2%	1.05 [0.87, 1.27]	2008
Balakier 2009	13	45	16	39	5.0%	0.70 [0.39, 1.27]	2009
Razi 2013	10	90	8	92	2.4%	1.28 [0.53, 3.09]	2013
Wan 2014	39	96	29	102	10.3%	1.43 [0.97, 2.11]	2014
Shi 2016	29	82	42	96	11.3%	0.81 [0.56, 1.17]	2016
Total (95% CI)		**1263**		**1216**	**100.0%**	**1.04 [0.90, 1.19]**	
Total events	391		361				

Heterogeneity: Tau² = 0.01; Chi² = 12.90, df = 11 (P = 0.30); I² = 15%

Test for overall effect: Z = 0.49 (P = 0.63)



Add-ons

Adjunct	Evidence
Sperm DNA fragmentation tests	Moderate - no value for clinical practise
Hyaluron acid or MACS	Moderate - possible clinical value
Assisted hatching	Low to moderate – probably no clinical value
Mitochondria DNA load measurement	
Time-lapse imaging	
Endometrial scratching	

CARE map (time-lapse)

Success rates are significantly higher with CAREmaps

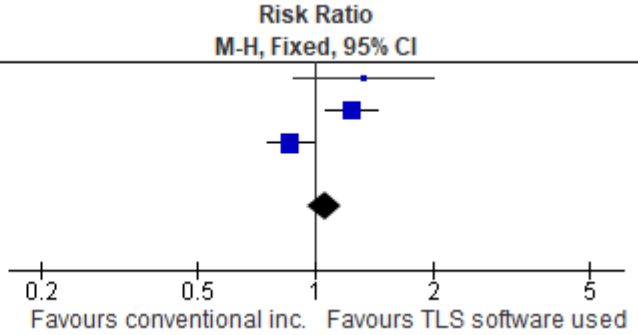
Age Range	Standard Incubation Birth Rates	CAREmaps® Birth Rates	Relative increase in birth rates with CAREmaps®
Below 35	42% (950 / 2262)	46% (270 / 587)	+11%
35 - 37	31% (296 / 958)	35% (116 / 333)	+12%
38 - 39	21% (127 / 605)	28% (66 / 236)	+35%
40 - 42	11% (53 / 483)	18% (33 / 186)	+64%
43 and 44	6% (5 / 79)	9% (3 / 35)	+35%
Over 39	10%	16%	+59%

This table shows the birth rates per embryo transfer for different female age categories for treatment with own eggs between 1/5/11 and 28/2/14 with the number of births and embryo transfers for the review shown in brackets. It compares birth rates for standard practice at CARE with birth rates when using CAREmaps which is an embryo selection method unique to CARE. Birth rates are compared per transfer procedure as CAREmaps is used to select embryos, so applied at the time of transfer.

Time-lapse - live birth

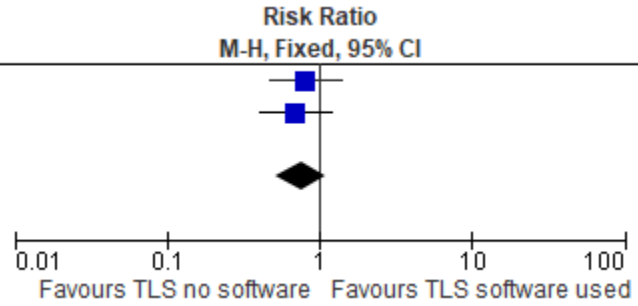
Study or Subgroup	TLS Events	TLS Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kovacs 2019	34	80	26	81	6.8%	1.32 [0.88, 1.99]
Rubio 2014	216	444	162	412	44.0%	1.24 [1.06, 1.44]
Yang 2018 (1)	162	300	188	300	49.2%	0.86 [0.75, 0.99]
Total (95% CI)		**824**		**793**	**100.0%**	**1.06 [0.96, 1.17]**
Total events	412		376			

Heterogeneity: Chi² = 13.90, df = 2 (P = 0.0010); I² = 86%
Test for overall effect: Z = 1.11 (P = 0.27)



Study or Subgroup	TLS Events	TLS Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kaser 2017 (1)	21	56	12	26	48.6%	0.81 [0.48, 1.39]
Kaser 2017 (2)	18	54	13	27	51.4%	0.69 [0.40, 1.19]
Total (95% CI)		**110**		**53**	**100.0%**	**0.75 [0.51, 1.10]**
Total events	39		25			

Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.47 (P = 0.14)

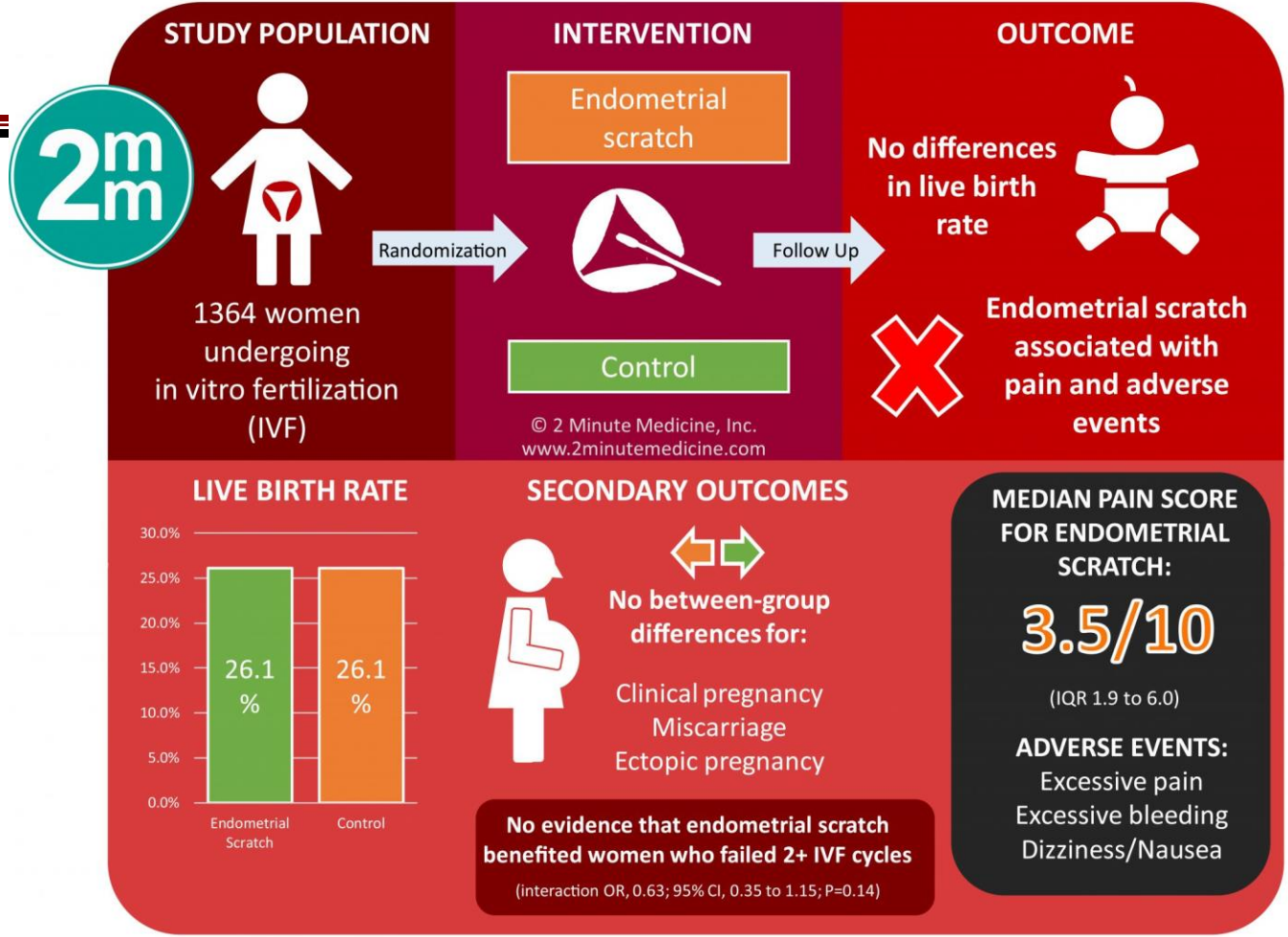


Time-lapse – zinnige zorg

Add-on	Evidence
Sperm DNA fragmentation tests	Moderate - no value for clinical practise
Hyaluron acid or MACS	Moderate - possible clinical value
Assisted hatching	Low to moderate – probably no clinical value
Mitochondria DNA load measurement	
Time-lapse imaging	Low - unclear
Endometrial scratching	

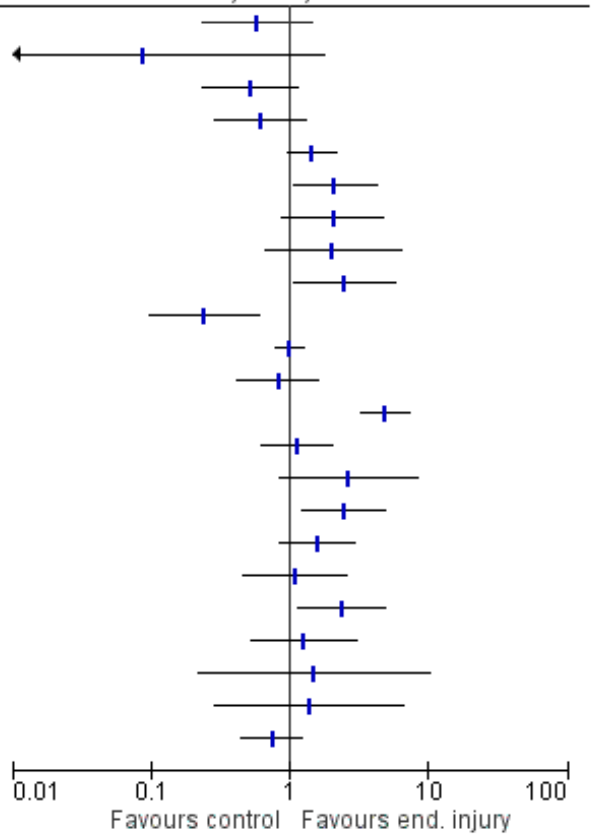
Endometrial schratching

A Randomized Trial of Endometrial Scratching before In Vitro Fertilization



Lensen et al. *NEJM*. January 2019.

