

Outcome and future of children born after ART

M. Aboulghar

Professor, Cairo University

Clinical Director, The Egyptian IVF
center

Possible effects on the babies could be from

1. Prematurity and multiple pregnancy
2. The procedure of SRT
3. Infertility

The *Medical Research Council Register* (2002) report on births resulting from assisted conception in Great Britain demonstrated a high incidence of preterm and low birth weight babies. This incidence remained high even when the analysis was restricted to singleton babies. Infertility per se can predispose to preterm birth and low birth weight.

Congenital malformation

Preterm birth and low birth weight among in vitro fertilization singletons: a systematic review and meta-analyses. (McDonald et al, 2009)

- Seventeen studies were included with 31,032 singletons conceived through IVF (+/- ICSI) and 81,119 spontaneously conceived singletons.
- IVF singletons had increased risks of PTB (RR 1.84, 95% CI 1.54, 2.21) and LBW (<2500g, RR 1.60, 95% CI 1.29, 1.98) (McDonald et al, 2009).

Singletons conceived through IVF or IVF/ICSI were at increased risk for late PTB (32-36 weeks, RR 1.52, 95% CI 1.01, 2.30), moderate PTB <32-33 weeks (RR 2.27, 95% CI 1.73, 2.97), very LBW (<1500 g, RR 2.65, 95% CI 1.83, 3.84), intrauterine growth restriction (RR 1.45, 95% CI 1.04, 2.00), and lower birth weights (-97 g, 95% CI -161 g, -33 g) (McDonald et al, 2009).

In conclusion, IVF singletons have significantly increased risks of PTB, LBW and other adverse perinatal outcomes compared to spontaneously conceived singletons after matching or controlling for maternal age at least (McDonald et al, 2009).

In vitro fertilization and preterm delivery, low birth weight, and admission to the neonatal intensive care unit: a prospective follow-up study (Wisborg et al 2010)

In a total of 20,080 liveborn singletons and after adjustments, it was found that there is a statistically significant increased risk of preterm delivery and very preterm delivery in women who conceived after IVF/ICSI compared with fertile women.

Perinatal outcome of singleton siblings born after assisted reproductive technology and spontaneous conception (Henningesen et al, 2001)

- The study compared the perinatal outcome of singleton siblings conceived differently.
- ART plays a role in mean birth weight and risk of low birth weight and preterm birth.

Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis
(Pinborg et al. 2013)

- Sixty five articles met the inclusion criteria.
- Subfertility is a major risk factor for adverse perinatal outcome in ART singletons, however, even in the same mother an ART singleton has a poorer outcome than the non-ART sibling.
- Factors related to the hormone stimulation and/or IVF methods may play a part.
- Longer culture times for embryos has a negative influence on the perinatal outcome.

The use of vaginal natural progesterone for prevention of preterm birth in IVF/ICSI pregnancies (Aboulghar et al, 2012)

- There was a significantly lower preterm birth rate in singleton pregnancies in the natural progesterone arm (OR 0.53, 95% CI 0.28 – 0.97) and no significant difference between both arms in twin pregnancies (OR 0.735, 95% CI 0.36-2)

Increased risk of preterm birth in singleton pregnancies after blastocyst vs day 3 embryo transfer: Canadian ART Register analysis

(Dar et al. 2013)

- Two recent studies, from Sweden and the USA reported an increased risk of preterm birth in singleton pregnancies after day 5/6 ET.
- There was a significant higher risk of preterm birth (<37 weeks) in singletons after extended embryo culture (Day 5/6) compared with cleavage stage (Day 3) transfer.
- Preterm birth rate <37 weeks was higher with day 5/6 versus day 3 transfers (17.2 versus 14.1%, $P < 0.001$).

Perinatal outcome of singleton pregnancies following IVF

(Stojnic et al 2013)

- The pregnancy outcome of 634 singleton pregnancies after IVF/ICSI were compared to 634 matched singleton controls.
- Total preterm delivery rate of IVF pregnancies was 9.3%, significantly higher than the control 5.85% ($t=2.33$, $p<0.05$), especially at the 30 – 32 weeks gestation period. The predominant mode of delivery after IVF pregnancy was cesarean section (80.75% vs 31.38% at spontaneously conceived).
- Singletons from IVF/ICSI pregnancies have poorer perinatal outcome associated with higher rates of Cesarean section.

The large comparative study by *Bonduelle et al. (2002)* was assuring that congenital anomalies are not increased in IVF (3.8%) and ICSI (3.4%) babies as compared to natural conceived babies.

The prevalence of major birth defects diagnosed by one year of age in infants conceived naturally or with use of ICSI or IVF showed that ART babies have increased risk with odds ratio of 2.0 (95% CI, 1.3 to 3.2) with ICSI and 2.0 (95% CI, 1.5 to 2.9) with IVF (*Hansen et al 2002*).

The increase in the risk of a major birth defect associated with assisted conception remained significant when only singleton or term singleton infants were considered (*Hansen et al 2002*).

