

# IVF Children – What do we really know?

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# Disclosures

- Founder of Auxogyn (Progyny)
- Founder of Ivigen

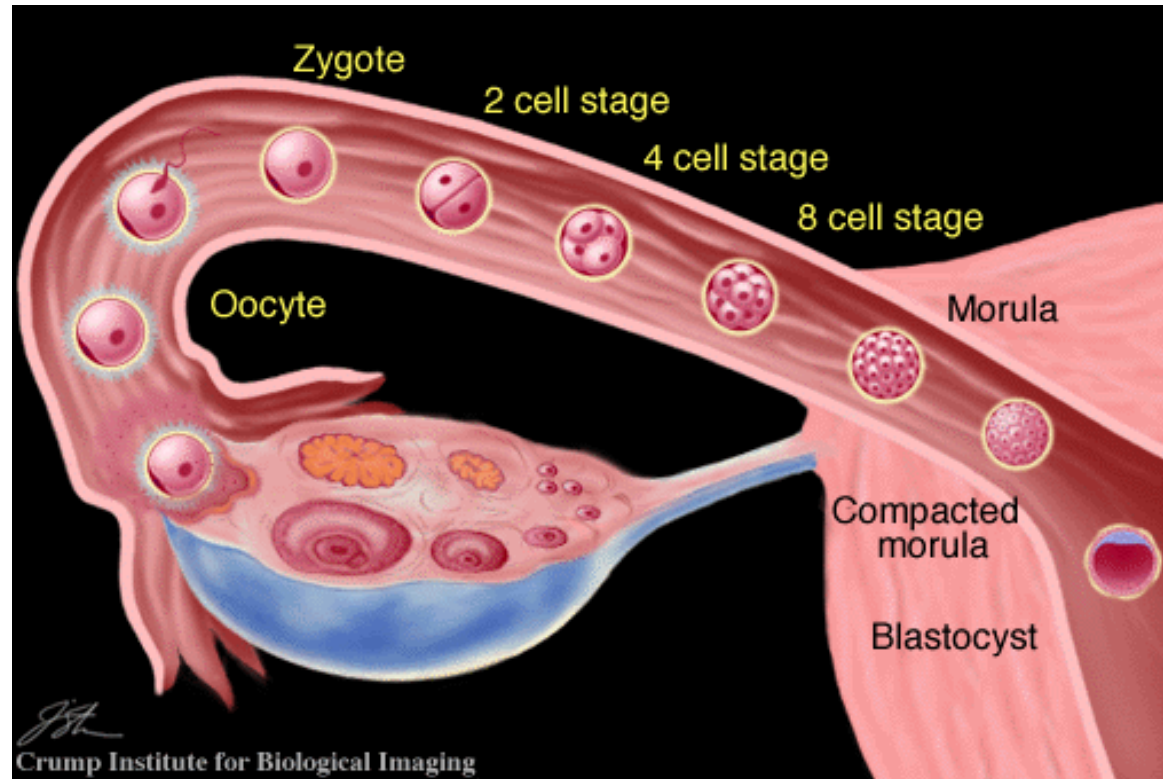


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# Is the lab a conduit from the Ovary to the Uterus?



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**It was but not anymore**

# What can we do?

- What do you need to be healthy?
  - Good genes
  - Good metabolism
  - Good environment (for development in vitro and in vivo)



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San Francisco Chronicle

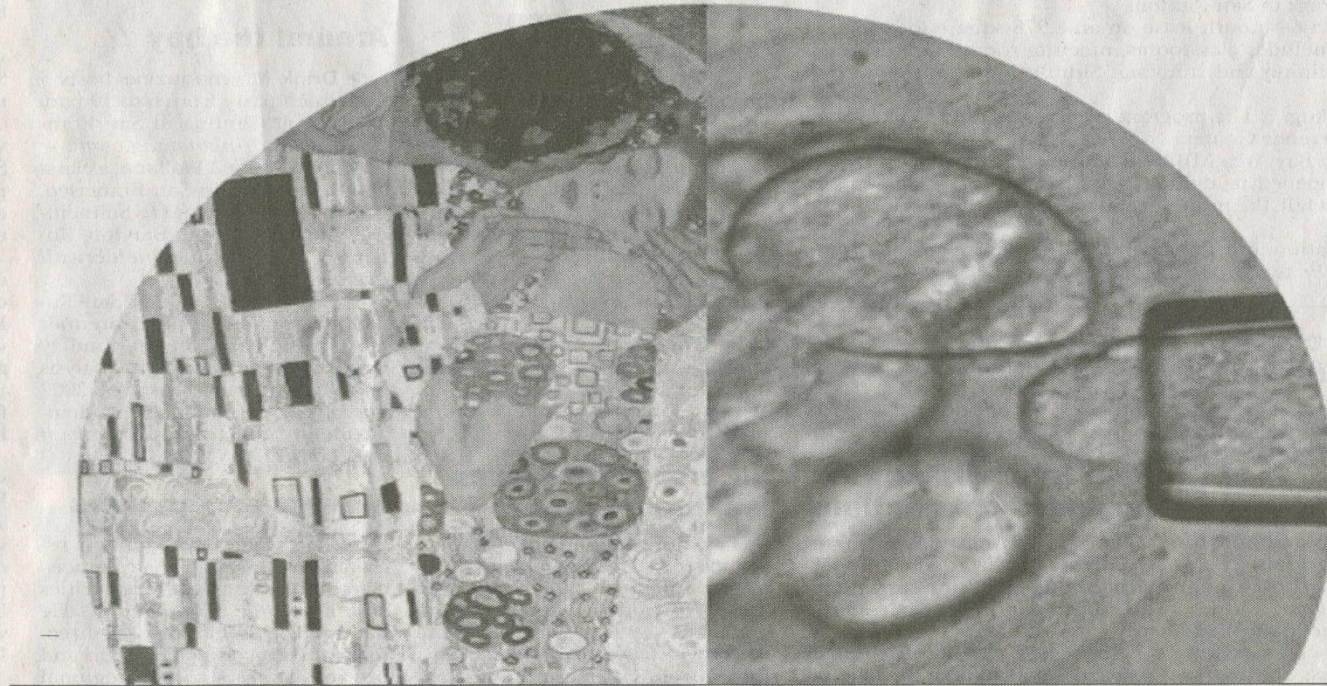
# BUSINESS

★★  
SECTION

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Sunday,  
June 1, 2008

Science is giving in vitro fertilization industry greater ability to screen embryos for illness and to advance stem cell research



*"The Kiss" by Gustav Klimt and illustration by ALLISON GHAMAN / The Chronicle*

## Is sex for reproduction becoming obsolete?



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# Chicken or the Egg?

