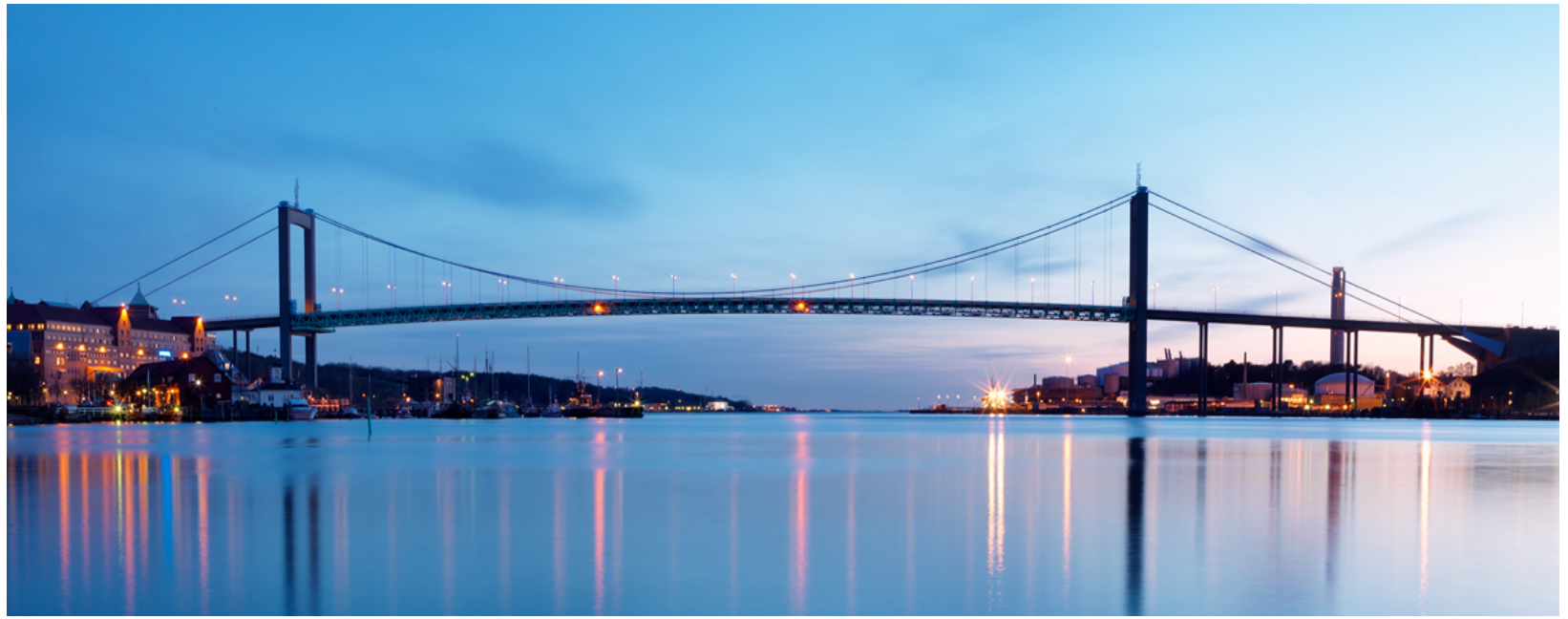
ART children – short and long term follow up



Christina Bergh

Gothenburg University, Sweden

Second Human Genome Germline Editing commission meeting
41-15 November, 2019, London

No conflicts of interest

Background

- >7 milj ART children born in the world

  (de Geyter, ICMART/ESHRE 2018, Barcelona)

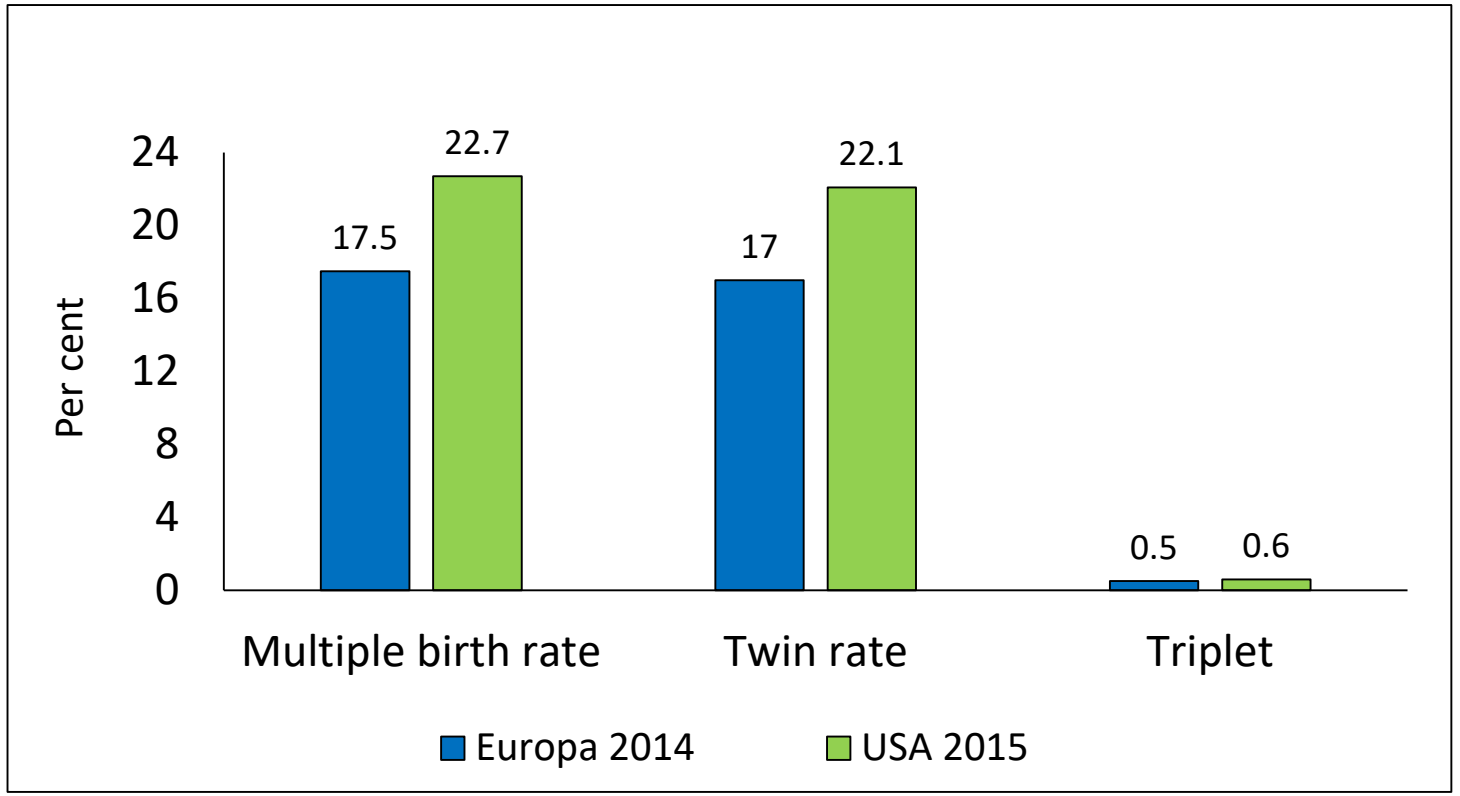
- Up to 6.4 % of national cohorts in Europa 2014

  (ESHRE /EIM data, de Geyter et al, Hum Reprod, 2018)

- >70 000 children born in Sweden

  (*www.qivf.se)*

Multiple birth after IVF in Europe and USA



De Geyter 2018
CDC, 2017

Singletons: ART vs spontaneous conception

Systematic reviews and meta-analyses

AOR or RR, 95% CI	Helmerhorst 2004	Jackson 2004	McGovern 2004	McDonald 2009	Pandey 2012	Qin 2017
No of studies, no of children	12* 5361	14* 12 114	27 14 748	15* 31 032	22** 27 819	52 181 741
<37 w	2.0 (1.8-2.3)	2.0 (1.7-2.2)	2.0 (1.8-2.2)	1.8 (1.5-2.2)	1.5 (1.5-1.6)	1.7
<32 w	3.3 (2.0-5.3)	3.1 (2.0-4.8)	2.5 (0.9-7.2)	2.3 (1.7-3.0)	1.7 (1.5-1.9)	2.0
<2500 g	1.7 (1.5-1.9)	1.8 (1.4-2.2)	-	1.6 (1.3-2.0)	1.6 (1.6-1.8)	1.5
<1500 g	3.0 (2.1-4.4)	2.7 (2.3-3.1)	-	2.6 (1.8-3.8)	1.9 (1.7-2.2)	2.0
SGA	1.4 (1.2-2.7)	1.6 (1.3-2.0)	-	1.4 (1.0-2.0)	1.4 (1.3-1.5)	1.2

*Cohort studies, matched or adjusted for at least maternal age

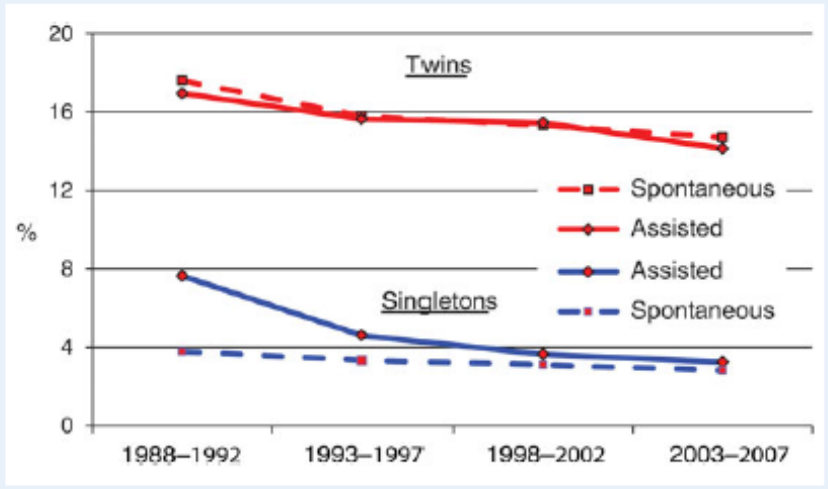
Human Reproduction, Vol.30, No.3 pp. 710–716, 2015
Advanced Access publication on January 20, 2015 doi:10.1093/humrep/deu345

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Trends in perinatal health after assisted reproduction: a Nordic study from the CoNARTaS group

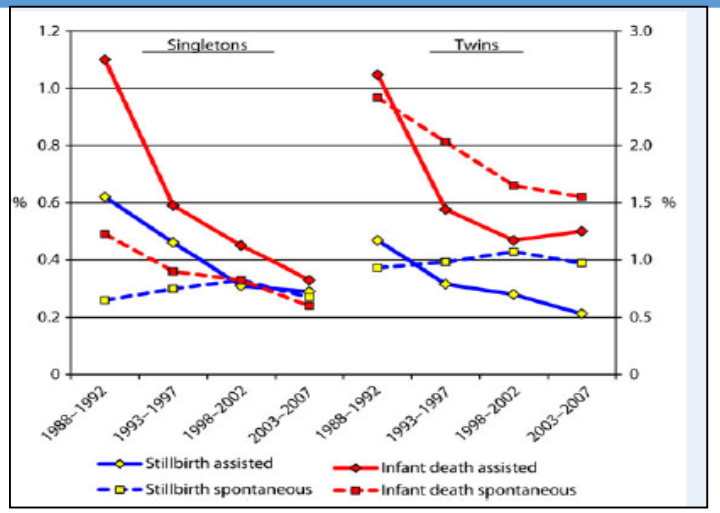
A.A. Henningsen[1,*], M. Gissler[2,3], R. Skjaerven[4,5], C. Bergh[6,7], A. Tiitinen[8], L.B. Romundstad[9,10], U.B. Wennerholm[11], O. Lidegaard[12], A. Nyboe Andersen[1], J.L. Forman[13], and A. Pinborg[14]

ART singleton and twins: SGA



ART singleton and twins : <37 weeks

ART singleton and twins: IUFD and death <1year



Human Reproduction Update, Vol.24, No.1 pp. 35–58, 2018
Advanced Access publication on November 13, 2017 doi:10.1093/humupd/dmx031

human reproduction update

Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer?

