

# Longer term outcome of IVF children

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ESHRE campus  
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## Background

Previous studies indicate

- an increased risk of major malformations in ART compared to natural conception
- low birthweight and prematurity among ART conceived children even after controlling for extensive maternal factors and multiple gestation

This outcome has been recently summarised in meta analyses

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## Remaining questions?

- Do **infertility treatments** have a direct effect on adverse outcomes?
  - Role of **ovarian stimulation** f.i.?
  - Does **embryo manipulation** (biopsy, assisted hatching, polar body biopsy) has an effect?
  - Do **culture** conditions play a role in imprinting disturbances?
- Are there increased risks for **adverse outcomes in childhood** (mediated by LBW or prematurity)?

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## Long-term follow-up studies

- Literature data of controlled studies on the developmental long-term outcome of ART children, which include a matching of plurality of gestation (Review Ludwig AK 2006)

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## Long-term follow-up studies

- Medical
- Neurological
- Cancer
- Development
- Behavior

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## Medical outcome: physical examination

Reference	Number ICSI / IVF / SC	Age	Physical examination
Belva 2006	150 / - / 147	8y	No difference phys ex, growth, BMI
Bonduelle 2005	540/437/538*	4 ½ - 5 ½y	No difference in phys examination, growth, vision, hearing
Brandes 1992	- / 116 / 116*	12 - 45m / 24m	No difference in growth
Koivurova 2003	- / 299/ 588	up to 3 years	IVF singletons smaller and lighter until 3 years
Mau 2006	236/ 173/ 1530 68/ 67/ 70	0- 36m 5y	No difference in growth No difference in growth
Pinborg 2003	634s+472tw/ 1132 SC	3 - 4y	No difference in hearing and vision
Saunders 1993	- / 289/ 146	2 y	No difference in growth
Stromberg 2002	- /5 680/ 11 360	>18m - 14y	Visual disorders singletons OR 2.6 (CI 0.8 - 6.0)
Wennerholm 1998	- /225 / 252*	< 18m	No difference in growth No more children < 2 SD

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\* Prospective study

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## Physical examination

- **None of the studies found differences** in the physical health up to 5 years
- The incidence of vision and hearing impairment was not increased in most studies
  - However one group (Stromberg et al.) found more severe vision impairment in IVF children up to 14 years (not significant)

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## Physical examination

- General growth (height, weight, head circumference) did not differ in IVF compared to SC children.
  - In one group catch up growth was still behind at 3y (Koivurova et al)
  - One study found IVF children slightly taller and higher levels of IGFII (Cutfield et al 2007)

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## Medical outcome: Illness / surgical intervention

Reference	Number ICSI / IVF / SC	Age	Illness / surgical intervention
Belva 2006	150 / - / 147*	8y	No difference phys ex, growth, BMI
Bonduelle 2005	540/437/538* > 32w gest	4 ½ - 5 ½y	<b>More</b> childhood illnesses / admissions / more surgery
Ericson 2002	- / 9 056 / 1 427	1-11y	<b>OR 1.40</b> hospital admissions (sing) at 6 years (astma, infect.)
Kallen 2006	11 283 / 16 120	1w - >11y	<b>OR 2.09</b> hospital admissions (adj mat age, parity, smoking)
Koivurova 2003	- / 299 / 588	up to 3 years	<b>OR 2.1</b> at least one illness (sing) <b>OR 3.1</b> hosp admissions
Pinborg 2004	5 139 / 10 239 twins	2 - 7y	No difference between IVF twins and SC twins
Saunders 1993	- / 289 / 146*	2y	No difference hospital admissions or surgery
Wennerholm 1998	- / 225 / 252*	< 18m	No difference in childhood illness or chronic disease

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\*Prospective study

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## Childhood disease in IVF

- More childhood disease in singletons, but contradicting results. Less difference in twins. More data needed
  - More childhood admissions up to 5 years were reported in IVF (and ICSI) (Bonduelle et al. 2005)
  - More children with at least 1 illness and cumulative incidence of diseases higher illnesses up to 3 years (Koivurova et al. 2003)
  - More children up to 6 years were hospitalised (asthma, infections) (Ericson et al. 2002)
  - Most studies did not find a higher incidence of childhood or chronic disease

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## Surgical interventions

- Some studies observed a higher rate of surgery at 5y (Bonduelle et al. 2004, 2005), while others did not
  - Some surgery was minor (tympanic drain, adenoidectomy). This could reflect a higher rate of minor infections
  - More genito-urinary surgery in ICSI boys corresponds to a higher rate of genito-urinary malformations

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## Long term FU studies on ICSI

Bonduelle et al. 2005

- Prospective controlled
- Multicentre EU study at 5y
  - 1515 ICSI, IVF and SC
  - Medical
  - Cognitive
  - Behavioral



