

Rischi di salute nei bambini concepiti con tecniche PMA

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Ministero dell'Università e della Ricerca



**UNIVERSITÀ
DI TORINO**

Prime segnalazioni rischi associati a PMA

Abstract

A total of 91 children (68 singletons, 20 twins and three triplets) who were conceived from cryopreserved embryos between 27 December 1989 and 18 January 1994, and 83 normally conceived control children (81 singletons and two twins) of a similar age, sex and social class, were assessed for minor congenital anomalies and major congenital malformations. Their development was assessed using the Griffiths Scales of Mental Development. The incidence of minor congenital anomalies (31.9% in the cryopreserved embryo group and 21.7% in the controls) and major congenital malformations (3.3 and 2.4% respectively) in our two groups of children was statistically similar. The relative risk (odds ratio and 95% confidence interval) in the cryopreserved embryo group compared with the controls was 1.7 (0.8, 3.3) for minor congenital anomalies and 1.4 (0.2, 8.5) for major congenital malformations. The minor congenital anomalies were mostly naevi and haemangiomas. **The major congenital malformations included Down's syndrome, Beckwith-Wiedemann syndrome and hypophosphataemic rickets in the cryopreserved embryo group** and hydronephrosis and gastroschisis in the controls. The Griffiths assessment showed that children from the cryopreserved embryo group and the controls were functioning at a similar level. The mean Griffiths quotient and subquotient values were greater than the standard 100 in children with or without congenital abnormalities. These results in the cryopreserved embryo group are reassuring in that the minor congenital anomaly and major congenital malformation rates were similar to those in normally conceived children of a similar age, sex and social class and their development was not adversely affected by cryopreservation.

Hum Reprod. 1995 Dec;10(12):3332-7.

Minor congenital anomalies, major congenital malformations and development in children conceived from cryopreserved embryos.

Sutcliffe AG¹, D'Souza SW, Cadman J, Richards B, McKinlay IA, Lieberman B.

The incidence of major and minor malformations in the two groups were similar

RR for minor malformations 1.7

RR for major malformations 1.4

One case of Beckwith Wiedemann Syndrome

Genomic Imprinting Defects and ART

J Assist Reprod Genet (2007) 24:131–136
DOI 10.1007/s10815-006-9096-3

GENETICS

Silver-Russell syndrome in a girl born after *in vitro* fertilization: partial hypermethylation at the differentially methylated region of *PEG1/MEST*

Masayo Kagami · Toshiro Nagai · Maki Fukami ·
Kazuki Yamazawa · Tsutomu Ogata

Pediatr Dev Pathol. 2008 Jul-Aug;11(4):329-31. doi: 10.2350/08-04-0458.1.

Silver-Russell syndrome following in vitro fertilization.

Douzqou S, Mingarelli R, Tarani L, De Crescenzo A, Riccio A.

Acta Paediatr. 2005 Aug;94(8):1163-5.

Increased risk of Silver-Russell syndrome after in vitro fertilization?

Svensson J, Björnståhl A, Ivarsson SA.

Am. J. Hum. Genet. 72:218–219, 2003

Another Case of Imprinting Defect in a Girl with Angelman Syndrome Who Was Conceived by Intracytoplasmic Sperm Injection

Am. J. Hum.

Report

Intracytoplasmic Sperm Injection May Increase the Risk of Imprinting Defects

Gerald F. Cox,^{1,2,*} Joachim Bürger,^{3,*} Va Lip,¹ Ulrike A. Mau,⁴ Karl Sperling and Bernhard Horsthemke⁵

Beckwith-Wiedemann syndrome

Most common overgrowth disorder

Neonatal macrosomia

Macroglossia

Abdominal wall defects

Hemihyperplasia

Capillary malformations

Embryonal tumors

Paradigm of overgrowth-cancer
predisposition syndromes

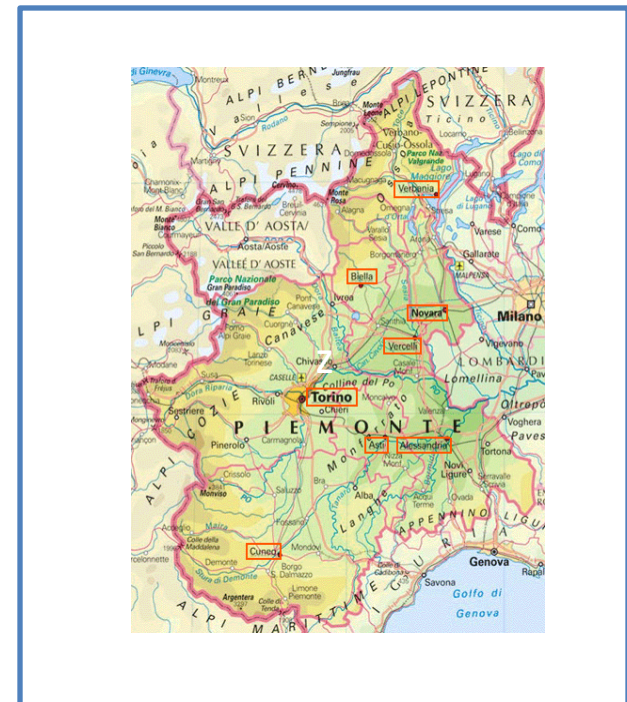
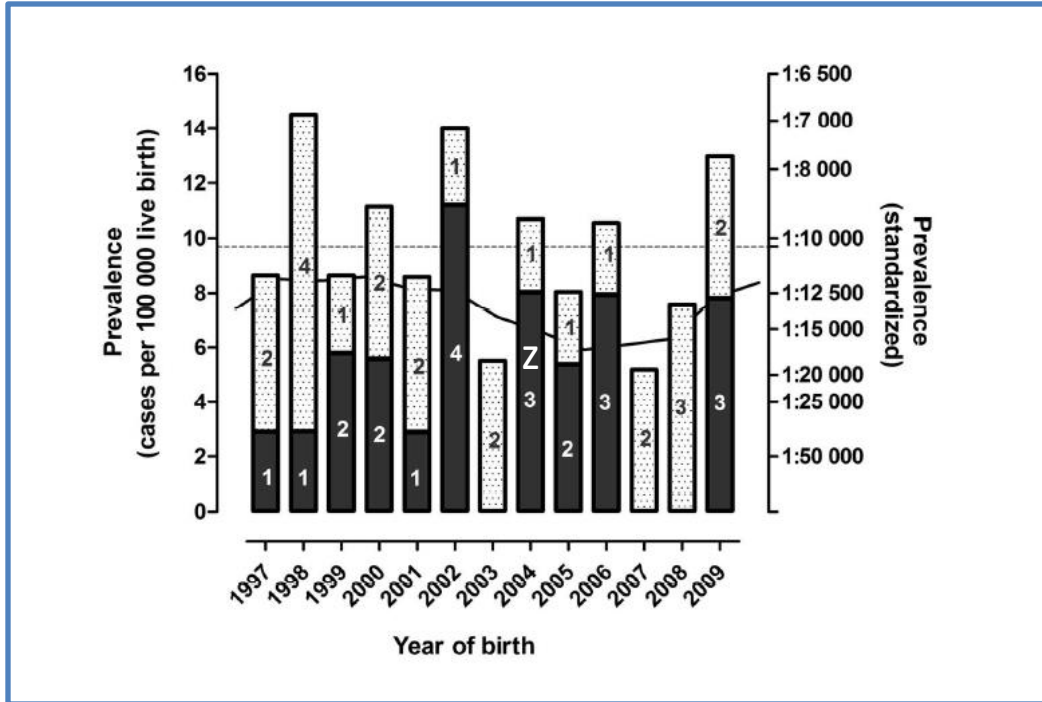
Beckwith and Wiedemann 1964



Epidemiology

Prevalence of Beckwith–Wiedemann Syndrome in North West of Italy

Alessandro Mussa,¹ Silvia Russo,² Agostina De Crescenzo,³ Nicoletta Chiesa,¹ Cristina Molinatto,¹ Angelo Selicorni,⁴ Lorenzo Richiardi,⁵ Lidia Larizza,^{2,6} Margherita Cirillo Silengo,¹ Andrea Riccio,^{3,7} and Giovanni Battista Ferrero^{4*}



Area	Years	Cases	Population	Prevalence
Italy (Piemont)	1996-2009	46	475,032	1:10,504

Neonatal features



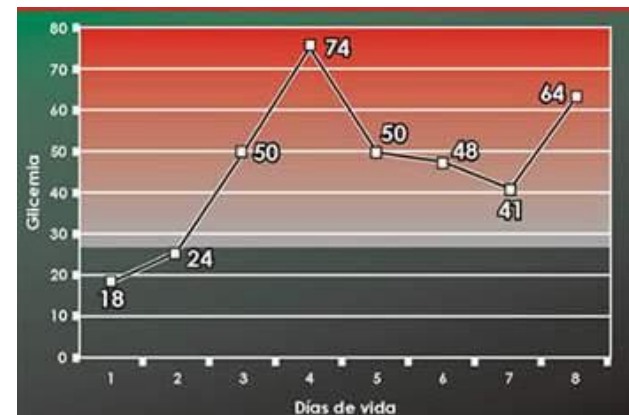
Macrosomia

Macroglossia

Abdominal wall defects

Hypoglicemia

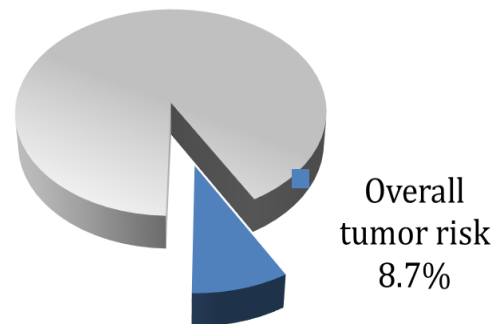
Severity of Hypoglicemia correlates with neurodevelopmental defects