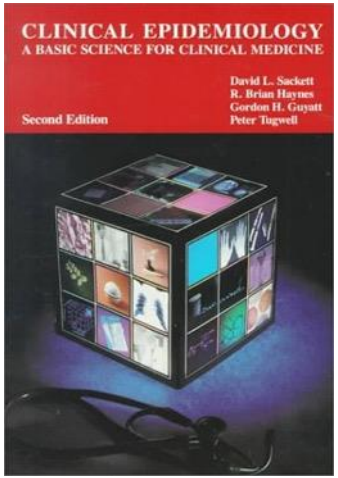
Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Odds Ratio M-H, Fixed, 95% CI
Aflatoonian 2016 (1)	10	50	15	50	0.58 [0.23, 1.46]
Baum 2012	0	18	4	18	0.09 [0.00, 1.75]
Eskew 2018	23	53	28	47	0.52 [0.23, 1.15]
Frantz 2019 (2)	14	98	20	93	0.61 [0.29, 1.29]
Gibreel 2015	91	193	74	194	1.45 [0.97, 2.17]
Gurgan 2018	27	153	14	152	2.11 [1.06, 4.21]
Guven 2014	19	62	11	62	2.05 [0.88, 4.77]
Hilton 2019	13	25	9	26	2.05 [0.66, 6.31]
Inal 2012	22	50	12	50	2.49 [1.06, 5.86]
Karimzade 2010 (3)	7	77	23	79	0.24 [0.10, 0.61]
Lensen 2019	180	690	176	674	1.00 [0.78, 1.27]
Liu 2017 (4)	25	70	29	72	0.82 [0.42, 1.62]
Mahran 2016	134	209	56	209	4.88 [3.22, 7.40]
Mak 2017 (5)	32	115	29	114	1.13 [0.63, 2.03]
Narvekar 2010	11	49	5	51	2.66 [0.85, 8.34]
Nastri 2013	33	79	18	79	2.43 [1.22, 4.85]
Polanski 2015	40	80	31	80	1.58 [0.84, 2.96]
Shahrokh-Tehraninejad 2016	14	60	13	60	1.10 [0.47, 2.59]
Shohayeb 2012	28	105	14	105	2.36 [1.16, 4.81]
TK 2017	14	55	12	56	1.25 [0.52, 3.02]
Wolff 2018	8	12	4	7	1.50 [0.22, 10.22]
Xu 2015	5	15	4	15	1.38 [0.29, 6.60]
Yeung 2014	39	150	48	150	0.75 [0.45, 1.23]

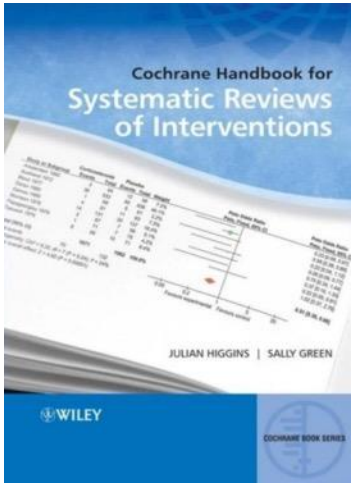


What is technology?

- Something new?
  - There is something new every year at ESHRE
  - Developments go very rapidly
- Something cool?
  - Many things strike us with awe
  - And they also strike our patients
- Something better?
  - A true innovation has a true (proven!) positive impact on the care we provide to our patients everyday
    - Not necessarily cool or perhaps not even new….

What is proof? – Evidence-based –





→ Grading the quality of evidence and the strength of recommendations

- http://www.gradeworkinggroup.org/

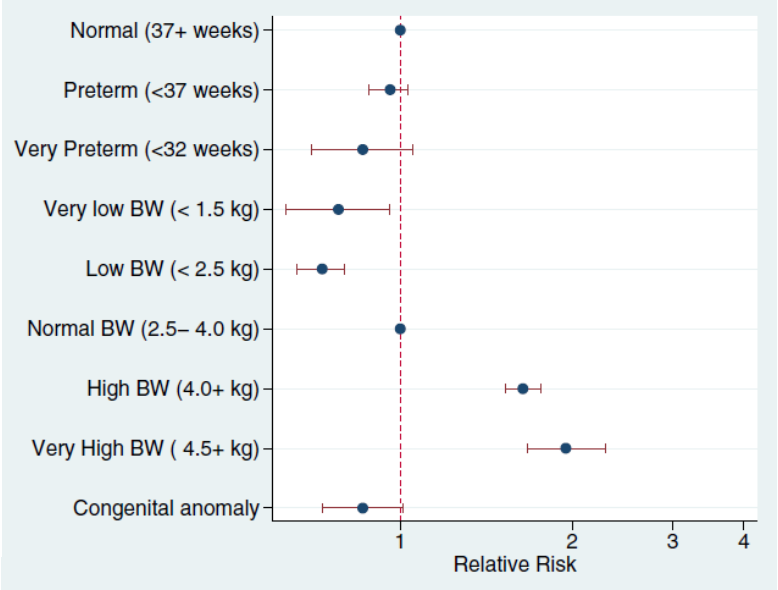
What is proof? – always RCTs? –

ORIGINAL ARTICLE: ASSISTED REPRODUCTION

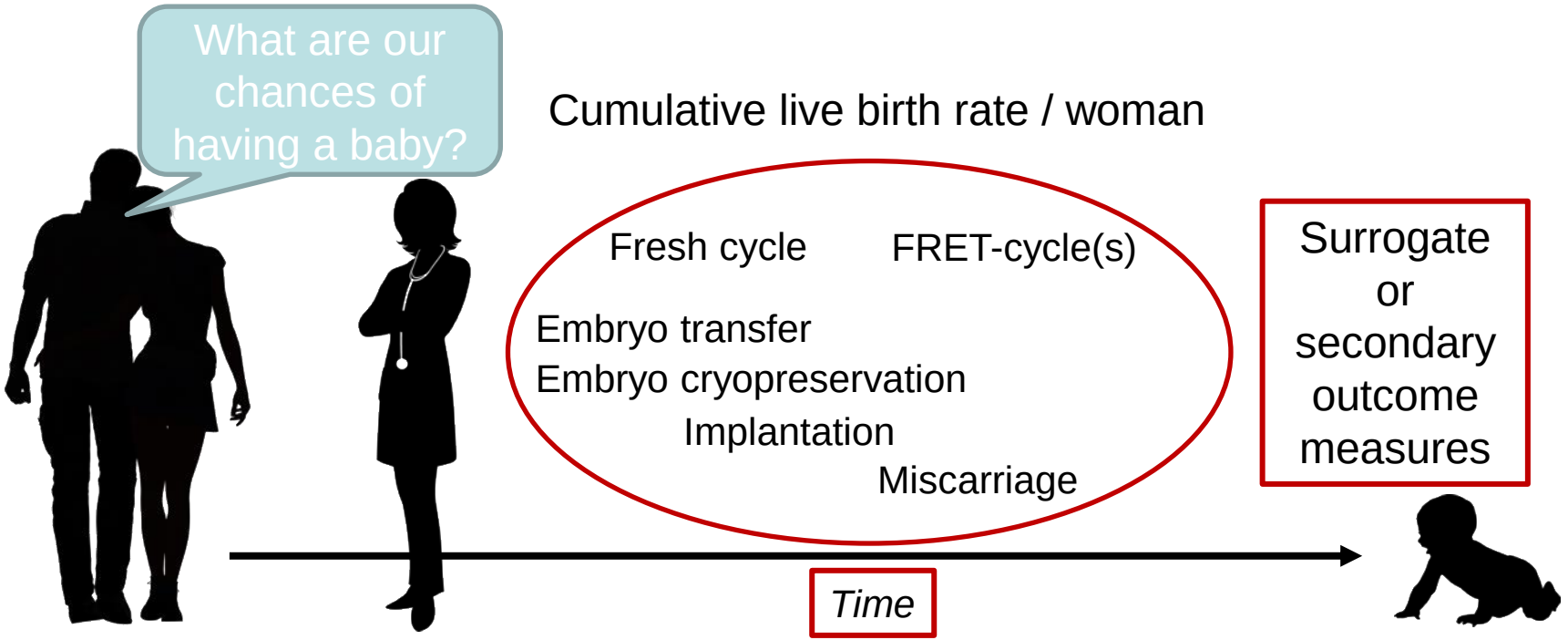
Obstetric and perinatal outcomes after either fresh or thawed frozen embryo transfer: an analysis of 112,432 singleton pregnancies recorded in the Human Fertilisation and Embryology Authority anonymized dataset

Abha Maheshwari, M.D.,[a] Edwin Amalraj Raja, Ph.D.,[b] and Siladitya Bhattacharya, M.D.[b]

[a] National Health Service Grampian; and [b] Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom



What is proof? – Outcomes –



Griesinger, HR (2016)

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What is proof? – Outcomes –

Implantation rate - Rate per transfer

The NEW ENGLAND JOURNAL of MEDICINE

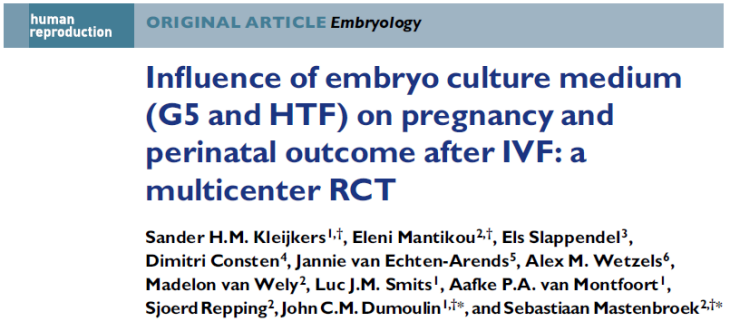
ESTABLISHED IN 1812 JULY 5, 2007 VOL. 357 NO. 1

In Vitro Fertilization with Preimplantation Genetic Screening

Sebastiaan Mastenbroek, M.Sc., Moniek Twisk, M.D., Jannie van Echten-Arends, Ph.D., Birgit Sikkema-Raddatz, Ph.D., Johanna C. Korevaar, Ph.D., Harold R. Verhoeve, M.D., Niels E.A. Vogel, M.D, Eus G.J.M. Arts, Ph.D., Jan W.A. de Vries, Ph.D., Patrick M. Bossuyt, Ph.D., Charles H.C.M. Buys, Ph.D., Maas Jan Heineman, M.D., Ph.D., Sjoerd Repping, Ph.D., and Fulco van der Veen, M.D., Ph.D.