The treatment or the patient?



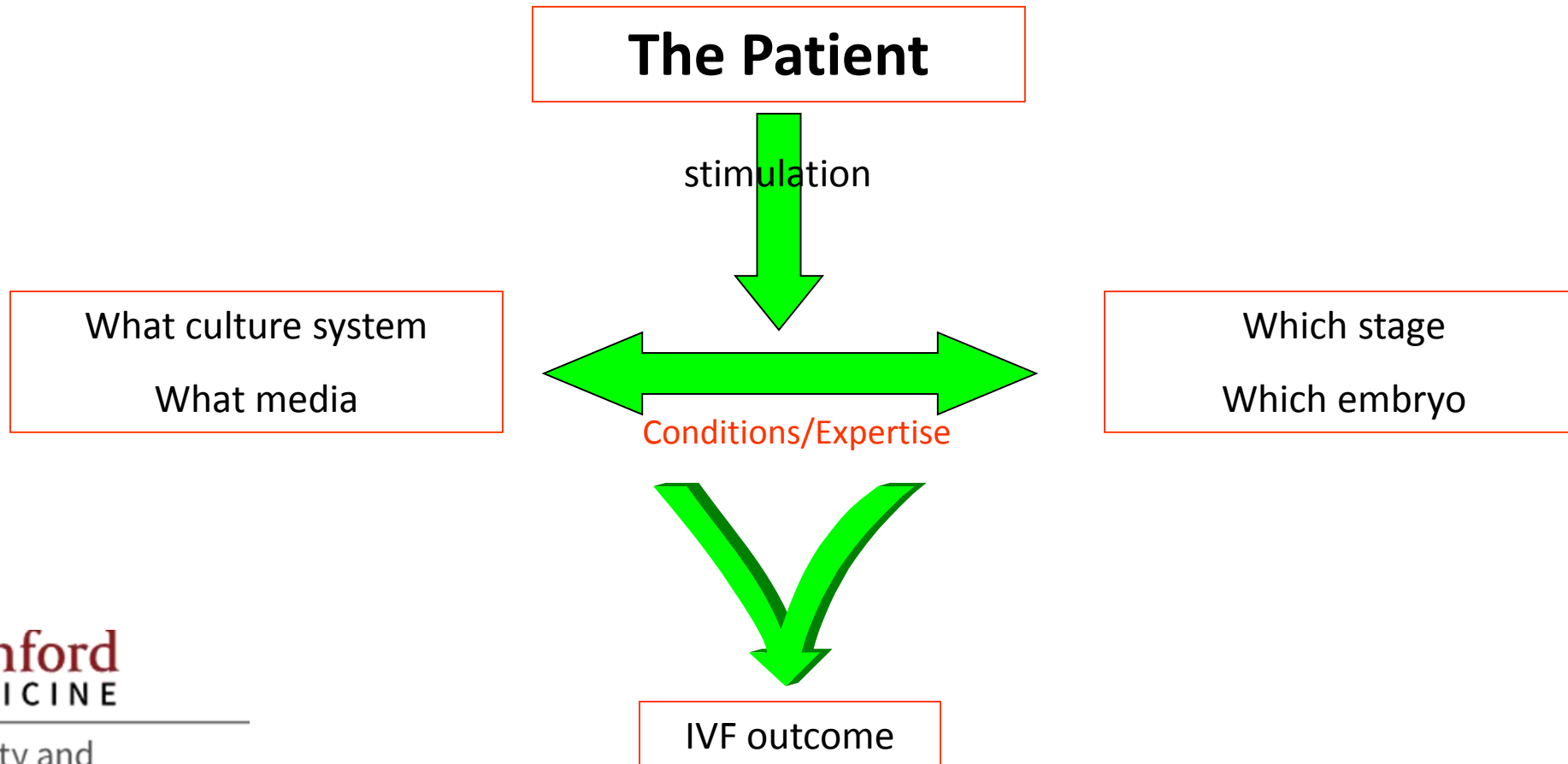
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# What's Important ?



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# How/when can you tell?

- After fertilization
- During pregnancy
- At birth
- Children
- Teen's
- Adults



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# Fertilization

- Pronuclear arrangement
- Fertilization mode/rate
- Genetics



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# Pregnancy

- NIPT
- Amnio/ CVS
- Quad screen
- Nuchal translucency
- Gestational age



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# Birth

- Gestational age
- Labor
- Baby position
- Type of delivery
- Weight
- Apgars
- Genetics



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# Children/Teens

- IQ
- Social
- Development



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# Adults

- Social
- Development
- Late onset disease
- Barker Hypothesis



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# Estimated IVF Birth Efficiency

- 7% of Follicles
- 13% of Oocytes
- 21% of Embryos (D3)
- 42% of Blastocysts



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# Models of Embryo Dysgenesis

- Maternal Nutritional Factors
  - Preimplantation maternal protein restriction reduces ICM and trophoctoderm cell numbers in rat blastocysts, and induces postnatal abnormal growth and hypertension.
  - Obese mice produce embryos with reduced IGF-IR, and small pups that later develop a MBS-like phenotype.
- IVF Culture Conditions
  - affect *in utero* fetal and placental development in mice.
  - influence expression of ICM genes (BMP4) crucial for fetal-placental development.
  - Modify birth weight of IVF singletons born after fresh ET



