Natural vs. artificial cycle FET and child outcomes

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Disclosures

- **Grants for research/donations**: Gedeon Richter, Ferring Pharmaceuticals, Merck
- **Lectures for:** Gedeon Richter, Ferring Pharmaceuticals, Merck, IBSA Pharma, Organon, Theramex
- **Scientific advisory boards:** Ferring Pharmaceuticals, Merck, Gedeon Richter, Cryos

CoNARTaS cohort 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.

Endometrial preparation protocols prior to FET

Artificial cycle Frozen Embryo Transfer (AC-FET)

Synonyms

- Artificial cycle FET
- Programmed cycle FET
- Substituted cycle FET
- Hormone replacement FET (HRT-FET)

Endometrial preparation protocols - other

- Natural cycle FET
- Modified natural cycle FET (hCG trigger)
- Stimulated cycle FET (FSH, hMG, letrozole, clomiphene)

CoNARTaS cohort: Retrospective population-based study

CoNARTaS
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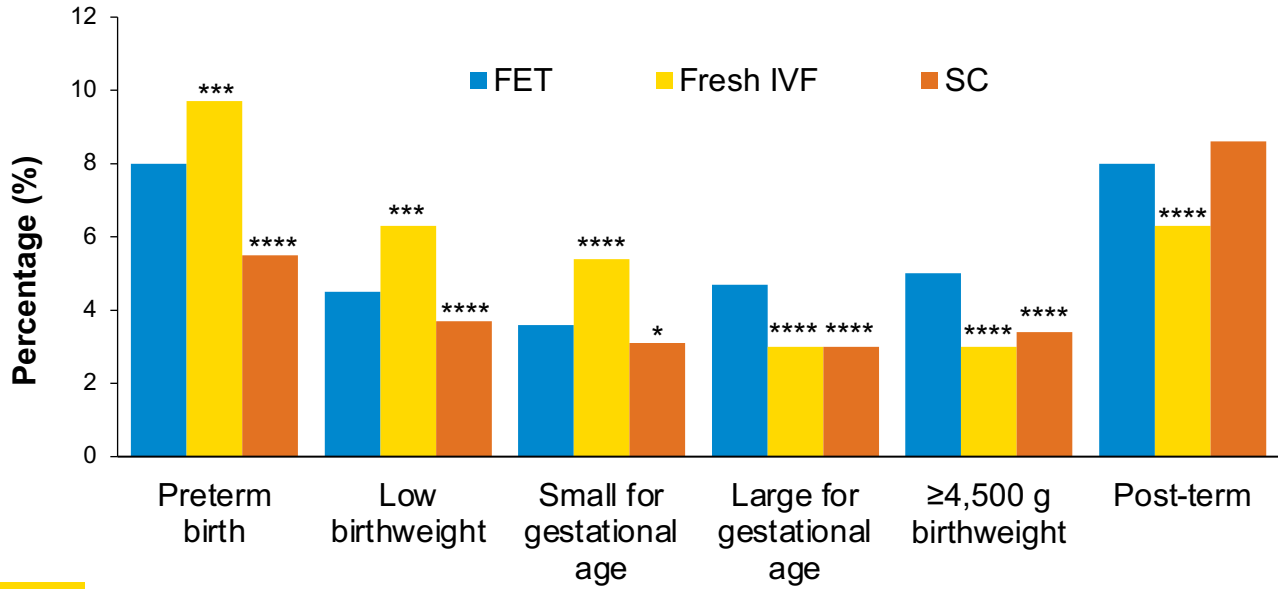
6,647
Singletons born after FET

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	Preterm birth	Low birthweight	Small for gestational age	Large for gestational age	≥4,500 g birthweight	Post-term
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.

Perinatal outcomes of children born after FET: Nordic cohort study from the CoNARTaS group

