



CE marking – (relevance for IVF?)

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Meeting between Comission, T&C CAs and Stakeholders
Brussels, 16th November 2017

One challenge for the IVF-clinic

- In the end, we feel responsible for:
 - Treatment related health issues for the couples treated
 - Treatment related health issues for the children born
- Do we need to worry?
 - Patient related factors
 - Hormonal treatment
 - Fertilization, embryo culture
 - Cryopreservation
 - Pregnancy
 - Postnatal life
- Most epidemiological studies reassuring

Products with (or without) a CE mark in IVF

- Sperm
- Oocytes
- Zygotes
- Embryos

Direct contact

Culture media
Enzyme solutions
Immobilization agents
ICSI needles

Culture media

Cryopreservation
solutions

Indirect contact

Tubes, Dishes
Pipettes, Needles
Incubators
Gas (O_2 , CO_2 , N_2)
Culture oil

Catheters
Storage vials
 N_2 vapour/liquid

IVF Culture media as a case

- IVF culture media comes in direct contact with gametes and embryos
 - In animal studies it has been shown that embryo culture, including the composition of the culture media, may have lifelong consequences for the health of the offspring
- Any published data suggesting that this may be an issue in human IVF ?

Two examples of different commercially available media for human IVF

CaCl ₂
MgSO ₄ ·7H ₂ O
KCl
NaCl
D-Glucose
Citrat·H ₂ O
NaH ₂ PO ₄
NaHCO ₃
Pyruvic acid
Penicilline
Streptomycine
Phenol red

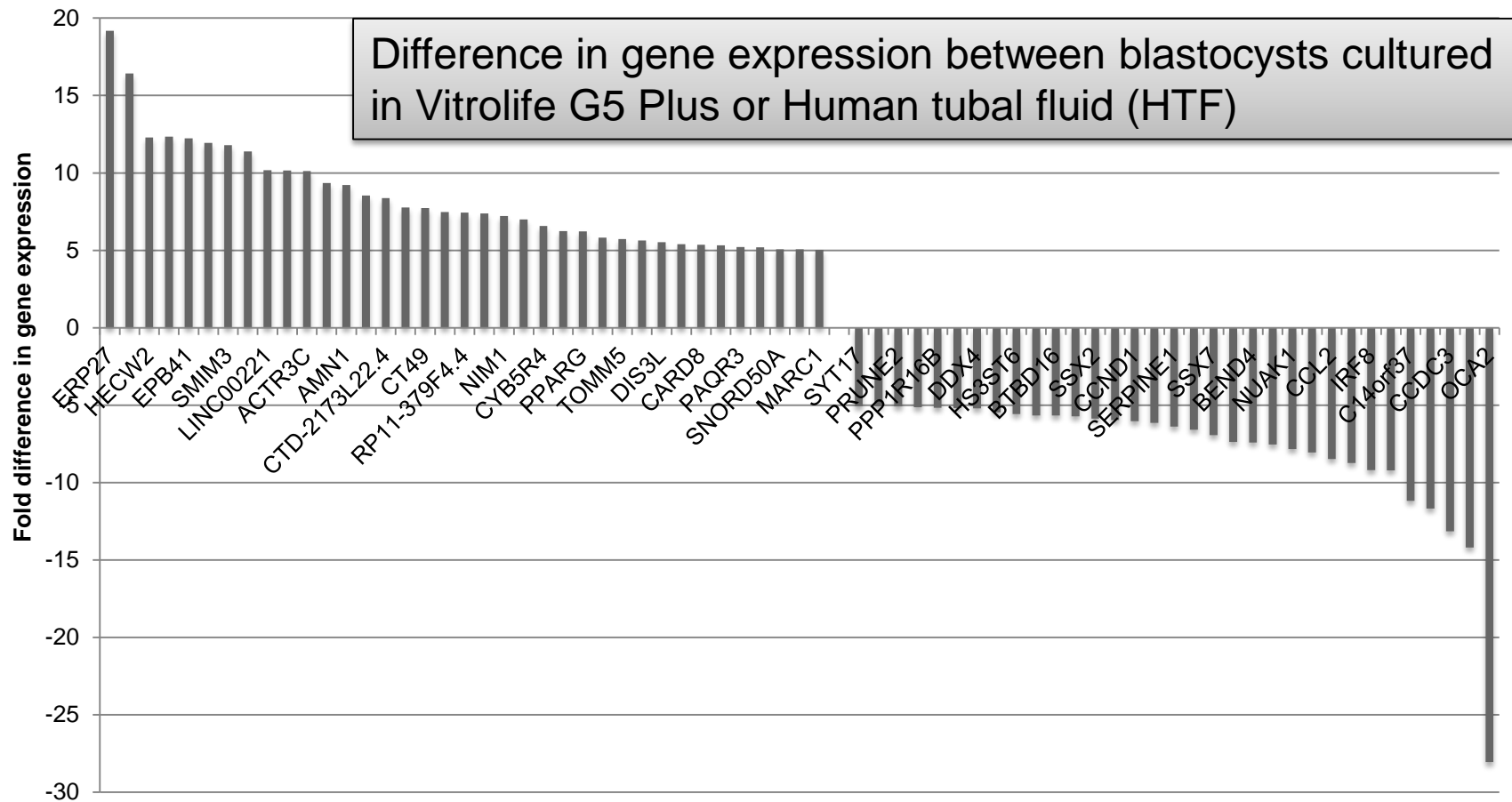
(NH ₄) ₆ MO ₇ O ₂₄ ·4 H ₂ O	D-Glucose	L-Arginie Cl	L-Methionine	MnSO ₄	NH ₄ VO ₃	Aurintricarboxylic acid
Acetic acid	Etanolamine	L-Asparagin·H ₂ O	L-Phenylalanine	MnSO ₄ ·H ₂ O	Ni(NO ₃) ₂ ·6H ₂ O	Fe(III)EDTA
CaCl ₂	Ethanol	L-Aspartat	L-Proline	Na Pyruvat	Nicotinamid	EDTA-Na ₂
Cholesterol	FeSO ₄ ·7H ₂ O	L-Cys Cl·H ₂ O	L-Serine	Na Selenit	Putrecine CL	HEPES
Cholin Cl	Folic acid	L-Glutamic acid	L-Threonine	Na-Citrat·2H ₂ O	Pyridoxine cl	Fe(III)EDTA
Citrat·H ₂ O	Hypoxantine	L-Glutamin	L-Tryptophan	Na ₂ HPO ₄	Riboflavin	L-Ala-L-Glut
Cobalamin	i-Inositol	L-Glycine	L-Tyrosine Na ₂	Na ₃ Citrat - 2H ₂ O	SeO ₂	Pluronic-F-68
CoCl ₂ ·6H ₂ O	KCl	L-Hist Cl·H ₂ O	L-Valine	NaCl	Thiamin-Cl	PVP 10
CuSO ₄ ·5H ₂ O	KCr(SO ₄) ₂ ·12H ₂ O	L-Isoleucine	Linoleic acid	NaH ₂ PO ₄	Thiocric cid	h-r-Insulin
D-Biotin	KH ₂ PO ₄	L-Leucine	MgCl ₂	NaHCO ₃	ZnSO ₄ ·7·H ₂ O	Penicillin
D-Ca Pantothenate	L-Alanine	L-Lysine	MgSO ₄ ·7H ₂ O	NH ₄ Al(SO ₄) ₂ ·12 H ₂ O	Phenol red ₃	Gentamycine

