

# Fertility NEWS

## ART associated with limited epigenetic variation that disappear by Adulthood

*"Should we be worried about IVF treatment?"*

**Introduction:** More than 7 million individuals have been conceived by Assisted Reproductive Technologies (ART) and there is some evidence that ART might be associated with rare imprinting disorders in early life outcomes. The periconception period and early embryogenesis are associated with widespread epigenetic remodelling, which can be influenced by ART, with effects on the developmental trajectory in utero, and potentially on health throughout life.

**Summary:** To investigate whether DNA methylation levels in blood differ between ART-conceived individuals relative to non-ART conceived individuals, Novakovic B *et al*<sup>1</sup> analysed epigenome-wide methylation data in neonatal (Guthrie spot) and adult peripheral whole blood using the EPIC array. DNA methylation status was generated for 149 neonatal and 158 adult ART-conceived individuals and for 58 neonatal and 75 adult non-ART conceived individuals. They profiled genome-wide DNA methylation in blood collected in the newborn period and in adulthood (age 22–35 years) from a unique longitudinal cohort of ART-conceived individuals, previously shown to have no differences in health outcomes in early adulthood compared with non-ART-conceived individuals. It showed evidence for specific ART-associated variation in methylation around birth, most of which occurred independently of embryo culturing. **ART-associated differential methylation at birth is largely attenuated in adulthood.** An interesting observation is that the *CHRNE* DMR at birth in both cohorts, was present in both IVF (with embryo culturing) and those who underwent IUI and GIFT procedures in the absence of culturing. This implies an effect of the ovarian stimulation or subfertility itself, rather than any of the additional embryo culturing processes associated with IVF. A similar direct effect of ovarian stimulation on offspring epigenetic profile have been reported for maternally imprinted regions and for LINE 1 methylation, which was decreased in association with high-dose hormone treatment.

**Conclusion:** ART conception is associated with limited epigenetic variation at birth that largely attenuates by adulthood. The epigenetic variation may be associated in part with ovarian stimulation, or infertility per se. Additional studies of larger sample size in both animal models and humans are required in order to replicate our findings. Even if the transient epigenetic changes associated with ART are replicated, the potential health implications should not be over-interpreted given the absence of any direct evidence for downstream functional consequences of the observed epigenetic change, and the lack of compelling evidence for altered health outcomes in adulthood.

**References:** 1. Novakovic B, et al. Assisted reproductive technologies are associated with limited epigenetic variation at birth that largely resolves by adulthood. *Nature Communications* 2 Sept. 2019



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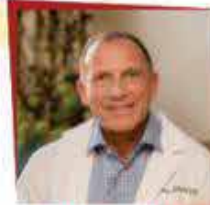
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