WEBINAIRE

Grossesse après FIV : Une grossesse comme les autres ?

Mardi 4 Avril 2023 • 12h00 à 14h00

Conséquences pour l'enfant

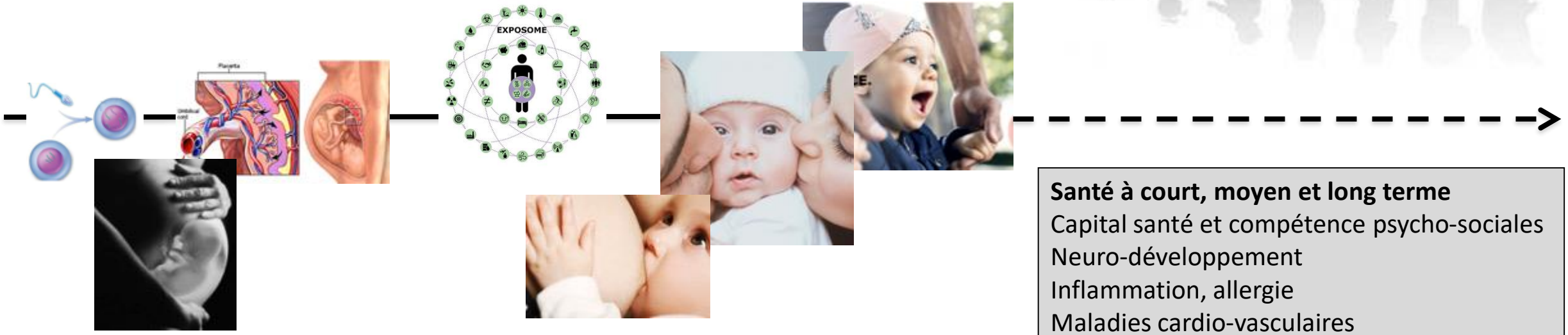
Géraldine Gascoin, Pédiatre - Toulouse

Concept de programmation fœtale
Mécanismes sous tendant ce concept: modifications épigénétiques
Revue de littérature sur complications court-moyen-long terme
Etudes sur Cohortes nouveau-nés prématurés
Take Home Messages

Developmental Origins of Behaviour, Health, and Disease (DOBHaD) concept

Période Pré/péri conceptionnelle et prénatale
Exposome
PMA
Prématurité
RCIU-preeclampsie
Obésité, Diabète
Stress psycho-sociaux et sociétaux

Période postnatale
Exposome
RCEU
Nutrition
Stress psycho-sociaux et sociétaux



Santé à court, moyen et long terme
Capital santé et compétence psycho-sociales
Neuro-développement
Inflammation, allergie
Maladies cardio-vasculaires
Maladies métaboliques, obésité, diabète

1000 jours

Programmation pré et péri conceptionnelle, intra-utérine, post-natale, transgénérationnelle

