AGGIORNAMENTO SU DIAGNOSI E TERAPIA DELLE EMOGLOBINOPATIE

Milano, 15 novembre 2024

Rischi di salute nei bambini concepiti con tecniche PMA

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DIPARTIMENTO DI ECCELLENZA
Ministero dell'Università e della Ricerca

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Orbassano (To)

UNIVERSITÀ DI TORINO

First report of Syndromic ART-children

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

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

Sutcliffe AG[1], D'Souza SW, Cadman J, Richards B, McKinlay IA, Lieberman B.

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

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* fertiliza partial hypermethylation at the differentially methylated region of *PEG1/MEST*

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

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

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

Silver-Russell syndrome following in vitro fertilization.

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

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 Horsthemke[5]

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

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

Svensson J, Björnståhl A, Ivarsson SA.

Beckwith-Wiedemann syndrome

Most common overgrowth disorder

Neonatal macrosomia

Macroglossia

Adbominal wall defects

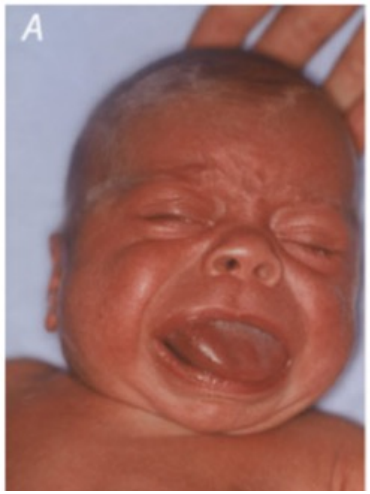
Hemihyperplasia

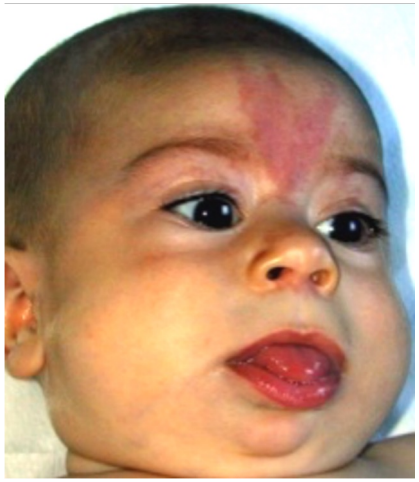
Capillary malformations

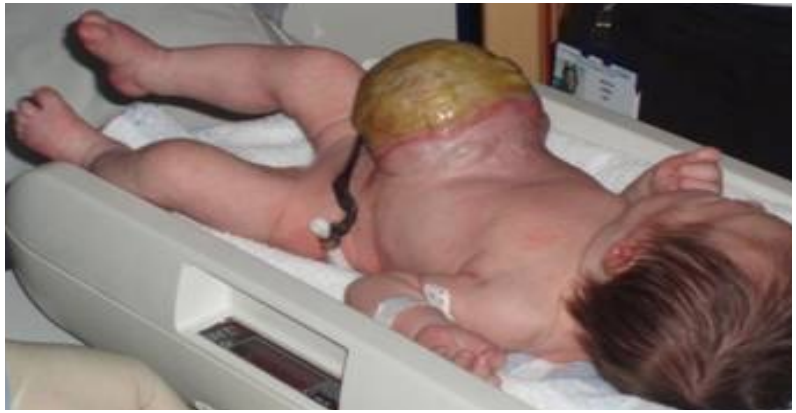
Embryonal tumors

Paradigm of overgrowth-cancer predisposition syndromes

Beckwith and Wiedemann 1964



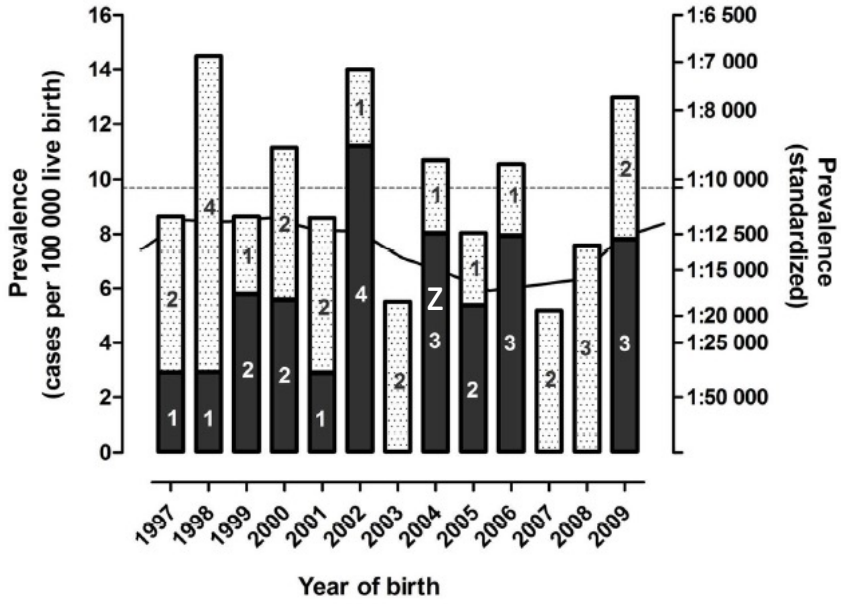


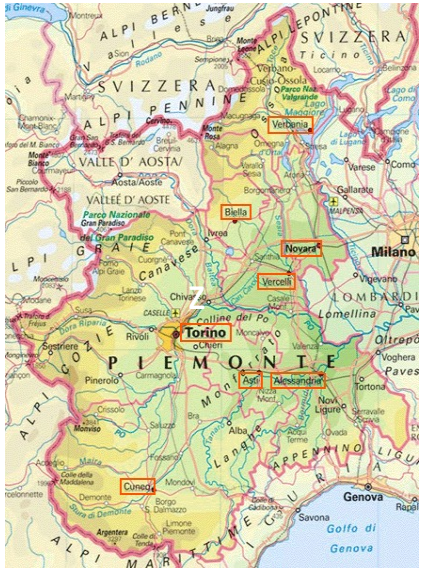


Epidemiology

Prevalence of Beckwith–Wiedemann Syndrome in North West of Italy

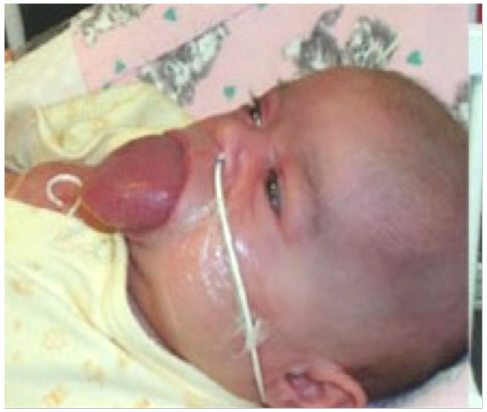
Alessandro Mussa,[1] Silvia Russo,[2] Agostina De Crescenzo,[3] Nicoletta Chiesa,[1] Cristina Molinatto,[1] Angelo Selicorni,[4] Lorenzo Richiardi,[5] Lidia Larizza,[2,6] Margherita Cirillo Silengo,[1] Andrea Riccio,[3,7] and Giovanni Battista Ferrero[1]*