CoNARTaS
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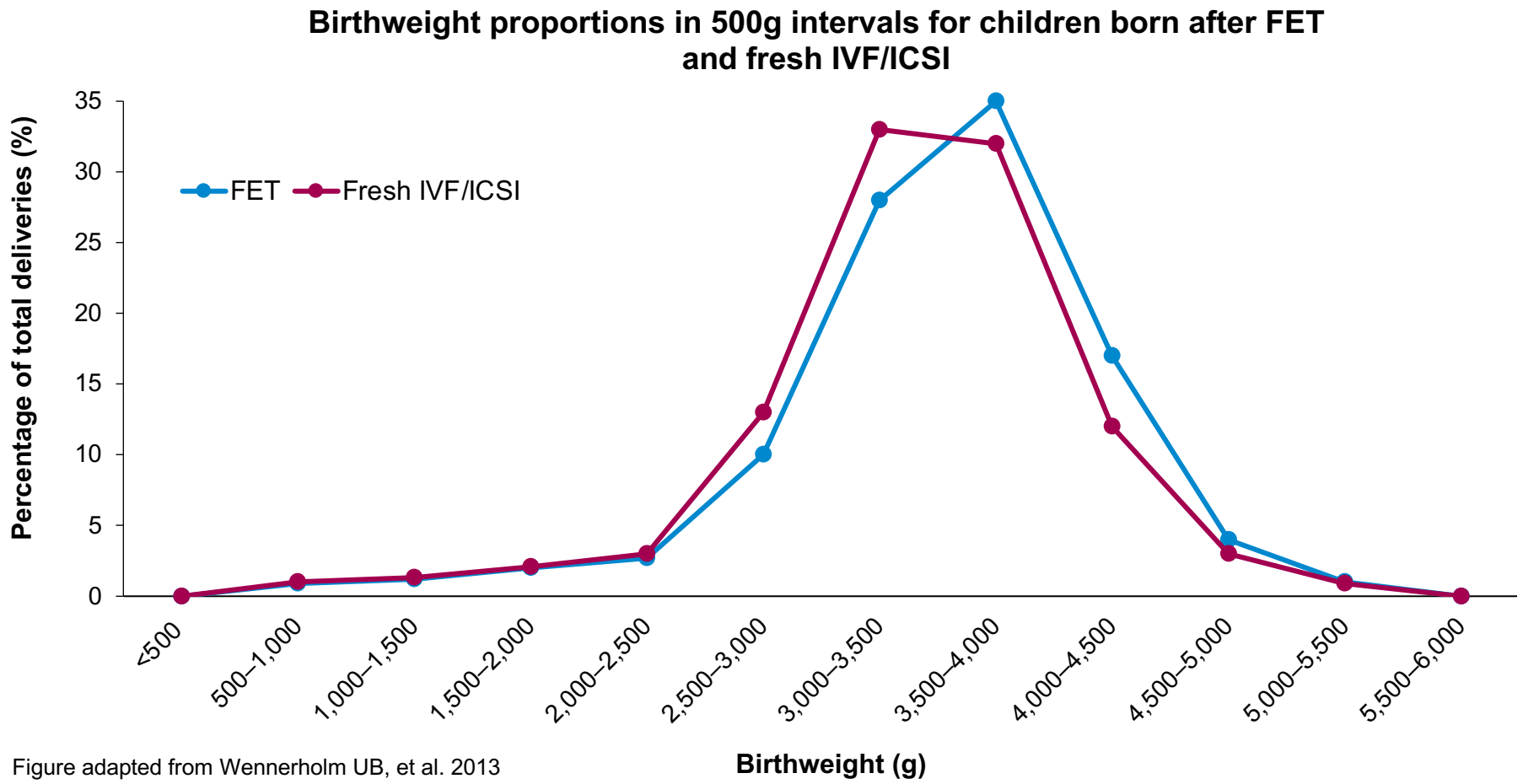


Figure adapted from Wennerholm UB, et al. 2013

Singletons born after FET (n=6,647) were compared with a control group of singletons born after fresh IVF and ICSI (n=42,242).

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

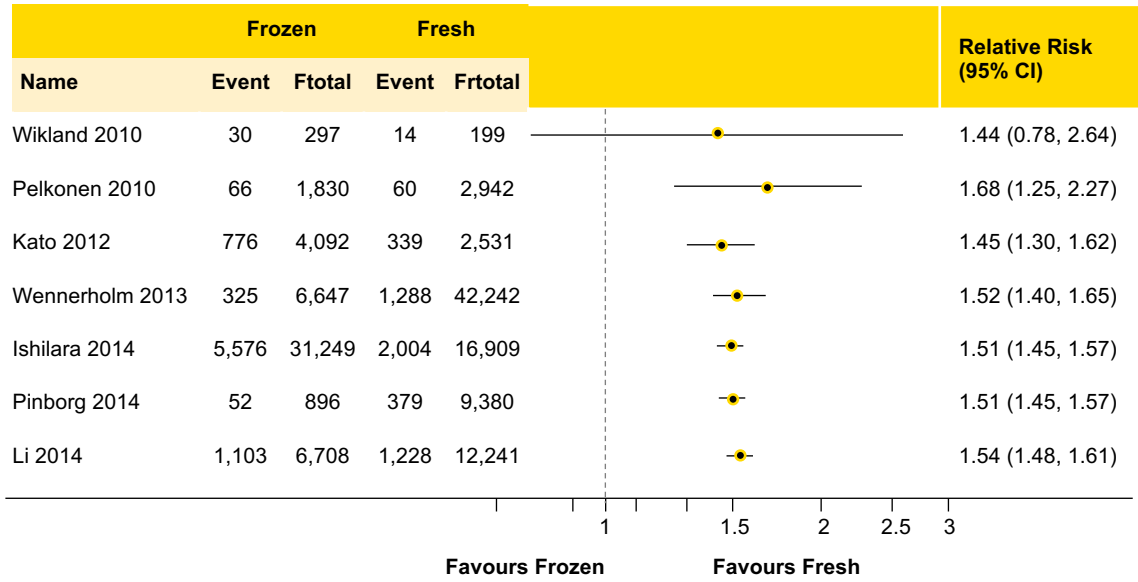
Wennerholm UB, et al. Hum Reprod 2013;28:2545–2553.

Is frozen embryo transfer better for mothers and babies?