Dénutrition / Surnutrition

PMA

Equilibre métabolique

Stress psycho-sociaux,
Santé psychique, Dépression

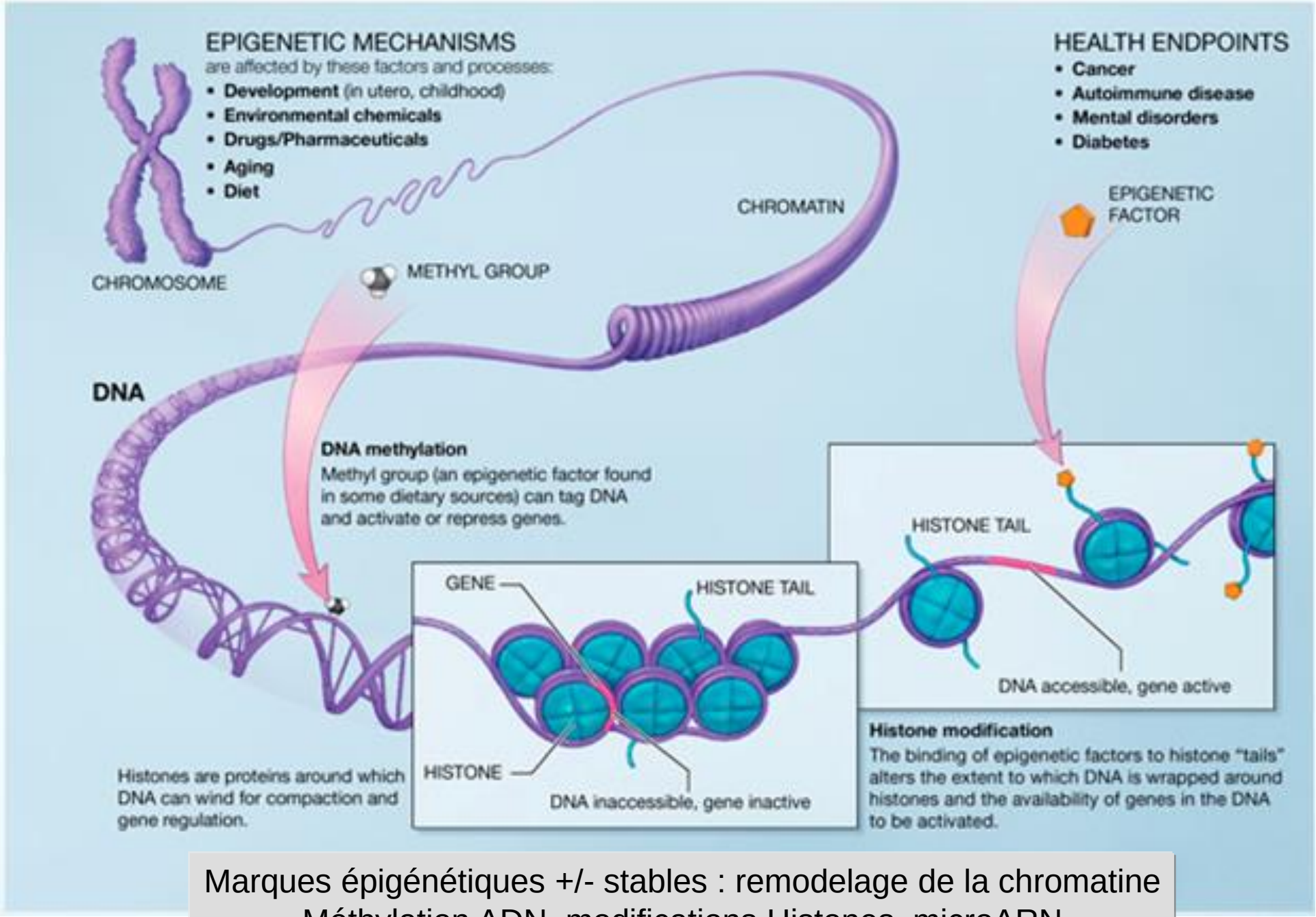
Infection, AB
Microbiote

Drogues, tabac

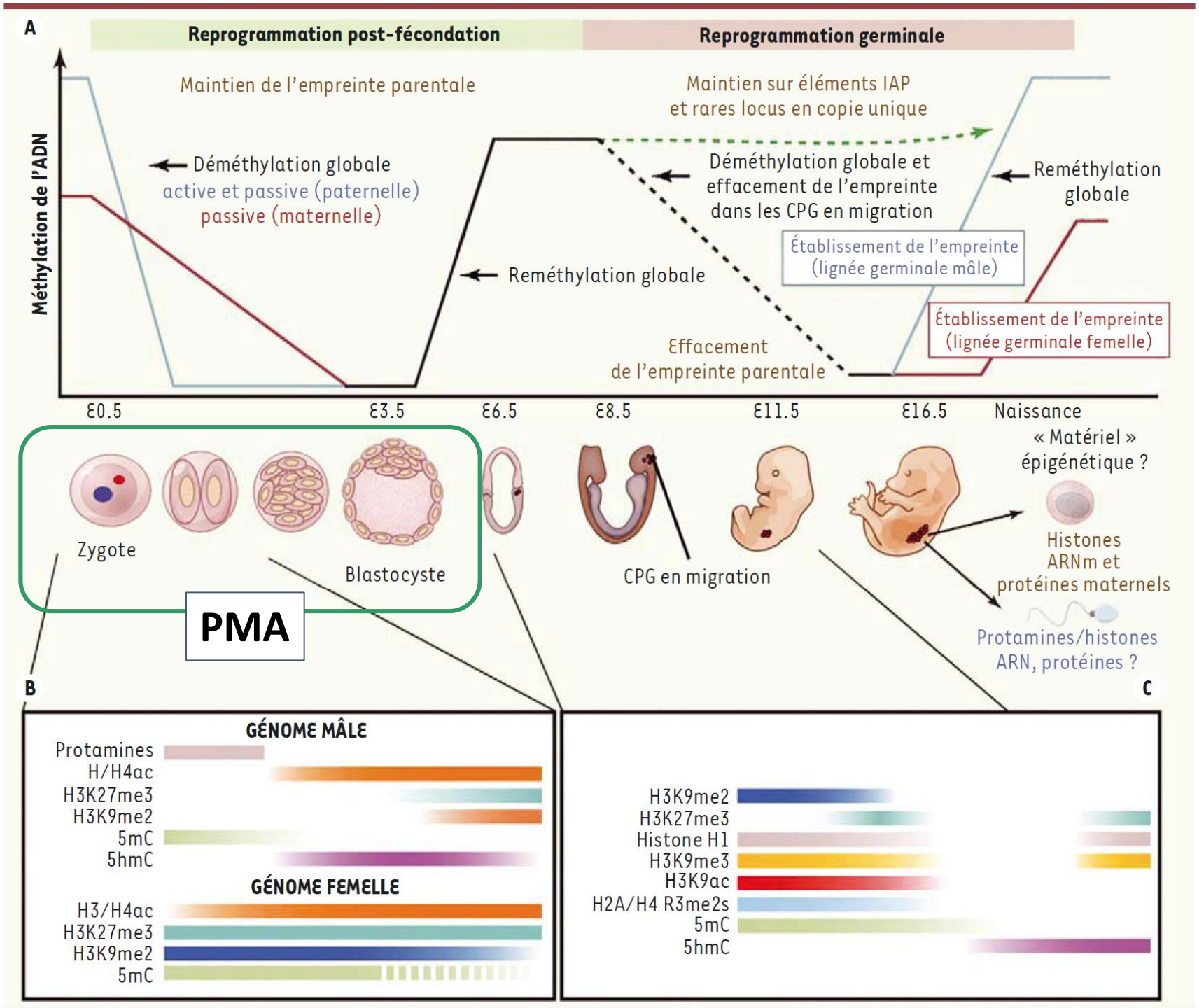
Toxiques environnementaux

MEDECINE PREDICTIVE…

Fenêtre de vulnérabilités … fenêtre d'opportunités

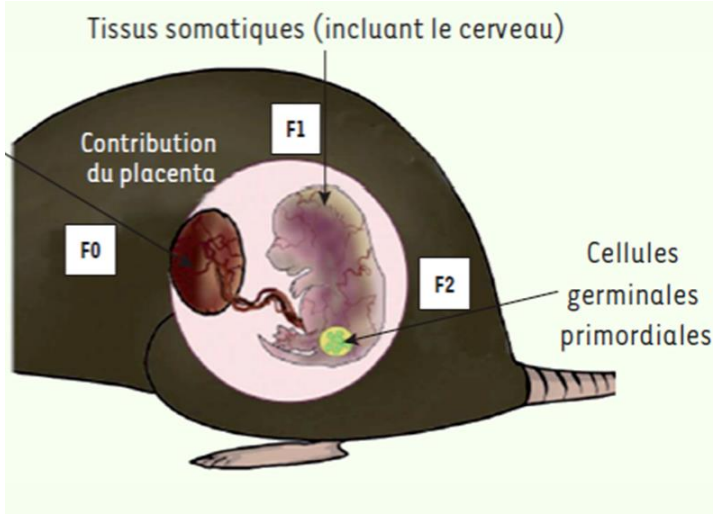


Marques épigénétiques +/- stables : remodelage de la chromatine
Méthylation ADN, modifications Histones, microARN



