

# Practitioner reporting of birth defects in children born following assisted reproductive technology: Does it still have a role in surveillance of birth defects?

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**BACKGROUND:** National assisted reproductive technology (ART) data collections that rely on practitioners' reports of birth defects have consistently reported lower proportions of children with birth defects than record linkage studies that link ART infants to birth and malformation registers. **METHODS:** We compared the birth defect data reported to the national Australian Assisted Conception Data Collection (ACDC) by practitioners at three Western Australian ART clinics with the birth defect data identified on the Western Australian Birth Defects Registry (WABDR) through record linkage of all the pregnancies conceived at these clinics to the WABDR. Cases are reported to the WABDR by multiple statutory and voluntary sources. **RESULTS:** We found that the national ACDC significantly underestimated the prevalence of birth defects in WA-born ART infants. Less than one-third of ART children identified with a major birth defect on the WABDR were reported to the ACDC. **CONCLUSIONS:** Although national ART data collections provide valuable information on pregnancy rates and short-term pregnancy outcomes such as multiple birth and birth weight, we strongly recommend that birth defect information used for patient counselling is preferentially drawn from large studies that have used record linkage to high-quality birth defect registers.

*Key words:* assisted reproductive technology/congenital malformations/IVF/national ART registers/surveillance

## Introduction

Data collection by national assisted reproductive technology (ART) registers provides information about the proportion of national births that are ART births, population access to ART in terms of cycles/million inhabitants, the relative importance of different ART techniques (such as IVF versus ICSI) and the age distribution of the women treated in a particular country. Individual clinics are able to compare their pregnancy, live birth and multiple birth rates to national figures, and national registers generally provide reliable information on birth weight, gestational age and perinatal mortality. However, as a source of information on birth defects in ART infants, national ART registers that rely on practitioners' reports of birth defects have consistently reported lower proportions of children with birth defects (1.1–3.9%) (Anonymous, 1995, 2000; Zegers-Hochschild, 2002; Dean and Sullivan, 2003) than record linkage studies that link ART infants to birth and malformation registers (4.3–8.9%) (Westergaard *et al.*, 1999; Hansen *et al.*, 2002; Kallen *et al.*, 2005; Klemetti *et al.*, 2005).

The publication describing a record linkage study between the Western Australian Reproductive Technology Register, the state Birth Register and the Western Australian Birth Defects Registry (WABDR) (Hansen *et al.*, 2002) generated much discussion (Barlow, 2002; Lambert, 2002; Mitchell, 2002; Schultz and Williams, 2002; Winston and Hardy, 2002; Kovalevsky *et al.*, 2003; Powell, 2003). This study found that 8.9% of ART children conceived at the three WA ART clinics between 1993 and 1997 were diagnosed with a major birth defect by 1 year of age.

National Australian data, by contrast, show a much lower prevalence (ranging from 2.0 to 3.9%) of reported birth defects for *all* Australian and New Zealand ART births between 1992 and 2000 (Lancaster *et al.*, 1995, 1997; Hurst *et al.*, 1997, 1999; Hurst and Lancaster, 2001a,b; Dean and Sullivan, 2003). This data source, which also includes information from the three WA clinics, is collated by the National Perinatal Statistics Unit of the Australian Institute of Health and Welfare. ART clinics are asked to follow-up outcomes of pregnancies,

collecting information on perinatal outcomes from each patient or their clinician. Because ART practitioners do not always provide care to women beyond their first trimester of pregnancy, the perinatal follow-up information may be obtained in a number of ways including direct contacting of mothers and/or treating doctors, patient self-report or hospital record review (Bryant *et al.*, 2004). During this period, Australia had neither nationally agreed guidelines for follow-up and notification of birth defects generally nor formal reporting guidelines for ART clinics. Instead, ART clinics were requested as part of the Assisted Conception Data Collection (ACDC) to report as much detail as was known about birth defects including from birth defect registration forms, autopsy reports and doctors' letters. To date, the utility of this follow-up has not been validated; however, many birth defects may be missed by data collections focusing on the perinatal period, as about one-third of the defects are not obvious at delivery and may be diagnosed weeks or even months later (Bower *et al.*, 2005).

In contrast, the WABDR collects information on birth defects diagnosed up to 6 years of age in WA-born infants (Bower *et al.*, 2005). Cases are reported by multiple statutory (Midwives' Notification of Birth Forms, Death Certificates, Hospital Morbidity Data System) and voluntary (private practitioners, genetics services, pathology services, cytogenetics services, ultrasound services, child and community health nurses and doctors and rural paediatric services) sources leading to a high level of ascertainment and accuracy. The BDR in South Australia, with similar methods, birth defect definition and inclusion/exclusion criteria, reports similar population rates of birth defects (Anonymous, 2005).

