Letter to the Editor

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Beckwith-Wiedemann Syndrome and IVF: A Case-Control Study

To the Editor:

A recent series of observations has suggested a link between in vitro fertilization (IVF) and imprinting disorders, such as Beckwith-Wiedemann syndrome (BWS [MIM 130650]) and Angelman syndrome (MIM 105830). BWS is a model imprinting disorder and is characterized by prenatal and/or postnatal overgrowth, macroglossia, abdominal-wall defects, neonatal hypoglycemia, hemihypertrophy, ear abnormalities, and an increased risk of embryonal tumors (DeBaun et al. 2002). An analysis of BWS registries from three centers has shown the proportion of individuals with BWS conceived using IVF to be 3/65 (DeBaun et al. 2003), 6/149 (Maher et al. 2003), and 6/149 (Gicquel et al. 2003). These data suggest that ~4% of individuals with BWS are conceived using IVF, a figure greater than the generally accepted usage of IVF in these centers. Further interpretation of these results has been limited because of a reliance by these studies on case records and questionnaire data to determine the method of conception in BWS cases, a lack of the use of appropriate controls, and a statistical significance that was either borderline (Gicquel et al. 2003; Maher et al. 2003) or not mentioned (DeBaun et al. 2003). A recent review of the epidemiology and molecular biology behind these and other related studies has highlighted the need for case-control studies in this area (Niemitz and Feinberg 2004). We report here the results of what we believe is the first case-control study done to test the null hypothesis that there is no difference between the rate of IVF in BWS cases and that in non-BWS controls, in an Australian population.

The present study was possible because the State of Victoria, Australia, is serviced by a single clinical genetics service and laboratory providing molecular tests for BWS. This allowed complete ascertainment of children born in Victoria between 1983 and 2003 and diagnosed with BWS by a clinical geneticist. Only cases meeting the DeBaun criteria (DeBaun and Tucker 1998) were included in this study. Appropriate controls were obtained using data from the Victorian Perinatal Data Collection Unit, which registers all births of >19-wk gestation. For each BWS case, four live-born controls were randomly selected from babies born within 1 mo of that case, in which parity was 1 and the maternal age was within 1 year of the risk-set case. Manual record linkage was then used to determine if the BWS cases and the controls were recorded in the databases of the providers of IVF services in Victoria, with the use of maternal names and the dates of birth of mothers and babies. Ethics approval was obtained from all sites providing data. Statistical significance of differences in proportions between groups was assessed using Epi Info, with results expressed as odds ratios (ORs) and as Fisher's-exact-test two-sided P values to account for cell sizes <5.

Among ~1,316,500 live births in Victoria between 1983 and 2003 (2003 data were estimated, as they were known to be very similar to 2002 data), 37 cases of BWS were detected, giving an overall BWS prevalence of ~1/35,580 live births for this period. The average maternal age for BWS cases was 27.0 years. Record linkage of the 37 BWS cases and 148 matched controls identified IVF as the method of conception in 4 BWS cases (10.81%) and in 1 control (0.67%), giving an OR of 17.8 (95% CI 1.8–432.9), and Fisher's-exact-test two-sided $P = .006$. The clinical and molecular features of the four patients with BWS conceived using IVF are listed in table 1, and the reasons for the use of IVF were varied (two unexplained infertility, one egg donation, and one oligospermia). Our results indicate that if a child has BWS, the odds that the child was conceived using IVF is ~18 times greater than that for a child without BWS, although the magnitude of this OR should be cautiously interpreted, given the wide CI. During the study period (1983–2003), 14,894 babies were born as a result of an IVF procedure (excluding gamete intrafallopian transfer). Using our population-based data, we can then estimate the absolute risk of having a live-born baby with BWS when IVF is used as the means of conception to be 4/14,894.

This study demonstrates that children conceived by IVF are significantly more likely to have BWS, compared with children conceived naturally. Our study design with a control group matched by maternal age has ensured that the rate of IVF procedures in the control (non-BWS) population is accurate for the entire study period, which

Table 1

Clinical Features of Four Patients Diagnosed with BWS Who Were Conceived Using IVF

	Finding in Patient			
Clinical Feature	1	2	3	4
Intracytoplasmic sperm injection	No	No	No	Yes
Frozen embryo	Yes	No	Yes	Yes
Day of transfer	2	2	2	2
Sex	Female	Male	Male	Female
Gestation (wk)	40	33	38	37
Macrosomia	Yes	Yes	Yes	No
Hypoglycemia	No	Yes	No	Yes
Macroglossia	Yes	Yes	Yes	Yes
Ear anomalies	Yes	No	Yes	Yes
Abdominal-wall defects	Exomphalos	No	Exomphalos	No
Hemihypertrophy	No	Yes	No	No
Isolated loss of methylation at *KVDMR1/LIT1*	Yes	Not performed	Yes	Yes

encompasses a time from infrequent use of IVF (0.2% of pregnancies in 1983) to more frequent use (3% in 2003). We can quantify, for the first time, the risk of BWS in our IVF population as ~1/4,000, or 9 times greater than in the general population. The mechanisms underlying this increased risk remain unclear, but this study and previous studies (DeBaun et al. 2003; Gicquel et al. 2003; Maher et al. 2003) have shown that patients with BWS conceived by IVF consistently show isolated hypomethylation at the maternal *KVDMR1/LIT1* locus at 11p15.5. By comparison, this molecular mechanism is observed in only 46% of our overall BWS population, with the remainder of BWS cases resulting from uniparental disomy of chromosome 11 (16%), biparental methylation of *H19DMR* (7%), or an unidentified mutation (31%). The preponderance of BWS cases conceived by IVF that show hypomethylation of maternal *KVDMR1/LIT1* suggests that collection of in vitro cultures might disturb methylation in the oocyte or early embryo, predisposing to maternal allele demethylation.

The fact that the overall risk of BWS in children conceived using IVF remains low and that BWS is, in most cases, associated with a good long-term outcome makes it unlikely that this finding will deter couples from using IVF. Nor does it seem necessary to offer prenatal diagnosis for BWS to couples undergoing IVF. Questions remain, however, about potential effects of IVF on other regions of the genome that are subject to epigenetic regulation. In this context, the observation of a possible association between IVF and Angelman syndrome, another disorder resulting from hypomethylation of the maternal genome, is of some concern (Cox et al. 2002; Orstavik et al. 2003). Although long-term follow-up data of children conceived by IVF are generally reassuring, it remains possible that alterations in genomic imprinting might have other unrecognized health implications for children and adults who were conceived by IVF. Our data reinforce the need for long-term follow-up studies of children conceived by IVF.

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Electronic-Database Information

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for BWS and Angelman syndrome)

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