J Assist Reprod Genet (2011) 28:489–493
DOI 10.1007/s10815-011-9561-5

COMMENTARY

Health of IVM children

Emre Basatemur · Alastair Sutcliffe

Received: 15 March 2011 / Accepted: 21 March 2011 / Published online: 7 April 2011

Introduction

In vitro maturation (IVM) is an emerging type of assisted reproductive technology (ART), in which immature as opposed to mature oocytes are collected from the ovaries and allowed to mature in vitro prior to fertilisation by either standard in vitro fertilisation (IVF) on intracytoplasmic sperm injection (ICSI). Since the first report of a human birth resulting from IVM in 1991 [1], it is estimated that over 1,300 babies have been born following the technique [2] (in contrast to an estimated 3 million babies conceived by standard IVF and ICSI over the last 30 years). IVM offers a number of potential benefits when compared to standard IVF, principally related to the avoidance of high doses of hormonal stimulation with gonadotrophins and GnRH analogues. In patients with polycystic ovary syndrome (PCOS) this avoids the risk of ovarian hyperstimulation syndrome (OHSS). The high costs of hormonal therapy also make IVM cheaper than conventional alternatives. Immature oocyte retrieval, without the need to wait for hormonal stimulation and in vivo maturation, offers the possibility of expedient oocyte cryopreservation for patients diagnosed with cancers without delaying cancer treatment. However, despite recent improvements, pregnancy rates with IVM remain lower than with conventional IVF, and higher miscarriage rates have been reported with IVM [2]. For these reasons IVM has yet to become widely used in the field of ART.

Given that IVM is not yet a mainstream ART technique, it is not surprising that there is very limited follow-up data regarding the health of children conceived following its use. This is in contrast to a significant volume of high quality studies that have followed-up children conceived following standard IVF and ICSI. In this article we discuss hypothetical concerns regarding the health of IVM children, and review the few studies published in this area.

Capsule Studies investigating the health of children born following in vitro maturation have generally been reassuring, however they are limited by size and study design.

E. Basatemur · A. Sutcliffe (✉)
General and Adolescent Paediatric Unit, Institute of Child Health,
University College London,
30 Guilford Street,
London WC1N 1EH, UK
e-mail: a.sutcliffe@ich.ucl.ac.uk

Health of IVF & ICSI children

High multiple pregnancy rates continue to be the single greatest factor adversely impacting upon the outcome of ART pregnancies [3, 4], with resulting increased risk of preterm delivery, low birth weight, and perinatal mortality. However, evidence regarding the health of ART singletons when compared to spontaneously conceived singletons is generally reassuring. The majority of studies investigating the risk of congenital malformations, neurodevelopmental outcome, physical health, growth, and psychosocial well-being in ART children are reassuring [5, 6]. Concerns have been raised that ART children may exhibit higher rates of cancer [7] and rare imprinting disorders [8] (such as Beckwith-Wiedemann Syndrome and Angelman Syndrome), however larger studies are required to confirm these associations. Risks of infertility and cardiovascular disease in later life remain unexplored areas of concern and require follow-up of cohorts of ART children to continue into adulthood.

Hypothetical risks for IVM children

There are various reasons why children conceived through ART might be exposed to greater health risks than naturally

conceived children. There is an increased risk of multiple pregnancy with ART [3], which is associated with increased risk of prematurity, low birthweight and perinatal morbidity. Couples undergoing ART are on average 5 years older than those who conceive spontaneously [9], and differences in the background biology of ART parents may confer health risks to their children. Procedural factors related to the infertility treatment itself may also have adverse consequences, for example exposure of sperm and embryos to in vitro environments may change their natural function.

A number of specific concerns have been raised regarding the effects of in vitro oocyte maturation on offspring health. Laboratory studies have reported high rates of chromosomal abnormalities in embryos fertilised following IVM [10], with a higher rate of abnormalities linked to longer period of maturation in vitro [11]. This may in part explain the higher rate of miscarriage observed in IVM pregnancies. In cattle IVM is a standard protocol for assisted reproduction, but is associated with a risk of 'large offspring syndrome' [12]. It has been proposed that the mechanism by which in vitro maturation causes this effect may be through inducing permanent changes in the expression of imprinted genes (epigenetic changes) [13, 14].

