The influence of the type of embryo culture medium on neonatal birthweight after single embryo transfer in IVF.

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Introduction

January 2009:
switch from HTF (Gynotec) to Sage® (CooperSurgical)

Validation process: birthweights babies

Introduction

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Birth weight in humans is associated with short and long term morbidity and mortality, and is therefore commonly used for the assessment of neonatal outcome. Land, 2006

Introduction

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ART singletons: ↑ risk adverse neonatal outcomes

Schieve et al., 2002; Helmerhorts et al., 2004; Jackson et al., 2004; Halliday 2007; Ceelen et al., 2008

- Low birthweight
- Preterm delivery

Why?

- Patient-related factors
- Technical procedures

Introduction

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Patient related factors influencing birthweight:

Lower birthweight:

- subfertility (no consensus in literature)
  Schieve et al., 2002; Wang et al., 2005; Romundstad et al., 2008; Jaques et al., 2010; Henningsen et al., 2011
- BMI of mother
- smoking
- alcohol consumption

King and Fabro, 1983; Andreasen et al., 2004; Odendaal et al., 2009

Higher birthweight

- gender (boys ↑ birthweight)
- ↑ parity
- ↑ gestational age

Oken et al., 2003

- ↑ blastomeres transferred embryo Liebermann, 2006

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Introduction

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Treatment related factors influencing birthweight:

- Ovarian hyperstimulation: trend towards ↓ birthweight
  Pelinck et al., 2010
- Embryo freezing and thawing:
  no lower birthweight and preterm delivery
  Wennerholm et al., 2009; Pelkonen et al., 2010; Henningsen et al., 2011
- Embryo culture medium

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Introduction

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Embryo culture medium

Dumoulin et al. (2010) and Nelissen et al. (2012):

- Vitrolife (GI.3): significant heavier infants than Cook®

Eaton et al. (2011):

- Global vs Vitrolife (GI.3 or GI.5): no differences

Aim

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AIM:

To compare birthweights of neonates after IVF treatment with a single-embryo transfer (SET), where fresh and frozen–thawed embryos were cultured in one of two commercially available types of media.

Sage Quinn's advantage protein plus	HTF (human tubal fluid) [Lonza/Gynotec] with 4 mg/ml HSA (human serum albumin) [=GPO Sanquin]

Results

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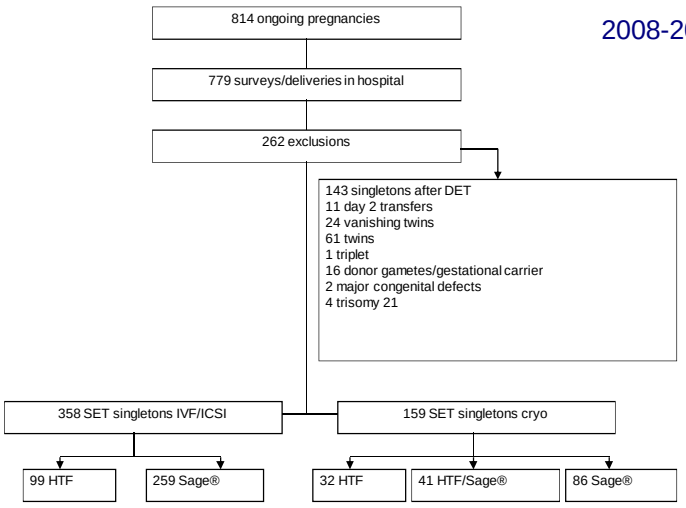

2008-2010

Results

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Table I Maternal characteristics and neonatal outcome of 358 fresh embryo transfers.

	HTF, *n* = 99	Sage®, *n* = 259	*P*-value
Maternal age (years)	34.0 (4.1)	34.2 (4.0)	0.75
Maternal BMI	23.9 (4.0), *n* = 89	24.1 (3.9), *n* = 241	0.79
Maternal smokers (%)	15.4, *n* = 99	17.5, *n* = 259	0.59
Birthweight (grams)	3446 (508)	3341 (575)	0.11
Small for gestational age (<10th percentile), *n* (%)	6 (6.1)	28 (10.8)	0.17
Large for gestational age (>90th percentile), *n* (%)	8 (8.1)	22 (8.5)	0.90
Z-score corrected for gestational age and gender	0.04 (0.87)	0.09 (0.99)	0.67
Z-score corrected for gestational age and parity	−0.02 (0.90)	0.08 (0.99)	0.38
Gestational age at birth (days)	278 (11)	275 (15)	0.06
Pregnancy duration (weeks), *n* (%)			
Term birth (≥37 weeks)	98 (99.0)	255 (98.5)	0.67
Preterm birth (<37 weeks)	1 (1.0)	2 (0.8)	
Very preterm birth (<32 weeks)	0 (0.0)	2 (0.8)	
Female infant, *n* (%)	45 (45.5)	127 (49.0)	0.67
Firstborn children, *n* (%)	74 (74.7)	196 (75.7)	0.86
Birthweight among firstborns (grams)	3388 (448), *n* = 74	3292 (579), *n* = 196	0.20
Number of cells per transferred embryo	7.7 (0.7)	8.0 (1.3)	0.01

Data are mean ± SD or *n* (%).

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Multiple linear regression analyses to analyse association with birthweight

- maternal age
- BMI
- smoking
- parity
- gestational age
- gender of the baby

significantly related to birthweight

- number of blastomeres of the transferred embryo
- type of culture media

Results

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Frozen-thawed single embryo transfers

Results

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Table II Maternal characteristics and neonatal outcome of 159 frozen–thawed embryo transfer cycles.

