Reprod Med Biol (2013) 12:151–158
DOI 10.1007/s12522-013-0156-y

REVIEW ARTICLE

# What are the risks of the assisted reproductive technologies (ART) and how can they be minimized?

**Robert W. Rebar**

Received: 8 March 2013 / Accepted: 19 May 2013 / Published online: 11 June 2013


**Abstract** Although assisted reproductive technologies (ART) have become established procedures performed around the world, there are still many unanswered questions regarding safety. Possible risks associated with infertility and ART include (1) those inherent to pregnancy, delivery, and childhood; (2) those associated with the infertility itself and its causes; and (3) risks iatrogenic to ART. Although there are many potential risks associated with ART, it has become clear that the major risk is multiple pregnancy and its consequences. Major efforts are warranted to reduce the risk of multiple gestations with IVF, but it is also clear that single-embryo transfer is not the solution in all cases. Moreover, several studies have now documented that perinatal outcomes are somewhat poorer in IVF singleton infants than in spontaneously conceived singletons, but it is not clear if this increased risk is due to the ART or the infertility. Concerns about the impact of abnormalities in genomic imprinting persist at this time, as do risks associated with the culture conditions and even our environment. Only time will tell if children born following ART are at any increased risk of developing certain chronic diseases as they age. In any case, the risks to IVF children and mothers are likely to remain higher than those for children and mothers conceived spontaneously without medical assistance. However, since there have been over 5 million births after ART worldwide, and the vast majority of pregnancies and children have been essentially "normal", it is obvious that any excess risk must be relatively small. The normality of most pregnancies mandates that extreme care be exercised in making any changes to current practice.

R. W. Rebar (✉)
The American Society for Reproductive Medicine,
1209 Montgomery Hwy, Birmingham, AL 35216, USA
e-mail: rrebar@asrm.org

**Keywords** ART · Embryo · IVF · Neonatal outcomes · Risk

## Introduction

This review will attempt to delineate potential risks associated with ART and consider how they might be minimized. The review is not intended to be all inclusive or a meta-analysis, but rather it represents one clinician's critical observations of a developing field. In order to address this topic, we will first consider the possible risks associated with infertility itself and then those associated with ART. We will consider the complications associated with multiple gestations, perhaps the greatest risk associated with ART, followed by a consideration of the risks of singleton births after in vitro fertilization (IVF). Because of concerns that ART may alter genomic imprinting, this issue will be considered next. Also to be considered are the risks associated with the culture of human gametes and embryos. These considerations will lead to the logical conclusion that ART, as currently practiced, is very safe. In fact the safety of ART is such that any future changes to current practice should be made only after controlled trials and careful analysis that any change will not be harmful.

## Possible risks associated with infertility and ART

First, it is important to consider all of the possible risks associated with infertility, and separately with ART. In general, as first suggested [1], there appear to be three distinct general areas of risk:

1. The risks inherent to pregnancy, delivery, and intrauterine development of the fetus. No one would argue

that conception and pregnancy do not have inherent risks for all couples.
2. Any risks associated with infertility and its causes. For example, it is well-documented that the risks of pregnancy increase with parental age. In addition, there are well-documented risks associated with polycystic ovarian syndrome and with oligospermia.
3. Any risks iatrogenic to ART itself. We will discuss many of those potential and theoretical risks in this review.

The logical conclusion from this listing is that pregnancies and children arising from ART will always be at slightly increased risk compared to spontaneous pregnancies.

## Potential risks iatrogenic to ART

Possible risks associated with the process of ART are listed in Table 1. All aspects of ART have potential risk. The risk inherent in ART that is associated with the greatest possibility of poor maternal and neonatal outcomes is multiple gestation. The Centers for Disease Control noted that ART accounts for only one percent of total babies born in the USA but accounts for 17 % of twins because couples undergoing ART are 27 times more likely to have twins than those conceiving spontaneously. Statistics document that the number of twin births in the United States rose by more than three-fourths over the period 1980–2004 [2]. In 2009, one in every 30 babies born in the US was a twin; that rate was one in 53 in 1980. About one-third of the increase can be accounted for by an increase in average maternal age, but two-thirds is likely due to treatment for infertility. To be sure, it would appear that most of this increase is due to the use of exogenous gonadotropins for "controlled ovarian hyperstimulation" in couples with unexplained infertility [3], but ART can lead to multiple pregnancies when multiple embryos are transferred.

