Recent Developments in the Transmission of Human Life

19-21 January 2023

Berlin, Germany

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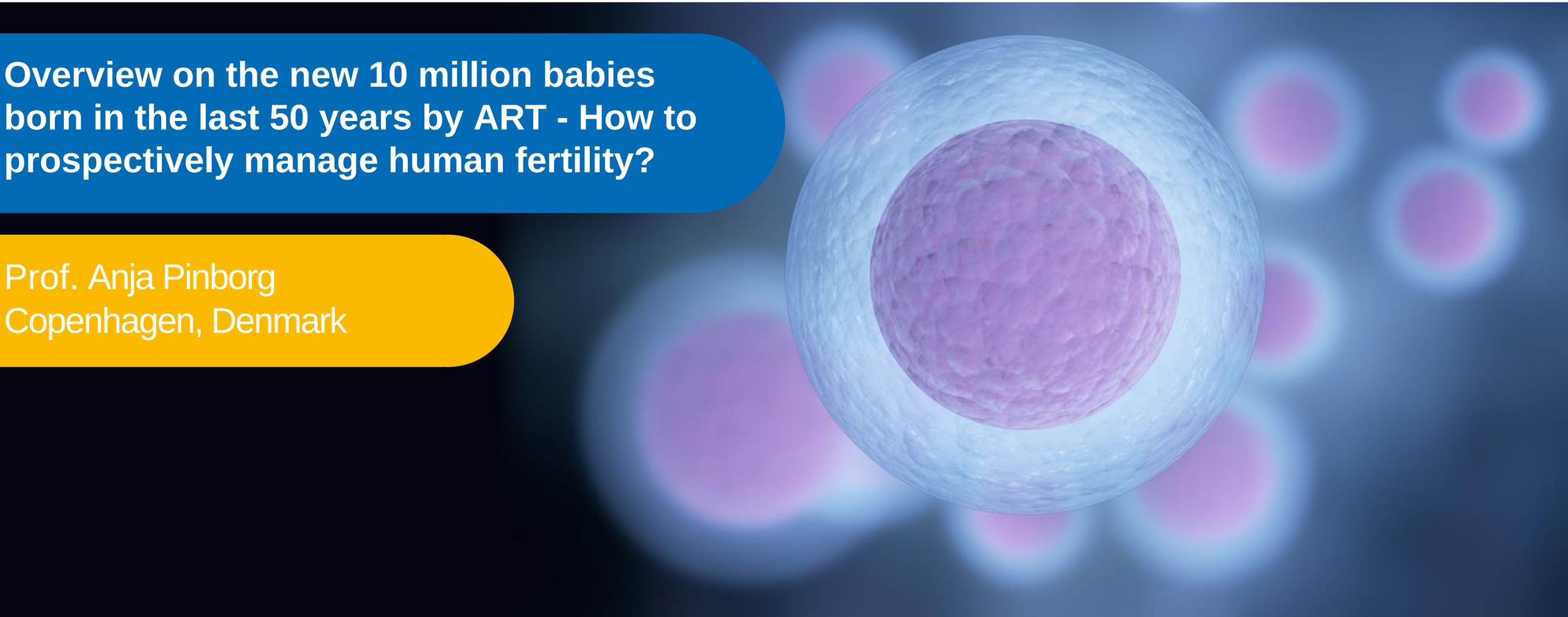
Recent Developments in the Transmission of Human Life

Overview on the new 10 million babies born in the last 50 years by ART - How to prospectively manage human fertility?

Prof. Anja Pinborg
Copenhagen, Denmark



Overview on the new 10 million babies born in the last 50 years by ART -How to prospectively manage human fertility?

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Fertility Dept., Rigshospitalet
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Faculty Disclosure

I received grants, contracts, honoraria or consultation fees from:

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- **Lectures for:** Gedeon Richter, Theramex, Ferring, Merck, IBSA Pharma, Organon
- **Scientific advisory boards:** Ferring, Merck, Gedeon Richter, Cryos

Content

- Short and long-term health in ART children
- Effect of various ART methods on child health
  - Fresh embryo transfer cycles
  - Frozen embryo transfer (FET) cycles
  - Egg donation
- How to prospectively manage human fertility?

CoNARTaS and European IVF Monitoring data

CoNARTaS
Committee of Nordic Assisted Reproductive Technology and Safety

Children born after ART in 2018[1] — 3–6%

ART children born after ICSI in 2015[2] — 40–50%

ART children born after cryopreservation in 2015[2] — 30–40%

Decrease in multiple pregnancies due to eSET policy

ART, assisted reproductive technology; eSET, elective single embryo transfer; ICSI, intracytoplasmic sperm injection.

1. Wyns C, et al. Hum Reprod Open 2022(3):hoac022; 2. Opdahl S, et al. Int J Epidemiol 2020;49:365–366f.

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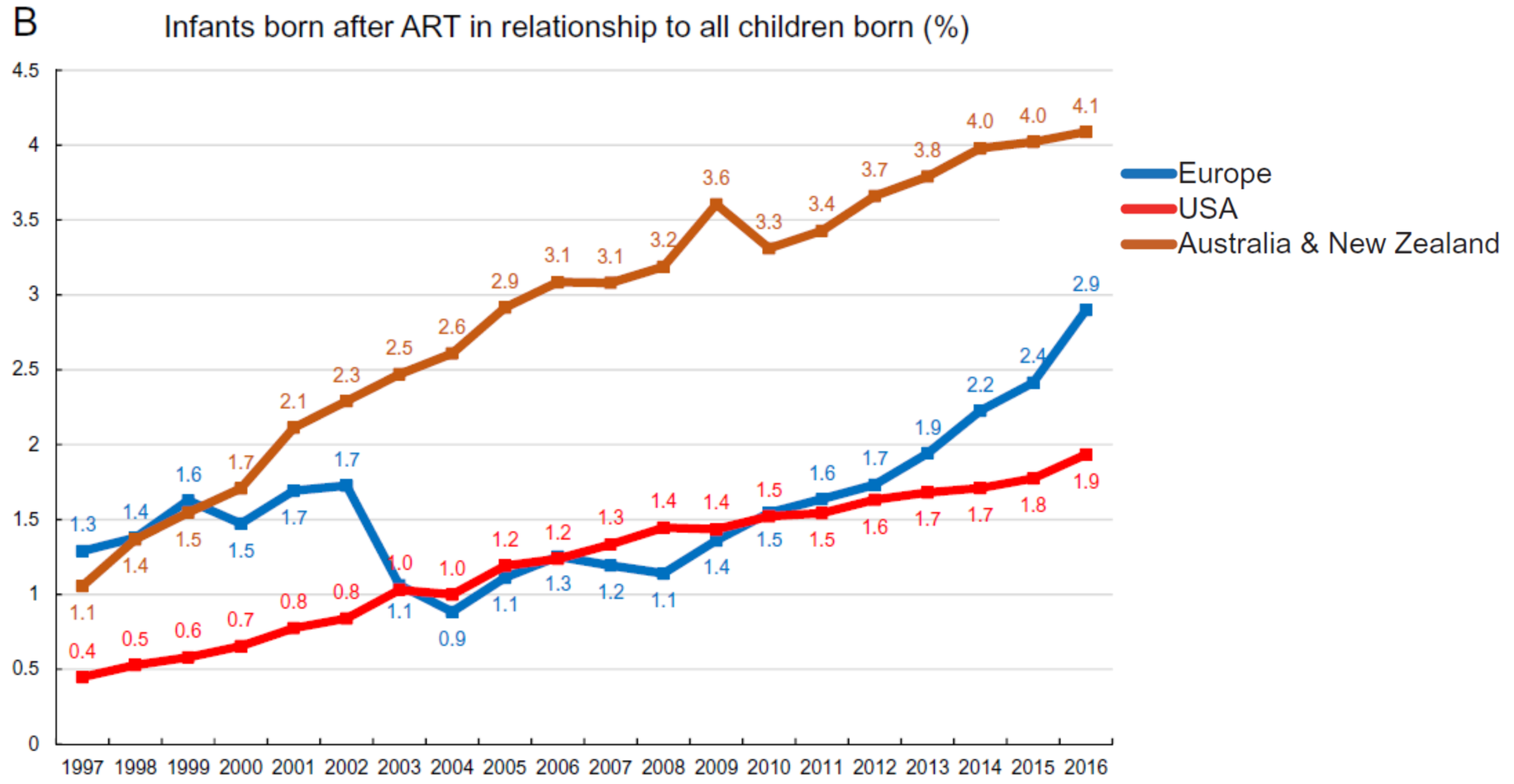
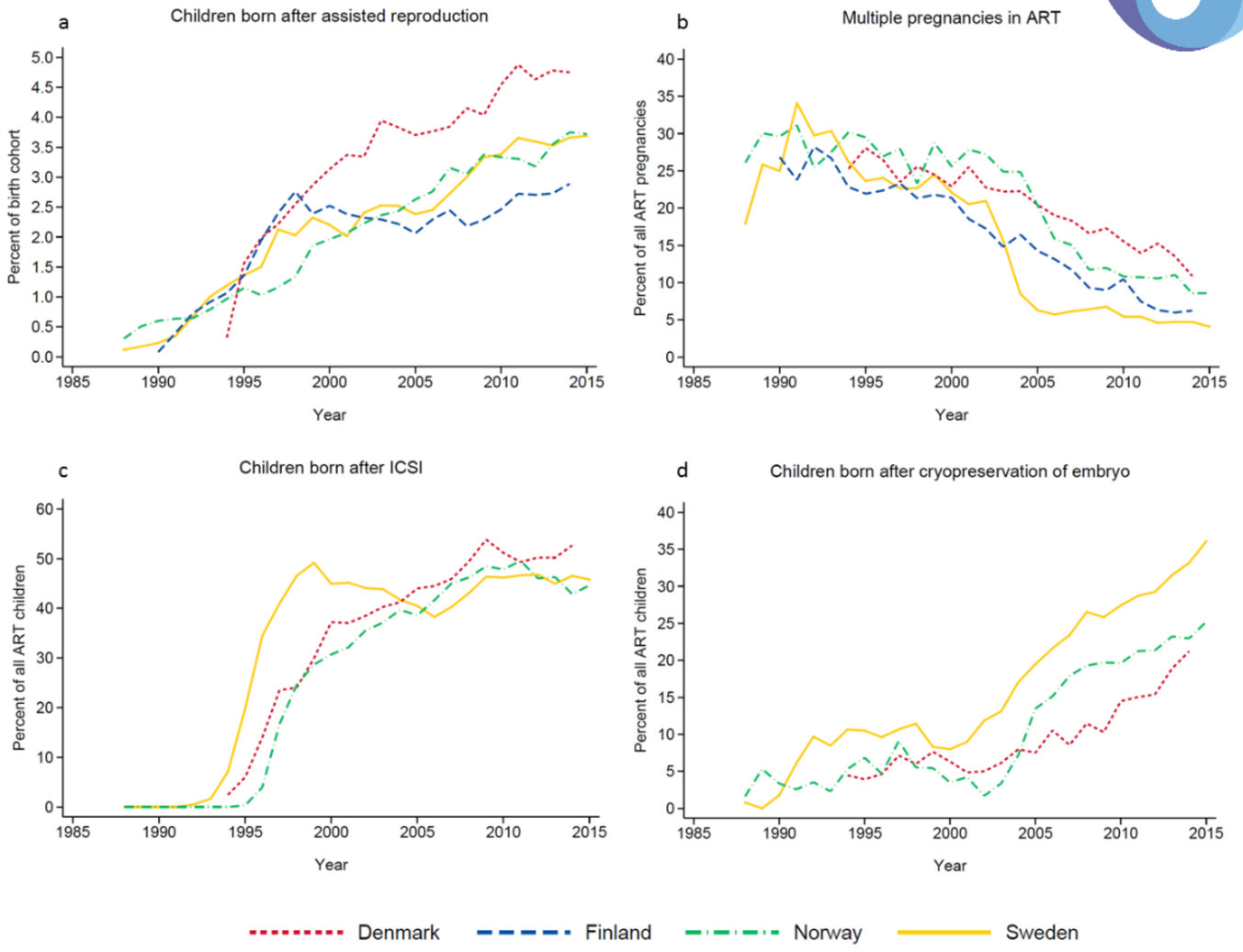
Changes in numbers of infants born after ART