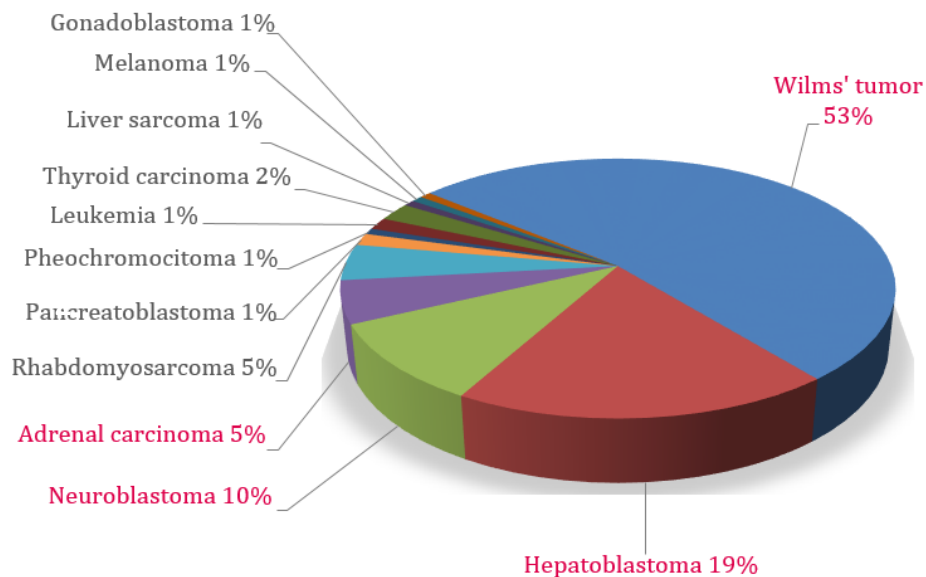
Tumor Risk in BWS

Approximately 8% of patients develop tumors.

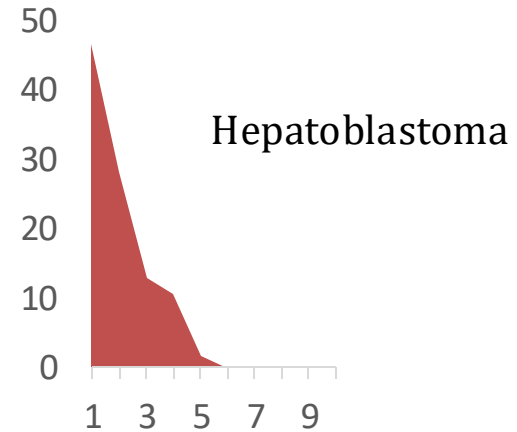
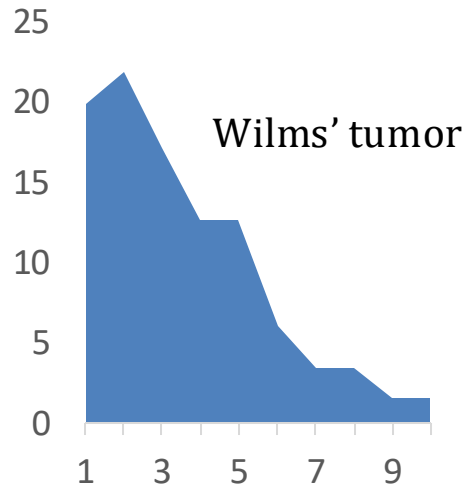
Mostly embryonal abdominal tumors



Wilms tumor	45%
Hepatoblastoma	20%
Adrenocortical carcinoma	7%
Rhabdomyosarcoma	6%
Neuroblastoma	5%
Pancreatoblastoma	3%
Renal cell carcinoma	2%
Pheochromocytoma	2%
Thyroid carcinoma	1%
Acute myeloid leukemia	1%
Acute lymphocytic leukemia	1%



Screening Oncologico

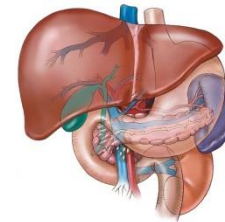


Ecografia addominale



Tumore di Wilms
ed Epatoblastoma

Dosaggio
 α -fetoproteina



Epatoblastoma

Associazione tra PMA e LOS

La LOS (Large-Offspring syndrome)

modello della Sindrome di Beckwith-Wiedemann

vitelli concepiti con PMA da vacche e tori normalmente fertili



Aberrant CpG methylation of the imprinting control region KvDMR1 detected in assisted reproductive technology-produced calves and pathogenesis of large offspring syndrome

Noboru Hori^{a,e,1}, Makoto Nagai^{a,1}, Muneyuki Hirayama^b, Tomokazu Hirai^c, Keisuke Matsuda^d, Michiko Hayashi^a, Takaichi Tanaka^e, Tadashi Ozawa^f, Shin-ichi Horike^{g,*}

ART and Beckwith Wiedemann Syndrome

TABLE 1 Epidemiology of BWS in Patients Conceived Naturally and Through ART in the Time Period 2005–2014

Conception	BWS	Non-BWS	Total Live Births	Risk (Per 1 000 000 Live Births)	Prevalence
ART	7	7877	7884	887.9	1:1126
Natural	31	371 957	371 988	83.3	1:12 000
Total	38	379 834	379 872	100.1	1:9997

10 – Fold Increased Risk of BWS in ART conceived children

Absolute Risk of 1:1000

ART and Beckwith Wiedemann Syndrome

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to couples considering ART-based reproductive choices: there is a clear increase in the relative risk of BWS, although the absolute risk for BWS is still small. As a final point, we highlight the need for awareness in the scientific community and in the general population of ART-associated health risks that should be taken into account in the complex cultural debate on human procreation, a major issue in modern public health politics.

Assisted Reproductive Technologies and Risk of Beckwith-Wiedemann Syndrome

Alessandro Mussa, MD, PhD,^{a,b} Cristina Molinatto, MD,^a Flavia Cerrato, PhD,^c Orazio Palumbo, PhD,^d Massimo Carella, PhD,^d Giuseppina Baldassarre, MD,^a Diana Carli, MD,^a Clementina Peris, MD,^e Andrea Riccio, MD, PhD,^e Giovanni Battista Ferrero, MD, PhD^a

BWS is an ART Associated Health Risk

birth even without macroglossia. Also of interest, although prematurity has been connected with BWS and is more represented in the IC2-LoM group,⁵² we detected no differences in gestational age at birth between ART and non-ART patients with BWS. As in many other studies, the IVF protocols were investigated without identifying the consistency of culture media, the procreation technique, or to couples considering ART-based reproductive choices: there is a clear increase in the relative risk of BWS, although the absolute risk for BWS is still small. As a final point, we highlight the need for awareness in the scientific community and in the general population of ART-associated health risks that should be taken into account in the complex cultural debate on human procreation, a major issue in modern public health politics.

PEDIATRICS[®]

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Assisted Reproductive Technologies
and Risk of Beckwith-Wiedemann
Syndrome

Alessandro Mussa, MD, PhD,^{1,2} Cristina Molinatto, MD,³ Flavia Cerrato, PhD,⁴ Orazio Palumbo, PhD,⁵ Massimo Carella, PhD,⁶ Giuseppina Baldassarre, MD,⁷ Diana Carli, MD,⁸ Clementina Peris, MD,⁹ Andrea Riccio, MD, PhD,² Giovanni Battista Ferrero, MD, PhD¹

Genomic Imprinting

Monoallelic – paternal or maternal - Expression of a gene

Molecular bases of this phenomenon are epi-genetic:

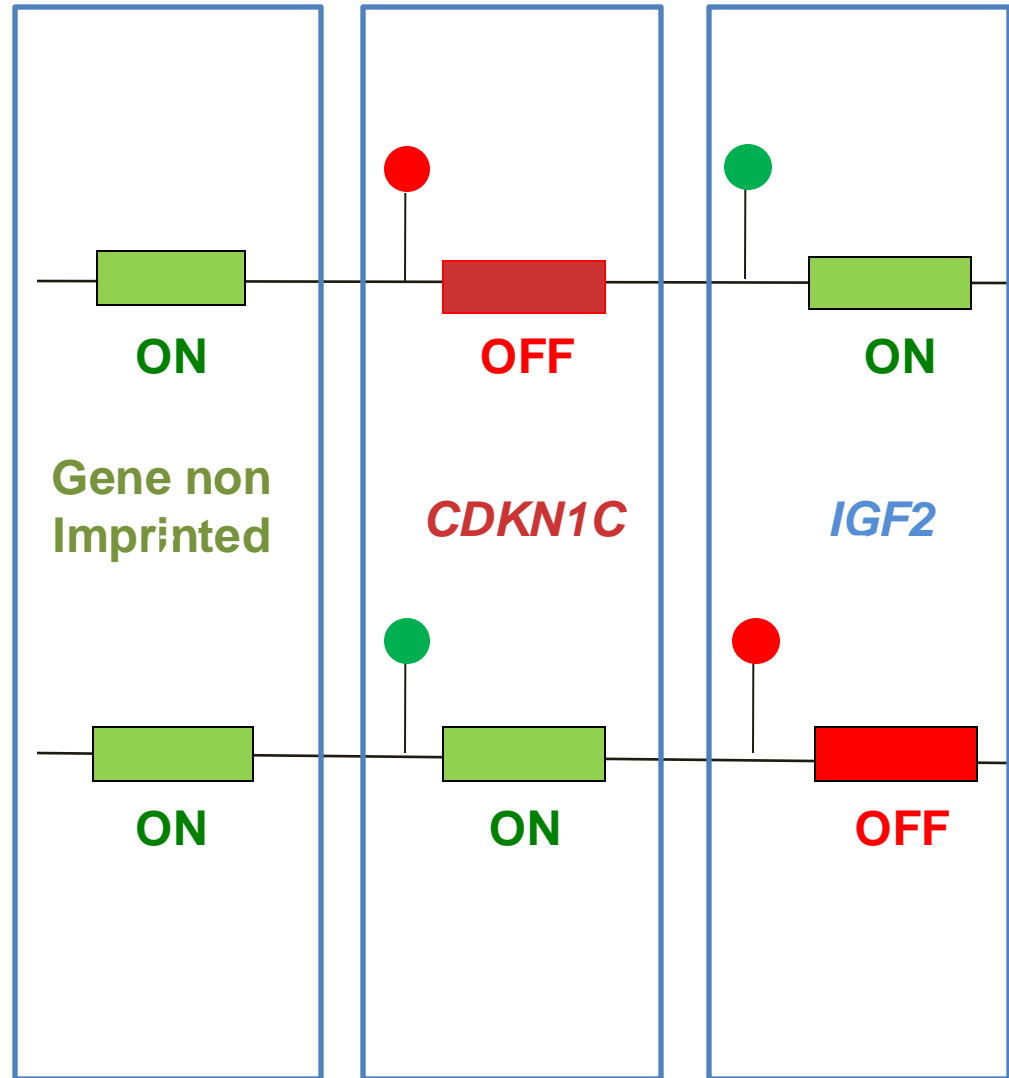
The different – male or female - parental origin of the allele is responsible for the differential expression in a tissue specific manner

This phenomenon is reversible during meiosis

Genomic Imprinting

Paternal Chromosome

Maternal Chromosome



Male and Female derived genomes have different biological features



Male Donkey

+



Female Horse

=

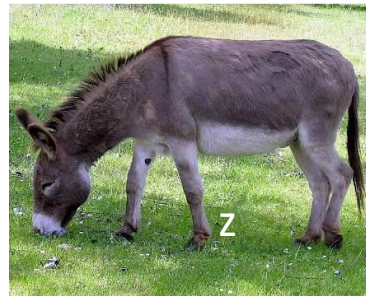


Mule



Male Horse

+



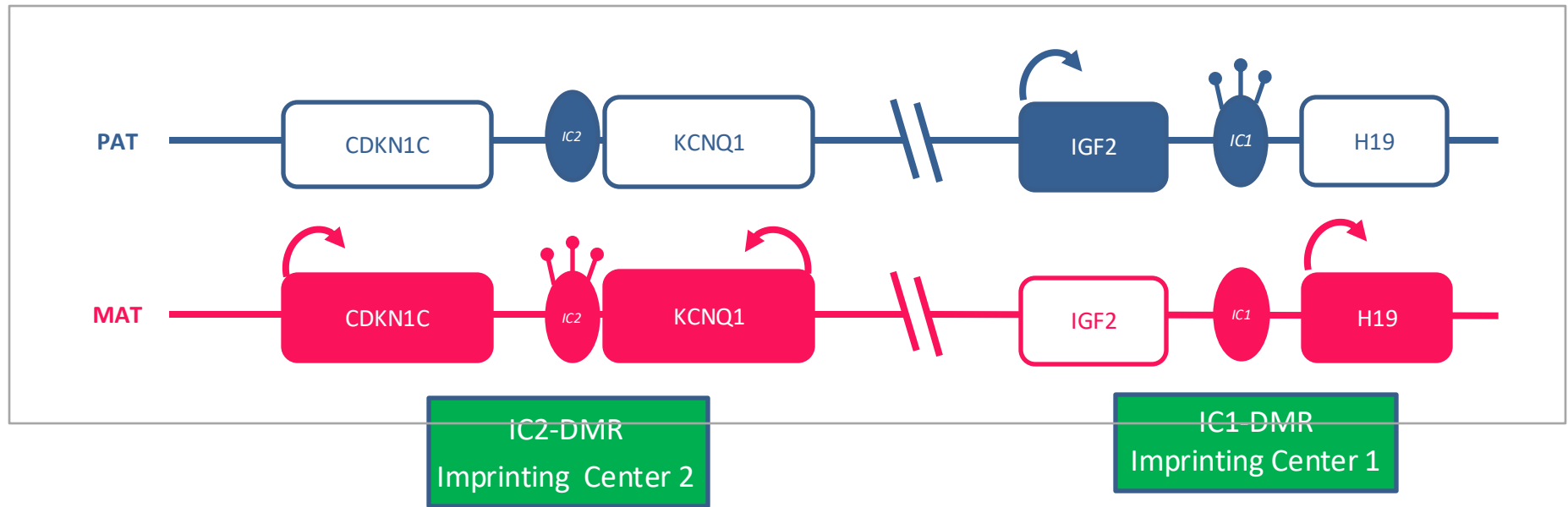
Female Donkey

=



Hinny

11p15 Chromosomal Region



CDKN1C Cyclin-dependent kinase inhibitor 1C

inhibitor of several
G1 cyclin/Cdk complexes and a
negative regulator
of cell proliferation.

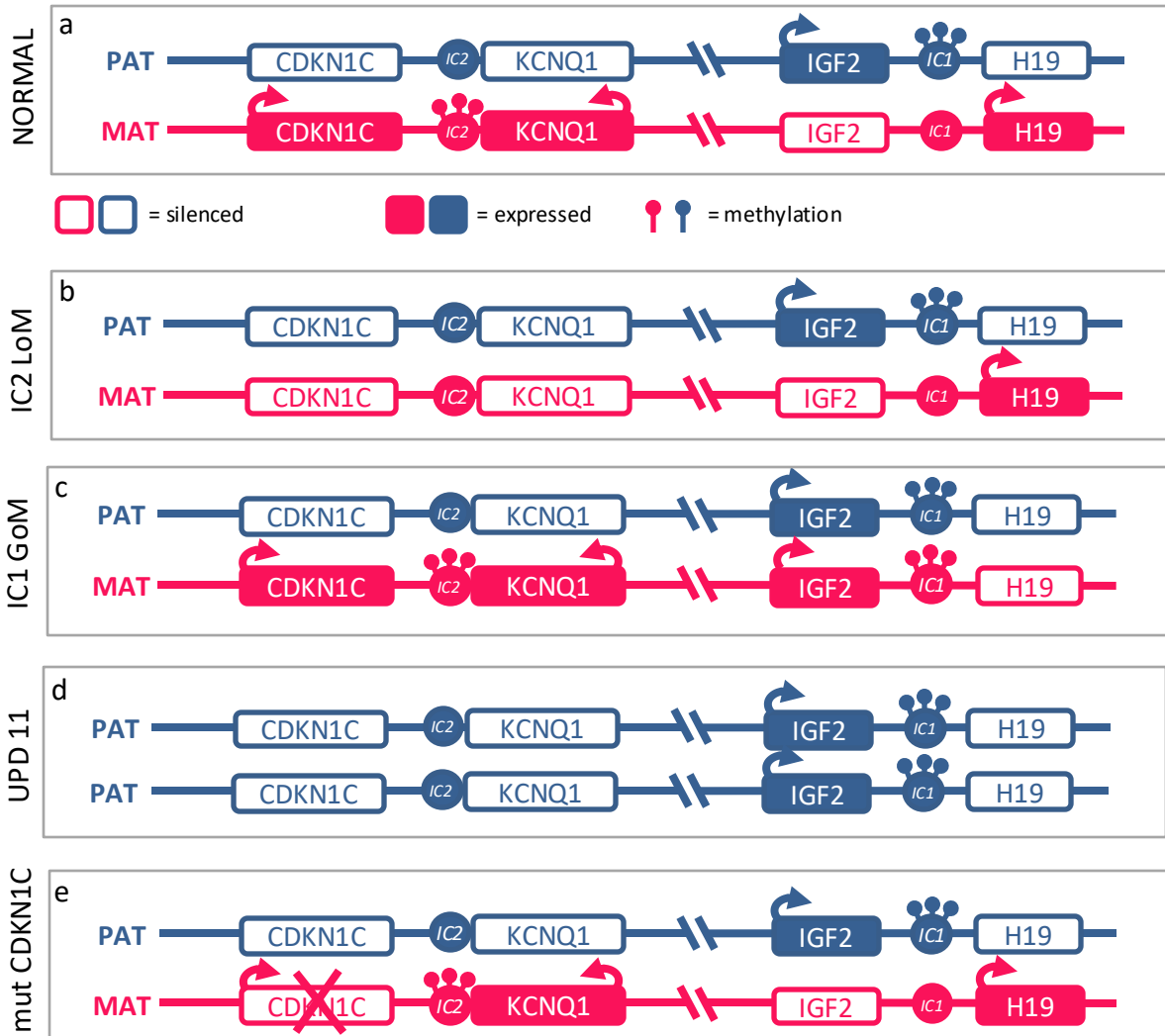
Insulin-like growth factor 2 IGF-2

Major fetal growth factor
insulin-like and
mitogenic activities

H19

a gene for a long noncoding RNA
negative regulator
of body weight and
cell proliferation.