**Table 1** Potential risks iatrogenic to ART

| |
|---|
| Hyperstimulation |
| Ovarian torsion |
| Infection, bleeding, and even death |
| Failure to conceive |
| Multiple gestation |
| Prematurity and "small for gestational age" infants |
| Birth defects |
| Health risks later in the life of children born after ART |
| Disorders of epigenetic imprinting |
| Risks from handling of gametes and embryos |
| Risks of culture |
| Risks associated with cryopreservation |
| Gamete and embryo "mix ups" |

### Risks of multiple pregnancies

Complications of multiple pregnancies include increased maternal morbidity and both fetal and neonatal morbidity and mortality [4]. The most important maternal complications of multiple gestation include pre-eclampsia, gestational diabetes, and preterm labor and delivery. Most of the excess perinatal morbidity and mortality is directly related to preterm birth. The problem of multiple pregnancy is not easily resolved by multifetal reduction, because reduction decreases, but does not eliminate, the risk of fetal growth restriction or loss of the entire pregnancy [5, 6].

### Elective single embryo transfer

If multiple gestation is best avoided, and multifetal reduction has significant difficulties, should elective single embryo transfer (eSET) become the "norm" in ART? Several studies have addressed this question. In a meta-analysis of "good prognosis" cycles only [7], one group noted that the odds of delivering a term singleton after eSET were approximately five-fold higher than following double embryo transfer (DET). Moreover, the odds of delivering a preterm infant were reduced three-fold, and the odds of delivering a low-birth weight (LBW) infant were reduced four-fold. After one fresh cycle, the live birth rate was lower with eSET (27 %) than with DET, but the multiple birth rate was also much lower (2 vs. 28 %). The authors noted that the cumulative live births after eSET followed by one frozen singleton embryo transfer (38 %) were similar to that after DET alone (42 %)—but this was based on data from patients from only two of the eight studies included in the analysis. There are other problems with this meta-analysis as well. As noted, only "good prognosis" patients, that is, those undergoing their first or second cycle of IVF, those with "good", well-developed embryos, and women $\leq$36 years of age, were included. Because the average age of women undergoing IVF in the US is over age 36, less than half of US women undergoing IVF in the US would have even been eligible for inclusion in the study! Moreover, only cycles in which cleavage stage embryos were transferred on day 2 or 3 were included.

One relatively small US program established a policy of mandatory single-embryo transfer (mSET) for all women under age 38 undergoing a fresh cycle with autologous oocytes: for all women undergoing a fresh cycle with donor oocytes, so long as there was no history of a failed fresh cycle, there were at least seven zygotes (i.e., 2 PN stage), and there was at least one good- or excellent-quality

blastocyst available for transfer in 2004 [8]. They compared the 5-year period immediately following the implementation of the policy to the 5-year immediately preceding the policy. Fully 75 % of those initially qualifying for mSET had it done; however, 25 % did not meet the blastocyst quality requirement. In all, mSET accounted for 28 % of all embryo transfers after implantation. The overall program live-birth rate from all transfers increased in the 5-year period after implementation to 51.1 % from 47.8 % in the preceding period—consistent with improvement in IVF success rates nationwide. The overall program multiple birth rate decreased from 32.7 to 18.3 % ($p < 0.0001$). The live-birth rate for the mSET cycles alone was 64.4 %, with only 3.4 % being multiple. The cumulative live-birth rate including transfer of cryopreserved embryos for all mSET couples was 83.8 %. This experience documents the feasibility of incorporating eSET into every practice but also emphasizes that even SET will not eliminate entirely the problem of multiple pregnancies with ART. These observations raise the question as to whether in the future this problem might be solved by dissociating oocyte collection cycles from transfer cycles and using frozen embryos only for transfer one at a time in subsequent normal cycles.

Although use of eSET reduces the risks of both maternal and neonatal complications, there have been suggestions that twins should be considered a desired outcome in IVF [9]. Using data from a Scandinavian registry, investigators compared outcomes in all reported twins after IVF with DET to those in women having two IVF singletons [10]. Preterm birth, very preterm birth, low birth weight, very low birth weight, and small for gestational age were dramatically increased for IVF twins compared with two IVF singletons with the same mother, with adjusted odds ratios ranging from 4 to 16. There were also significantly higher rates of respiratory complications, sepsis, and jaundice among the IVF twins. Significantly higher rates of preeclampsia, preterm premature rupture of membranes, and cesarean section were seen in the twin pregnancies as well.

A recent population study examining outcomes after IVF in Australia and New Zealand reported that the adjusted risk of perinatal mortality for all births following fresh DET was 58 % higher than for births following fresh SET [11].

## Increased risks of singleton births after ART

What appears to be true, based on several publications, is that even singleton births after ART are associated with increased risks such as low birth weight and prematurity, independent of maternal age and fetal number, but it must be acknowledged that the risks are far greater with multiple gestations. Utilizing data from the SART/ASRM/CDC database in the United States, Schieve et al. noted that among singleton infants born at ≥37 weeks of gestation, those conceived with ART had a risk of low birth weight that was 2.6 times the general population [95 % confidence interval (CI) 2.4–2.7] [12]. This observation has been confirmed and expanded in several subsequent studies and meta-analyses.