Follow-up of IVM children

A number of studies have been published regarding outcomes in children born following IVM [15–19]. They report on perinatal outcomes in offspring including gestational age and birthweight (Table 1), the incidence of congenital and chromosomal anomalies (Table 2), as well as growth and development up to 2 years of age (Table 3).

Cha et al. reported outcomes from 38 IVM pregnancies [15]. Their study did not have a control group. There were 14 miscarriages (36.8%) and 24 live births (63.2%). Of the live births, 20 were singletons and 4 twins. In the singletons, mean gestational age was 38.4 weeks (range 33–41.6) and mean birthweight was 3.25 kg (range 1.75–4.1 kg). The authors report that this is comparable to Korean population means of 38 weeks gestational age and 3.17 kg birthweight. There were three fetuses with congenital anomalies in their cohort of 38 pregnancies (7.9%). One of these was a hydrops fetalis diagnosed antenatally, with a termination of pregnancy performed at 16 weeks gestation. One fetus of a twin pregnancy had an antenatally diagnosed omphalocele and died in utero at 14 weeks gestation, with subsequent karyotype identifying 45X/46XY mosaicism. The third fetus had a cleft palate and was delivered at term without any complications.

A similar uncontrolled study from Denmark reported perinatal outcomes and karyotype in a cohort of 47 IVM children [16]. 45 of the children were singletons and there were 2 twins. Three were delivered preterm (6.4%); a singleton delivered at 32+4 weeks by Caesarean section for severe maternal pre-eclampsia with a birthweight of 1.75 kg, and a set of twins delivered vaginally at 34 weeks gestation with birthweights of 2.24 kg and 2.06 kg. The remaining babies were born at term with a median gestational age of 40 weeks (range 37–42 weeks). The median birthweight in the term babies was 3.72 kg (range 2.90 to 5.29 kg). Only one baby had a congenital malformation (2.1%), which was a soft palate in an otherwise healthy child. Chromosomal analysis was performed in 34 cases, of which 13 were obtained antenatally

Table 1 Perinatal outcomes in IVM children

Study	Cohort Size (n)	Control Group	Multiple Pregnancies	Gestational Age at Delivery (weeks)*	Birth weight (kg)*
Cha 2005 [15]	28 IVM	None	20 singleton	Singletons=38.4	Singletons=3.2 kg
			4 twin	Twins=36.1	Twins=2.4 kg
Mikkelsen 2005 [16]	47 IVM	None	45 singleton	44 term	Median for term
			1 twin	3 preterm	babies=3.7 kg
Söderström-Anttila 2006 [17]	46 IVM	None	40 singleton	Singletons=40.2	Singletons=3.6 kg
			3 twin	Twins=36.7	Twins=2.6 kg
Shu-Chi 2006 [18]	21 IVM	21 SC	17 singleton	IVM=38.1	IVM=3.1 kg
			2 twin	SC=38.1	SC=3.1 kg
Buckett 2007 [19]	55 IVM	338 SC	Twin rates:	Singletons:	Singletons:
			IVM=21%	IVM=39+3	IVM=3.48 kg
	217 IVF		IVF=20%	IVF=38+3	IVF=3.21 kg
	160 ICSI		ICSI=17%	ICSI=38+0	ICSI=3.16 kg
			SC=1.7%	SC=39+6	SC=3.26 kg

*Means

SC Spontaneously conceived, *IVM* in-vitro maturation, *IVF* in vitro fertilization, *ICSI* intracytoplasmic sperm injection

Table 2 Karyotype and congenital anomalies in IVM children

Study	Cohort Size (n)	Control Group	Karyotype	Congenital Anomalies
Cha 2005 [15]	28 IVM	None	–	3 congenital anomalies from a total of 38 pregnancies (7.9%): 1 hydrops fetalis 1 omphalocele 1 cleft palate
Mikkelsen 2005 [16]	47 IVM	None	Normal in 33/34 cases. The abnormal case was a small pericentric inversion in chromosome 20 inherited from the father, no clinical abnormality in the baby.	Cleft palate in one baby
Söderström-Anttila 2006 [17]	46 IVM	None	–	No congenital anomalies observed
Shu-Chi 2006 [18]	21 IVM	21 SC	Normal karyotype in all cases	No major congenital anomalies in either group Odds ratios for any congenital anomaly:
Buckett 2007 [19]	55 IVM 217 IVF 160 ICSI	350 SC	–	IVM=1.42 (0.52–3.91) IVF=1.21 (0.63–2.32) ICSI=1.69 (0.88–3.26)

SC Spontaneously conceived, *IVM* in-vitro maturation, *IVF* in vitro fertilization, *ICSI* intracytoplasmic sperm injection

by chorionic villous sampling or amniocentesis, and 21 were obtained at delivery from cord blood. Karyotype was normal in all cases, except for one baby with a small pericentiric inversion in chromosome 20 which was inherited from the father. The baby had no clinical abnormalities.

