IVF: It’s the Hormones
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The hormone regimen used to bump up egg production during in vitro fertilization (IVF) may have an effect on the blood pressure of the resulting children, according to a new analysis. The study suggests that the hormone regimen, rather than other aspects of in vitro fertilization, such as embryo culture, underlies findings indicating that the cardiometabolic health of offspring is compromised.

Three studies have reported elevated blood pressure in IVF children, although two studies have not seen such an effect. The two studies, however, showed other problems with cardiometabolic health, such as an increased risk of vascular dysfunction. Overall, the data hint that children born from IVF have poorer cardiometabolic outcomes than children conceived naturally—a difference that is not attributable to factors such as prematurity or low birth weight, which also occur more frequently in IVF offspring.

In the two new analyses, Jorien Seggers et al. and Sacha La Bastide-Van Gemert et al. examined systolic blood pressure in 194 children conceived using different methods and crunched the data using two separate statistical approaches. Both analyses showed that children born from IVF following controlled ovarian hyperstimulation (a hormonal regimen that boosts ovulation rate) had higher blood pressure at age four than children born from modified natural-cycle IVF, which does not involve the same hormonal procedures. The difference was about 13 percentile points and was not due to factors such as weight of the mother. The data also hinted that IVF children conceived through ovarian hyperstimulation may have also slightly more subcutaneous fat, an indicator of poor metabolic health.

The findings suggest that the hormonal boost of conventional IVF procedures may affect the health of the oocyte and ultimately the health of the resulting offspring. This conclusion was bolstered by the observation that there was no difference in blood pressure between children from modified natural-cycle IVF and children conceived naturally by subfertile couples, suggesting that the in vitro aspects of the procedure did not affect blood pressure.

The researchers speculate that ovarian hyperstimulation might have epigenetic effects on the DNA of the oocyte, which undergoes epigenetic modifications during maturation. They point to studies in mice suggesting that ovarian hyperstimulation results in epigenetic disturbances, and studies in humans showing that IVF is associated with epigenetic modifications in phenotypically normal offspring.

The findings raise many basic research questions, but also highlight the need for further clinical studies. The new studies also suffer from several drawbacks; for instance, there was a low number of study subjects, and the researchers could not rule out an effect due to the criteria used to select women to receive hyperstimulation versus natural-cycle IVF.


Single-Cell Technique Peers into Oocyte DNA
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Geneticists have applied a pioneer DNA sequencing technique to determine the genetic makeup of single human oocytes. The DNA is collected from polar bodies extruded from the oocyte, showcasing the technique as a noninvasive way to screen an egg’s genes prior to assisted reproduction.

Current methods to assess oocyte or embryo DNA for assisted reproduction are limited. One common method involves removing a cell from the early embryo and checking its DNA for gross abnormalities, such as missing chromosomes. But this method of pre-implantation genetic diagnosis has drawbacks, including that it requires microsurgery of the embryo, there are concerns that it may disrupt development, and it has not been possible to simultaneously obtain both sequence data and information on aneuploidy.

In the new study, Yu Hou et al. deployed a technique recently developed to sequence DNA from a single cell. The technique involves a unique step that enables uniform levels of DNA amplification, regardless of sequence, called multiple annealing and looping-based amplification cycles (MALBAC). MALBAC overcomes the problem of amplification bias that has plagued previous methods of single-cell sequencing.

Using oocytes donated by eight healthy women, the researchers found that by sequencing the DNA of the polar bodies, they could predict the sequence of the DNA in the oocyte pronucleus. Using DNA information from the polar bodies, the researchers could accurately identify 91 to 95 percent of single nucleotide polymorphisms (SNPs) in the pronucleus in each donor. The technique also enabled the researchers to detect chromosomal abnormalities, such as extra or missing chromosomes and translocations.

The cost of detecting these larger-scale changes is about the same as that of current methods of pre-implantation genetic diagnosis, the researchers say. Whole-genome sequencing, however, is much more costly and technologies will have to improve for that approach to become feasible on a large scale. Meanwhile, the researchers have begun a small clinical trial to determine whether the method improves the success rates of in vitro fertilization in women who have genetic diseases or who have suffered multiple miscarriages.

The technique not only has clinical potential, but it also will enable researchers to answer longstanding basic research questions. For instance, in the current study, the researchers calculated that the average rate of chromosome crossover in the oocyte was 43 crossovers per haploid cell—about 1.65 times that of sperm.