Jackson et al. [13] conducted a meta-analysis compiling data from 15 studies comprising 12,283 IVF and 1.9 million spontaneously conceived singletons. IVF singletons were associated with significantly higher odds of perinatal mortality [odds ratio (OR) 2.2], preterm delivery (2.0), low birth weight (1.8), very low birth weight (2.7), and small for gestational age (1.6). Helmerhorst et al. [14] compiled data from eight studies including 4,582 IVF and 5,641 natural births (some of the data overlap with data included in the previously discussed meta-analysis [13]). After IVF, singletons had a relative risk of 3.27 for very preterm (<32 weeks' gestation) and 2.04 for preterm (<37 weeks' gestation) birth. Relative risks were 3.00 for very low birth weight (<1,500 g), 1.70 for low birth weight (<2,500 g), 1.40 for small for gestational age, 1.54 for being delivered by cesarean section, 1.27 for admission to a neonatal intensive care unit, and 1.68 for perinatal mortality. What not one of these retrospective analyses can do is provide information about causality. It is possible, and there is evidence to suggest that will be discussed later, that infertile couples are inherently at greater risk during pregnancy than are fertile couples. Moreover, that ethnic differences may exist in the risks associated with IVF pregnancies is raised by a report utilizing the 2006 registry database of the Japan Society of Obstetrics and Gynecology failing to find any dramatically increased adjusted risks of perinatal death, low birth weight, small for gestational age, congenital malformation, or sex ratio when comparing singleton IVF pregnancies with singleton spontaneous conceptions [15].

There is accumulating evidence that the altered hormonal milieu or intrauterine environment associated with the cycle during which oocytes are stimulated, collected and transferred may be in part responsible for the worse neonatal outcomes associated with ART. Using the SART database, Kalra et al. [16] noted that the odds of having a low birth weight infant (odds ratio 1.35; 95 CI 1.20–1.51), of having a low birth weight infant at term (1.73; 1.37–2.03) and having a low birth weight infant preterm (1.49; 1.24–1.78) were all higher in singleton infants conceived following fresh embryo transfer (ET) compared to those born after frozen embryo transfer (FET). This association was stronger comparing fresh ET and FET in the same patients (4.66; 1.18–18.38). Consistent with the hypothesis that the environment at the time of embryo transfer may in part mediate this increased risk was the

observation that the percentage of infants with low birth weight was no different in donor recipients, regardless of fresh ET or FET [17]. Similarly, data from one large Australian clinic indicate no difference in birth weight between infants born following FET (3,352 g) and non-ART infants (3,341 g); in contrast, infants born following fresh ET were smaller (3,185 g) [18].

That the hormonal milieu may also increase maternal risks is suggested by data indicating that the risks of venous thromboembolism (VTE) and pulmonary embolism (PE) are increased in pregnancies after IVF [19]. Utilizing data from Swedish registries collected over almost 20 years and involving almost 24,000 first pregnancies after IVF and matched to almost 117,000 spontaneous first pregnancies, these investigators reported that proportion of women pregnant for the first time after undergoing IVF with VTE was 4.2 per 1,000 compared with 2.5 per 1,000 for those conceiving and subsequently delivering for the first time spontaneously. The risk for VTE was increased during the entire pregnancy ($p < 0.001$; hazard ratio, HR, 1.77; 95 % CI 1.41–2.23), but especially during the first trimester (HR 4.05; 95 % CI 2.54–6.46). Risks for the two groups did not differ both before pregnancy and after delivery. Risk for PE, based on many fewer cases, also was increased after IVF ($p < 0.0034$; HR 1.42; 95 % CI 0.86–2.36) and once more was particularly increased in the first trimester (HR 6.97; 95 % CI 2.21–21.96). Multivariate analysis considering smoking, singleton or multiple pregnancy, body mass index, education, marital status, and maternal age among others did not alter the main finding. Multiple pregnancies only seemed to further increase the incidence of VTE above that of singletons.

Data from the Swedish birth registry indicate that infants born after blastocyst transfer are at higher risk for both preterm birth (OR 1.35; 95 % CI 1.07–1.71) and congenital malformations (OR 1.4; 1.14–1.81) compared to infants born after cleavage-stage transfer [20]. Utilizing data from the Society for Assisted Reproductive Technologies for 2004–2006, Kalra et al. [21] also have noted that singleton IVF births after blastocyst transfer, as compared with cleavage-stage transfer, were at increased risk for preterm delivery (18.6 vs. 14.4 %, adjusted OR, 1.39; $p < 0.001$) and very preterm delivery (2.8 vs. 2.2 %, adjusted OR 1.35; $p < 0.001$) but not low birth weight (10.3 vs. 9.1 %; adjusted OR 1.10; $p = 0.06$). These findings persisted in comparing twin births. The authors suggest that blastocyst transfer may not be warranted unless it results in a reduction in multiple births. Could it be that these increased risks are due, as animal data to be discussed later suggest, to imprinting abnormalities resulting from prolonged culture? However, it should be noted that, in contrast, Australian investigators found no statistically significant differences in a retrospective cohort study between transfers on days 5 and 6 (blastocyst) and days 2 and 4 (cleavage-stage) for all maternal and perinatal outcomes [22].

