The authors collected data from 2004−2013 that addressed a transition period between slow-freezing protocols and vitrification of gametes and embryos. It is now established that vitrification is superior to slow freezing in terms of blastocyst survival rates and ART outcomes. Furthermore, vitrified embryos carry a decreased risk of being delivered preterm and with low birthweight. Specifically, when evaluated, pregnancies delivered after vitrified embryos and oocytes were not at an increased risk of obstetric or puerperal complications and appear to have higher birthweight when compared with slow-frozen or freshly transferred embryos.[4] Because of these advancements in oocyte and embryo cryopreservation, most of the frozen gametes and embryos that now lead to transfer in the United States are vitrified.

Despite these factors, we thank the authors for a well-prepared study that will prove an invaluable tool for counseling patients who undergo ART in the many years to come. ■

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REPLY

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We thank Drs Pier, Ligon, and Levy for their interest in our study and their thoughtful comments. We agree that SGA is an important consideration. However, neither freezing an embryo nor thawing a frozen embryo are physiologically normal states and potentially are associated with subtle changes, some of which have yet to be identified and may only manifest in early childhood or adolesence. Furthermore, the long-term health of offspring conceived after vitrification is essentially unknown because, as the authors point out, vitrification has not been practiced widely until recently. In our analysis of 7795 pairs of singleton siblings conceived with in vitro fertilization (IVF), the adjusted difference in birthweight when both siblings were from fresh embryos was ≥81 g; whereas when the first was from a fresh embryo and the second from a frozen embryo, the frozen−fresh birthweight difference was ≥222 g, and the risk of LGA increased (frozen vs fresh: adjusted odds ratio, 1.74; 95% confidence interval, 1.45−2.08).[1] In a recent analysis of fetal growth, frozen embryos had greater estimated fetal weight than the reference curve in all 3 trimesters compared with fresh embryos from IVF, intracytoplasmic sperm injection, and intrauterine insemination, which had greater than reference weights for only the first 2 trimesters.[2] The implications of this altered accelerated fetal growth for health during childhood and young adulthood are unknown.

In addition to potential consequences of protocol choices on offpsring, factors that affect maternal health must be considered. As shown in our analysis, the use of donor oocytes or frozen embryos are associated with the highest risks for severe maternal morbidity, which includes blood transfusion, unplanned hysterectomy, and hysterectomy after cesarean delivery, and reflect alterations in placental structure and function. In pregnancies that use donor oocytes or frozen embryos, clinical data strongly implicate the absence of the corpus luteum as a potential explanation for the increased risk of placental complications and preeclampsia that is seen with frozen embryo transfers.[3] The pathogenesis of preeclampsia in many women, especially those with early-onset preeclampsia, involves impaired placentation in early pregnancy and provokes an abnormal maternal response that manifests as endothelial dysfunction with the clinical signs of new-onset hypertension and proteinuria or impaired function of other organs. There is a continuing need for refinement of IVF protocols to reduce these morbidities and to close the gap between IVF-conceived and spontaneously conceived outcomes. ■

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