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Commentary

Ovulation induction, assisted conception and childhood cancer. Is there a link?

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Infertility is currently a major clinical problem, and a recent report from the World Health Organisation (WHO) suggests that 80 million people are affected worldwide [1]. Since 1978, nearly one million babies have been born worldwide following assisted reproductive technologies (ART). The development of ART and in particular intra-cytoplasmic sperm injection (ICSI) has revolutionised the treatment for couples with male factor infertility. It has been estimated that in some European countries up to 5% of all births are now due to ART [1], but there are still some concerns about the safety of ART [2].

This excellent Review of the current, albeit limited, evidence for the safety of ART in survivors of childhood cancer is very welcome [3]. The nature of *in vitro* fertilisation involves potentially toxic exposure (particularly hormonal) to the sperm, egg, zygote and embryo. It is known that defective imprinting may have a role in the development of some childhood cancers, including Wilms tumour, Retinoblastoma, and embryonal Rhabdomyosarcoma. There is now increasing evidence that this epigenetic phenomenon of imprinting may be affected by ART, especially by the more invasive procedures such as ICSI, *in vitro* maturation, assisted hatching and blastocyst transfer. The limited evidence about the relationship between ART conception and the risk of childhood cancer predates these ''invasive'' techniques where the risk of defective imprinting is likely to be higher [4].

There is now increasing evidence that syndromes caused by imprinting errors occur more frequently after ART. Several recent studies have reported an unexpectedly high incidence of the overgrowth syndrome Beckwith-Wiedemann syndrome (BWS) in children conceived using ART. Six of 149 cases, three from IVF and three from ICSI pregnancies, were reported from a British Registry [5]. These reported frequencies are very high for such a rare congenital condition (0.13 per 10 000 live births). Children with BWS are at increased risk of developing various types of childhood cancer; Wilms' tumour is the most common and occurs in 11% of children with BWS before the age of 4 years.

There is now an urgent requirement for more detailed investigation into the long-term outcomes of ART, particularly the risk of developing cancer. There are two ways in which such a link can be investigated. The less satisfactory, because the methodology is open to potentially serious bias, would be a case-control study design to identify cases of childhood cancer through the national children's cancer registry, with controls matched for age and gender, and asking the parents to report the conception history using a questionnaire. There are some ethical difficulties in requesting this kind of sensitive information from parents of children who have or have had cancer, especially if the child has died.

The second option, which is scientifically more attractive, but may be obstructed by legal issues, involves a linkage between outcome data following ART and cancer registration data. In the United Kingdom (UK), the Human Fertility and Embryology Authority (HFEA) has a register of children born following ART. Success rates and short-term outcome data are available on its web-site (www.hfea.gov.uk). The data are confidential, under the Human Fertilization and Embryology Act (1990), so direct access is not possible without a change in legislation. However, the individual outcome data

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could be linked in an anonymised fashion to the UK's national children's cancer register. This strategy would provide the evidence we require to reassure us that the explosion in the use of ART, and in particular ICSI, is safe. Given the real concerns expressed in the review by Lightfoot and colleagues [3], it is therefore crucial that researchers are given access to the data held by the HFEA.

Competing interests

No competing interests declared.

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