	HTF, $n = 32$	HTF/Sage®, $n = 41$	Sage®, $n = 86$	*P*-value
Maternal age (years)	34.8 (4.4)	35.2 (3.4)	34.1 (3.8)	0.59
Maternal BMI	23.3 (3.8), $n = 32$	23.4 (4.0), $n = 37$	24.1 (3.6), $n = 83$	0.33
Maternal smokers, *n* (%)	4 (12.5), $n = 32$	5 (12.2), $n = 41$	14 (16.2), $n = 86$	0.74
Birthweight (grams)	3547 (513), $n = 32$	3700 (543), $n = 41$	3550 (571), $n = 86$	0.46
Small for gestational age (<10th percentile), *n* (%)	2 (6.3)[a]	2 (4.9)[a]	2 (2.3)	<0.05*
Large for gestational age (>90th percentile), *n* (%)	2 (6.3)	12 (29.3)	13 (15.1)	0.09
Z-score corrected for gestational age and gender	0.27 (0.91)	0.49 (1.08)	0.31 (1.01)	0.65
Z-score corrected for gestational age and parity	0.26 (0.91)	0.47 (1.06)	0.38 (1.00)	0.66
Gestational age at birth (days)	278 (11)	279 (8)	277 (13)	0.37
Pregnancy duration (weeks), *n* (%)				
Term birth (≥37 weeks)	30 (93.8)	40 (97.6)	80 (93.0)	0.40
Preterm birth (<37 weeks)	2 (6.3)	1 (2.4)	5 (5.8)	
Very preterm birth (<32 weeks)	0 (0)	0 (0)	1 (1.2)	
Female infant, *n* (%)	16 (50.0)	18 (43.9)	48 (55.8)	0.90
Firstborn children, *n* (%)	14 (43.8)[a]	9 (22.0)[b]	64 (74.4)[a, b]	<0.001*
Birthweight among firstborns (grams)	3512 (495), $n = 14$	3361 (509), $n = 9$	3470 (584), $n = 64$	0.37

Data are mean ± SD or *n* (%).
*Pairs of means that are significantly different from each other in a Bonferroni multiple comparison test are marked ([a, b]).

Results

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Fresh versus frozen-thawed embryo transfers

Results

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Table III Maternal characteristics and neonatal outcome of 358 fresh and 159 frozen–thawed embryo transfers.

	Fresh SET, *n* = 358	Frozen–thawed SET, *n* = 159	*P*-value
Maternal age (years)	33.0 (3.8)	34.5 (3.8)	<0.0001
Maternal BMI	24.2 (4.1), *n* = 330	23.7 (3.6), *n* = 159	0.32
Maternal smokers, *n* (%)	56 (17.2), *n* = 325	23 (15.6), *n* = 147	0.67
Birthweight (grams)	3370 (558)	3588 (553)	<0.0001
Small for gestational age (<10th percentile), *n* (%)	34 (9.5)	6 (3.8)	0.03
Large for gestational age (>90th percentile), *n* (%)	30 (8.4)	27 (17.0)	0.004
Z-score corrected for gestational age and gender	−0.03 (0.94)	0.35 (1.00)	<0.0001
Z-score corrected for gestational age and parity	0.03 (0.94)	0.38 (0.99)	<0.0001
Gestational age at birth (days)	276 (14)	278 (11)	0.14
Pregnancy duration (weeks), *n* (%)			
Term birth (≥37 weeks)	337 (94.1)	150 (94.3)	0.73
Preterm birth (<37 weeks)	16 (4.5)	8 (5.0)	
Very preterm birth (<32 weeks)	5 (1.4)	1 (0.6)	
Female infant, *n* (%)	172 (48.0)	82 (51.6)	0.46
Firstborn children, *n* (%)	270 (75.4)	87 (54.7)	<0.0001
Birthweight among firstborns (grams)	3319 (547)	3466 (559)	0.03

Data are mean ± SD or *n* (%).

Discussion

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HTF + HSA: simple, one medium culture system
Sage®: more complex, sequential culture system

HTF protein source:

HSA (human serum albumine) 4 mg/ml

Sage® protein source:

fertilization: HSA 3 mg/ml
cleavage: SPS (serum protein substitute) 5 mg/ml
blastocyst: SPS 5 mg/ml

Sage® addition of essential[1] and non-essential[2] amino acids

1 arginine, l-cystine dihydrochloride, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, tyrosine, valine

2 alanyl-glutamine, asparagine, aspartic acid, glycine, proline, serine

Discussion

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Dumoulin et al. (2010) and Nelissen et al. (2012):

Vitrolife (GI.3): significant heavier infants than Cook®

Vitrolife embryos significantly ↑ mean nr. blastomeres

Vitrolife mothers significantly taller and heavier in fresh embryo transfer group

Eaton et al. (2011):

Global vs Vitrolife (GI.3 or GI.5): no differences

Discussion

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Singletons frozen-thawed SET
significant higher mean birthweight
than singletons fresh SET

- Confirmation previous studies
- More natural uterine environment
- Cryo SET day 5, fresh SET day 3
  day ET no effect on mean birthweight Kaussche 2001, Schwärzler 2004

more LGA and less SGA babies

- Cleavage stage vs blastocyst
  no ↑ LGA and SGA babies in fresh transfers Kallén 2010, Fernando 2012

Conclusion

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Type of medium (HTF or Sage) does not significantly influence mean birthweight in singletons born after fresh or frozen-thawed single embryo transfer

Embryo freezing and thawing:
⇒significantly higher mean birthweight