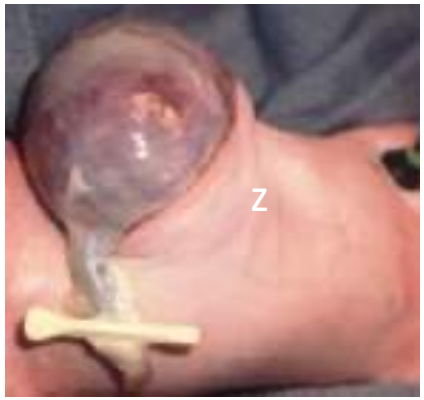




Area	Years	Cases	Population	Prevalence
Italy (Piemunt)	1996-2009	46	475,032	1:10,504

Neonatal features





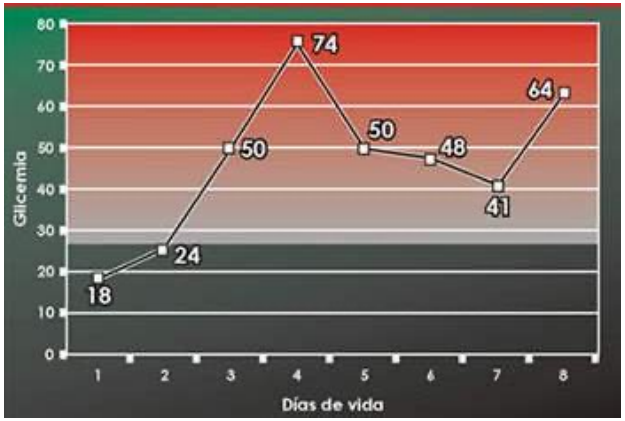
Macrosomia

Macroglossia

Abdominal wall defects

Hypoglicemia

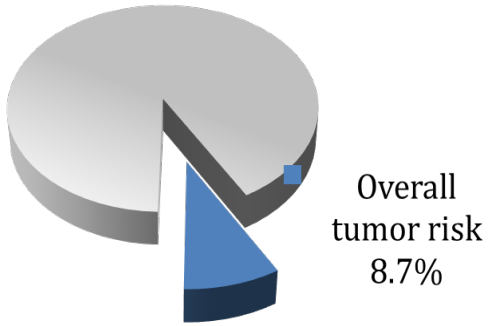
Severity of Hypoglicemia correlates with neurodevelopmental defects



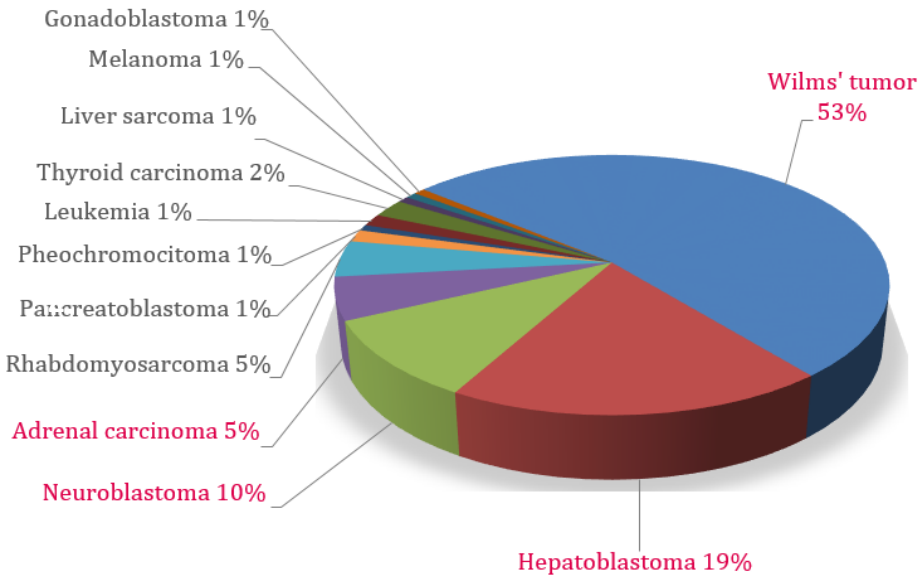
Tumor Risk in BWS

Approximately 8% of patients develop tumors.

Mostly embryonal abdominal tumors

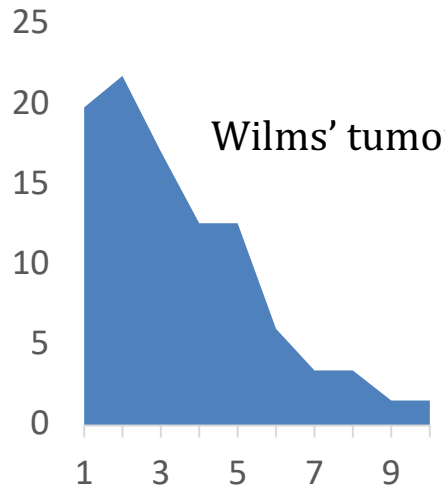


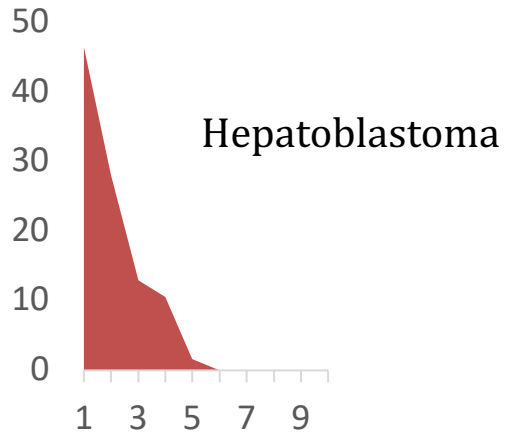
Wilms tumor	45%
Hepatoblastoma	20%
Adrenocortical carcinoma	7%
Rhabdomyosarcoma	6%
Neuroblastoma	5%
Pancreatoblastoma	3%
Renal cell carcinoma	2%
Pheochromocytoma	2%
Thyroid carcinoma	1%
Acute myeloid leukemia	1%
Acute lymphocytic leukemia	1%



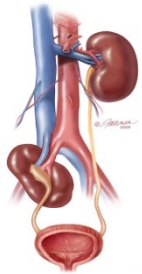
Lapunzina P. Risk of tumorigenesis in overgrowth syndromes: a comprehensive review. Am J Med Genet C . 2005 Aug 15;137C(1):53-71

Oncologic surveillance



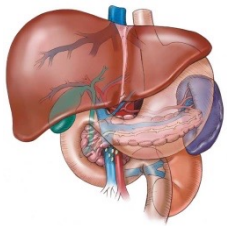


Ecografia addominale



Tumore di Wilms
ed Epatoblastoma

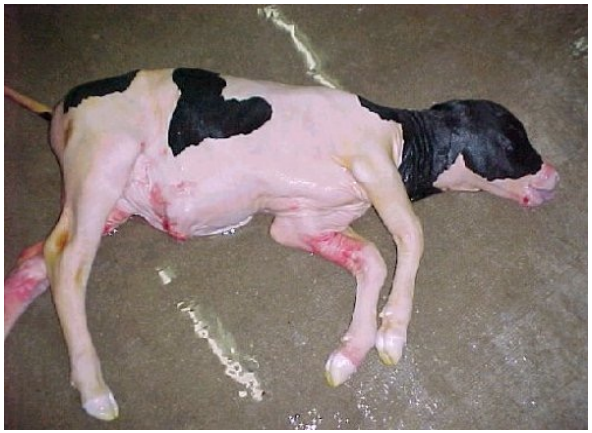
Dosaggio
α-fetoproteina



Epatoblastoma

ART and Large Offspring Syndrome (LOS)

LOS is a model of Beckwith-Wiedemann Syndrome
Observed in
ART conceived calves obtained from
gametes harvested from fertile cows and bulls



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,*]

BWS in ART Children

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 children

Absolute Risk of 1:1000

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,[c] Giovanni Battista Ferrero, MD, PhD[a]

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.