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## Major malformations at 5 years

	ICSI n 540	IVF n 437	Control n 538	p-value
Neonatal	3.3%	2.1%	1.9%	ns
Childhood	<b>3.0%<sup>1</sup></b>	2.3%	0.4% <sup>1</sup>	<sup>1</sup> 0.001
Total major malformation	<b>6.3%<sup>2</sup></b>	4.3%	2.2% <sup>2</sup>	<sup>2</sup> 0.001

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## Major malformations at 5 years

Increase in ICSI > IVF > control children

- Not detected at birth
- Partially due to increased defects in uro-genital system
- Higher malformation rate in ICSI boys 8.2% > girls 3.6%

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## Medical History at 5 y

	ICSI	IVF	NC
Hospital Admissions (%)	<b>31*</b>	28	20*
Surgery (%)	<b>24*</b>	22	14*
Medication (%)	13	12	12
Therapy (%) Speech, Physiotherapy, Psychological	<b>12*</b>	9	5*

\*Significant ICSI vs NC

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## Growth Parameters at 5 y

	ICSI	IVF	NC
Mean (SD) Height, cms	111 (5.5)	111 (5.0)	111 (5.3)
Mean (SD) Weight, kgs	19.5 (3.2)	19.3 (2.8)	19.7 (3.0)
Mean (SD) Head Circumf, cms	51.6 (1.6)	51.8 (1.4)	51.5 (1.4)

NS ICSI vs IVF and NC

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## Long-term follow-up studies

- Medical
- Neurological
- Cancer
- Development
- Behavior

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## Neurological outcome

Reference	Number ICSI/IVF /SC	Age	Neurological outcome
Belva 2006	150 / - / 147*	8y	No difference
Bonduelle 2005	540 / 437 / 538* > 32w gest	4 ½ - 5 ½y	No difference
Ericson 2002	9 056 / 1 427	1-11y	<b>OR 1.7 (1.1-2.7) cerebral palsy</b> OR N.S. for mental retardation
Kallen 2006	16 280 / pop	up to 11y	Neurologic problems related to prem
Lidegaard	6 052 / 442 345	4 ½ IVF 4.1 SC	<b>OR 1.8 (1.2-2.8) cerebral palsy</b>
Pinborg 2004	3 393 / 10 239	2 - 7y	OR N.S. neurological ex. in twins
Saunders 1993	289 / 146*	2y	OR N.S. neurological sequelae
Stromberg 2002	5 680 / 11 360	>18m - 14y	<b>OR 1.4 (1.0-2.1) disability sing</b> <b>OR 1.4 (1.0-2.1) cerebr. palsy s.</b>
Wennerholm 1998	- / 225 / 252*	< 18m	No difference No difference in eye disorder

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## Neurological outcome

- **In singletons**, three large cohort studies reported an increased risk of cerebral palsy 1.7 – 2.8 fold, based on registry data with longer FU period (up to 14y)
  - Other (smaller) studies based on examination at 2 - 5 y, did not find differences
- **IVF twins** did not show differences in neurological disabilities compared to SC twins

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## Long-term follow-up studies

- Medical
- Neurological
- **Cancer**
- Development
- Behaviour

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## Cancer

Reference	Number IVF (ICSI) / SC	Age	Cancer
Bergh 2006	5 856	1 - 14y	No difference
Brinton 2004	51 063 Infertility	10y	SIR 1.14 (0.8 – 1.5)
Bruinsma 2000	5 247	0 - 15y	SIR 1.39 (0.62 – 3.09)
Doyle 1998	2 507	8.6y	SIR 0.57 (0.07-2.06)
Ericson 2002	9 056 / 1 427	1-11y	OR 0.88 (0.44-1.58)
Kallen 2006	> 16 000 / pop	up to 11y	No difference
Klip 2001	9 479 IVF + STIM / 7 532	>18m – 14y	SIR 1.0
Lidegaard 2005	6 052 / 442 345	4 ½ IVF 4.1 SC	0 Cases
Pinborg 2004	3 393tw / 10 239s	2 - 7y	0 Cases
Moll 2003			5 Cases of retinoblastoma RR 7.2 (2.4 – 17.0)

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## Cancer

- No controlled samples of sufficient size and a long FU period to assess childhood cancer
- There seems to be no increased risk, however the evidence remains suggestive
  - The RR reported for retinoblastoma (Moll) has been widely questioned (clustering of data, based on estimation of IVF pregnancies)
  - Few studies suggest an increased risk of neuroblastoma or leukaemia in children of women treated with infertility drugs. Larger cohort studies contradict this

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## Long-term follow-up studies

- Medical
- Neurological
- Cancer
- Development
- Behavior

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## Cognitive / motor development