## Risks of birth defects after ART

There are also other studies indicating that the incidence of major birth defects after IVF might be increased. However, such observations are confounded by the facts that there is no standard definition as to what comprises major birth defects and virtually every study has defined them differently. Moreover, tabulation of information about birth defects is invariably incomplete.

Olson et al. [23] published a retrospective study from a single center over a 13-year period. They noted that 90 of 1,462 IVF children (6.6 %) had a major defect compared to 369 of 8,422 naturally conceived children (4.4 %) for an adjusted odds ratio (OR) of 1.30 (95 % CI 1.00–167). The odds ratio was also elevated when analysis was limited to singletons at 1.44 (95 % CI 0.98–2.12). There seemed to be a significantly greater proportion of cardiovascular and musculoskeletal defects and syndrome diagnoses after IVF. This study was criticized because of the high incidence of birth defects even in the naturally conceived children, but the same definition was applied to both groups.

More recently, Davies et al. [24] reported a population-wide cohort study from a single Australian state over 17 years including over 308,000 births, with over 6,100 from ART. Compared to women conceiving spontaneously, women who used ART were older, more likely to be nulliparous and of a higher socioeconomic status, and were more likely to have a stillbirth, to deliver by cesarean section and before 32 or 37 weeks' gestation, and to have singleton children with a lower mean birth weight. After multivariate adjustment for several potential confounders, the odds ratio (OR) for any birth defect in assisted conception (513 defects, 8.3 %) was 1.28 (95 % CI 1.16–1.41) compared to spontaneous pregnancies (17,546 defects, 5.8 %). Births after IVF alone and IVF with ICSI together had an odds ratio after adjustment of 1.24 (95 % CI 1.09–1.41). When the two were analyzed separately, risk was increased only with IVF with ICSI (OR 1.57; 95 % CI 1.30–1.90). Births in women with a prior ART pregnancy were also at increased risk (OR 1.25; 95 % CI 1.01–1.56), and women with a prior history of infertility without ART had a borderline increased risk (OR 1.29; 95 % CI 0.99–1.68).

Data from the large study by Davies et al. [24] are largely reassuring and confirm previous smaller studies published previously. One difficulty lies with the identification and recording of birth defects, which are high because of inclusion of disorders that are not normally included (such as hemangiomas). The data also indicate that couples with infertility have a small increased risk of birth

defects—even without ART. Lastly, the increase risk in IVF cycles with ICSI is biologically plausible because of the increased incidence of genetic defects in infertile men.

Hansen et al. [25] presented evidence from Western Australia that major defects resulting from ART may be decreasing with time (as the technology improves?). Investigators examined the prevalence of major birth defects diagnosed by age six for all ART compared to all non-ART births and terminations for anomalies from 1994 to 2006. A major birth defect was diagnosed in 172 ART singletons (8.7 %) and 11,078 non-ART singletons (5.4 %) for an odds ratio of 1.53 (95 % CI 1.30–1.79). Of note is the fact that 10.9 % of ART births had a major defect for the time interval 1994–1998; the prevalence decreased to 7.5 % between 1999 and 2002. The prevalence of birth defects in non-ART singletons decreased nonsignificantly from 5.6 to 5.2 % during the same intervals.

What is noteworthy about all these studies of birth defects following ART is that the increased odds ratios are similar among all of the published studies.

Concerns have also been raised about the possibility that cancer risk is increased in children and young adults conceived by IVF [26]. Fifty-three cases of cancer were identified in 26,692 children born after IVF in Sweden between 1982 and 2005, against approximately 38 expected based on the incidence in approximately 2.5 million total birth for an odds ratio of 1.42 (95 % CI 1.09–1.87). There were 18 hematologic malignancies (of which 15 were acute lymphocytic leukemia), 17 eye or central nervous system malignancies, and 12 other solid malignancies. The remaining six had Langerhans cell-type histiocytosis against one expected. This small study requires confirmation before any increased risk of cancer after IVF is proven.

A meta-analysis involving eight cohort studies including almost 750,000 participants failed to find a significant association between cancer risk and women undergoing IVF [27]. Utilizing data from Western Australia, other investigators found no evidence of an increased risk of ovarian cancer following IVF in women who give birth but some uncertainty (nonsignificant) regarding ovarian cancer following IVF in women remaining nulliparous [28].