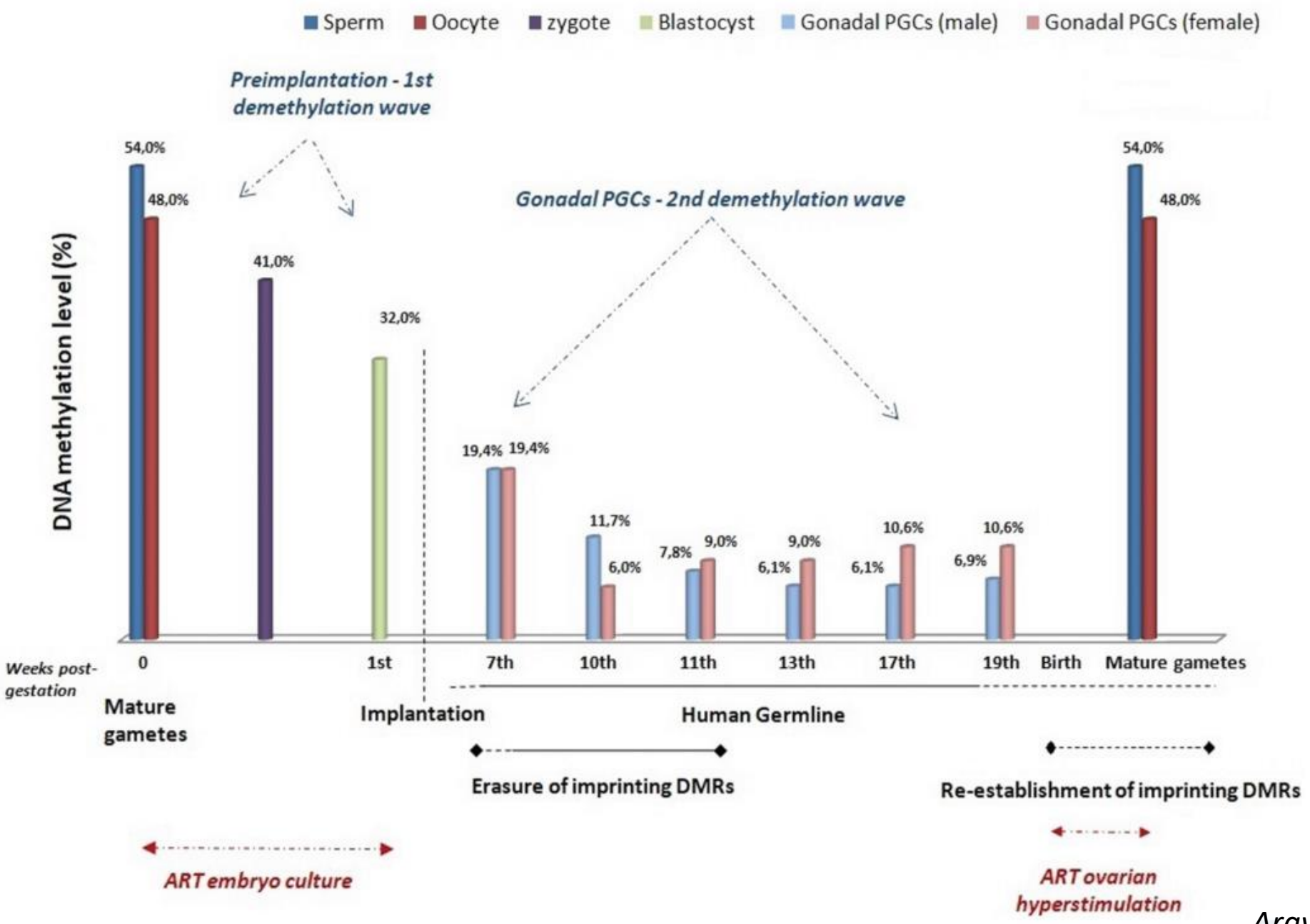
Mémoires de l'exposition précoce à un environnement défavorable