Reference	Number ICSI / IVF / SC	Age y	Scale	Development
Bowen 1998	89 / 84 / 80	13m	Bayley MDI+PDI	MDI lower in ICSI
Bonduelle 2003	378 / 138 / -	2y	Bayley	No difference
Brandes 1992	- / 116 / 116	12-45m	Stanford Binet	No difference
Leunens 2006	109 / - / 90 s	10y	WISC-R	No difference
Leslie 2003	97 / 80 / 110	5y	WIPPSI-R	No difference
Knoester 2006	81 / 80 / 85	5-8y	RAKIT shorted	ICSI lower then CS
Place 2003	66 / 52 / 59	5y	Brunnet-Lezine	No difference
Ponjaert 2004	300 / 0 / 266	5y	WIPPSI-R	No difference
Ponjaert 2005	500 / 437 / 538	4.5-5.5y	WIPPSI-R + MSCA	No difference
Sutcliffe 2001	208 / - / 221	1.5y	Griffiths	No difference

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## Cognitive / motor development

- No differences were found in cognitive development in all studies but two (Bowen, Knoester).
- The Bowen study was re-conducted at 5 years (Leslie) and no differences were found
- No delay in motor development was found
- There is **no evidence** to support a delay cognitive or motor development in all ART children (IVF and ICSI)

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## Long-term follow-up studies

- Medical
- Neurological
- Cancer
- Development
- Behavior / Family relation

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## Behaviour and family relation

Reference	Number ICSI / IVF / SC	Age y	Behaviour
Barnes 2004	500 / 437 / 538	4.5-5.5y	No difference
Golombok 2002	102IVF/ 102adop/ 102SC	11-12y	No difference
Golombok 1996	116IVF/ 116DI/ 115adop/ 120SC	4-8y	No difference
Ponjaert 2004	300 / 0 / 266	5y	No difference

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## Socio-emotional development and family relationships

- Barnes et al. 2004
- Family relations

Questionnaires were given to parents  
500 ICSI / 437 IVF / 538 SC



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## Parent well-being and family functioning

Questionnaires were given to parents

- On parent-child relation
  - Stress in parent-child interactions (PSI)
  - Parental Acceptance-Rejection (PARQ) (warmth, hostility, neglect and acceptance)
- On family relationship
  - Parental mental health problems (GHQ)
  - Marital satisfaction (DAS)
  - Commitment to parenting and work (Greenberger)

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## Results

- No evidence of increased child behavioural problems (CBCL)
- No evidence of more stress in families who have used ICSI or IVF (PSI)
- Less criticism and rejection in parent-child relation (Parq), remaining in regression analysis

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## Behaviour / Family relation

- Only a few studies have addressed socio-emotional development. Regarding child behaviour **none** of the controlled studies found a difference between IVF and SC children up to 12 years.
- The largest study (Barnes) involving 1520 children ages 4-5y suggested that parents value their experience of parenting more and their work less than SC parents.

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## Conclusions 1

- General **growth** (height, weight, head circumference) and health (including hearing and vision) do not differ in IVF compared to NC children
- Some studies find more childhood **illnesses** and/or hospital admissions (in singletons); others do not.
  - A lower birthweight and lower gestational age, compared to matched controls, may contribute to these findings.

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## Conclusions 2

- An increased risk of **neurological** problems such as cerebral palsy was found in some large registry based studies in IVF children.
  - This was partially due to the higher number of twins born, to LBW and to lower gestational age also found in singletons.
  - However an effect of IVF, the parents' infertility or other factors not adjusted for in the studies cannot be excluded.

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## Conclusions 3

- An increased need for **surgical** intervention may be due to an increase in malformation rate.
- There seems to be no increased risk for childhood **cancer** in IVF children. However there are insufficient controlled studies to be conclusive.

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## Conclusions 4

- There is no evidence for **developmental** or motor delay in children born after IVF (and born >32 weeks gestation) or ICSI
- Overall there is sufficient evidence that IVF and ICSI children up to school-age have similar temperaments and **behaviour**

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## Long-term follow-up studies

### Questions to be further addressed

- Medical outcome :
  - long term risk in adult life (Barker hypothesis?)
  - long term risk of infertility and reproduction?
- Neurological complication
  - estimation of quantity
  - mechanism (infertility per se, prematurity/LBW, treatment)
- Imprinting disorders
  - estimation of quantity and mechanism

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## Long-term follow-up studies

### Questions to be addressed

- Cancer :
  - Long life time risk ?
  - Role of imprinted genes ?
- Development / behavior
  - Behavioral disorders linked to prematurity or infertility?
  - Family functioning during puberty?

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  - psychologists
  - data managers
  - cytologists, molecular biologists, embryologist
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