Molecular defects in BWS: 11p15.5



Normal

60% **IC2 LoM**
Hypomethylation

10% **IC1 GOM**
Hypermethylation

25% **Paternal**
Uniparental Disomy

5% **CDKN1c LOF**
mutation

Epigenetica

The developmental biologist Conrad Waddington¹⁰⁷ first defined 'epigenetics' in the 1940s as "...the interactions of genes with their environment which bring the phenotype into being." Holliday and Pugh¹⁰⁸ proposed in 1975 that covalent chemical DNA modifications, including methylation of cytosine-guanine (CpG) dinucleotides, were the molecular mechanisms behind Conrad's hypothesis. The further revelations that X inactivation in mammals and genomic imprinting are regulated by epigenetic mechanisms highlighted the heritable nature of epigenetic gene-regulation mechanisms^{109,110}. Therefore, in the 1990s, epigenetics was described as the study of changes in gene expression that occur not by changing the DNA sequence, but by modifying DNA methylation and remodelling chromatin¹¹¹.

The genomics revolution inspired the investigation of global, rather than local, gene analyses, and the term 'epigenomics' was coined as the study of the "...effects of chromatin structure, including the higher order of chromatin folding and attachment to the nuclear matrix, packaging of DNA around nucleosomes, covalent modifications of histone tails (acetylation, methylation, phosphorylation, ubiquitination), and DNA methylation."¹¹² The resistance of some gene loci to methylation reprogramming during embryogenesis revealed the possibility that epigenetic modifications are inherited not only during somatic-cell division, but also in the subsequent generation³¹⁻³⁴.

Epigenetica

Waddington, 1940:

interazione di geni e ambiente che permette lo sviluppo del fenotipo

Holliday and Pugh, 1975:

modificazioni chimiche covalenti, compresa la metilazione dei dinucleotidi CpG

Inattivazione del cromosoma X e Imprinting genomico dimostrarono l'ereditarietà dei meccanismi epigenetici coinvolti nella regolazione dell'espressione genica

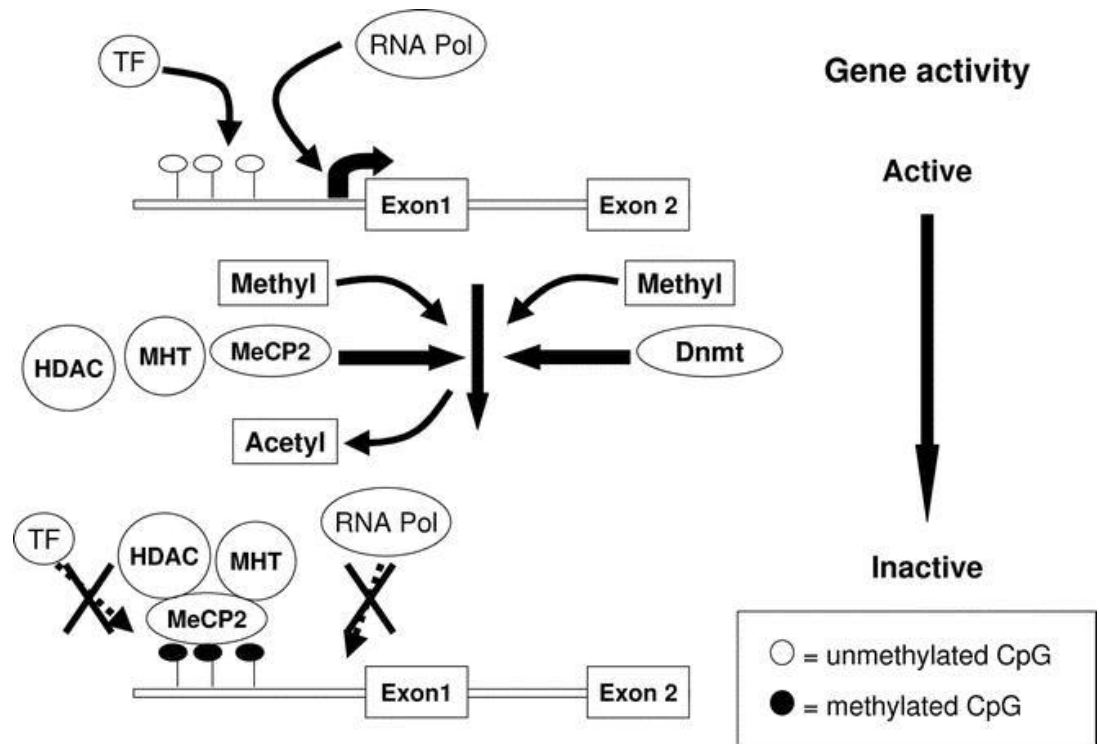
Epigenomica: ulteriore sviluppo del concetto

coinvolgimento della struttura cromatinica e le modificazioni covalenti degli istoni

DNA Methylation

DNA methylation

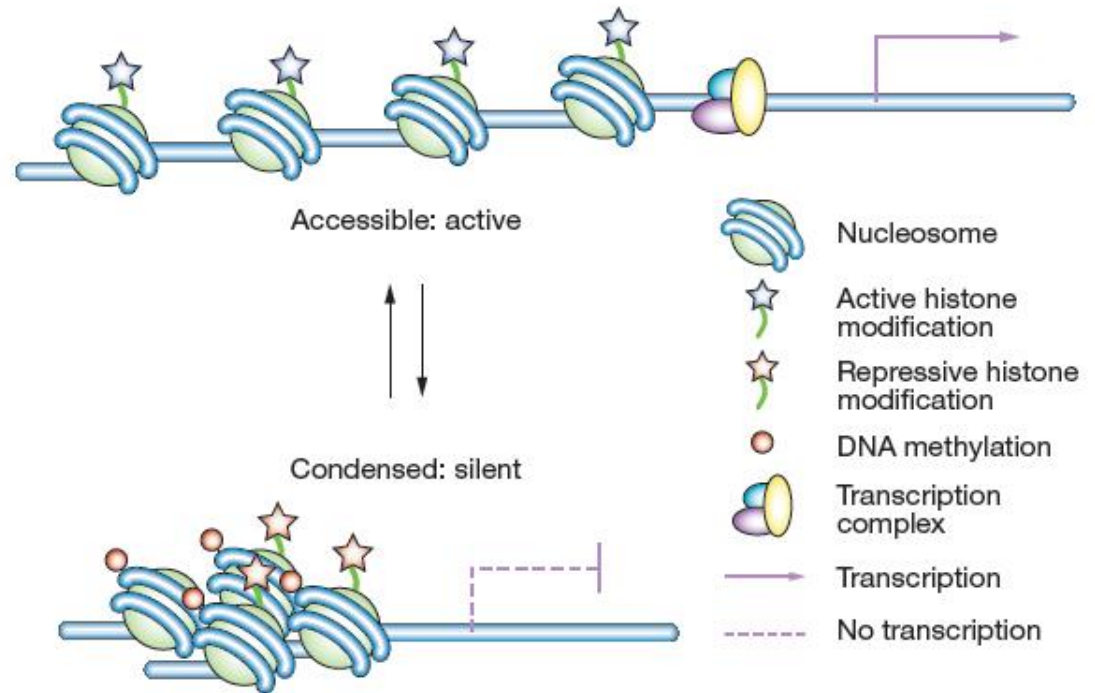
This refers to the enzymatic attachment of a methyl group (CH_3) to a cytosine base that is followed by a guanosine (the CpG dinucleotide). Methylation is believed to be associated with the silencing of genes. Disruption of methylation pharmacologically or genetically by inactivating the methyltransferase enzymes results in reactivation of gene expression at silent loci. Plausible mechanisms for methylation-associated silencing include one whereby binding of transcription factors is precluded, and one whereby methyl-group-binding proteins and associated protein complexes that remodel chromatin locally are recruited.



Histone Modifications

Histone modifications

DNA wraps around the core histones H2A, H2B, H3 and H4, forming the nucleosome. Histone tails protrude from this structure and act as potential binding sites for enzymes and proteins. Acetylation, by histone acetyltransferases, of lysine (K) residues present within the N-terminal tails of H3 and H4 correlates with an active chromatin state and gene expression; their deacetylation, carried out by histone deacetylases, is associated with



Developmental Plasticity



Apis mellifera

Larve identiche NUTRITE in modo differente

Api operaie = miele e polline

Ape regina = pappa reale

Induzione del fenotipo tramite meccanismi complessi
che regolano la metilazione

siRNA per Dnmt3 che modula l' epigenotipo

Nelle fasi precoci dello sviluppo avvengono modificazioni
Nell'espressione genica che risultano in fenotipi diversi
Indotte dall'ambiente - nutrienti

Dutch famine of 1944–1945: the Hongerwinter



da 1800 Kcal/ die a 400-800 kcal / die

Long term effects of the Dutch Famine



Molecular and Cellular Endocrinology 185 (2001) 93–98



Molecular and Cellular Endocrinology
www.elsevier.com/locate/mce

Effects of prenatal exposure to the Dutch famine on adult disease
in later life: an overview

Tessa J. Roseboom *, Jan H.P. van der Meulen, Anita C.J. Ravelli, Clive Osmond,
David J.P. Barker, Otto P. Bleker

Department of Clinical Epidemiology, Academic Medical Centre, Amsterdam, The Netherlands

Early onset of coronary artery disease after prenatal exposure to the
Dutch famine^{1–3}