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Collier 2009, Zhang 2008, Piane 2010, Fleming 2004, Jungheim 2010, Behr 2004,  
Giritharan 2012, Nelissen 2012

# Fresh vs Frozen Cycle outcomes

- Success rate.
- Birth weight
- Ectopic rate

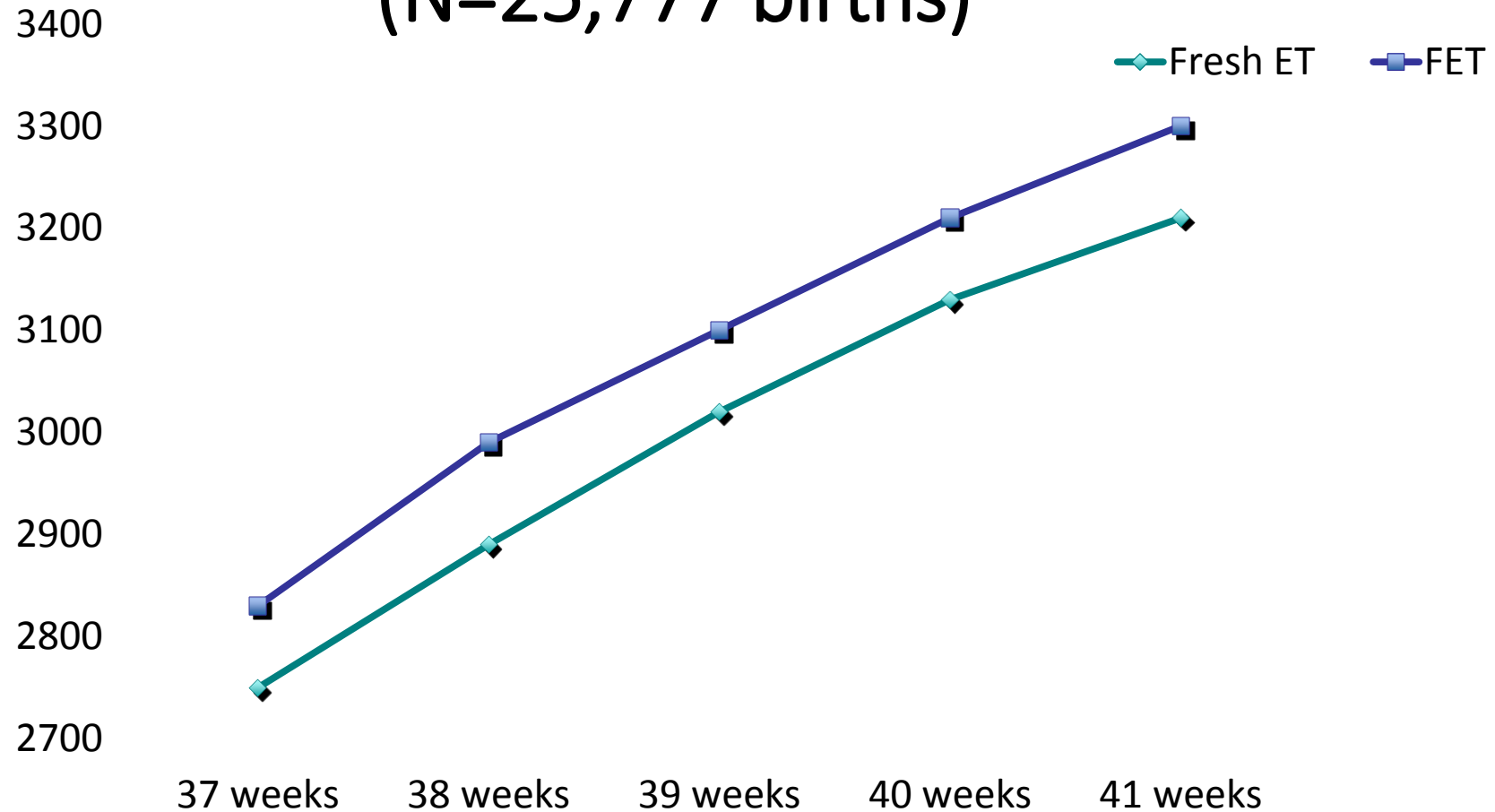


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# Mean Birth Weight of Term IVF Singletons (N=25,777 births)



Mean difference, 90.9 grams



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# Placental Abnormalities in IVF Pregnancies

- Greater placental thickness, increased bilobate and succenturiate morphology and abnormal cord insertion
- larger placentas and a higher placental weight/birthweight ratios
- Decreased second trimester placental perfusion
- Placental protein abnormalities
- Reduced pregnancy associated plasma protein A



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Jauniaux 1990, Daniel 1999, Sellers-Lopez 2010 , Collier 2009, Zhang 2008, Piane 2010, Amor 2009, Haavaldsen 2012

# Serum E2 during IVF & Abnormal Placentation

Elevated E2 during COH-IVF is associated with greater odds of developing pre-eclampsia and delivery of an SGA singleton, perhaps from abnormal remodeling of the spiral artery and trophoblast invasion. *Imudia 2012*

