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Review

The impact of assisted reproductive technologies on intra-uterine growth and birth defects in singletons

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S U M M A R Y

Pooled odds ratios from meta-analyses of infants born following assisted reproductive technologies (ART) compared with non-ART singletons show increases in low birth weight, preterm birth, small for gestational age, and birth defects. Although there have been small reductions in recent data, odds associated with these outcomes are still higher for ART singletons. Both ART procedures and underlying infertility contribute to these increased risks. Outcomes appear better for frozen–thawed compared with fresh embryo transfers, but are poorer than for non-ART infants. There is a concerning increase in large-for-gestational-age infants born following frozen–thawed embryo transfer and limited data on the effects of embryo vitrification used instead of slow-freezing techniques. Using large datasets, we now need to investigate risks of individual birth defects and disentangle the inter-related effects of different types of infertility and the multiple aspects of ART. Greater understanding of the causes of adverse ART outcomes and identification of modifiable risk factors may lead to further reductions in the disparities in outcome between ART and non-ART infants.

1. Introduction

Intrauterine growth is usually estimated using gestational age and weight at birth, which are routinely recorded on all births in most countries where assisted reproductive technologies (ART) have been introduced. It is therefore not surprising that the possible effects of ART on these two measures were reported soon after the first ART birth in 1978. For example, in 1985, the Australian In Vitro Fertilisation Collaborative Group [1] reported that 19% of 108 ART singletons in Australia were born before 37 weeks of gestation and 19% had a birth weight <2500 g, about three times the population rates at that time of preterm birth (PTB) and low birth weight (LBW). Although there were also early reports on birth defects following ART, they were based on small numbers of affected children, as birth defects are relatively rare. Hence, risk estimates were imprecise and often interpreted as showing no increase because the difference was not statistically significant. It took until the mid-2000s for the increased risk of birth defects in ART-conceived infants to be generally acknowledged [2,3].

ART has changed greatly since those early days. Techniques have altered, advanced and multiplied, pregnancy success rates have increased considerably, and more couples are using ART and for an increasing list of indications – there are now estimated to be more than five million ART children worldwide. This article surveys the systematic reviews and meta-analyses on intrauterine growth and birth defects in ART compared with non-ART singletons and discusses the possible reasons for the differences found, again using evidence from systematic reviews and meta-analyses where available. We report on recent reductions in risk of these outcomes and discuss two emerging issues: (i) the shift towards frozen–thawed embryos, and (ii) the risk of excessive intrauterine growth.

2. Systematic reviews and meta-analyses

2.1. Intrauterine growth

Poor intrauterine growth is a predictor of adverse perinatal (and later) outcomes and is usually estimated using infant weight and gestation at the time of birth. Whereas the advent of prenatal ultrasound scanning has allowed serial measurement of growth during pregnancy, all the population studies included in the systematic reviews have used weight and gestation at birth to assess intrauterine growth.

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Table 1
Pooled estimates and 95% confidence intervals derived from the meta-analyses of six systematic reviews examining intrauterine growth in ART compared with non-ART singletons.

	Helmerhorst et al. [4]	Jackson et al. [5]	McGovern et al. [8]	McDonald et al. [7]	McDonald et al. [6]	Pandey et al. [9]
Years included in literature search	1985–2002	1978–Oct 2002	1965–2000	1966–Oct 2003	1978–June 2008	1978–2011
No. of studies in meta-analysis of preterm birth[a]	12	14	27	10	15	22
No. of ART infants in meta-analysis of preterm birth[b]	5361	12,114	14,748	3055	<31,032[b]	27,819
Preterm birth (<37 weeks)	2.0 (1.8–2.3)	2.0 (1.7–2.2)	2.0 (1.8–2.2)	1.9 (1.4–2.7)	1.8 (1.5–2.2)	1.5 (1.5–1.6)
Very preterm birth (<32 weeks)	3.3 (2.0–5.3)	3.1 (2.0–4.8)	2.5 (0.9–7.2)	3.0 (1.5–5.8)	2.3 (1.7–3.0)	1.7 (1.5–1.9)
Low birth weight (<2500 g)	1.7 (1.5–1.9)	1.8 (1.4–2.2)	–	1.4 (1.0–1.9)	1.6 (1.3–2.0)	1.6 (1.6–1.8)
Very low birth weight (<1500 g)	3.0 (2.1–4.4)	2.7 (2.3–3.1)	–	3.8 (2.5–5.8)	2.6 (1.8–3.8)	1.9 (1.7–2.2)
Small for gestational age	1.4 (1.2–2.7)	1.6 (1.3–2.0)	–	1.6 (1.2–2.1)	1.4 (1.0–2.0)	1.4 (1.3–1.5)

ART, assisted reproductive technologies.
[a] An indicator of the number of studies included in different meta-analyses. This varies widely depending on the outcome under study. For example, in the Pandey et al. [9]. meta-analysis 22 studies reported on preterm birth and 19 on low birth weight, but only seven reported on small for gestational age.
[b] A rough indicator of the number of ART infants included in different meta-analyses. For the meta-analysis by McDonald et al. [6] it was not possible to determine the exact number of ART infants included in the meta-analysis of preterm birth which included 15 of the 17 studies. The total number of infants in all 17 studies was 31,032.