*Rebecca C Painter, Susanne R de Rooij, Patrick M Bossuyt, Timothy A Simmers, Clive Osmond, David J Barker,
Otto P Bleker, and Tessa J Roseboom*

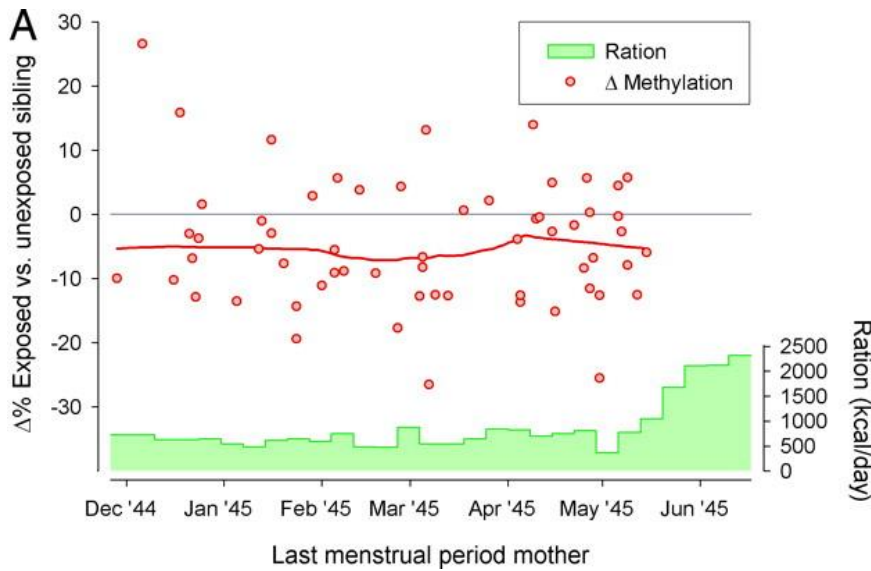
Obesita'

Anomalie metabolismo glicidico e lipidico

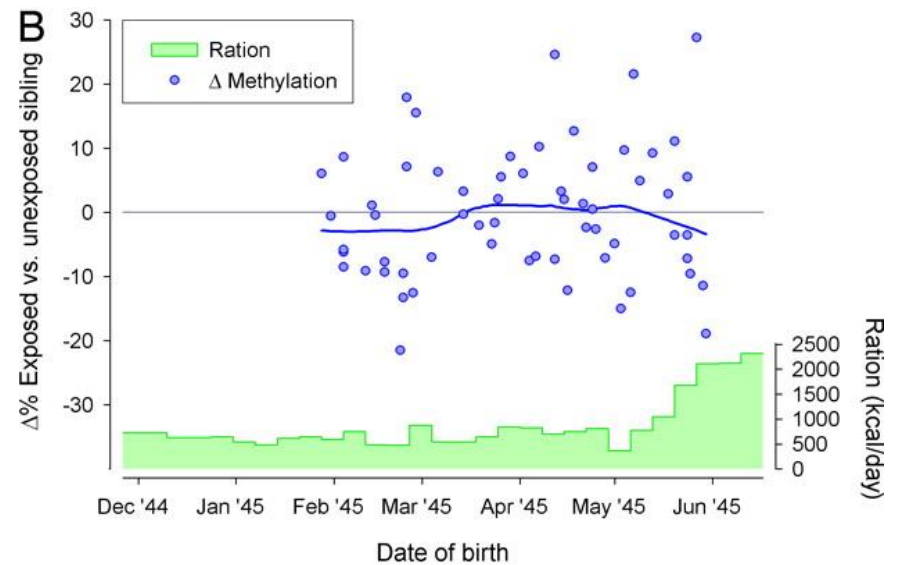
Disturbi dell'Umore

Epigenetic Anomalies correlates with Famine

A) Conceived during the Famine



B) Born during the famine



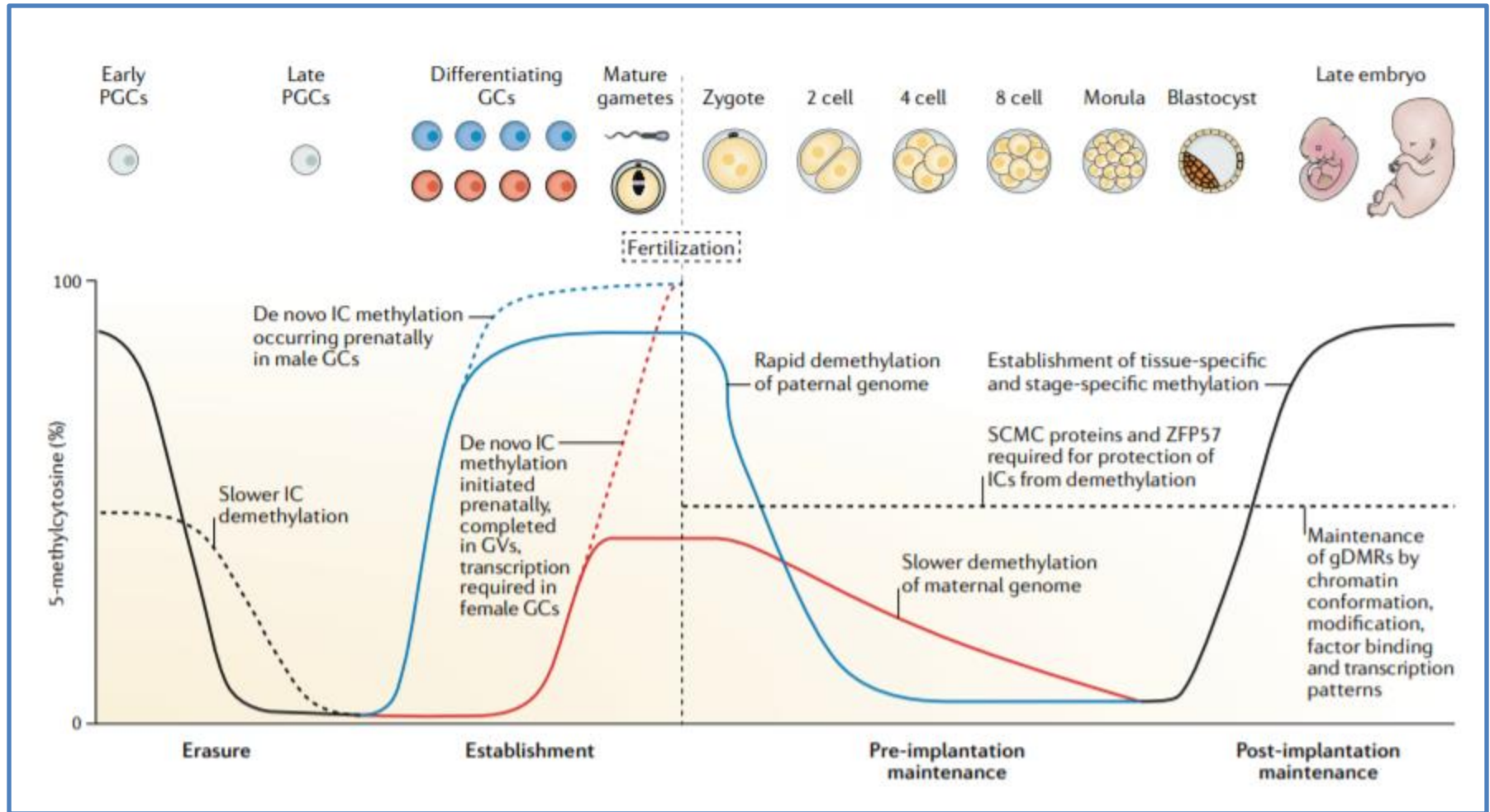
A) Periconceptual exposure:

Difference in methylation according to the mother's last menstrual period before conception of the famine-exposed individual.

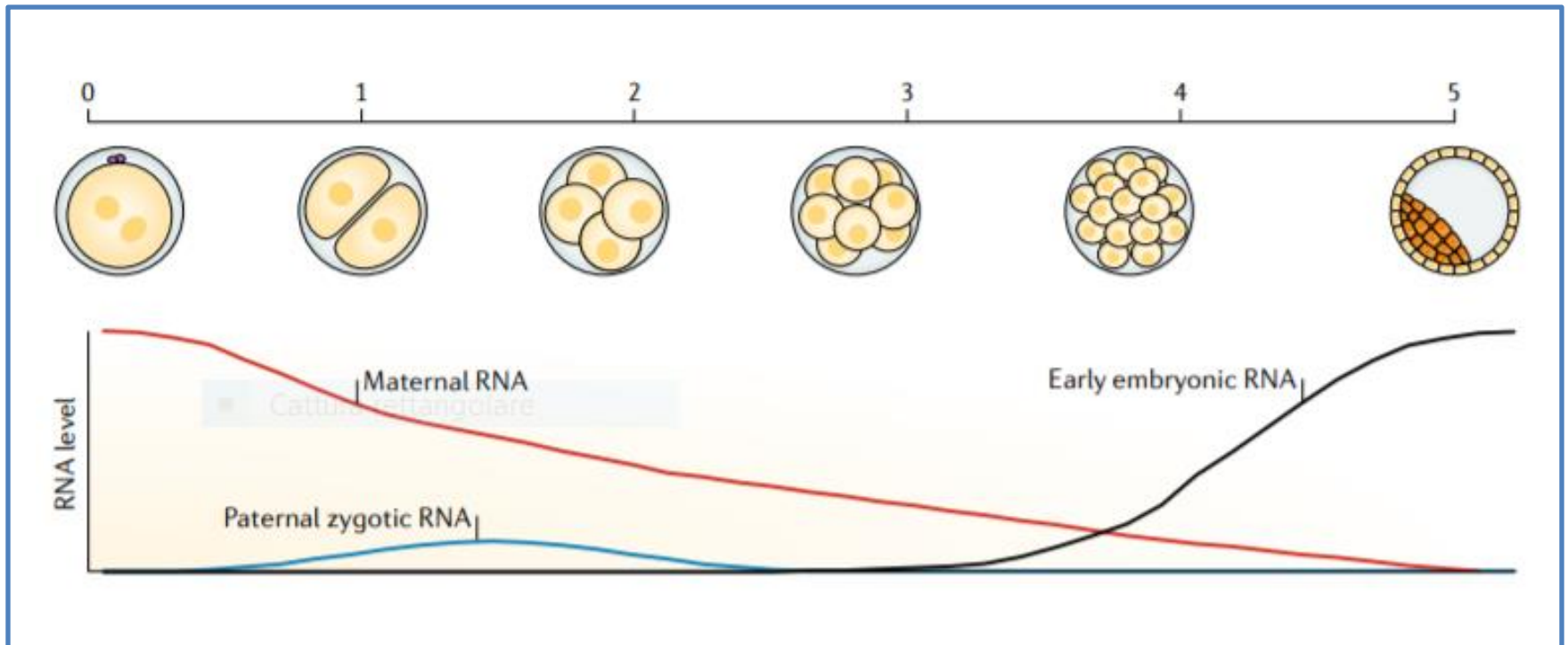
A) Exposure late in gestation:

