Well begun is half done

OCTOBER 4, 2010

**Environment Special:**
The oceans—why 70% of our planet is in danger

**Afghanistan:**
After a flawed election, how the world can help

# TIME

## How the first nine months shape the rest of your life

The new science of fetal origins

BY ANNIE MURPHY PAUL

www.time.com

**Early**

Glucose metabolism

Obesity

Lipid profile

Coagulation

Coronary heart disease

Breast cancer

Stress responsiveness

Food preference

Depression

Cognition

Schizophrenia

Reproductive success

**Mid**

Glucose metabolism

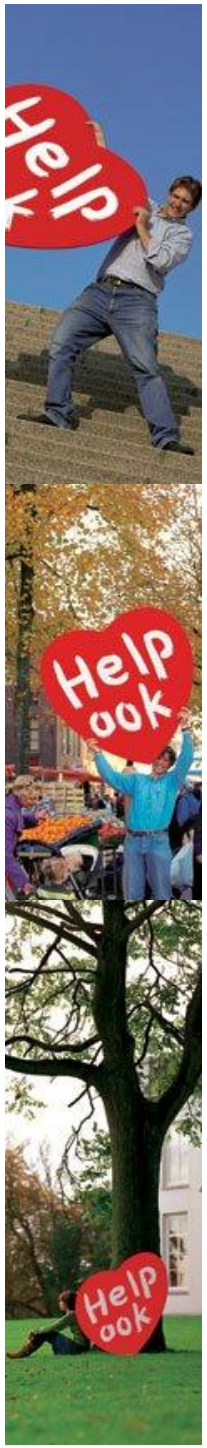
Obstructive airways disease

Microalbuminurea

Reproductive success

**Late**

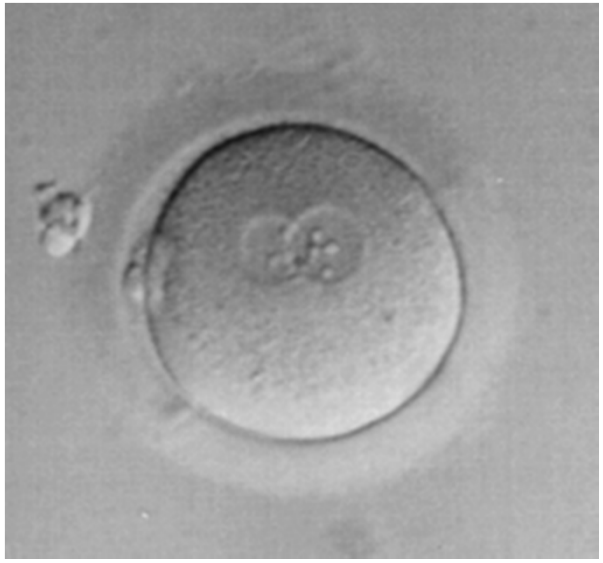
Glucose metabolism




Nederlandse Hartstichting

# “Prevention of CHD starts with the birth of a childwish”


# The embryo is sensitive to its environment



Evening News

Meet Louise, the world's first test-tube arrival

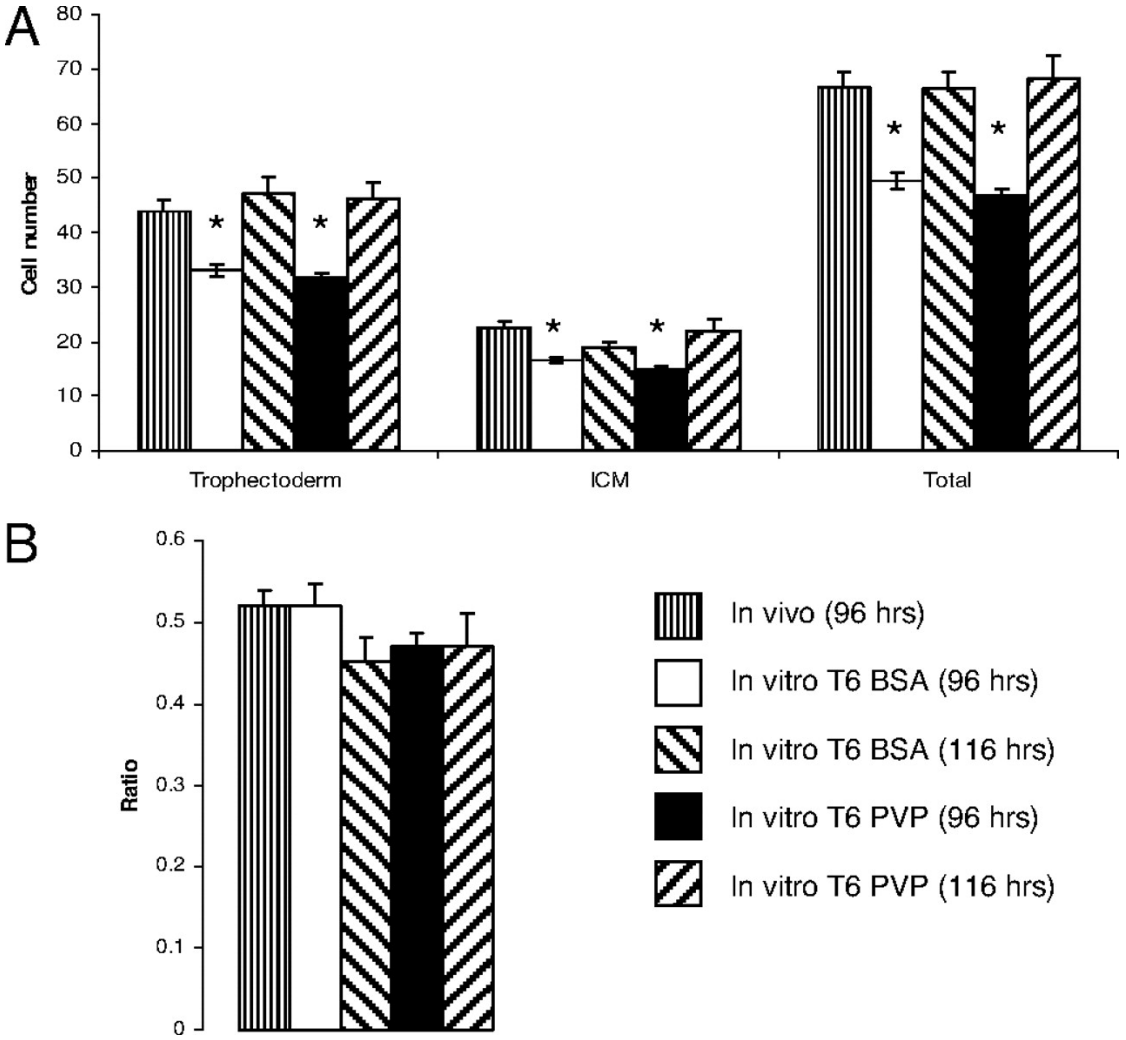
SUPERBABE

Wide-eyed Louise Brown pictured in hospital 18 hours after she was born. Today she's doing well. See Page Three