A third uncontrolled study, this time from Finland, followed up a cohort of 46 IVM babies up to 2 years of age, looking at growth and development in the children [17]. 40 were singletons, with 3 sets of twins. Mean gestational age was 40.2 weeks in the singletons and 36.7 in the twins. Four of the 43 pregnancies resulted in preterm delivery (9.3%). Mean birthweight was 3.55 kg in the singletons and 2.62 kg in the twins, figures which the authors report to be comparable to Finnish national means. No congenital anomalies were observed in the cohort. Karyotyping was performed in only four cases, of which three were normal and one child was found to have a

Table 3 Growth and development in IVM children

Study	Cohort Size (n)	Control Group	Growth (compared to national means)	Development
Söderström-Anttila 2006 [17]	46 IVM	None	- Mean height age 2 years: girls=+0.1 SD boys=+0.2 SD - Mean height-related weight age 2 years: girls=+1.1 percentile boys=−1.3 percentiles	BSID at age 2: - Normal in 34/35 children - Mild developmental delay in 1/35.
Shu-Chi 2006 [18]	21 IVM	21 SC	–	BSID at 6–24 months: - Mean Mental Development Index scores not significantly different between IVM (92.7) or SC (97.2) groups (p=0.07). - Mean Psychomotor Development Index scores not significantly different between IVM (96.7) or SC (96.2) groups (p=0.82).

SC Spontaneously conceived, *IVM* in-vitro maturation, *BSID* Bayley Scales of Infant Developments

balanced translocation between chromosomes 1 and 8 which was inherited from the mother. The children were subsequently followed up at 1 year and 2 years of age. At both time points the height and weight of the children was comparable to Finnish population standards. At 2 years mean height was +0.1 SD (range −2.0 to +2.3) from the population mean for girls, and +0.2 SD (range −0.6 to +0.6) for boys. Mean height-related weight at the same age was +1.1 percentiles (range −14 to +20) from the national mean for girls, and −1.3 percentiles (range −10 to +7) for boys. Developmental assessment was performed using Bayley Scales of Infant Development at age 2 years in 35 of the children (76%). In 34 cases (97%) developmental was considered to be adequate (mental development index score >85), with one child demonstrating mild developmental delay (mental development index score of 82).

There are two published follow-up studies of IVM children in which there are control groups of spontaneously conceived (SC) children [18, 19]. Shi-Chi et al. followed up a cohort of 21 IVM children and 21 SC controls [18]. They make no reference to matching between the groups with regards to parental characteristics. In the IVM group there were 17 singletons and two pairs of twins. There were no significant differences between the groups with regards to gestational age at birth (mean 38.1 weeks in both groups) or birthweight (mean 3.07 kg in IVM group, 3.13 kg in SC group). Karyotyping was performed in all of the children and was normal in all cases. There were no major congenital malformations in either group, although two children in the IVM group had minor anomalies (one had a 3 cm breast nodule, the other had a 2 cm auricular haemangioma). The children were followed up for developmental assessment using Bayley Scales between 6–24 months of age. Mean mental development index scores were lower in the IVM group (92.7±SD of 10.5) than the SC group (97.2±8.9), although this did not reach statistical significance (p=0.07). There was no difference in mean psychomotor development index scores between the two groups (IVM=96.7±8.9, SC=96.2±7.1, p=0.82).