Changes in the numbers of infants born after IVF, ICSI and FET.

De Geyter C *et al.*, Hum Reprod 2020



(Opdahl S et al., Int J Epidemiol 2020)

Human Reproduction, Vol.36, No.8, pp. 2358–2370, 2021
Advance Access Publication on May 29, 2021 doi:10.1093/humrep/deab122

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Cerebral palsy in ART children has declined substantially over time: a Nordic study from the CoNARTaS group

Anne Lærke Spangmose [1,*], Lene Hee Christensen [1], Anna-Karina Aaris Henningsen [1], Julie Forman [2], Signe Opdahl [3], Liv Bente Romundstad [3,4], Kate Himmelmann [5], Christina Bergh [6], Ulla-Britt Wennerholm [6], Aila Tiitinen [7], Mika Gissler [8,9], and Anja Pinborg [1]

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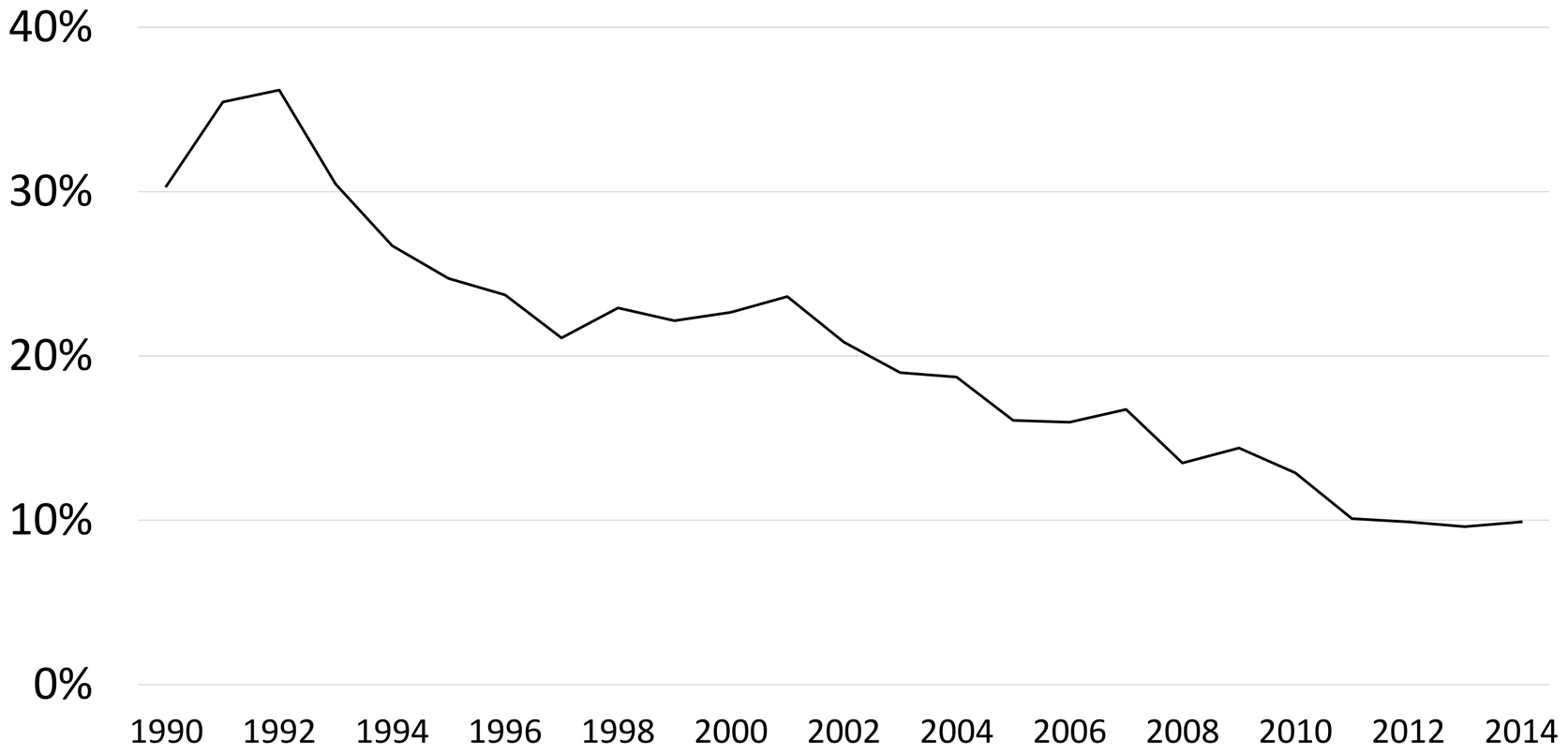
CoNARTaS
Committee of Nordic Assisted Reproductive Technology and Safety

ART deliveries with gestational age < 37 weeks



(Spangmose AL et al., Hum Reprod 2021)

Cerebral palsy – All children

Birth year	ART no./1000	Spontaneous conception no./1000	Crude OR (95% CI)	**Adjusted OR* (95% CI)**
1990–1993	**12.5**	**4.3**	**2.92 (2.17–3.84)**	**2.76 (2.03–3.67)**
1994–1998	8.2	4.3	1.94 (1.64–2.27)	1.80 (1.49–2.14)
1999–2002	7.6	3.9	1.94 (1.65–2.27)	1.73 (1.46–2.03)
2003–2006	6.0	3.2	1.90 (1.60–2.24)	1.65 (1.37–1.96)
2007–2010	**3.5**	**2.7**	**1.31 (1.06–1.58)**	**1.21 (0.97–1.49)**
2011–2014	3.4	**2.1**	1.63 (1.22–2.13)	1.39 (1.01–1.87)
Total	5.9	3.5	1.68 (1.55–1.82)	1.56 (1.44–1.70)

*Adjusted for parity, child's sex, country, maternal age and smoking during pregnancy

(Spangmose AL et al., Hum Reprod 2021)

Journal of the American Heart Association

J Am Heart Assoc. 2022;11:e022658. DOI: 10.1161/JAHA.121.022658

ORIGINAL RESEARCH

In-Hospital Complications in Pregnancies Conceived by Assisted Reproductive Technology

Pensée Wu, MBChB, MD(Res); Garima V. Sharma, MD; Laxmi S. Mehta, MD; Carolyn A. Chew-Graham, MBChB, MD; Gina P. Lundberg, MD; Kara A. Nerenberg, MD, MSc; Michelle M. Graham, MD; Lucy C. Chappell, MB BCh, PhD; Umesh T. Kadam, MBChB, PhD; Kelvin P. Jordan, PhD; Mamas A. Mamas, BM BCh, DPhil

BACKGROUND: Assisted reproductive technology (ART) has emerged as a common treatment option for infertility, a problem that affects an estimated 48 million couples worldwide. Advancing maternal age with increasing prepregnancy cardiovascular risk factors, such as chronic hypertension, obesity, and diabetes, has raised concerns about pregnancy complications associated with ART. However, in-hospital complications following pregnancies conceived by ART are poorly described.

METHODS AND RESULTS: To assess the patient characteristics, obstetric outcomes, vascular complications and temporal trends of pregnancies conceived by ART, we analyzed hospital deliveries conceived with or without ART between January 1, 2008, and December 31, 2016, from the United States National Inpatient Sample database. We included 106 248 deliveries conceived with ART and 34 167 246 deliveries conceived without ART. Women who conceived with ART were older (35 versus 28 years; *P*<0.0001) and had more comorbidities. ART-conceived pregnancies were independently associated with vascular complications (acute kidney injury: adjusted odds ratio [aOR], 2.52; 95% CI 1.99–3.19; and arrhythmia: aOR, 1.65; 95% CI, 1.46–1.86), and adverse obstetric outcomes (placental abruption: aOR, 1.57; 95% CI, 1.41–1.74; cesarean delivery: aOR, 1.38; 95% CI, 1.33–1.43; and preterm birth: aOR, 1.26; 95% CI, 1.20–1.32), including in subgroups without cardiovascular disease risk factors or without multifetal pregnancies. Higher hospital charges ($18 705 versus $11 983; *P*<0.0001) were incurred compared with women who conceived without ART.

CONCLUSIONS: Pregnancies conceived by ART have higher risks of adverse obstetric outcomes and vascular complications compared with spontaneous conception. Clinicians should have detailed discussions on the associated complications of ART in women during prepregnancy counseling.