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

[1]Aberdeen Maternity Hospital NHS Grampian, AB 25 2ZL, Scotland, UK [2]CARE Fertility Nottingham, John Webster House, 6 Lawrence Drive, Nottingham Business Park, Nottingham NG8 6PZ, UK [3]School of Medicine and Dentistry, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK

*Correspondence address. Aberdeen Maternity Hospital NHS Grampian, AB 25 2ZL, Scotland, UK. E-mail: abha.maheshwari@abdn.ac.uk
orcid.org/0000-0002-3652-2447

Submitted on July 31, 2017; resubmitted on September 19, 2017; editorial decision on October 5, 2017; accepted on October 9, 2017

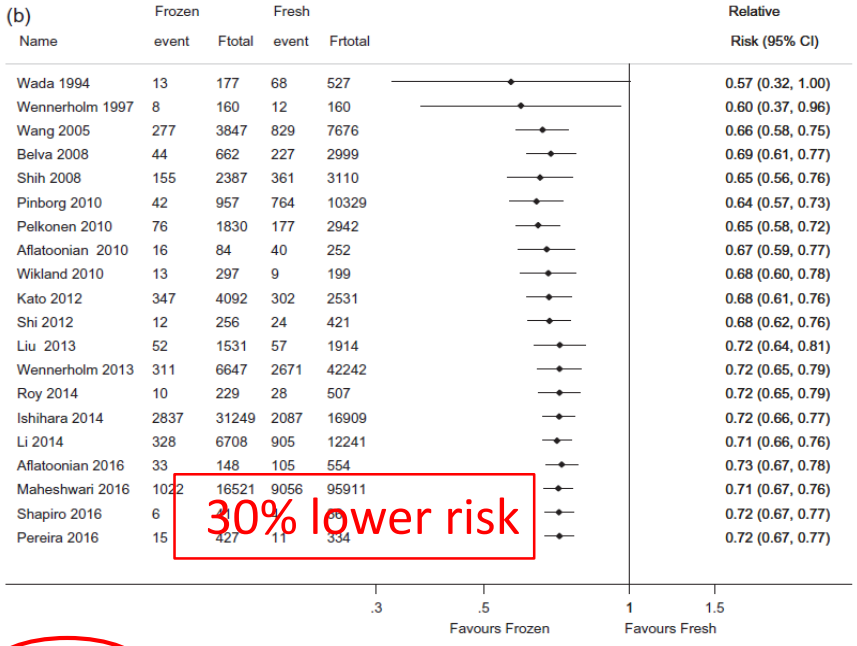


Figure 3 Low birth weight (less than 2500g): (**a**) meta-analysis and (**b**) cumulative meta-analysis.

Lower risk-small babies!

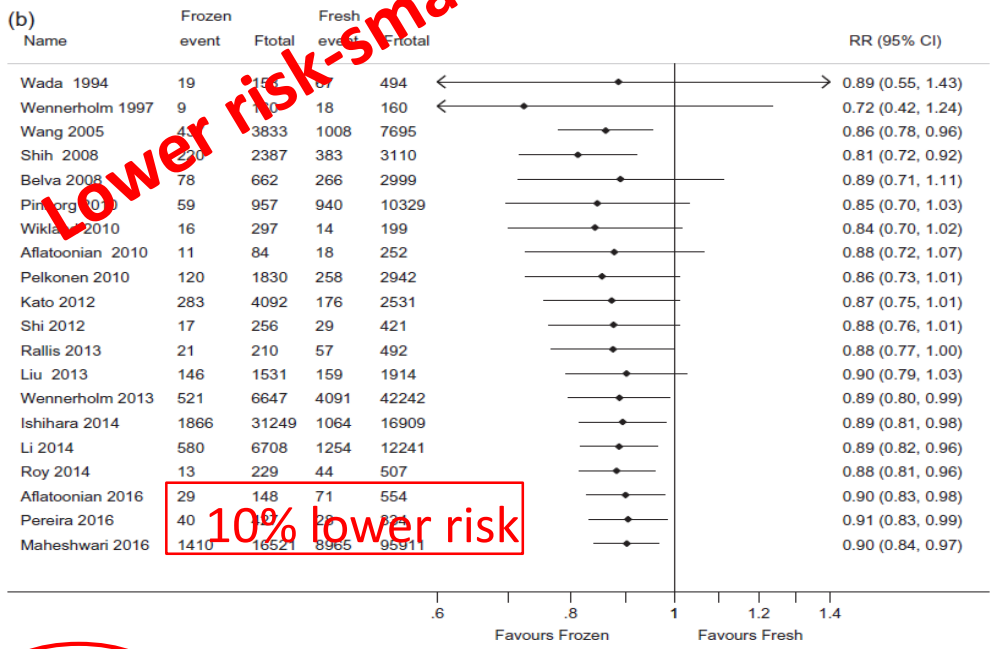


Figure 8 Preterm delivery (at less than 37 weeks): (**a**) meta-analysis and (**b**) cumulative meta-analysis.

Human Reproduction Update, Vol.24, No.1 pp. 35–58, 2018
Advanced Access publication on November 13, 2017 doi:10.1093/humupd/dmx031

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Advanced Access publication on November 13, 2017 doi:10.1093/humupd/dmx031

human reproduction update

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[1]Aberdeen Maternity Hospital NHS Grampian, AB 25 2ZL, Scotland, UK [2]CARE Fertility Nottingham, John Webster House, 6 Lawrence Drive, Nottingham Business Park, Nottingham NG8 6PZ, UK [3]School of Medicine and Dentistry, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK

*Correspondence address. Aberdeen Maternity Hospital NHS Grampian, AB 25 2ZL, Scotland, UK. E-mail: abha.maheshwari@abdn.ac.uk orcid.org/0000-0002-3652-2447

Submitted on July 31, 2017; resubmitted on September 19, 2017; editorial decision on October 5, 2017; accepted on October 9, 2017

Higher risk-big babies!

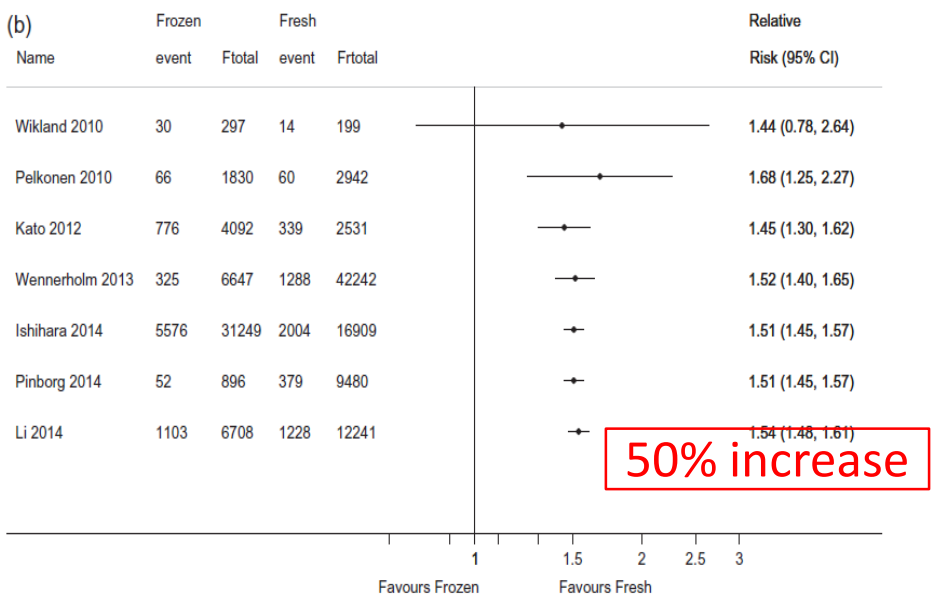


Figure 5 Large for gestational age: (**a**) meta-analysis and (**b**) cumulative meta-analysis.

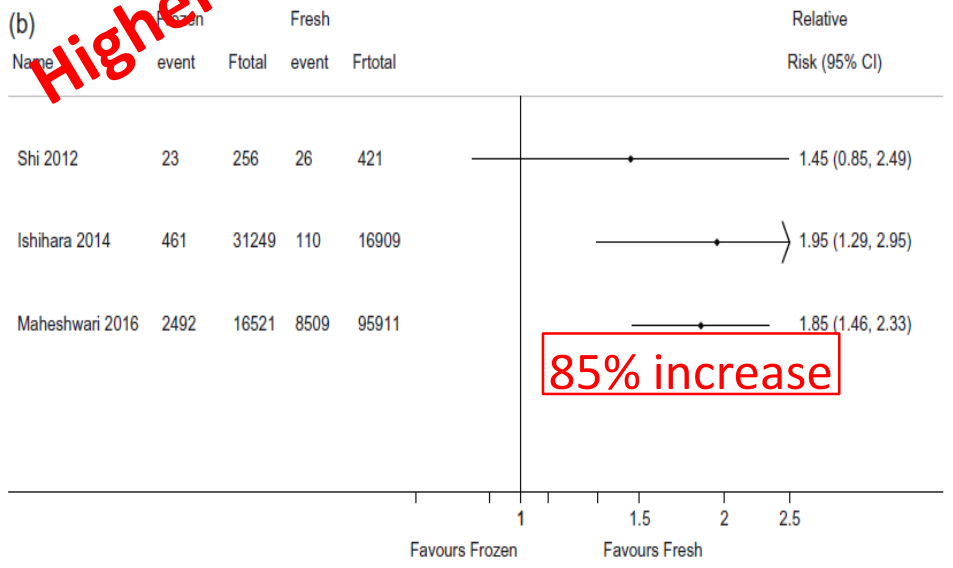


Figure 6 High birth weight (more than 4000g): (**a**) meta-analysis and (**b**) cumulative meta-analysis.

Birth defects

Singletons: ART vs spontaneous conception
Systematic reviews och meta-analyses

	Rimm 2004	Hansen 2005*	McDonald 2005	Pandey 2012*	Hansen 2013*	Qin 2016	Zhao 2019
No of studies and ART children	IVF: 82 064 ICSI: 63 948	15 13 059	7 4 031	7 4 382	23 48 944	28 77697	46 112 913
Birth defects AOR or RR (95% CI)	IVF: 1.5 (0.8-2.7) ICSI: 1.3 (0.9-2.0)	1.3 (1.2-1.5)	1.4 (1.1-1.9)	1.7 (1.3-2.1)	1.4 (1.3-1.4)	1.4 (1.3-1.5)	1.4 (1.3-1.5)

*Cohort studies, matched or adjusted

ART 30-70% increased risk

AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS ORIGINAL RESEARCH ARTICLE

Trends over time in congenital malformations in live-born children conceived after assisted reproductive technology

ANNA-KARINA A. HENNINGSEN[1], CHRISTINA BERGH[2], ROLV SKJAERVEN[3,4], AILA TIITINEN[5], ULLA-BRITT WENNERHOLM[6], LIV B. ROMUNDSTAD[7,8,9], MIKA GISSLER[10,11], SIGNE OPDAHL[8,9], ANDERS NYBOE ANDERSEN[1], ØJVIND LIDEGAARD[12], JULIE L. FORMAN[13] & ANJA PINBORG[14]

	ART N=61 281	SC N=350 811	AOR*	95% CI
Percent of children with serious birth defects**	3.4%	2.9%	1.2	1.1-1.2
Heart	0.63%	0.50%	1.3	1.1-1.4
Gastro-intestinal	0.28%	0.22%	1.3	1.1-1.5
Urogenital	0.24%	0.17%	1.4	1.2-1.7

*Adjusted for maternal age, parity, year of birth, country and gender

** Defined after Eurocat

Henningsen et al, 2018

AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS ORIGINAL RESEARCH ARTICLE

Trends over time in congenital malformations in live-born children conceived after assisted reproductive technology

ANNA-KARINA A. HENNINGSEN[1], CHRISTINA BERGH[2], ROLV SKJAERVEN[3,4], AILA TIITINEN[5], ULLA-BRITT WENNERHOLM[6], LIV B. ROMUNDSTAD[7,8,9], MIKA GISSLER[10,11], SIGNE OPDAHL[8,9], ANDERS NYBOE ANDERSEN[1], ØJVIND LIDEGAARD[12], JULIE L. FORMAN[13] & ANJA PINBORG[14]

Table 2. Risk of any major malformation in different time periods according to mode of conception and plurality.

