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Editorial

Biology matters in gestational age dating: lessons from assisted reproductive technology pregnancies

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Emerging evidence from Norway on ART pregnancy biology and gestational age determination

In this issue of *Ultrasound in Obstetrics and Gynecology*, Gjerdevik *et al.* report a population-based study of gestational age (GA) determination in assisted reproductive technology (ART) pregnancies, including more than 163 000 spontaneously conceived pregnancies and over 4000 ART pregnancies from the Norwegian Medical Birth Registry between 2015 and 2021[1]. ART-based pregnancy dating utilizing the oocyte fertilization date and the embryo transfer date was compared with population-based ultrasound dating. After recalibrating the ART model to assume a 15-day rather than a 14-day follicular-phase duration, median GA discrepancies between ART-based and ultrasound dating were minimal, with individual pairwise GA differences ≤ 1 day in just under half of pregnancies and ≤ 2 days in roughly two-thirds. In practical terms, GA dating therefore appears largely reconcilable across conception modes once this modest adjustment is introduced.

Gjerdevik *et al.* then evaluated biological pregnancy duration using Kaplan–Meier time-to-event analyses, treating spontaneous births as events and nonspontaneous births (inductions and elective Cesarean deliveries) as censored observations, an approach that avoids systematic bias toward shorter gestations. Median ultrasound-based GA at birth in frozen embryo transfer (ET) pregnancies was 286.1 days, exceeding that of fresh ET pregnancies by 3.3 days and that of spontaneously conceived pregnancies by 2.7 days. Frozen ET pregnancies also displayed a lower proportion of spontaneous labor onset (56% of frozen ET pregnancies *vs* 65% of fresh ET pregnancies *vs* 69% of spontaneously conceived pregnancies) and a higher proportion of nonspontaneous post-term births. Meanwhile, ART- and ultrasound-based classification of preterm birth showed > 98% concordance. Stratified analysis confirmed that the gestational gap between frozen and fresh ET pregnancies persisted in both those fertilized using *in-vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) cycles (median gestational prolongation of 3.6 days and 2.7 days, respectively), whereas IVF *vs* ICSI differences were negligible within ET type. Sensitivity analyses and competing-risks models did not materially alter these findings, indicating that the prolonged gestation observed in frozen ET pregnancies reflects biological characteristics rather than scheduled obstetric intervention.

Taken together, the results of this Norwegian study show that, while ART-based and ultrasound dating can be harmonized statistically, ART pregnancies, especially frozen ET pregnancies, exhibit distinct downstream patterns of fetal growth velocity and timing of parturition. Importantly, these findings do not challenge the accuracy of first-trimester ultrasound dating *per se*, but rather question its biological neutrality across different modes of conception.

Interpretation in context

The study of Gjerdevik *et al.*[1] intersects with a broader question in obstetric imaging: to what extent should biological variation in early growth be normalized for the purpose of GA dating? For decades, crown–rump length (CRL) in the first trimester has been treated as a neutral chronometer, yet prospective ART cohorts show that early size differences are not merely technical artifacts. Previous work has demonstrated that CRL is consistently greater in frozen ET compared with fresh ET pregnancies between 6 and 14 weeks[2]. Ginod *et al.* also reported similar findings in a cohort stratified by conception mode[3]. Importantly, these early growth differences do not dissipate, but rather persist later in gestation: frozen ET pregnancies tend to have higher estimated fetal weight and birth weight compared with fresh ET pregnancies[3,4], and population-based comparisons show a right-sided shift in birth-weight distribution relative to spontaneously conceived pregnancies[5].

These observations support the idea that CRL differences in frozen ET pregnancies compared with fresh ET and spontaneously conceived pregnancies anticipate subsequent intrauterine growth and reflect differences in the intrauterine environment rather than random variation. Attempts to normalize GA solely based on CRL across conception modes therefore risk suppressing informative biological variability. The later delivery of frozen ET pregnancies in the Norwegian study[1] fits naturally into this continuum and is an argument against

treating ART pregnancy cohorts as neutral reference groups for spontaneously conceived pregnancies.