Non-ART

ART

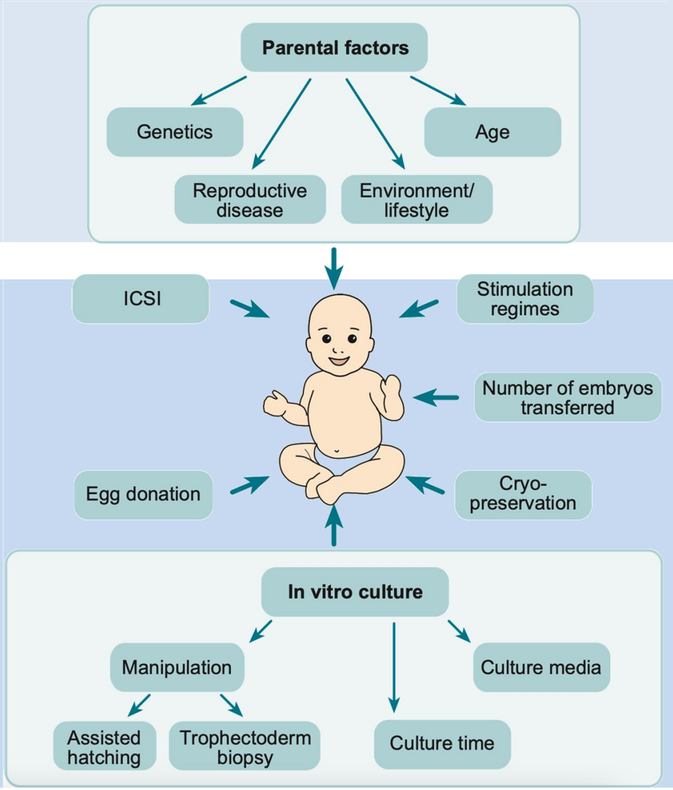
Comorbidities, %			
Chronic kidney disease	0.06	0.06	0.96
Congenital heart disease	0.12	0.30	<0.0001*
Congestive heart failure	0.05	0.07	0.18
Current preeclampsia/ eclampsia	4.42	10.33	<0.0001*
Depression	2.21	2.88	<0.0001*
Diabetes	1.10	1.16	0.49
Dyslipidemia	0.12	0.42	<0.0001*
Hypertension	2.20	3.67	<0.0001*
Multifetal pregnancy	1.95	28.70	<0.0001*
Obesity	5.52	6.36	0.0002*
Previous MI	0.01	0.01	0.90
Previous TIA/stroke	0.06	0.12	0.0001*
Smoker	7.68	3.66	<0.0001*
Valvular disease	0.28	0.75	<0.0001*

Potential causes for adverse health outcomes in ART children

Parental characteristics

ART treatment

per se



(Berntsen S. et al., Hum Reprod Upd 2019)

CoNARTaS cohort: Retrospective population-based

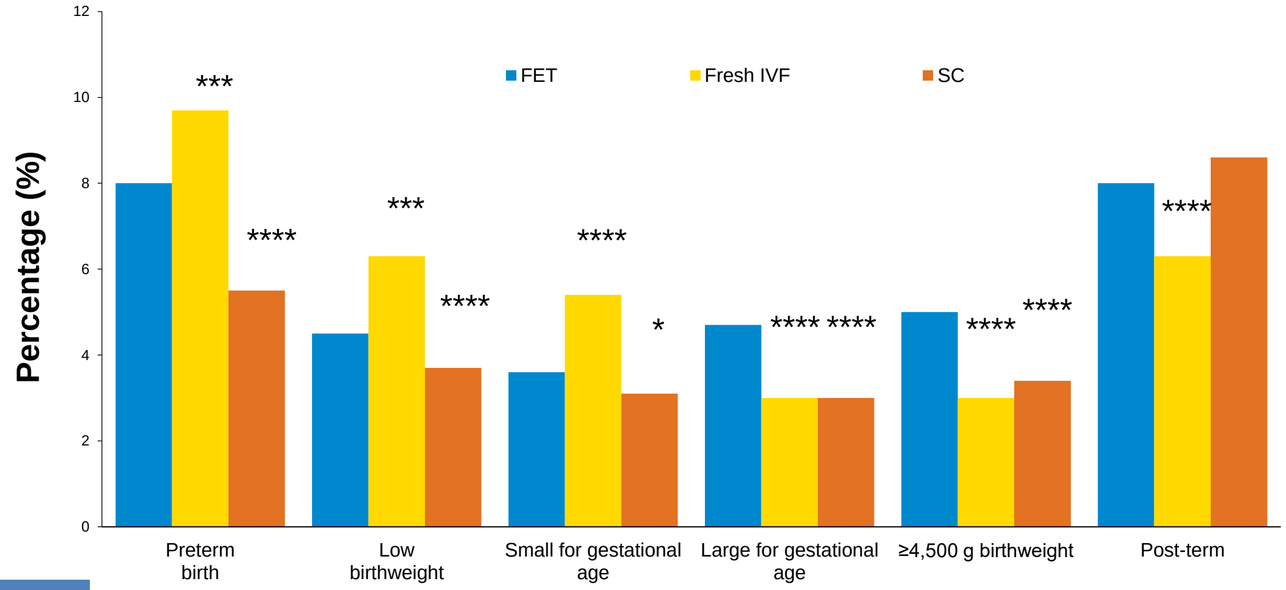
CoNARTaS
Committee of Nordic Assisted Reproductive Technology and Safety

6,647
Singletons born after FET

42,242
Singletons born after fresh IVF/ICSI

288,542
Singletons born after SC

Distribution of gestational age and birthweight in children born after FET, fresh IVF and spontaneous conception



	Adjusted p-value					
FET vs fresh IVF/ICSI	0.0003	0.0007	<0.0001	<0.0001	<0.0001	<0.0001
FET vs SC	<0.0001	<0.0001	0.02	<0.0001	<0.0001	-

*p<0.05; ***p<0.001; ****p<0.0001. Data obtained by linkage to the national Medical Birth Registries.

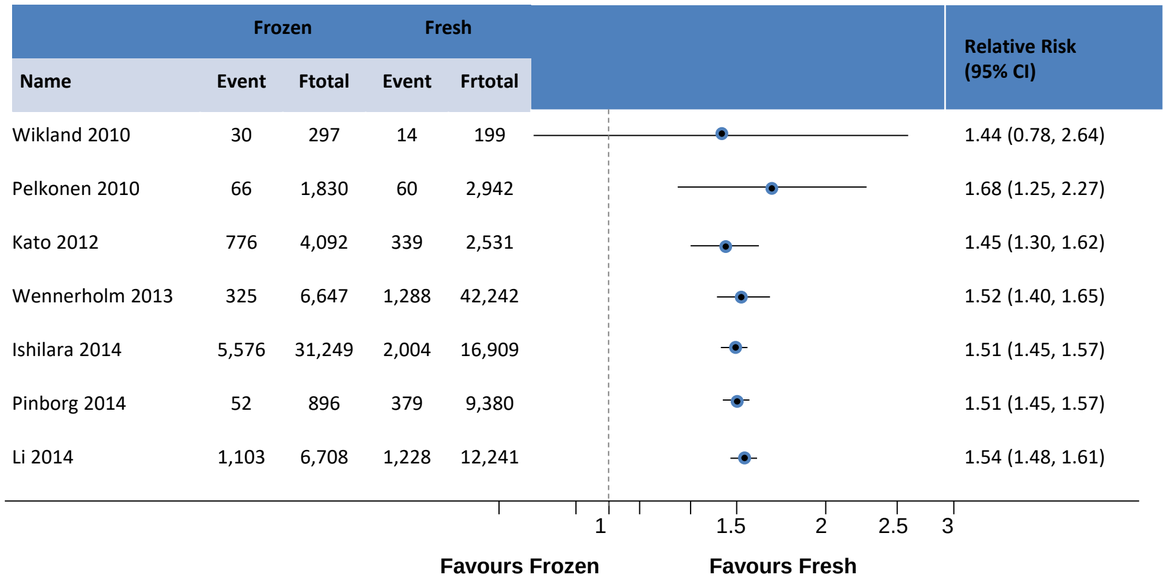
FET, frozen embryo transfer; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation; SC, spontaneous conception.

Wennerholm UB, et al. Hum Reprod 2013;28:2545–2553.

Large-for-gestational age in singletons born after frozen vs. fresh embryo transfer

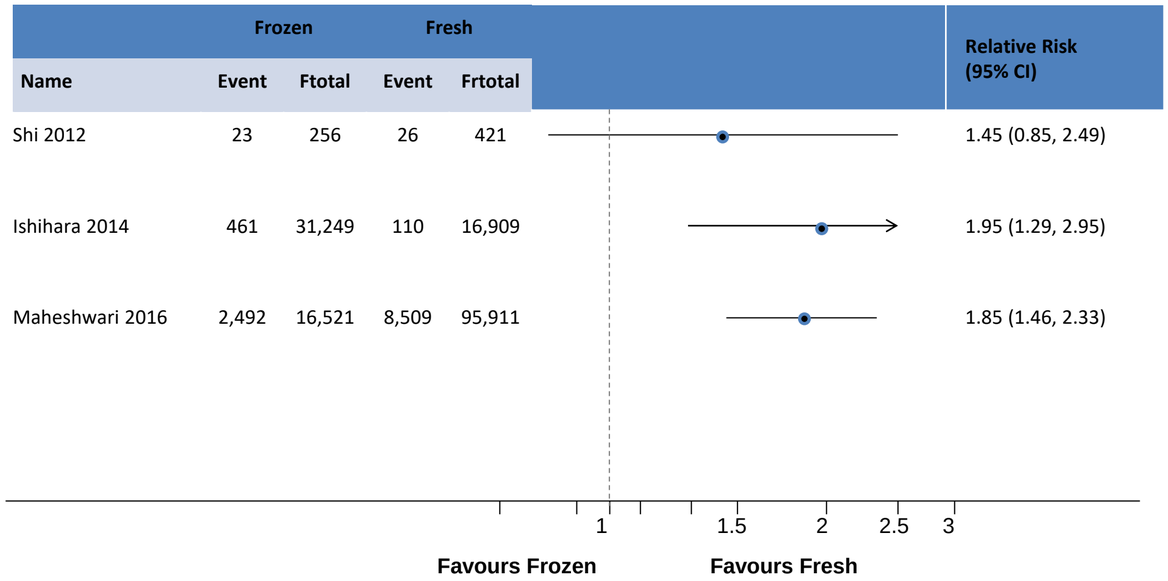
Relative risk of large for gestational age babies based on a cumulative meta-analysis