	Any major congenital malformation							
	1988-1992				1993-1997			
	ART, n(%)	SC, n(%)	aOR[a]	[95%CI]	ART, n(%)	SC, n(%)	aOR[a]	[95%CI]
Singletons	49 (2.22)	272 (1.69)	1.36	[0.96-1.91]	234 (2.22)	1340 (1.97)	1.04	[0.89-1.22]
Twins	32 (2.28)	406 (1.85)	1.19	[0.80-1.78]	236 (3.58)	1144 (3.67)	0.87	[0.74-1.02]
All	81 (2.25)	678 (1.79)	1.16	[0.90-1.50]	470 (2.75)	2484 (2.50)	1.02	[0.91-1.14]
	1998-2002				2003-2007			
	ART, n(%)	SC, n(%)	aOR[a]	[95%CI]	ART, n(%)	SC, n(%)	aOR[a]	[95%CI]
Singletons	697 (3.57)	3734 (3.15)	1.13	[1.03-1.23]	1119 (3.87)	4858 (3.29)	1.16	[1.08-1.24]
Twins	634 (5.59)	1634 (4.95)	1.02	[0.91-1.14]	625 (6.53)	2288 (6.29)	0.91	[0.82-1.01]
All	1331 (4.31)	5368 (3.54)	1.17	[1.10-1.26]	1744 (4.53)	7146 (3.89)	1.12	[1.05-1.18]

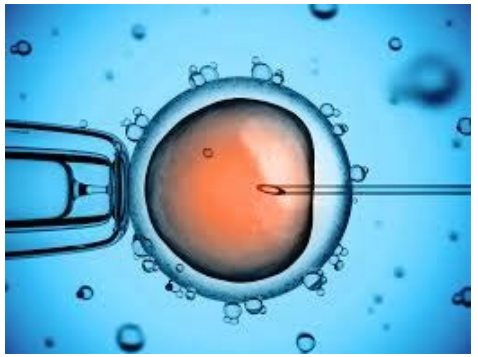
[a]Adjusted for parity (0 versus ≥1), year of birth, maternal age, child's sex and country.

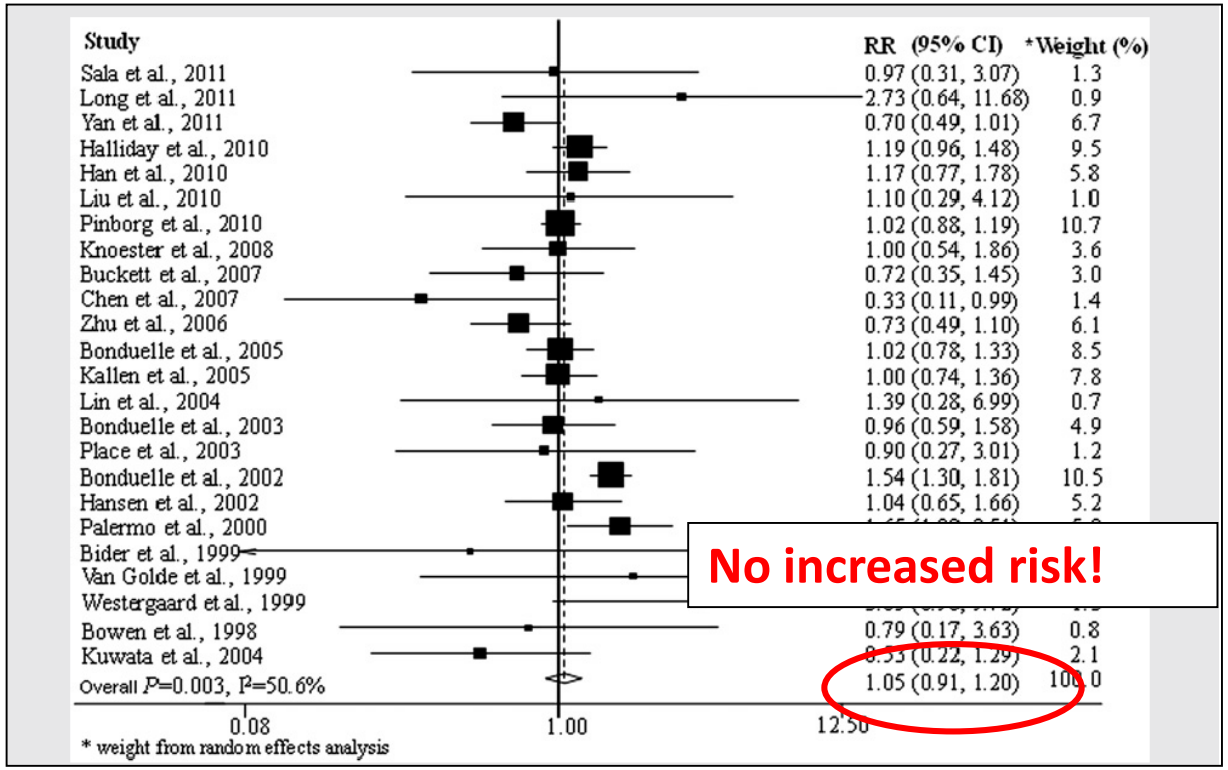
ART, assisted reproductive technology; SC, spontaneous conception; aOR, adjusted odds ratio; CI, confidence interval.

No trend over time!

Birth defects:

ICSI compared to IVF





24 studies, N=27 754 ICSI, N=46 890 IVF

Wen et al., Fertil Steril 2012

Longterm follow up

- Growth
- Cognitive and psychomotor development
- Mental disorders
- Autism
- School performances
- Cancer
- Cardiovascular risks
- Diabetes mellitus
- Puberty development

BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.15456
www.bjog.org

Systematic review

Childhood growth of singletons conceived following in vitro fertilisation or intracytoplasmic sperm injection: a systematic review and meta-analysis

B Bay,[a,b] J Lyngsø,[c] L Hohwü,[d] US Kesmodel[e,f]

[a] The Fertility Clinic, Regional Hospital Horsens, Horsens, Denmark [b] Department of Obstetrics and Gynaecology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark [c] Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark [d] Department of Health Science and Technology, Public Health and Epidemiology Group, Aalborg University, Aalborg, Denmark [e] Department of Obstetrics and Gynaecology, Herlev and Gentofte Hospital, Herlev, Denmark [f] Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence: B Bay, The Fertility Clinic, Regional Hospital Horsens, Sundvej 30, 8700 Horsens, Denmark. Email: bjornbay@me.com

Accepted 3 August 2018. Published Online 10 October 2018.

20 studies, 13 in meta-analysis

Max follow up-22 years

ART: 3972 children

SC: 11 012 children


BJOG An International Journal of Obstetrics and Gynaecology

Systematic review

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B Bay,[a,b] J Lyngso,[c] L Hohwü,[d] US Kesmodel[e,f]

Weight

Study or Subgroup	IVF/ICSI Mean [Kg]	IVF/ICSI SD [Kg]	IVF/ICSI Total	Spontaneous conceived Mean [Kg]	Spontaneous conceived SD [Kg]	Spontaneous conceived Total	Weight	Mean Difference IV, Random, 95% CI [Kg]
Basatemur (2010)	41.3	10.2	158	40.5	12	67	0.4%	0.80 [-2.48, 4.08]
Belva (2007)	29.2	6.2	150	28.9	5.2	147	2.1%	0.30 [-1.00, 1.60]
Bonduelle (2004)	19.5	6.5	292	19.7	3.6	260	4.2%	-0.20 [-1.06, 0.66]
Bonduelle (2005)	19.4	3	977	19.7	3	538	14.9%	-0.30 [-0.62, 0.02]
Celeen (2008)	47.6	16.4	233	46.3	14.7	233	0.5%	1.30 [-1.53, 4.13]
Desmyttere, (2008)	13.4	1.7	70	13.5	1.5	70	8.7%	-0.10 [-0.63, 0.43]
Halliday (2014)	69.6	13.9	531	72.7	15.9	528	1.1%	-3.10 [-4.90, -1.30]
Kai 2006 (cohort a)	15	1.7	129	15	1.7	1177	15.2%	0.00 [-0.31, 0.31]
Kai 2006 (cohort b)	19.2	2.5	135	18.6	2	70	6.9%	0.60 [-0.03, 1.23]
Knoester (2008)	23.5	3.9	166	23.8	3.8	85	3.3%	-0.30 [-1.30, 0.70]
Koivurova (2003)	14.9	1.8	150	15.3	1.9	280	13.2%	-0.40 [-0.76, -0.04]
Ludwig (2009)	21.2	3.2	276	21.4	4.1	273	7.1%	-0.20 [-0.82, 0.42]
Pontesilli, (2015)	21.1	3.2	28	21.4	4.4	2244	2.4%	-0.30 [-1.50, 0.90]
Woldringh (2011)	16.3	2.2	677	16.5	3.1	5040	20.0%	-0.20 [-0.39, -0.01]
Total (95% CI)			**3972**			**11012**	**100.0%**	**-0.16 [-0.36, 0.03]**

Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 21.41$, df = 13 ($P = 0.07$); $I^2 = 39\%$

Test for overall effect: $Z = 1.65$ ($P = 0.10$)

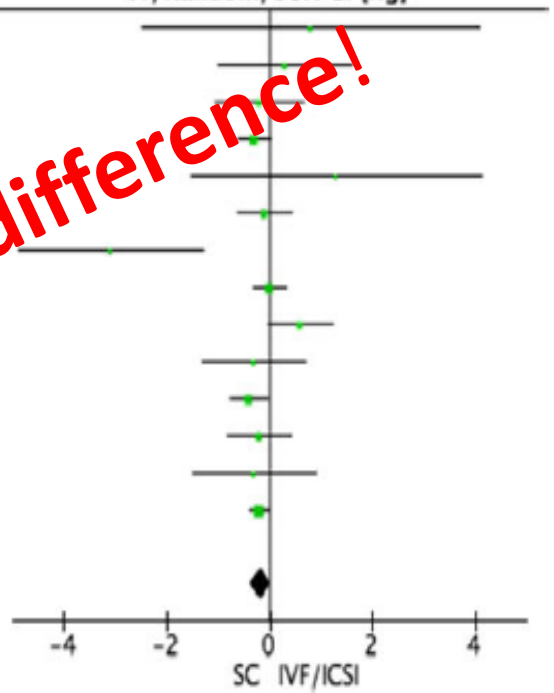

Figure 2. Forest plot comparing childhood weight among children conceived following in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) with spontaneously conceived children (SC) using a random-effect model.


