Vital signs: when twin bliss doesn't measure up

The gestational age is usually derived from the time elapsed since the last menstrual period (LMP). However, clinicians often rely on fetal biometry obtained in early pregnancy to achieve a better estimate of the true gestational age (GA) because menstrual cycles can display a great degree of variability both within and between patients, making a calendar-based GA unreliable. Of course, when the LMP-derived GA is reset based on fetal biometry, the assumption is that fetal growth has been normal up until then, and this is obviously not always the case.

In vitro fertilization (IVF) pregnancies, on the other hand, have a conception date that is known with great precision. Our group has relied on this to develop a new and more accurate reference crown–rump length (CRL) chart based on IVF dates in a large singleton IVF cohort (1). We found that six commonly used reference charts, including the one used in the study of Bardin et al. (2), show inaccuracies in their ability to date IVF pregnancies. So the known conception date of IVF pregnancies allows us in a unique way to study the intrinsic and external factors that influence fetal growth. This is further aided by the fact that there is very little normal biologic variation in fetal size in the first trimester, so any discrepancy between the measured and predicted biometry in IVF pregnancies points to an abnormal growth pattern.

In the study of Bardin et al. (2), the investigators went one step farther. They restricted their study cohort to women who had conceived a dichorionic diamniotic IVF twin gestation. This allowed them to compare not only the intrafetal size discordance (ΔGA), which was defined as a difference between the actual GA calculated by ovum pickup date and the evaluated GA by CRL for each of the twins, but also the intertwin size discrepancy (ΔGap), defined as a difference in CRL-based gestational age between both twins. The study's main aim was to evaluate the outcomes (live birth, GA at birth, and birthweight percentile) of the fetuses affected by intrafetal or intertwin size discrepancy. The authors reported that the main findings of their study suggest that there is an association of fetal size discrepancy and the number of live-born fetuses at delivery, as well as with birthweight percentiles. Let's look at their findings.

The first clear observation the authors make is that the average ΔGA for the whole cohort was −1.5 days—that is, the embryos were collectively lagging 1.5 days behind the dates calculated based on the ovum pickup. This is, however, entirely consistent with our own study (1), which showed that the CRL reference measurements published in 1992 by Hadlock et al. are approximately 1 day behind the true IVF dates. It is known that placentation is different in IVF pregnancies, but this seems to have no clinically relevant impact on the fetal biometry, at least in the first trimester.

The second clear observation in Table 2 of their study is that the prognosis of any embryo is very guarded if the CRL is lagging 4 or more days behind. Again, these findings are not surprising and have been reported before. A validated discriminant forecasting model based on almost 10,000 IVF pregnancies clearly identified CRL as a major prognostic factor (3). The findings reported in the new study also do not clearly establish that the intertwin size discrepancy in itself is all that useful. As expected, the ΔGap was actually smaller (though not statistically significant) for twin pregnancies where there was no live birth compared with those where there was one live birth.

The authors also argue that their data support an association between ΔGA for the smaller twin and its birthweight percentile but not in the larger twin (no association was found between ΔGap and birthweight discordancy between the twins). They accept that the correlation is very weak, with a correlation coefficient $R = 0.154$ ($P=.013$), which means that only 2.4% ($R^2 = 0.024$) of the total variability in birthweight percentile is explained by ΔGA. Furthermore, eyeballing Figure 1 in their article makes it obvious that the correlation (if any exists) is predominantly determined by the extreme outlier with a negative ΔGA of more than 25 days (in the lower left corner of the graph). Removing the extreme outliers in a sensitivity analysis will most likely make the statistical significance disappear. It would also be interesting to have more clinical details on this case as it is quite remarkable that this fetus was eventually delivered. The fetus had a growth delay of a month by CRL, and if it was measured at 14 weeks its CRL would have been approximately 33 mm instead of 85 mm (if measured at 10 weeks: approximately 2 mm instead of 33 mm).

So should we be worried? Although the study of Bardin et al. does not allow us to draw conclusions regarding the underlying cause when a growth delay was observed, there is evidence from a large cohort of CRL-discordant twin pregnancies that the risk of aneuploidy is increased 11-fold in the smaller twin. However, it is reassuring to see that this study confirms previous findings that a fetus with a small CRL in the first trimester is not likely to affect the outcome of the other normal-sized twin.

Although the study of Bardin et al. concurs with a previously published meta-analysis of 17 studies (4) that CRL discordance between twins is associated with an increased risk for birthweight discordance (relative risk, 2.2; 95% confidence interval, 1.9–2.6), it is important to point out that not all studies agree. Our own study found no birthweight discordance among fetuses that had a discordant CRL measured early in the first trimester between 6 and 9 weeks (5). More importantly, the meta-analysis concluded that when used alone to screen for adverse pregnancy outcome, the predictive accuracy of CRL discordance was too low for each of the outcomes explored to be clinically useful. It looks like that conclusion still stands.

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