## Risks associated with infertility itself

In an important study, Jaques et al. examined pregnancy outcomes in 2,171 women who had singleton non-ART births within 5 years of registering at an IVF clinic for infertility treatment compared to 4,363 controls [29]. After adjustment, the subfertile women had increased odds of hypertension or preeclampsia (1.29; 95 % CI 1.02–1.61), antepartum hemorrhage (1.41; 1.05–1.89), perinatal death (2.19; 1.10–4.36), low birth weight (1.44; 1.11–1.85), preterm birth <37 weeks (1.32; 1.05–1.67), preterm birth <31 weeks (2.37; 1.35–4.13), and cesarean delivery (1.56; 1.37–1.77). There was also weak evidence for increased birth defects (1.30; 0.98–1.72) and gestational diabetes (1.25; 0.96–1.63).

This study emphasizes that, at this time, we cannot be certain as to what risks are increased in infertile couples and what risks are increased by ART itself. The data emphasize the need to inform infertile couples of their potential increased risk and of the potential increased risks associated with ART. Still, the vast majority of children born both to infertile couples and following ART are normal—and this, too, should be discussed with patients.

## Are disorders of genomic imprinting associated with ART?

Reports suggested that two recognized disorders of genomic imprinting, Angelman syndrome [30] and Beckwith–Wiedemann syndrome [31–33] might be increased in children conceived by ART. These observations were consistent with numerous studies in animal embryos, primarily mouse, which have documented errors in genomic imprinting with IVF [34]. It is now clear that the absolute incidence in humans is low, <1 in 12,000, but counseling of this possible association is warranted [34]. To date, most studies have failed to find imprinting errors in children born after ART, despite the apparent increased association of these syndromes [35–37].

Scientists are even now attempting to determine what the mechanism might be for this association with abnormal syndromes. Turan et al. [38] noted that placentas of in vitro conceived embryos are derived from fewer stem cells than those conceived in vivo. The investigators questioned whether the smaller placentas resulted from imprinting disorders possibly associated with IVF. These data and this hypothesis, however, does not square with the observation derived from the Medical Birth Registry of Norway that placentas and placental weight/birth weight ratios in pregnancies conceived by ART were overall significantly larger than those in spontaneously conceived pregnancies [39]. It has also been suggested that unfaithful maintenance of DNA methylation marks following fertilization might involve the dysregulation of a trans-acting factor altered by ART [40].

Although the mechanism for any potential disorders associated with ART may be unknown at this time, it is possible to theorize several causes associated with infertility and ART that might lead to imprinting disorders. Some of these are listed in Table 2.

**Table 2** Potential causes of disorders of epigenetic imprinting in ART

| |
|---|
| Causes of infertility |
| Hormonal hyperstimulation |
| Use of GnRH analogs |
| Fertilization in vitro |
| Abnormal spermatozoa |
| ICSI |
| Micromanipulation of gametes |
| Exposure to culture medium—or to a particular component |
| Culture conditions (oxygen, carbon dioxide, and nitrogen concentrations; temperature; pollutants) |
| Maturation of gametes in vitro |
| Timing of embryo transfer |
| Cryopreservation of gametes and embryos |

## Risks associated with the culture of gametes and embryos

There are also potential risks associated with the culture of gametes and embryos. One must consider potential effects from culture conditions, especially temperature and atmosphere; the culture media; and the effects of contaminants and pollutants.

There is controversy as to whether the concentration of oxygen in the culture atmosphere can impact the culture. Three studies suggest an effect. Embryos from 230 first cycles randomly cultured in 5 % oxygen resulted in more live births (57.4 %) than those randomly cultured in 20 % oxygen (42.6 %) [41]. In the second study, of embryos from 396 women randomized, culture with 5 % oxygen resulted in a 42 % live birth rate compared to a 32 % live birth rate in embryos cultured in 20 % oxygen [42]. In the third study, randomized culture of embryos from 326 women in 5 % oxygen resulted in a higher proportion of good day 2 embryos (54.7 %) compared to those from 321 women cultured in 20 % oxygen, but the ongoing pregnancy rates were not different (31.6 vs. 27.1 %) [43]. The NIH-supported Reproductive Medicine Network in the United States is now conducting another larger, randomized study.

With regard to culture media, most IVF labs worldwide now use commercially prepared "proprietary" media, which is well-tested and undergoes strict quality control but for which the exact composition is unknown. This, quite obviously, makes it difficult to assess if there are any detrimental or beneficial effects of any particular component. That there may well be significant differences among the various media utilized is indicated by one study noting that, in one small Dutch study ($n = 188$), birth weights were significantly higher for embryos cultured in "Vitrolife" media (3453 g) compared to those cultured in "Cook" media (3208 g) [44]. These findings have been confirmed in a subsequent study by the same group [45]. In contrast, other investigators failed to detect any difference in birth weights in a retrospective study comparing embryos cultured in human tubal fluid with added human serum albumin to Sage® Quinn's advantage protein plus medium [46].