BJOG An International Journal of Obstetrics and Gynaecology

Systematic review

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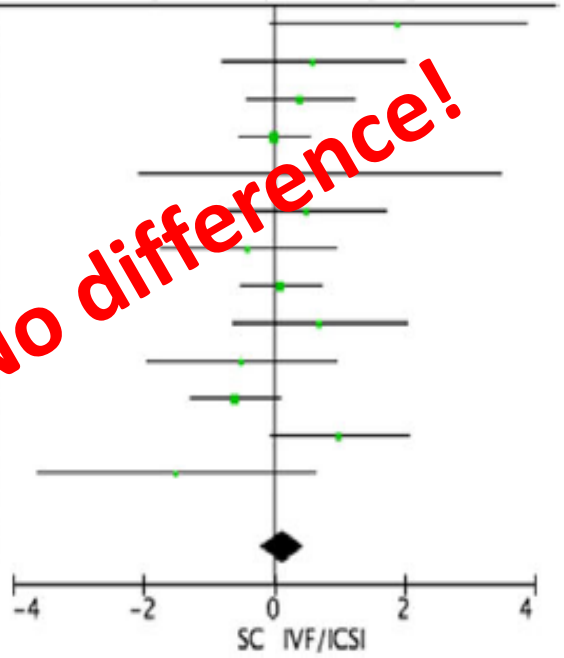
Height

Study or Subgroup	IVF/ICSI Mean [cm]	IVF/ICSI SD [cm]	IVF/ICSI Total	Spontaneous conceived Mean [cm]	Spontaneous conceived SD [cm]	Spontaneous conceived Total	Weight	Mean Difference IV, Random, 95% CI [cm]
Basatemur (2010)	147.8	7.1	156	145.9	6.8	67	2.7%	1.90 [-0.07, 3.87]
Belva (2007)	133.4	6.1	150	132.8	6.2	147	4.9%	0.60 [-0.80, 2.00]
Bonduelle (2004)	112.4	5.3	299	112	4.7	261	11.2%	0.40 [-0.43, 1.23]
Bonduelle (2005)	111	5.6	977	111	5	538	18.1%	0.00 [-0.55, 0.55]
Celeen (2008)	156.1	15	233	155.4	15.6	233	1.4%	0.70 [-2.08, 3.48]
Desmyttere, (2008)	91.9	3.9	70	91.4	3.4	70	6.3%	0.50 [-0.71, 1.71]
Halliday (2014)	172.7	10.9	518	173.1	11.2	514	5.3%	-0.40 [-1.75, 0.95]
Kai 2006 cohort a)	96.8	3.4	129	96.7	3.7	1177	15.9%	0.10 [-0.52, 0.72]
Kai 2006 (cohort b)	110.8	5.2	135	110.1	4.3	70	5.3%	0.70 [-0.64, 2.04]
Knoester (2008)	120.9	5.7	166	121.4	5.5	85	4.6%	-0.50 [-1.96, 0.96]
Kolvurova (2003)	96.5	3.4	150	97.1	3.6	280	14.2%	-0.60 [-1.29, 0.09]
Ludwig (2009)	116	6.6	276	115	6.1	273	7.8%	1.00 [-0.06, 2.06]
Pontesilli, (2015)	116.7	5.7	28	118.2	7.5	2244	2.3%	-1.50 [-3.63, 0.63]
Total (95% CI)			**3287**			**5959**	**100.0%**	**0.13 [-0.20, 0.47]**

Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 15.76$, df = 12 ($P = 0.20$); $I^2 = 24\%$

Test for overall effect: $Z = 0.78$ ($P = 0.44$)



No difference!

Figure 3. Forest plot comparing childhood height among children conceived following in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) with spontaneously conceived children (SC) using a random-effect model.

Cognitive and psychomotor development

Human Reproduction Update, Vol.14, No.3 pp. 219–231, 2008
doi:10.1093/humupd/dmn005
Advance Access publication March 26, 2008

Neuromotor, cognitive, language and behavioural outcome in children born following IVF or ICSI–a systematic review

K.J. Middelburg[1,5], M.J. Heineman[2,3], A.F. Bos[4] and M. Hadders-Algra[1]

[1]Department of Paediatrics, Division of Developmental Neurology, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands; [2]Department of Obstetrics and Gynaecology, University Medical Center Groningen, Groningen, The Netherlands; [3]Department of Obstetrics and Gynaecology, Academic Medical Center, Amsterdam, The Netherlands; [4]Department of Paediatrics, Division of Neonatology, University Medical Center Groningen, Groningen, The Netherlands

Assisted reproduction and child neurodevelopmental outcomes: a systematic review

Bjørn Bay, M.D.,[a,b] Erik Lykke Mortensen, M.Sc.,[c] and Ulrik Schiøler Kesmodel, Ph.D.[b]

[a] Section of Epidemiology, School of Public Health, and [b] Fertility Clinic, Department of Obstetrics and Gynecology, Institute of Clinical Medicine, Aarhus University, Aarhus; and [c] Institute of Public Health and Center for Health Aging, University of Copenhagen, Copenhagen, Denmark

Fertil&Steril 2013

Human Reproduction Update, Vol.19, No.3 pp. 244–250, 2013
Advanced Access publication on February 28, 2013 doi:10.1093/humupd/dmt002

human reproduction update

The longer-term health outcomes for children born as a result of IVF treatment. Part II–Mental health and development outcomes

Roger Hart[1,2,*] and Robert J. Norman[3]

Human Reproduction, Vol.32, No.7 pp. 1489–1507, 2017
Advanced Access publication on May 4, 2017 doi:10.1093/humrep/dex085

human reproduction

REVIEW *Reproductive epidemiology*

The impact of specific fertility treatments on cognitive development in childhood and adolescence: a systematic review

Alice R. Rumbold[1,*], Vivienne M. Moore[1,2], Melissa J. Whitrow[1,2], Tassia K. Oswald[1,3], Lisa J. Moran[1,4], Renae C. Fernandez[1,2], Kurt T. Barnhart[5], and Michael J. Davies[1]

[1]Robinson Research Institute, The University of Adelaide, Adelaide, South Australia 5005, Australia [2]School of Public Health, The University of Adelaide, Adelaide, South Australia 5005, Australia [3]School of Psychology, The University of Adelaide, Adelaide, South Australia 5005, Australia [4]Monash Centre for Health Research Implementation, Monash University, Melbourne, Victoria 3163, Australia [5]Division of Reproductive Endocrinology and Infertility, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA

*Correspondence address. Robinson Research Institute, The University of Adelaide, Adelaide, South Australia, Australia.
E-mail: alice.rumbold@adelaide.edu.au

Age ≥4 years, 35 studies

Conflicting results

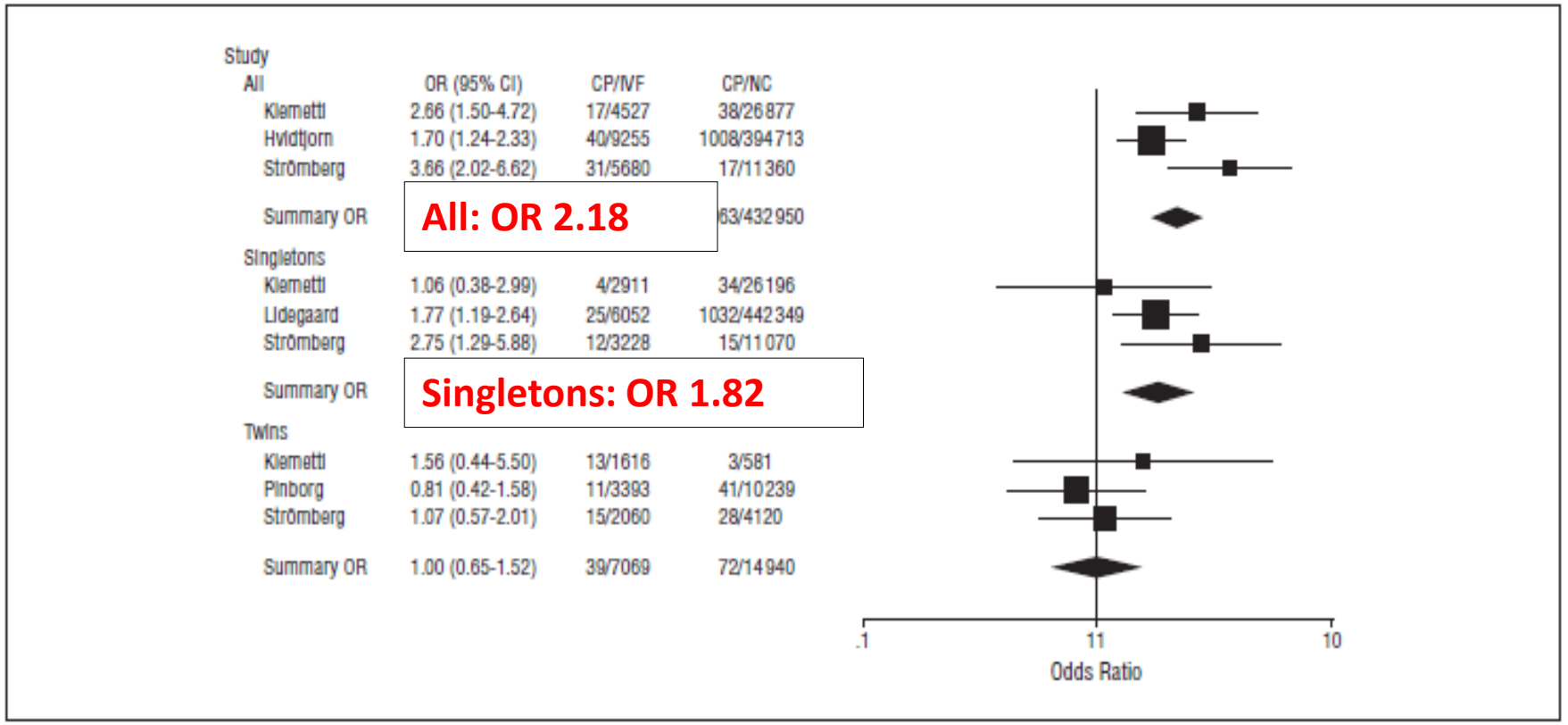
IVF vs spontaneous conception

ICSI vs spontaneous conception and vs IVF

-disappeared after adjustment for multiples

-only observed in subgroups

ART and neurological impairment Cerebral Palsy



Hvidtjorn et al, Arch Ped Adolesc Med 2009

Cerebral palsy

In vitro fertilization in Sweden: child morbidity including cancer risk

Bengt Källén, Ph.D.,[a] *Orvar Finnström, Ph.D.,*[b] *Karl-Gösta Nygren, Ph.D.,*[c] *and Petra Otterblad Olausson, Ph.D.*[d]

[a] Tornblad Institute, University of Lund, Lund; [b] Department of Pediatrics, University Hospital, Linköping; [c] Fertility Clinic, Sophiahemmet, Stockholm; and [d] Centre for Epidemiology, National Board of Health and Welfare, Stockholm, Sweden

Crude OR: 1.89 (1.37-2.60)
Adjusted OR: 1.14 (0.72-1.81)

N=16 000 ART

Human Reproduction, Vol.25, No.8 pp. 2115–2123, 2010
Advanced Access publication on June 16, 2010 doi:10.1093/humrep/deq070

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Multiplicity and early gestational age contribute to an increased risk of cerebral palsy from assisted conception: a population-based cohort study

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Crude OR: 2.34 (1.81-3.01)
Adjusted OR:1.07 (0.78-1.47)
(adjusted for multiplicity and gestational age)

N=33 000 ART

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Cerebral palsy after assisted reproductive technology: a cohort study

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This article is commented on by Källén on page 9 of this issue.

Table II: Birth prevalence and odds of cerebral palsy (CP) by conception type

	ART CP/ART (birth prevalence proportion per 1000 live births)	Naturally conceived CP/naturally conceived (birth prevalence proportion per 1000 live births)	ART compared with naturally conceived crude OR (95% CI)	ART compared with naturally conceived adjusted* OR (95% CI)
Whole group	21/2914 (7.2/1000 LB)	514/208 746 (2.5/1000 LB)	2.9 (1.9–4.6)	2.6 (1.6–4.0)
Singletons GA	10/1927 (5.2/1000 LB)	468/203 352 (2.3/1000 LB)	2.3 (1.2–4.2)	2.0 (1.1–3.9)
<32wks	6/47 (127.7/1000 LB)	81/1561 (51.9/1000 LB)	2.7 (1.1–6.5)	2.7 (1.0–6.9)
32–36wks	1/209 (4.8/1000 LB)	61/11 032 (5.5/1000 LB)	0.9 (0.1–6.3)	0.9 (0.1–6.8)
≥37wks	3/1671 (1.8/1000 LB)	326/190 748 (1.7/1000 LB)	1.1 (0.3–3.3)	1.0 (0.3–3.1)

EDITOR'S CHOICE

Risk of autism spectrum disorders in children born after assisted conception: a population-based follow-up study

D Hvidtjørn,[1] J Grove,[1] D Schendel,[2] L A Schieve,[2] C Sværke,[1] E Ernst,[3] P Thorsen[1]

ELSEVIER

Official Journal of the European Paediatric Neurology Society

Original article

Is there an increased risk for drug treated attent hyperactivity disorder in children born after in v fertilization?