In Finland, Gissler *et al.* (2004) have shown that national data collected from all ART clinics underestimate birth defects in ART infants compared with the Finnish Malformations Register. The ART clinic statistics suggest a prevalence of major birth defects of 1.6%, whereas data linking the Finnish Birth and Malformations Register suggest a prevalence of 4.2%.

On the basis of these data from Finland, the results of the Western Australian record linkage study and the differences between methods of ascertainment used by the national ACDC and the WABDR, we reasoned that the Australian ACDC may underestimate the prevalence of birth defects in children born following ART in WA.

To test this, we compared the birth defect data reported to the national ACDC by the three WA ART clinics with the birth defect data identified on the WABDR through record linkage of all the pregnancies conceived at these clinics to the WABDR.

## Materials and methods

The three WA ART clinics provided de-identified details of all birth defects reported to the ACDC for the study period (1993–1997). The ACDC was an Australian and New Zealand data collection of pregnancies following ART; only Australian data were included in this study. These data were compared to the major birth defects identified in the record linkage study of all the pregnancies conceived at these clinics between 1993 and 1997 to the WABDR (Hansen *et al.*, 2002). For the record linkage study, data from the statutory WA Assisted Reproductive Technology Register were used to identify all ART

pregnancies of at least 20 weeks duration and any terminations of pregnancy (regardless of the length of gestation). These were linked to the State Birth Register that collects information on all infants delivered in WA at 20 weeks gestation or later. Finally, all births and terminations were linked to the WABDR, so that de-identified records of birth defects were available for all infants and terminations for which a link was found within the BDR. A birth defect on the WABDR is defined as a structural or functional abnormality that is present at conception or occurs before the end of pregnancy and is diagnosed by 6 years of age. Most minor defects are excluded unless they are disfiguring or require treatment (Bower *et al.*, 2005). Conditions that are not considered birth defects by the WABDR (e.g. umbilical hernia) have not been considered in this article, nor have children with minor birth defects only.

As the original linkage study collected information on birth defects diagnosed up to 1 year of age although ART clinics generally only obtain information about birth defects diagnosed at or before birth, comparisons between the two reporting sources were also made with defects restricted to those diagnosed antenatally or at birth.

We used McNemar's chi-square test to compare the proportion of children with defects identified using the different data sources.

This study was covered by ethics approval from the King Edward Memorial Hospital/Princess Margaret Hospital Ethics Committee.

## Results

There were 1138 children born following conception by IVF or ICSI treatment in WA ART clinics between 1993 and 1997. The clinics reported 32 infants with major birth defects to the national ACDC (giving a birth defect prevalence of 2.8%). There were 101 of the 1138 infants notified to the WABDR with a major birth defect diagnosed by 1 year of age (birth defect prevalence 8.9%), a statistically significant difference [McNemar  $\chi^2 = 60.1$  (1 df),  $P < 0.001$ ] (Table I). Overall, only 27.7% of children with a major birth defect identified on the WABDR by 1 year of age were reported to the national ACDC. Four children with birth defects were reported to the national ACDC but were not included on the WABDR. Three of these had conditions (patent ductus arteriosus, hip dysplasia and inherited Robertsonian translocation) that staff of the BDR would check to determine whether they were registrable. The WABDR has strict criteria for the inclusion of these conditions (Bower *et al.*, 1987, 2005; Bower and Ramsay, 1994), and it may be that they were not met in these cases. The fourth condition is a registrable one and hence appears to have been missed by the BDR.

Defects that were not reported included 21 infants with musculoskeletal defects such as congenital dislocation of the hip (CDH) and talipes equinovarus, 21 infants with genitourinary

**Table I.** Number of children reported with a major birth defect according to different data sources; the national Australian Assisted Conception Data Collection (ACDC) and the Western Australian Birth Defects Registry (WABDR)

	Australian ACDC		Total
	Defect—Yes	Defect—No	
WABDR			
Defect—Yes	28	73	101
Defect—No	4	1033	1037
Total	32	1106	1138

McNemar  $\chi^2 = 60.1$  (1 df),  $P < 0.001$ .

defects such as undescended testes (UDT) and hypospadias, five infants with cardiovascular defects such as ventricular septal defect and coarctation of the aorta, five infants with chromosomal defects such as Trisomy 21 and four infants with gastro-intestinal defects such as cleft lip and palate and pyloric stenosis. Seventeen infants were diagnosed with other defects including nervous system and respiratory system defects, haemangiomas and abnormalities of the eyes.