Singletons born after frozen versus fresh embryo transfer

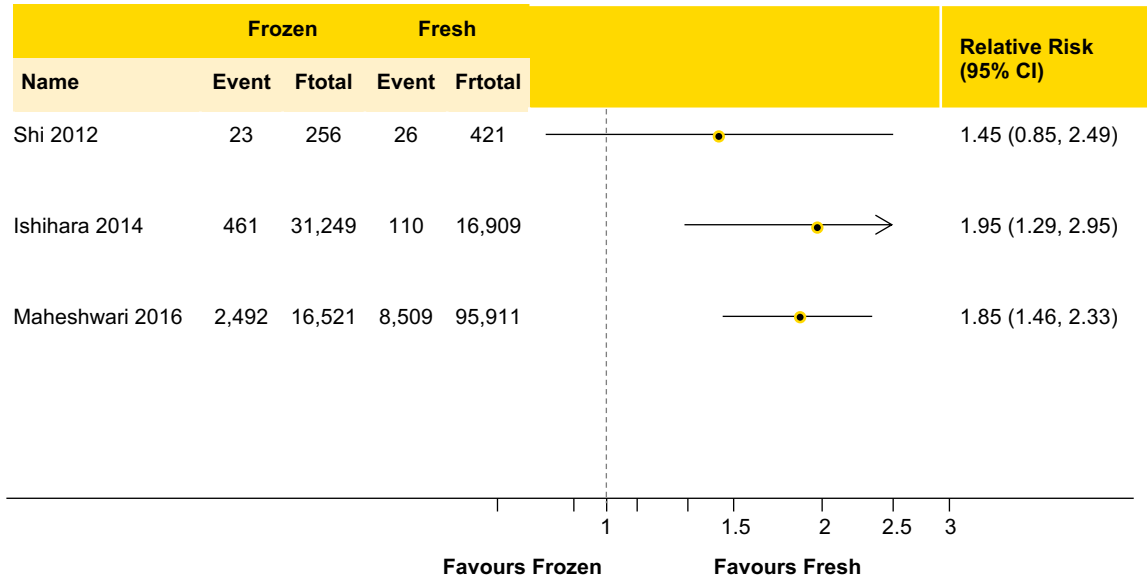
Relative risk of large for gestational age babies based on a cumulative meta-analysis

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.

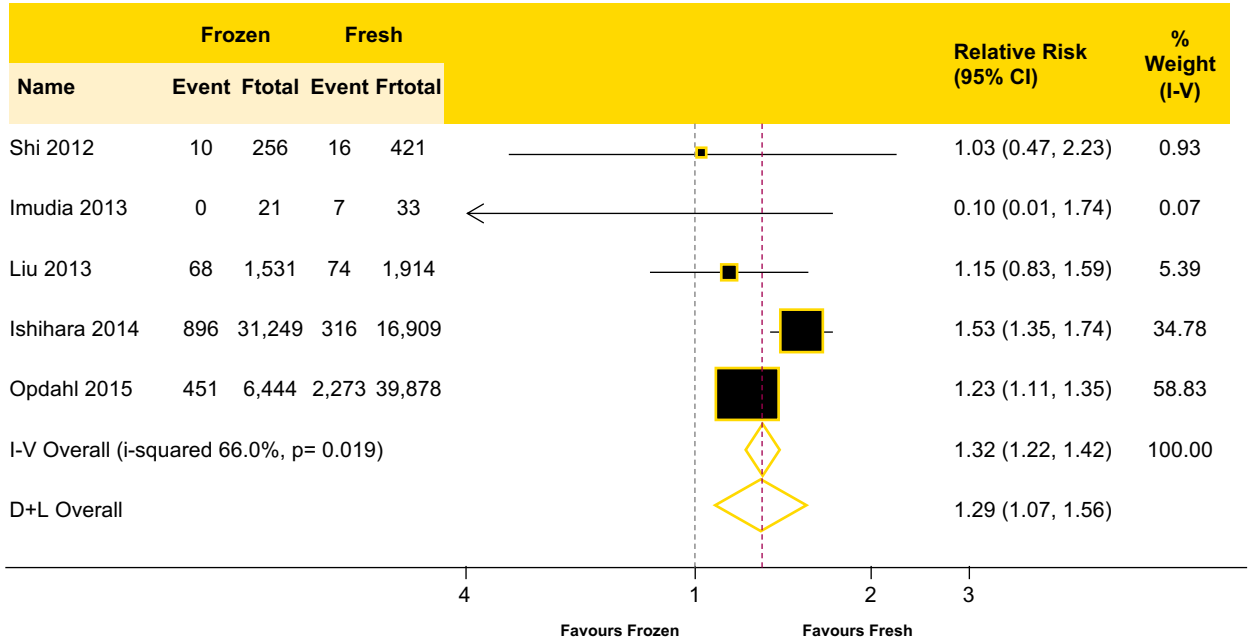
Figures from Maheshwari A, et al. 2018.

Hypertensive disorders of pregnancy*: Frozen versus fresh embryo transfer pregnancies