A.J. Bengt Källén [a,*], O. Otto Finnström [b], Anna P. Lindam [c], Emma M Karl-Gösta Nygren [d], Petra M. Otterblad Olausson [c]

Human Reproduction, Vol.28, No.3 pp. 812–818, 2013

Advanced Access publication on January 4, 2013 doi:10.1093/humrep/des43

human reproduction

ORIGINAL ARTICLE Rep

Advanced Access publication on October 29, 2015 doi:10.1093/humrep/dev273

human reproduction

ORIGINAL ARTICLE *Infertility*

Mental health and developmental outcomes for children born after ART: a comparative prospective study on child gender and treatment type

Raija-Leena Punamäki[1,*], Aila Tiitinen[2,3], Jallu Lindblom[1], Leila Unkila-Kallio[2,3], Marjo Flykt[1], Mervi Vänskä[1], Piia Poikkeus[2,3], and Maija Tulppala[2]

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Autism spectrum disorders in IVF children: a national case–control study in Finland

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JAMA July 3, 2013 Volume 310, Number 1

Research

Original Investigation

Autism and Mental Retardation Among Offspring Born After In Vitro Fertilization

Sven Sandin, MSc; Karl-Gösta Nygren, PhD; Anastasia Iliadou, PhD; Christina M. Hultman, PhD; Abraham Reichenberg, PhD

IVF/ICSI: 30 959, SC: 2 541 125, 1982-2007
Follow up at 1.5-10 years. ICD 9, 10 diagnoses in Patient Registry

	per 100 000 person year		RR (95% CI)
Autism	19.0	15.6	1.14 (0.94-1.39
Singleton	14.4	15.0	0.89 (0.68-1.17)
Mental retardation	46.3	39.8	1.18 (1.01-1.36)
Singleton	38.8	38.5	1.01 (0.83-1.24)

Human Reproduction, Vol.30, No.2 pp. 454–465, 2015
Advanced Access publication on December 17, 2014 doi:10.1093/humrep/deu338

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Association of assisted reproductive technology (ART) treatment and parental infertility diagnosis with autism in ART-conceived children

D.M. Kissin[1,*], Y. Zhang[1], S.L. Boulet[1], C. Fountain[2], P. Bearman[3], L. Schieve[4], M. Yeargin-Allsopp[4], and D.J. Jamieson[1]

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1997-2006,
N=42 383 ART children, up to 5 years

Autism in ART Singleton: 0.8%
ICSI: adjusted HR 1.65 (1.08-2.56) (IVF as ref)

BMJ

BMJ 2013;347:f3978 doi: 10.1136/bmj.f3978 (Published 5 July 2013) Page 1 of 11

RESEARCH

Fertility treatment and risk of childhood and adolescent mental disorders: register based cohort study

OPEN ACCESS

Bjørn Bay *PhD student*[1 2], Erik Lykke Mortensen *professor*[3], Dorte Hvidtjørn *midwife*[4], Ulrik Schiøler Kesmodel *consultant*[1 2]

No increase for IVF/ICSI!

Hazard rates and 95% CIs for mental disorders[*†] in children aged 0−17 years according to type of infertility treatment, hormones, gametes and aetiology of infertility compared with spontaneously conceived children

	No of exposed	Any psychiatric diagnosis (n=23,278)	Mental retardation (n=3371)	Disorders of psychological development (n=11,794)	Behaviour and emotional disorders (n=16,432)	Other/unspecified psychiatry disorders (n=682)
Procedure[‡]						
OI/IUI	18,148	**1.20 (1.11 to 1.31)**	1.02 (0.81 to 1.28)	**1.17 (1.05 to 1.31)**	**1.22 (1.11 to 1.34)**	1.16 (0.72 to 1.87)
IVF	9532	1.01 (0.90 to 1.15)	0.88 (0.63 to 1.24)	0.98 (0.83 to 1.15)	1.06 (0.91 to 1.23)	1.14 (0.56 to 2.29)
ICSI	4201	1.08 (0.90 to 1.31)	0.81 (0.47 to 1.42)	1.17 (0.92 to 1.49)	1.10 (0.87 to 1.38)	0.33 (0.05 to 2.45)

*As defined by ICD-10 (applicable in study period); [†]adjusted for maternal age, parity, education al level, smoking in pregnancy, maternal psychiatric history, birth year, child's sex and multipclicity; [‡]specific type of treatment missing in 117 children in IVF/ICSI group; 163 had egg donation and 978 were fertilised with frozen egg without specification of treatment type (IVF or ICSI).

Human Reproduction, Vol.33, No.10 pp. 1948–1959, 2018
Advanced Access publication on August 28, 2018 doi:10.1093/humrep/dey273

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

School performance in singletons born after assisted reproductive technology

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1985-2001

N=8323 ART

1 499 667 SC

Singletons

Finishing 9th grade school-15-16 years

Table II School performance in ninth grade for singletons born after assisted reproduction techniques (ART) and spontaneous conception (SC) and graduated 2000–2016.

	ART singletons			SC singletons		
	All *n* = 8323	Male *n* = 4220	Female *n* = 4103	All *n* = 1 499 667	Male *n* = 767 554	Female *n* = 732 113
Total score*, all subjects, year of test						
All years, 2000–2016, mean score (SD)	230.2 (57.2)	219.2 (56.9)	241.6 (55.4)	209.7 (63.9)	198.7 (62.0)	221.2 (63.9)
mean percentile (SD)	60.2 (27.7)	60.4 (27.9)	60.4 (27.5)	50.2 (29.0)	50.1 (28.9)	50.4 (29.1)
2000–2012, mean total score (SD)	225.9 (59.1)	214.5 (58.7)	237.7 (57.1)	207.1 (64.5)	196.2 (62.4)	218.6 (64.7)
mean percentile (SD)	59.0 (28.4)	58.7 (28.8)	59.5 (28.0)	50.3 (29.0)	50.1 (28.9)	50.5 (29.1)
	n = 3914	*n* = 1995	*n* = 1919	*n* = 1 192 109	*n* = 609 326	*n* = 582 783
2013–2016, mean total score (SD)	234.1 (55.3)	223.4 (54.9)	245.1 (53.6)	219.6 (60.5)	208.3 (59.1)	231.5 (59.6)
mean percentile (SD)	57.4 (28.3)	57.8 (28.3)	57.2 (28.6)	50.1 (29.0)	50.0 (28.8)	50.2 (29.0)
	n = 4409	*n* = 2225	*n* = 2184	*n* = 308 556	*n* = 158 228	*n* = 149 328
Mathematics**						
All years 2000–2016, mean score (SD)	13.3 (4.6)	13.0 (4.7)	13.5 (4.5)	12.1 (4.8)	11.9 (4.8)	12.3 (4.8)
mean percentile (SD)	61.1 (28.4)	60.9 (28.4)	61.4 (28.5)	53.2 (28.7)	52.9 (28.4)	53.5 (29.0)
Swedish**						
All years, 2000–2016, mean score (SD)	14.2 (4.4)	13.1 (4.2)	15.4 (4.2)	12.8 (4.9)	11.7 (4.7)	14.1 (4.8)
mean percentile (SD)	63.0 (28.3)	61.4 (27.2)	65.2 (29.0)	53.8 (29.6)	51.8 (27.9)	55.9 (30.8)
English**						
All years, 2000–2016, mean score (SD)	15.1 (4.3)	14.9 (4.3)	15.4 (4.2)	13.5 (4.8)	13.1 (4.9)	13.9 (4.8)
mean percentile (SD)	66.4 (28.6)	66.4 (28.2)	66.5 (29.1)	55.0 (30.4)	54.2 (29.9)	55.8 (30.8)
Physical education**						
All years, 2000–2016, mean score, (SD)	14.6 (4.7)	14.8 (4.6)	14.4 (4.7)	13.6 (5.3)	14.0 (5.3)	13.2 (5.3)
mean percentile (SD)	62.2 (29.5)	62.1 (30.4)	62.4 (28.4)	56.2 (31.2)	57.1 (31.7)	55.3 (30.7)

Mean total score (0–320) and mean grades (0–20) for specific subjects.
* Total score 0–320.
** Score 0–20 (fail = 0 p, pass = 10 p, pass with distinction = 15 p, pass with special distinction = 20 p).

10% higher for ART!

Table IV School performance in ninth grade, children graduated 2000–2016.

	ART vs SC					
	All		Male		Female	
	Crude mean difference (95% CI), *P*-value	Adjusted* mean difference (95% CI) *P*-value	Crude mean difference (95% CI), *P*-value	Adjusted* mean difference (95% CI), *P*-value	Crude mean difference (95% CI), *P*-value	Adjusted* mean difference (95% CI), *P*-value
Total score, all subjects, all years 2000–2016	10.0 (9.4 to 10.6) *P* < 0.0001	−0.72(−1.31 to −0.12) *P* = 0.018	10.3 (9.5 to 11.1) *P* < 0.0001	−0.36 (−1.21 to 0.49) *P* = 0.41	10.0(9.2 to 10.8) *P* < 0.0001	−1.22 (−2.1 to −0.36) *P* = 0.005
Mathematics All years 2000–2016	7.9 (7.3 to 8.6) *P* < 0.0001	−0.56 (−1.19 to 0.06) *P* = 0.08	7.9 (7.1 to 8.8) *P* < 0.0001	−0.27 (−1.1 to 0.6) *P* = 0.54	7.9 (7.1 to 8.8) *P* < 0.0001	−0.90 (−1.8 to 0.002) *P* = 0.051
Swedish All years 2000–2016	9.2 (8.6 to 9.8) *P* < 0.0001	−0.51 (−1.1 to 0.09) *P* = 0.10	9.6 (8.8 to 10.4) *P* < 0.0001	0.11 (−0.74 to 0.95) *P* = 0.81	9.3 (8.4 to 10.2) *P* < 0.0001	−1.2 (−2.2 to −0.29) *P* = 0.01
English All years 2000–2016	11.4 (10.8–12.1) *P* < 0.0001	0.03 (−0.62 to 0.69) *P* = 0.92	12.2 (11.3 to 13.0) *P* < 0.0001	0.54 (−0.37 to 1.45) *P* = 0.24	10.7 (9.8 to 11.6) *P* < 0.0001	−0.47 (−1.43 to 0.48) *P* = 0.33
Physical education All years 2000–2016	6.0 (5.4 to 6.6) *P* < 0.0001	−0.48 (−1.2 to 0.23) *P* = 0.19	5.0 (4.1 to 5.9) *P* < 0.0001	−0.004 (−1.02 to 1.01) *P* = 0.99	7.1 (6.3 to 8.0) *P* < 0.0001	−0.98 (−1.95 to 0.002) *P* = 0.051

Crude and adjusted mean difference in total score, all subjects and in Mathematics, English, Swedish and physical education (percentiles, 1–100).
*Adjusted for maternal age, paternal age, parental region of birth, parity, smoking during pregnancy, parental level of education, socioeconomic status, year of birth.

Adjusted analysis-slightly lower!