- Increased implantation rate
- Decreased live birth rate

Fertilization



human reproduction ORIGINAL ARTICLE *Embryology*

Influence of embryo culture medium (G5 and HTF) on pregnancy and perinatal outcome after IVF: a multicenter RCT

Sander H.M. Kleijkers[1,†], Eleni Mantikou[2,†], Els Slappendel[3], Dimitri Consten[4], Jannie van Echten-Arends[5], Alex M. Wetzels[6], Madelon van Wely[2], Luc J.M. Smits[1], Aafke P.A. van Montfoort[1], Sjoerd Repping[2], John C.M. Dumoulin[1,†*], and Sebastiaan Mastenbroek[2,†*]

- Increased fertilization rate
- Decreased live birth rate

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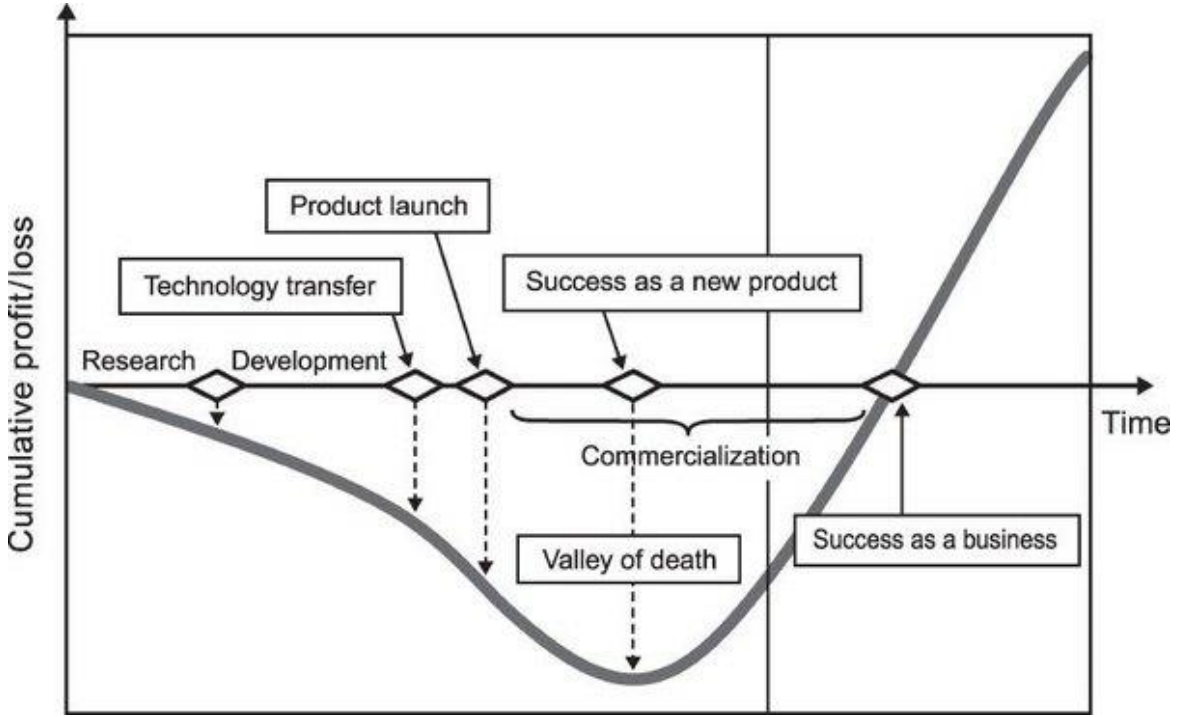
What is commercialization? – conflict of interest –

- To have or represent a financial interest in the use of treatments, diagnostics, add-ons, drugs
  - Unavoidable in a capitalist economy
  - Companies
  - Commercial private clinics
  - Or combinations (professors at private clinics)

- Not bad per se (drives innovation)
  - Should always be clearly presented
  - Conflict of interest slide, declaration
  - Should be taken into account when weighing the evidence

What is commercialization? – goal –

- To make a profit as fast and as large as possible



Example: PGS in the beginning…

FERTILITY AND STERILITY®
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Published by Elsevier Science Inc.

Vol. 68, No. 6, December 1997
Printed on acid-free paper in U. S. A.

Preimplantation genetic diagnosis increases the implantation rate in human in vitro fertilization by avoiding the transfer of chromosomally abnormal embryos

Luca Gianaroli, M.D.
M. Cristina Magli, M.Sc.
Anna Pia Ferraretti, Ph.D.
Agnese Fiorentino, B.Sc.
John Garrisi, Ph.D.
Santiago Munné, Ph.D.

Preimplantation genetic diagnosis significantly reduces pregnancy loss in infertile couples: a multicenter study

Santiago Munné, Ph.D.,[a] Jill Fischer, M.Sc.,[a] Alison Warner, M.Sc.,[a] Serena Chen, M.D.,[b] Christo Zouves, M.D.,[c] Jacques Cohen, Ph.D.,[a] and the Referring Centers PGD Group

Fertility and Sterility® Vol. 85, No. 2, February 2006

Improved implantation after preimplantation genetic diagnosis of aneuploidy

Authors: Santiago Munné[1]; Mireia Sandalinas[2]; Tomas Escudero[2]; Esther Velilla[2]; Renee Walmsley[2]; Sasha Sadowy[2]; Jacques Cohen[2]; David Sable[2]
Source: Reproductive BioMedicine Online, Volume 7, Number 1, July 2003, pp. 91-97(7)

Human Reproduction vol.14 no.9 pp.2191–2199, 1999

OUTSTANDING CONTRIBUTION

Positive outcome after preimplantation diagnosis of aneuploidy in human embryos*

Santiago Munné[1,4], Cristina Magli[2], Jacques Cohen[1], Paula Morton[3], Sasha Sadowy[1], Luca Gianaroli[2], Michael Tucker[3], Carmen Márquez[1], David Sable[1], Anna Pia Ferraretti[2], Joe B.Massey[3] and Richard Scott[1]

Human Reproduction vol.15 no.9 pp.2003–2007, 2000

Healthy births and ongoing pregnancies obtained by preimplantation genetic diagnosis in patients with advanced maternal age and recurrent implantation failure

S.Kahraman[1,4], M.Bahçe[2], H. Şamlr[3], N.İmirzalıoğlu[2], K.Yakısn[1], G.Cengiz[1] and E.Dönmez[1]

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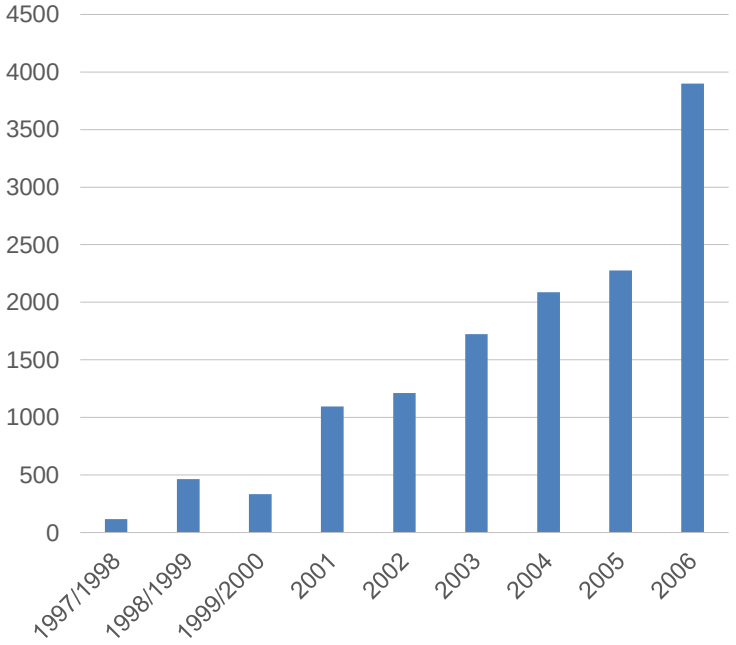
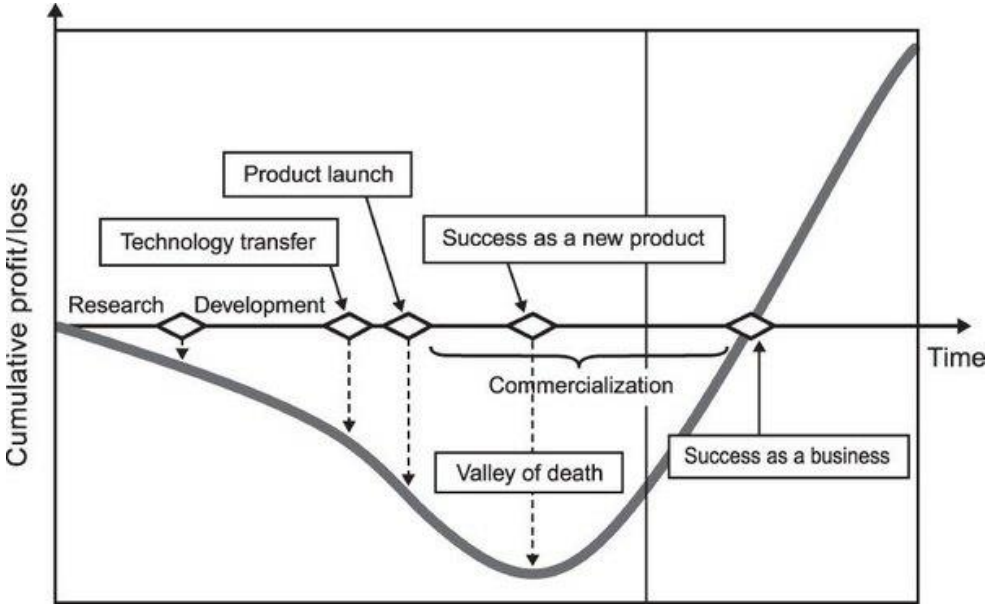
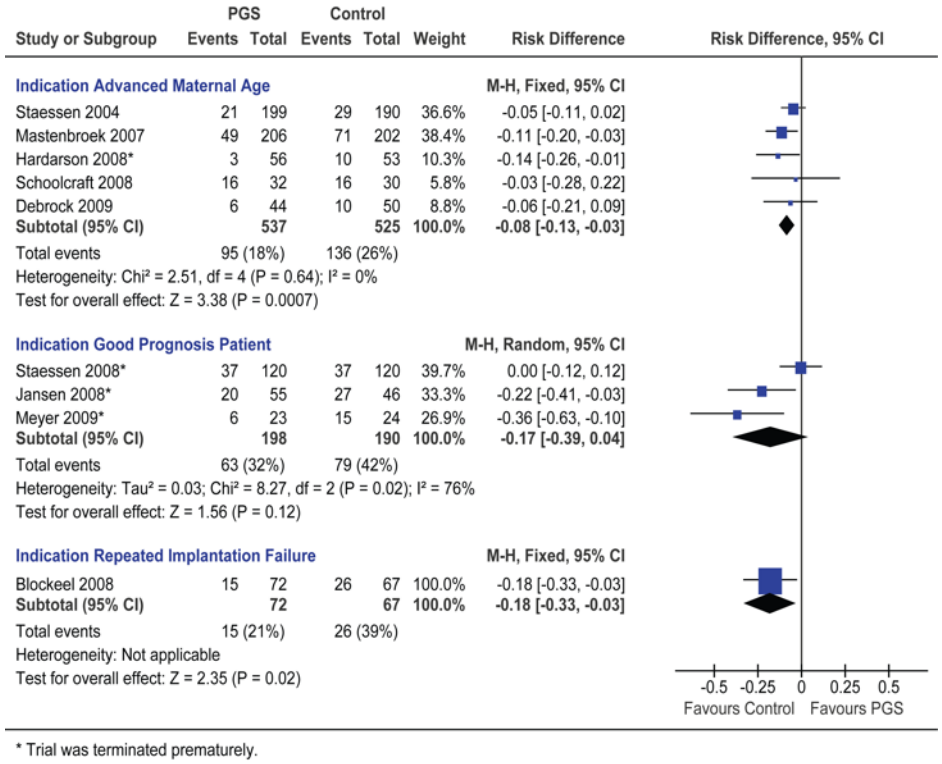
Use of PGS