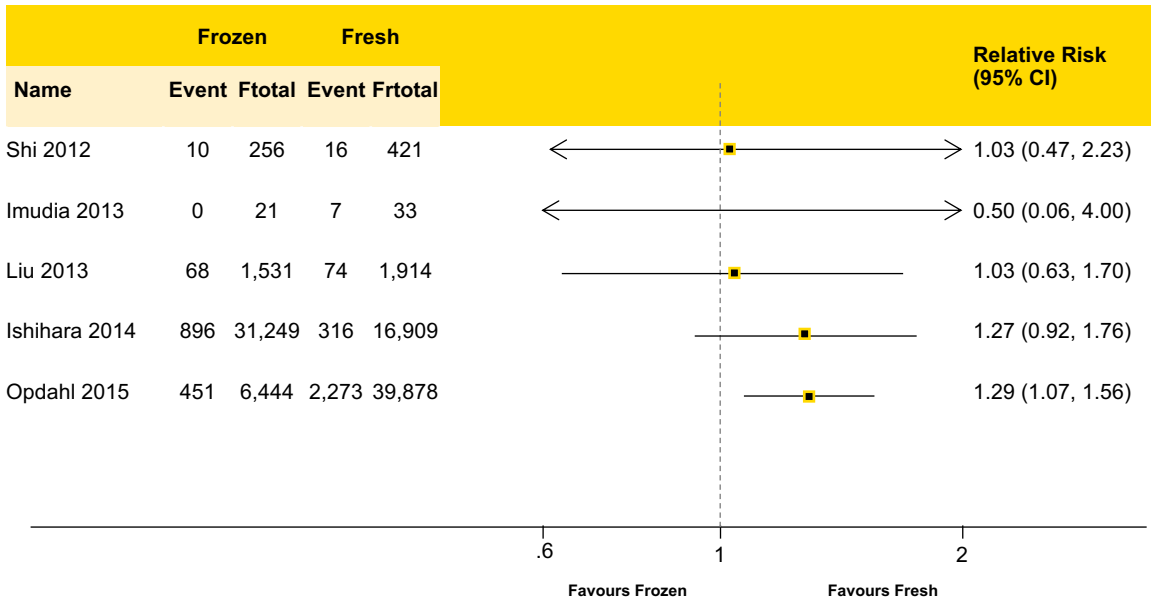
Relative risk of HDP among frozen versus fresh ET

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.

Perinatal outcome of singleton siblings born after assisted reproductive technology 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

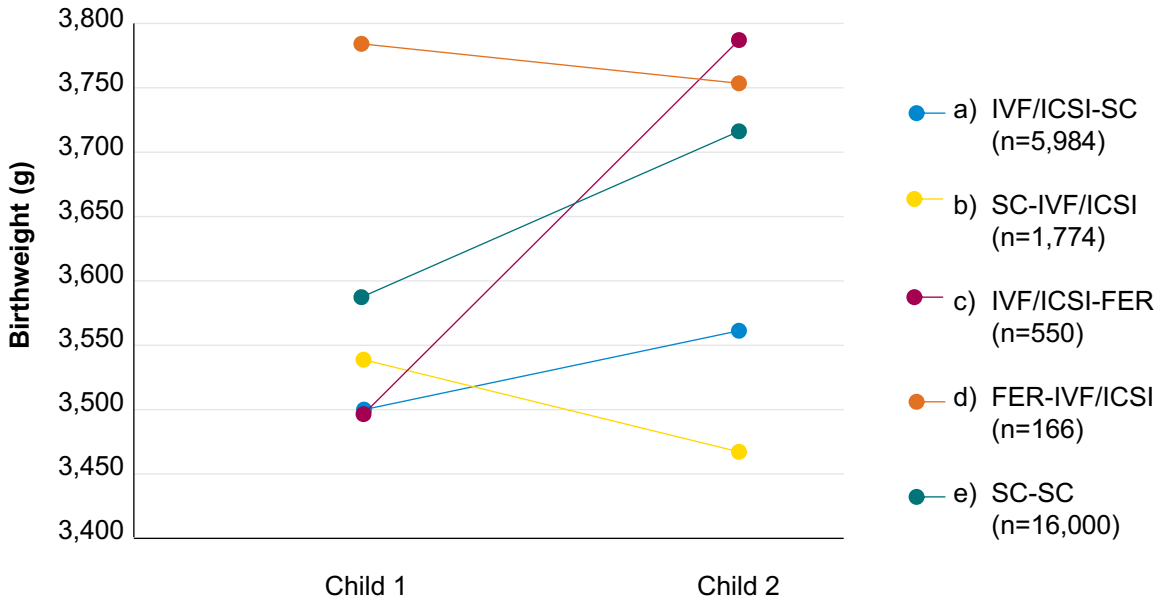


Figure adapted from Henningsen AKA, et al. 2011

*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.

Obstetric and perinatal outcomes following programmed compared with natural FET cycles: A systematic review and meta-analysis

Obstetric and perinatal risk estimates comparing programmed FET cycles versus natural FET cycles

Hypertensive disorders of pregnancy

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)

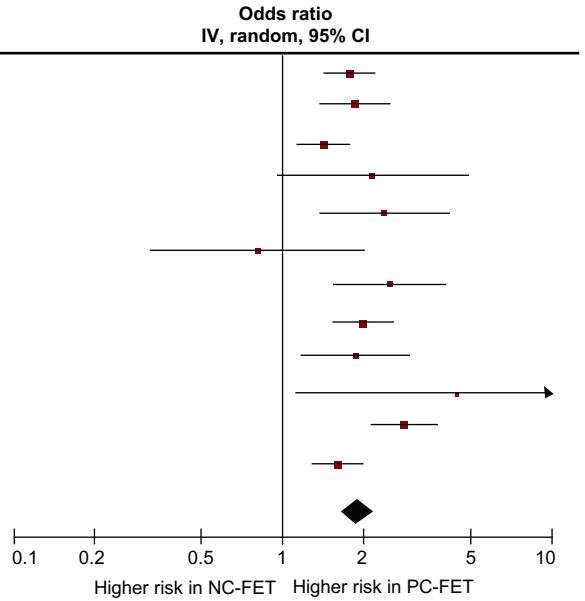


Figure from Busnelli A, et al. 2022

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.