Difference in methylation according to the date of birth of the famine-exposed individual. To describe the difference in methylation according to estimated conception and birth dates, a lowess curve (red or blue) is drawn. The average distributed rations (in kcal/day) between December 1944 and June 1945 are depicted in green.

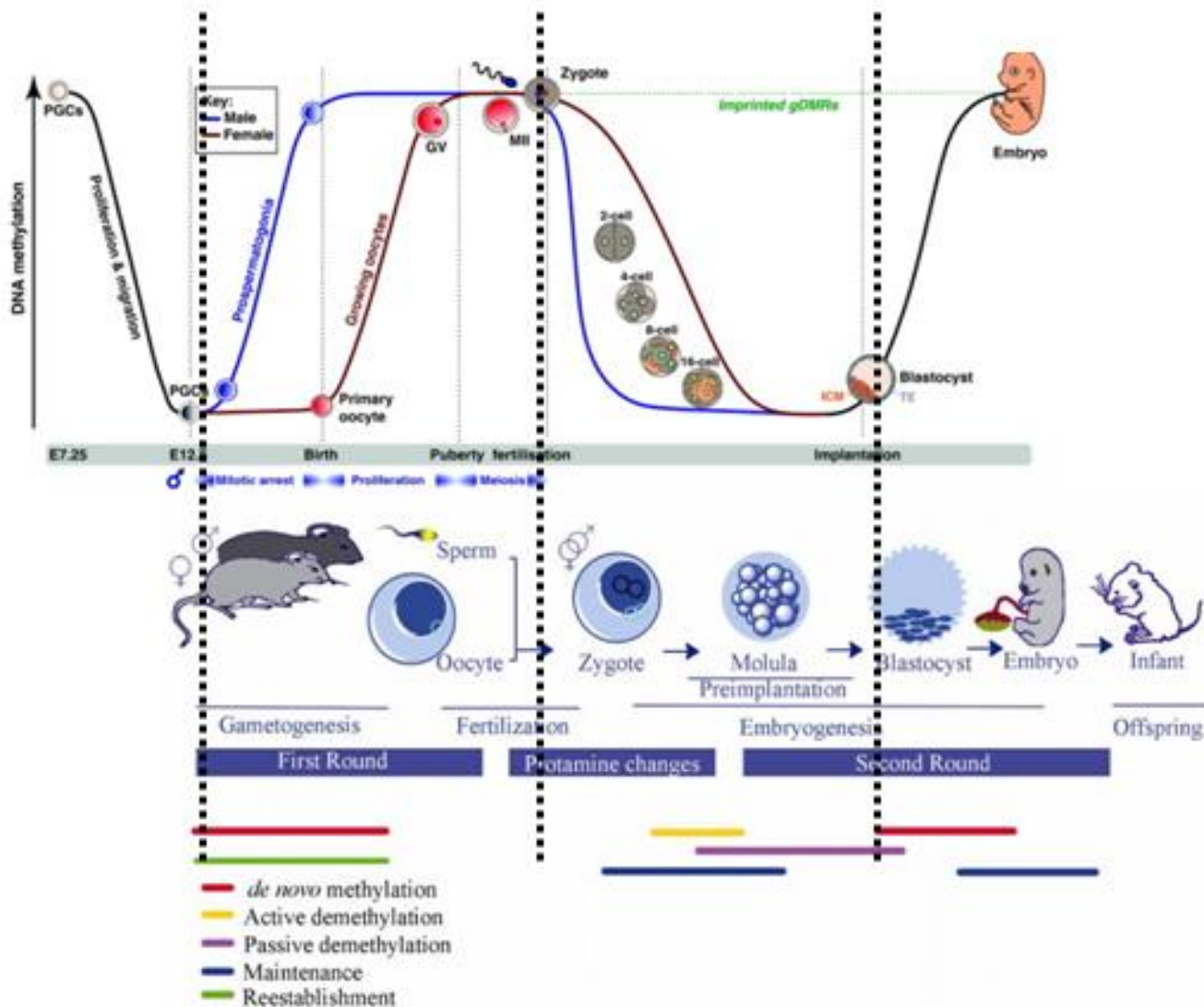
Epi-genotype Establishment



Epi-genotypic reprogramming and Zygote genome activation Establishment



Epi-genotype establishment and ART



Fetal Origin of Adult disease

Reviews of Reproduction (1997) 2, 105–112

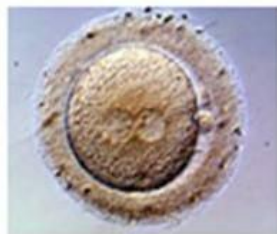
Fetal undernutrition and disease in later life

David J. P. Barker and Phillipa M. Clark

*MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital,
Southampton, SO16 6YD, UK*

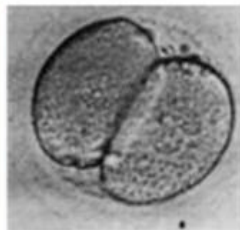
Recent findings suggest that coronary heart disease and stroke, and the associated conditions, hypertension and non-insulin dependent diabetes, originate through impaired growth and development during fetal life and infancy. These diseases may be consequences of 'programming', whereby a stimulus or insult at a critical, sensitive period of early life results in long-term changes in physiology or metabolism. Animal studies provide many examples of programming, which occurs because the systems and organs of the body mature during periods of rapid growth in fetal life and infancy. There are critical windows of time during which maturation must be achieved; and failure of maturation is largely irrecoverable.

Hypothesis for the Etiology of primary Epimutations



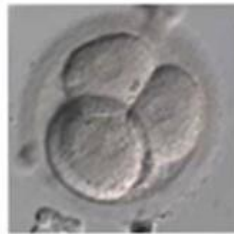
zygote

mouse D0
human D1



2-cell

D1
D1-2



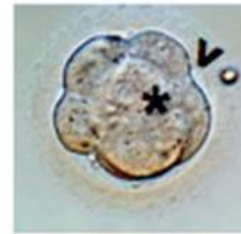
4-cell

D1-2
D2



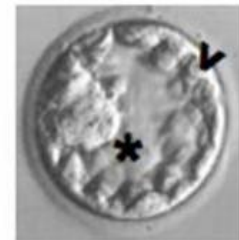
multi-cell

D2
D3



morula

D2-3
D3-4



blastocyst

D3-4
D5

* inner cells of the morula form the inner cell mass; ^ outer cells of the morula form the trophoblast

Images are courtesy of Dr. B. Behr and the Stanford University IVF clinic.

Maternal genetics factors

Protein expressed in oocyte

Ovum biologic features

Environmental factors pre and post conception

Perinatal Health risk associated with ART

LBW-ELBW

SGA

emorragia antepartum

disturbi ipertensivi della gravidanza

PROM

diabete gestazionale

gravidanze gemellari

Broncodisplasia
Enterite necrotizzante
Sepsi
Emorragia cerebrale
Paralisi cerebrale
Retinopatia

FIVET > ICSI

nell'ICSI la maggior parte delle donne è sana dal punto di vista riproduttivo, il che potrebbe dare un esito perinatale più favorevole.

