

A multivariate analysis of large-for-gestation risk factors in IVF and naturally conceived singletons

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Introduction

- IVF frozen-thawed ET (FET) outcome reassuring
 - IVF „FET babies“ higher birthweight, less pregnancy and perinatal complications in comparison to „fresh IVF babies“

- Wennerholm UB, Henningsen AK, Romundstad LB, Bergh C, Pinborg A, Skjaerven R et al. Perinatal outcomes of children born after frozen-thawed embryo transfer: a Nordic cohort study from the CoNARTaS group. Hum Reprod 2014
- Ishihara O, Araki R, Kuwahara A, Itakura A, Saito H, Adamson GD. Impact of frozen-thawed single-blastocyst transfer on maternal and neonatal outcome: an analysis of 277,042 single-embryo transfer cycles from 2008 to 2010 in Japan. Fertil Steril 2014
- Henningsen AK, Pinborg A, Lidegaard Ø, Vestergaard C, Forman JL, Andersen AN. Perinatal outcome of singleton siblings born after assisted reproductive technology and spontaneous conception: Danish national sibling-cohort study. Fertil Steril 2011
- Healy DL, Breheny S, Halliday J, Jaques A, Rushford D, Garrett C et al. Prevalence and risk factors for obstetric haemorrhage in 6730 singleton births after assisted reproductive technology in Victoria Australia. Hum Reprod 2010
- Belva F, Henriët S, Van den Abbeel E, Camus M, Devroey P, Van der Elst J, et al. Neonatal outcome of 937 children born after transfer of cryopreserved embryos obtained by ICSI and IVF and comparison with outcome data of fresh ICSI and IVF cycles. Hum Reprod 2008
- Pelkonen S, Koivunen R, Gissler M, Nuojua-Huttunen S, Suikkari AM, Hydén-Granskog C et al. Perinatal outcome of children born after frozen and fresh embryo transfer: the Finnish cohort study 1995-2006. Hum Reprod 2010
- Maheshwari A, Pandey S, Shetty A, Hamilton M, Bhattacharya S. Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen-thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis. Fertil Steril 2012



Introduction

- Higher risk for birth of singletons being large for gestational age (LGA)

- Wennerholm UB, Henningsen AK, Romundstad LB, et al. Perinatal outcomes of children born after frozen-thawed embryo transfer: a Nordic cohort study from the CoNARTaSgroup. Hum Reprod 2013.
- Ishihara O, Araki R, Kuwahara A, et al. Impact of frozen-thawed single-blastocyst transfer on maternal and neonatal outcome: an analysis of 277,042 single-embryo transfer cycles from 2008 to 2010 in Japan. Fertil Steril 2014;101(1):128-33.
- Henningsen AK, Pinborg A, Lidgaard Ø, et al. Perinatal outcome of singleton siblings born after assisted reproductive technology and spontaneous conception: Danish national sibling-cohort study. Fertil Steril 2011
- Korosec S, Ban Frangez H., Virant-Klun I et al. Singleton pregnancy outcomes after in vitro fertilization with fresh or frozen-thawed embryo transfer and incidence of placenta praevia. Biomed Res Int 2014
- Pinborg A, Henningsen AA, Loft A, et al.. Large baby syndrome in singletons born after frozen embryo transfer (FET): is it due to maternal factors or the cryotechnique? Hum Reprod 2014
- Li Z, Wang YA, Ledger W, Sullivan EA. Birthweight percentiles by gestational age for births following assisted reproductive technology in Australia and New Zealand, 2002-2010. Hum Reprod 2014
- Marino JL, Moore VM, Willson KJ, et al. Perinatal outcomes by mode of assisted conception and sub-fertility in an Australian data linkage cohort. PLoS One 2014
- Sazonova A, Källén K, Thurin-Kjellberg A, et al. Obstetric outcome in singletons after in vitro fertilization with cryopreserved/thawed embryos. Hum Reprod 2012.
- Hansen M, Bower C. The impact of assisted reproductive technologies on intra-uterine growth and birth defects in singletons. Semin Fetal Neonatal Med 2014.
- Wennerholm UB, Söderström-Anttila V, Bergh C, et al. Children born after cryopreservation of embryos or oocytes: a systematic review of outcome data. Hum Reprod 2009.