Modifiant l'expression de gènes pendant toute la vie, voire 3 générations



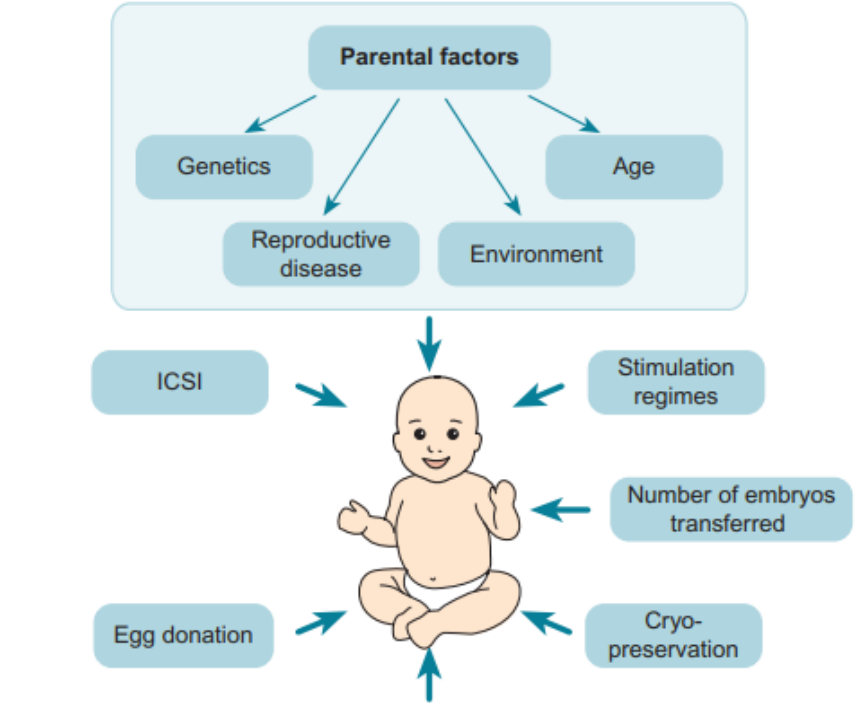
Junien, Med Scie 2016

Human DNA methylation process

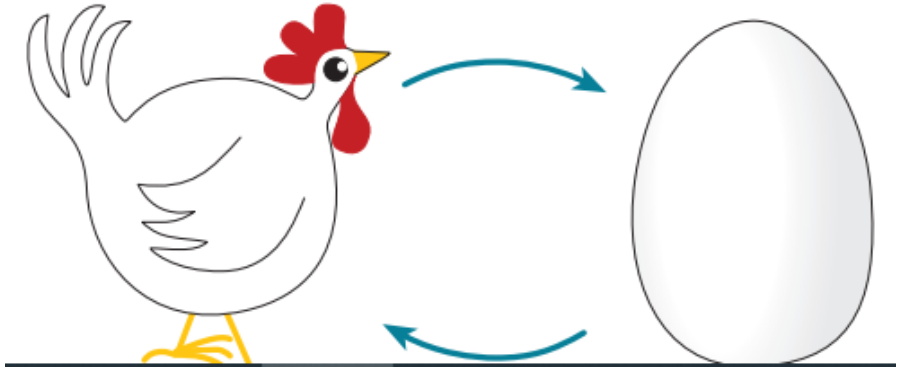


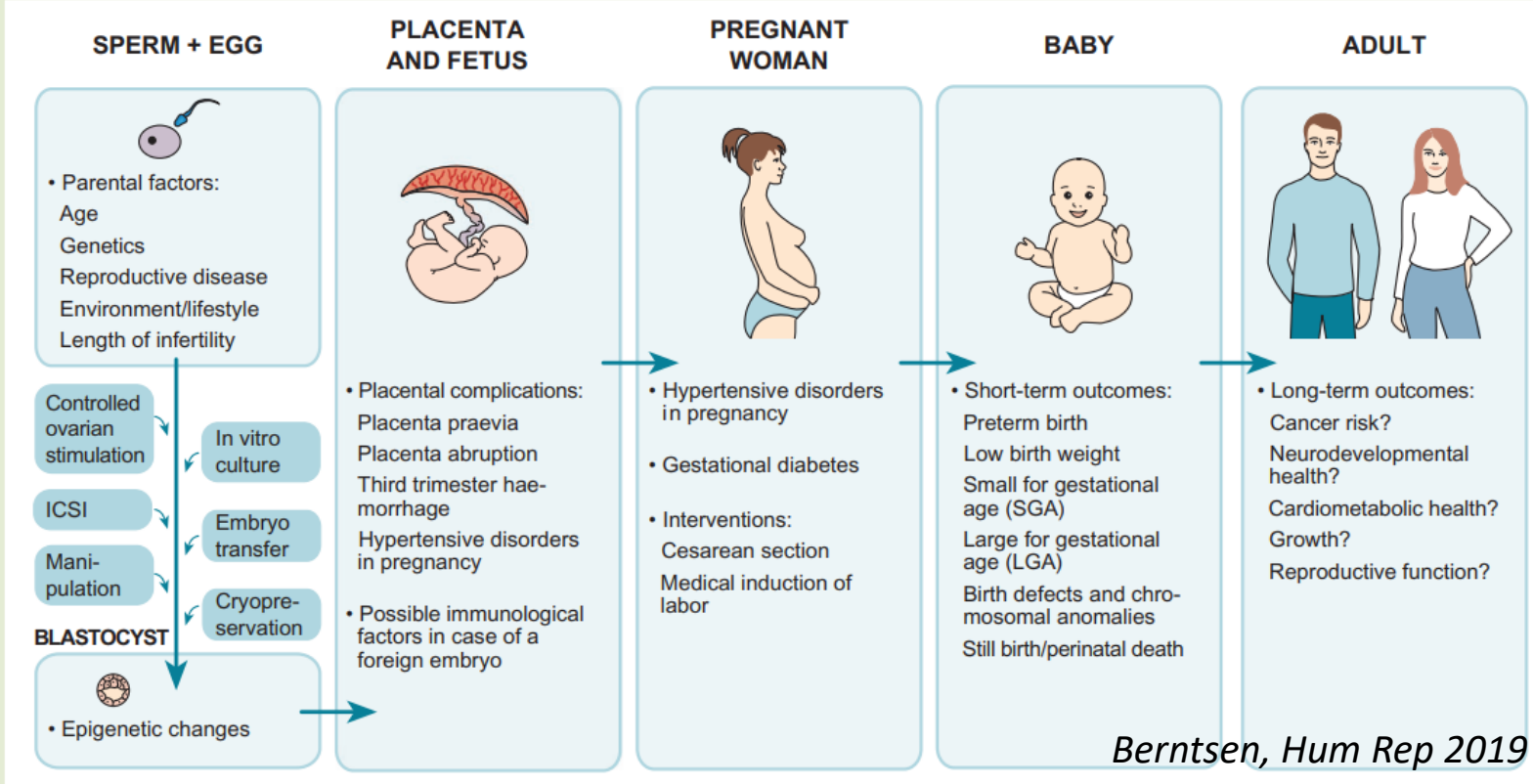
Argyraki, Hum Rep 2019

PMA / infertilité : l'œuf ou la poule?



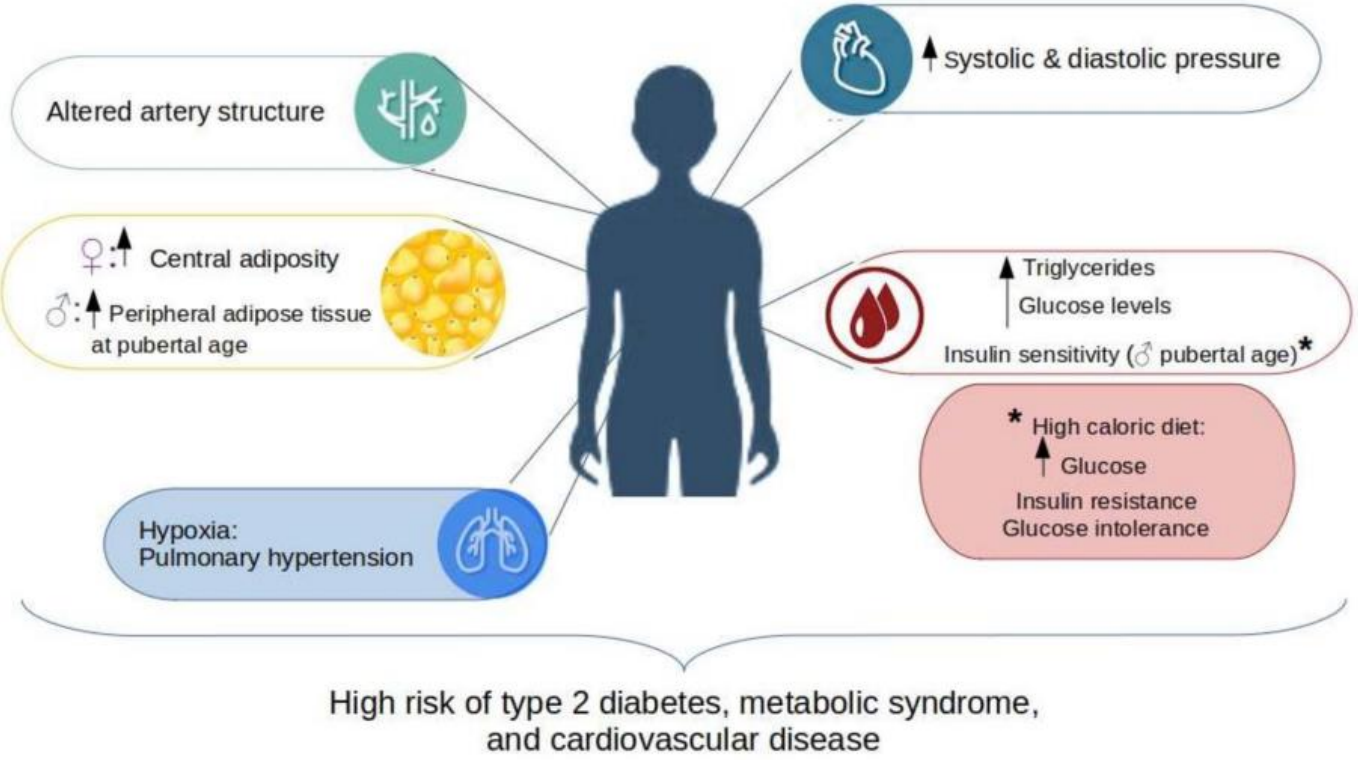
>10 millions enfants nés de PMA depuis 1978, 2-6% des grossesses en Europe
Augmentation du risque **HTA et maladies cardiovasculaires**
Données **rassurantes pour croissance, risques de cancer**
Résultats **discordants** sur **neurodéveloppement**, disparaissant après ajustements
Données limitées sur fertilité: **oligospermie, pas d'effet chez fille**
Effets croisés/médiés/cumulés: infertilité, techniques PMA, prématurité, PAG/RCIU
Groupe contrôle: couples hypofertiles, fratrie sans PMA