12 ingredients

+ serum Albumin

78 ingredients

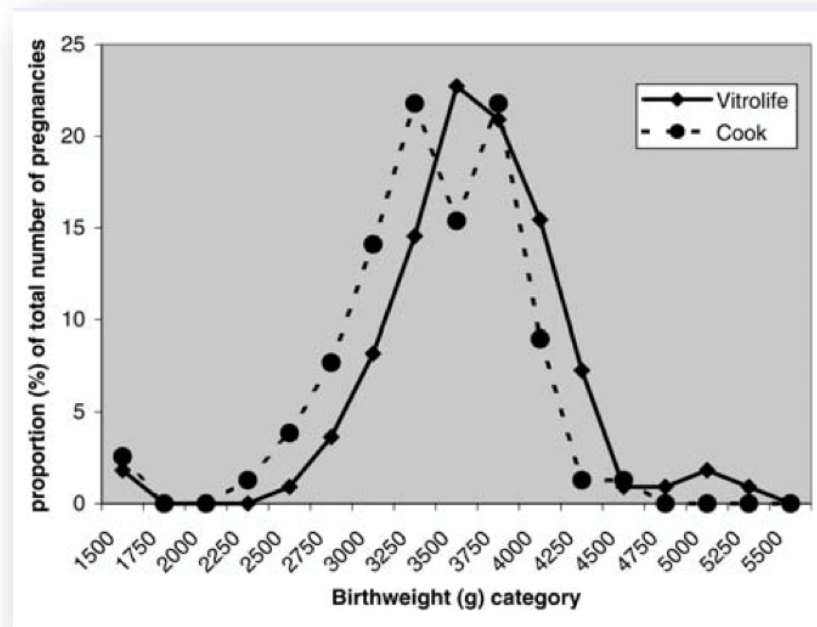
Difference in gene expression of embryos in two culture media from a Dutch prospective randomized multicentre trial



Can culture media influence birth weight?