Among 16280 IVF children including 30% conceived after ICSI, a 42% excess of congenital malformation was found in infants born after IVF during the period 1982-2001 in Sweden as compared to natural registry (*Kallen et al. 2005*).

Twenty four studies had data on birth defects in children conceived by IVF (46,890) compared with those by ICSI (27,754), which provided an overall no risk difference.

There is no risk difference between children conceived by IVF and/or ICSI
(Wen et al 2012)

The risk for specific congenital heart defects associated with assisted reproductive techniques: a population-based evaluation (Tararbit et al 2013)

- Exposure to ARTs was significantly higher for tetralogy of Fallot than controls (6.6 vs. 3.5%, $P = 0.002$).
- No statistically significant association were found for the other congenital heart diseases.

Mental, psychomotor, neurologic, and
behavioral outcomes of 2-year-old
children born after preimplantation
genetic screening
(Middelburg et al 2001)

- Conception with PGS does not seem to be associated with impaired mental, psychomotor, or behavioral outcomes by age 2 years.

Morphologic abnormalities in 2-year-old children born after IVF/ICSI with PGS (Beukers et al, 2013)

- No statistically significant differences were found in minor anomalies between children after IVF/ICSI with or without PGS.
- There is <2.5% chance of $\geq 10\%$ more major abnormalities in children born after PGS.

Ovarian hyperstimulation and the in vitro procedure do not affect neurological outcome in infancy (Middleburg et al 2009)

- In a prospective assessor-blinded cohort study, the authors found no effects of IVF/ICSI on neurological outcome in children aged 4 – 18 months.
- Continuation of follow-up in older and larger groups of children is still recommended.

Children born after cryopreservation of embryos or oocytes: a systematic review of outcome data (Wennerholm et al 2009)

- In this systematic review most studies found comparable malformation rates between frozen and fresh IVF/ICSI.

Infant outcome of 957 signletons born after frozen embryo replacement (Pinborg et al 2010)

- No significant difference in the prevalence rates of birth defects, neurological sequelae, and imprinting-related diseases were observed between the cryo and the two control groups.
- However, higher malformaiton and cerebral palsy rates were observed in the total Fresh vs. non-ART group.

Fedder et al 2013

- The study group consisted of 466 children born after surgical retrieval of sperm, while the control groups consisted of 8967 ICSI with ejaculated sperm, 17592 IVF and 63854 normally conceived children.
- The total rate of congenital malformations in the surgically retrieved sperm group was 7.7% and did not differ significantly from any of the control groups.

Reproductive technologies and the risk of birth defects (Davies et al., 2012)

- Of the 308974 births, 6163 resulted from assisted conception. The unadjusted odds ratio for any birth defect in pregnancies involving assisted conception (513 defects, 8.3%) as compared with pregnancies not involving assisted (17,546 defects, 5.8%) was 1.47 (95% CI, 1.33-1.62).
- A history of infertility, either with or without assisted conception, was also significantly associated with birth defects.

Chromosomal abnormalities and ICSI babies

Bonduelle et al (2002) found 1.66% de novo aberrations in 1.586 fetuses and claimed that this increased incidence over the normal population is due to the increased sex chromosomal abnormalities seen among ICSI fetuses.

In a prospective controlled study of karyotyping for 430 consecutive babies conceived through ICSI, the authors found that ICSI carries a small but significant increased risk of abnormal karyotyping to the offspring. This risk (3.5%) appears to be equally distributed between autosomal and sex chromosome anomalies (*Aboulghar et al. 2001*)

ICSI chromosomal anomalies

Bonduell et al., 1999	2.6%
Loft et al, 1999	3.4%
In't Veld et al., 1995	33%
Van Opstal et al., 1997	12%
Aboulghar et al., 2001	3.5%

Imprinting disorders in ART babies

There is increasing evidence that genetic factors in infertile couples as well as environmental factors (hormones and culture media) can have adverse effects on epigenetic processes controlling implantation, placentation, organ formation and fetal growth (Horsthemke and Ludwig 2005).

Three recent studies reported unexpectedly high incidence of Beckwith-Wiedemann syndrome (BWS) in children conceived with ARTs. Six cases were reported from a British BWS registry, the same numbers were recorded in a French registry and seven children have been reported in the USA. These frequencies are extraordinarily high for such a rare congenital condition (Gosden et al 2003)

So far, follow-up studies of cohorts of children conceived by ART have not revealed an increased risk of imprinting disorders. However, imprinting disorders are so rare that a slight to moderate increase in incidence after ART can not be detected in single center or nationwide follow-up studies (Horsthemke and Ludwig 2005).

Imprinting disorders and assisted reproductive technology (Manipalviratn et al, 2009)

- Because of the absolute incidence of imprinting disorders is small (<1:12,000 births), routine screening for imprinting disorders in children conceived by ART is not recommended.

Conclusion

- Single IVF/ICSI pregnancies are associated with increased incidence of preterm labor and higher perinatal risk.
- IVF/ICSI babies are associated with increased risk of congenital malformation and chromosomal abnormalities.