54% increase in risk



Relative risk of babies born with high birth weight >4,000 g based on a cumulative meta-analysis

85% increase in risk



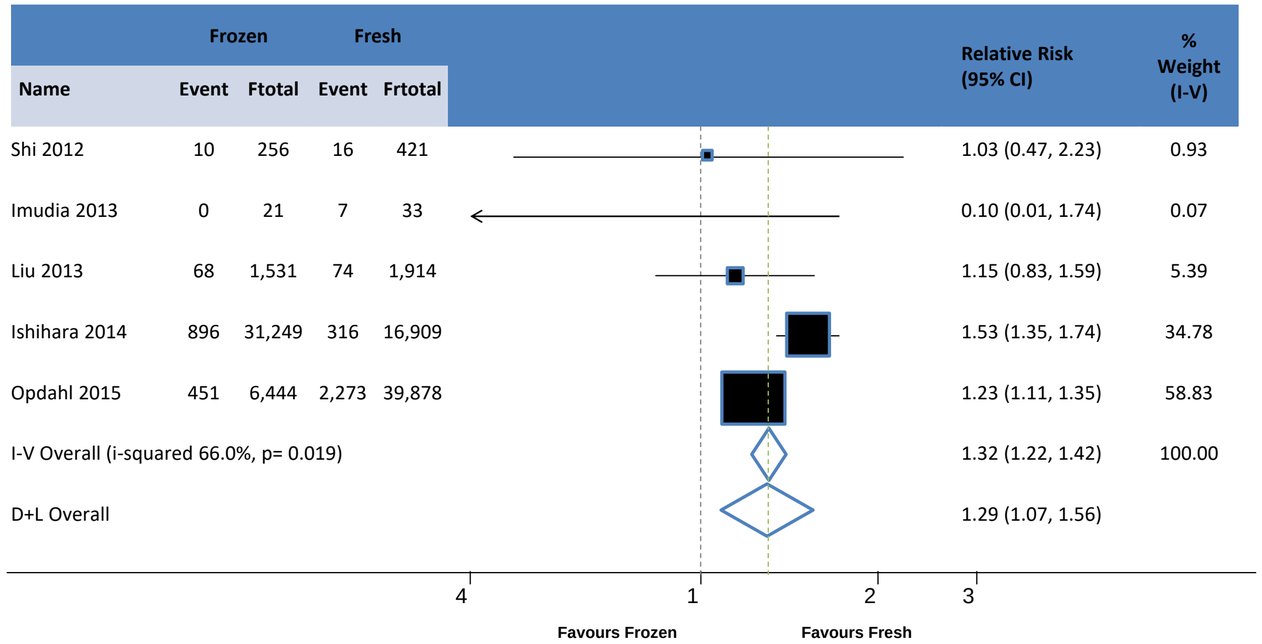
CI, confidence interval; F, frozen; Fr, fresh.
Maheshwari A, et al. Hum Reprod Update 2018;24:35–58.

Figures from Maheshwari A, et al. 2018.

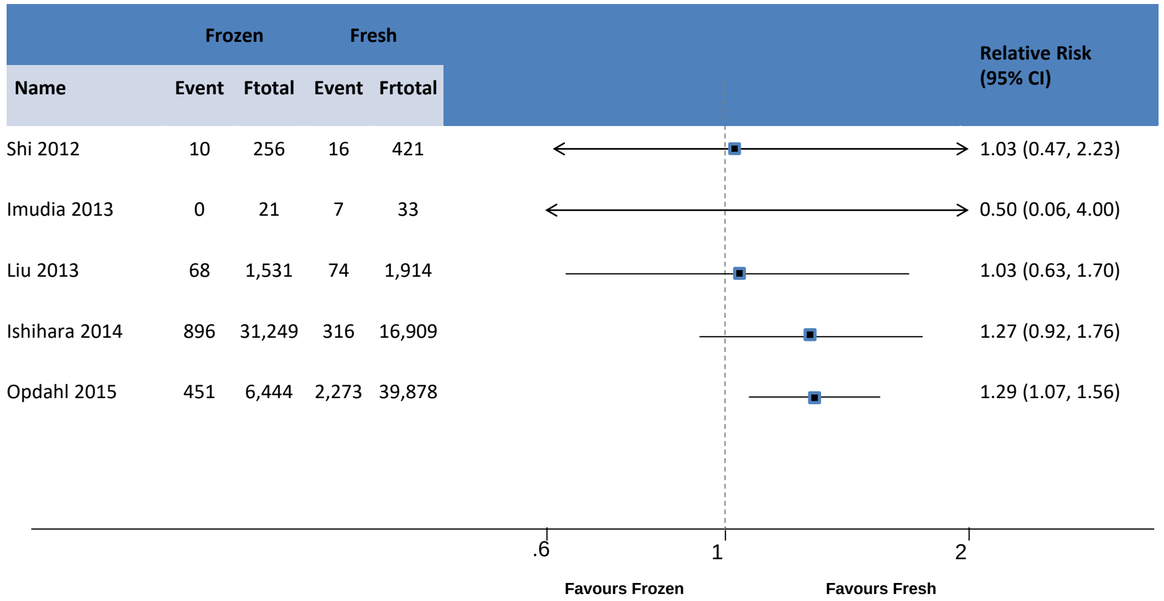
Relative risk of hypertensive disorder of of pregnancy in frozen versus fresh ET

29% increase in risk among frozen embryo transfer

Based on meta-analysis



Based on cumulative meta-analysis



*Hypertensive disorders of pregnancy included pregnancy-induced hypertension, preeclampsia and eclampsia.
CI, confidence interval; HDP, hypertensive disorders of pregnancy; F, frozen; Fr, fresh.
Maheshwari A, et al. Hum Reprod Update 2018;24:35–58.

Figures from Maheshwari A, et al. 2018.

Birth weight of singleton siblings born after ART and spontaneous conception: Danish national sibling-cohort study

NATIONAL POPULATION-BASED REGISTRY STUDY

- 13,692 sibling pairs born after IVF/ICSI/FER

OR

- Spontaneous conception, subcategorised into five groups according to succession

Main outcome measures

Birth weight, gestational age, low birth weight (<2,500 g), preterm birth (<37 weeks gestation) and perinatal deaths

Birthweight* in siblings from cohorts a–e

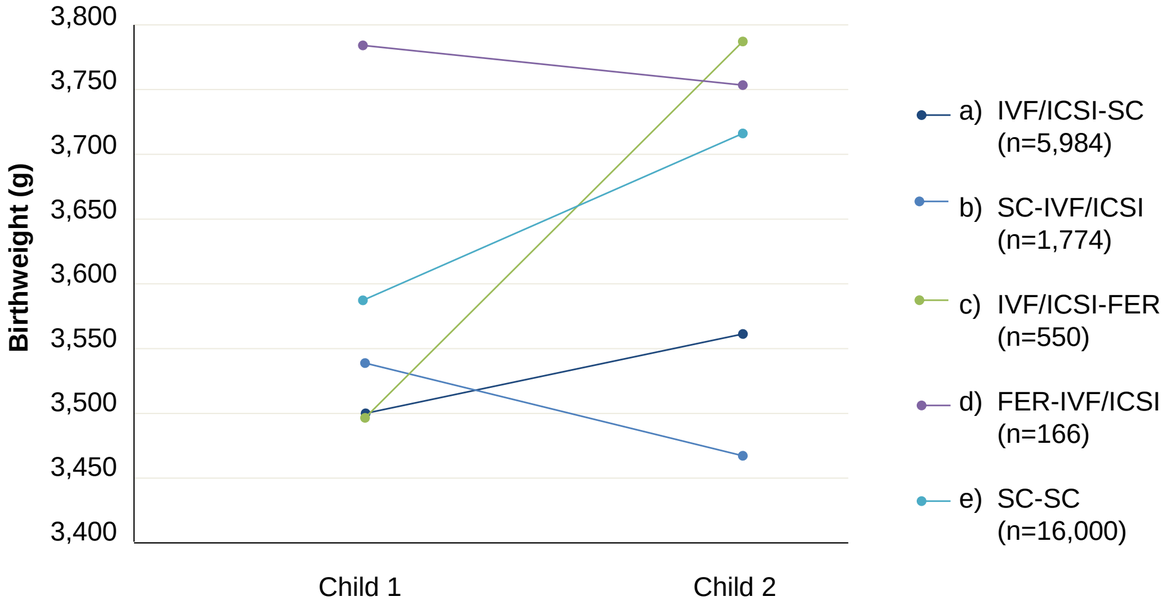


Figure adapted from Henningsen AKA, et al. 2011

*Adjustments are made for maternal age, parity, year of birth and sex. As mean birthweight depends on these factors, the estimated mean values are reported for a male child born by a nulliparous mother, 30–34 years old, between 1999 and 2002.

FER, frozen embryo replacement; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation; SC, spontaneous conception.

Henningsen AKA, et al. Fertil Steril 2011;95:959–963.