# Large offspring syndrome animal husbandry

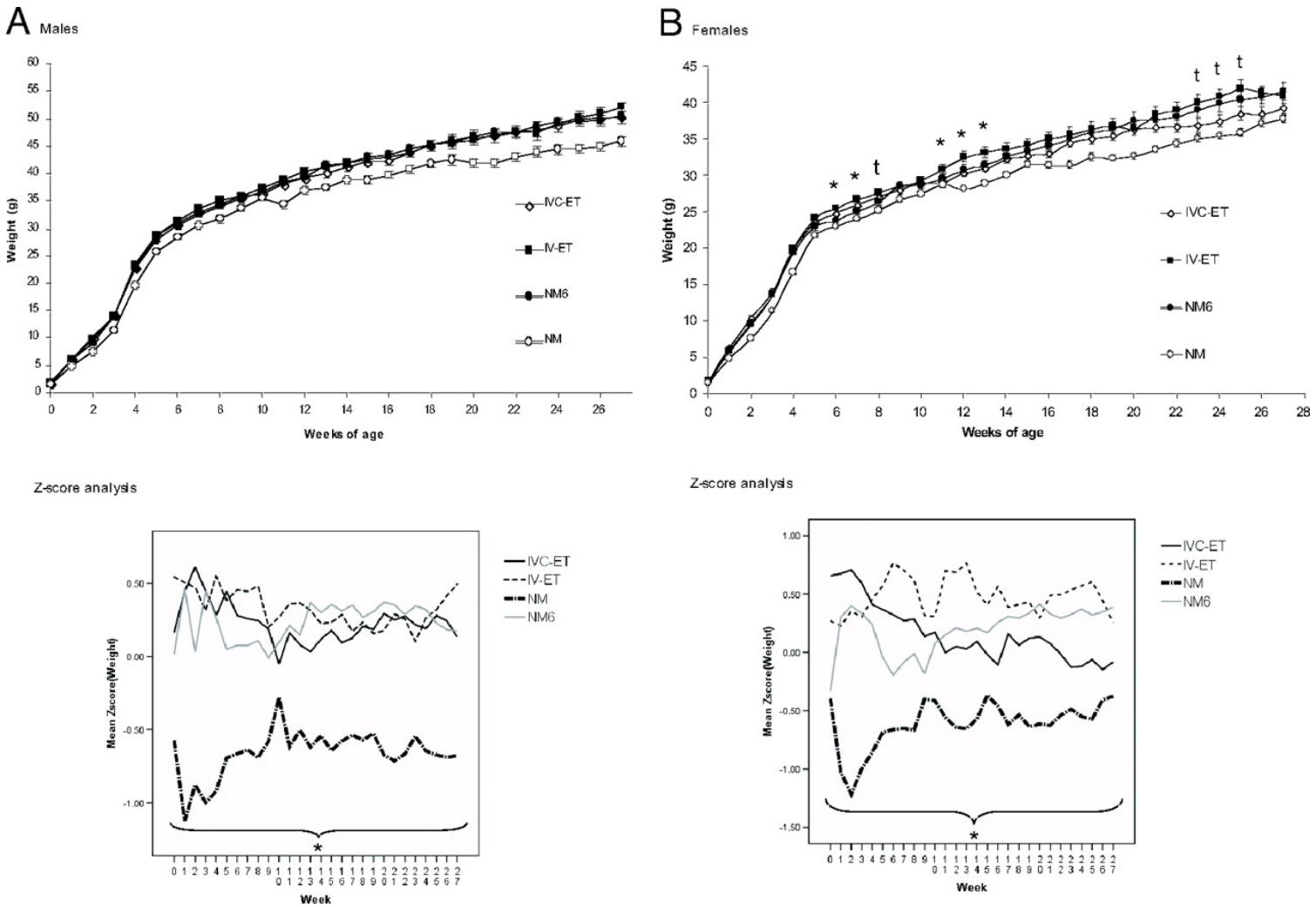
# Mouse embryo culture induces changes in postnatal phenotype including raised systolic blood pressure

