have increased dramatically. There is therefore no guarantee that recommending IOL at 39 weeks gestation for all nulliparous women would reduce the national cesarean delivery rate or indeed be acceptable to most pregnant women.

That being said, there are consistent findings across a variety of settings that term elective IOL, when compared with expectant management, leads to either a reduction or no difference in cesarean deliveries.\(^3,4\) Additionally, in a recent systematic review, the findings from previous cohort studies that examined this question essentially found a similar effect size to the randomized trials.\(^5\) Thus, although the impact on cesarean delivery in lower intervention settings may have a lower absolute impact, there is no evidence to suggest it may lead to harm. However, going forward, a better understanding of the economic, resource, and long-term implications of elective induction at term will be important areas for investigation.

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Fresh in vitro fertilization cycles increase risk of small-for-gestational age; frozen cycles increase risk of large-for-gestational age: Which is worse?

TO THE EDITORS: We enthusiastically read the article entitled “Risk of severe maternal morbidity by maternal fertility status: a US study in 8 states” by Luke et al.\(^1\) The aim of this study was to evaluate the risk of maternal morbidity by maternal fertility status and, for in vitro fertilization pregnancies, by oocyte source and embryo state combination. The study concluded that risk of severe maternal morbidity is increased for subfertile and in vitro fertilization births, particularly in pregnancies that are not autologous, fresh assisted reproductive technology (ART) treatment cycles.

In this article, Luke et al.\(^1\) reference a connection between frozen cycles and large-for-gestational age (LGA) neonates. What is not mentioned is the accepted relationship between fresh cycles and small-for-gestational age (SGA).\(^2\) Aberrant fetal growth, in either extreme, is linked with offspring complications. LGA is associated with delivery trauma and stillbirth, although there are conflicting reports regarding actual LGA mortality rates. On the other hand, SGA is associated with anomalies, amniotic fluid abnormalities, stillbirth, neonatal acidosis, seizures, and death. SGA neonates may be at greater risk for neurodevelopmental delays and cardiovascular disease later in life. A 2010 retrospective analysis evaluated 123,383 diverse live births and concluded that SGA, but not LGA, was associated with increased mortality rates. In fact, appropriate-for-gestational age and LGA neonates had similar likelihoods of death.\(^3\) Therefore, we caution citing aberrant fetal growth as an argument for favoring fresh over frozen in vitro fertilization cycles without properly considering other elements that may be more relevant.
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. 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

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 adolescence. 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). 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 intruterine insemination, which had greater than reference weights for only the first 2 trimesters. 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 offspring, 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. 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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