Outcomes following programmed compared with natural FET cycles[1]

	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]

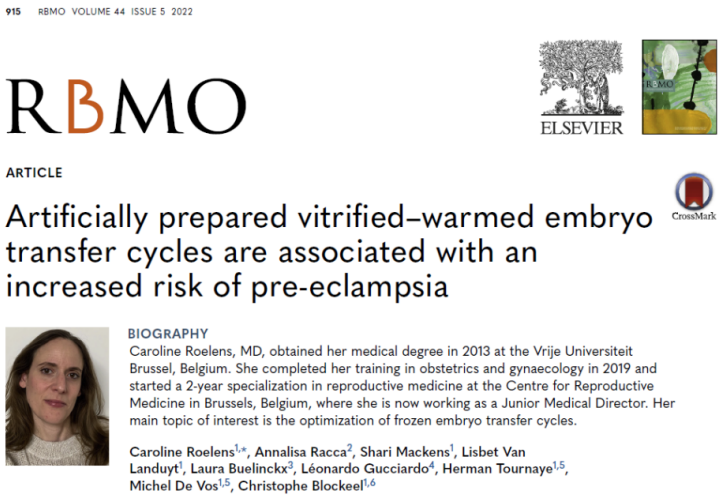
CI, confidence interval; FET, frozen embryo transfer; HDP, hypertensive disorders of pregnancy; PE, preeclampsia; PPH, post-partum haemorrhage.

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 and pre-eclampsia

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

- 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)


915 RBMO VOLUME 44 ISSUE 5 2022

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ELSEVIER

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]

- Incidence 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)

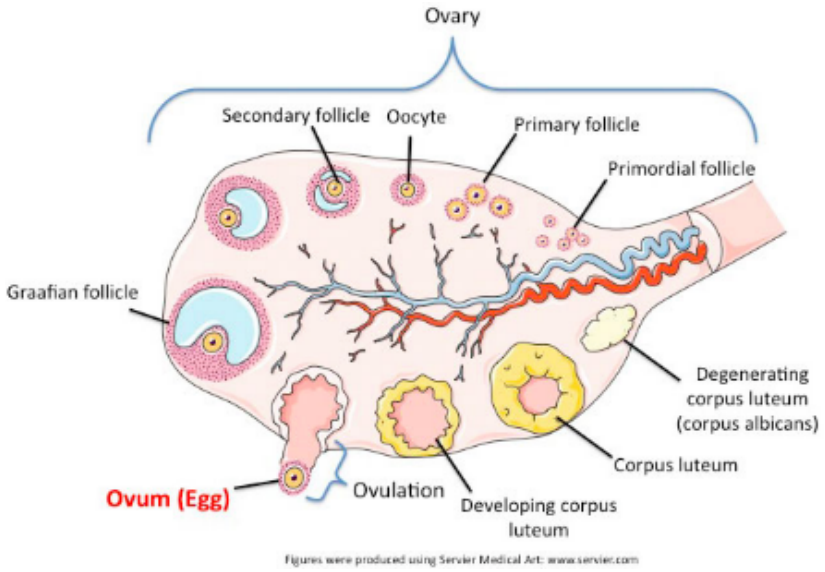
Original Article

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†

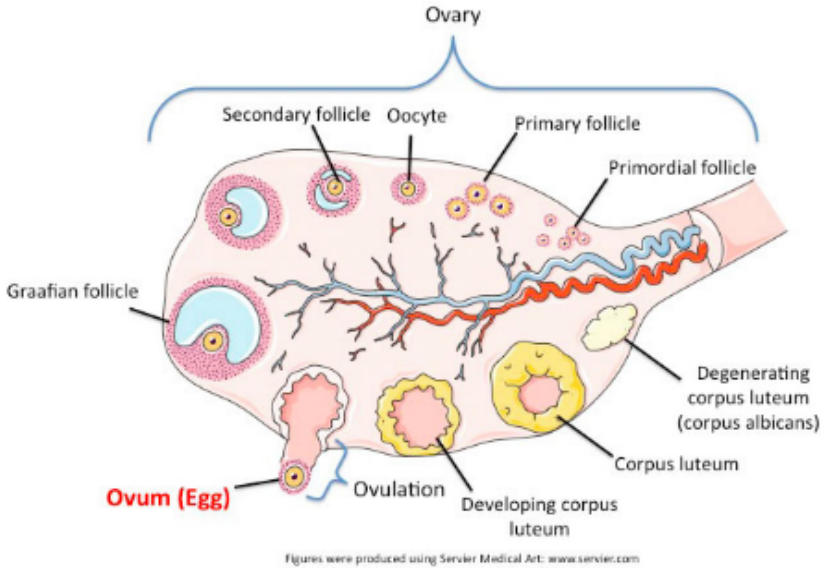
(Versen-Höynck et al., Hypertension 2019; 73, 640-49)

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)



Which FET protocol would be optimal?

Veronica

- 38-year-old patient
- Cycle length: 40–50 days
- AMH 25 pmol/L
- Patient has systemic lupus erythematosus currently without symptoms?

AMH, anti-Müllerian hormone; FET, frozen embryo transfer.

Which FET protocol would be optimal?

Anna

- 28-year-old patient
- Cycle length 40–50 days
- AMH 45 pmol/L
- Healthy and taking no medication

AMH, anti-Müllerian hormone; FET, frozen embryo transfer.

Long-term health and growth in childhood following frozen embryo transfer

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.

Cardiovascular function and metabolism

FET

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.