**Embryos developing in culture have fewer cells than those developing in vivo.**



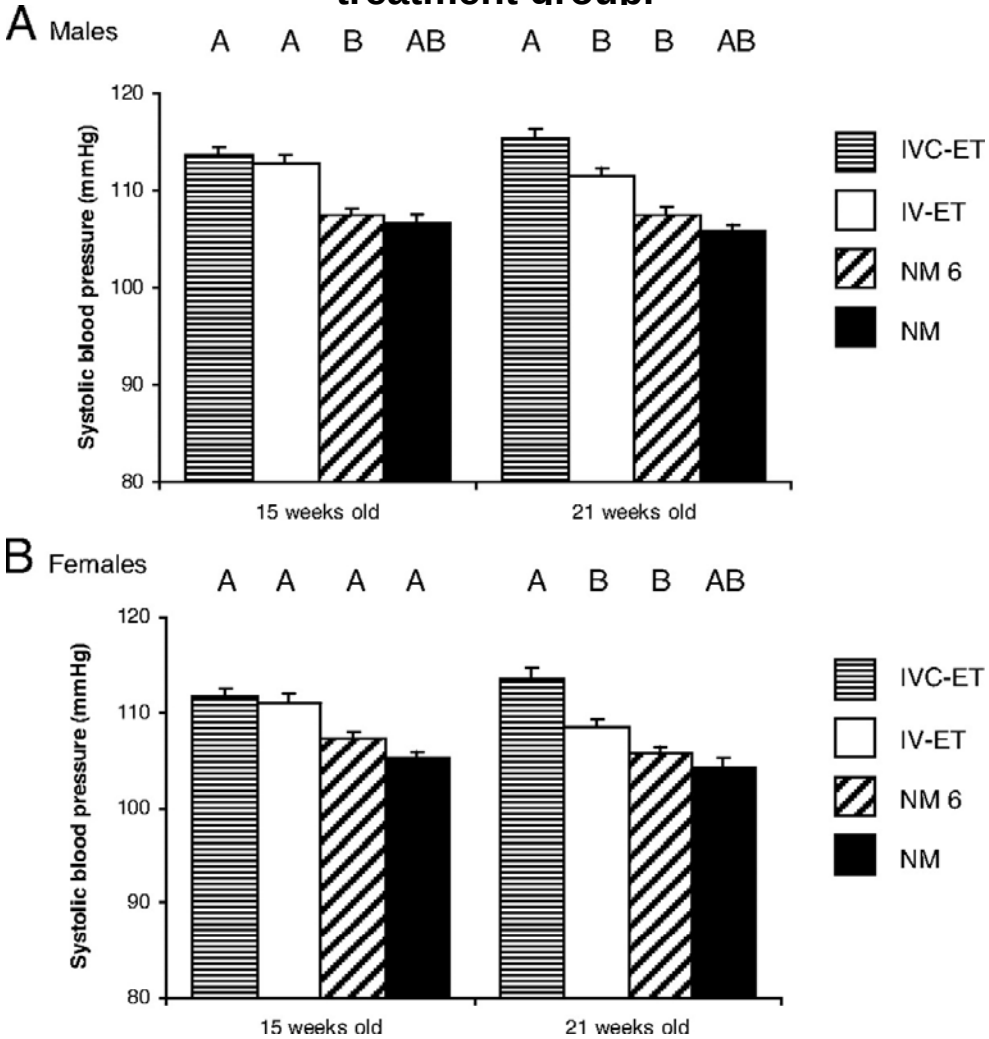

**Watkins A J et al. PNAS 2007;104:5449-5454**

# Embryo culture and transfer treatments have minimal effect on postnatal growth.



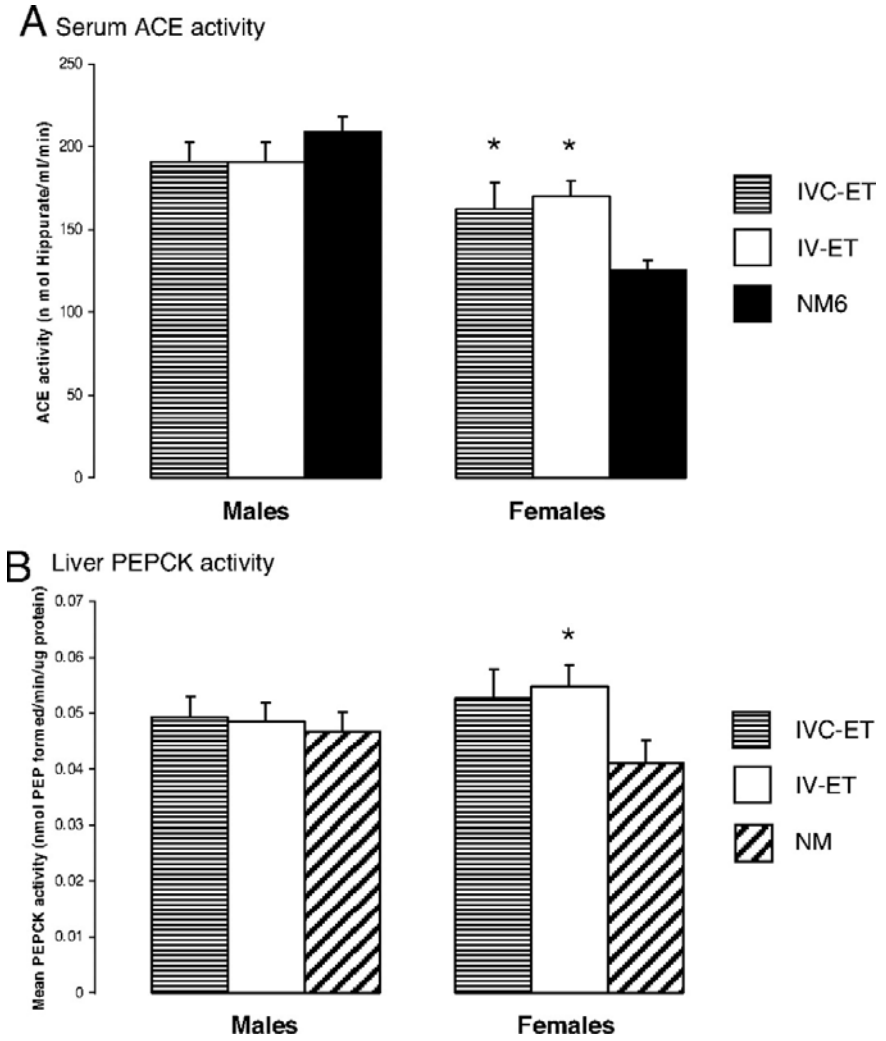

Watkins A J et al. PNAS 2007;104:5449-5454

**Embryo culture and transfer treatments induce elevation in postnatal SBP. Mean (±SEM) SBP of male (n = 20–31 per