Hypertensive disorders of pregnancy
Risk estimates comparing programmed FET *vs.* natural FET cycles

Study or subgroup	log[odds ratio]	SE	Weight	Odds ratio IV, random, 95% CI	Year
Ernstad 2019	0.5766	0.1117	13.7%	1.78 [1.43–2.22]	2019
Jing 2019	0.6195	0.1506	11.0%	1.86 [1.38–2.50]	2019
Saito 2019	0.3577	0.1156	13.5%	1.43 [1.14–1.79]	2019
von Versen-Höynck 2019	0.7716	0.4182	2.8%	2.16 [0.95–4.91]	2019
Makhijani 2020	0.8713	0.2839	5.2%	2.39 [1.37–4.17]	2020
Pan 2020	–0.2148	0.4683	2.3%	0.81 [0.32–2.02]	2020
Wang 2020b	0.9208	0.2446	6.4%	2.51 [1.55–4.06]	2020
Zong 2020	0.6931	0.1333	12.2%	2.00 [1.54–2.60]	2020
Asserhøj 2020	0.6259	0.2393	6.6%	1.87 [1.17–2.99]	2020
Zaat 2021	1.5041	0.7099	1.1%	4.50 [1.12–18.09]	2021
Hu 2021	1.0438	0.1516	11.0%	2.84 [2.11–3.82]	2021
Li 2021	0.4819	0.1062	14.2%	1.62 [1.31–1.99]	2021
Total (95% CI)			**100.0%**	**1.90 [1.64–2.20]**	

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 22.19$, df = 11 (p=0.02); $I^2 = 50\%$
Test for overall effect: Z = 8.49 (p<0.00001)

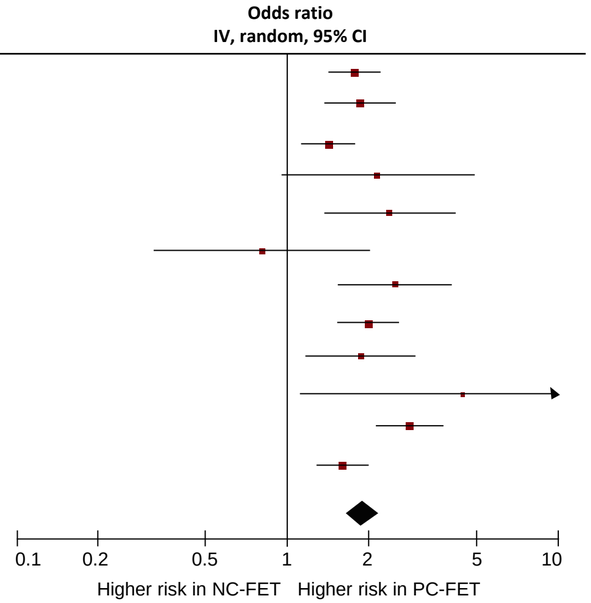


Figure from Busnelli A, et al. 2022

CI, confidence interval; FET, frozen embryo transfer; IV, inverse variance; NC-FET, natural FET cycles; PC-FET, programmed FET cycles; SE, standard error.
Busnelli A, et al. Hum Reprod 2022;37:1619–1641.

Hypertensive disorders of pregnancy
Risk estimates comparing programmed FET *vs.* natural FET cycles

	Pooled odds ratio (95% CI)	p-value	Quality of Evidence*
Hypertensive disorders of pregnancy	1.90 (1.64–2.20)	<0.00001	Very low quality
Preeclampsia	2.11 (1.87–2.39)	<0.00001	Low quality
Post-partum haemorrhage	2.53 (2.19–2.93)	<0.00001	Low quality
Post-term birth	1.90 (1.25–2.90)	0.003	Very low quality
Macrosomia	1.18 (1.05–1.32)	0.007	Very low quality
Large for gestational age	1.08 (1.01–1.16)	0.02	Very low quality
Placenta accreta	6.29 (2.75–14.4)	<0.0001	Very low quality

*Quality of evidence of evidence assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[2]
CI, confidence interval; FET, frozen embryo transfer; HDP, hypertensive disorders of pregnancy; PE, preeclampsia; PPH, post-partum haemorrhage.
1. Busnelli A, et al. Hum Reprod 2022;37:1619–1641; 2. Atkins D, et al. BMJ 2004;328:1490.

Artificially prepared vitrified-warmed embryo transfer cycles are associated with an increased risk of pre-eclampsi

915 RBMO VOLUME 44 ISSUE 5 2022

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ARTICLE

Artificially prepared vitrified–warmed embryo transfer cycles are associated with an increased risk of pre-eclampsia

BIOGRAPHY

Caroline Roelens, MD, obtained her medical degree in 2013 at the Vrije Universiteit Brussel, Belgium. She completed her training in obstetrics and gynaecology in 2019 and started a 2-year specialization in reproductive medicine at the Centre for Reproductive Medicine in Brussels, Belgium, where she is now working as a Junior Medical Director. Her main topic of interest is the optimization of frozen embryo transfer cycles.

Caroline Roelens[1,*], Annalisa Racca[2], Shari Mackens[1], Lisbet Van Landuyt[1], Laura Buelinckx[3], Léonardo Gucciardo[4], Herman Tournaye[1,5], Michel De Vos[1,5], Christophe Blockeel[1,6]

- VUB Bruxelles
- 536 women from 2010-2019 all delivered at the same institution
  - 325 Natural cycle FET (NC-FET)
  - 211 Artificial cycle FET (AC-FET)

- Single vitrified/warmed blastocyst transfer
- Prevalence of pre-eclampsia in AC-FET 11.8% vs. 3.7% in NC-FET ($p<0.001$)

- The risk of pre-clampsia in AC-FET vs. NC-FET: Adjusted odds ratio: 2.9 (95%CI 1.4-6.0)(P=0.005) (Adjustments for oocyte recipient cycles, African ethnicity and PCOS)

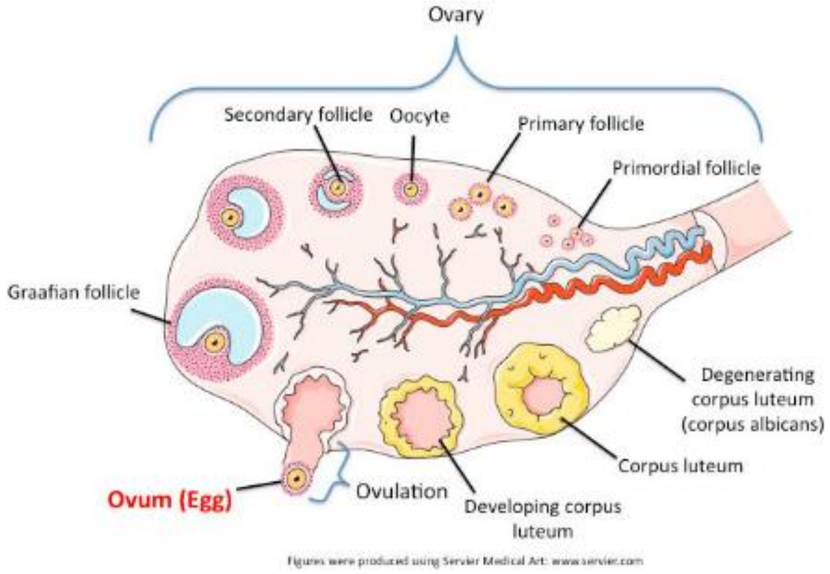
(Roelens C et al., RBMOnline 2022: 44(5):915-22)

Effect of Mode of Conception on Maternal Serum Relaxin, Creatinine, and Sodium Concentrations in an Infertile Population

Reproductive Sciences
2019, Vol. 26(3) 412-419

DOI: 10.1177/1933719118776792
journals.sagepub.com/home/rsx
SAGE

Frauke von Versen-Höynck, MD, MS[1,2], Nairi K. Strauch, MS[1], Jing Liu, PhD[3], Yueh-Yun Chi, PhD[3], Maureen Keller-Woods, PhD[4], Kirk P. Conrad, MD[5,6], and Valerie L. Baker, MD[1]



In programmed FET cycles with no corpus luteum

- Relaxin is undetectable
- Creatinine, sodium and total CO_2 are higher with no corpus luteum

Relaxin (6-kDA peptide hormone) is produced in the corpus luteum

- Maternal systemic and renal vasodilation in pregnancy
- Increase glomerular filtration

Versen-Höynck et al., Hypertension 2019

Preeclampsia

Increased Preeclampsia Risk and Reduced Aortic Compliance With In Vitro Fertilization Cycles in the Absence of a Corpus Luteum

Frauke von Versen-Höynck,* Amelia M. Schaub,* Yueh-Yun Chi, Kuei-Hsun Chiu, Jing Liu, Melissa Lingis, R. Stan Williams, Alice Rhoton-Vlasak, Wilmer W. Nichols, Raquel R. Fleischmann, Wendy Zhang, Virginia D. Winn, Mark S. Segal, Kirk P. Conrad,† Valerie L. Baker†

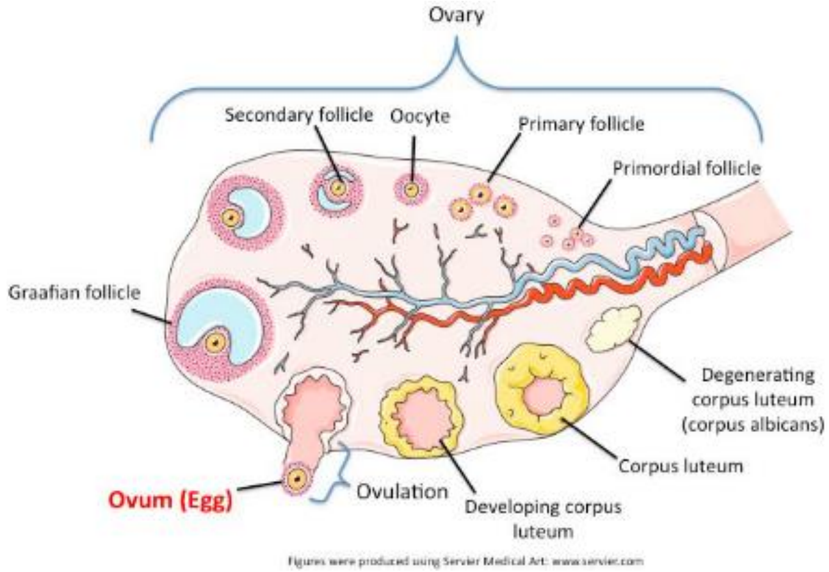
(Versen-Höynck et al., Hypertension 2019; 73, 640-49)

Pregnancy

Absent or Excessive Corpus Luteum Number Is Associated With Altered Maternal Vascular Health in Early Pregnancy

Frauke von Versen-Höynck, Purnima Narasimhan, Elif Seda Selamet Tierney, Nadine Martinez, Kirk P. Conrad, Valerie L. Baker, Virginia D. Winn

(Versen-Höynck et al., Hypertension 2019; 73, 680-90)



BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.14257
www.bjog.org

Systematic review

Egg donation

Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis

M Storgaard,[a] A Loft,[b] C Bergh,[c] UB Wennerholm,[d] V Söderström-Anttila,[e] LB Romundstad,[f,g] K Aittomaki,[h] N Oldereid,[i] J Forman,[j] A Pinborg[k]

Adjusted odds ratio aOR (95%CI)	Singletons OD vs. IVF/ICSI	Multiples OD vs. IVF/ICSI	Singletons OD vs. natural conception
Preeclampsia	2.11 (1.42-3.15)	3.31 (1.61-6.80)	2.30 (1.09-4.87)
Preterm birth	1.75 (1.39-2.20)	-	
Low birth weight	1.53 (1.16-2.01)	-	

(Storgaard M et la., Br J Obstet Gynecol 2017, 124, 561-72)

Human Reproduction Update, Vol.25, No.2 pp. 137–158, 2019
Advanced Access publication on February 12, 2019 doi:10.1093/humupd/dmz001

human reproduction update GRAND THEME REVIEW

The health of children conceived by ART: 'the chicken or the egg?'