ESHRE PGD Consortium Data Collections

Meta-analysis PGS 2011



Study or Subgroup	PGS Events	PGS Total	Control Events	Control Total	Weight	Risk Difference
Indication Advanced Maternal Age						M-H, Fixed, 95% CI
Staessen 2004	21	199	29	190	36.6%	-0.05 [-0.11, 0.02]
Mastenbroek 2007	49	206	71	202	38.4%	-0.11 [-0.20, -0.03]
Hardarson 2008*	3	56	10	53	10.3%	-0.14 [-0.26, -0.01]
Schoolcraft 2008	16	32	16	30	5.8%	-0.03 [-0.28, 0.22]
Debrock 2009	6	44	10	50	8.8%	-0.06 [-0.21, 0.09]
Subtotal (95% CI)		**537**		**525**	**100.0%**	**-0.08 [-0.13, -0.03]**
Total events	95 (18%)		136 (26%)			
Heterogeneity: Chi² = 2.51, df = 4 (P = 0.64); I² = 0%						
Test for overall effect: Z = 3.38 (P = 0.0007)						
Indication Good Prognosis Patient						M-H, Random, 95% CI
Staessen 2008*	37	120	37	120	39.7%	0.00 [-0.12, 0.12]
Jansen 2008*	20	55	27	46	33.3%	-0.22 [-0.41, -0.03]
Meyer 2009*	6	23	15	24	26.9%	-0.36 [-0.63, -0.10]
Subtotal (95% CI)		**198**		**190**	**100.0%**	**-0.17 [-0.39, 0.04]**
Total events	63 (32%)		79 (42%)			
Heterogeneity: Tau² = 0.03; Chi² = 8.27, df = 2 (P = 0.02); I² = 76%						
Test for overall effect: Z = 1.56 (P = 0.12)						
Indication Repeated Implantation Failure						M-H, Fixed, 95% CI
Blockeel 2008	15	72	26	67	100.0%	-0.18 [-0.33, -0.03]
Subtotal (95% CI)		**72**		**67**	**100.0%**	**-0.18 [-0.33, -0.03]**
Total events	15 (21%)		26 (39%)			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.35 (P = 0.02)						

* Trial was terminated prematurely.

Mastenbroek, et al., HRU (2011)

PGS 2.0

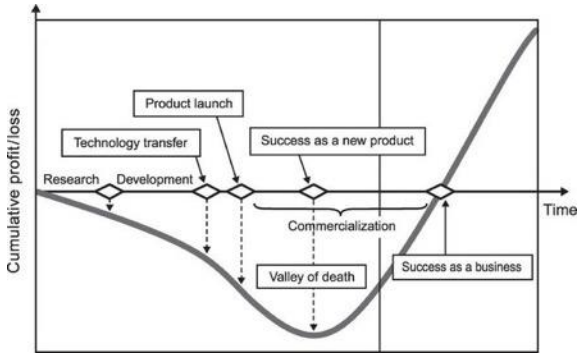
Mastenbroek & Repping, HR (2014)

PGS 2.0

Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: a randomized controlled trial

Richard T. Scott Jr., M.D.,[a,b] Kathleen M. Upham, B.S.,[a] Eric J. Forman, M.D.,[b] Kathleen H. Hong, M.D.,[b] Katherine L. Scott, M.S.,[a,c] Deanne Taylor, Ph.D.,[a,b] Xin Tao, M.S.,[a] and Nathan R. Treff, Ph.D.[a,b]

[a] Reproductive Medicine Associates of New Jersey, Morristown, New Jersey; [b] Division of Reproductive Endocrinology, Department of Obstetrics, Gynecology, and Reproductive Science, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, New Jersey; and [c] Atlantic Reproductive Medicine Specialists, Raleigh, North Carolina



In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial

Eric J. Forman, M.D.,[a,b] Kathleen H. Hong, M.D.,[a,b] Kathleen M. Ferry, B.Sc.,[a] Xin Tao, M.Sc.,[a] Deanne Taylor, Ph.D.,[a] Brynn Levy, Ph.D.,[a,c] Nathan R. Treff, Ph.D.,[a,b] and Richard T. Scott Jr., M.D.[a,b]

[a] Reproductive Medicine Associates of New Jersey, Department of Reproductive Endocrinology, Basking Ridge, New Jersey; [b] UMDNJ-Robert Wood Johnson Medical School, Department of Obstetrics, Gynecology & Reproductive Sciences, New Brunswick, New Jersey; and [c] Department of Pathology, Columbia University, College of Physicians and Surgeons, New York, New York

RESEARCH ARTICLE Open Access

Randomized comparison of next-generation sequencing and array comparative genomic hybridization for preimplantation genetic screening: a pilot study

Zhihong Yang[1,2,5*], James Lin[2], John Zhang[3], Wai leng Fong[4], Pei Li[5], Rong Zhao[5], Xiaohong Liu[5], William Podevin[6], Yanping Kuang[7] and Jiaen Liu[5]

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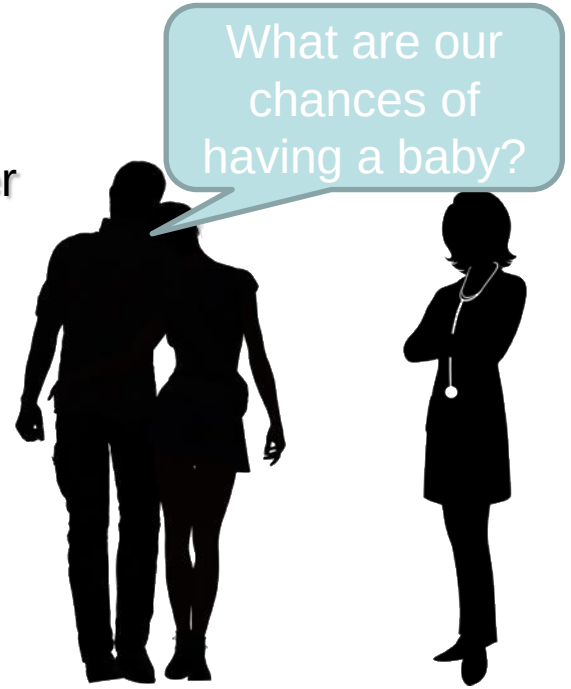
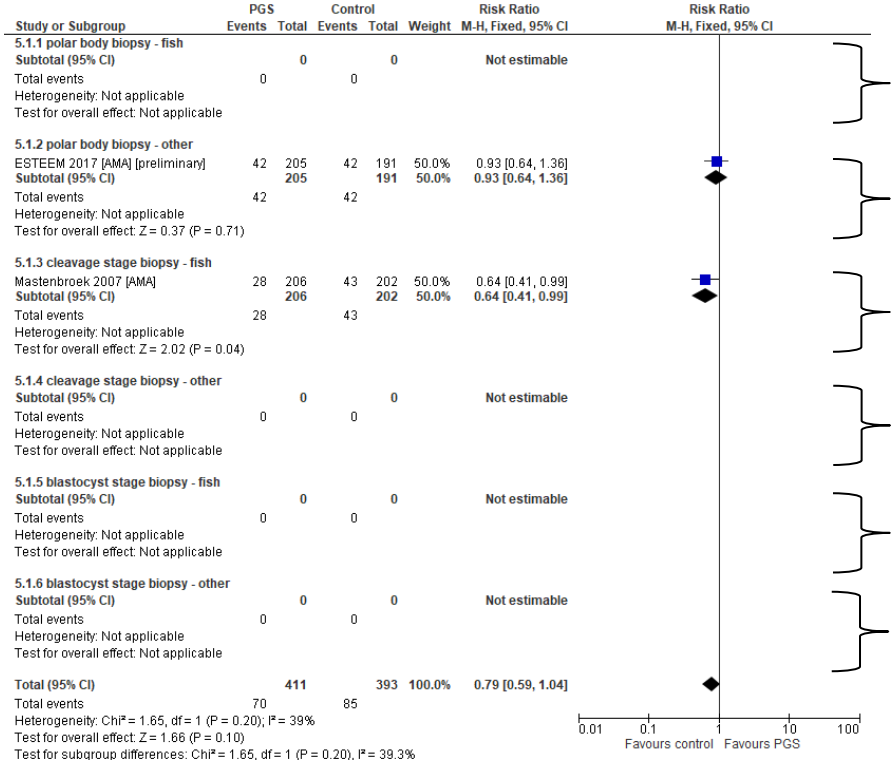
Cumulative live birth rate per woman