Reasons?

- Maternal characteristics (BMI, GDM, lifestyle)
- Embryo selection (extreme circumstances)
- Placentation differences (endometrium)
- Underlying epigenetic disturbances?

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human
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ORIGINAL ARTICLE *Reproductive epidemiology*

Large baby syndrome in singletons born after frozen embryo transfer (FET): is it due to maternal factors or the cryotechnique?

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etics 8:6, 591–601; June 2013; © 2013 Landes Bioscience

RESEARCH PAPER

Large offspring syndrome

A bovine model for the human loss-of-imprinting overgrowth syndrome Beckwith-Wiedemann

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Division of Animal Sciences; University of Missouri; Columbia, MO USA

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Advanced Access publication on June 11, 2013 doi:10.1093/humrep/det251

human
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ORIGINAL ARTICLE *Infertility*

Factors affecting the outcome of frozen–thawed embryo transfer

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Aim

The aim of the study was to analyze **independent LGA risk factors** and to identify those specifically connected to the IVF techniques.



Study design

- Retrospective cohort case-matched study
- The IVF performed between 2004 - 2011 University Medical Centre Ljubljana.
- National Perinatal Data System
- 4508 singleton pregnancies and births
- 1127 IVF
 - 211 FET, 916 fresh ET
- 3381 naturally conceived controls
 - 3 controls for each IVF pregnancy,
 - matched by maternal age, parity and maternity hospital



Study design

- Logistic regression models
- the risk factors for LGA in FET, fresh ET and natural controls
- Factors observed: smoking, hypertension, multiparity, BMI, gestational diabetes (GDM), IVF / ICSI fertilization, single/double ET



Results

	FET N=211	FET controls N=633	Fresh ET N=916	Fresh controls N=2748
LGA (above 90 th centile) N (%)	31 (14,7)	55 (8,7)	86 (9,4)	249 (9,1)
P value	0.017*		0.791	
LGA (above 95 th centile) N (%)	21 (10,0)	31 (4,9)	45 (4,9)	141 (5,1)
P value	0.012*		0,862	

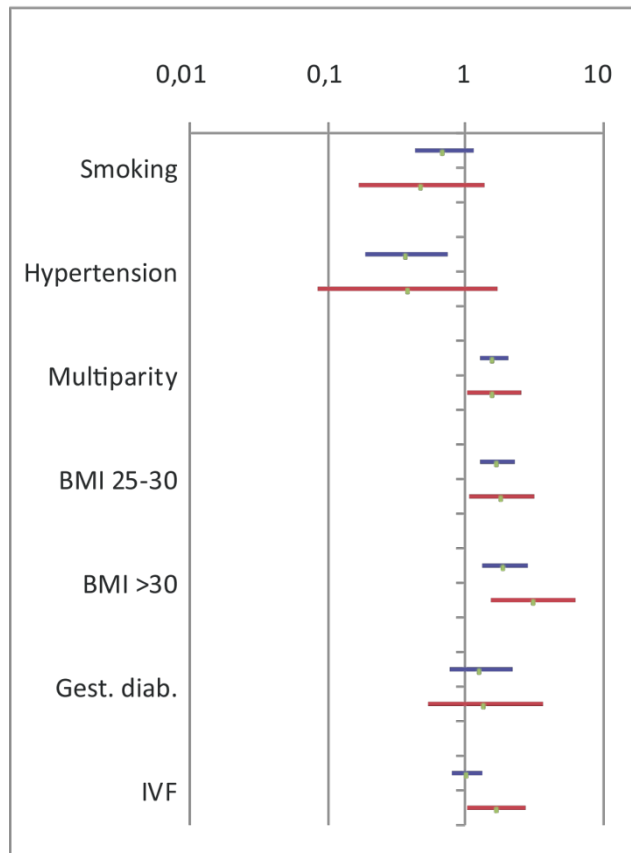
FET- frozen-thawed embryo transfer, fresh ET – fresh embryo transfer, LGA – large for gestation birthweight*-statistically significant (p < 0.05), as revealed by Chi-square test.