Long-term risks in children born large for gestational age

Systematic review and meta-analysis

High birthweight and LGA were associated with increased risks of:

Certain malignancies in childhood (e.g. breast cancer and leukaemia)*	Several psychiatric disorders	Hypertension in childhood	Type 1 or 2 diabetes

While the increases in risk are moderate, they should be considered when making decisions about fresh and frozen ART cycles

These risks are of general importance due to the increasing prevalence of high birthweight babies

*Low to moderate increase.
ART, assisted reproductive technology; CI, confidence interval; LGA, large for gestational age.
Magnusson A, et al. Front Pediatr 2021;9:675775.

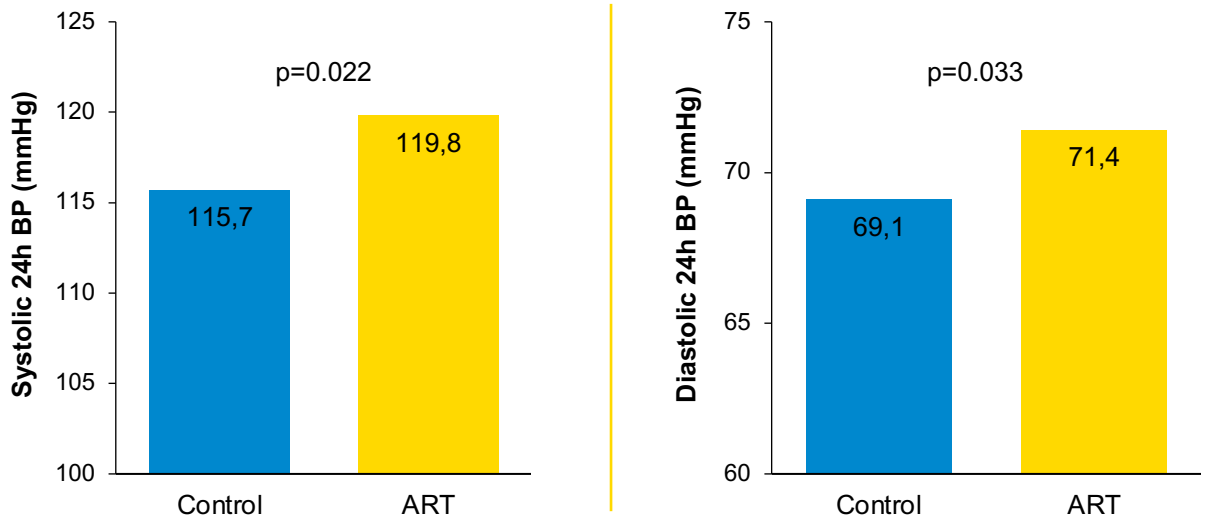
Association of ART with arterial hypertension during adolescence

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)



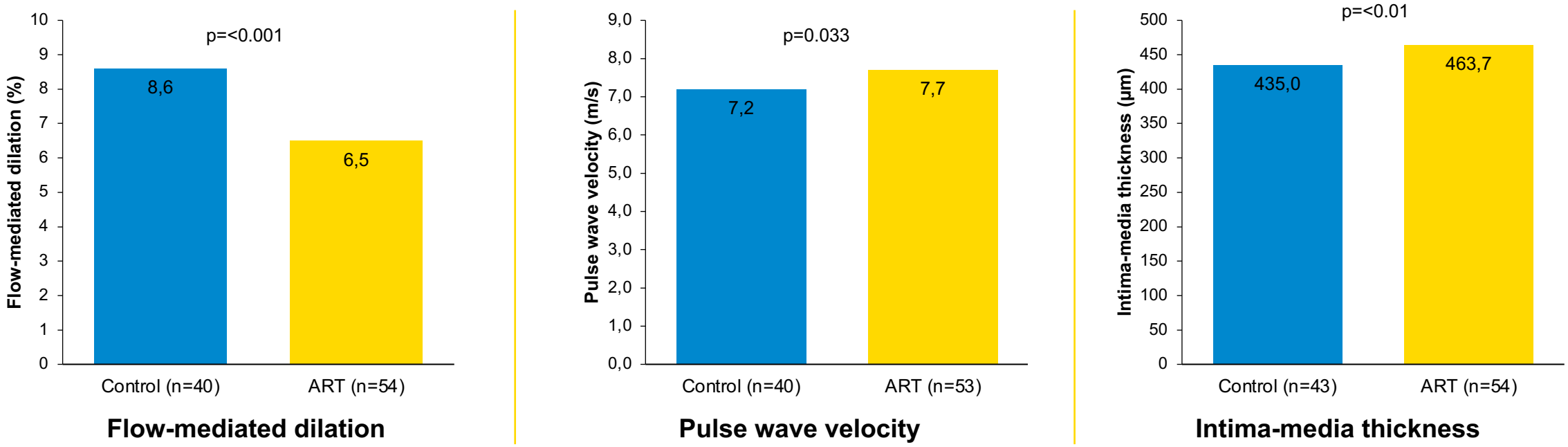
Systolic and diastolic 24-hour ambulatory blood pressure was **significantly higher** in **subjects conceived through ART** than in control subjects

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)



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)

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)

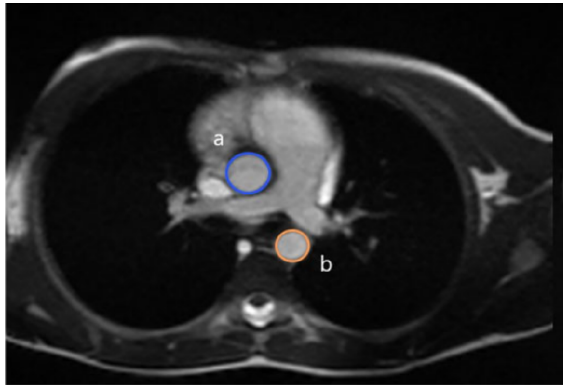
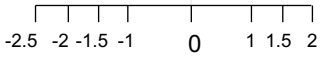


Figure showing cross-sectional CMR image of ascending aorta (a) and descending aorta (b) from Mizrak I, et al. 2022.

