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Review

Birth defects and assisted reproductive technologies

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SUMMARY

Assisted reproductive technologies (ART) using in-vitro fertilization (IVF) account for ~1% of births in the USA and as much as 3–4% in Europe or Australia. Initially studies involved infants prospectively examined in an early cohort of US births, with salutary results. Later studies began to show the frequency of birth defects to be increased. In meta-analysis, odds ratio was >1.0, with the 95% confidence limit not extending to <1.0. Although ART are associated with a 30% increase in birth defects; subfertile couples achieving pregnancy without ART show a 20% increase. It thus appears that the increase in birth defects is due less, if at all, to ART protocols per se than to the biological perturbations that generated the infertility that necessitated ART to achieve pregnancy. There is consensus that traditional IVF and intracytoplasmic sperm injection (ICSI)/IVF show the same overall risk notwithstanding increased sex chromosome abnormalities in both procedures and increased hypospadias in ICSI. No other organ system seems disproportionately affected. There is no additive risk in ART twins compared with non-ART twins, nor in embryos having been cryopreserved. The increased risk observed had not appeared to dissuade couples from attempting to have their own children.

1. Introduction

Assisted reproductive technologies (ART) using in-vitro fertilization (IVF) account for about 1% of births in the USA and as much as 3–4% in Europe or Australia. More than five million babies are estimated worldwide to have been born through ART. Scientific and medical advances are increasing pregnancy rates, and the prevalence of ART births can confidentially be expected to continue to increase. Even prior to the pioneering efforts of Edwards and Steptoe that resulted in the first success in 1978, concern had been raised over whether infants born by ART would universally be abnormal. This fear has largely been mitigated, and attention is now focused on more nuanced questions.

The initial studies involved infants carefully examined in an early cohort of US births, with results salutary although sample sizes were small [1]. Population-based studies from Australia by Lancaster [2] showed a 2.9% frequency, reassuringly that expected for the general population. The first large population study was by Westergaard et al. [3], who compared 2245 ART births in 1994–1995 with 2245 controls. The odds ratio (OR) was 1.04 with the 95% confidence interval (CI) 0.78–1.39 (non-significant). Other studies of this era generally failed to show deleterious effects (Table 1) [3–5]. Studies reported in the 2000s began to show frequency of birth defects to be increased (Table 2). The OR in these studies was often >1.0, with the 95% CI not extending across the 1.0 isobar [6–15]. Thus, there evolved the present consensus that increased birth defects are indeed positively associated with ART. The major question at present is whether this increase is due to ART protocols per se or merely reflective of the biological perturbations that generated the infertility that necessitated ART to achieve pregnancy.

In this communication, we shall first consider the frequency of congenital anomalies in offspring of ART pregnancies, stratified by specific subgroups depending on technique. We shall also comment on the pitfalls that make difficult definitive conclusions concerning the explanation for anomalies detected.

2. Frequency of anomalies in ART pregnancies

Almost 50 cohort studies have addressed the question of anomalies in ART pregnancies, as referenced elsewhere [16–19]. Initial studies naturally focused on IVF alone, because not until the mid-1990s could male infertility be managed by intracytoplasmic sperm injection (ICSI) followed by traditional IVF. In the 1990s and early 2000s, one could confidently conclude the overall risk was not, say, a two- or three-fold increase above the accepted population baseline of 2–3%. However, more precise statements could not be made.

Notwithstanding general reassurance, this author and others pointed out pitfalls that could sway opinions on safety in either

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Table 1
Earlier population-based studies of anomalies in assisted reproductive technology pregnancies.

Study	Years of sample accrual	Adjusted OR (95% CI)	Statistical significance	Country
Dhont et al. [4]	1986–2002	1.25 (0.96–1.64)	No	Belgium
Westergaard et al. [3]	1994–1995	1.04 (0.78–1.39)	No	Sweden
Anthony et al. [5]	1995–1996	1.03 (0.86–1.23)	No	Netherlands

OR, odds ratio; CI, confidence interval.
The initial population-based studies depend on data in registries. Ascertainment varied between studies with respect to duration of time in which anomalies were sought and definition of major defects. The interval of accumulated ART registry cases does not in any report correspond to the extant laboratory and ovulation stimulation protocols used in 2014.

direction [20,21]. It was in particular appreciated that power to detect a significantly increased frequency of anomalies was not possible due to small sample size.

Table 2 shows later population-based studies on which this altered conclusion began to be based [6–15]. All were based on registries that recorded cohorts of births, from which those with anomalies could be stratified. A caveat is that the definition of birth defects among registries varies, usually involving International Classification of Diseases (ICD)-based diagnosis codes not well suited to distinguish major from minor anomalies. ICD codes at birth are not robust in detecting subtle anomalies not externally visible, nor in excluding inherited syndromes or chromosomal anomalies. Neither is plausibly due to ART. Not always followed is the pragmatic, accepted, definition of a major birth defect as one that causes death, functional impairment or (if structural) requires surgery.