Genomic Imprinting

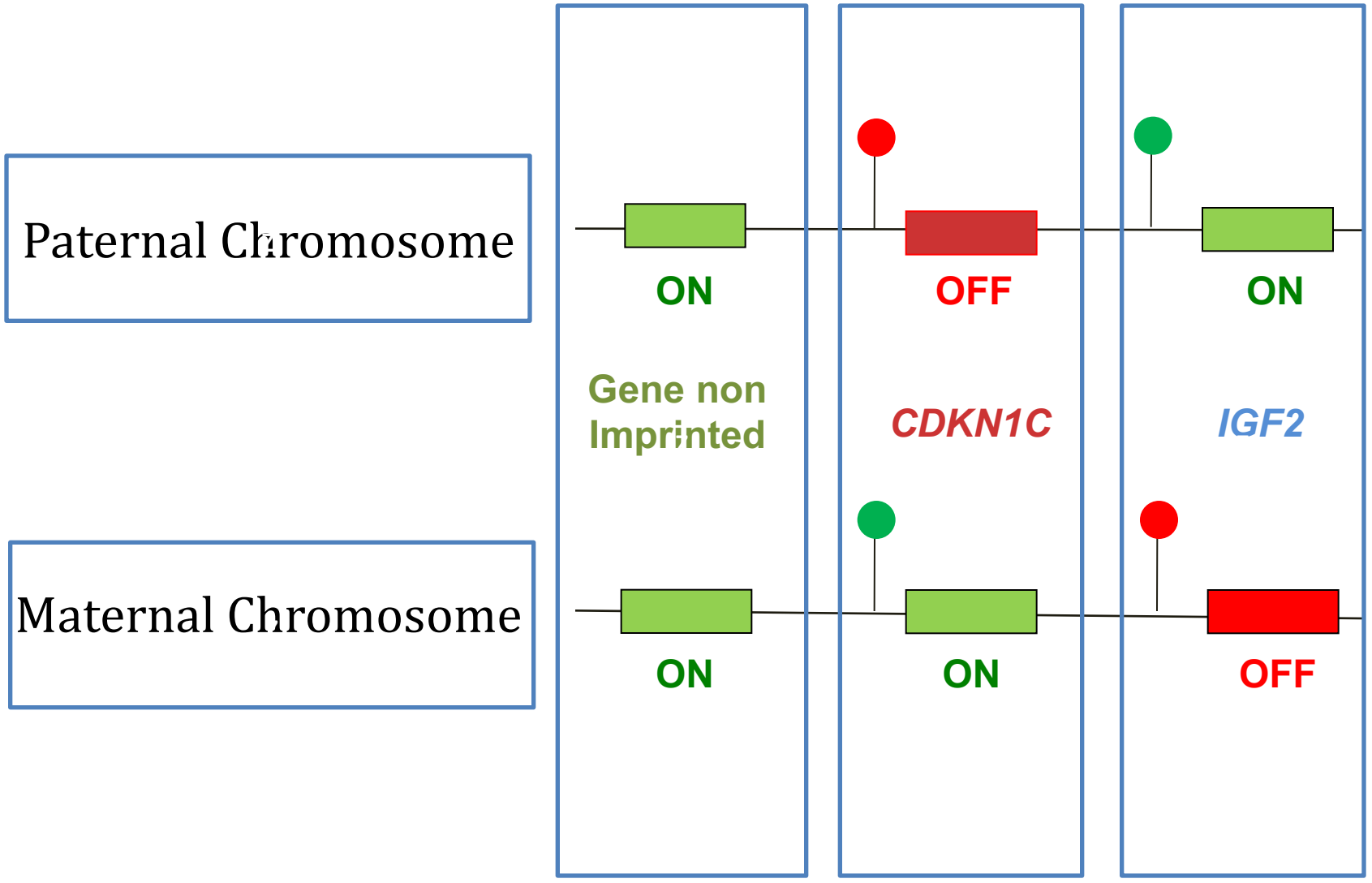
Monoallelic – paternal or maternal - Expression of a gene

Molecular bases of this phenomenon are epi-genetic:

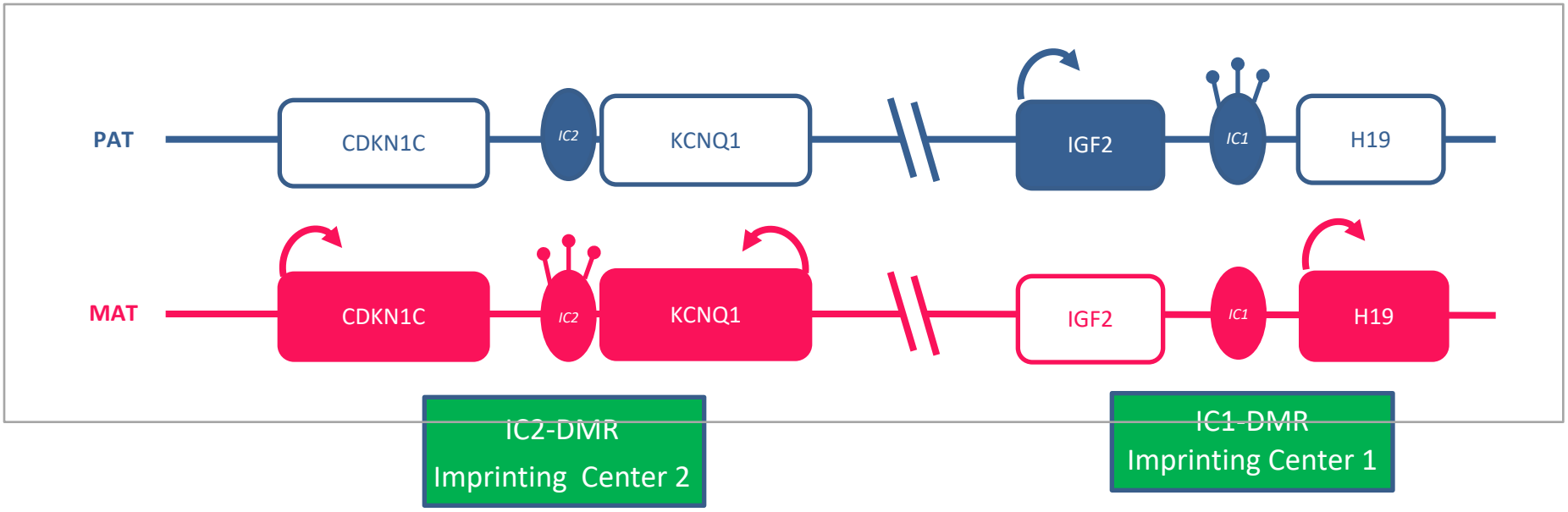
The different – male or female - parental origin
of the allele is responsible for the differential expression
in a tissue specific manner