- From the Vitrolife arm of the study:
 - Foetuses larger
 - On average 240g heavier at birth
 - Children
 - On average 0,5 kg heavier at 2 years of age
 - Still differences at age of 9
 - Weight and waist circumference

Two commercially available culture media from Vitrolife or COOK



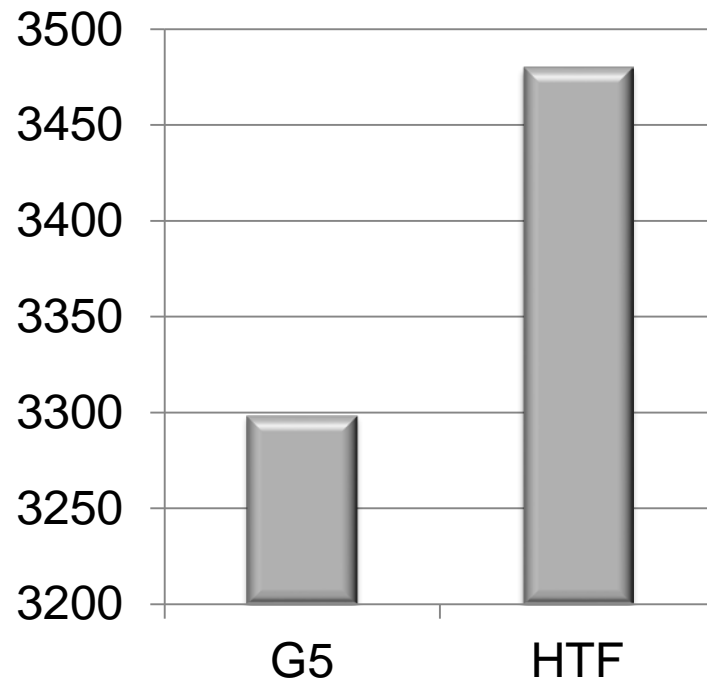
Dumoulin et al., 2010, Nelissen, et al., 2011, 2013
Van Montfoort, 2017, Zandstra 2017

Influence of embryo culture medium (G5 and HTF) on pregnancy and perinatal outcome after IVF: a multicenter RCT

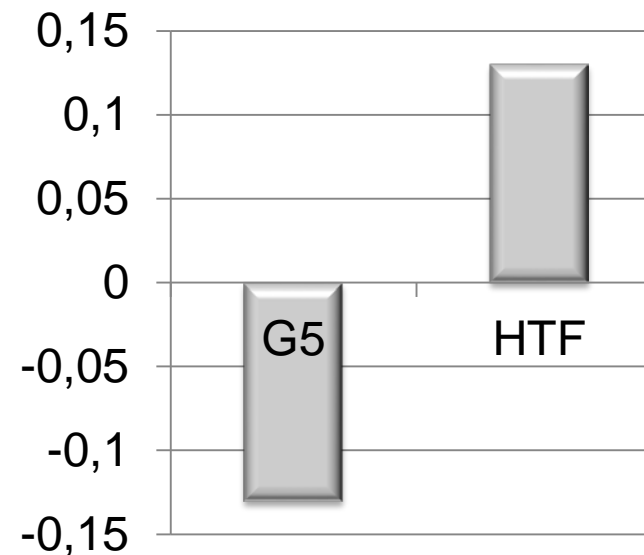
Multicenter, prospective
Randomized, double-blind
836 patients randomized
383 children

Kleijkers et al. 2016

Birth weight all



Z-score birth weights



Significantly different

Culture media influence phenotype

–formulations are kept secret to us

- We have data showing that the composition of IVF-culture media influence the phenotype of the offspring
 - Too early to say if this represents a health issue
 - Data from animal experiments suggest that we cannot exclude this
- The composition of culture media is **unknown** to us
 - The media companies change the formulations almost at will
 - Not substantiated by relevant clinical data
- Impossible to study the relationship between culture media compositions and phenotype and health of the offspring
 - This type of studies are urgently needed

IVF-clinics - regulation

- IVF lab is partially regulated
 - Safety, traceability (Tissue Directive)
 - Performance is not regulated
- The IVF clinics rapidly introduce consumables, technology and procedures, which have little or no documentation
 - Regulation does not interfere here.
 - The Industry knows this and behave accordingly
- Is this, in reality, a “Goods and Services” sector?

CE mark does it help ?

- Notifying body
 - Private companies can issue CE marks
 - In the industry some are known to be “easy” and quality standards are not equivalent?
 - Difficult to know for us who has issued a CE-mark for a given product
- Regulated by the CE-mark
 - Production, QC,
 - The media company’ rationale for the composition of various products
 - The media company’s opinion/data on safety
 - Some clinical data (in our opinion not much needed)
- We have no information about follow-up and post market surveillance
 - If it happens, the outcome are kept secret

CE mark does it help ?

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- Regulation does not interfere here.
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What do we want?

- Not necessarily a very rigorous system with detailed regulations
 - Difficult to develop and to enforce
- We want transparency
 - The name of the notifying body
 - The data provided by the media company prior to obtaining a CE mark
 - The composition including the concentration of each ingredient in the culture media
 - Notification when media composition is changed including
 - rationale and the new composition
 - Data from post market surveillance