- Exclusion of studies that
  - do not report on outcome of FRET-cyles
  - only report on patients who received a transfer

- What is the chance of a live birth per woman per cycle started?
  - Exclusion of studies that report on PGS with multiple OPUs for single ET



Cumulative live birth rate (one OPU per IVF)



PB - fish

PB - array cgh ngs

cleavage - fish

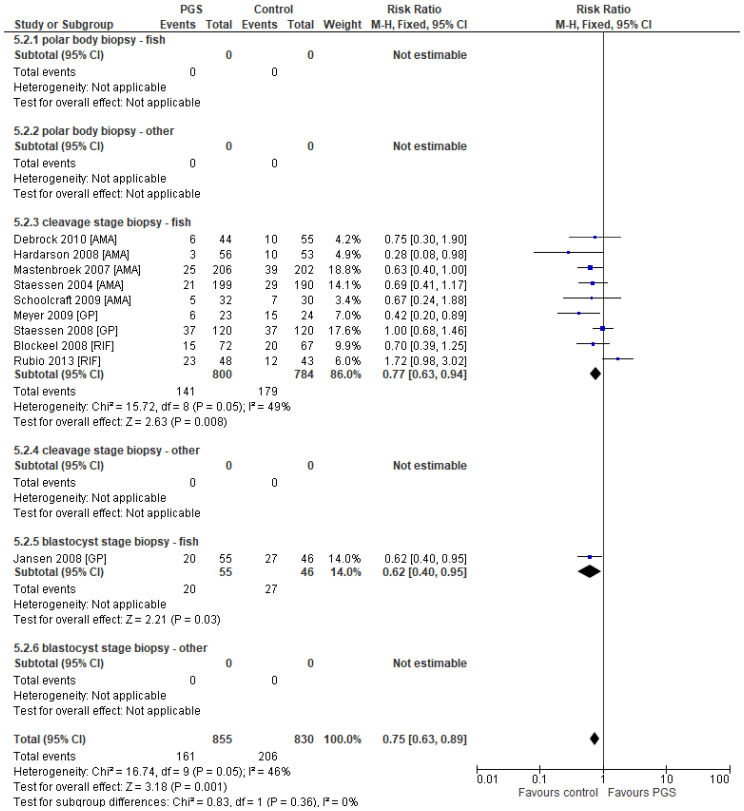
cleavage – array cgh ngs

blastocyst - fish

blastocyst - array cgh ngs

Mastenbroek & Repping, preliminary Cochrane update

Live birth rate per first transfer (one OPU per IVF)



PB - fish

PB - array cgh ngs

cleavage - fish

cleavage – array cgh ngs

blastocyst - fish

blastocyst - array cgh ngs

Mastenbroek & Repping, preliminary Cochrane update

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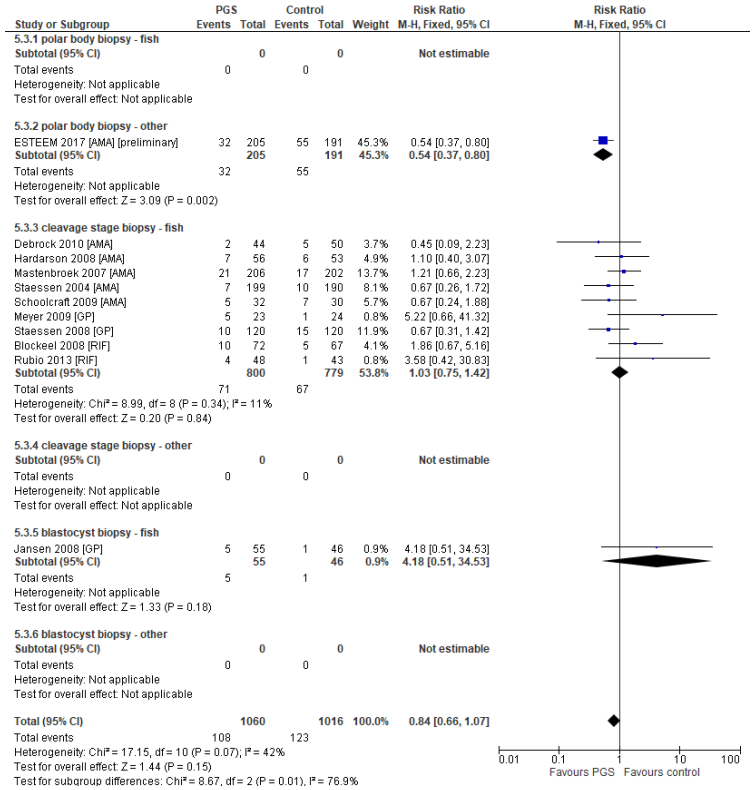
Miscarriage rate (one OPU per IVF)



PB - fish

PB - array cgh ngs

cleavage - fish

cleavage – array cgh ngs

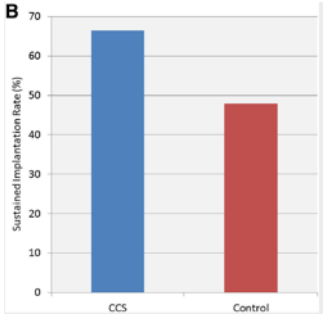
blastocyst - fish

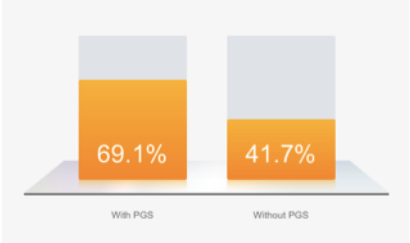
blastocyst - array cgh ngs

Mastenbroek & Repping, preliminary Cochrane update

Secondary outcomes: implantation rate

- Implantation rate is higher in PGS cycles
  - Scott 80% vs 63%
  - Yang 69% vs 42%
  - Mastenbroek[a] 17% vs 15%
  - Staessen 17% vs 12%
  - Rubio 53% vs 28%
  - ESTEEM[b] 18% vs 11%





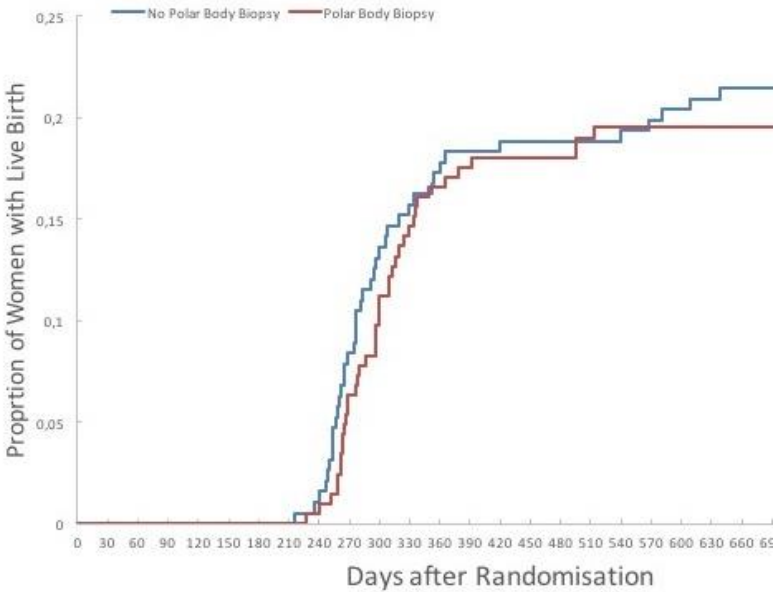
[a] excluding transfers of unknown embryos
[b] aggregate of fresh and frozen embryos

Secondary outcomes: time to pregnancy

- No effect on time to pregnancy (limited data!)

Supplemental Table 4: Number of transfers and time to pregnancy for a healthy baby at home.

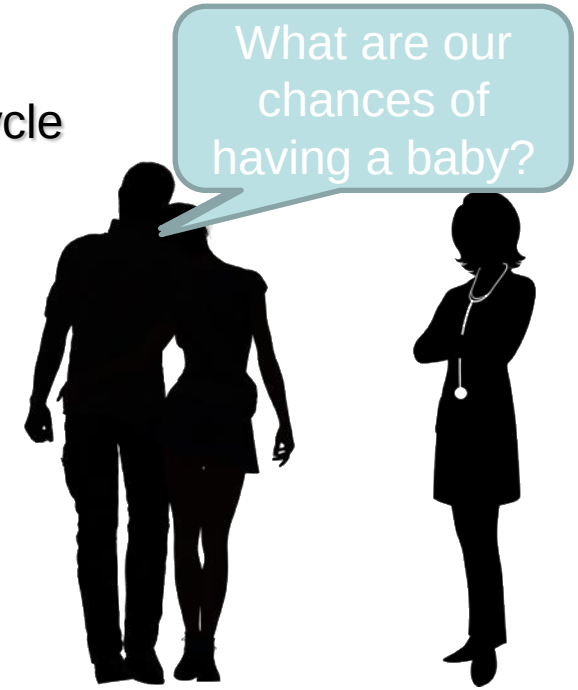
	PGD-A	Non PGD-A	*p-value*
Number of pregnancies at the first attempt	36	23	---
Number pregnancies after transfer of cryopreserved embryos	1	10	---
Mean time to ongoing pregnancy (SD, weeks)	4.5 (4.1)	5.8 (4.5)	*NS*
Mean number of transfer attempts (SD)	1.0 (0.2)	1.3 (0.4)	*<0.0001*