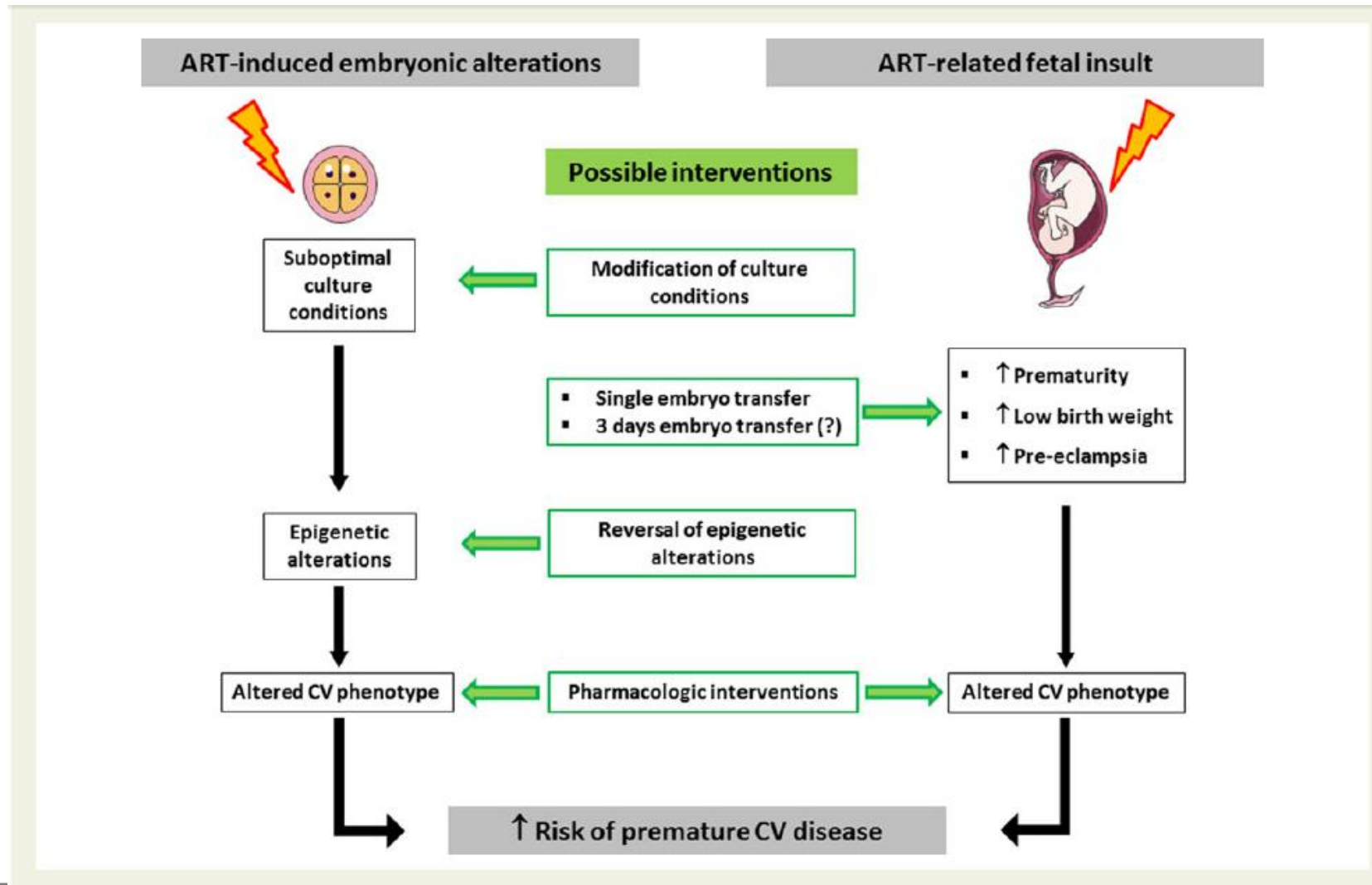
Elevated E2 levels in vitro impair growth of human first trimester cytotrophoblast, suggesting that abnormal spiral artery remodeling from high E2 exposure is due to impaired trophoblast survival. *Skafar 2012*



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# The Barker Hypothesis

- Fetal under nutrition causes disproportional fetal growth and programs later coronary heart disease.
- Death from CHD rose in individuals small at birth (<2500 gm) due to growth failure rather than prematurity.
- Trends in CHD by birth weight are paralleled by similar trends in diabetes and hypertension (metabolic syndrome).
- Highest prevalence of diabetes occurs in people who are small at birth and become obese as adults.
- Highest blood pressures occur in people who at birth are **small for gestational age** and have large placentas.
- Fetal under nutrition slows cell division during critical time intervals in various target tissues by altering cell number, function or distribution.



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**The Barker hypothesis:** Low birth weight is related to increased risk of major organ disease in the adulthood

Low birth weight

Congenital abnormalities in animals

Singleton infants and multiple pregnancies

Imprinting genes

Expression of imprinted genes in animal models

?