One study raises the possibility that the air quality in the region in which the IVF is carried out may affect the results. Legro et al. [47] used air quality monitors from the US Environmental Protection Agency to estimate pollutants at addresses of 7,403 women undergoing first-cycle IVF using laboratories in the northeastern United States. Increases in the concentration of nitrogen oxide at the patient's address and at the IVF laboratory lowered chances of pregnancy and live birth. Increased ozone concentrations during ovulation induction at the patient's address increased chances of subsequent live birth but decreased odds of live birth when increased exposure occurred from embryo transfer to live birth. Fine particulate matter at the IVF laboratory during embryo culture decreased conception rates but not live births. These observations clearly demand confirmation and expansion.

The effects of cigarette smoking on IVF success have been well-documented. A meta-analysis of 2,314 first IVF cycles from eight studies showed that odds of pregnancy were almost halved by smoking [48]. In another study, couples (one or both) who ever smoked had an adjusted relative rate, RR, of 2.41 of not achieving an IVF pregnancy and 3.76 of not achieving a live birth [49]. Moreover, couples smoking more than 5 years had a RR of 4.27 of not achieving a pregnancy. The number of oocytes retrieved decreased by 40 % for couples and 46 % for men smoking the week of IVF. In still another study, smoking was associated with a significantly lower live birth rate and a significantly higher rate of miscarriage compared to the rates in non-smokers [50].

Alcohol consumption also may affect IVF success. Data from a self-administered questionnaire completed by 2,545 couples undergoing 4,729 cycles were analyzed [51]. Women drinking four or more drinks per week had 16 % less odds of a live birth compared to those who drank less. For couples in which both partners drank four or more per week, odds of a live birth were 21 % lower than those in which both partners drank less.

## Development of children conceived by ART

Data continue to accumulate regarding the development of children born as a result of ART. Two studies are indicative of what is known about the development and performance of these children. Ludwig et al. [52] noted that

children born after ART are "generally healthy and are developmentally similar to children born after spontaneous conception". Mains reported that children aged 8–17 years born after IVF scored higher on standardized achievement tests in the state of Iowa than did their matched peers, suggesting that IVF does not have a negative effect on cognitive development [53].

## Final thoughts

It is clear from this review that the risks to IVF children and their mothers are likely to remain higher than those for children and mothers who do not require treatment for conception. Because there have now been over 5 million births after ART worldwide, and the vast majority of these pregnancies and children have been essentially "normal", it is obvious that any excess risks must be relatively small.

However, the fact that almost all ART pregnancies have been "normal" mandates that extreme care be exercised in making any changes to current practice. Clinicians should understand that the atmosphere in this field has changed: there is no place for changing protocols in the absence of controlled trials documenting benefit. It is important for research to continue, but the research must be responsible: with such research, progress in this field should continue.