treatment) (A) and female (n = 19–31) (B) offspring from 6–10 litters per treatment group.**



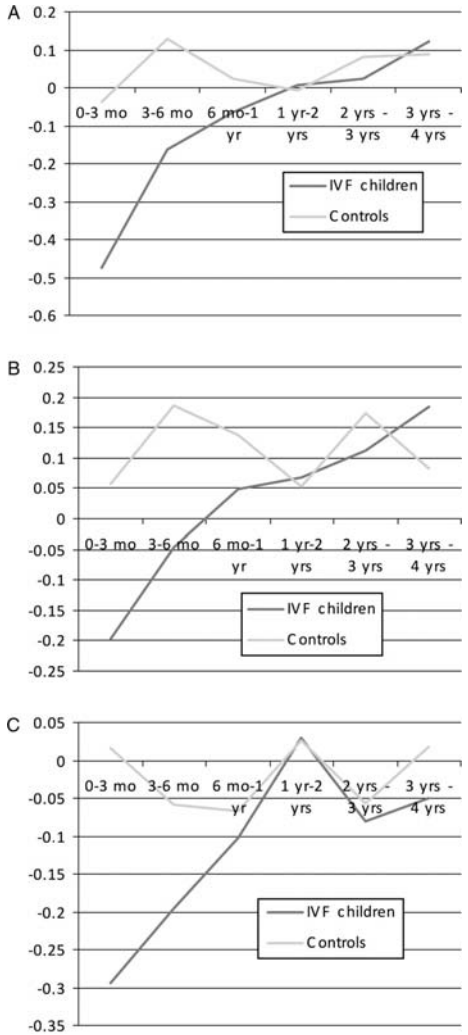

**Watkins A J et al. PNAS 2007;104:5449-5454**

**Embryo culture and/or transfer cause elevation in female offspring serum ACE and PEPCK activities.**




**Watkins A J et al. PNAS 2007;104:5449-5454**

**Postnatal measurements of weight (n = 5380, A), height (n = 4559 B) and BMI (n = 4540, C) of 193 IVF and 199 control children.**