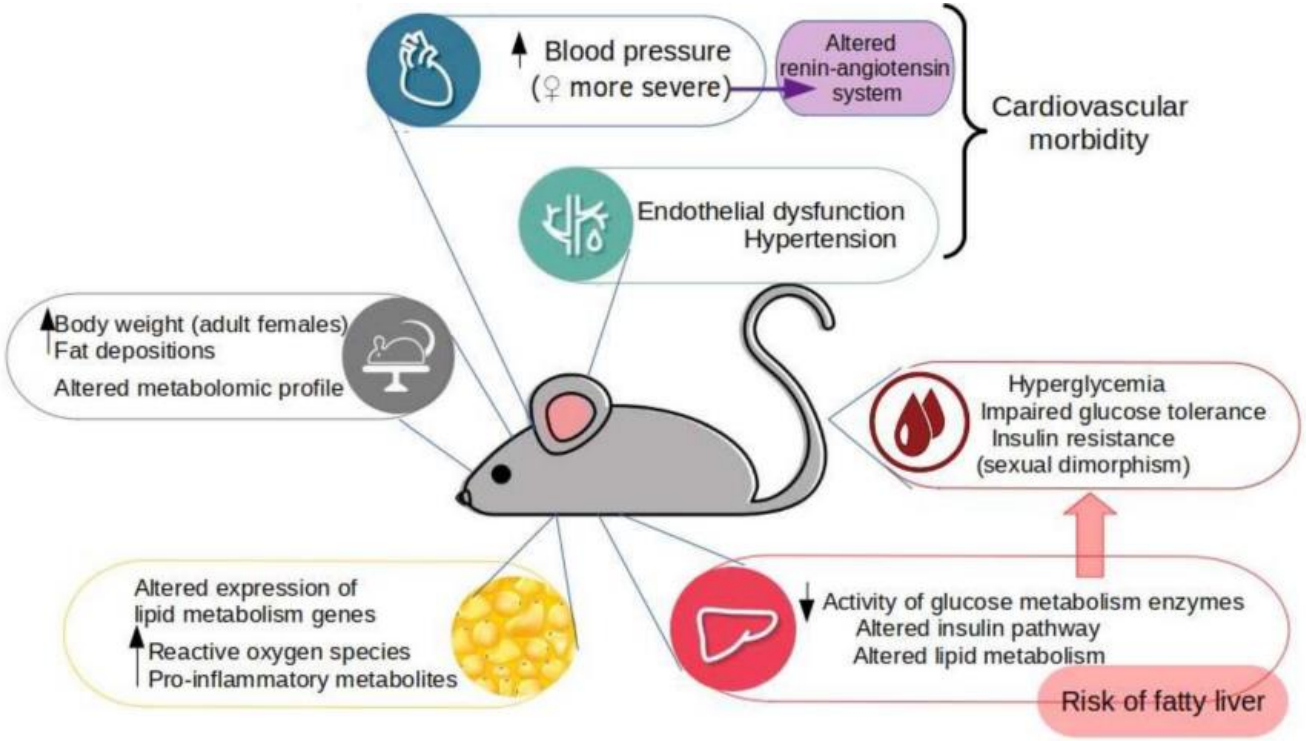
Berntsen, Hum Rep 2019

PMA et devenir cardiovasculaire et métabolique



Enfants en bonne santé
Effets à l'adolescence
Nécessité ++ **études de suivi**
Les altérations pourraient survenir plus tard dans la vie et influencer le développement de la **maladie de l'adulte**

Etudes chez l'animal permettent d'isoler les effets médiés par l'hypofertilité parentale
Confirmation des effets observés sur cohorte humaine
Effets à long terme avec **syndrome métabolique**
Effets transgénérationnels?
Marque épigénétique persistant sur 2 générations



Heber, Bio Reprod 2021

PMA : grossesse – accouchement – nouveau-né

Pregnancy complications	ART Method	References
Deleterious effects:		
Placental abruption	IVF, ICSI	(Isaksson, 2002; Katalinic, 2004; Luke, 2017; Vermey, 2019; Cochrane, 2020; Petersen, 2020)
Placenta previa	IVF, ICSI	(Isaksson, 2002; Katalinic, 2004; Luke, 2017; Vermey, 2019; Cochrane, 2020; Petersen, 2020)
Preterm rupture of membranes	IVF, ICSI	(Katalinic, 2004; Pandey, 2012)
Ante/postpartum hemorrhages	IVF, ICSI	(Pandey, 2012, Luke, 2017)
Poly/oligohydramnios	ICSI	(Katalinic, 2004)
Caesarean sections	IVF, ICSI	(Chaveeva, 2011; Pandey, 2012, Luke, 2017)
Preterm deliveries	IVF, ICSI	(Pandey, 2012; Ombelet, 2016; Luke, 2017; Hwang, 2018; Chang, 2020; Cochrane, 2020)
Preeclampsia/hypertension	IVF, ICSI	(Katalinic, 2004, Chaveeva, 2011; Pandey, 2012; Almasi-Hashiani, 2019; Petersen,2020)
Gestational diabetes mellitus	IVF, ICSI	(Chaveeva, 2011; Pandey, 2012; reviewed in Mohammadi, 2020)
Early abortion	IVF, ICSI, IUI, OI ,FET	(Brandes, 2011)
Neutral effects:		
No risk of LBW, perinatal morbidity/mortality or rate of malformations	IVF	(Vasario, 2010)
No risk of obstetric complications	IVF, ICSI, IUI, OI	(Elfituri, 2021)
Placenta outcomes		
Deleterious effects:		
Morphological changes, increased weight, efficiency & thickness	IVF, ICSI	(Daniel, 1999; Haavaldsen, 2012; Eskild, 2013)
Abnormal umbilical cord insertion	IVF, ICSI	(Daniel, 1999; Yanaihara, 2018; Cochrane, 2020)
Epigenetic changes, methylation/gene expression of imprinted genes	IVF, ICSI	(Katari, 2009; Menezo, 2010; Turan, 2010; Vermeiden, 2013; Nelissen, 2013, 2014; Choux, 2015, 2018, Sakian, 2015; Dong, 2019; Chi, 2020)
Altered expression of transmembrane transporters	IVF	(Zhang, 2010)
Neutral effects:		
Normal weight	IVF, ICSI	(Yanaihara, 2018; Dong, 2019)
Perinatal outcomes		
Deleterious effects:		
Reduced birth weight & SGA	IVF, ICSI	(Isaksson, 2002; Katalinic, 2004; Sakka, 2010; Chaveeva, 2011; Pandey, 2012; Ombelet, 2016; Luke, 2017; Hwang, 2018; Chang, 2020; Cochrane, 2020; Magnus, 2021)
Congenital anomalies	IVF, ICSI	(Hansen, 2012; Pandey, 2012; Donzelli, 2015; Hwang, 2018; Valenzuela-Alcaraz, 2019; Chang, 2020)
Infectious diseases	ART	(Hwang, 2018)
Increased perinatal mortality	IVF, ICSI	(Isaksson, 2002, Pandey, 2012; Ombelet, 2016; Hwang, 2018)
Cardiovascular changes	IVF, ICSI	(Valenzuela-Alcaraz, 2013, 2018; Guo, 2017; Hwang, 2018; Chang, 2020)
Dilated atria, cardiac and vascular remodeling	IVF, ICSI	(Valenzuela-Alcaraz, 2013, 2018)
Neutral effects:		
No risk of birth defects	IVF, ICSI	(Davies, 2012; Levi Setti, 2016)
Normal birth weight	IVF, ICSI	(Levi Setti, 2016)
No increase in perinatal mortality	IVF, ICSI	(Chaveeva, 2011)
Normal perinatal outcomes	IVF, ICSI, IUI, OI	(Elfituri, 2021)
Positive effects:		
Reduced risk of SGA	IVF, ICSI, IUI	(Glatthorn, 2021)