## References


1. Nygren K-G. The clinical significance and durability of current knowledge. In: Hedon B, Mettler L, Tinneberg H-R, editors. 2010 Proceedings of the IFFS 20th World Congress on Fertility and Sterility. Munich: LUKON—VerlagsgesellschaftmbH; 2010. p. 13–9.
2. Martin JA, Hamilton BE, Osterman MJ. Three decades of twin births in the United States, 1980–2009. NCHS Data Brief 2012; p. 1–8.
3. Jones HW Jr. The use of controlled ovarian hyperstimulation (COH) in clinical in vitro fertilization: the role of Georgeanna Seegar Jones. Fertil Steril. 2008;90:e1–3.
4. Multiple gestation associated with infertility therapy: an American Society for Reproductive Medicine Practice Committee opinion. Fertil Steril. 2012;97:825–34.
5. Torok O, Lapinski R, Salafia CM, Bernasko J, Berkowitz RL. Multifetal pregnancy reduction is not associated with an increased risk of intrauterine growth restriction, except for very-high-order multiples. Am J Obstet Gynecol. 1998;179:221–5.
6. Evans MI, Britt DW. Fetal reduction. Semin Perinatol. 2005;29: 321–9.
7. McLernon DJ, Harrild K, Bergh C, Davies MJ, de Neubourg D, Dumoulin JC, et al. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. BMJ. 2010;341:c6945.
8. Kresowik JD, Stegmann BJ, Sparks AE, Ryan GL, van Voorhis BJ. Five-years of a mandatory single-embryo transfer (mSET) policy dramatically reduces twinning rate without lowering pregnancy rates. Fertil Steril. 2011;96:1367–9.
9. Gleicher N, Barad D. Twin pregnancy, contrary to consensus, is a desirable outcome in infertility. Fertil Steril. 2009;91:2426–31.
10. Sazonova A, Källen K, Thurin-Kjellberg A, Wennerholm UB, Bergh C. Neonatal and maternal outcomes comparing women undergoing two in vitro fertilization (IVF) singleton pregnancies and women undergoing one IVF twin pregnancy. Fertil Steril. 2013;99(3):731–7.
11. Sullivan EA, Wang YA, Hayward I, Chambers GM, Illingworth P, McBain J, et al. Single embryo transfer reduces the risk of perinatal mortality, a population study. Hum Reprod. 2012;27: 3609–15.
12. Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. Low and very low birth weight in infants conceived with use of assisted reproductive technology. N Engl J Med. 2002; 346(10):731–7.
13. Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol. 2004;103(3):551–63.
14. Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. BMJ. 2004;328(7434):261.
15. Fujii M, Matsuoka R, Bergel E, van der Poel S, Okai T. Perinatal risk in singleton pregnancies after in vitro fertilization. Fertil Steril. 2010;94:2113–7.
16. Kalra SK, Ratcliffe SJ, Coutifaris C, Molinaro T, Barnhart KT. Ovarian stimulation and low birth weight in newborns conceived through in vitro fertilization. Obstet Gynecol. 2011;118(4):863–71.
17. Gibbons WE, Cedars M, Ness RB, Society for Assisted Reproductive Technologies Writing Group. Toward understanding obstetrical outcome in advanced assisted reproduction: varying sperm, oocyte, and uterine source and diagnosis. Fertil Steril. 2011;95(5):1645–9.
18. Shih W, Rushford DD, Bourne H, Garrett C, McBain JC, Healy DL, et al. Factors affecting low birthweight after assisted reproduction technology: difference between transfer of fresh and cryopreserved embryos suggests an adverse effect of oocyte collection. Hum Reprod. 2008;23:1644–53.
19. Henriksson P, Westerlund E, Wallen H, Brandt L, Hovatta O, Ekbom A. Incidence of pulmonary and venous thromboembolism in pregnancies after in vitro fertilisation: cross sectional study. BMJ. 2013;346:e8632.
20. Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Olausson PO. Blastocyst versus cleavage stage transfer in in vitro fertilization: differences in neonatal outcome? Fertil Steril. 2010;94:1680–3.
21. Kalra SK, Ratcliffe SJ, Barnhart KT, Coutifaris C. Extended embryo culture and an increased risk of preterm delivery. Obstet Gynecol. 2012;120:69–75.
22. Fernando D, Halliday JL, Breheny S, Healy DL. Outcomes of singleton births after blastocyst versus nonblastocyst transfer in assisted reproductive technology. Fertil Steril. 2012;97:579–84.
23. Olson CK, Keppler-Noreuil KM, Romitti PA, Budelier WT, Ryan G, Sparks AE, et al. In vitro fertilization is associated with an increase in major birth defects. Fertil Steril. 2005;84:1308–15.
24. Davies MJ, Moore VM, Willson KJ, Van Essen P, Priest K, Scott H, Haan EA, Chan A. Reproductive technologies and the risk of birth defects. N Engl J Med. 2012;366(19):1803–13.
25. Hansen M, Kurinczuk JJ, de Klerk N, Burton P, Bower C. Assisted reproductive technology and major birth defects in Western Australia. Obstet Gynecol. 2012;120:852–63.
26. Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Olausson PO. Cancer risk in children and young adults conceived by in vitro fertilization. Pediatrics. 2010;126:270–6.
27. Li LL, Zhou J, Qian XJ, Chen YD. Meta-analysis on the possible association between in vitro fertilization and cancer risk. Int J Gynecol Cancer. 2013;23:16–24.