Sine Berntsen[1], Viveca Söderström-Anttila[2], Ulla-Britt Wennerholm[3], Hannele Laivuori[4,5,6,7], Anne Loft[8], Nan B. Oldereid[9], Liv Bente Romundstad[10,11], Christina Bergh[12], and Anja Pinborg[8,*]

Egg donation

- Hypertensive disorder of pregnancy 16-40% and 2-3-fold higher risk
- Low birth weight and prematurity 2-3-fold higher
- Malformations no increase
- Genetically foreign fetus induces immunological reactions and placental pathology
- HLA matching between donor and recipient might prevent the immunologic mis-match
- Endometrial preparation without a corpus luteum may cause preeclampsia

(Berntsen S. et al., Hum Reprod Upd 2019, 25, 137-58)

Long-term health in ART children

- Academic performance
- Cerebral palsy and autism spectrum disorders
- Cancer
- Cardiovascular function & metabolism

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

A.L. Spangmose[1,*], S.S. Malchau[1], L. Schmidt[2], D. Vassard[2], S. Rasmussen[1], A. Loft[3], J. Forman[4], and A. Pinborg[1]

	ART singletons N=2544	Non-ART singletons N=4985	ART twins N=1676	*P*-values	
				Singletons ART vs. Non-ART	ART Singletons vs. Twins
Test score, mean (SD)	7.16 (2.41)	6.74 (2.46)	7.21 (2.31)	**<0.01**	**0.47**

Mean difference ART vs. Non-ART singletons +0.41 (95%CI 0.30-0.53)

Mean difference adjusted -0.15 (95%CI -0.29-(-0.02))*

*Adjustment for maternal age, parity, cohabiting status, parental highest educational and occupational level, ethnicity, child sex, area of residence, graduation year

Academic performance in adolescents aged 15–16 years born after FET compared with fresh-ET: A Danish nationwide registry-based cohort study

9th grade school performance scores in singletons born after FET versus fresh-ET (1995–2001)

	Crude mean test score		Singletons FET versus fresh-ET			
	Singletons		Model 1		Model 2	
	FET N=396	Fresh-ET N=5,507	Crude mean difference* (95% CI)	p-value	Adjusted mean difference† (95% CI)	p-value
Overall scores	7.44 (2.33)	7.29 (2.40)	0.11 (–0.11–0.34)	0.33	0.12 (–0.09–0.34)	0.25

The crude and adjusted mean test scores were similar in singletons born after FET and fresh-ET

*Data were compared using linear mixed models to adjust for correlation within siblings. †Adjusted for the following covariates: maternal age, parity, cohabiting status, ethnicity, highest educational and occupational level of the parents, area of residence, child gender and graduation year.

CI, confidence interval; ET, embryo transfer; FET, frozen embryo transfer.

Spangmose AL, et al. BJOG 2019;126:261–269.

Early Autism Spectrum Disorders in Children Born to Fertile, Subfertile, and ART-Treated Women

(ART N = 10,147, Subfertile N = 8072 and Fertile births N = 441,898)

Prevalence of Autism Spectrum Disorder among Singletons, by Fertility Groups, Massachusetts Birth July 1, 2004–December 31, 2010

Demographic Characteristics	Autism N (%)	No Autism N (%)	p-value
Fertility Group			
Fertile	4,363 (1.0)	437,535 (99.0)	Ref
Subfertile	88 (1.1)	7,984 (98.9)	0.35
ART	120 (1.2)	10,027 (98.8)	<0.05
ICSI	50 (1.3)	3,854 (98.7)	0.07
IVF	49 (1.0)	4,785 (99.0)	0.85

	Natural Direct effect	
	OR (95% CI)	P-value
ART vs. Fertile	1.07 (0.88, 1.30)	0.49
Subfertile vs. Fertile	1.11 (0.89, 1.38)	0.35
ICSI vs. Fertile	1.13 (0.84, 1.51)	0.43
IVF vs. Fertile	0.91 (0.68, 1.22)	0.53

[a]Models adjusted for maternal demographics (maternal paternal age, race, education, marital status, nativity), insurance, smoking, prenatal care, parity, gender, method of delivery, chronic and pregnancy hypertension, gestational and chronic diabetes, breech. Data with missing covariates are excluded in all models.

(Diop H et al., Matern Child Health J. 2019 Nov;23(11):1489-1499)

Human Reproduction, Vol.35, No.5, pp. 1178–1184, 2020
Advance Access Publication on May 12, 2020 doi:10.1093/humrep/deaa039

human reproduction **ORIGINAL ARTICLE** ***Reproductive epidemiology***

Imprinting disorders in children born after ART: a Nordic study from the CoNARTaS group

A.A. Henningsen[1,*], M. Gissler[2,3], S. Rasmussen[1], S. Opdahl[4], U.B. Wennerholm[5], A.L. Spangmose[1], A. Tiitinen[6], C. Bergh[5], L.B. Romundstad[4,7], H. Laivuori[8,9,10], J.L. Forman[11], A. Pinborg[1], and Ø. Lidegaard[12]

Table II Risk of Prader–Willi syndrome, Silver-Russel syndrome, Beckwith–Wiedemann syndrome and Angelman syndrome in Finnish and Danish children born from 1990/1994 to 2014.

	Prader-Willi syndrome	Silver-Russell syndrome	Beckwith-Wiedemann syndrome	Angelman syndrome	All four imprinting disorders
Assisted reproductive technology (ART)					
Children born	74 621	74 621	74 621	74 621	74 621
Imprinting	5	<3#	8	<3#	16
Rate/10000	0.67	0.27	1.07	0.27	2.14
Natural conception (NC)					
Children born	2 775 239	2 775 239	2 775 239	2 775 239	2 775 239
Imprinting	138	67	97	70	372
Rate/10000	0.50	0.24	0.35	0.25	1.34
ART versus NC					
Crude odds ratio	1.35	1.11	3.07	0.53	1.60
[95%CI]	[0.55–3.29]	[0.27–4.53]	[1.49–6.31]	[0.07–3.82]	[0.97–2.65]
Adj.* odds ratio	1.03	0.82	2.84	0.51	1.35
[95%CI]	[0.37–2.84]	[0.20–3.43]	[1.34–6.01]	[0.07–3.74]	[0.80–2.29]

#Due to Danish law on health data, we are not allowed to show data on groups of less than three individuals.
*Adjustments were made for maternal age, parity (nulliparous versus multiparous), year of birth, child's sex, BMI, smoking and country.

Cardiovascular function and metabolism

Frozen Embryo Transfer

Increased risk of being born LGA[1]

LGA

Obesity and insulin resistance

Metabolic syndrome[2]

FET, frozen embryo transfer; LGA, large for gestational age.

1. Pinborg A, et al. Hum Reprod 2014;29:618–627; 2. Johnsson IW, et al. Pediatr Obes 2015;10:77–83.

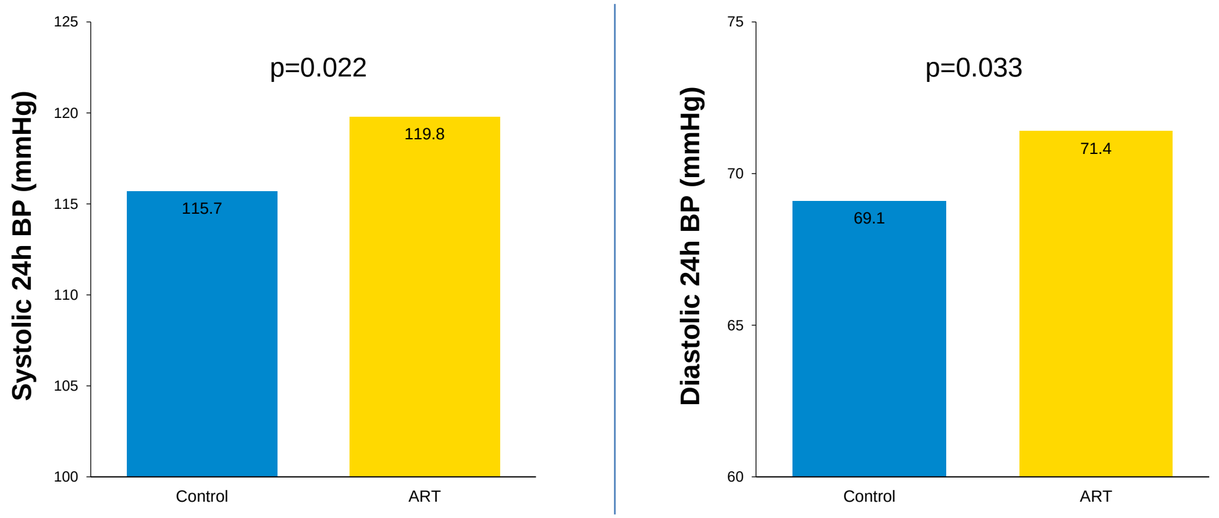
Association of ART with arterial hypertension during adolescence

5 years after an initial study, vascular function and 24-hour ambulatory BP was monitored in:

- 54 ART-conceived subjects
- 43 control subjects

- **8 of the 52 ART-conceived subjects** fulfilled the criteria for the diagnosis of arterial hypertension (>130/80 mmHg and/or >95th percentile)
- Only **1 of the 40 control subjects** fulfilled these criteria (p=0.041)

24-hour ambulatory blood pressure in ART (n=52) and control subjects (n=43)