Schroeder, Front cell Dev Bio 2022

PMA : Enfance

Childhood	ART Method	References
Cardiovascular & Metabolic health		
Deleterious effects:		
Elevated blood pressure & triglyceride levels	IVF, ICSI	(Ceelen, 2008a; Sakka, 2010; Pontesilli, 2015; Guo, 2017; Valenzuela-Alcaraz, 2019; Cui, 2020; Zandstra, 2020)
Elevated glucose	IVF, ICSI	(Ceelen, 2008a; Pontesilli, 2015; Cui, 2020)
Vascular dysfunction	IVF, ICSI	(Scherrer, 2012; Guo, 2017; Cui, 2020; Zandstra, 2020)
Altered growth patterns	IVF, ICSI	(Ceelen, 2008a; Green, 2013; Magnus, 2021; Roseboom and Eriksson, 2021; Magnus, 2021)
Elevated body fat	ICSI	(Belva, 2007; reviewed in Hart and Norman, 2013)
Elevated peripheral fat and skinfolds	IVF	(Ceelen, 2007)
Congenital malformations	ICSI	(Belva, 2007)
Neutral effects:		
Normal blood pressure	ART	(Scherrer, 2012)
Normal BMI, lipid profile, GTT & ITT	IVF, ART	(Sakka, 2010; Scherrer, 2012)
Favorable lipid profile and normal fat mass	IVF	(Miles, 2007)
Neurodevelopmental health		
Deleterious effects:		
Developmental delay and risk of cerebral palsy	IVF	(Strömberg, 2002)
High risk of autism	ART	(Fountain, 2015; reviewed in Liu, 2017)
Neutral effects:		
No risk of ADHD	IVF, ICSI	(Farhi, 2021a, 2021b)
Normal school performance	IVF, ICSI	(Wagenaar, 2008; Punamäki, 2016; Norrman, 2018; Luke, 2020)
Normal cognitive function and verbal skills	IVF, ICSI	(Belva, 2007; Carson, 2010; Punamäki, 2016; Farhi, 2021a)
Normal psychomotor development	IVF, ICSI	(Belva, 2007; Nekkebroeck, 2008; Carson, 2010; Sánchez-Soler, 2020)
No mental retardation or autistic disorders	IVF, ICSI	(Sandin, 2013; Lung, 2018; Jenabi, 2020; Farhi, 2021b)
Positive effects:		
Reduced risk of autism	ART	(Maimburg and Vaeth, 2007)
Lower odds of adverse neurodevelopmental (cognitive and language) outcomes	IVF, ICSI, ET, IUI	(Roychoudhury, 2021)

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PMA : adolescence et jeune adulte

Adolescence		
Deleterious effects:		
High blood pressure	IVF	(Ceelen, 2008a)
High fasting glucose	IVF	(Ceelen, 2008a)
Higher LH and DHEAs in girls	IVF	(Ceelen, 2008b)
Higher bone age/chronological age in girls	IVF	(Ceelen, 2008b)
Elevated body fat in girls	ICSI	(Belva, 2012a)
Neutral effects:		
Healthy bone mineral composition/high peripheral fat	IVF	(Ceelen, 2007)
Normal height, weight and BMI	IVF, ICSI , other	(Magnus, 2021)
Healthy blood pressure	ICSI	(Belva, 2007, 2012b)
Normal metabolic outcomes	ICSI	(Belva, 2019)
Normal gonadal function/pubertal development	IVF, ICSI	(Belva, 2007, 2019; Ceelen, 2008b)

Young Adults		
Deleterious effects:		
Lower glucose sensitivity after acute overfeeding	IVF	(Chen, 2014)
Increased systolic BP after acute overfeeding	IVF	(Chen, 2014)
Low HDL in men	ICSI	(Belva, 2018)
Low sperm count, abnormal exocrine function	ICSI	(Belva, 2019)
Neutral effects:		
Normal gonadal function	ICSI	(Belva, 2019)
Normal basal metabolic health	IVF, ICSI	(Chen, 2014; Halliday, 2014; Belva, 2018; Juonala, 2020)
Normal cholesterol/triglycerides/insulin & BP	IVF, ICSI	(Chen, 2014; Belva, 2018; Juonala, 2020)
Positive effects:		
Lower chance of psychiatric diagnosis	IVF, ICSI, IUI, OI , FET	(Rissanen, 2020)

Schroeder, Front cell Dev Bio 2022

Prématurité et PMA : Devenir à 2 ans

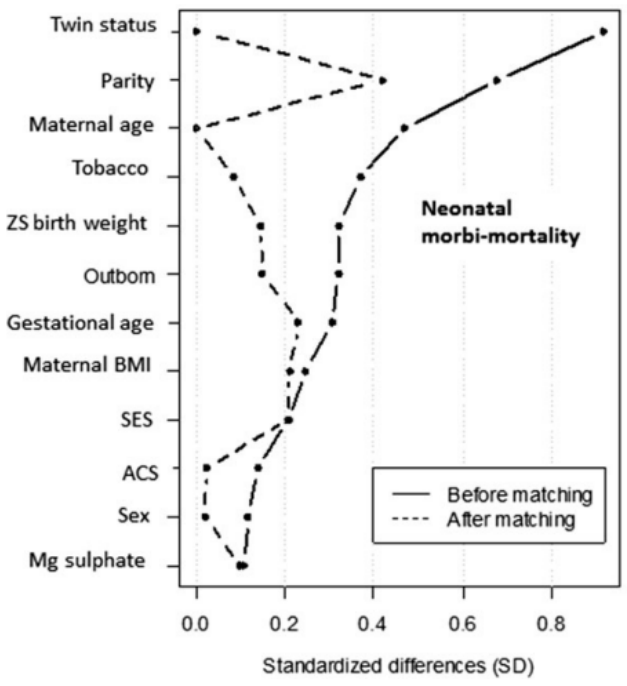
grandir ensemble
RÉSEAU SÉCURITÉ NAISSANCE
PAYS DE LA LOIRE