Human Reproduction, Vol.33, No.10 pp. 1948–1959, 2018
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human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

School performance in singletons born after assisted reproductive technology

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Submitted on June 4, 2018; resubmitted on July 26, 2018; accepted on August 2, 2018

	ART n=8323	SC n=1499667	aOR 95% CI
Approved in Mathematics, Swedish, English Qualified to enter secondary school	93.5%	88.8%	1.05 (0.95-1.17)
Poor school performance	7.2%	13.5%	0.98 (0.89-1.09)

Cancer risk among children born after assisted conception

Study period	Cohort size	Average follow-up	Observed cancers	Expected cancers	Risk	95% CI
1992-2008	**106013**	**6.6y**	**108**	**109.7**	**SIR=0.98**	**0.81-1.19**
Hepato-blastoma			6	1.8	SIR=3.64	1.34-7.93
Rhabdomyo-sarcoma			10	3.8	SIR=2.62	1.26-4.82

Williams CL, Sutcliffe A et al, NEJM, 2013

Human Reproduction, Vol.29, No.9 pp. 2050–2057, 2014
Advanced Access publication on July 2, 2014 doi:10.1093/humrep/deu143

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Cancer in children and young adults born after assisted reproductive technology: a Nordic cohort study from the Committee of Nordic ART and Safety (CoNARTaS)

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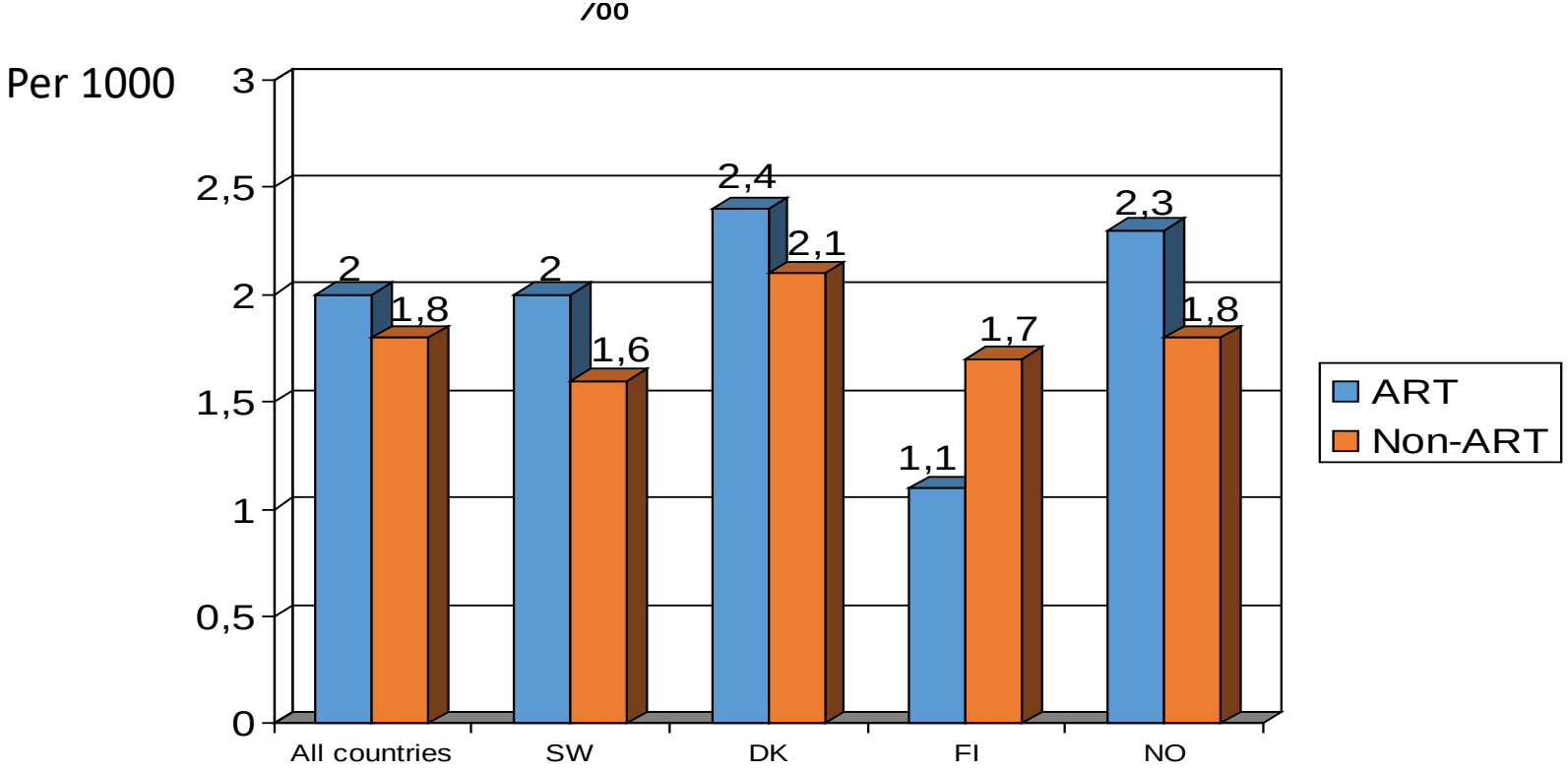

ART: 91 796
SC:358 419
1982-2007
Follow up: 9.5 years

Hazard ratio (95% CI) for cancer in children born after ART vs non-ART

	ART n	**Non-ART** n	**Crude***	**Adjusted****
Any cancer	181	638	1.16 (0.87-1.55)	1.14 (0.85-1.53)

* Age at diagnosis and time of follow-up incorporated
** Adjustment for country

University of Gothenburg

JAMA Pediatr. doi:10.1001/jamapediatrics.2019.0392
Published online April 1, 2019.

Research

JAMA Pediatrics | Original Investigation

Association of In Vitro Fertilization With Childhood Cancer in the United States

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	ART	**Spontaneous conception**
Children	275 686	2 266 847
Cancer/ 1000 000 person-year	251.9	192.7

Follow up:
ART: 4.5 years
SC: 4.7 years

Table 2. Data on the Rates of Cancer by Study Group for All Children (Singleton and Multiple Births Combined)[a]

Cancer	Cases, No.		Cancer Rate/1 000 000 Person-Years		HR (95% CI)[b]
	IVF	Non-IVF	IVF	Non-IVF	
Any cancer	321	2042	251.9	192.7	1.17 (1.00-1.36)
Leukemia	93	707	73.0	66.7	0.93 (0.70-1.22)
ALL	72	534	56.5	50.4	0.96 (0.71-1.32)
AML	13	108	10.2	10.2	0.74 (0.35-1.53)
Lymphoma	22	139	17.3	13.1	1.00 (0.56-1.80)
CNS cancer	59	383	46.3	36.1	1.26 (0.89-1.79)
Astrocytoma	34	197	26.7	18.6	1.50 (0.95-2.36)
Ependymoma	5	48	3.9	4.5	0.53 (0.16-1.72)
Intracranial embryonal tumors	13	83	10.2	7.8	1.41 (0.67-2.95)
Neuroblastoma	47	260	36.9	24.5	1.10 (0.74-1.65)
Retinoblastoma	14	127	11.0	12.0	1.11 (0.57-2.18)
Renal cancer	28	186	22.0	17.6	1.10 (0.66-1.84)
Hepatic cancer	23	60	18.1	5.7	2.46 (1.29-4.70)
Soft-tissue sarcoma	18	97	14.1	9.2	1.50 (0.81-2.84)
Germ cell tumors	11	43	8.6	4.1	2.13 (0.91-4.96)
Embryonal tumors[c]	131	746	102.8	70.4	1.28 (1.01-1.63)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; HR, hazard ratio; IVF, in vitro fertilization.

[a] The final population included 275 686 children in the IVF group (1 274 070 person-years; 209 586 births) and 2 266 847 children in the non-IVF group (10 596 144 person-years; 2 230 378 births).

[b] Adjusted for state of birth, maternal race and ethnicity, maternal educational level (college graduate vs less than college graduate), maternal age, and child's sex; missing data for maternal race (4.3%) and educational level (2.2%) were replaced by a category labeled "missing" in each variable.

[c] Neuroblastoma, retinoblastoma, nephroblastoma, hepatoblastoma, embryonal rhabdomyosarcoma, pulmonary and pleuropulmonary blastoma, medulloblastoma, primitive neuroectodermal tumor, medulloepithelioma, and atypical teratoid and rhabdoid tumor.

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human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Risk of cancer in children and young adults conceived by assisted reproductive technology

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1980-2001, OMEGA, 21 years follow up
ART: 24269
SC:13761
Subfertile:9660

231 cancer (93, 92, 46)
ART vs subfertile: HR 1.0 (0.72-1.38)
ART vs general population: SIR:1.11 (0.90-1.36)

ARTICLE IN PRESS

ORIGINAL ARTICLE: ENVIRONMENT AND EPIDEMIOLOGY

Fertil &Steril 2017

Cardiovascular and metabolic profiles of offspring conceived by assisted reproductive technologies: a systematic review and meta-analysis

Xiao-Yan Guo, M.D.,[a] Xin-Mei Liu, Ph.D.,[b,c] Li Jin, Ph.D.,[b,c] Ting-Ting Wang, Ph.D.,[b,c] Kamran Ullah, Ph.D.,[d] Jian-Zhong Sheng, M.D., Ph.D.,[d] and He-Feng Huang, M.D.[a,b,c]

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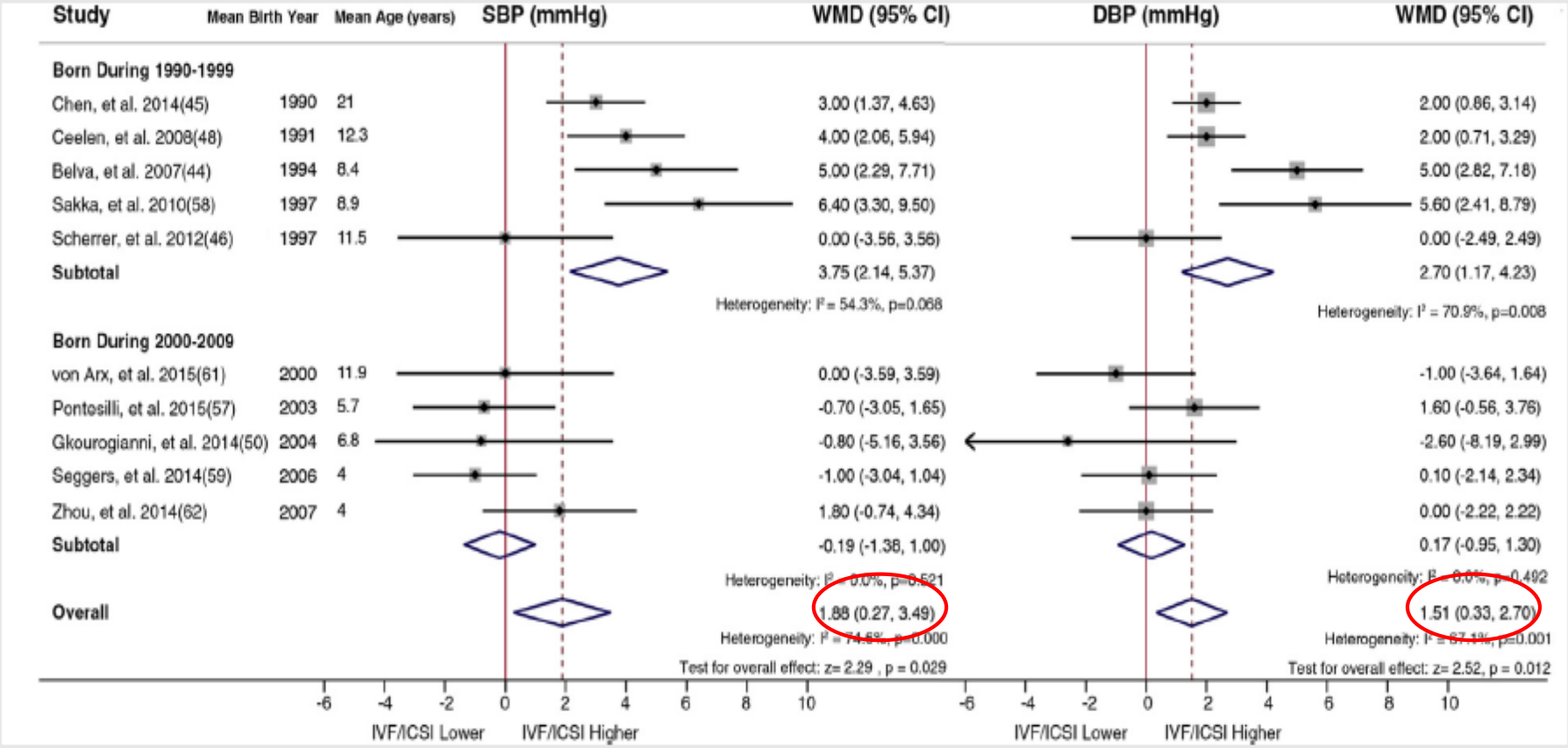
19 studies