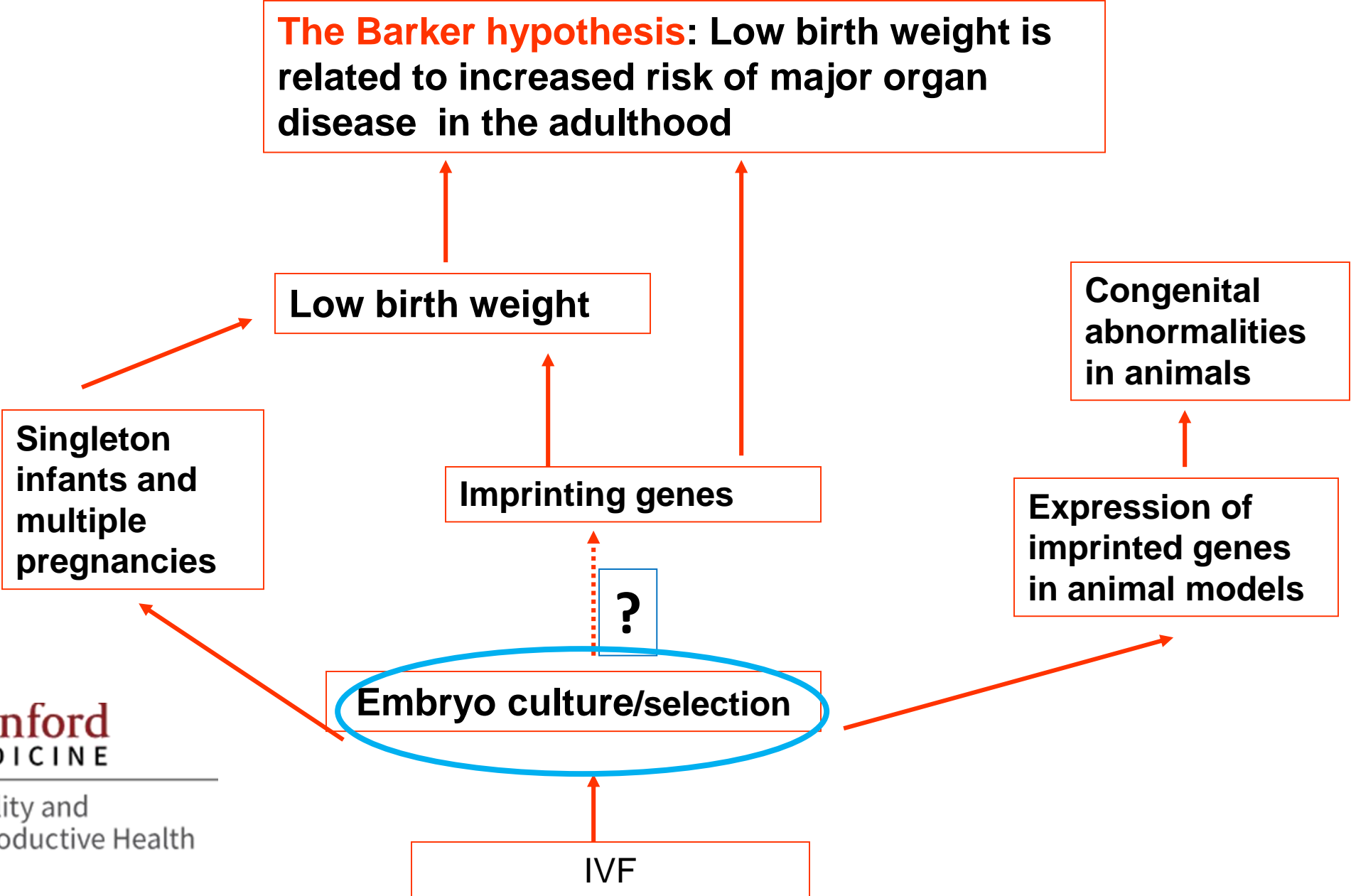
Embryo culture/selection

IVF



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# Dutch Famine 1944-1945

## People exposed to famine

- in early gestation have a more atherogenic lipid profile, and a higher BMI and waist circumference at 50 yrs (women),
- in mid- to late-gestation have reduced glucose tolerance, and
- in late gestation with protein restriction have higher blood pressure.



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Ravelli 1998, 1999, Roseboom 2001

# Genetic testing explosion

- Preconception carrier screening
- Cancer genetics (BRCA, Lynch)
- Cardiac genetics ( Marfans)
- Neuro developmental genetics (Fragile X)
- High density arrays for fetal/neonatal anomalies
- Whole exome sequencing



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# How Can We Optimize the Health of Our IVF Offspring?

- Optimize maternal nutrition and lifestyle before conception.
- Investigate *in vitro* conditions that alter genes crucial for fetal-placental development.
- Reduce supraphysiological levels of circulating estradiol that accompany ovarian stimulation for IVF.
- Single embryo transfer
- Frozen embryo transfer



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[www.sciencedirect.com](http://www.sciencedirect.com)  
[www.rbmonline.com](http://www.rbmonline.com)



## REVIEW

# Health outcomes of children born after IVF/ICSI: a review of current expert opinion and literature



BCJM Fauser <sup>a,\*</sup>, P Devroey <sup>b</sup>, K Diedrich <sup>c</sup>, B Balaban <sup>d</sup>, M Bonduelle <sup>e</sup>,  
HA Delemarre-van de Waal <sup>f</sup>, C Estella <sup>g,h</sup>, D Ezcurra <sup>i</sup>, JPM Geraedts <sup>j</sup>,  
CM Howles <sup>i</sup>, L Lerner-Geva <sup>k</sup>, J Serna <sup>l</sup>, D Wells <sup>m</sup>, Evian Annual  
Reproduction (EVAR) Workshop Group 2011

**Table 2** Birth defect rates in infants (singletons and multiples) after transfer of frozen and fresh IVF and ICSI early cleavage-stage embryos.

<i>Group</i>	<i>Cryopreserved cycles</i>	<i>Fresh cycles</i>
Belva et al. (2008)		
IVF	12/390 (3.1)	112/2955 (3.8)
ICSI	35/547 (6.4)	96/2840 (3.4)
Källén et al. (2005) <sup>a</sup>		
IVF	81/1055 (7.7)	832/10,228 (8.1)
ICSI	36/419 (8.6)	392/4530 (8.7)

Values are *n*/total (%).

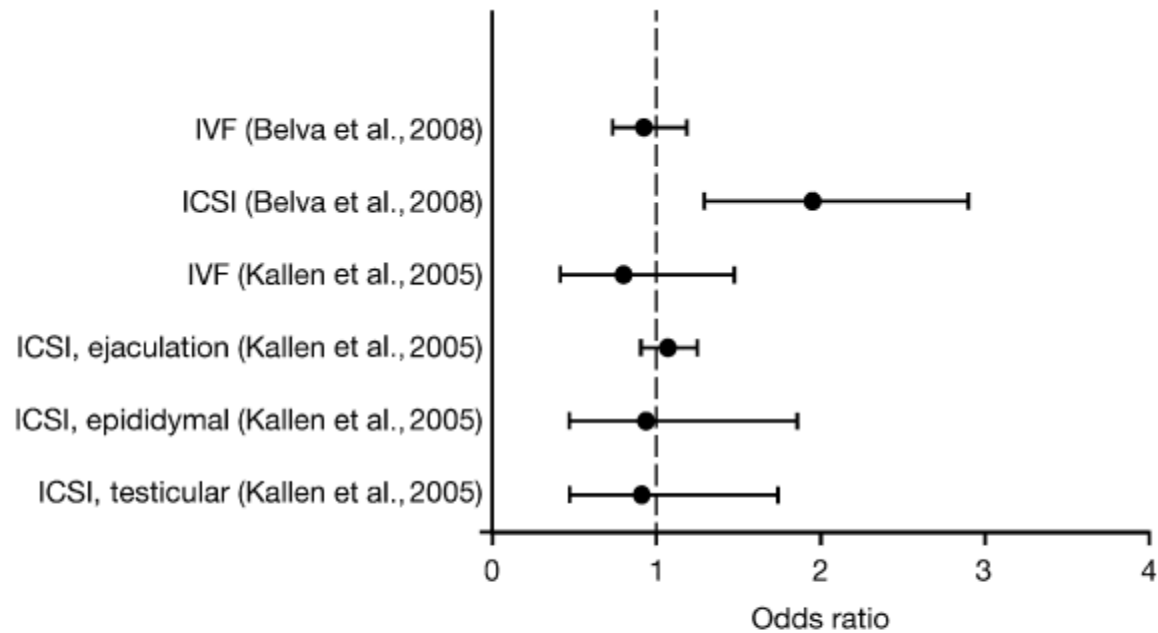
ICSI = intracytoplasmic sperm injection.