Singletons – Adjusted Relative Risk

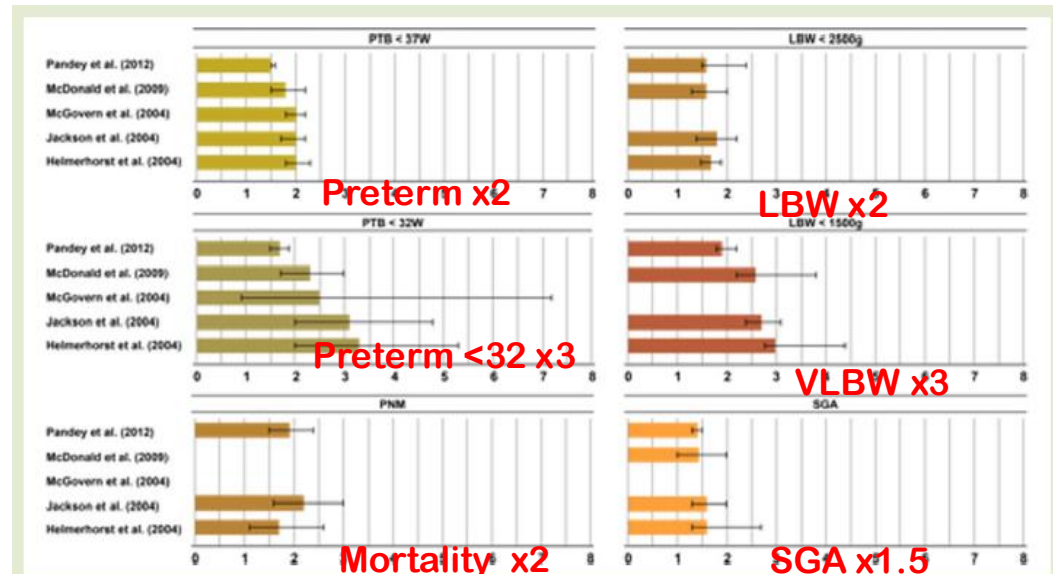
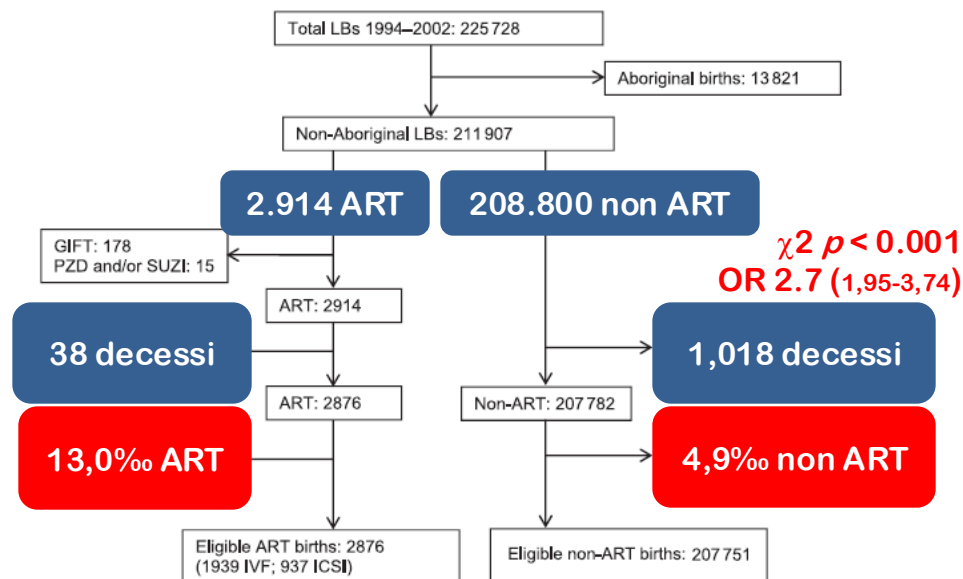


Figure 2 Perinatal outcomes in singletons born after ART versus singletons born without ART. Outcomes are depicted as bars showing the adjusted risks (x-axes) with 95% CI (error bars). PTB, preterm birth; LBW, low birthweight; SGA, small for gestational age; PNM, perinatal mortality.

Perinatal Death risk associated with ART

Phys. = 4,9 / 1000
ART = 13 / 1000



Mortalità IVF/ICSI vs concepimento spontaneo

Hansen et al. 2009	OR 1.8 (0.4–8.8)
Kallen et al. 2005	OR 1.13 (0.90–1.43)
Klemetti et al. 2006	IVF, 9.0 per 1,000; SC, 4.1 per 1,000
Koivurova et al. 2003	IVF 13.1 per 1,000 vs 5.2/1,000
Pinborg et al. 2003	IVF/ICSI 3.7 per 1,000; SC, 2.0 per 1,000

	ART	Non-ART
Neonatale	10,6‰	2,7‰
1-6 mesi	1,0‰	0,9‰
6-12 mesi	-	0,3‰
12 mesi -7 anni	1,3‰	1,0‰

Cancer risk and ART

Table 2. Observed vs. Expected Cancers for All Cancers and According to Cancer Type.*

Cancer Type and ICCC-3 Group†	No. of Person-Years of Follow-up	No. of Observed Cancers‡	No. of Expected Cancers	Standardized Incidence Ratio (95% CI)
All cancers: groups I to X	700,705	108	109.7	0.98 (0.81–1.19)
Leukemia: group I	701,047	34	37.5	0.91 (0.63–1.27)
CNS tumors: group III	701,138	22	25.8	0.85 (0.54–1.29)
Neuroblastoma: group IV	701,165	9	10.2	0.88 (0.40–1.68)
Retinoblastoma: group V	701,193	<5	—	0.59 (0.12–1.73)
Renal tumors: group VI	701,162	8	8.5	0.94 (0.41–1.86)
Hepatic tumors: group VII	701,165	6	1.8	3.27 (1.20–7.12)§
Bone tumors and extraosseous sarcomas: groups VIII and IX	701,134	20	8.6	2.34 (1.43–3.61)¶
Osteosarcoma: group VIIla	701,206	<5	—	2.95 (0.61–8.62)
Ewing's sarcoma: groups VIIlc and IXd, divisions 1 and 2	701,202	<5	—	2.47 (0.67–6.32)
Rhabdomyosarcoma: group IXa	701,162	10	3.8	2.62 (1.26–4.82)§
Other sarcomas: groups VIIlb; VIIId; VIIle; IXb; IXc; IXd, divisions 3–11; and IXe	701,205	<5	—	1.42 (0.29–4.15)
Germ-cell tumors: group X	701,203	<5	—	0.56 (0.07–2.03)

There was no increase in the overall risk of cancer
Increased risk of hepatoblastoma and rhabdomyosarcoma were detected but with a small absolute risk

Results are reassuring.
The small but significant increased risk of hepatoblastoma detected was associated with low birthweight, a known risk factor for this tumour type. It should be emphasized that the absolute risks are very small.

Intellectual disability and ART

TABLE 2 Risk of ID in Children Who Were Conceived Using ART Compared With Non-ART-Conceived Children

	ART ID/ART ^a (Prevalence Proportion per 1000 LBs)	Non-ART ID/Non-ART (Prevalence Proportion per 1000 LBs)	RR (95% CI), Crude	RR (95% CI), Fully Adjusted ^b
Overall ID	60/2876 (20.9)	3491/207 751 (16.8)	1.24 (0.96–1.60)	1.58 (1.19–2.11)
Mild or moderate	52/2868 (18.1)	3261/207 521 (15.7)	1.15 (0.88–1.51)	1.51 (1.11–2.06)
Severe	8/2824 (2.8)	230/204 490 (1.1)	2.52 (1.25–5.09)	2.55 (1.19–5.44)
All singletons, wk	37/1909 (19.3)	3361/202 457 (16.6)	1.17 (0.85–1.61)	1.56 (1.10–2.21)
≥37	24/1665 (14.4)	2956/190 219 (15.5)	0.93 (0.62–1.38)	1.30 (0.85–1.99)
32–36	8/207 (38.6)	313/10915 (28.7)	1.35 (0.68–2.68)	1.62 (0.79–3.34)
<32	5/37 (135.1)	92/1316 (69.9)	1.93 (0.84–4.47)	2.50 (0.93–6.75)
All twins, wk	21/891 (23.6)	122/5133 (23.8)	0.99 (0.63–1.57)	1.47 (0.82–2.61)
≥37	6/353 (17.0)	51/2403 (21.2)	0.80 (0.35–1.85)	1.03 (0.35–3.04)
32–36	7/445 (15.7)	47/2325 (20.2)	0.78 (0.35–1.71)	1.06 (0.44–2.55)
<32	8/93 (86.0)	24/405 (59.3)	1.45 (0.67–3.13)	2.85 (1.22–6.65)
IVF	31/1939 (16.0)	3491/207 751 (16.8)	0.95 (0.67–1.35)	1.17 (0.79–1.73)
ICSI	29/937 (30.9)	3491/207 751 (16.8)	1.84 (1.29–2.64)	2.54 (1.69–3.83)
Fresh embryos	36/1757 (20.5)	3491/207 751 (16.8)	1.22 (0.88–1.69)	1.58 (1.11–2.26)
Frozen embryos	24/1119 (21.4)	3491/207 751 (16.8)	1.28 (0.86–1.90)	1.64 (1.09–2.48)



Comprehensive meta-analysis reveals association between multiple imprinting disorders and conception by assisted reproductive technology