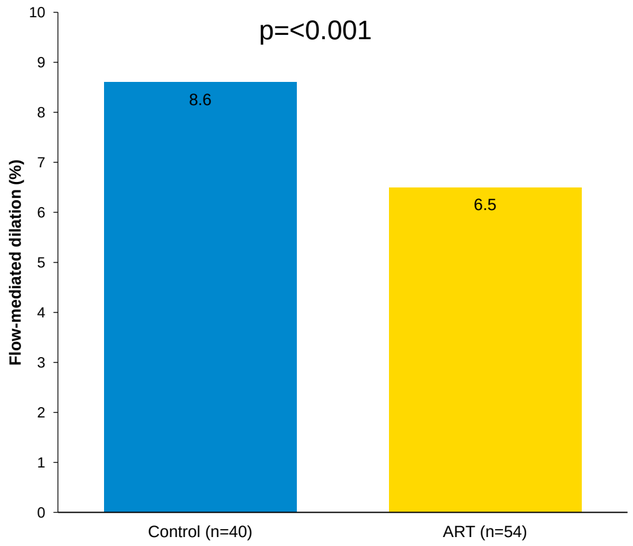


Systolic and diastolic 24-hour ambulatory blood pressure was **significantly higher** in **subjects conceived through ART** than in control subjects

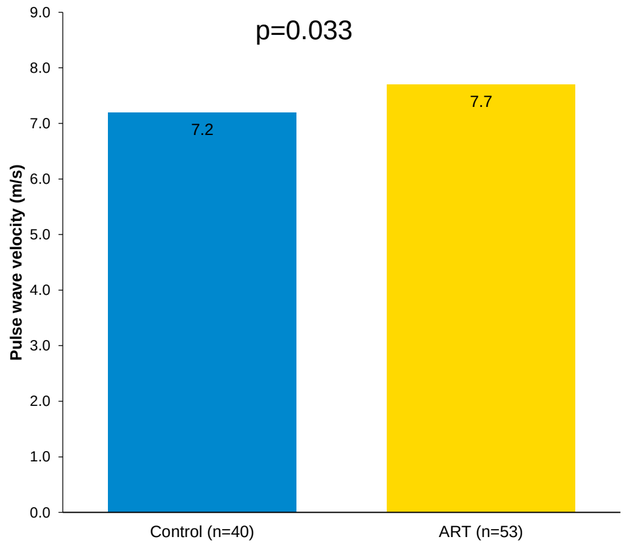
Figure adapted from Meister TA, et al. 2018

ART, assisted reproductive technology; BP, blood pressure.
Meister TA, et al. J Am Coll Cardiol 2018;72:1267–1274.

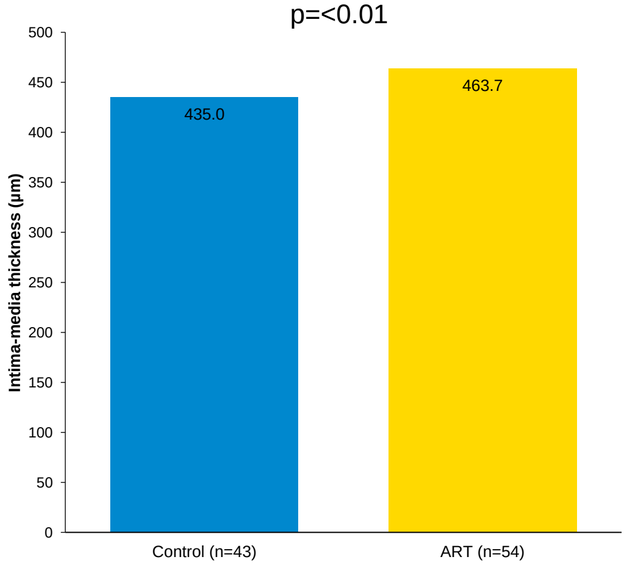
Premature vascular ageing in ART children persists into adulthood (5-year follow-up)



Flow-mediated dilation



Pulse wave velocity



Intima-media thickness

ART-induced vascular aging persists in healthy and young adults, without any other detectable cardiovascular risk factors and progresses to arterial hypertension

ART, assisted reproductive technology.
Meister TA, et al. J Am Coll Cardiol 2018;72:1267–1274.

Figure adapted from Meister TA, et al. 2018

Health in Children born after Assisted Reproductive Technology (HiCART)

HiCART

Health in Childhood following Assisted Reproductive Technology

Cardiovascular function in 8–9-year-old singletons born after frozen and fresh embryo transfer

Study period 2018 to 2020

8–9-year-old singletons conceived after FET, fresh-ET and NC (50 children in each group)

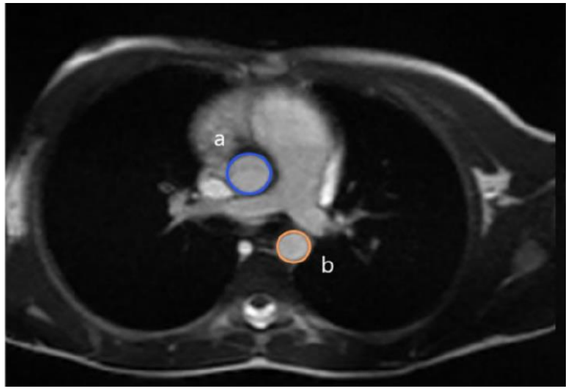
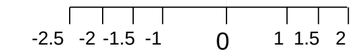


Figure showing cross-sectional CMR image of ascending aorta (a) and descending aorta (b) from Mizrak I, et al. 2022.

Multivariate linear regression models for ascending aorta distensibility*

	Beta estimate	95% confidence interval
FET versus NC		
Model 0	-0.69	-1.80–0.42
Model 1	-0.70	-1.79–0.40
Model 2	-0.68	-1.81–0.45
Model 3	-0.77	-1.98–0.44
Fresh-ET versus NC		
Model 0	0.35	-0.76–1.45
Model 1	0.31	-0.79–1.41
Model 2	0.33	-0.79–1.45
Model 3	0.23	-0.96–1.41
FET versus fresh-ET		
Model 0	-1.03	-2.14–0.07
Model 1	-1.01	-2.11–0.09
Model 2	-1.01	-2.15–0.13
Model 3	-0.99	-2.20–0.21



← Less distensible aorta ascendens More distensible aorta ascendens →

Figure adapted from Mizrak I, et al. 2022

*A beta estimate and its 95% confidence interval are presented for each model. A positive/negative beta estimate means an increase/decrease in aortic distensibility. Model 0: ascending aorta distensibility versus study groups, Model 1: model 0 adjusted for child sex and age, Model 2: Model 1 adjusted for maternal BMI at early pregnancy, Model 3: Model 2 adjusted for maternal educational level.

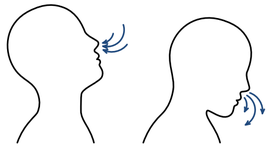
BMI, body mass index; ET, embryo transfer; FET, frozen embryo transfer; NC, natural conception.

Mizrak I, et al. Hum Reprod 2022;37:600–611.

Cardiovascular autonomic nervous function in children born with frozen or fresh embryo transfer

PHYSIOLOGICAL PROVOCATION MANOEUVRES

Active standing



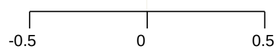
Deep breathing

The Valsalva maneuver

Children conceived with frozen embryo transfer have normal autonomic cardiovascular regulation

Heart rate response to physiological provocation maneuvers

	Beta estimate	95% confidence interval
FET versus NC		
Active standing test	-0.09	-0.24–0.06
Deep breathing	-0.00	-0.15–0.14
Valsalva maneuver	0.28	-0.04–0.60
Fresh-ET versus NC		
Active standing test	-0.11	-0.25–0.03
Deep breathing	0.03	-0.12–0.18
Valsalva maneuver	0.04	-0.26–0.34
FET versus fresh-ET		
Active standing test	0.02	0.12–0.16
Deep breathing	-0.03	-0.16–0.09
Valsalva maneuver	0.24	-0.04–0.52



Adjusted data presented as beta estimate and 95% confidence interval		
FET versus NC	**Fresh-ET versus NC**	**FET versus fresh-ET**
-0.06 (-8.70–8.58)	2.04 (-6.31–10.40)	-2.10 (-10.23–6.04)

Figure adapted from Mizrak I, et al. 2022

ET, embryo transfer; FET, frozen embryo transfer; NC, natural conception.

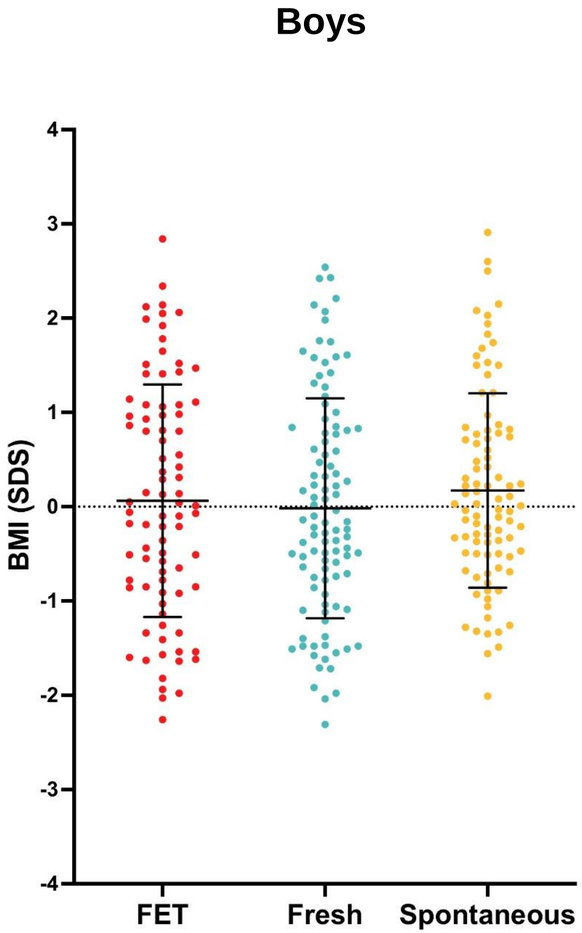
Mizrak I, et al. Presented at ESHRE 2022. P-772.