<sup>a</sup>Fresh IVF = 1.00, adjusted for year of birth, maternal age and number of infants in birth.



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**Figure 1** Odds ratios for birth defects after transfer of frozen and fresh IVF and ICSI early cleavage-stage embryos. ICSI = intracytoplasmic sperm injection (Belva et al., 2008; Källén et al., 2005).



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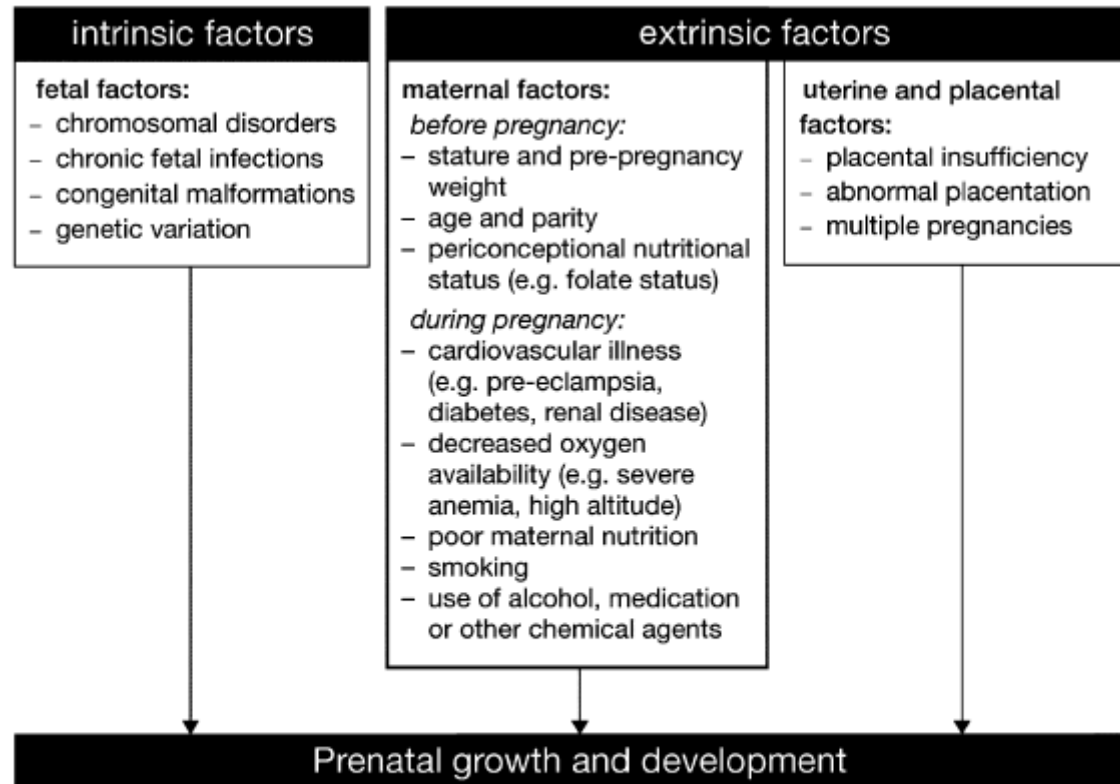
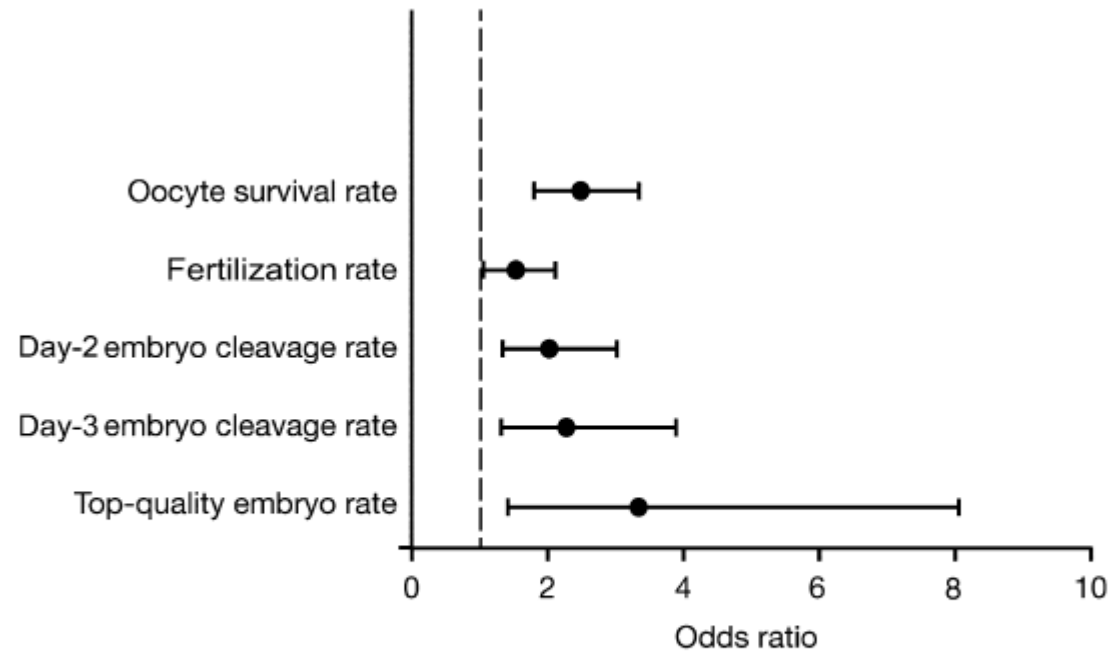


Figure 2 Biological factors influencing growth and development. Adapted from: [Ceelen et al., 2008b](#).