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Abstract

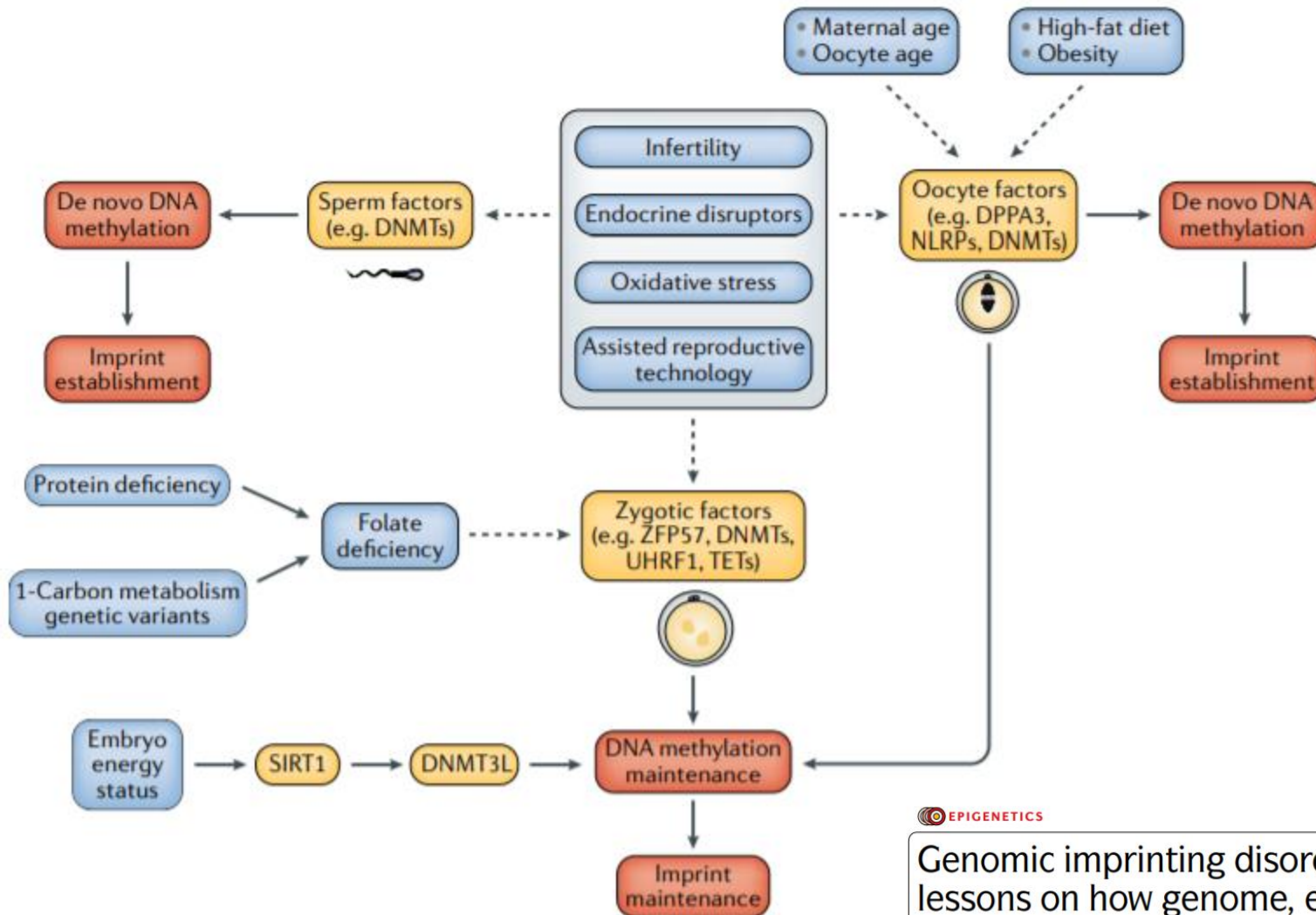
Purpose To determine whether a history of conception by assisted reproductive technology (ART) is associated with occurrence of one or more imprinting disorders of either maternal or paternal origin.

Methods We implemented a systematic review of scholarly literature followed by comprehensive meta-analysis to quantitatively synthesize data from reports relating to use of ART to occurrence of any imprinting disorder of humans, including Beckwith-Wiedemann (BWS), Angelman (AS), Prader-Willi (PWS), and Silver-Russell (SRS) syndromes, as well as transient neonatal diabetes mellitus (TNDB) and sporadic retinoblasoma (RB).

Results The systematic review identified 13 reports presenting unique data from 23 studies that related conception following ART to occurrence of imprinting disorders. Multiple studies of four disorder were identified, for which meta-analysis yielded the following summary estimates of associations with a history of ART: AS, summary odds ratio (sOR) = 4.7 (95% confidence interval (CI) 2.6–8.5, 4 studies); BWS, sOR = 5.8 (95% CI 3.1–11.1, 8 studies); PWS, sOR = 2.2 (95% CI 1.6–3.0, 6 studies); SRS, sOR = 11.3 (95% CI 4.5–28.5, 3 studies). Only one study reported on each of TNDB and RB.

Conclusion Published data reveal positive associations between history of ART conception and each of four imprinting disorders. Reasons for these associations warrant further investigation.

Genome – Epigenome – Environment

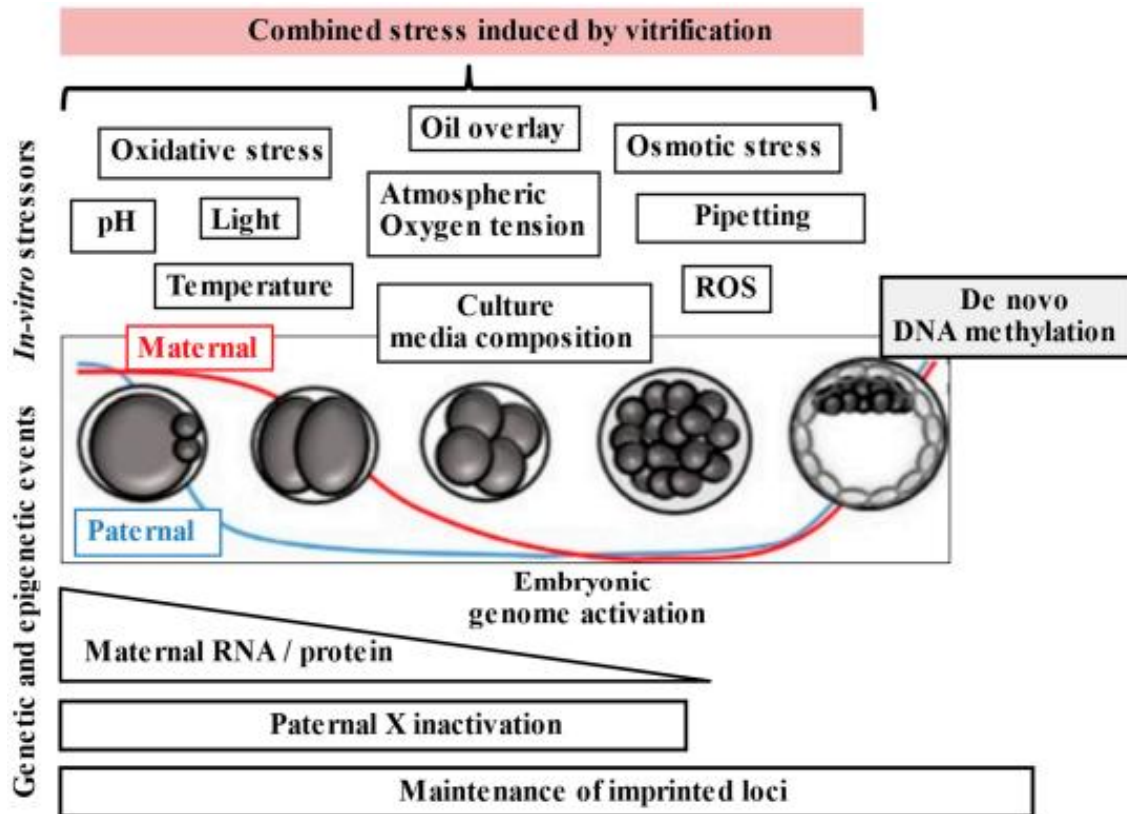


EPIGENETICS

Genomic imprinting disorders:
lessons on how genome, epigenome
and environment interact

David Monk¹, Deborah J. G. Mackay², Thomas Eggermann³, Eamonn R. Maher⁴
and Andrea Riccio^{5*}

Genome – Epigenome – Environment





FATEFUL IMPRINTS

A mysterious method of gene control, and the rare diseases it causes, is shedding its secrets

Studying these rare diseases “can open a new way to understand the imprinting phenomenon, to see how, in the beginning of the development of the embryo, the embryo answers to stimuli” that regulate how its genes behave, says Giovanni Battista Ferrero, a pediatrician at the University of Turin in Italy. “That is one of the next big challenges in science.”

Conclusions

ART is associated with Genomic Imprinting Defects

10 times RR of Beckwith Wiedemann Syndrome in ART conceived children

Open questions :

Correlation of Imprinting defects with the other Health risks

Role of techniques in respect of pre-existing pathological condition

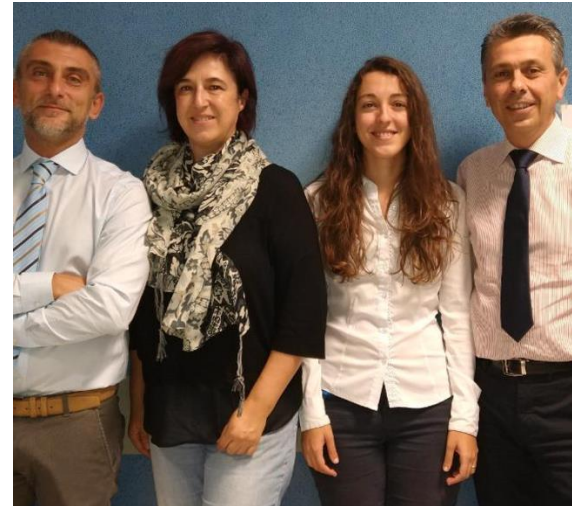
Long term effects in respect of the Developmental Origin of Health Diseases

Model for the study of Genome – Epigenome – Environment interactions

Ringraziamenti

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