Logistic model for independent factors influencing LGA (90th c.)

Red line: FET with controls

Blue line: fresh ET with controls.



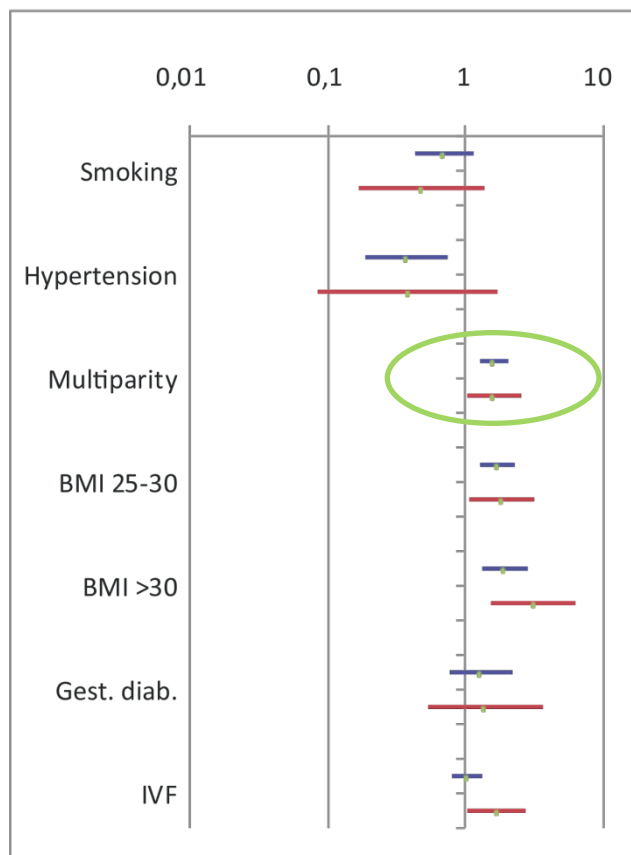
OR with 95% c.i.

All cases

Logistic model for independent factors influencing LGA (90th c.)

Red line: FET with controls

Blue line: fresh ET with controls.