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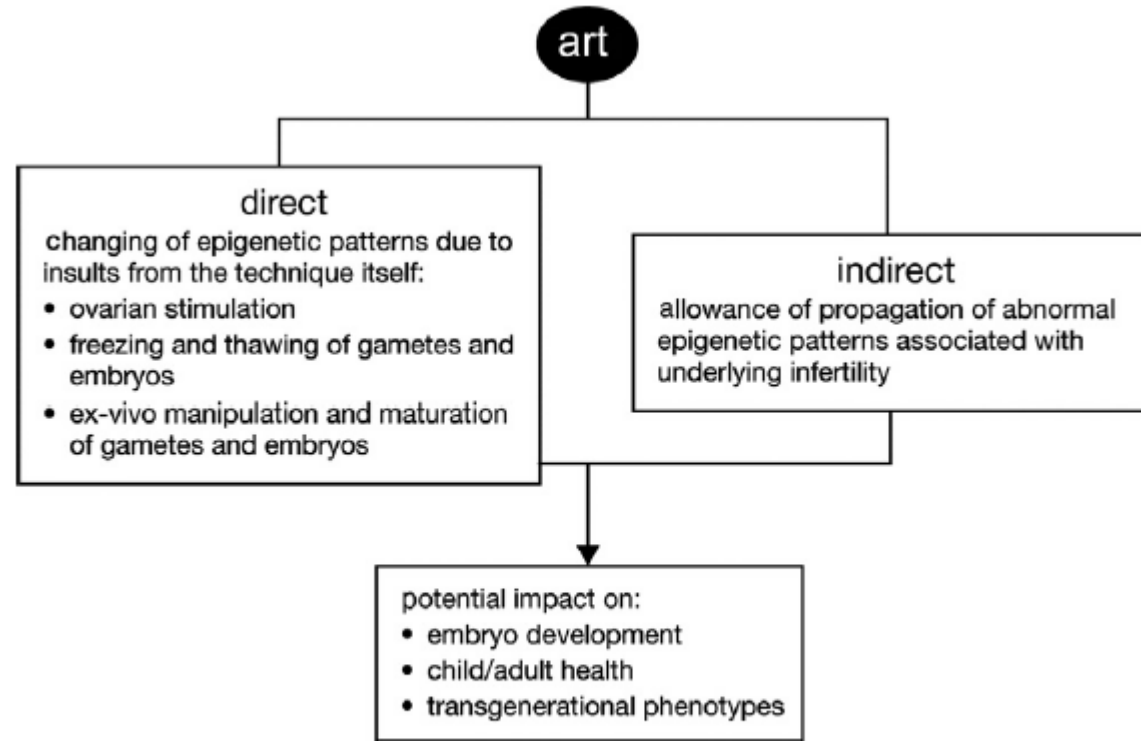
**Figure 3** Results from a meta-analysis of five studies involving 4282 vitrified oocytes, 3524 fresh oocytes and 361 slow-frozen oocytes (2005–2009). Adapted from: [Cobo and Diaz, 2011](#).



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**Figure 4** Assisted reproduction treatment and potential alterations of the phenotypical fetal/adult programme.

