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Letter to the Editor

Unveiling early predictors of adverse birth outcomes: the potential and limits of embryonic growth metrics

Editors,

The article 'Embryonic size and growth and adverse birth outcomes: the Rotterdam Periconception Cohort' by Roelants *et al.* (2024) provides valuable insights into the early predictors of adverse birth outcomes, specifically preterm birth and small-for-gestational-age (SGA) infants. Their study represents a leap forward in utilizing advanced imaging, including 3D-ultrasound (3D-US) and virtual reality (VR), to monitor crown–rump length (CRL) and embryonic volume (EV) in early gestation (Roelants *et al.*, 2024). Such an approach holds significant potential for early identification of pregnancies at risk, aligning with the Developmental Origins of Health and Disease (DOHaD) paradigm that underscores the importance of the periconceptional period on fetal and lifelong health (Barker, 2007).

Moreover, Roelants *et al.* demonstrate a robust association between a CRL below the 20th percentile at 7 weeks and an increased risk of SGA at birth, while also acknowledging that EV, despite its larger relative growth, did not show equivalent predictive accuracy. This prompts a deeper exploration of the unique properties and limitations of CRL and EV as markers. While the study underscores the correlation between smaller embryonic CRL and SGA, future research could further investigate the developmental trajectory of EV, especially in the context of multifactorial influences like maternal health and environmental exposures. Such a multi-dimensional approach would extend beyond morphological markers, incorporating molecular and genetic factors that may further elucidate the link between early embryonic growth and birth outcomes (Stephenson *et al.*, 2018).

In addition, a significant proportion (44%) of the cohort was conceived via ART, introducing a set of variables unique to this population. ART pregnancies are associated with distinctive periconceptional influences, including hormonal stimulation and potential epigenetic alterations, which could inherently affect CRL and EV metrics (Fleming *et al.*, 2018). Furthermore, the predominantly Western demographic within a tertiary hospital setting may limit the generalizability of the findings. Including broader demographic and ethnic variability would be critical for validating CRL and EV as universal markers for adverse birth outcomes, given the reported variability in fetal growth patterns across populations (Bottomley *et al.*, 2009).

Furthermore, the study's use of longitudinal growth trajectories for CRL and EV offers an advanced method for evaluating embryonic development, yet the observed value addition over cross-sectional measurements was limited. Considering that fetal growth is influenced by genetic, nutritional, and epigenetic factors, incorporating additional data points and possibly extending the monitoring period into the second trimester could enhance predictive precision. Longitudinal tracking of CRL and EV trajectories may benefit from integrating growth patterns with maternal biomarkers, such as circulating placental growth factor or maternal inflammatory markers, which have shown relevance to pregnancy outcomes (Van Uitert *et al.*, 2013). Such a layered approach could support personalized care pathways, helping identify higher-risk pregnancies earlier and more accurately.

Additionally, the study highlights the accuracy of 3D-US and VR for CRL and EV measurements, though the necessity of high-quality equipment and skilled operators may limit broader application. Future advancements in automated image analysis, augmented by artificial intelligence, could enhance the practicality of these measurements, making early predictive assessments more accessible in routine obstetric care (Rousian *et al.*, 2021). Additionally, including Bland–Altman analysis for inter-observer variability would provide a more granular understanding of measurement reproducibility in clinical settings, facilitating the potential adoption of these techniques.

Building on these findings, Roelants *et al.*'s findings are foundational for developing early interventions targeting at-risk pregnancies. Prospective trials could investigate the efficacy of lifestyle and nutritional interventions, initiated during the periconceptional period, to optimize CRL and EV metrics, thus potentially reducing adverse birth outcomes (Oostingh *et al.*, 2020). Furthermore, as a tool in clinical practice, predictive models incorporating CRL and EV growth parameters alongside maternal characteristics could support obstetricians in tailoring antenatal care, potentially offering more frequent monitoring or specialized support for those at heightened risk.

In conclusion, the study by Roelants *et al.* opens new avenues for early pregnancy monitoring but also highlights the need for broader validation and enhanced predictive methodologies. As the field progresses, integrating embryonic growth metrics with genetic and environmental data may enable a truly comprehensive approach to fetal risk assessment and intervention in the earliest stages of pregnancy.

Conflict of interest

The authors have no conflicts of interest.

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