This phenomenon is reversible during meiosis

Genomic Imprinting



11p15 Chromosomal Region



CDKN1C
Cyclin-dependent kinase inhibitor 1C

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

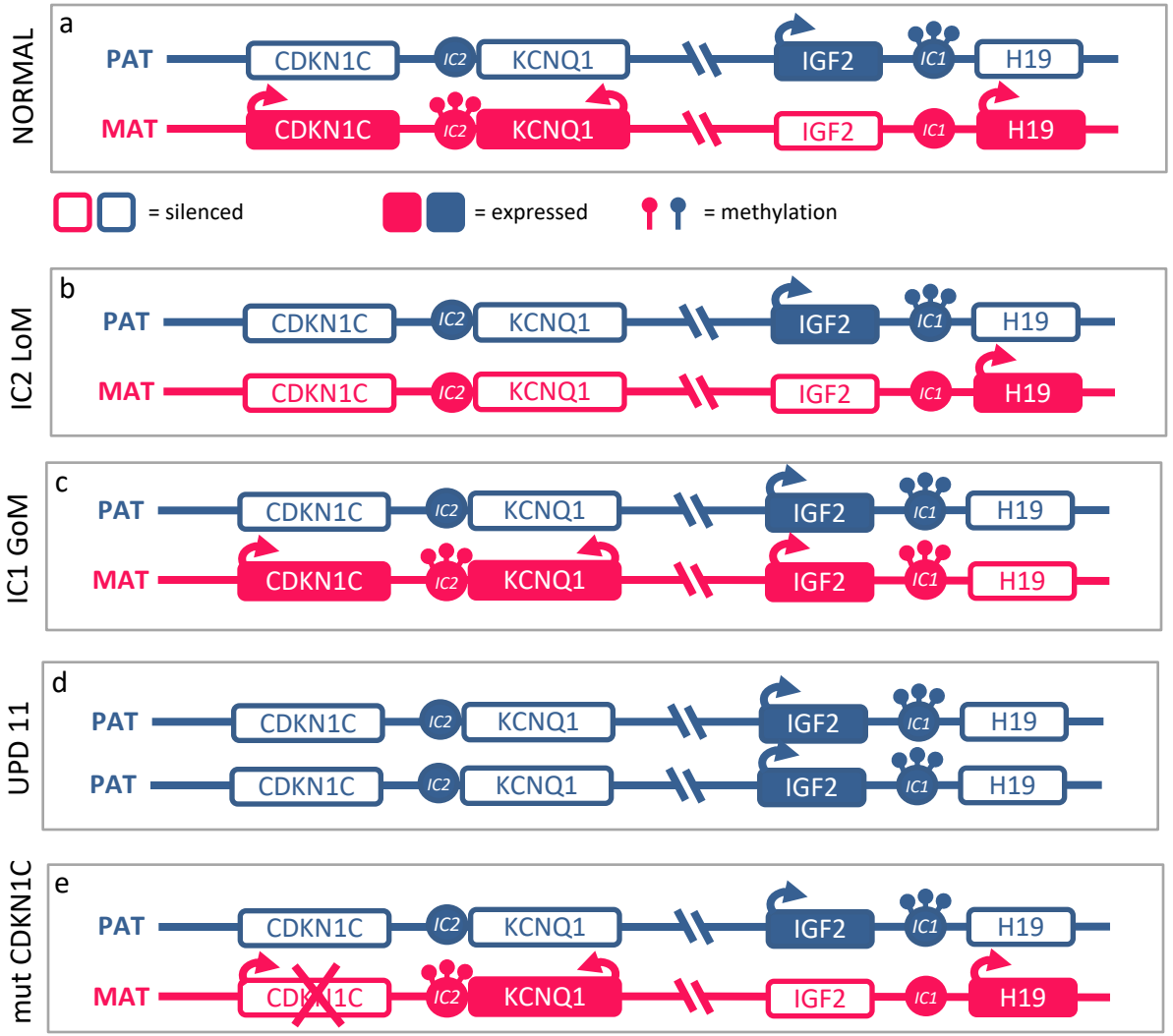
Insulin-like growth factor 2
IGF-2

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**

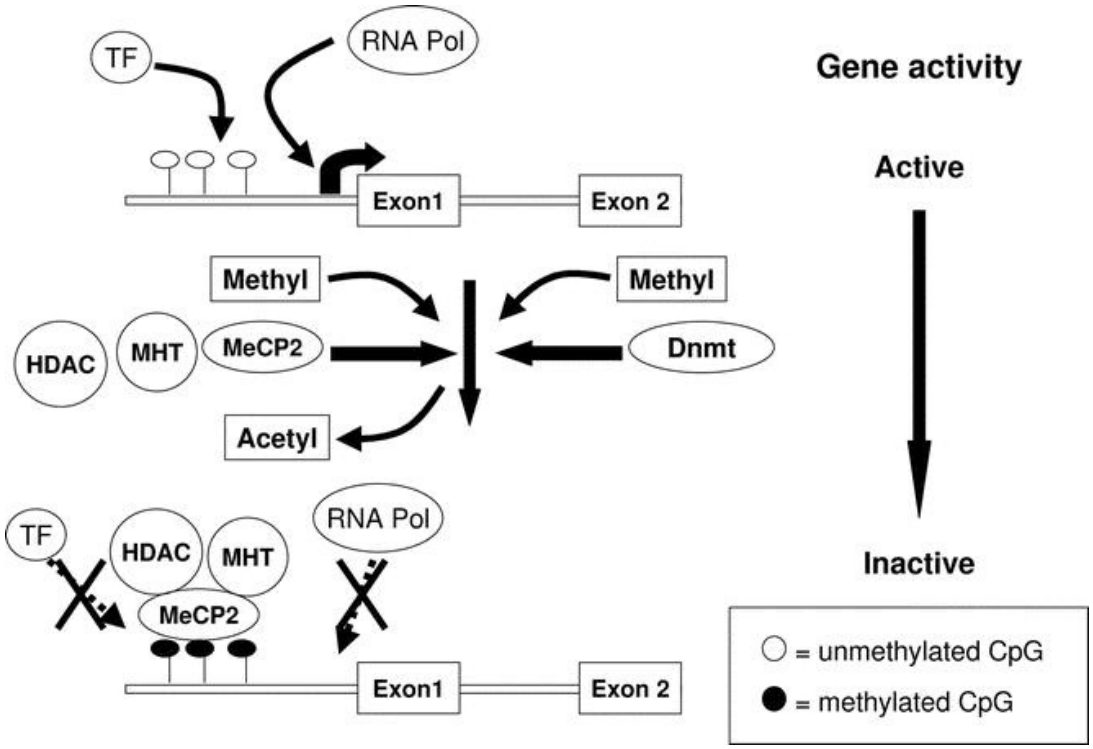
25% **Paternal Uniparental Disomy**

5% CDKN1c LOF mutation

Weksberg R et al.. Eur J Hum Genet. 2010;18:8-14
Mussa A et al. Prospettive in Pediatria, 2013,