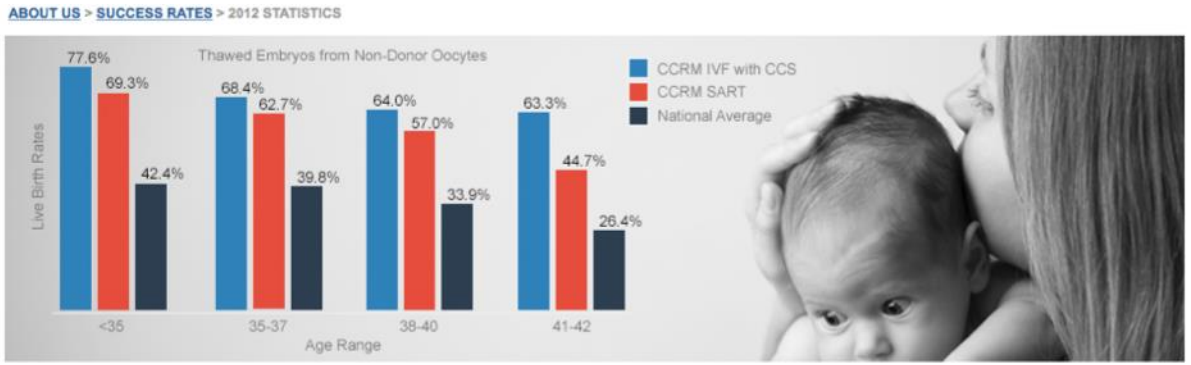
Rubio, F&S (2017), ESTEEM data (ESHRE 2017)

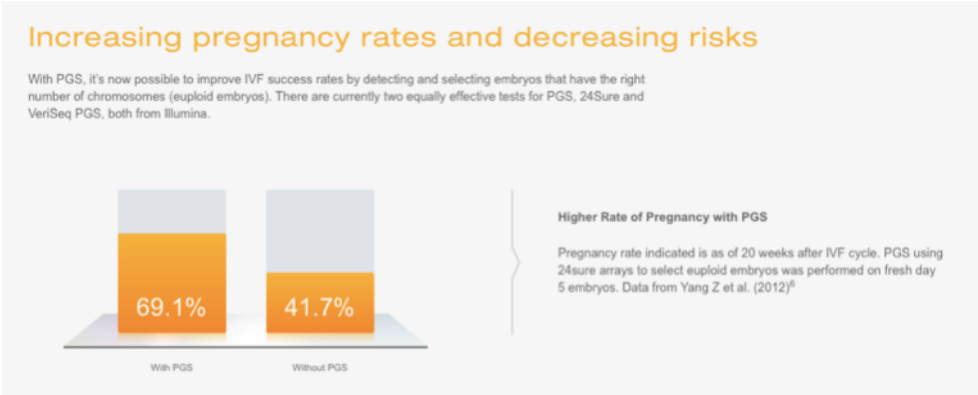
How should we inform patients?

- No increase in chances of having a baby
  - PGS 1.0 will decrease LBR per started cycle
  - PGS 2.0 almost no data, no increase
- Secondary outcomes
  - More no transfer, less transfers
  - Less embryos cryopreserved
  - Higher implantation rate per embryo
  - Perhaps fewer miscarriages
  - No effect on time to pregnancy
- High costs, invasive procedure……



How do we inform patients?





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http://www.colocrm.com, http://www.illumina.com

How do we inform patients?

- First: the baby!
- Then the famous trustworthy professor
- Then the (wrong) numbers
- Who can resist?

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http://www.illumina.com

How do we inform patients?

Improve your reproductive success with the specific selection of chromosomally normal embryos

Increase in implantation rate: Some embryos that are chromosomally abnormal will fail to implant into a woman's uterus. Therefore, by transferring chromosomally normal embryos, PGS using an array can increase the implantation rate.

Reduction in miscarriage rate: In the general population, 20% of all clinical pregnancies miscarry and about half are chromosomally abnormal. Since PGS evaluates numerical changes in chromosome numbers and large chromosome imbalances, embryo with chromosome abnormalities will not be transferred. Therefore, especially, in high-ris groups, PGS reduces the risk of miscarriage.

Increase in the chance of delivering a healthy baby: Some pregnancies with chromosome abnormalities will result in the birth of a child with multiple serious anomalies. Therefore, PGS can increase the chance of delivering a healthy baby by assisting physicians in identifying chromosomally healthy embryos for transfer. These conditions can also be detected by chorionic villus sampling (CVS) or amniocentesis later during the pregnancy.

Decrease in time to achieve a pregnancy: With this approach, the time to achieve healthy live-born decreases compared to a regular IVF cycle, avoiding multiple frozen embryo transfers before the transfer of the implanting embryo.

PGS 24 Chromosomes

Have a successful pregnancy and a healthy baby by selecting chromosomally normal embryos

Employing PGS for aneuploidy screening in IVF can double ongoing pregnancy rates.

Data summary of cycles performed at IVI Group 2011-2012 (with and without PGS). Cycles# AMA 880, IF 187, RM 204, MF 116. Pregnancy of 12 weeks gestation or more.

2.5x higher	Advanced maternal age
2.3x higher	Implantation failure
1.7x higher	Recurrent miscarriage
1.6x higher	Male factor

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http://www.igenomics.com

How do we inform customers?

- We try everything to make them buy our products

  “No worries! You can trust us!”

Commercialization….

- The benefits

▪ **In Vitro Fertilization (IVF)**

IVF Package Fees	Price
CCRM IVF Package (Starts at Lupron consult and ends after first pregnancy test)	$ 7,975
Fertility Laboratories of Colorado (FLC)	$ 5,105
South Denver Anesthesia Services	$ 430
Medications (Paid directly to the pharmacy of your choice)	$ 3,500 to 6,500 (approximate)
Total Estimated Cost of IVF Cycle	$ 17,010 to 20,010

▪ **IVF with Comprehensive Chromosome Screening (CCS)**

IVF With CCS Package Fees	Price
CCRM IVF Package (Starts at Lupron consult and ends after first pregnancy test)	$ 7,975
Fertility Laboratories of Colorado (FLC)	$ 14,080
*CCS and ICSI Included	
South Denver Anesthesia Services	$ 430
Medications (Paid directly to the pharmacy of your choice)	$ 4,300 to 8,500 (approximate)
Total Estimated Cost of IVF Cycle with CCS	$ 27,285 to 31,485

$ 8975

- PGS/CCS at CCRM in 2013
  - 3309 cycles * 0.85 (cycles with CCS) * $ 8975 = **$ 25,246,675**

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http://www.colocrm.com, http://www.sart.org, PPT Repping ASRM/ESHRE 2015

Who benefits from PGS?

- The companies!
  - 1/1/2013: $50.63
  - 7/1/2017: $174.13
  - 344%

www.marketwatch.com, Illumina Inc.

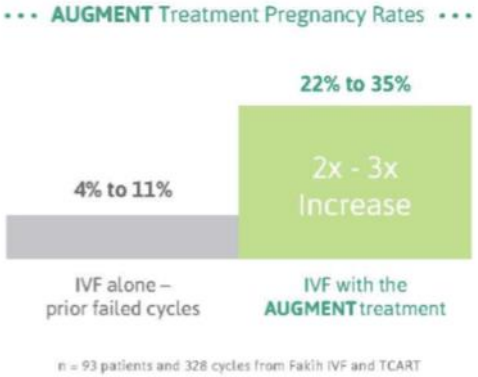
AUGMENTATION

The AUGMENT℠ Treatment

3x Improvement vs. Patients' Previous IVF History

Women with a poor prognosis who tried IVF alone had a 4%-11% clinical pregnancy rate. **For these same women who failed at least one prior IVF cycle and used the AUGMENT treatment, the clinical pregnancy rate was 22%-35%.** That's a 2-3 fold improvement over their historic rates.[1]

Ask your doctor if the **AUGMENT** treatment is right for you.



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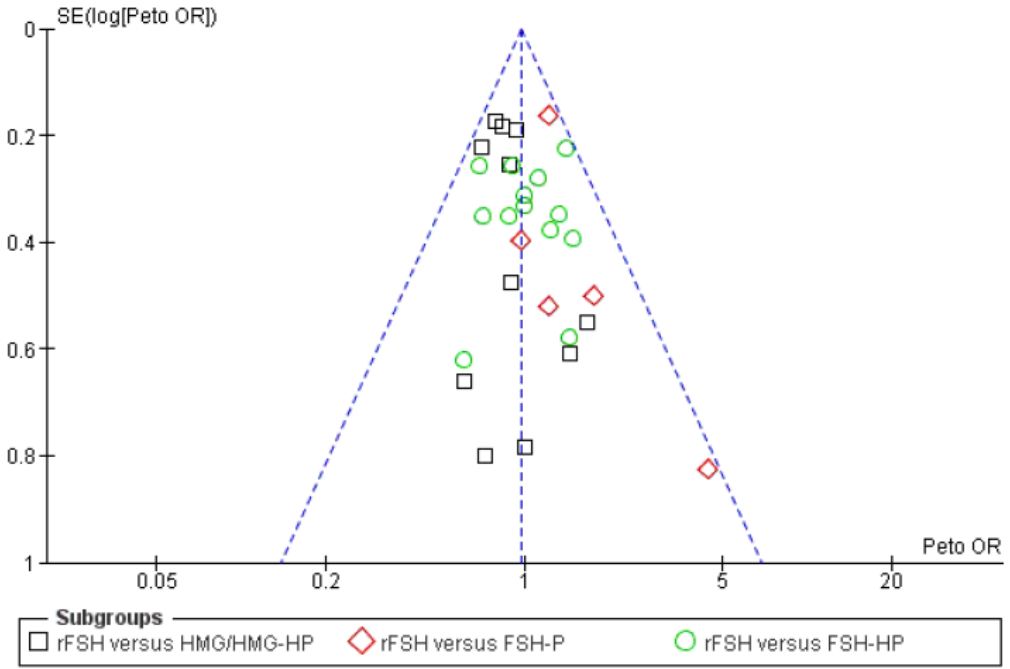
http://www.ovascience.com