2,112 IVF/ICSI children

4,096 SC children

FIGURE 1

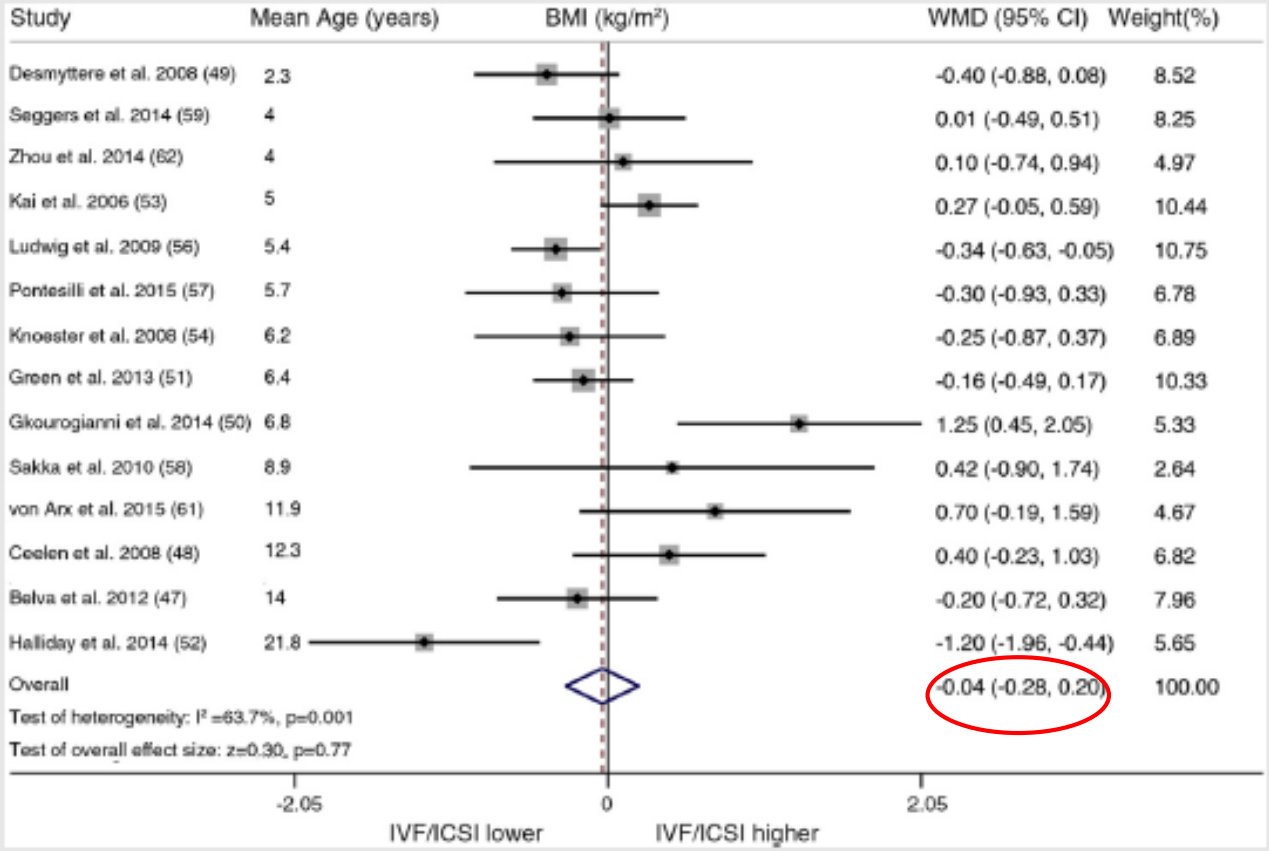


Systolic and diastolic blood pressure of 872 IVF-ICSI offspring versus 3,034 naturally conceived offspring. Studies are arranged and grouped by mean birth year of the children. Random effects model was used. CI = confidence interval; DBP = systolic diastolic blood pressure; SBP = systolic blood pressure; WMD = weighted mean difference.

Guo. Cardiometabolic profile of ART offspring. Fertil Steril 2016.

Guo *et al,* 2017

FIGURE 2



Body mass index of 1,914 IVF-ICSI offspring versus 3,881 naturally conceived offspring. Studies are arranged according to mean age of the subjects. Random effects model was used. CI = confidence interval; WMD = weighted mean difference.

Guo. Cardiometabolic profile of ART offspring. Fertil Steril 2016.

Guo *et al*, 2017

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Systemic and Pulmonary Vascular Dysfunction in Children Conceived by Assisted Reproductive Technologies

Urs Scherrer, MD*; Stefano F. Rimoldi, MD*; Emrush Rexhaj, MD; Thomas Stuber, MD; Hervé Duplain, MD; Sophie Garcin, MD; Stefano F. de Marchi, MD; Pascal Nicod, MD; Marc Germond, MD; Yves Allemann, MD*; Claudio Sartori, MD*

- IVF singletons (n=65) and spontaneously conceived singletons (n=57)
- General vascular dysfunction in the systemic and pulmonary circulation
  - Intima thickness in the carotic artery ↑
  - Pressure in the pulmonary artery ↑

(Circulation 2012)

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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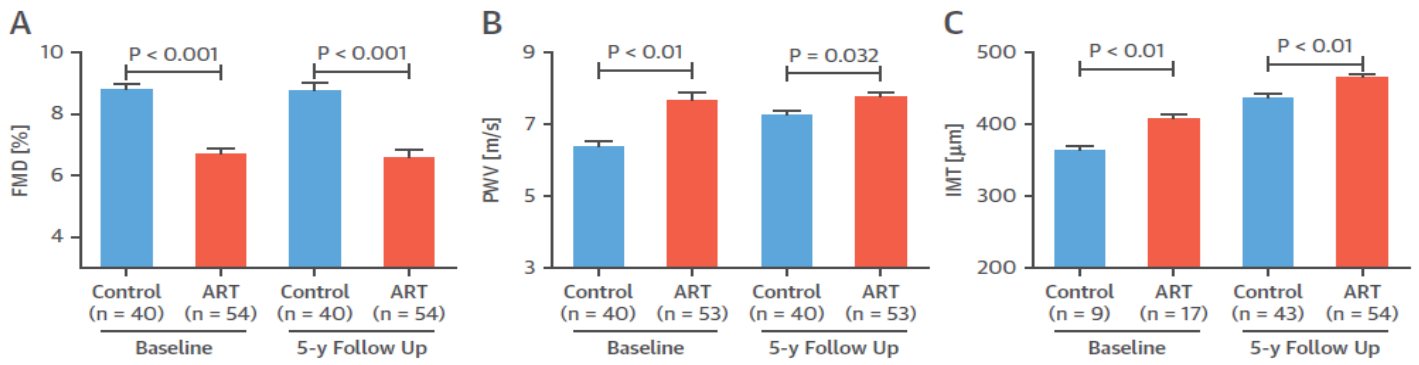
SPECIAL FOCUS ISSUE: BLOOD PRESSURE

Association of Assisted Reproductive Technologies With Arterial Hypertension During Adolescence

Théo A. Meister, MD,[a,*] Stefano F. Rimoldi, MD,[a,*] Rodrigo Soria, MD,[a] Robert von Arx, MD,[a] Franz H. Messerli, MD,[a] Claudio Sartori, MD,[b] Urs Scherrer, MD,[a,c,†] Emrush Rexhaj, MD[a,†]

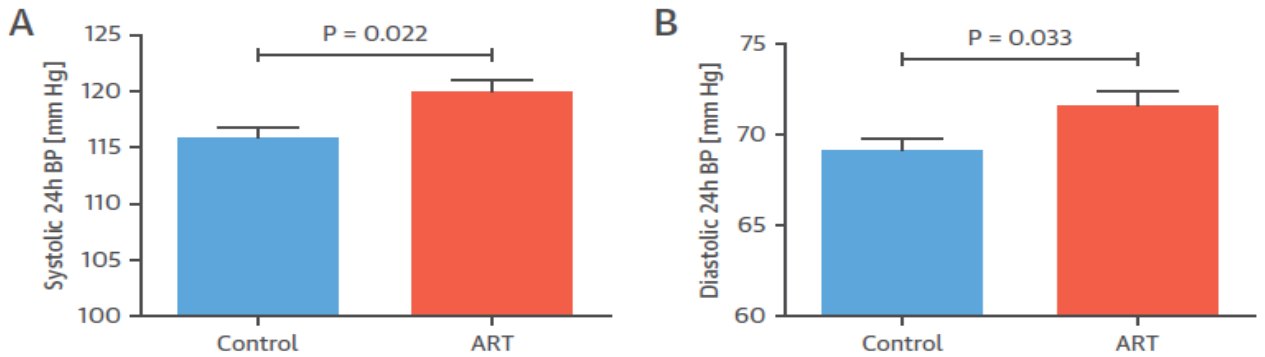
54 ART, 43 SC singletons
5-year follow up (16-17 years old)

FIGURE 1 Premature Vascular Aging in ART Children Persists Into Young Adulthood



(A) Flow-mediated dilation (FMD, **(B)** pulse wave velocity (PVW), and **(C)** intima-media thickness (IMT) at baseline (mean ± SD age, control 11.8 ± 2.2 years; assisted reproductive technologies [ART] 10.9 ± 2.4 years) and at 5-year follow-up (mean age; control 17.6 ± 2.7 years; assisted reproductive technologies 16.6 ± 2.4 year) in subjects conceived through assisted reproductive technologies and naturally conceived control subjects. Premature vascular aging, as evidenced by impaired flow-mediated dilation and by increased pulse wave velocity and intima-media thickness, persists at 5-years follow up in subjects conceived through assisted reproductive technologies. Data are shown as mean ± SD.

FIGURE 2 24-h Ambulatory BP in ART and Control Subjects



(A) Systolic and **(B)** diastolic 24-h ambulatory blood pressure (BP) was significantly higher in subjects conceived through assisted reproductive technologies (ART) (n = 52) than in control subjects (n = 43). Data are shown as mean ± SD.

Fertility treatment and childhood type 1 diabetes mellitus: a nationwide cohort study of 565,116 live births

Laura Ozer Kettner, M.D.,[a] Niels Bjerregaard Matthiesen, Ph.D.,[a] Cecilia Høst Ramlau-Hansen, Ph.D.,[b] Ulrik Schiøler Kesmodel, Ph.D.,[c] Bjørn Bay, Ph.D.,[d] and Tine Brink Henriksen, Ph.D.[a]

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TABLE 2

Associations between types of fertility treatment and childhood type 1 diabetes mellitus in 565,116 singleton pregnancies, Denmark, 1995–2003.

Exposure	Pregnancies, n (%)	Diabetes, n (%)	Person-years at risk	HR	HR (95% CI) adjusted[a]
No fertility treatment	541,641 (95.9)	1,928 (0.4)	7,581,754	1.00 (reference)	1.00 (reference)
OI or IUI	14,985 (2.7)	54 (0.4)	202,015	1.06	1.01 (0.77–1.32)
IVF or ICSI	8,490 (1.5)	29 (0.3)	112,850	1.03	0.99 (0.67–1.45)

Note: CI = confidence interval; HR = hazard rate ratio; ICSI = intracytoplasmic sperm injection; IUI = intrauterine insemination; IVF = in vitro fertilization; OI = ovulation induction.

[a] Adjusted for maternal age at birth, maternal smoking during pregnancy, maternal education, maternal ethnicity, maternal and paternal type 1 diabetes mellitus, and child's year of birth.

Kettner. Fertility treatment and type 1 diabetes. Fertil Steril 2016.