Sixty percent (44/73) of the defects not reported to the national ACDC by the WA clinics were diagnosed antenatally or in the first week of life, the remainder being diagnosed within the first year of life. When we restricted the birth defects to those that were diagnosed antenatally or within the first week of life, the clinics reported 22 infants with major birth defects to the national ACDC, and there were 66 IVF or ICSI infants notified to the WABDR. This means that only one-third of the children who were reported to the WABDR with a major birth defect diagnosed at, or before, birth were notified to the national ACDC by the WA clinics.

Where a child was reported to both data sources with a birth defect(s), it was noted that more detail was often provided to the WABDR than to the national ACDC. For example, the accompanying heart defects in children with chromosomal anomalies were not reported to the national ACDC.

## Discussion

We found that the ACDC significantly underestimated the prevalence of birth defects in WA-born ART infants. Less than one-third of ART children identified with a major birth defect on the WABDR were reported to the national ACDC. There are several explanations for the differences.

First, the common practice of patients being referred back to their obstetrician for pregnancy care meant that many ART practitioners did not follow all pregnant patients through to delivery (Bryant *et al.*, 2004). Even when it was known that a birth occurred, validated information about the presence or absence of birth defects was not necessarily available. The birth defect field is left blank on the Australian ACDC if no birth defect is reported. Thus, it is not known whether the information on birth defects was not collected or whether it was sought, but no birth defect was identified. This limited the utility of the collection to estimate the extent of missing birth defect data. In contrast, in the Western Australian record linkage study, there were no losses to follow-up with respect to ART births within the State. All WA-born ART infants were linked to the BDR to determine whether they had been diagnosed with a birth defect.

Second, a shorter length of follow-up by ART practitioners could lead to under-ascertainment of defects that are not clinically obvious at birth. Birth defect data extracted from the WABDR for this study include defects diagnosed up to 1 year of age. The national ACDC, by contrast, did not provide instructions on the data reporting form as to the length of follow-up required for the reporting of birth defect data and the date of diagnosis of a malformation is not recorded in this collection. However, because the data were collated by the National Perinatal Statistics Unit, it might reasonably have

been assumed that the collection referred only to birth defects identified in the perinatal period. If clinics generally obtained information about defects diagnosed at or shortly after delivery, defects that are not clinically obvious at birth will be under-ascertained in comparison with reports from the WABDR. Although this may have occurred to some extent, it cannot explain the entire difference between the registers because 60% of the defects that were not reported to the national ACDC were diagnosed at birth or antenatally.

Furthermore, some infants with defects that would certainly have been clinically obvious at birth (such as Trisomy 21 and cleft lip and palate) were not reported to the national ACDC. Gissler *et al.* (2004) also reported that under-ascertainment in the national Finnish ART data was evident for specific major birth defects that are clinically obvious at birth (such as Trisomy 21, cleft palate and neural tube defects). This again suggests that shorter length of follow-up is not the sole explanation for under-ascertainment of birth defects in ART clinician data. When we restricted our comparison to defects diagnosed antenatally or at birth (to allow for a shorter follow-up period by ART clinicians), the difference in prevalence estimates remained statistically significant.

Third, most clinics during this period obtained information on birth defects by telephoning the mother (Bryant *et al.*, 2004). In contrast, the WABDR seeks notifications from multiple statutory and non-statutory sources (Bower *et al.*, 2005). Using data from the large Atlanta Birth Defects Case-Control study, Rasmussen *et al.* (1990) were able to show that only 61% of mothers whose child had a major birth defect gave responses at telephone interview that could be coded as denoting a major birth defect. The most important factor influencing the sensitivity of maternal response was the type of birth defect: for those defects that have life-long effects on the family (e.g. Trisomy 21 and spina bifida), the sensitivity of maternal responses was high, whereas sensitivity was low for those defects in which treatment usually takes place shortly after birth with good results (e.g. hypospadias and talipes equinovarus) or where the defect was lethal (e.g. anencephaly). Maternal race, education, age and baby's birth status (live or stillborn) also influenced maternal response. Although a random selection of ART treatment cycle data reported to the Australian ACDC are validated against clinic records by the Reproductive Technology Accreditation Committee in their triennial clinic inspections (Bryant *et al.*, 2004), maternal report (or the absence of maternal report) of birth defects cannot be validated in this way. Validation of birth defect data would require examination of obstetric and paediatric records—an expensive and time-consuming process.