Recombinant FSH vs Urinary FSH

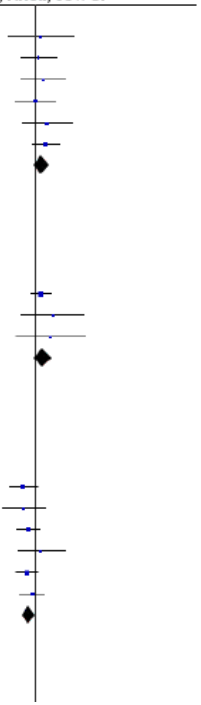
Figure 3. Funnel plot of comparison: 1 rFSH versus urinary gonadotrophins, outcome: 1.1 Live birth (or pregnancy ongoing beyond 20 weeks).



van Wely, et al, Cochrane (2011)

Recombinant FSH vs Urinary FSH

Study or Subgroup	rFSH Events	rFSH Total	Urinary gonadotrophins Events	Urinary gonadotrophins Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year	Peto Odds Ratio Peto, Fixed, 95% CI
1.4.1 Serono								
RHFSHG 1995	9	60	8	63	1.1%	1.21 [0.44, 3.36]	1995	
Bergh 1997	40	119	36	116	4.0%	1.12 [0.65, 1.94]	1996	
Lenton 2000	27	83	20	75	2.6%	1.32 [0.67, 2.61]	2000	
Frydman 2000	25	139	25	139	3.2%	1.00 [0.54, 1.84]	2000	
Franco 2000	21	60	16	60	2.0%	1.47 [0.69, 3.19]	2000	
Schats 2000	56	247	43	249	6.1%	1.40 [0.90, 2.18]	2000	
Subtotal (95% CI)		**708**		**702**	**19.0%**	**1.25 [0.97, 1.61]**		
Total events	178		148					
Heterogeneity: Chi² = 1.12, df = 5 (P = 0.95); I² = 0%								
Test for overall effect: Z = 1.75 (P = 0.08)								
1.4.2 Organon								
Out 1995	124	615	71	412	11.7%	1.21 [0.88, 1.66]	1995	
Hedon 1995	15	60	6	39	1.2%	1.77 [0.66, 4.71]	1995	
Jansen 1998	12	54	5	35	1.0%	1.66 [0.57, 4.87]	1998	
Subtotal (95% CI)		**729**		**486**	**14.0%**	**1.28 [0.96, 1.71]**		
Total events	151		82					
Heterogeneity: Chi² = 0.76, df = 2 (P = 0.68); I² = 0%								
Test for overall effect: Z = 1.66 (P = 0.10)								
1.4.3 Ferring								
Westergaard 2001	53	190	67	189	6.4%	0.71 [0.46, 1.09]	2001	
Dickey 2002	14	58	37	119	2.5%	0.71 [0.36, 1.42]	2002	
EISG 2002	67	386	80	395	9.2%	0.83 [0.58, 1.18]	2002	
Dickey 2003	24	60	21	60	2.2%	1.24 [0.59, 2.58]	2003	
Andersen 2006	82	368	97	363	10.5%	0.79 [0.56, 1.10]	2006	
Hompes 2008	71	317	74	312	8.6%	0.93 [0.64, 1.35]	2008	
Subtotal (95% CI)		**1379**		**1438**	**39.4%**	**0.83 [0.70, 0.98]**		
Total events	311		376					
Heterogeneity: Chi² = 2.29, df = 5 (P = 0.81); I² = 0%								
Test for overall effect: Z = 2.15 (P = 0.03)								



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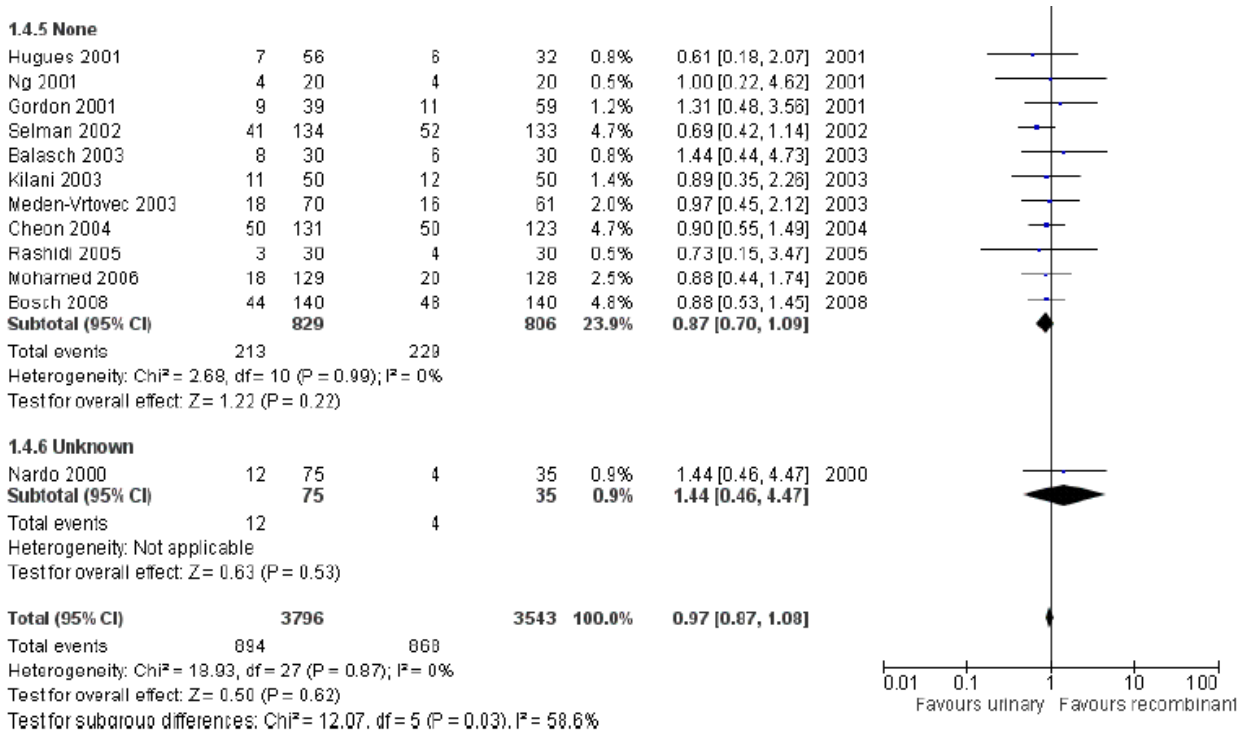
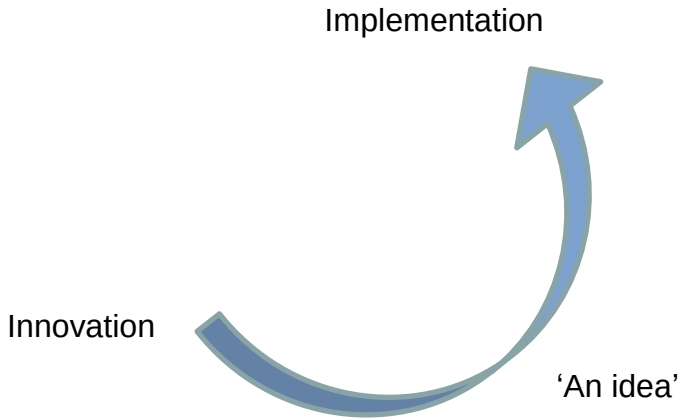
Recombinant FSH vs Urinary FSH



1.4.5 None							
Hugues 2001	7	56	6	32	0.8%	0.61 [0.18, 2.07]	2001
Ng 2001	4	20	4	20	0.5%	1.00 [0.22, 4.62]	2001
Gordon 2001	9	39	11	59	1.2%	1.31 [0.48, 3.56]	2001
Selman 2002	41	134	52	133	4.7%	0.69 [0.42, 1.14]	2002
Balasch 2003	8	30	6	30	0.8%	1.44 [0.44, 4.73]	2003
Kilani 2003	11	50	12	50	1.4%	0.89 [0.35, 2.26]	2003
Meden-Vrtovec 2003	18	70	16	61	2.0%	0.97 [0.45, 2.12]	2003
Cheon 2004	50	131	50	123	4.7%	0.90 [0.55, 1.49]	2004
Rashidi 2005	3	30	4	30	0.5%	0.73 [0.15, 3.47]	2005
Mohamed 2006	18	129	20	128	2.5%	0.88 [0.44, 1.74]	2006
Bosch 2008	44	140	48	140	4.8%	0.88 [0.53, 1.45]	2008
Subtotal (95% CI)		**829**		**806**	**23.9%**	**0.87 [0.70, 1.09]**	
Total events	213		229				
Heterogeneity: Chi² = 2.68, df = 10 (P = 0.99); I² = 0%							
Test for overall effect: Z = 1.22 (P = 0.22)							
1.4.6 Unknown							
Nardo 2000	12	75	4	35	0.9%	1.44 [0.46, 4.47]	2000
Subtotal (95% CI)		**75**		**35**	**0.9%**	**1.44 [0.46, 4.47]**	
Total events	12		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.63 (P = 0.53)							
Total (95% CI)		**3796**		**3543**	**100.0%**	**0.97 [0.87, 1.08]**	
Total events	894		868				
Heterogeneity: Chi² = 18.93, df = 27 (P = 0.87); I² = 0%							
Test for overall effect: Z = 0.50 (P = 0.62)							
Test for subgroup differences: Chi² = 12.07, df = 5 (P = 0.03), I² = 58.6%							

van Wely, et al, Cochrane (2011)