Type 1 Diabetes in Children born after Assisted Reproductive Technology: a register based national cohort study

Emma Norrman, MD[9], Max Petzold, PhD[2], Tine Dalsgaard Clausen, MD, PhD[3], Anna-Karina Henningsen, MD[4], Signe Opdahl, MD, PhD[5], Anja Pinborg, MD, PhD[4], Annika Rosengren, MD, PhD[6] Christina Bergh, MD, PhD[7,8], Ulla-Britt Wennerholm, MD, PhD[1,8]

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	ART	SC
	n=47,938	n=3,090,602
DM1	202	17,916
per 100 000 person years	43.4	35.5

aHR (ART vs SC):1.07 (0.93-1.23)

aHR (FET vs fresh): 1.52 (1.08-2.14)

aHR (FET vs SC):1.41 (1.05 to 1.89)

Norrman, accepted 2019

Reproductive health in ICSI
Pubertal development

- 116 ICSI boys and 115 SC boys, 14 years old
- Genital development and pubic hair development comparable

- 101 ICSI girls and 108 SC girls, 14 years old
- Mean (SD) age for menarche 13.1 (1.2) and 13.1 (1.4) years
- Pubic hair development comparable
- Breast development was less advanced in ICSI

Belva *et al.,* Hum Reprod 2012

Reproductive health in ICSI

- 54 ICSI men and 57 SC men, 18-22 years old
- Reproductive hormones:
- FSH, LH, testosterone, and inhibin B comparable
- Semen parameters:
- Lower semen parameters in ICSI cohort
- Concentration <15 million/ml: AOR 2.7 (95% CI 1.1-6.7)
- Total count <39 million: AOR 4.3 (95% CI 1.7-11.3)

- 71 ICSI women and 81 SC women, 18-22 years old
- Reproductive hormones:
  AMH, FSH, LH, and DHEAS comparable
- Mean follicle count/ovary comparable

Belva *et al.*, 2016 2017

KEY MESSSAGES - short term outcomes

- Neonatal outcome (PTB, LBW) -increased rates
- Congenital birth defects - increased rate
- ICSI-IVF-No differences
- Cryopreservation-lower PTB/LBW, higher LGA

KEY MESSAGES – long term outcomes

- Growth-no difference
- Cancer no/small increased risk
- Neuro-developmental diseases- no increased risk
- Academic performance-reassuring
- Autism-reassuring
- SBP and DBP slightly higher
- Cardiac diastolic function suboptimal and vessels thickness was higher
- BMI and lipid metabolism similar
- Type 1 Diabetes-increased for FET

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Thank’s!

London 14-15 November, 2019

University of Gothenburg

London 14-15 November, 2019

Cardiometabolic differences in children born after IVF

(8-18 year-old, matched age and gender)

	IVF N=225	Controls (subfertile) N=225	P-value
SBT	109±11	105±1	<0.001
DBT	61±7	59±7	<0.001
Fasting glucose	5.0± 0.4	4.8±0.4	<0.005

Ceelen *et al*, 2008

Are ICSI adolescents at risk for increased adiposity?

(14-year old ICSI singletons and spontaneous conception, n=233)

Result: ICSI girls more central, peripheral and total adiposity

Belva *et al*, 2012

SCIENTIFIC REPORTS

OPEN

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Published: 07 April 2017

Association between assisted reproductive technology and the risk of autism spectrum disorders in the offspring: a meta-analysis

Liang liu*, Junwei Gao*, Xie He, Yulong Cai, Lian Wang & Xiaotang Fan

11 studies

N=46 249 ART children

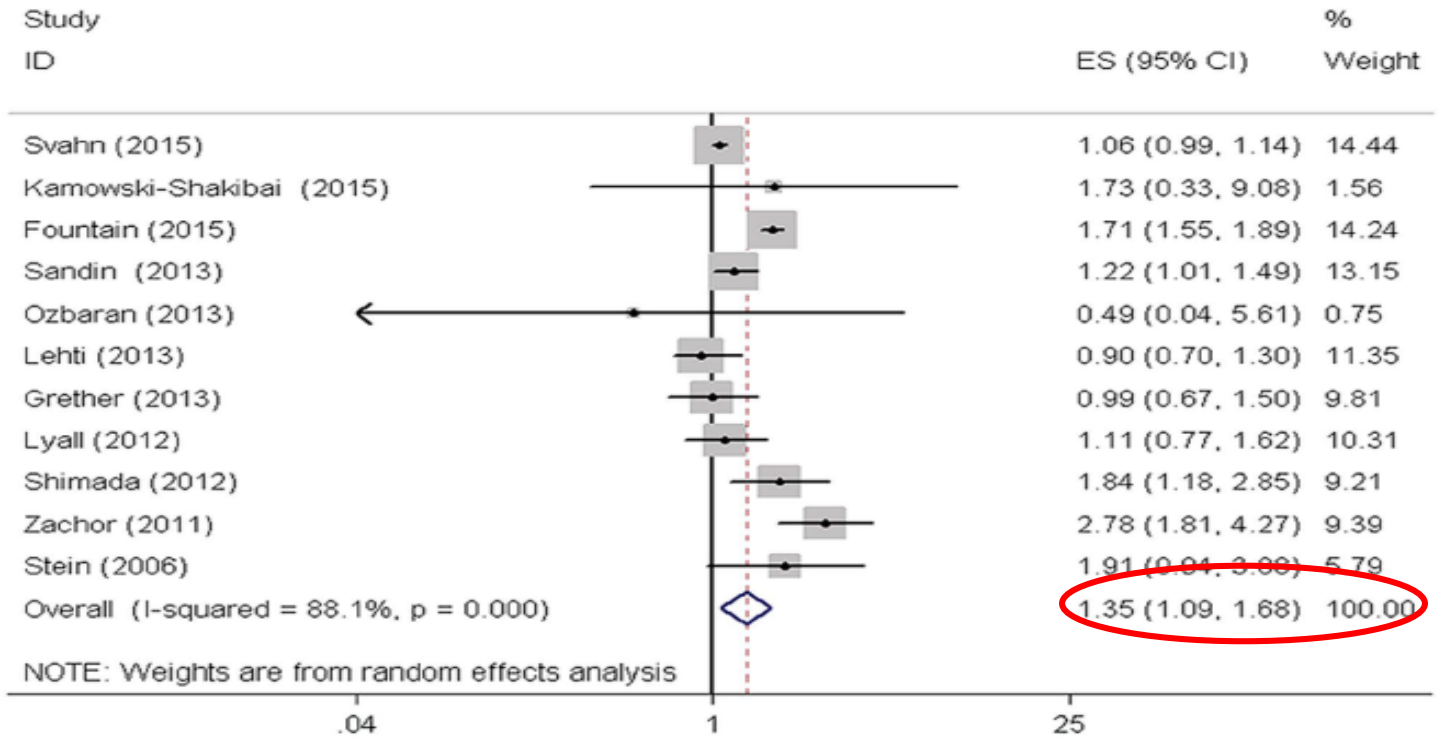

Figure 2. Forest plot of ASDs risk associated with ART using. ASDs, autism spectrum disorders; CI, confidence interval.

No increase when
adjusted for multiplicity!

Human Reproduction, Vol.32, No.2 pp. 447–456, 2017
Advanced Access publication on January 5, 2017 doi: 10.1093/humrep/dew334

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Academic performance in adolescents born after ART—a nationwide registry-based cohort study

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Epidemiology

Academic performance in adolescents aged 15–16 years born after frozen embryo transfer compared with fresh embryo transfer: a nationwide registry-based cohort study

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Cardiovascular and metabolic profiles of offspring conceived by assisted reproductive technologies: a systematic review and meta-analysis

Xiao-Yan Guo, M.D.,[a] Xin-Mei Liu, Ph.D.,[b,c] Li Jin, Ph.D.,[b,c] Ting-Ting Wang, Ph.D.,[b,c] Kamran Ullah, Ph.D.,[d] Jian-Zhong Sheng, M.D., Ph.D.,[d] and He-Feng Huang, M.D.[a,b,c]

- Small increase in SBP and DBP
- Cardiac diastolic function suboptimal and vessels thickness was higher
- Increased insulin levels, no difference in glucose
- No difference in BMI and lipid metabolism
- Indicates a certain risk of cardiovascular disease which calls for further investigation

ORIGINAL ARTICLES
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Long-Term Cardiovascular Morbidity in Children Born Following Fertility Treatment

Sivan Reut Shiloh, BSc[1], Eyal Sheiner, MD, PhD[1], Tamar Wainstock, PhD[2], Asnat Walfisch, MD[1], Idit Segal, MD[3], Daniella Landau, MD[4], and Avi Harlev, MD[1]

Population based cohort, Israel
Hospitilization up to age 13 years
Singletons: 2603 IVF, 237 863 Spontaneous conception

CVD:15 (0.6%) vs 1476 (0.6%)
aHR 1.05 (0.63-1.74)

AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS ORIGINAL RESEARCH ARTICLE

Type 1 diabetes risk in children born to women with fertility problems: a cohort study in 1.5 million Danish children

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Table 2. Relative risks (HRs) and 95% confidence intervals (95% CIs) for type 1 diabetes according to maternal fertility status.

	N_{cases}	N_{all}	HR[a]	(95% CI)	HR[b]	(95% CI)
Maternal fertility problems						
No	5176	1 440 126	1.00	—	1.00	—
Yes	313	110 393	1.09	(0.97–1.22)	1.01	(0.90–1.13)
Birth year						
1987–93						
No	2298	427 209	1.00	—	1.00	—
Yes	61	12 546	0.92	(0.72–1.19)	0.90	(0.70–1.16)
1994–2010						
No	2878	1 012 917	1.00	—	1.00	—
Yes	252	97 847	1.09	(0.96–1.24)	1.05	(0.92–1.19)
Age at diagnosis						
<1 years						
No	85	1 440 126	1.00	—	1.00	—
Yes	6	110 393	0.92	(0.40–2.11)	0.86	(0.37–1.99)
1–15 years						
No	4251	1 428 332	1.00	—	1.00	—
Yes	286	109 210	1.12	(1.00–1.27)	1.04	(0.92–1.17)
>15 years						
No	840	656 335	1.00	—	1.00	—
Yes	21	26 383	0.81	(0.52–1.25)	0.79	(0.51–1.21)

[a]Crude unadjusted model.
[b]Adjusted for birth year, sex and history of parental type 1 diabetes.

Type 1 Diabetes in Children born after Assisted Reproductive Technology: a register based national cohort study

Emma Norrman, MD[1,9], Max Petzold, PhD[2], Tine Dalsgaard Clausen, MD, PhD[3], Anna-Karina Henningsen, MD[4], Signe Opdahl, MD, PhD[5], Anja Pinborg, MD, PhD[4], Annika Rosengren, MD, PhD[6] Christina Bergh, MD, PhD[7,8], Ulla-Britt Wennerholm, MD, PhD[1,8]

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- Year of birth 1985 to 2015
- Singletons born after ART (n=47 938)
- Singletons born after SC (n=3 090 602)
- ART: 36 727 fresh embryo transfer, 11 211 frozen embryo transfer

National registries

IVF-registries

- Medical Birth Registry
- National Patient Registry
- SWEDIABKIDS
- National Diabetes Register
- Swedish Prescribed Drug Register
- SCB (Swedish Central Bureau)

Association between ART and type 1 diabetes in singletons born in Sweden between 1985 and 2015

	All ART n= 47 938	SC n= 3,090,602
Type 1 diabetes n, % (n= 18 118)	202	17 916
Person-years at risk	465 450	50 471 136
HR (95% CI) crude ART vs SC	**1.23** (1.07 to 1.42)	1.00 (reference)
HR (95% CI) adjusted[a] ART versus SC	1.13 (0.98 to 1.30)	1.00 (reference)
HR (95% CI) adjusted[b] ART versus SC	**1.07** (0.93 to 1.23)	1.00 (reference)

[a]Adjusted for calendar year of birth

[b]Adjusted for maternal age, sex, year of birth, maternal smoking, maternal country of birth and educational level, type 1 diabetes of the parents

Association between frozen embryo transfer and type 1 diabetes in singletons born in Sweden between 1985 and 2015

	IVF/ICSI frozen N= 11,211	IVF/ICSI fresh N= 36,727	Spontaneous conception N= 3,090,602
Type 1 diabetes N=202 (%)	45 (0.40)	157 (0.43)	17,916 (0.58)
Person-years at risk	83,181	382,269	50,471,136
HR (95% CI) crude Frozen versus fresh IVF/ICSI	**1.48** (1.06 to 2.07)	1.00 (reference)	
HR (95% CI) adjusted[b] Frozen versus fresh IVF/ICSI	**1.52** (1.08 to 2.14)	1.00 (reference)	
HR (95% CI) crude Frozen IVF/ICSI versus SC	**1.65** (1.23 to 2.21)		1.00 (reference)
HR (95% CI) adjusted[b] Frozen IVF/ICSI versus SC	**1.41** (1.05 to 1.89)		1.00 (reference)

[b]Adjusted for maternal age, sex, year of birth, maternal smoking, maternal country of birth and educational level, type 1 diabetes of the parents

ANDROLOGY

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REVIEW ARTICLE

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Long-term follow-up of ICSI-conceived offspring compared with spontaneously conceived offspring: a systematic review of health outcomes beyond the neonatal period

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48 studies

Neurodevelopment
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