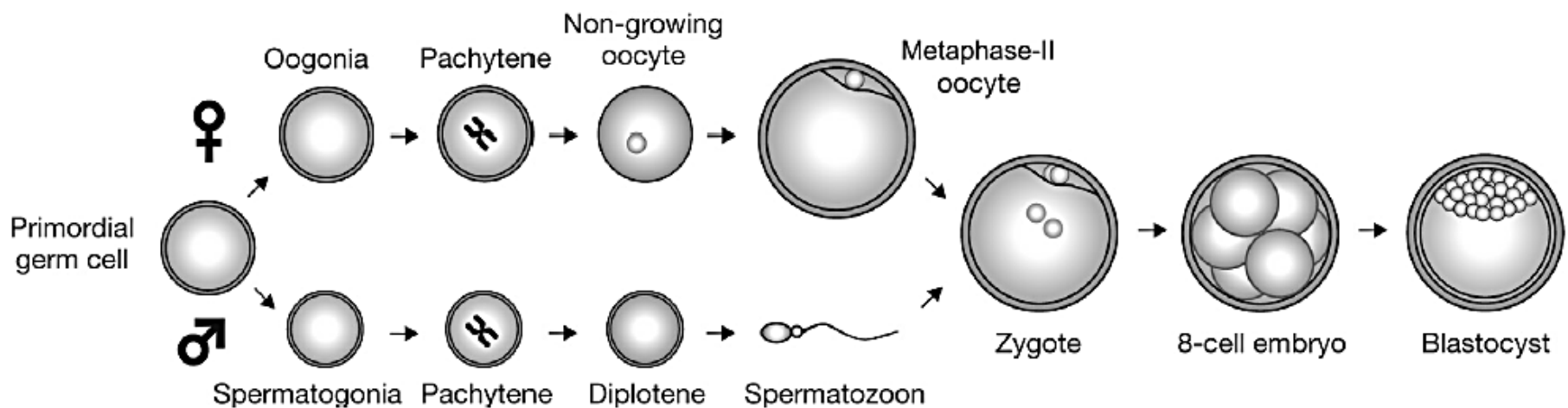
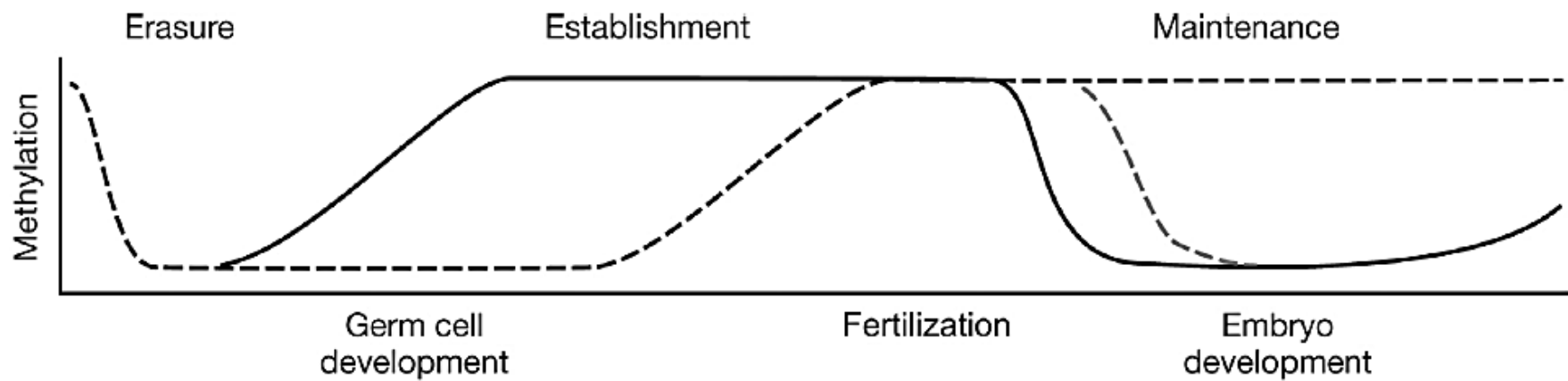


Figure 5 Stages of imprinting in early life. Adapted from: Gosden et al., 2003.



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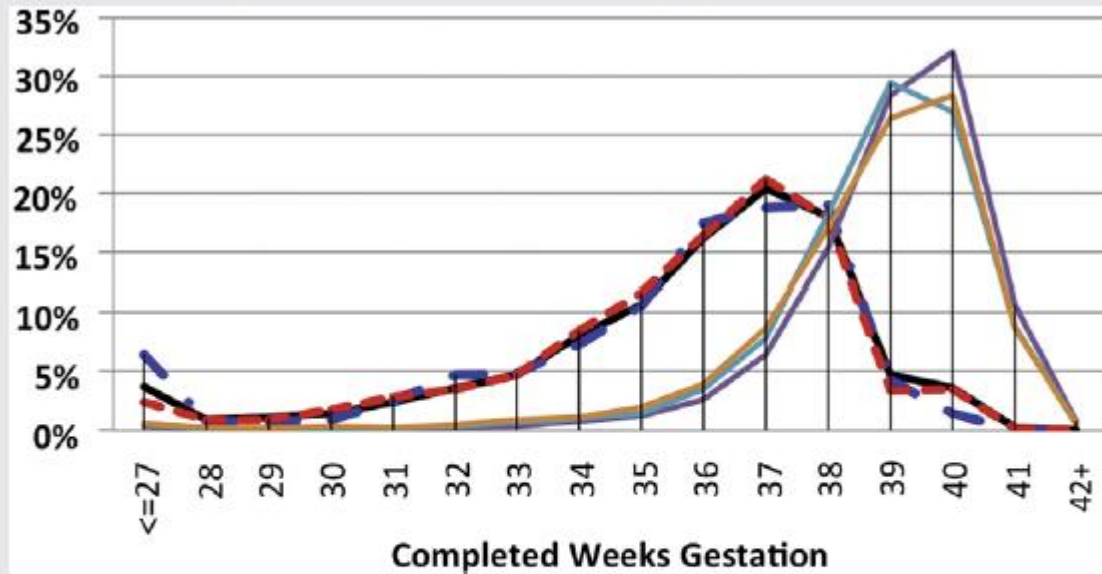
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# Perinatal outcomes associated with assisted reproductive technology: the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART)

Eugene Declercq, Ph.D.,<sup>a</sup> Barbara Luke, Sc.D., M.P.H.,<sup>b</sup> Candice Belanoff, Sc.D.,<sup>a</sup> Howard Cabral, Ph.D.,<sup>a</sup> Hafsatu Diop, M.D.,<sup>c</sup> Daksha Gopal, M.P.H.,<sup>a</sup> Lan Hoang, M.P.H.,<sup>a</sup> Milton Kotelchuck, Ph.D.,<sup>d</sup> Judy E. Stern, Ph.D.,<sup>e</sup> and Mark D. Hornstein, M.D.<sup>f</sup>

<sup>a</sup> Boston University School of Public Health, Boston, Massachusetts; <sup>b</sup> Michigan State University, East Lansing, Michigan; <sup>c</sup> Massachusetts Department of Public Health, Boston, Massachusetts; <sup>d</sup> Mass General Hospital for Children, Harvard Medical School, Boston, Massachusetts; <sup>e</sup> Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire; and <sup>f</sup> Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts





Gestational age distribution, by fertility groups, singletons, and twins. *Solid black: fertile twin; dashed blue: subfertile twin; dashed red: assisted reproductive technology (ART) twin; solid purple: fertile singleton; solid teal: subfertile singleton; solid orange: ART singleton.*  
 Declercq. *Perinatal outcomes associated with ART. Fertil Steril* 2015.



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# Conclusions

- People don't do IVF because they don't like sex
- If you need IVF it's safe when performed responsibly
- IVF does contribute to poorer neonatal (and potentially long term) outcomes.
- Difficult to separate the chicken and the egg



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