28. Stewart LM, Holman CD, Aboagye-Sarfo P, Finn JC, Preen DB, Hart R. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. Gynecol Oncol. 2013;128(2):260–4.
29. Jaques AM, Amor DJ, Baker HW, Healy DL, Ukoumunne OC, Breheny S, et al. Adverse obstetric and perinatal outcomes in subfertile women conceiving without assisted reproductive technologies. Fertil Steril. 2010;94:2674–9.
30. Cox GF, Burger J, Lip V, Mau UA, Sperling K, Wu BL, et al. Intracytoplasmic sperm injection may increase the risk of imprinting defects. Am J Hum Genet. 2002;71:162–4.
31. DeBaun MR, Niemitz EL, Feinberg AP. Association of in vitro fertilization with Beckwith-Wiedemann syndrome and epigenetic alterations of LIT1 and H19. Am J Hum Genet. 2003;72:156–60.
32. Maher ER, Brueton LA, Bowdin SC, Luharia A, et al. Beckwith-Wiedemann syndrome and assisted reproductive technology (ART). J Med Genet. 2003;40:62–4.
33. Gicquel C, Gaston V, Mendelbaum J, Siffrio JP, Flahault A, Le Bouc Y. In vitro fertilization may increase the risk of Beckwith-Wiedemann syndrome related to the abnormal imprinting of the KCNQ1OT gene. Am J Hum Genet. 2003;72:1338–41.
34. Manipalviratn S, DeCherney A, Segars J. Imprinting disorders and assisted reproductive technology. Fertil Steril. 2009;91: 305–15.
35. Zheng HY, Shi XY, Wang LL, Wu YQ, Chen SL, Zhang L. Study of DNA methylation patterns of imprinted genes in children born after assisted reproductive technologies reveals no imprinting errors: a pilot study. Exp Ther Med. 2011;2:751–5.
36. Feng C, Tian S, Zhang Y, He J, Zhu XM, Zhang D, et al. General imprinting status is stable in assisted reproduction-conceived offspring. Fertil Steril. 2011;96:1417–23.
37. Oliver VF, Miles HL, Cutfield WS, Hofman PL, Ludgate JL, Morison IM. Defects in imprinting and genome-wide DNA methylation are not common in the in vitro fertilization population. Fertil Steril. 2012;97:147–53.
38. Turan N, Katari S, Gerson LF, Chalian R, Foster MW, Gaughan JP, et al. Inter- and intra-individual variation in allele-specific DNA methylation and gene expression in children conceived using assisted reproductive technology. PLoS Genet. 2010;6: e1001033.
39. Haavaldsen C, Tanbo T, Eskild A. Placental weight in singleton pregnancies with and without assisted reproductive technology: a population study of 536,567 pregnancies. Hum Reprod. 2012;27:576–82.
40. Wakeling EL, Amero SA, Alders M, Bliek J, Forsythe E, Kumar S, et al. Epigenotype-phenotype correlations in Silver-Russell syndrome. J Med Genet. 2010;47:760–8.
41. Meintjes M, Chantilis SJ, Douglas JD, Rodriguez AJ, Guerami AR, Bookout DM, et al. A controlled randomized trial evaluating the effect of lowered incubator oxygen tension on live births in a predominantly blastocyst transfer program. Hum Reprod. 2009;24:300–7.
42. Waldenström U, Engström AB, Hellberg D, Nilsson S. Low-oxygen compared with high-oxygen atmosphere in blastocyst culture, a prospective randomized study. Fertil Steril. 2009;91(6): 2461–5.
43. Kovacic B, Sajko MC, Vlaisavljevic V. A prospective, randomized trial on the effect of atmospheric versus reduced oxygen concentration on the outcome of intracytoplasmic sperm injection cycles. Fertil Steril. 2010;94:511–9.
44. Dumoulin JC, Land JA, Van Montfoort AP, Nelissen EC, Coonen E, Derhaag JG, et al. Effect of in vitro culture of human embryos on birthweight of newborns. Hum Reprod. 2010;25:605–12.
45. Nelissen EC, Van Montfoort AP, Coonen E, Derhaag JG, Geraedts JP, Smits LJ, et al. Further evidence that culture media affect perinatal outcome: findings after transfer of fresh and cryopreserved embryos. Hum Reprod. 2012;27:1966–76.
46. Vergouw CG, Kostelijk EH, Doejaaren E, Hompes PG, Lambalk CB, Schats R. The influence of the type of embryo culture medium on neonatal birthweight after single embryo transfer in IVF. Hum Reprod. 2012;27:2619–26.
47. Legro RS, Sauer MV, Mottla GL, Richter KS, Li X, Dodson WC, et al. Effect of air quality on assisted human reproduction. Hum Reprod. 2010;25:1317–24.
48. Feichtinger W, Papalambrou K, Poehl M, Krischker U, Neumann K. Smoking and in vitro fertilization: a meta-analysis. J Assist Reprod Genet. 1997;14:596–9.
49. Klonoff-Cohen H, Natarajan L, Marrs R, Yee B. Effects of female and male smoking on success rates of IVF and gamete intra-fallopian transfer. Hum Reprod. 2001;16:1382–90.
50. Lintsen AM, Pasker-de Jong PC, de Boer EJ, Burger CW, Jansen CA, Braat DD, et al. Effects of subfertility cause, smoking and body weight on the success rate of IVF. Hum Reprod. 2005;20:1867–75.
51. Rossi BV, Berry KF, Hornstein MD, Cramer DW, Ehrlich S, Missmer SA. Effect of alcohol consumption on in vitro fertilization. Obstet Gynecol. 2011;117:136–42.
52. Ludwig AK, Sutcliffe AG, Diedrich K, Ludwig M. Post-neonatal health and development of children born after assisted reproduction: a systematic review of controlled studies. Eur J Obstet Gynecol Reprod Biol. 2006;127:3–25.
53. Mains L, Zimmerman M, Blaine J, Stegmann B, Sparks A, Ansley T, et al. Achievement test performance in children conceived by IVF. Hum Reprod. 2010;25:2605–11.