HiCART study: Body mass index at 7–10 years of age

Health in Childhood following Assisted Reproductive Technology

Body mass index (SDS)

	FET Mean (SD)	Fresh Mean (SD)	Spontaneos Mean (SD)
Girls	0.21 (1.09)	0.02 (1.03)	0.15 (0.99)
Boys	0.06 (1.23)	-0.02 (1.17)	0.17 (1.03)



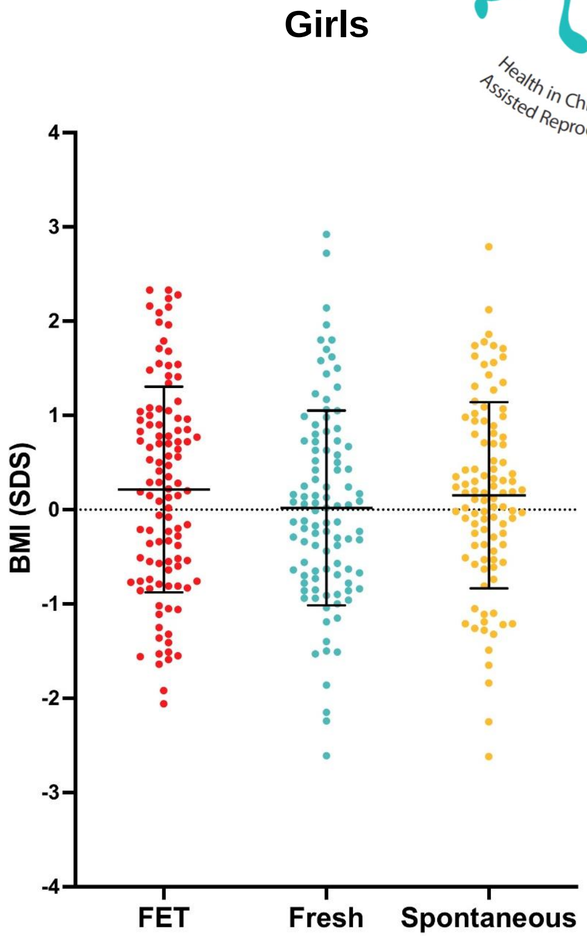


Figure from Asserhoej L, et al. 2022.

N=200 frozen embryos (n=90 boys, n=110 girls), N=203 fresh embryos (n=102 boys, n=101 girls)

FET, frozen embryo transfer; SD(S), standard deviation (scores).

Asserhoej L, et al. Presented at ESHRE 2022. Abstract O-086 and unpublished data.

PLOS MEDICINE

CoNARTaS
Committee of Nordic Assisted Reproductive Technology and Safety

RESEARCH ARTICLE

Cancer in children born after frozen-thawed embryo transfer: A cohort study

Nona Sargisian[1], Birgitta Lannering[2], Max Petzold[3], Signe Opdahl[4], Mika Gissler[5,6], Anja Pinborg[7], Anna-Karina Aaris Henningsen[7], Aila Tiitinen[8], Liv Bente Romundstad[9,10], Anne Lærke Spangmose[7], Christina Bergh[1☯], Ulla-Britt Wennerholm[1☯*]

Cancer type (ICCC-3 category)[a]	ART N = 171,774 children N = 1,705,772 person-years			Spontaneous conception N = 7,772,474 children N = 97,027,051 person-years			ART vs. spontaneous conception	
	No. of children with cancer	IR		No. of children with cancer	IR		Crude HR (95% CI) p-value	Adjusted HR[b] (95% CI) p-value
		Per 1,000 children	Per 100,000 person- years		Per 1,000 children	Per 100,000 person-years		
Any cancer (I–XII)	329	1.92	19.29	16,184	2.08	16.68	1.13 (1.01 to 1.26) 0.03	1.08 (0.96 to 1.21) 0.18

[b]Adjusted for sex, plurality, year of birth, country, maternal age, and parity

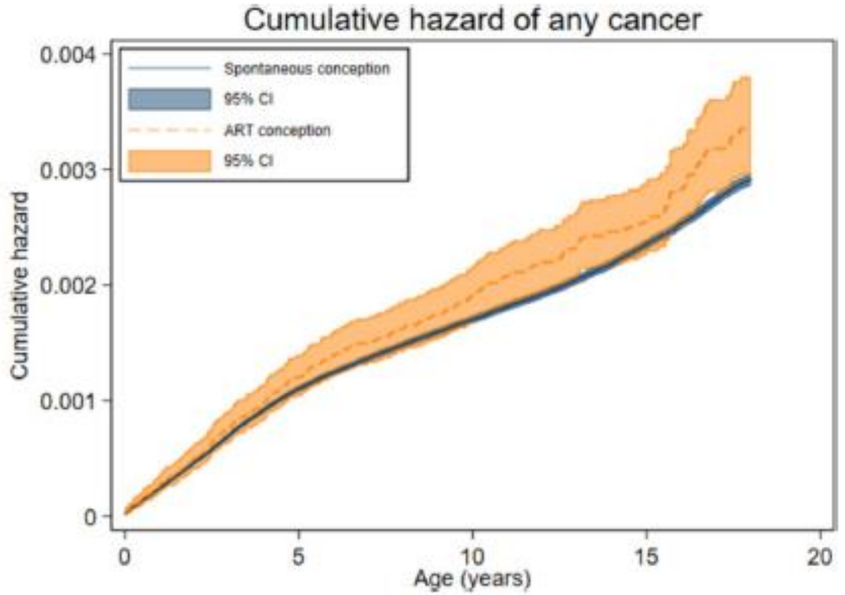


Fig 3. Cumulative hazard of first cancer (any type) up to 18 years for spontaneously and ART-conceived children born in Denmark (1994–2014), Finland (1990–2014), Norway (1984–2015), and Sweden (1985–2015). Crude hazard ratio 1.13; 95% CI 1.01 to 1.26, $p = 0.03$. ART, assisted reproduction technology; CI, confidence interval.

Citation: Sargisian N, Lannering B, Petzold M, Opdahl S, Gissler M, Pinborg A, et al. (2022) Cancer in children born after frozen-thawed embryo transfer: A cohort study. PLoS Med 19(9): e1004078. https://doi.org/10.1371/journal.pmed.1004078

Sargasian et al., PLoS Med 19 (9): e1004078 (2022)

PLOS MEDICINE

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RESEARCH ARTICLE

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- Children born after FET had a higher risk of cancer (48 cases; IR 30.1/100.000 person-years)
- aHR 1.59 (95%CI 1.15-2.20)(p=0.005) compared to fresh embryo transfer
- aHR 1.65 (95%CI 1.24-2.19)(p=0.001) compared to natural conception
- Adjustment for macrosomia, birth weight, or major birth defect attenuated the association marginally
- Higher risk of leukaemia

IR = Incidence rate, aHR = adjusted hazard ratio

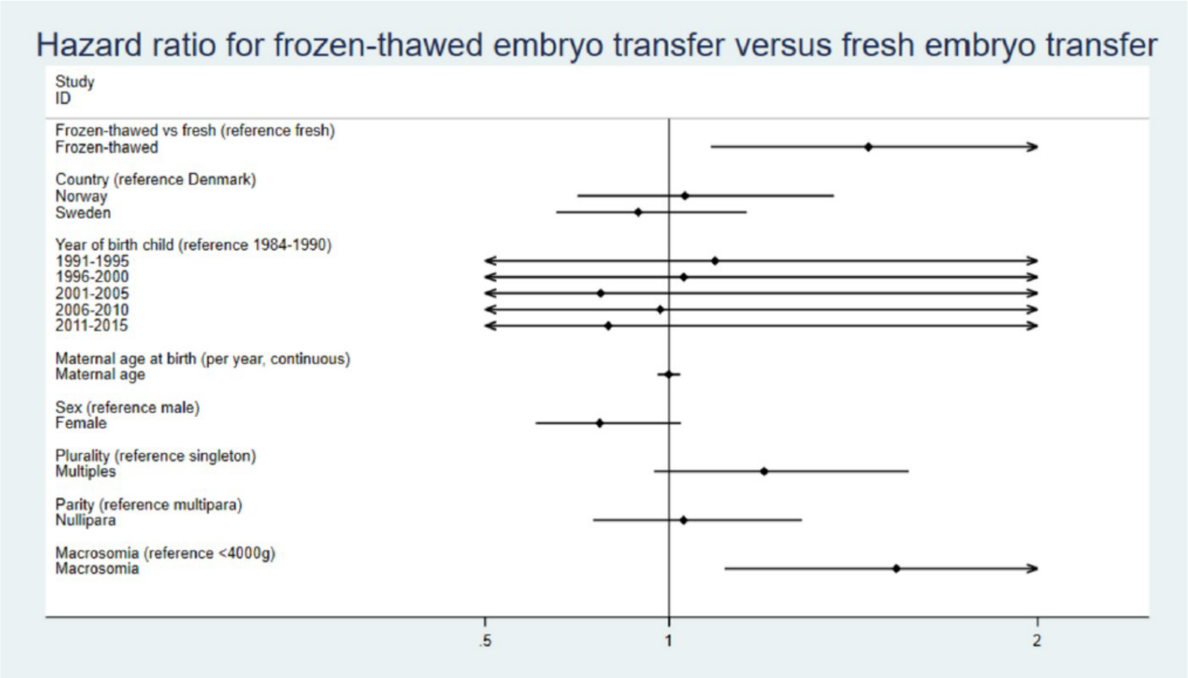

Fig 4. HRs with 95% CI for independent covariates including macrosomia for risk of cancer in children born after FET versus fresh embryo transfer. CI, confidence interval; FET, frozen-thawed embryo transfer; HR, hazard ratio.

Sargasian et al., PLoS Med 19 (9): e1004078 (2022)

Overview on the new 10 million babies born in the last 50 years by ART

Take-home messages

- ✓ The single embryo transfer strategy has lowered the risk of preterm birth and preeclampsia in ART in general
- ✓ Risk of preeclampsia is 2-3 fold increased after FET and OD
- ✓ Programmed/artificial cycle FET has the highest risk of preeclampsia
- ✓ A corpus luteum is important for the early pregnancy development
- ✓ Long term health risks in ART children are reassuring but need further attention
- ✓ Cardiometabolic health after ART may be compromised

How to prospectively manage human fertility?

Use natural or modified natural FET cycles if possible[1]

In case of anovulation use stimulated FET with letrozole or low dose gonadotrophins[2]*

In egg donation, only use single embryo transfer in FET[3]*

Use single embryo transfer

Use cycle segmentation (freeze-all) when needed due to increased risk of OHHS or uterine pathology

*Speaker's personal opinion.
FET, frozen embryo transfer.
1. Glujovsky D, et al. Cochrane Database Syst Rev 2020;20:CD006359; 2. Li SJ, et al. Arch Gynecol Obstet 2014;289:687–693; 3. Marklund A, et al. J Womens Health (Larchmt) 2018;27:939–945.

THANK YOU

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