DNA Methylation

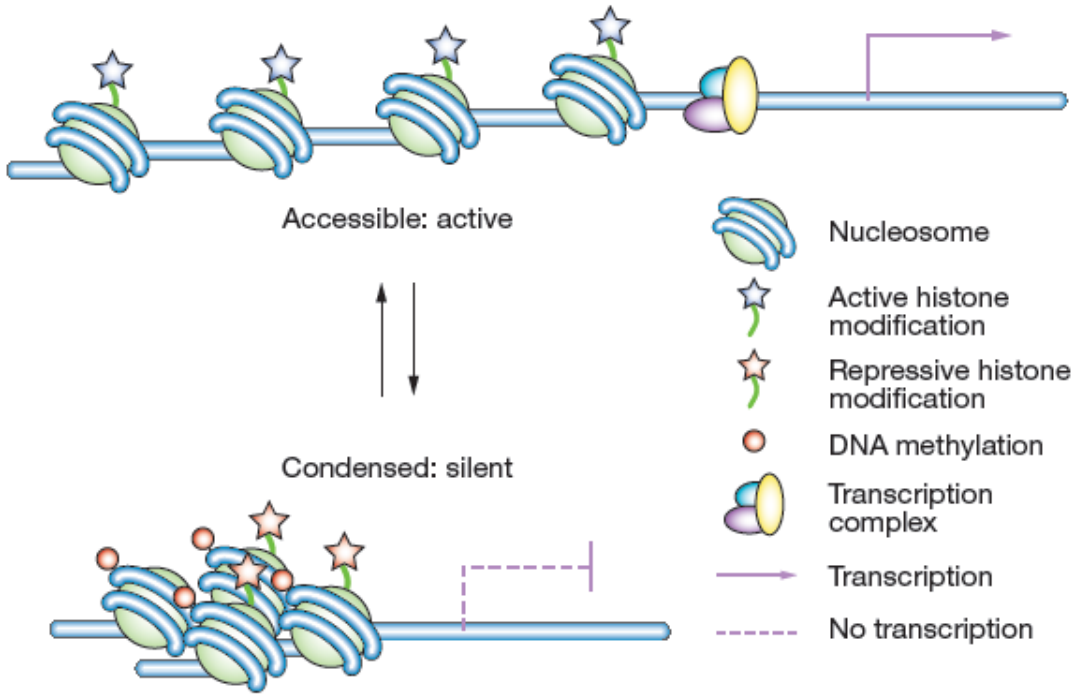
DNA methylation
This refers to the enzymatic attachment of a methyl group (CH_3) to a cytosine base that is followed by a guanosine (the CpG dinucleotide). Methylation is believed to be associated with the silencing of genes. Disruption of methylation pharmacologically or genetically by inactivating 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

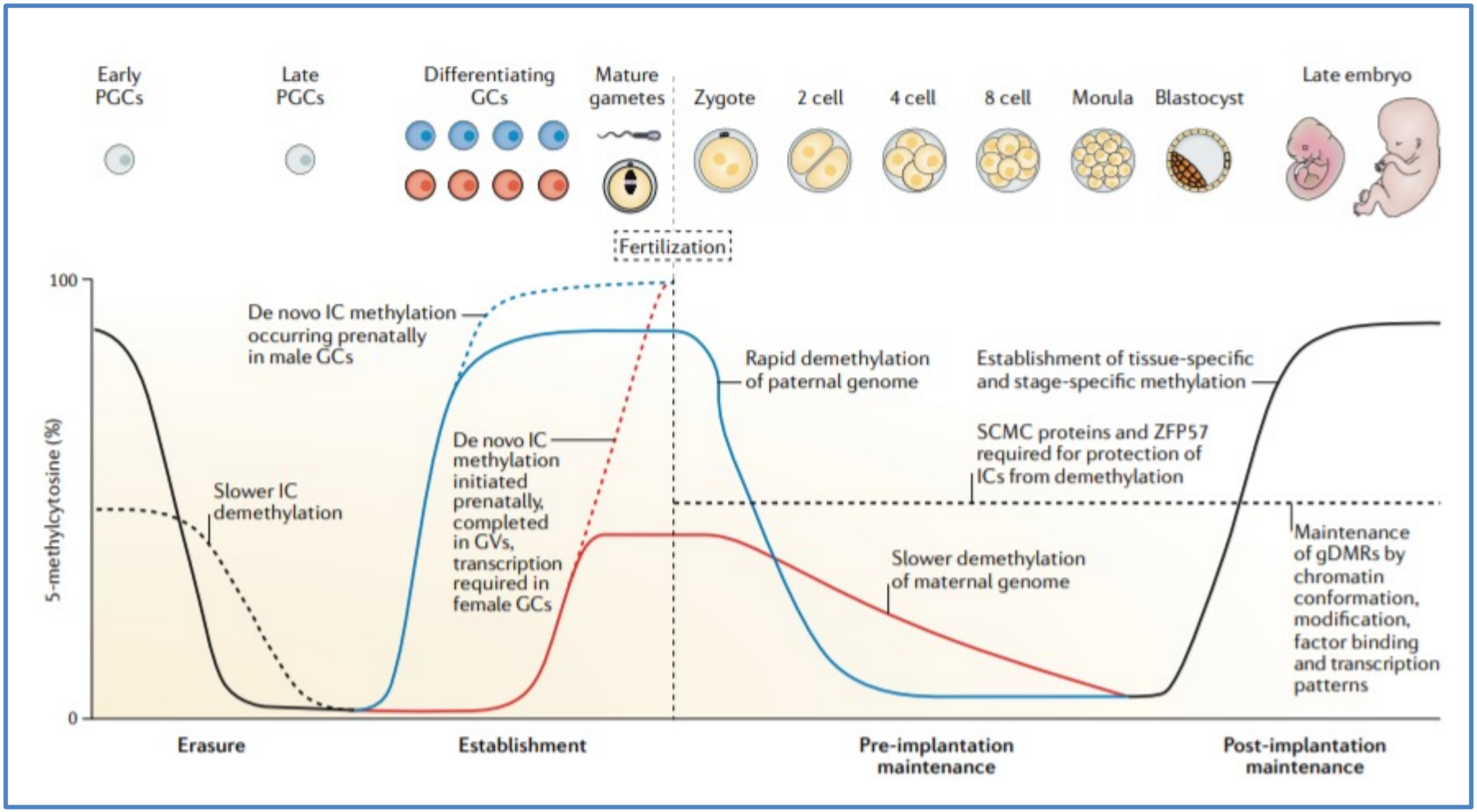
Api operaie = miele e polline
Ape regina = pappa reale