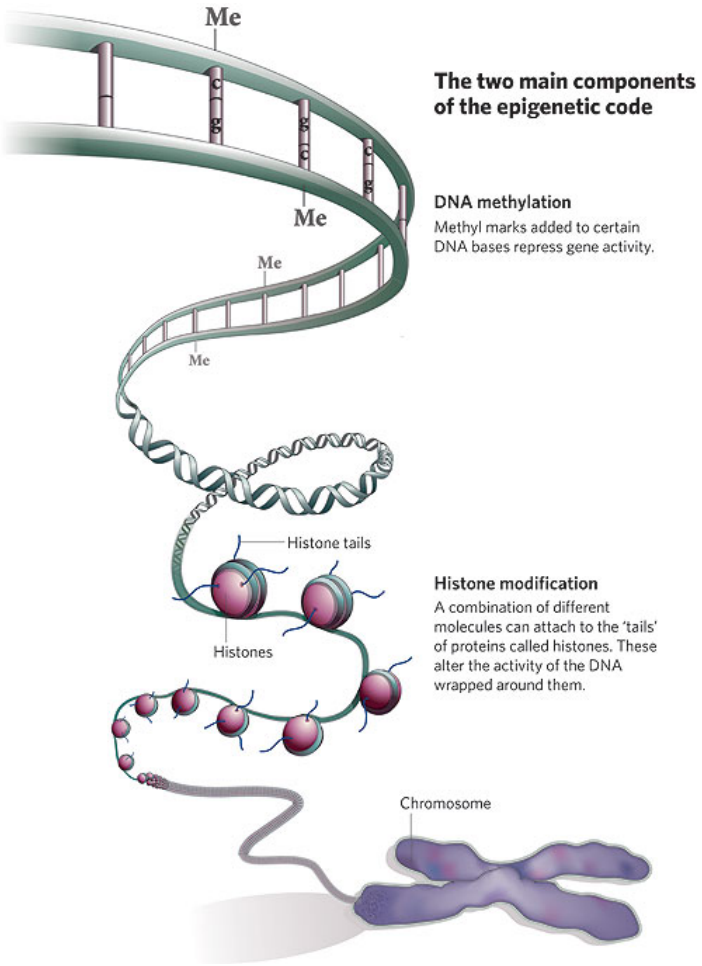



**Ceelen M et al. Hum. Reprod. 2009;24:2788-2795**



human reproduction

# epigenetics



# Epigenetic changes after IVF

Table 1. Comparison of reported neuroendocrine findings in children born after ARTs in comparison to naturally conceived controls