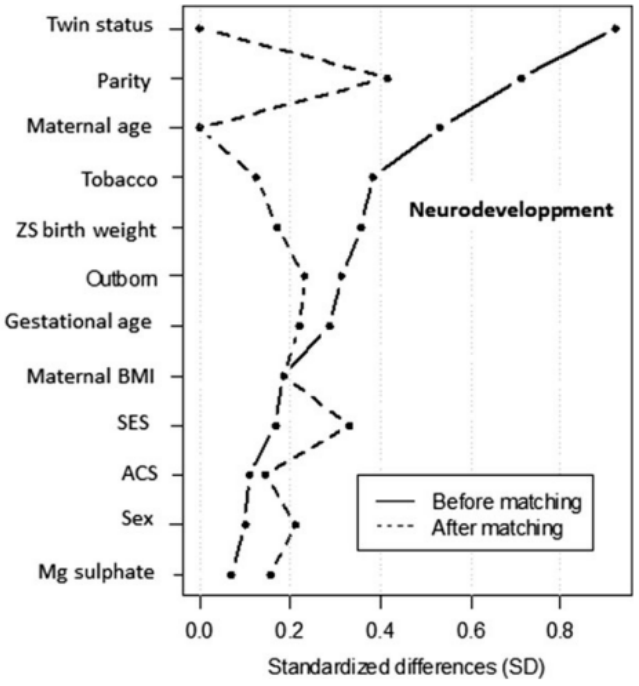
836 infants born <34 weeks GA
→ 68 infants not enrolled in the LIFT cohort

768 infants enrolled in the LIFT cohort
→ 25 infants with malformative pathologies
→ 40 infants with incomplete medical records (age of the mother n = 25, birth weight n = 3, parity n = 4, antenatal treatments n = 13)

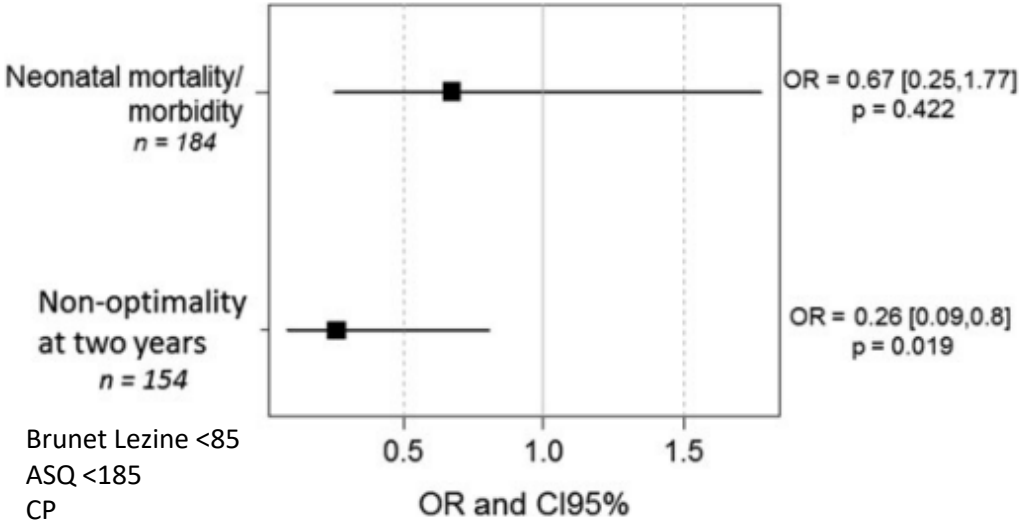
703 infants included in the study
→ 37 infants died before discharge
→ 93 infants lost to follow-up

573 infants followed at 2 years of corrected age





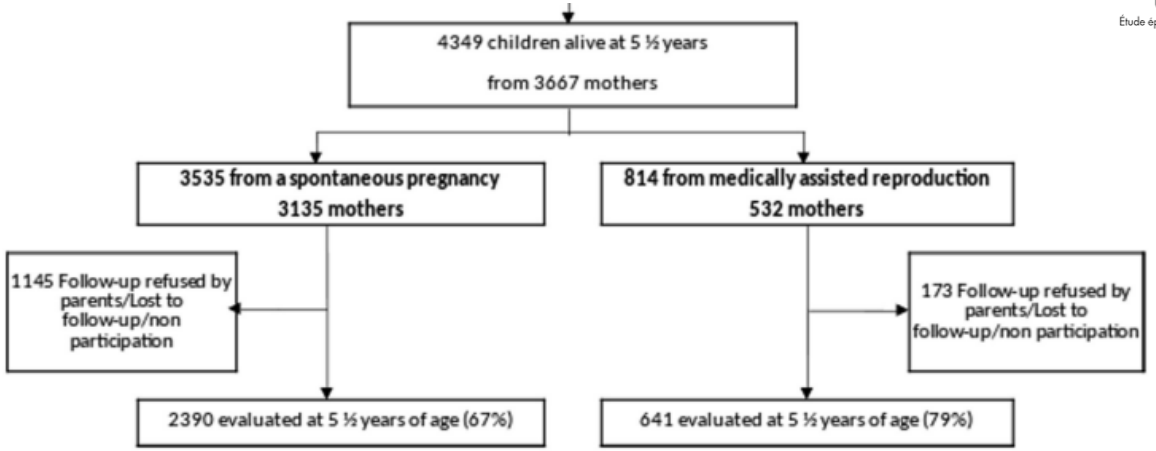
Pas d'augmentation de la morbi-mortalité NN
Amélioration du devenir neuro à 2 ans



Brunet Lezine <85
ASQ <185
CP

Molines, Hum Rep 2018

Prématurité et PMA : Devenir à 5 ans
Pas de différence CP, cognitif, neurosensoriel et coordination
Ajustement sur facteurs sociodémographiques



Characteristics of the 3667 mothers with children in the EPIPAGE-2 cohort surviving to 5½ years of age according to mode of conception, after multiple imputation