A second line of evidence concerns uterine perfusion and placental vascular adaptation. ART pregnancies provide a rare insight into how endocrine conditions influence placentation. Fresh ET cycles occur in a supraphysiological hormonal milieu following controlled ovarian stimulation, whereas frozen ET cycles implant embryos into more controlled endometrial environments. Previous studies have demonstrated a lower uterine artery pulsatility index in frozen ET pregnancies compared with fresh ET pregnancies[6–9], particularly in those that undergo artificial endometrial preparation (when the corpus luteum is absent). Such perfusion patterns align with fetal-growth and birth-weight phenotypes[4,5], and now also with the prolonged gestation demonstrated in frozen ET pregnancies in the Norwegian cohort[1]. Together, these findings are consistent with the notion that frozen ET pregnancies exhibit more efficient placental function, whereas fresh ET pregnancies show comparatively reduced placental performance.

Recent work linking placental function to the timing of parturition further strengthens this interpretation. In two complementary studies in women without clinical pre-eclampsia, a higher pre-eclampsia risk, estimated using Fetal Medicine Foundation (FMF) multimodal models, was associated with earlier spontaneous labor onset, both preterm and at term or post-term[10,11]. These findings support a mechanistic model in which spontaneous labor may operate as an adaptive response to subclinical placental dysfunction, enabling delivery when the placental reserve declines. According to Gjerdevik *et al.*[1], the birth distributions of fresh and frozen ET pregnancies diverge predominantly during the term-to-post-term period, but previous major work has also demonstrated similar differences during the preterm period, a pattern precisely in line with this framework[12].

One important caveat is that frozen ET pregnancies are associated with a higher rate of diagnosed pre-eclampsia compared with fresh ET pregnancies, which may appear contradictory. However, pre-eclampsia is a heterogeneous syndrome with distinct vascular and placental endotypes and, in this context, the cardiovascular component, shaped by hormonal milieu and absence of corpora lutea, may predominate over primary placental insufficiency, with longer pregnancy duration playing an additional role.

Insights for future research

Several points arise from these findings that are relevant for future research. First, the temporal dynamics of divergence between ART and spontaneously conceived pregnancies warrant further study, as early CRL differences arise during placentation and maternal vascular adaptation. Second, the endocrine–vascular interface in ART pregnancies remains underexplored and could be interrogated through longitudinal ultrasound examination, Doppler assessment, endocrine and molecular profiling, and standardized endometrial protocols. Third, if conception mode influences growth, placentation and labor timing, then clinical surveillance and labor induction thresholds may require refinement. For example, the timing and clinical utility of third-trimester ultrasound, already under renewed scrutiny[13], do not map identically across ART and spontaneously conceived pregnancies due to different risks of preterm birth[12] and growth abnormalities[3–5]. Moreover, methodological studies comparing CRL and biparietal diameter for first-trimester dating[14,15] reinforce that improved precision does not eliminate biological diversity; rather, it forces us to engage with it. Finally, recent applications of the FMF pre-eclampsia risk model also suggest potential future intersections between pregnancy dating, placental risk stratification, clinical surveillance and labor induction policies of ART pregnancies[16,17].

Conclusion

The study of Gjerdevik *et al.*[1] shows that GA differences in ART pregnancies reflect underlying biological variation. Although ART-based and ultrasound dating can be harmonized statistically, pregnancies conceived via ART, especially after frozen ET, follow distinct growth trajectories and tend to be delivered later than naturally conceived pregnancies. CRL variation between the two conception modes captures developmental velocity and aligns with uterine perfusion as an indicator of placental efficiency, while the timing of labor may represent adaptive responses to subclinical placental dysfunction. These findings argue against treating ART pregnancies as interchangeable with spontaneously conceived pregnancies for GA calibration. Recognizing this biological variation is important for accurate GA estimation and for optimal management of ART pregnancies.

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