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.

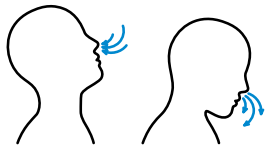
Mizrak I, et al. Hum Reprod 2022;37:600–611.

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

HiCART
Health in Childhood following Assisted Reproductive Technology

PHYSIOLOGICAL PROVOCATION MANOEUVRES

Active standing



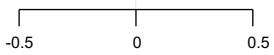
Deep breathing

The Valsalva maneuver

Children conceived with frozen embryo transfer have normal autonomic cardiovascular regulation

Heart rate response to physiological provocation

	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.

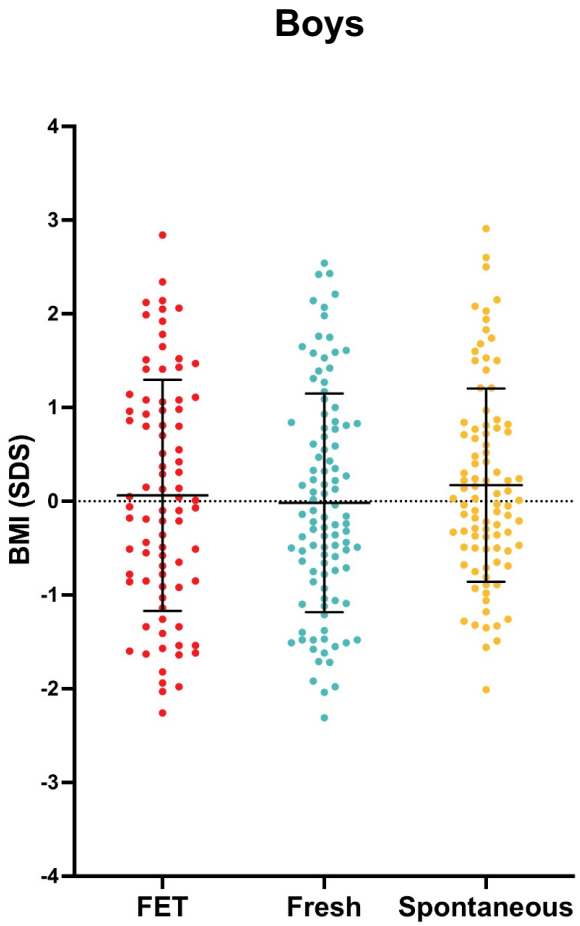
Mizrak I, et al. Presented at ESHRE 2022. P-772.

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)



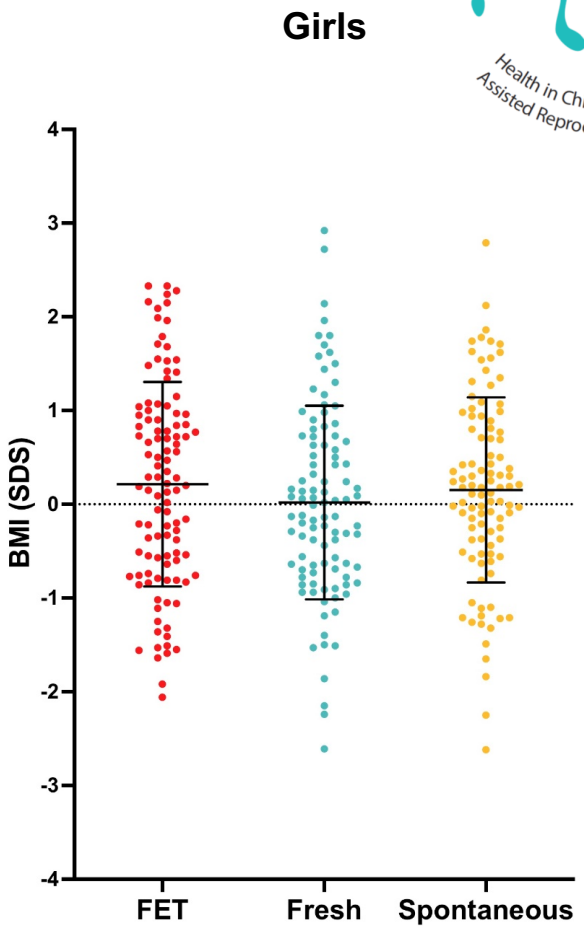


Figure from Asserhoej L, et al. 2022.