Induzione del fenotipo tramite meccanismi complessi che regolano la metilazione

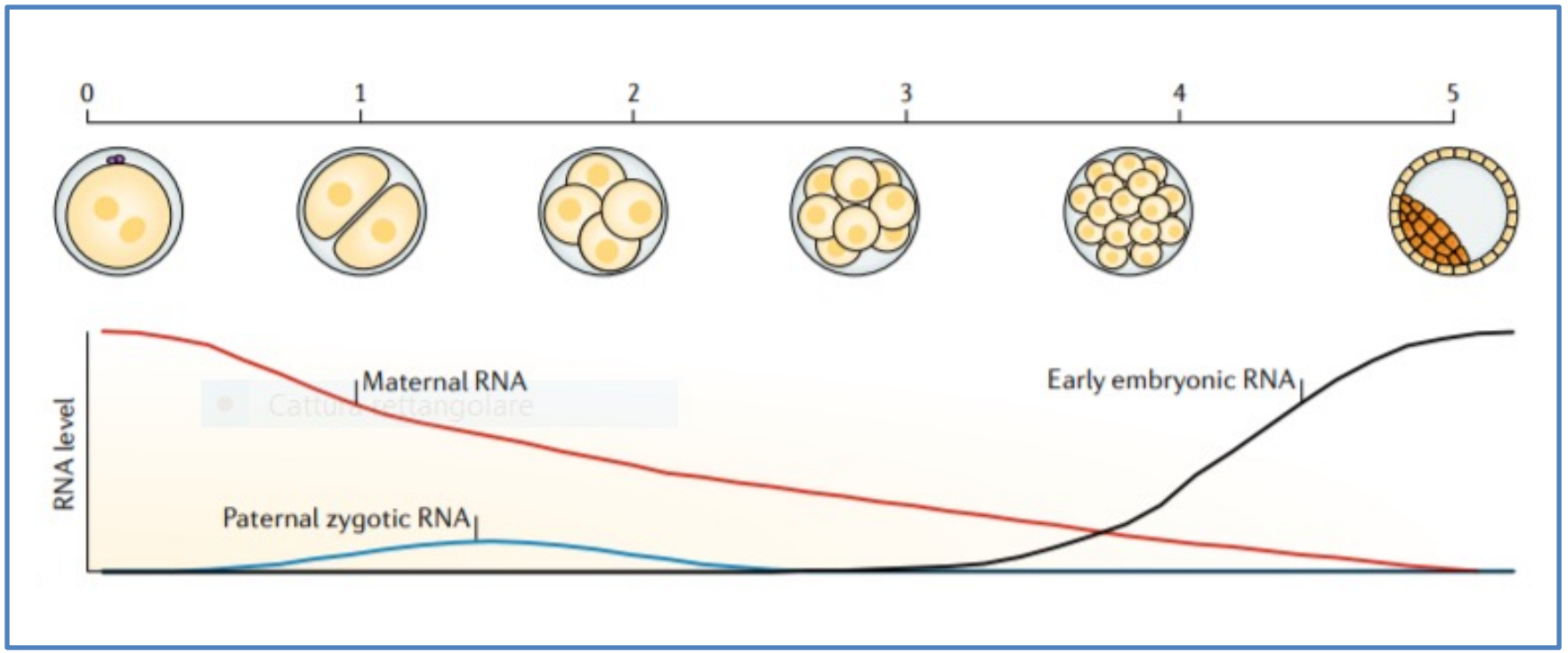
siRNA per Dnmt3 che modula l' epigenotipo