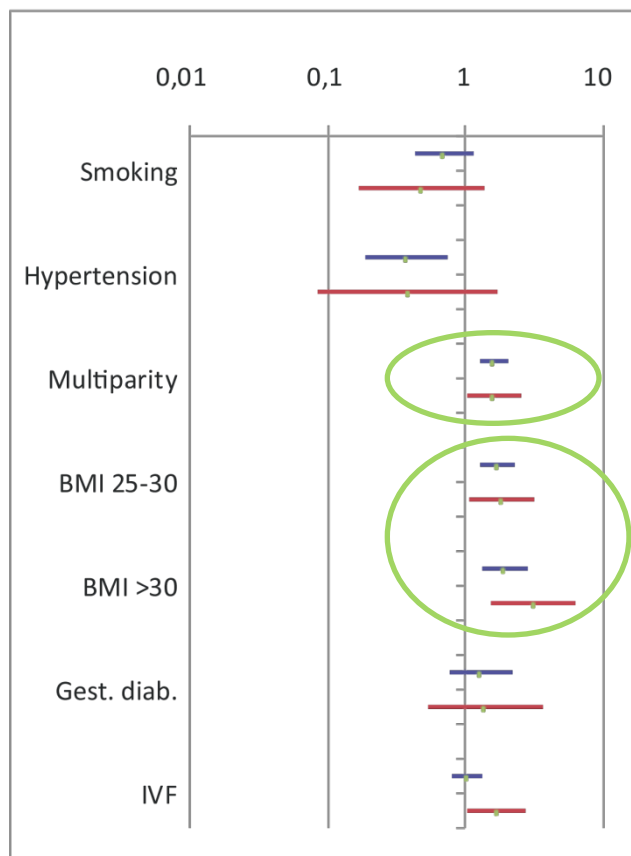
All cases

SIGNIFICANT FACTORS			
	p-value	OR	95% C.I
FET and controls			
multiparity	0,039	1,615	1,023 - 2,550
BMI 25-30	0,026	1,851	1,078 - 3,177
BMI over 30	0,002	3,124	1,521 - 6,417
FET procedure (IVF)	0,032	1,697	1,047 - 2,752
Fresh ET and controls			
hypertension	0,006	0,377	0,189 - ,751
multiparity	0,001	1,610	1,266 - 2,047
BMI 25-30	0,000	1,709	1,293 - 2,258
BMI over 30	0,001	1,933	1,319 - 2,832

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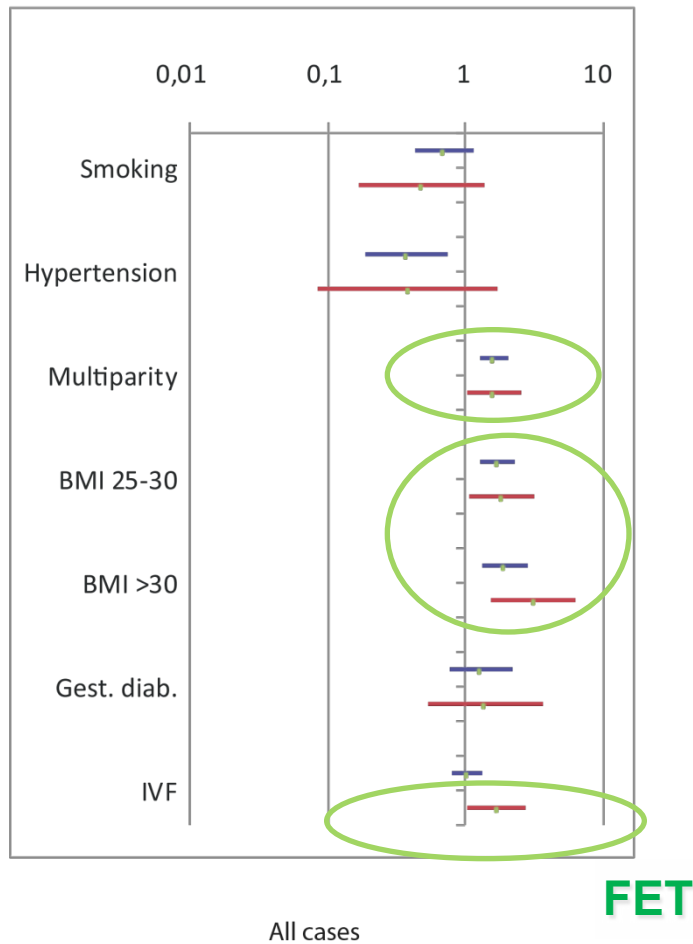
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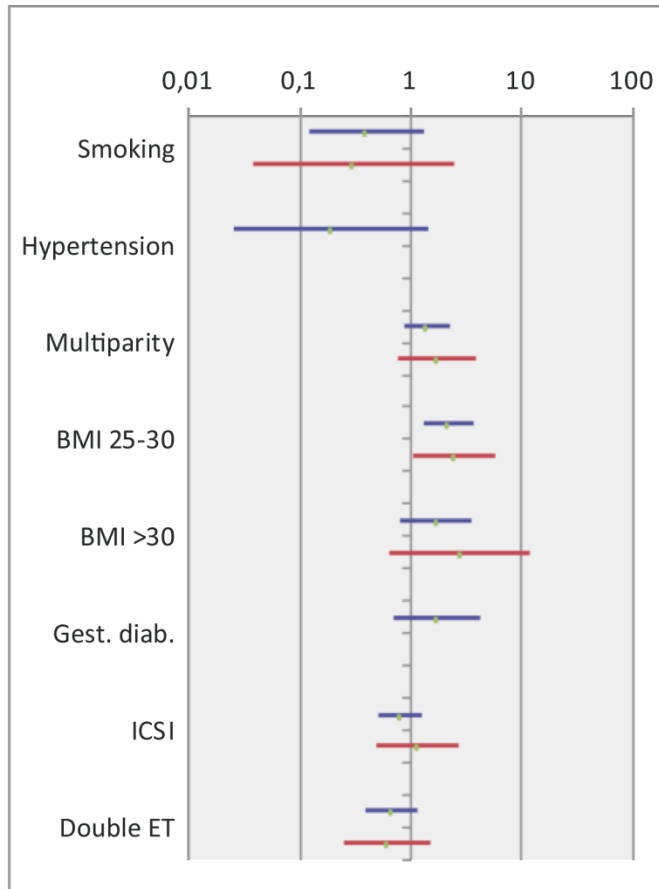