The number of children with major birth defects in this study ( $n = 101$  on the WABDR) was too small to allow detailed examination of particular maternal or infant characteristics which may have influenced the reporting of birth defects to the national register. We did search for trends in these data however and found, in agreement with Rasmussen *et al.* (1990), that maternal age, race and baby's birth status may have influenced reporting to some extent. In addition, birth defects in children who may be more closely examined in the perinatal period such as multiple births, low birthweight babies and

preterm births appeared to be more often reported to the national register, although none of these comparisons reached statistical significance.

Lastly, some defects may not be considered as notifiable birth defects by ART clinicians. For example, Kallen *et al.* (2005) in their most recent analysis of malformations in Swedish ART births presented results with and without the exclusion of some conditions such as CDH and UDT, which were considered relatively common, variable in registration and sometimes associated with preterm birth. In contrast, the WABDR would include these two conditions if they met a number of criteria. For example, UDT are included on the register if they require surgery. This prevents the registration of cases with testes that are simply retractile and descend spontaneously without surgery. Similarly, cases of CDH are registered if they require abduction splinting, surgery or both. Children with 'clicky hips' or for whom the sole treatment prescribed is the use of double diapers are excluded (Bower *et al.*, 1987). As no definition or guidance is provided to Australian ART clinicians as to what constitutes a birth defect for the purposes of the national ACDC, judgements may vary from clinic to clinic about which defects they should or should not report. This was demonstrated when only one of three WA clinics reported cases of CDH or UDT to the national ACDC despite at least one child at all three clinics being reported to the WABDR with each of these defects. Conversely, some more minor conditions that are not registrable on the WABDR were reported to the national ACDC (such as umbilical hernia and bilateral hydrocoeles).

In summary, it is likely that these four reasons have all contributed to the under-ascertainment of birth defects on the Australian ACDC. This finding is supported by similar data from Finland (Gissler *et al.*, 2004).

The data used to undertake the comparison of registers in this article are now at least 8-years old, but we believe that birth defect reporting patterns from ART clinics in Australia are unlikely to have changed substantially over time. For example, estimates of birth defect prevalence from the national ACDC for the years 1998, 1999 and 2000 were 2.0, 2.0 and 3.9%, respectively (Hurst and Lancaster, 2001a,b; Dean and Sullivan, 2003). Similarly, estimates of birth defect prevalence from other national ART registers reliant on practitioner's report (such as the French, German, USA and Latin American registers) have all been consistently low (Anonymous, 1995, 2000; Schroder and Ludwig, 2002; Zegers-Hochschild, 2002). It has previously been suggested that these registers are likely to underestimate the prevalence of birth defects in ART infants (Schieve *et al.*, 2000; Schroder and Ludwig, 2002; Franco *et al.*, 2004). In fact, the Centers for Disease Control and Prevention (CDC) in the USA have published a commentary warning of the very serious limitations of published estimates of birth defects and deaths among US ART infants, based on data collected by the US Society for Assisted Reproductive Technology (SART) (Schieve *et al.*, 2000).

There is no doubt that national ART registers with data contributed by ART practitioners provide valuable information on pregnancy rates and pregnancy outcomes such as multiple birth, birthweight, gestation and perinatal mortality and

because of this are much broader in scope than a State-based BDR. This validation study however confirms the importance of surveillance of birth defects following ART by dedicated Birth Defect Registers and highlights the limitations of ART data sets that rely solely on practitioner reports of birth defects. Indeed, like SART, the new ART data collection Australian and New Zealand Assisted Reproduction Database (ANZARD) implemented in Australia in 2002 no longer publishes data on birth defects because of the lack of specificity of source of notification, lack of validation of diagnosis and variable quality in ascertainment. ANZARD also suggests that previously published data on birth defects in Assisted Conception reports from the Australian ACDC be interpreted with caution because of the limitations described above (Waters *et al.*, 2006).

For countries without established Birth Defect Registers, ART registers with excellent follow-up may play a role in birth defect monitoring, providing the limitations of these collections are acknowledged. However, for Australia, we strongly recommend that information used for patient counselling is preferentially drawn from large studies that have used record linkage to high-quality birth defect registers.

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### Contributors

M.H. compared the data from the two data sources, conducted the data analyses and drafted the report. M.H., C.B. and A.M.J. contributed to the study design. A.M.J., P.B., S.J. and J.Y. provided summaries of birth defect data submitted by their clinics to the National Perinatal Statistics Unit (NPSU). E.S. provided information on the ACDC. All the authors contributed to the interpretation of the data, and all were involved in the critical revision of the article.

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