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

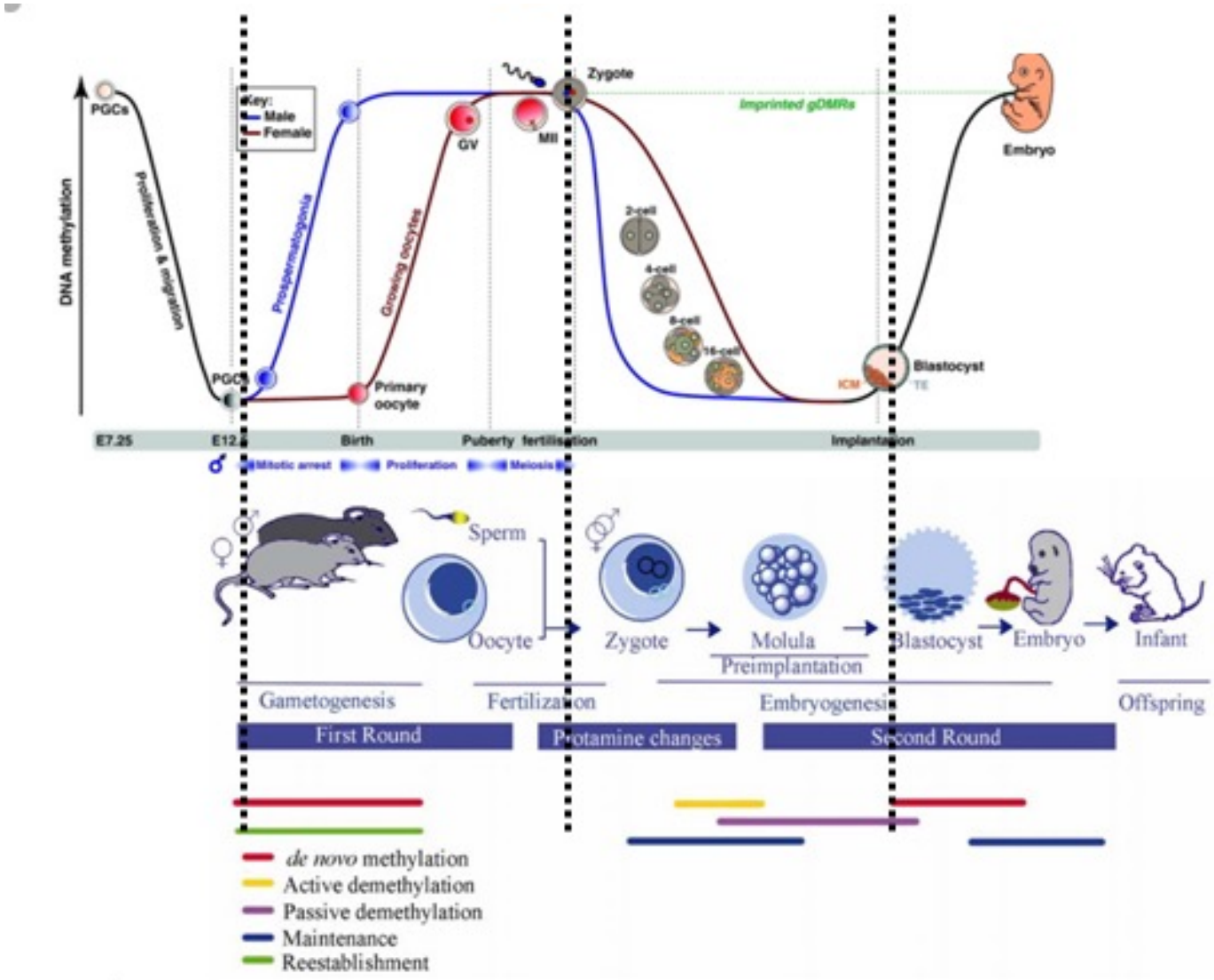
Epi-genotype Establishment



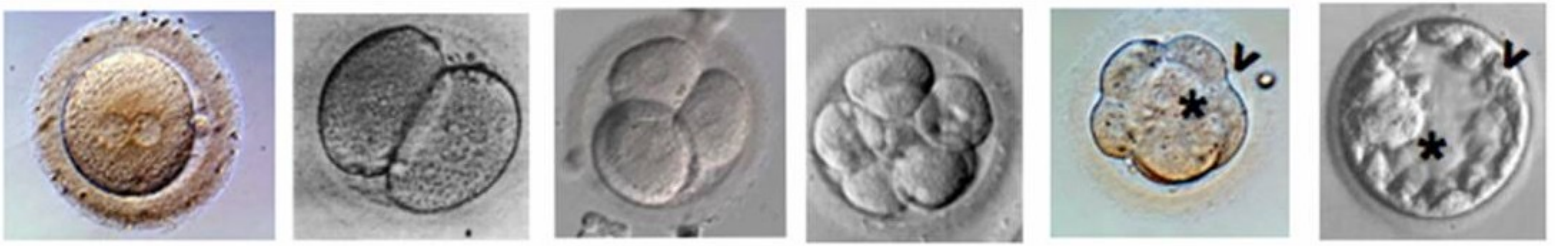
Epi-genotipic reprogramming and Zygote genome activation Establishment



Epi –genotype establishment and ART



Hypothesis for the Etiology of primary Epimutations



zygote	2-cell	4-cell	multi-cell	morula	blastocyst
mouse D0	D1	D1-2	D2	D2-3	D3-4
human D1	D1-2	D2	D3	D3-4	D5

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

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

Environmental factors pre and post conception
Maternal genetics factors
Protein expressed in oocyte
Ovum biologic features

Journal of Assisted Reproduction and Genetics (2018) 35:943–952
https://doi.org/10.1007/s10815-018-1173-x

REVIEW

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

Victoria K. Cortessis[1,2] · Moosa Azadian[1] · James Buxbaum[3] · Fatimata Sanogo[1] · Ashley Y. Song[1] · Intira Sriprasert[1] · Pengxiao C. Wei[1] · Jing Yu[1] · Karine Chung[2] · Kimberly D. Siegmund[1]

Received: 14 December 2017 / Accepted: 23 March 2018 / Published online: 25 April 2018

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.

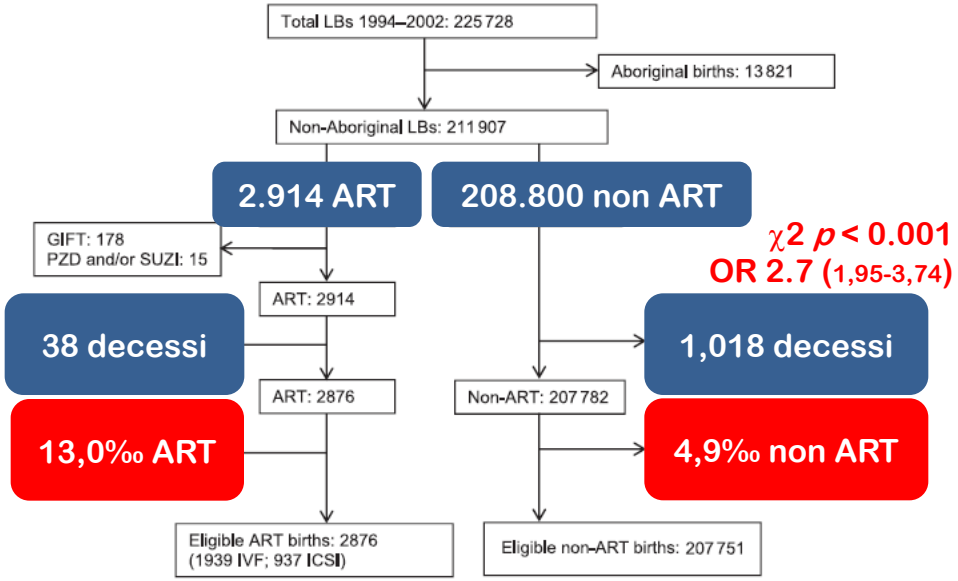
Methods We implemented a systematic review of scholarly literature followed by comprehensive meta-analysis to quantitatively synthesize data from reports relating to use of ART to occurrence of any imprinting disorder of humans, including Beckwith-Wiedemann (BWS), Angelman (AS), Prader-Willi (PWS), and 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.

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‰

PEDIATRICS®
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Intellectual Disability in Children Conceived Using Assisted Reproductive Technology

Michele Hansen, PhD, MPH,[a] Kathryn R. Greenop, PhD,[a] Jenny Bourke, MPH,[a] Gareth Baynam, MBBS, PhD,[a,b,c,d,e] Roger J. Hart, MD, CREI,[e,f,g] Helen Leonard, MBChB, MPH[a]

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 VIIIa	701,206	<5	—	2.95 (0.61–8.62)
Ewing's sarcoma: groups VIIIc 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 VIIIb; VIIId; VIIIe; 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.

N ENGL J MED 369;19 NEJM.ORG NOVEMBER 7, 2013

Cancer Risk among Children Born after Assisted Conception

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)	313/10 915 (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)