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

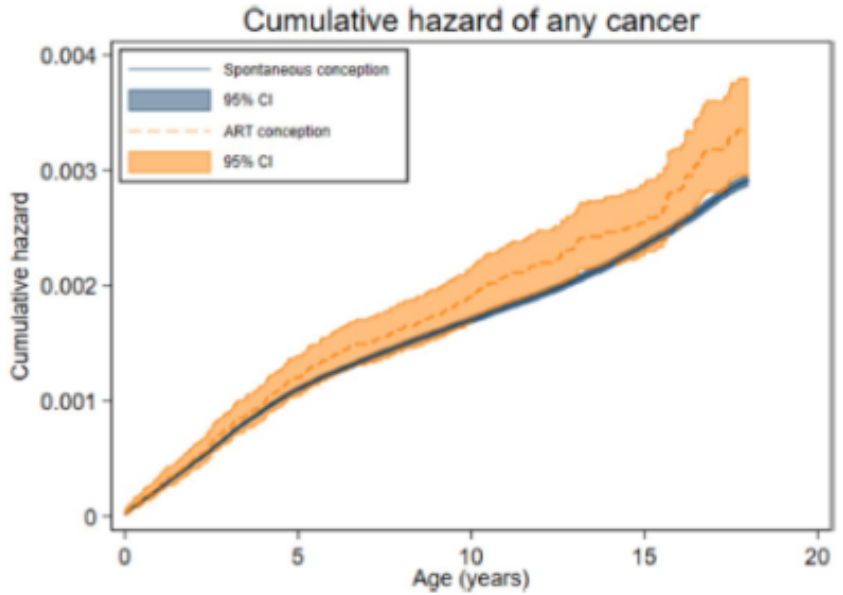


Fig 3. Cumulative hazard of first cancer (any type) up to 18 years for spontaneously and ART-conceived children born in Denmark (1994–2014), Finland (1990–2014), Norway (1984–2015), and Sweden (1985–2015). Crude hazard ratio 1.13; 95% CI 1.01 to 1.26, $p = 0.03$. ART, assisted reproduction technology;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

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Committee of Nordic Assisted Reproductive Technology and Safety

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

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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

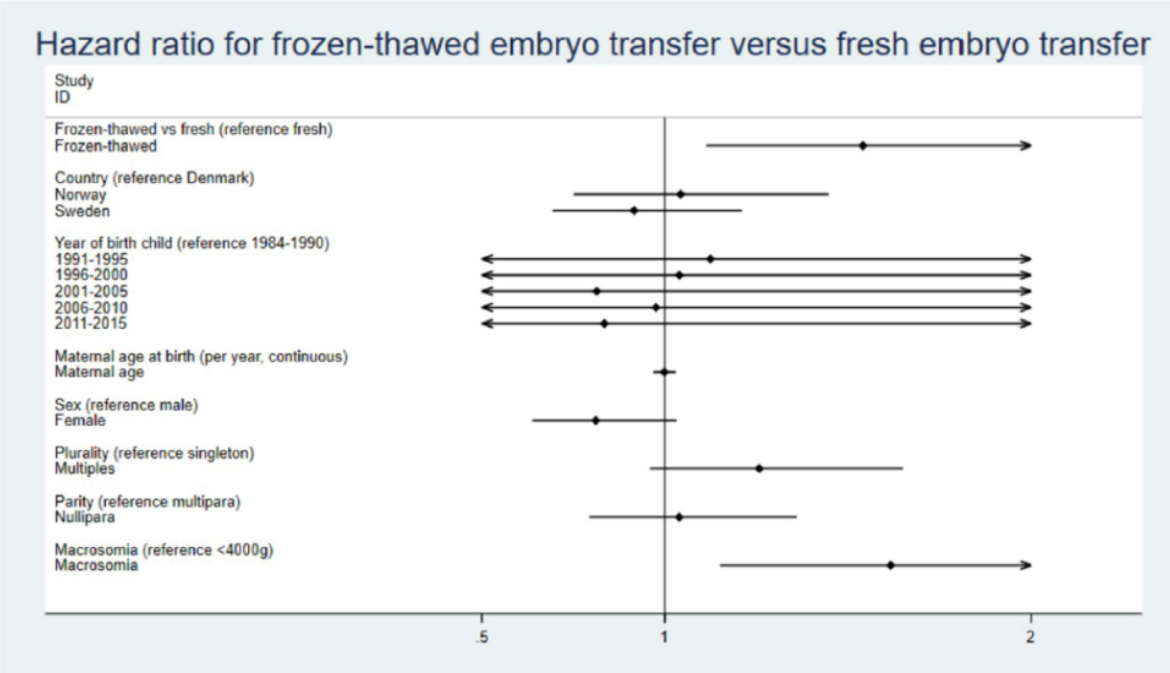

Fig 4. HRs with 95% CI for independent covariates including macrosomia for risk of cancer in children born after FET versus fresh embryo transfer. CI, confidence interval; FET, frozen-thawed embryo transfer; HR, hazard ratio.

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How to minimise the risk of FET protocols

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

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

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

*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.

Conclusions

1. There is a higher risk of large for gestational age, macrosomia in preeclampsia and post-partum haemorrhage after FET and programmed FET compared with fresh ET or natural cycle FET[1,2]
2. A similar academic performance at school in children born after FET and fresh-ET has been observed[3]
3. The cardiovascular health of children born after FET aged between 8–9 years is reassuring[4]
4. BMI in children born after FET is reassuring

ET, embryo transfer; FET, frozen embryo transfer.

1. Pinborg A, et al. Hum Reprod 2014;29:618–627; 2. Busnelli A, et al. Hum Reprod 2022;37:1619–1641; 3. Spangmose AL, et al. BJOG 2019;126:261–269;
4. Mizrak I, et al. Presented at ESHRE 2022. P-772.

Thank you

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