Characteristic	Spontaneous N mothers=3135	MAR[a] N mothers=532	IO or IUI N mothers=254	IVF or IVF-ICSI N mothers=278
Age, mean (95% confidence interval)	29.4 (29.2–29.7)	32.0 (31.5–32.6)	31.4 (30.4–32.3)	32.6 (32.0–33.2)
Primiparous	49.9 (47.5–52.3)	77.0 (72.3–81.8)	74.8 (67.8–81.7)	79.0 (72.4–85.6)
Born in France	78.8 (76.9–80.7)	84.8 (81.0–88.6)	85.5 (80.3–90.8)	84.1 (78.6–89.6)
Smoked during pregnancy	23.5 (21.5–25.5)	8.8 (5.5–12.1)	9.2 (4.5–14.0)	8.4 (3.8–13.0)
Level of education				
Less than high school	36.7 (34.4–39.0)	22.1 (17.3–27.0)	25.7 (18.1–33.3)	19.0 (12.8–25.2)
High school	23.3 (21.3–25.4)	15.9 (11.7–20.1)	15.4 (9.7–21.1)	16.3 (10.3–22.3)
1–2 y of graduate studies	17.9 (16.0–19.8)	21.0 (16.3–25.6)	23.7 (16.4–31.0)	18.6 (12.8–24.4)
≥3 y of graduate studies	22.0 (20.0–24.1)	41.0 (35.3–46.8)	35.2 (27.0–43.4)	46.1 (38.1–54.0)
Occupational activity during pregnancy	61.7 (59.4–64.0)	80.1 (75.5–84.6)	74.7 (67.3–82.0)	84.8 (79.2–90.3)
Cohabiting with partner at delivery	88.9 (87.4–90.4)	97.3 (95.4–99.2)	96.5 (93.4–99.5)	98.1 (95.8–100)
Parents' socioeconomic status[b]				
Executive	18.7 (16.8–20.6)	34.8 (29.2–40.3)	28.8 (21–36.6)	40.0 (32.2–47.8)
Intermediate	19.9 (18.0–21.9)	27.6 (22.3–33.0)	31.6 (23.5–39.8)	24.1 (17.1–31.2)
Administration	28.9 (26.8–31.1)	24 (19.0–29.0)	23.3 (16.1–30.6)	24.6 (17.7–31.5)
Service, trade	15.8 (14.0–17.5)	7.1 (4.2–10.0)	7.5 (3.1–12.0)	6.7 (2.9–10.5)
Worker	12.8 (11.2–14.3)	5.8 (3.2–8.3)	7.3 (3.0–11.5)	4.5 (1.6–7.4)
Unemployed	3.9 (3.0–4.8)	0.8 (0.0–1.8)	1.5 (0.0–3.6)	0.2 (0.0–0.8)

Association between mode of conception and neurodevelopmental outcome measures for 4349 children from the EPIPAGE-2 cohort surviving at 5½ years—multivariate analysis after multiple imputation

Epipage 2
Étude épidémiologique sur les petits âges gestationnels

Outcome (Model)	MAR[a] (N children=814) vs spontaneous conception (N children=3535): OR or mean difference (95% CI)[b]	*P* value	IO or IUI (N children=381) vs spontaneous conception (N children=3535): OR or mean difference (95% CI)[b]	*P* value	IVF or IVF-ICSI (N children=433) vs spontaneous conception (N children=3535): OR or mean difference (95% CI)[b]	*P* value
Cerebral palsy						
Adjusted for GA and antenatal steroids	0.85 (0.59–1.24)	.41	0.89 (0.53–1.50)	.67	0.81 (0.49–1.35)	.42
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	1.00 (0.67–1.49)	.99	0.99 (0.59–1.69)	.99	1.00 (0.58–1.72)	.99
FSIQ[d]						
Mean difference (95% CI)						
Adjusted for GA and antenatal steroids	3.8 (2.4–5.3)	<.001	3.3 (1.3–5.3)	.002	4.3 (2.4–6.3)	<.001
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	−0.3 (−1.7 to 1.1)	.66	0.0 (−1.9 to 1.9)	.99	−0.6 (−2.5 to 1.3)	.52
<1 SD (<93)[e]						
Adjusted for GA and antenatal steroids	0.64 (0.53–0.77)	<.001	0.61 (0.46–0.80)	<.001	0.66 (0.52–0.85)	.001
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.99 (0.80–1.23)	.94	0.84 (0.62–1.15)	.28	1.15 (0.87–1.52)	.32
< 2 SD (<79)[e]						
Adjusted for GA and antenatal steroids	0.67 (0.51–0.88)	.004	0.69 (0.47–1.02)	.060	0.64 (0.44–0.94)	.023
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	1.14 (0.83–1.56)	.42	1.04 (0.69–1.57)	.86	1.26 (0.82–1.93)	.30
Severe and moderate neurodevelopmental impairment[f]						
Adjusted for GA and antenatal steroids	0.68 (0.53–0.88)	.003	0.72 (0.51–1.02)	.066	0.64 (0.45–0.91)	.013
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	1.09 (0.82–1.45)	.56	1.04 (0.72–1.51)	.83	1.14 (0.77–1.68)	.51
Developmental coordination disorders[g]						
Total MABC-2 score, mean difference (95% CI)						
Adjusted for GA and antenatal steroids	0.2 (−0.1 to 0.5)	.28	0.1 (−0.3 to 0.5)	.67	0.2 (−0.2 to 0.6)	.25
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.1 (−0.3 to 0.4)	.74	0.0 (−0.4 to 0.5)	.92	0.1 (−0.3 to 0.5)	.69
Total MABC-2 score <fifth percentile[e]						
Adjusted for GA and antenatal steroids	0.76 (0.51–1.11)	.16	0.77 (0.45–1.31)	.34	0.74 (0.43–1.28)	.28
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.75 (0.50–1.12)	.16	0.77 (0.45–1.31)	.33	0.73 (0.41–1.29)	.28

Verhaeghe, AJOG 2022

Conclusion

Human Reproduction Update, Vol.25, No.2 pp. 137–158, 2019
Advanced Access publication on February 12, 2019 doi:10.1093/humupd/dmz001

human reproduction update

GRAND THEME REVIEW

The health of children conceived by ART: 'the chicken or the egg?'

Sine Berntsen[1], Viveca Söderström-Anttila[2], Ulla-Britt Wennerholm[3], Hannele Laivuori[4,5,6,7], Anne Loft[8], Nan B. Oldereid[9], Liv Bente Romundstad[10,11], Christina Bergh[12], and Anja Pinborg[8,*]

- Augmentation modérée des complications périnatales chez singleton (PAG, prématurité)
- Peu d'études sur le suivi à long terme (1978, 45 ans!)
- Données limitées sur un surrisque cardiovasculaire et métabolique
- Origines multiples de ces complications: combinaison de l'hypofertilité du couple et des techniques par elles-mêmes
- Effet démontré d'un excès de morbi-mortalité sur les grossesses multiples, éviter ++ transfert de plusieurs embryons/blastocystes
- Beaucoup de questions : nouvelles techniques, effet trans-générationnel…
- Nécessité de registres nationaux et de suivi à long terme +++