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Growth trajectories in twins: FMF models validation on a Danish national cohort

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Objective

To describe fetal growth in dichorionic diamniotic (DCDA) and monochorionic diamniotic (MCDA) twin pregnancies in relation to the singleton growth reference by FMF. Moreover, to develop chorionicity-specific models of fetal growth from an FMF twin cohort and to externally validate these models on a Danish national cohort of twin pregnancies.

Methods

A cohort of DCDA and MCDA twin pregnancies from 1) FMF King's College Hospital, London, UK, 2) Medway Maritime Hospital, Kent, UK, 3) Grenada, and 4) Sofia, Bulgaria, between 2003 and 2021. The inclusion criteria were pregnancies with known pregnancy outcomes and resulting in two liveborn children. We excluded all pregnancies that were terminated, had a miscarriage before 24^{+0} weeks, stillbirth from 24^{+0} weeks, intrauterine fetal demise of one fetus, were treated by fetal reduction or had missing outcome information. Delivery from 37^{+0} weeks gestation was defined as term delivery in DCDA twins and from 36^{+0} weeks in MCDA pregnancies. These cut-offs were determined according to most national and international guidelines for the chorionicity-specific recommended time of delivery in twin pregnancies. Delivery before these cut-offs were defined as preterm delivery, and all pregnancies delivered preterm were considered complicated, particularly those delivered before 32^{+0} (severe preterm) and 28^{+0} weeks (extreme preterm). Scheduled visits were defined as 4-weekly in DCDA twins from 20 weeks and 2-weekly in MCDA from 16 weeks. Non-scheduled visits were defined as visits in between the previously defined intervals. Pregnancies with non-scheduled visits were assumed to be more likely associated with complications. To describe the chorionicity-specific fetal growth in twin pregnancies, the reference cohort was defined as uncomplicated twin pregnancies delivered at 37^{+0} or 36^{+0} weeks or later in DCDA or MCDA twins, respectively. Moreover, the reference cohort for fetal growth was only assessed at scheduled visits. The estimated fetal weights were calculated using the Hadlock 3 formulae, requiring details of gestational age, head circumference, abdominal circumference, and femur length. The estimated fetal weights were normalized as Z-scores calculated by the FMF reference for singletons. Reference distributions for growth in DCDA and MCDA twins relative to singletons were obtained by computing singleton z-scores for EFW in twin pregnancies. The models were fitted as Bayesian hierarchical models using Markov Chain Monte Carlo (MCMC) simulation. The models were Hierarchical Gaussian with three levels, 1) pregnancy, 2) fetus and 3) visit, and they were fitted to singleton z-scores for DCDA and MCDA twins over scheduled visits in pregnancies delivered from 37^{+0} and 36^{+0} weeks, respectively. The Bayesian approach has benefits in the form of high flexibility, production of clear direct and indirect inference, the possibility to utilize all available information, and avoiding the problems associated with null hypothesis testing and its reliance on p-values. The statistical software package R was used for data analyses. The R package mvtnorm was used for multivariate Gaussian statistics. Model fitting was done using the software WinBUGS. Diagnostics were produced to assess the adequacy of the model. This included summary statistics and Gaussian probability plots of z-scores EFW in MC and DC twins. Distributions of z-scores were produced for scheduled and non-scheduled visits according to gestational age at delivery. The chorionicity-specific models were validated on a retrospective register-based national Danish cohort of DCDA and MCDA twin pregnancies between 2008 and 2018. The inclusion and exclusion criteria were identical to the training cohort, as were the definitions of term and preterm delivery and scheduled and non-scheduled visits. The validation was performed by an overall and individual evaluation for scheduled visits in terms of distributions, z-score means with 10^{th} and 90^{th} percentile, and standard deviation (SD). The models fitted to the FMF data were used to determine singleton and twin z-scores for the Danish population data. In addition, the goodness of fit to the Danish data was assessed by comparison of observed and fitted percentiles.

Results

The training cohort consisted of 3,323 (75.7%) DCDA and 1,068 (24.3%) MCDA twin pregnancies. The model was fitted to EFW measurements from 1,869 (56.2%) DCDA twin pregnancies delivered at 37^{+0} weeks or later and 601 (56.3%) MCDA twin pregnancies delivered at 36^{+0} weeks or later. A total of 7,762 scans in DCDA twins were included, with a mean of 0.83 per pregnancy at each of the five scheduled visits. A total of 5,381 scans in MCDA twins were included, with a mean of 0.81 per pregnancy at each of the eleven scheduled visits. The fitted models found twins to be smaller than singletons at the earliest visits, however, most notably in MCDA twins. In both chorionicities, the smallness was improved until 28 weeks in DCDA and 24 weeks in MCDA. Both chorionicities had a continuous decline in growth from these gestational ages compared to singletons. Evaluation of the models on pregnancies delivered before 37^{+0} weeks in DCDA and before 36^{+0} weeks in MCDA twins showed left-shifted distributions at each of the scheduled visits, corresponding to the fetuses being considered smaller. These findings were even more prominent when looking at pregnancies delivered before 32^{+0} or 28^{+0} weeks. The same pattern was found for the evaluation of non-scheduled visits. The validation cohort consisted of 8,609 DCDA and 1,675 MCDA twin pregnancies. Overall, 95,787 growth scans were performed in DCDA twins, of which 62.4% (5,518) pregnancies had one or more non-scheduled scans performed and 60.0% (5,307) pregnancies delivered at 37^{+0} weeks or later. Overall, 31,632 growth scans were performed in MCDA twins, of 47.5% (862) pregnancies had one or more non-scheduled scans performed and 58.0% (1,052) pregnancies delivered at 36^{+0} weeks or later. We found an overall good fit of the models in the validation cohort. However, DCDA twins were smaller in the validation cohort at the 20-week scheduled visits.

Conclusion

Our study produced fetal growth trajectories from fitted models in DCDA and MCDA twin pregnancies relative to fetal growth in singletons. In doing so, we were still pertaining details of growth restriction on the singleton reference and avoiding normalization of smallness in twin pregnancies. In addition, the models were externally validated on a national Danish cohort, with an overall good fit. Therefore, we believe these models can be used to assess growth in DCDA and MCDA twin pregnancies.