Reviewing several studies will suffice as illustrative. In 2005 Klemetti et al. [7] published Finnish registry of IVF and ICSI cases delivered in 1996–1999, finding the adjusted OR for all birth defects to be 1.31 (95% CI: 1.10–1.57), when comparing 4459 cases and 27 078 controls. In 2007, Pinborg et al. [9] used Danish registry data to derive an OR of 1.24 (95% CI: 1.09–1.43). In 2005 Kallen et al. [6,12] published an analysis of Swedish registries (1982–1999) data and in 2010 analysed cases for the years 2001–2007. The latter study showed OR of 1.25 (95% CI: 1.5–1.37) based on 15 570 cases [12].

Outside of Scandinavia, the region generating greatest attention is Australia, befitting the country's sentinel role in developing ART. In 2002 Hansen et al. reported Western Australia cases, reprising this in 2012 [14,22]. Their 2012 report of Western Australia registry data involved ART cases delivered 1994–2002, an interval of significance given many changes having since occurred in laboratory methodology. This study was laudatory, however, in trying to take into account anomalies in pregnancy terminations. Both the 2911 ART cases and the 210 997 non-ART cases were followed for 6 years. A 'major birth defect' was found in 8.7% of ART cases and 5.4 of non-ART cases (OR: 1.53; 95% CI: 1.30–1.79). Rates were not different in unlike sex twins (obligatory dizygosity) (OR: 1.08; 95% CI: 0.77–1.51). The 5.4% birth defects in the control group is at odds with general acceptance, absent comprehensive laboratory assessments such as array comparative genomic hybridization. These authors concluded also that there has been a decrease in the prevalence of birth defects compared with their earlier cohort (1994–1998) [14,23]. One explanation may simply be greater appreciation between major and minor anomalies. Plausible scientific reasons include changes in culture media, better regulation of heat and CO_2 in incubators, and differential ovulation stimulation regimes.

A second Australian group extending interval of ascertainment to 5 years was that of Davies et al. [13], who used registry data of 308 974 births in South Australia (Adelaide). Minor defects were excluded unless they required treatment or were 'disfiguring'. Among 6163 ART offspring were 513 with anomalies (8.4%), compared with 5.8% in non-ART births. The adjusted OR was 1.28 (95% CI: 1.16–1.41). OR was 1.26 for IVF alone, and 1.77 for ICSI/IVF. It would be of interest to know the temporal sequence in which the cumulative absolute frequency of birth defects occurred, i.e. ascertainment at birth versus later.

Of special interest to US readers is the report of Kelley-Quon et al. [15], who used the California Patient Discharge Linked Birth Cohort Database that lists anomalies by ICD-9 codes. This study involved 4795 infants born in 2006–2007 after ART, compared with 46 025 naturally conceived in the same interval. The overall rate of 'major congenital abnormalities' was 9.0% vs 6.6% (OR: 1.25; 95% CI: 1.12–1.39; $P < 0.001$). Incidence of birth defects this high bespeaks inclusion of many minor anomalies. In this author's opinion, this alone casts doubt on conclusions that ORs were significantly increased for certain organ-specific anomalies: eye, head and neck, heart and genitourinary track.

These limitations notwithstanding, meta-analyses reached similar arithmetic conclusions: Rimm et al. [16]: 1.29 (95% CI: 1.01–1.67); Hansen et al. [17,19], risk ratio: 1.32 (95% CI: 1.24–

Table 2
Later population-based studies on anomalies in assisted reproductive technology (ART) pregnancies (2005–2013).

Study	Years of sample accrual	Adjusted OR (95% CI)	Statistical significance	Country
Kallen et al. [6]	1982–2001	1.44 (1.32–1.57)	Yes	Sweden
Davies et al. [13]	1986–2002	1.24 (1.09–1.41)	Yes	Australia (Adelaide)
Halliday et al. [11]	1991–2004	1.36 (1.19–1.55)	Yes	Australia (Parkville)
Hansen et al. [14]	1994–2002	1.53 (1.30–1.79)	Yes	Australia (Perth)
Pinborg et al. [9]	1995–2000	1.24 (0.97–1.58)	No	Denmark
Klemetti et al. [7]	1996–1999	1.31 (1.10–1.57)	Yes	Finland
Ombolet et al. [8]	1997–2003	1.11 (0.08–1.58)	No	Belgium
Kallen et al. [12]	2001–2007	1.25 (1.15–1.37)	Yes	Sweden
Kelley-Quon et al. [15]	2006–2007	1.25 (1.21–1.39)	Yes	USA (California)
Fuji et al. [10]	2006	1.17 (0.81–1.69)	No	Japan

OR, odds ratio; CI, confidence interval.
These population-based studies depend on data in registries. Ascertainment varied with respect to duration of time in which anomalies were sought and definition of major defects. The interval of accumulated ART registry cases does not in any report correspond to the extant laboratory and ovulation stimulation protocols used in 2013.