CLINICAL VIGNETTE

Cardiovascular Screening for a Patient Conceived through Assisted Reproductive Technology

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A cardiologist (MK) was recently asked to consult on a 22-year-old patient who was conceived through Assisted Reproductive Technology (ART). Her mother was unable to conceive spontaneously due anatomic abnormalities of her fallopian tubes. The patient had no known medical problems. However, she was concerned that individuals conceived through ART were at increased risk of heart disease relative to the general population and inquired if she needed any preventative screening. This patient's query prompted a review of the available data.

The world's first "test tube baby" Louise Brown was born on July 25, 1978 at Oldham General Hospital in England. Since then, more than 5 million children have been conceived through ART as novel in-vitro fertilization techniques have been developed, medication regimens further refined, costs have decreased, and the process has generally become more culturally accepted by the public.[1] Current statistics indicate that 2% of all births worldwide and 1% of live births in the US at this time are attributable to ART.[2]

Pregnancies conceived by ART are at higher risk for adverse birth outcomes relative to spontaneous conception: these include multiple births, low birth weight, and pre-term delivery.[3,4] ART may also impair placental development and function, thus affecting intrauterine fetal growth.[5-8] Concerns have been raised about the health of the offspring born via ART, including an increased risk of birth defects, cancers, delayed growth, and developmental disorders. As children of ART are getting older there is growing concern about the frequency of age-related disorders including type 2 diabetes and cardiovascular disease.[9-14]

Specifically looking at cardiovascular disease, multiple studies have shown elevated systolic and diastolic blood pressures in children conceived through ART.[15-16] A study by *Celeen et al.* looked at the differences in systolic and diastolic blood pressure in ART-conceived children.[15] In their population of 8 to 18-year olds, there was a significant difference in both systolic (3-4 mm Hg) and diastolic (1-2 mm Hg) blood pressure readings relative to the age and weight-matched controls that were spontaneously conceived.

While these numbers may sound minimal, increased blood pressure is associated with a higher long-term risk of stroke and cardiovascular disease. Lowering the mean systolic blood pressure by 2 mm Hg corresponds to an 8% reduction in the risk of stroke.[17] In the same study by Celeen et al., ART children had a significantly higher sum of skin folds, which correlated to increased body fat and higher glucose levels. Height, weight, and BMI were comparable between the two populations.[15]

With regard to cardiac structure and function, von Arx et al showed increased right ventricular dysfunction in children and adolescents conceived by ART relative to controls.[18] An additional 2012 study showed systemic and pulmonary vascular dysfunction in 7 to 18-year-olds conceived through ART when compared with age-matched controls.[19] As ART-conceived children grow, there is speculation that these individuals may be at higher risk for developing type 2 diabetes and metabolic syndrome.[16,19-22] Studies to date have been small and have measured different parameters. Celeen et al reported that ART may impair fasting blood glucose metabolism, irrespective of early life factors.[15] Sakka et al showed no increase in insulin resistance in ART-conceived children, however, this population had significantly higher triglyceride levels.[16] It is unclear which of these metabolic abnormalities result from the ART versus the hereditary metabolic profile of the parents. Some metabolic illnesses are associated with an inability to conceive, i.e. polycystic ovarian syndrome.

Hormonal abnormalities in ART-conceived children may be due to the high circulating maternal gonadotropins which are used to stimulate oocyte maturation during the ART process. A condition called OHSS (Ovarian Hyperstimulation Syndrome) can occur during the stimulation of ovaries in ART and is associated with supraphysiologic maternal estradiol and progesterone levels. This lasts throughout the first trimester and can lead to intravascular depletion of fluid with oliguria, electrolyte imbalance, and thromboembolic phenomenon in the mother, the effects of which may be transferred to the fetus.[22,23]

Epigenetic changes may also play a role in metabolic functioning of ART-conceived children. Epigenetics is defined as heritable changes in gene expression without alterations in DNA sequence.[24] Epigenetic modifications regulate the spatial and temporal gene expressions necessary during embryonic, fetal, and post-natal development.[2] There are two recognized instances of epigenetic manipulation during gametogenesis and early pre-implantation. Manipulation of the oocyte or blastocyst during ART may impair this process, the effects of which may persist into or only become manifest during adulthood.[26,27]

Returning to our patient, a thorough history was obtained. She had normal vital signs and a normal physical examination. Based on the literature reviewed, no cardiac functional or structural testing was clinically indicated. I encouraged regular preventive visits with her PCP as well as a healthy lifestyle with exercise and a mindful diet, and follow-up for routine age-related preventative screenings.

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