The largest, and best designed study of outcomes in IVM children to date is from a group based at the McGill University in Montréal [19]. They report on obstetric outcomes and congenital anomalies in three separate ART cohorts; 55 IVM, 217 IVF, and 160 ICSI. All ART pregnancies were matched with spontaneously conceived controls, with matching on maternal age and parity, with a resulting cohort of 350 SC children. Multiple pregnancy rates were significantly greater each of the ART groups when compared to controls (p<0.001), but there were no significant differences between IVM, IVF, and ICSI pregnancies. Twin rates were 21% for IVM, 20% for IVF, 17% for ICSI and 1.7% for SC. Triplet rates were 5% for IVM, 3% for IVF, 3% for ICSI, and 0% for SC. Mean birthweight of all infants (singleton and multiples) was similar among the three ART groups (IVM=2.81 kg, IVF=2.83 kg, ICSI=2.81 kg), but significantly lower than in controls (3.23 kg). However, when only singletons were considered, mean birthweight in IVM infants (3.48 kg) was significantly higher than in IVF (3.21 kg), ICSI (3.16 kg), and SC (3.26 kg) infants (p=0.048). Gestational age at delivery among all infants (singletons and multiples) was similar among all ART groups, but significantly lower than in controls. Interestingly, when only singletons were considered, IVF and ICSI infants had a lower mean gestational age at delivery than SC controls, but IVM infants did not. There were no statistically significant differences in incidence of congenital anomalies between each of the ART groups and the SC group.

Conclusions

IVM is an emerging technique in ART, and in recent years the first studies investigating outcomes in children conceived by following IVM have been published. These reports are generally reassuring. Multiple pregnancy rates are no higher than in standard IVF or ICSI. Most studies have reported gestational age at birth and birthweight that is comparable with the general population. However, the report by Buckett et al. of higher birthweights in IVM singletons compared to SC singletons highlights the need for larger studies and emphasises the importance of future studies investigating potential epigenetic differences in IVM children [19]. Studies to date have not identified an alarming rate of congenital anomalies in IVM children, and the two studies which have followed up children to the age of 2 years have provided reassuring results regarding their growth and development.

It is important to note that these studies are significantly limited in their size and study design. Most of the studies are uncontrolled, and thus do not allow direct comparison between outcomes in IVM children with other ART children or spontaneously children. Furthermore, the IVM cohort sizes range between just 21 and 55, meaning that the studies are insufficiently powered to reliably identify differences between the study groups. Given these limitations, we must be cautious in drawing conclusions from the current literature. Many early outcome studies of IVF children had similar shortcomings, yet over the last decade a considerable number of high quality studies have been published investigating the health of IVF and ICSI children. As IVM gains more widespread use, it is important that larger and better designed studies investigating the health of these children are undertaken.

References

1. Cha KY, Koo JJ, Ko JJ, et al. Fertil Steril. 1991;55(1):109.
2. Suikkari AM. Curr Opin Obstet Gynecol. 2008;20(3):242.
3. Wright VC, Chang J, Jeng G, et al. MMWR Surveill Summ. 2008;57(5):1.
4. Andersen AN, Goossens V, Ferraretti AP, et al. Hum Reprod (Oxford, England). 2008;23(4):756.
5. Basatemur E, Sutcliffe A. Placenta. 2008;29(Suppl B):135.
6. Sutcliffe AG, Ludwig M. Lancet. 2007;370(9584):351.
7. Kallen B, Finnstrom O, Lindam A, et al. Pediatrics. 2010;126(2):270.
8. Sutcliffe AG, Peters CJ, Bowdin S, et al. Hum Reprod (Oxford, England). 2006;21(4):1009.
9. Katalinic A, Rosch C, Ludwig M. Fertil Steril. 2004;81(6):1604.
10. Nogueira D, Staessen C, Van de Velde H, et al. Fertil Steril. 2000;74(2):295.
11. Zhang XY, Ata B, Son WY, et al. *Reproductive biomedicine online*. 2010;21(4):552.
12. McEvoy TG, Sinclair KD, Young LE, et al. Hum Fertil (Cambridge, England). 2000;3(4):238.
13. Young LE, Fernandes K, McEvoy TG, et al. Nat Genet. 2001;27(2):153.
14. Kerjean A, Couvert P, Heams T, et al. Eur J Hum Genet. 2003;11(7):493.
15. Cha KY, Chung HM, Lee DR, et al. Fertil Steril. 2005;83(5):1461.
16. Mikkelsen AL. Reprod Biomed Online. 2005;10(5):593.
17. Soderstrom-Anttila V, Salokorpi T, Pihlaja M, et al. Hum Reprod (Oxford, England). 2006;21(6):1508.
18. Shu-Chi M, Jiann-Loung H, Yu-Hung L, et al. Early Hum Dev. 2006;82(10):677.
19. Buckett WM, Chian RC, Holzer H, et al. Obstet Gynecol. 2007;110(4):885.