There have now been six systematic reviews (with meta-analyses) including comparisons of weight and gestation at birth in ART and non-ART singletons (Table 1) [4–9].

2.2. Gestation

The pooled odds ratios (ORs) from each of the reviews show an increase in PTB (<37 weeks of gestation), with around a two-fold increase in all but the most recent review, in which the OR was 1.5 (Table 1) [9]. All these estimates of effect have 95% confidence intervals (CIs) that exclude unity and are therefore all statistically significant.

The pooled ORs for very PTB (<32 weeks) were even more elevated – around two-and-a-half to three times that of non-ART singletons in the earliest reviews and again lower (1.7) but still statistically significant in the most recent review [9].

2.3. Birth weight

The findings for LBW and small for gestational age (SGA) show increased ORs (1.4–1.8 for LBW; 1.4–1.6 for SGA) and the ORs in the Pandey et al. [9] review were similar. For very LBW the pooled ORs were around 3, falling to around 2 in the recent review (Table 1) [9].

2.4. Birth defects

There have been six systematic reviews with meta-analyses of birth defects and ART in singletons (or singletons and multiples combined), compared with their non-ART counterparts (Table 2) [2,3,7,9–11]. The pooled ORs show a 30–70% increase in birth defects (ORs: 1.3–1.7), with slightly lower pooled ORs for studies examining singletons and multiples combined (ORs: 1.3–1.4). Although some individual studies (the earlier ones in particular) had methodological limitations and most of them were small, there are now many large, well-conducted studies examining the risk of birth defects in ART infants, and the pooled ORs from each meta-analysis are similar. This may be partly due to the inclusion of very large population-based studies from Scandinavia, Germany and Australia that carry considerable weight in the analyses. Data from the large Swedish ART cohort [12], for example, contributed 34% of all ART infants in our recent meta-analysis [10].

Increased risks of anatomically grouped birth defects (e.g. cardiovascular, musculoskeletal, gastrointestinal, urogenital) in ART compared with non-ART singletons were found in pooled data from a meta-analysis [11]. There have been no meta-analyses of individual birth defects, although there was a review of the increased association between ART and rare imprinting disorders such as Beckwith–Wiedemann and Angelman syndromes, consistent with animal studies demonstrating alteration in gene imprinting of embryos cultured in vitro [13].

Two studies have reported on the association of birth defects and ART over time [12,14] and both have found a reduction in risk among more recent births. In the Swedish study, the risk ratio decreased from 1.5 (1986–2001) to 1.3 (2001–2006), whereas in our Australian study the OR decreased from 1.9 (1994–1998) to 1.3 (1999–2002). A study from Finland using a more recent birth

Table 2
Pooled estimates (95% confidence intervals) derived from the meta-analyses of six systematic reviews examining birth defects in ART compared with non-ART singletons (or singletons and multiples together).[a]

	Rimm et al. [3]	Hansen et al. [2]	McDonald et al. [7]	Pandey et al. [9]	Wen et al. [11]	Hansen et al. [10]
Singletons						
Years included in literature search	1990–Sep 2003	1978–Mar 2003	1966–Oct 2003	1978–2011	1978–Sep 2011	1978–Sep 2012
No. of studies in meta-analysis	IVF: 8 ICSI: 6	15	7	7	–	23
No. of ART infants in meta-analysis	IVF: 2064 ICSI: 3948	13,059	4031	4382	–	48,944
Birth defects	IVF: 1.5 (0.8–2.7) ICSI: 1.3 (0.9–2.0)	1.3 (1.2–1.5)	1.4 (1.1–1.9)	1.7 (1.3–2.1)	–	1.4 (1.3–1.4)
Singletons and multiples together						
No. of studies in meta-analysis	19	25			46	45
No. of ART infants in meta-analysis	35,578	28,638			124,468	92,671
Birth defects	1.3 (1.0–1.7)	1.3 (1.2–1.4)			1.4 (1.3–1.5)	1.3 (1.2–1.4)

ART, assisted reproductive technologies.
[a] Adapted from Hansen et al. [10].