PEDIATRICS
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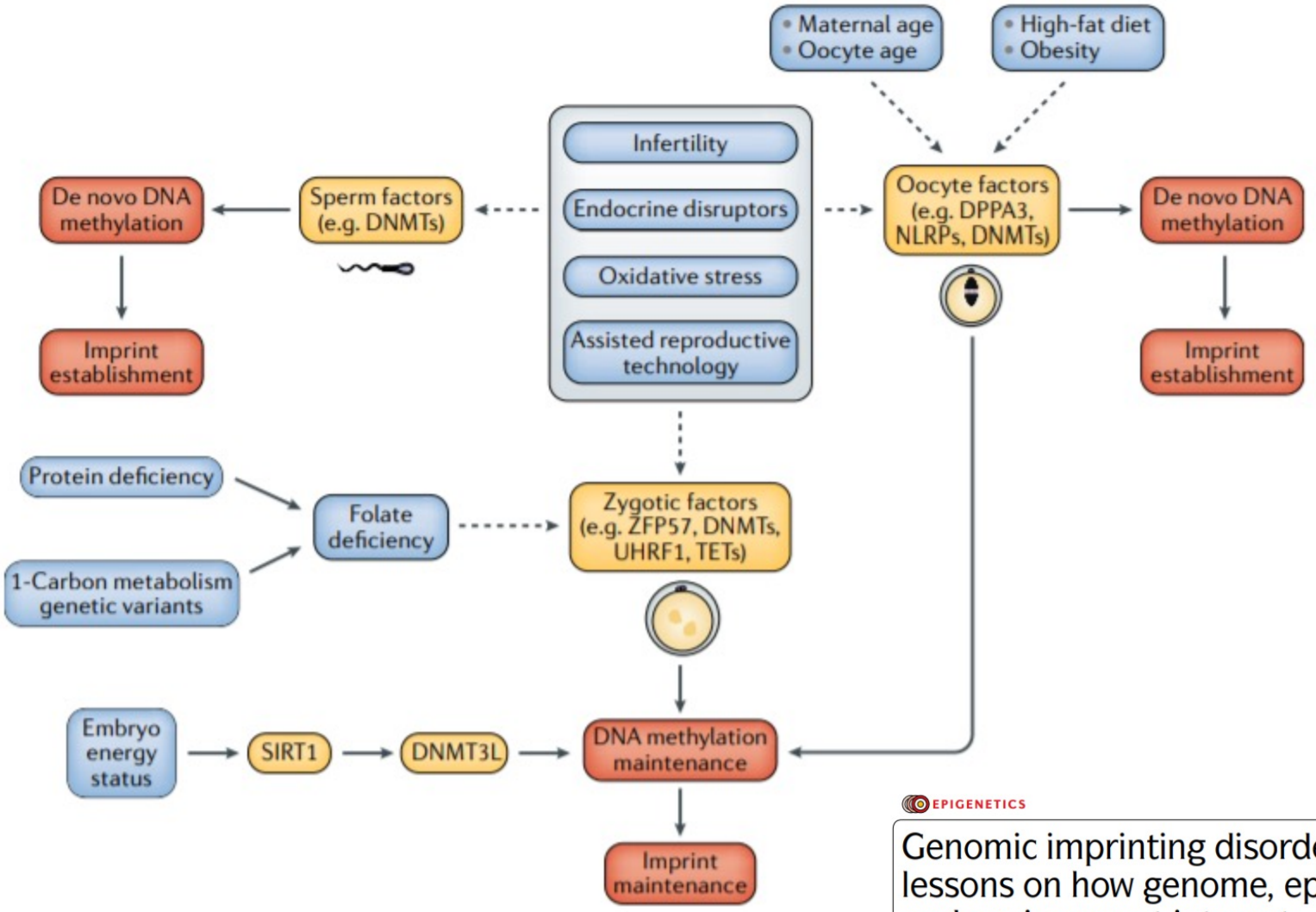
Intellectual Disability in Children Conceived Using Assisted Reproductive Technology

Michele Hansen, PhD, MPH,[a] Kathryn R. Greenop, PhD,[a] Jenny Bourke, MPH,[a] Gareth Baynam, MBBS, PhD,[a,b,c,d,e] Roger J. Hart, MD, CREI,[e,f,g] Helen Leonard, MBChB, MPH[a]

Genome – Epigenome – Environment

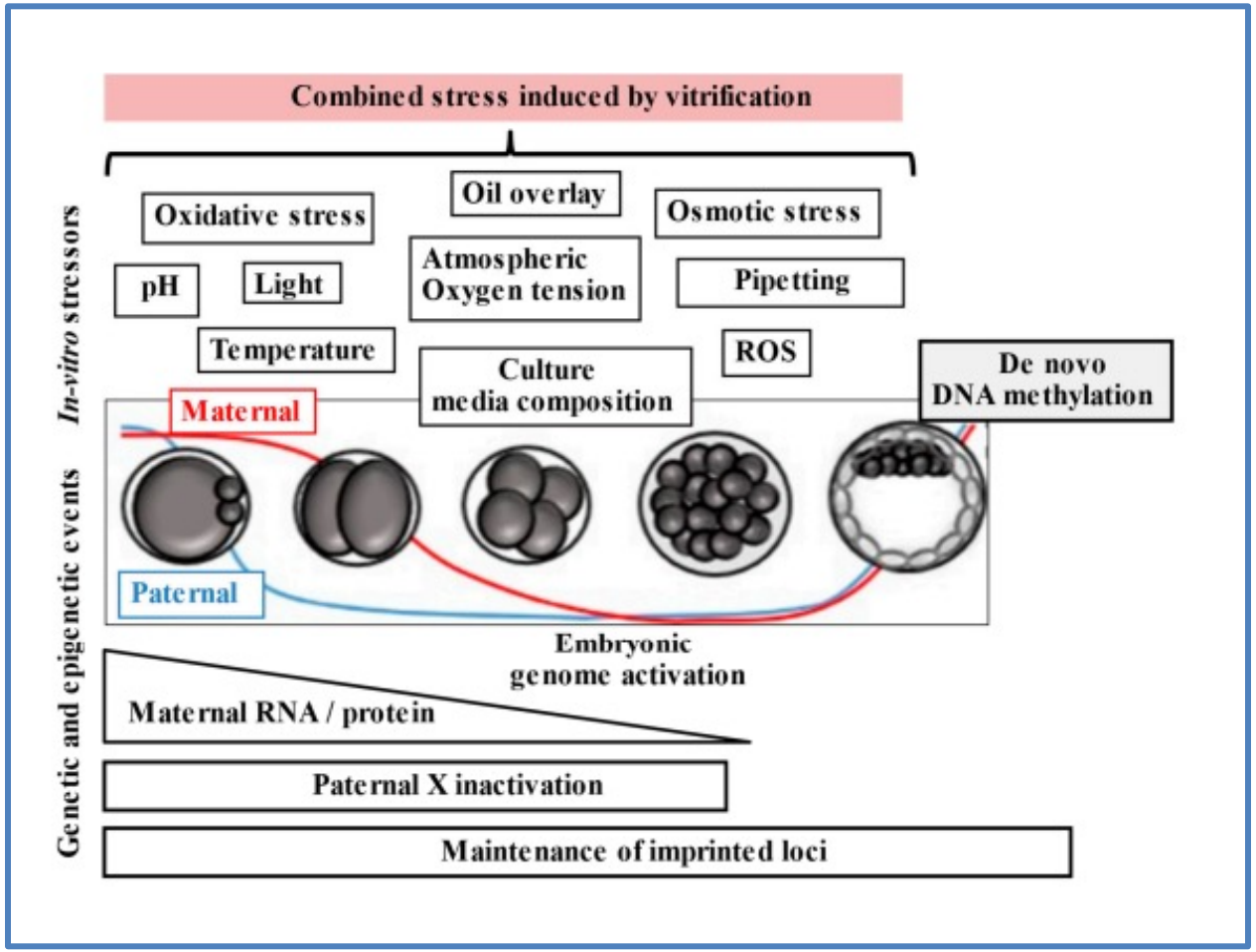


EPIGENETICS

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

David Monk[1], Deborah J. G. Mackay[2], Thomas Eggermann[3], Eamonn R. Maher[4] and Andrea Riccio[5]*

Genome – Epigenome – Environment



Journal of Clinical Medicine
MDPI
Review

Can Cryopreservation in Assisted Reproductive Technology (ART) Induce Epigenetic Changes to Gametes and Embryos?

Romualdo Sciorio [1,*], Claudio Manna [2], Patricia Fauque [3,4] and Paolo Rinaudo [5]

Conclusions

ART is associated with Genomic Imprinting Defects

10 times RR of Beckwith Wiedemann Syndrome in ART conceived children

Open questions :

Role of techniques in respect of pre-existing pathological condition

Association of ART with other Health risks

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

Model for the study of Genome – Epigenome – Enviroment interactions

FEATURES

FATEFUL IMPRINTS

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

Aknowledgments

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