The route of innovation



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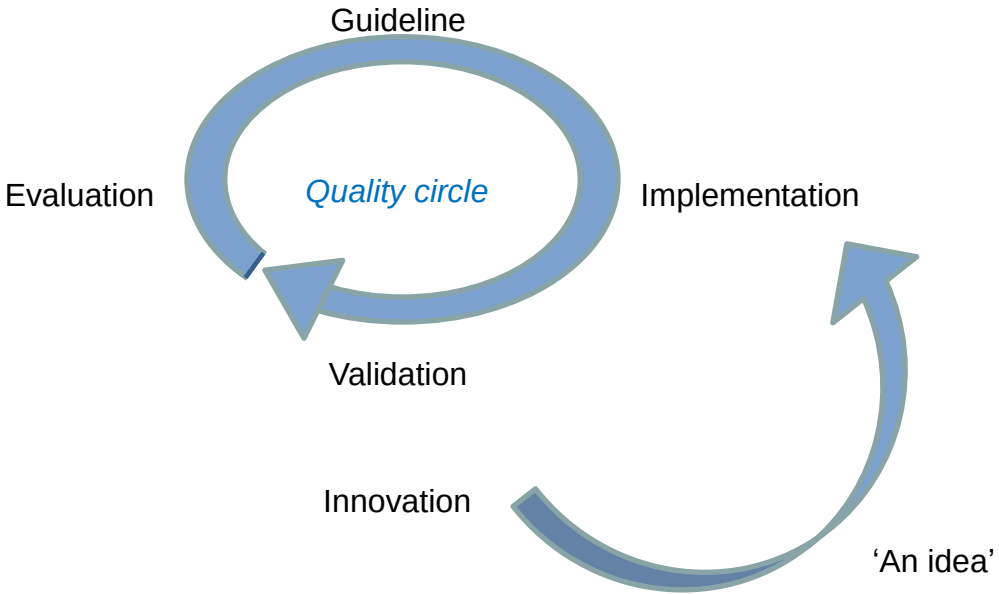
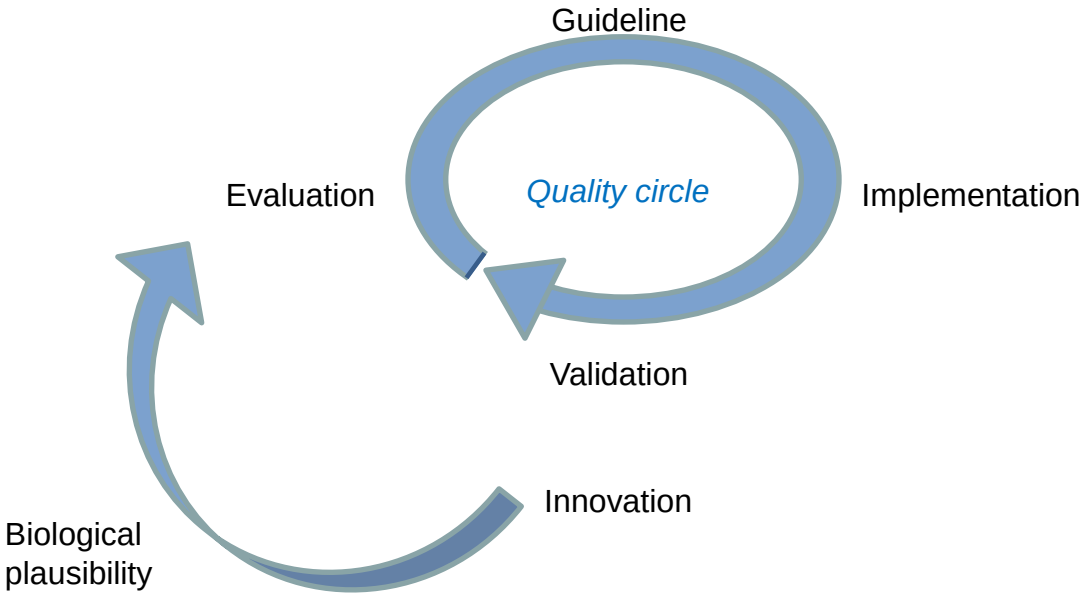
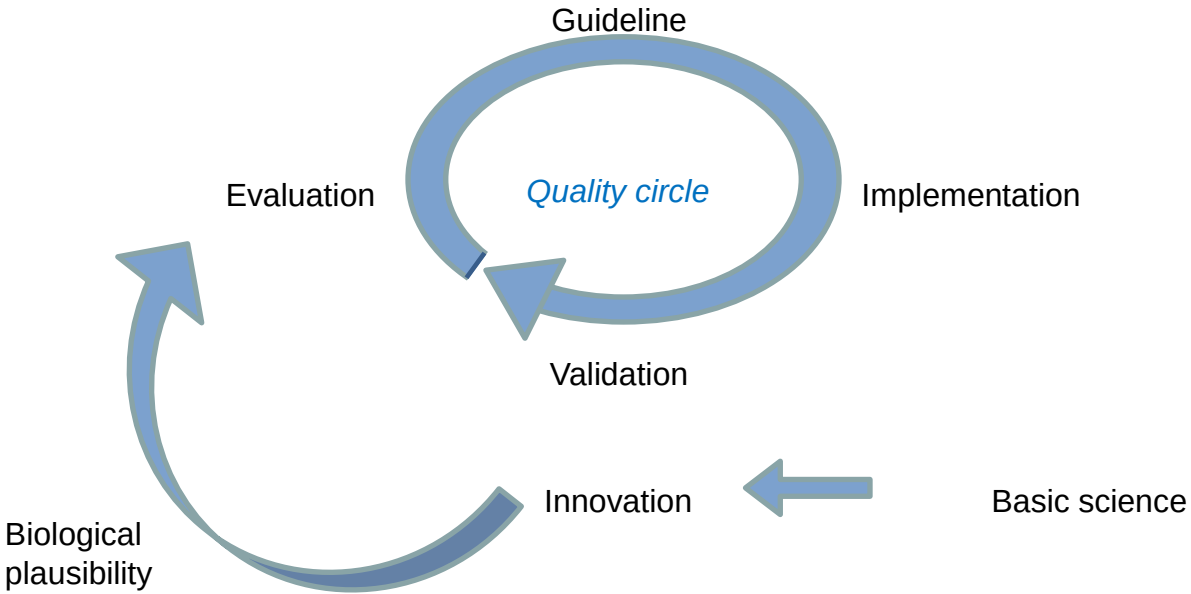
The route of innovation



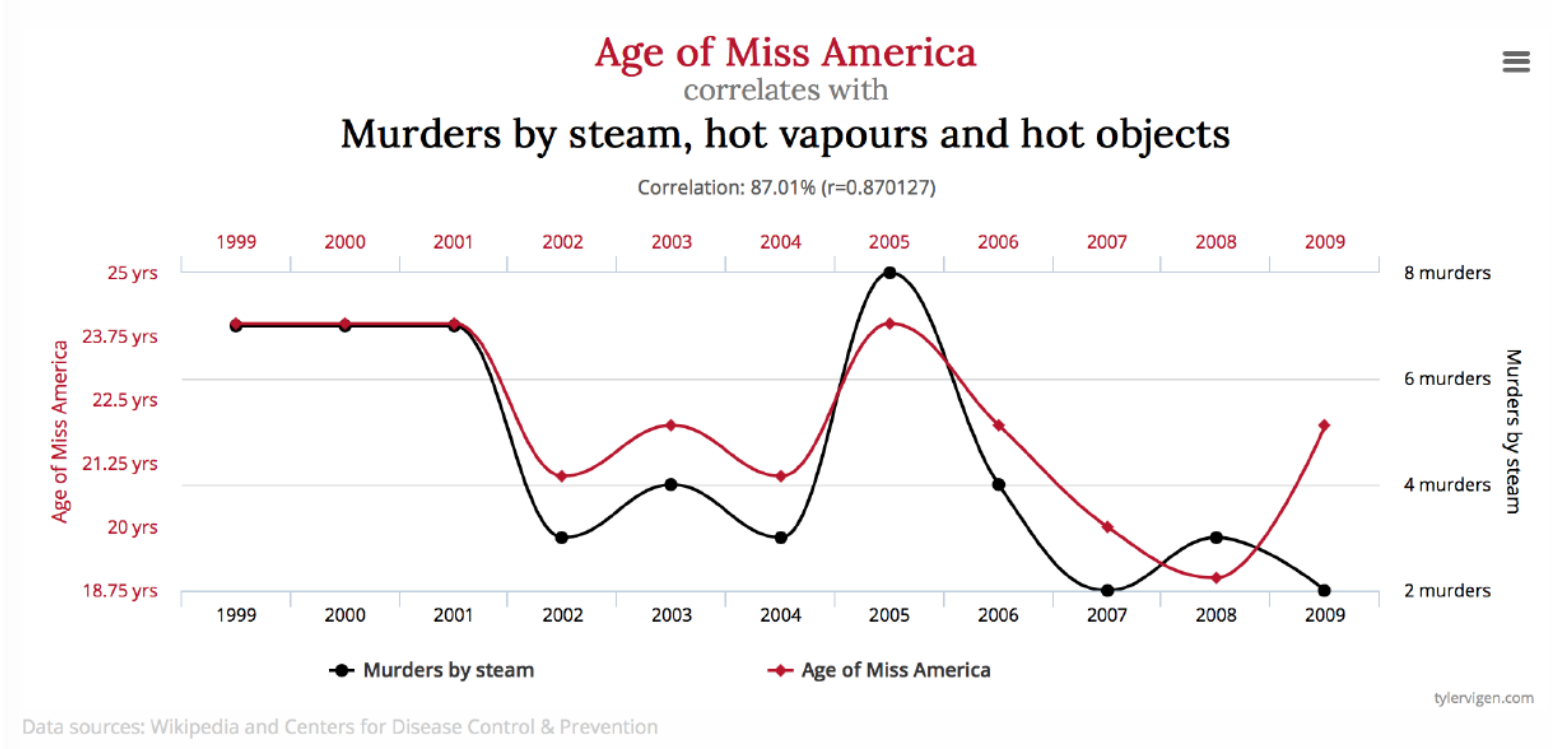
The route of innovation



The route of innovation



Biological plausibility…



Moral obligation

Responsible innovation requires making potentially risky reproductive technologies the subject of research, ideally proceeding through the steps of preclinical investigations, clinical trials and (long-term) follow-up studies.

The liability in this is often left to the patient by means of ‘informed consent’. But it is simply too easy to just hide behind the demand of the patient. The problem here is that a patient could agree with being treated with a technique of unknown effectiveness, but the clinician still remains responsible for what he or she does.

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Dondorp and de Wert, HR (2011)