| Characteristic | ART versus controls | References |
|---|---|---|
| *Growth* | | |
| Birthweight | ↓ | Bergh et al. (1999), Miles et al. (2007), Ceelen et al. (2007a), Sakka et al. (2009a) |
| Gestational age | ↓ | Ceelen et al. (2007a), Sakka et al. (2009a) |
| Gestational age | ≈ | Miles et al. (2007) |
| Postnatal growth | ≈ | Kai et al. (2006), Ceelen et al. (2007a, 2007b, 2008a), Sakka et al. (2009a) |
| Postnatal growth | ↑ | Miles et al. (2007) |
| IGF-I in childhood | ≈ | Kai et al. (2006), Sakka et al. (2009a) |
| IGFBP3 in childhood | ≈ | Kai et al. (2006) |
| *Cardiometabolic status* | | |
| Systolic BP | ↑ | Ceelen et al.( 2008a), Sakka et al. (2009a) |
| Diastolic BP | ↑ | Ceelen et al. (2008a), Sakka et al. (2009a) |
| Fasting blood glucose | ↑ | Ceelen et al. (2008a) |
| Fasting blood glucose | ≈ | Miles et al. (2007), Sakka et al. (2009a) |
| Triglycerides | ↓ | Miles et al. (2007) |
| Triglycerides | ↑ | Sakka et al. (2009a) |
| HDL | ↑ | Miles et al. (2007) |
| HDL | ≈ | Sakka et al. (2009a) |
| Adiponectin | ≈ | Sakka et al., 2009a |
| Leptin | ≈ | Sakka et al. (2009a) |
| HsCRP | ≈ | Sakka et al. (2009a) |
| IL-6 | ≈ | Sakka et al. (2009a) |
| *Puberty* | | |
| Timing and progression | ≈ | Ceelen et al. (2008b) |
| *Precocious adrenarche* | | |
| DHEA-S | ↑ | Ceelen et al. (2008b) |
| DHEA-S | ↑, only in SGA-ART | Sakka et al. (2009a) |
| *Thyroid function* | | |
| TSH | ↑ | Sakka et al. (2009b) |
| T3, T4 | ≈ | Sakka et al. (2009b) |

Abbreviations/explanations of symbols: ART, assisted reproductive technologies; IGF-I, insulin-like growth factor I; IGFBP3, insulin-like growth factor binding protein 3; BP, blood pressure; HDL, high-density lipoprotein; IL-6, high-sensitivity interleukin-6; hsCRP, high-sensitivity C-reactive protein; SGA, small for gestational age; DHEA-S, dehydroepiandrosterone-sulphate; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; ↑, increased; ↓, reduced; ≈, similar; no statistical difference.

| | IVF children | | Controls | | *P* value |
|---|---|---|---|---|---|
| Perinatal characteristics | | | | | |
| No. of subjects | 225 | | 225 | | |
| Birth weight (kg) | 3.22 | | 3.44 | | 0.001 |
| | | | | | |
| Age (yr) | 12.3 | | 12.3 | | 0.35 |
| Gender (% male) | 49 | | 49 | | 1.00 |
| Height (cm) | 156.4 | | 155.8 | | 0.39 |
| Body weight (kg) | 47.8 | | 46.7 | | 0.19 |
| BMI (kg/m2) | 19.1 | | 18.7 | | 0.25 |
| Sum of skinfolds (mm) | 40.5 | | 36.9 | | 0.04 |
| | | | | | |
| Systolic blood pressure (mm Hg) | | 109 | | 105 | 0.001 |
| Diastolic blood pressure (mm Hg) | | 61 | | 59 | 0.001 |
| Heart rate (beats per min) | 74 | | 72 | | 0.02 |
| | | | | | |
| Fasting glucose (mmol/liter) | 5.0 | | 4.8 | | 0.005 |

# Cardiometabolic differences in children born after IVF: follow-up study

**Ceelen et al (2008)**
**J Clin Endocrinol Metab 93: 1682-1688**

Comparison of 225 children born after IVF
with a control group of 225 spontaneously conceived children matched for age and sex.
All children (mean age at the time of follow-up 12.3 years, range 8–18 years) were born to parents with suboptimal fertility.

Systolic and diastolic blood pressures, the sum of skin-fold thicknesses and fasting glucose levels were all significantly higher in children conceived following IVF than in controls.

| | IVF | Controls |
|---|---|---|
| **Systolic blood pressure (mm Hg)** | **109** | **104** |
| **Diastolic blood pressure** | **61** | **59** |
| **Fasting blood glucose (mM)** | **5.0** | **4.8** |

**… the periconception period might contain a critical time window during which cardiometabolic function could be perturbed …**
**(highlighting) the importance of continued monitoring of the postnatal development of children born after IVF.**