

Looking Farther Afield

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The Egg and Me(thylation)

Several recent studies have investigated the potential association between assisted reproductive technology (ART) and risk of childhood cancer (e.g., retinoblastoma) or genetic syndromes at high risk of malignancy [e.g., Beckwith-Wiedemann syndrome (BWS); refs. 1, 2]. Most recently, Halliday et al. (3) conducted a case-control study in Victoria, Australia to measure the association between ART and BWS. Of 1.3 million live births during the period 1983 to 2003, 37 cases of BWS were born (confirmed by clinical geneticists) for an overall population prevalence of ~1 case per 35,500 births. These cases were each matched (age, maternal age, and parity) to four live-born controls. Record linkage was done with the providers of ART services in Victoria to determine which infants were conceived using ART methods. Of the 37 BWS cases, 4 were conceived by ART compared with 1 of 148 matched controls (odds ratio, 17.8; 95% confidence interval, 1.8-432.9). In the context of all 14,894 live births conceived by ART during this time period, the absolute risk of BWS was ~1 case per 4,000 births or about nine times higher than in the general population. As the authors note, previous reports of ART-associated BWS consistently show hypomethylation of the maternal KvDMR1/LIT1 locus at 11p15.5 (4, 5). In contrast, this mechanism is only observed in ~45% of the overall BWS population. It is possible that the process of ART preferentially results in maternal allele demethylation, which would have important implications not only for BWS but also for childhood cancer.

Sperm Count, Too!

Genomic imprinting, or the preferential expression of a gene depending on the parent of origin, results from the differential methylation of CpG islands. The imprint is erased during gametogenesis through demethylation and reset later according to the parent of origin of the transmitted chromosome. Demethylation of maternally transmitted alleles is a mechanism by which some genetic disorders and malignancy arise. Although demethylation has been described in the maternal allele (see

above), there has been little evidence that this phenomenon occurs in the paternal allele. Marques et al. (6) examined spermatozoan DNA from 123 individuals (27 normozoospermic and 96 oligozoospermic, including 46 moderately affected and 50 severely affected) undergoing routine analysis for infertility. Methylation profiles were studied in two imprinted genes: *MEST* (maternally imprinted) and *H19* (paternally imprinted). For *MEST*, maternal imprinting was correctly erased in all 123 samples. In contrast, although the *H19* paternal imprint was correctly erased in the normozoospermic samples, 8 (17%) of the moderately affected and 15 (30%) of the severely affected men showed incomplete methylation. The authors conclude that abnormal spermatogenesis is associated with a rise in methylation defects at *H19*. Because the maternal imprint was correctly erased for *MEST*, this may indicate that changes in DNA methyltransferase activity are responsible for hypospermatogenesis. Importantly, there is coordinated regulation of expression of *IGFII* (a maternally imprinted gene) by repressor binding sites on the *H19* gene (7). Thus, paternal *H19* hypomethylation could lead to the inactivation of both *IGFII* genes, which could have deleterious consequences during fetal development.

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