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Logistic model for independent factors influencing LGA (90th c.) in IVF singletons only

Red line: FET

Blue line: fresh ET



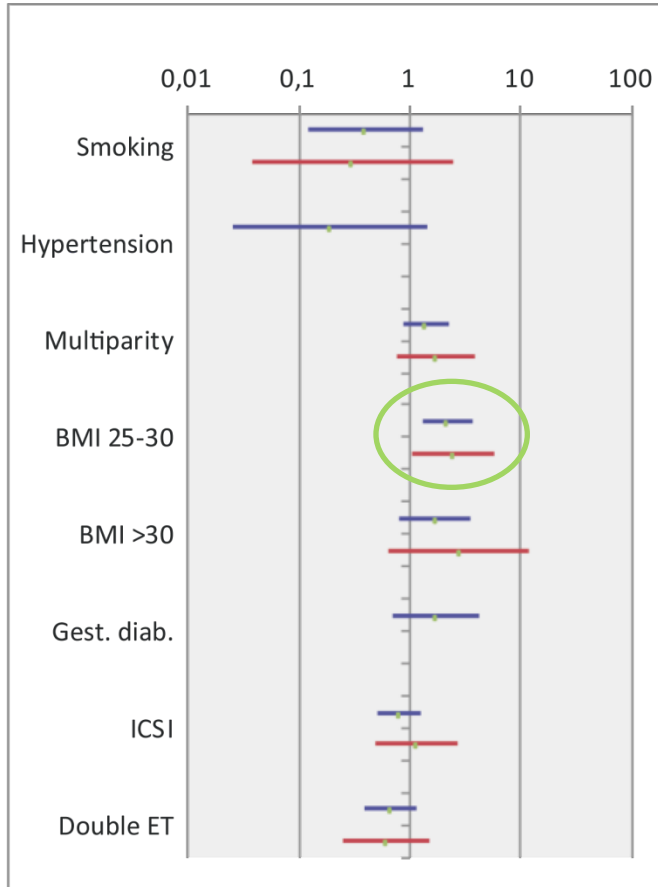
OR with 95% c.i.

IVF only

Logistic model for independent factors influencing LGA (90th c.) in IVF singletons only

Red line: FET

Blue line: fresh ET



IVF only

SIGNIFICANT FACTORS			
	p-value	OR	95% C.I
FET			
BMI 25-30	0.043	2.460	1.030-5.857
Fresh ET			
BMI 25-30	0.003	2.188	1.297-3.691

Results

- **FET** was found to be a **significant independent risk factor** for LGA similarly as the **BMI and multiparity** in the IVF singletons.
- ICSI had practically no effect on LGA occurrence, whereas the double ET insignificantly reduced the LGA risk.



Conclusions

- Besides maternal BMI and parity, FET is a significant independent LGA risk factor for the birth of a LGA singleton.
- Other observed IVF factors, ICSI and double ET, do not influence LGA risk significantly.
- The most obvious for higher LGA rate after FET procedure are being excluded.



Further investigation

- Maternal characteristics
 - excluded?
- Placentation differences
 - natural cycle endometrium
- Embryo selection
 - vitrification vs. slow freezing
- Epigenetic disturbances?
- Multifactorial?

