Akolekar Ranjit (Orcid ID: 0000-0001-7265-5442)
Syngelaki Argyro (Orcid ID: 0000-0001-5856-6072)
Kristensen Steffen Ernesto (Orcid ID: 0000-0003-4633-4738)

Fetal Medicine Foundation charts for fetal growth in twins

A. Wright[1], D. Wright[1], P. Chaveeva[2], F. S. Molina[3], R. Akolekar[4], A. Syngelaki,[5] O. B. Petersen[6,7], S. E. Kristensen[6,7] and K. H. Nicolaides[5].

[1]Institute of Health Research, University of Exeter, Exeter, UK

[2]Fetal Medicine Unit, Shterev Hospital, Sofia, Bulgaria

[3]Fetal Medicine Unit, Hospital Universitario San Cecilio, Granada, Spain

[4]Fetal Medicine Unit, Medway Maritime Hospital, Gillingham, UK

[5]Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK

[6]Center for Fetal Medicine, Pregnancy and Ultrasound, Department of Obstetrics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

[7]Faculty of Health and Medical Sciences, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Corresponding author

Professor KH Nicolaides,

Fetal Medicine Research Institute, King's College Hospital,

16-20 Windsor Walk, Denmark Hill, London SE5 8BB

email: kypros@fetalmedicine.com

Running head

Fetal growth in twin pregnancies

Keywords

Twin pregnancies; Fetal growth; Fetal growth restriction; Twin reference distributions; Singleton reference distributions; Growth monitoring; Premature birth; Monochorionic twins; Dichorionic twins.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.27514

CONTRIBUTION

What are the novel findings of this work?

This study presents models designed to derive chorionicity-specific fetal growth trajectories in twin pregnancies, comparing these to the growth dynamics observed in singleton pregnancies. Dichorionic twins, and to a greater extent, monochorionic twins, tend to exhibit reduced but changing fetal growth compared to their singleton counterparts. Furthermore, the discrepancy in growth trajectories between twin and singleton pregnancies intensifies with advancing gestational age.

What are the clinical implications of this work?

Utilizing singleton growth charts as a reference for evaluating fetal size in twin pregnancies provides a standardized benchmark, enabling a consistent classification of fetal size regardless of whether the fetus originates from a singleton or twin pregnancy. Combined with twin-specific reference ranges, this method offers a comprehensive evaluation, particularly when fetal growth is visualized on the singleton percentile scale. These comparative perspectives hold clinical utility and can serve as valuable tools in obstetric practice to optimize fetal growth assessment in twin pregnancies.

ABSTRACT

Objectives: To derive reference distributions of estimated fetal weight (EFW) in twins relative to singletons.

Methods: Gestational age and chorionicity-specific reference distributions for singleton percentiles and EFW were fitted to data on 4,391 twin pregnancies with two liveborn fetuses from four European centres; there were 3,323 dichorionic (DC) and 1,068 monochorionic diamniotic (MCDA) twin pregnancies. Gestational age was derived using the larger of the two crown-rump length measurements obtained during the first trimester of pregnancy. The EFW was obtained from ultrasound measurements of head circumference, abdominal circumference, and femur length using the Hadlock formula. Singleton percentiles were obtained using the Fetal Medicine Foundation population weight charts for singleton percentiles. Hierarchical models were fitted to singleton z-scores with autoregressive terms for serial correlations within and between twins; separate models were fitted to DC and MCDA twins.

Results: Fetuses from twin pregnancies tended to be smaller than singletons at the earliest gestations; 16 weeks for MCDA and 20 weeks for DC twins. This was followed by a period of catch-up growth to around 24 weeks. After that, both DC and MCDA twins showed reduced growth. In DC twins, the EFW corresponding to the 50th percentile was on the 50th percentile of singleton pregnancies at 24 weeks, the 43rd percentile at 28 weeks, the 31st percentile at 32 weeks, and the 22nd percentile at 36 weeks. In MCDA twins, the EFW corresponding to the 50th percentile was on the 36th percentile of singleton pregnancies at 24 weeks, the 29th at 28 weeks, the 19th at 32 weeks, and the 12th at 36 weeks.

Conclusions: In DC and, to a greater extent, MCDA twin pregnancies, fetal growth demonstrates a comparatively lower rate than that observed in singleton pregnancies. Furthermore, the divergence in growth trajectories between twin and singleton pregnancies becomes more pronounced as gestational age increases.

INTRODUCTION

Twin pregnancies, which account for 1.5-2.0% of all pregnancies, are associated with substantially increased risks of adverse pregnancy outcomes by comparison with singleton pregnancies, including fetal loss <24 weeks' gestation, perinatal death at ≥24 weeks, preterm birth, fetal growth restriction and preeclampsia[1-3]. Consequently, it is recommended that twin pregnancies, especially monochorionic twins, have considerably closer antenatal surveillance[4, 5]. In the UK, singleton pregnancies have two routine ultrasound examinations, one at around 12 weeks and another at 20 weeks. In contrast, in dichorionic (DC) twins, ultrasound scans are carried out at 12 and 20 weeks and every four weeks thereafter until delivery, and in monochorionic diamniotic (MCDA) twins, ultrasound scans are performed at 12 weeks and every two weeks from the 16th week onwards[4].

We have previously reported on developing the Fetal Medicine Foundation fetal and neonatal population weight charts[6]. This study aims to examine the pattern of growth of fetuses from DC and MCDA twin pregnancies relative to our singleton chart.

METHODS

Study population

This study includes data from 4,391 twin pregnancies obtained from King's College Hospital, London, UK (April 2003 to August 2021), Medway Maritime Hospital, Kent, UK (January 2007 to September 2021), Shterev Hospital, Sofia, Bulgaria (September 2011 to August 2021) and Hospital Universitario San Cecilio, Granada, Spain (January 2009 to May 2021). Pregnancy dating was based on the fetal crown-rump length of the largest twins, determined by trained sonographers according to a standardized protocol. A total of 40,784 scans were included, and estimated fetal weight (EFW) was calculated using the measurements of head circumference, abdominal circumference, and femur length based on the formula developed by Hadlock *et al.*[7].

Statistical methods

The primary purpose of the analysis was to model the growth, as measured by EFW, in twin pregnancies relative to singletons. To avoid selection bias from including non-routine scans, the model fitting was restricted to measurements taken during routine ultrasound examinations with deliveries at ≥37+0 weeks for DC twins and ≥36+0 weeks for MCDA twins. The data comprise longitudinal measurements of EFW for twins, with measurements every two weeks from 16 to 36 weeks in MCDA twins and every 4 weeks from 20 to 36 weeks in DC twins. Because measurements were not made at every scheduled visit, the data are unbalanced. This was dealt with using a Bayesian approach where missing visit data were included as unknown quantities in the model.

Reference distributions for growth in twins relative to singletons were obtained by fitting separate models to singleton z-scores[6] for EFW in DC and MCDA twins. These provide direct models for growth in DC and MCDA twins relative to singletons. The fitted mean, which is a function of gestational age, represents the mean singleton z-score. This can be transformed into singleton percentiles so, for example, if at a particular gestation, the fitted mean of the singleton z scores is -1, the median EFW of twin pregnancies at that gestation corresponds to the 16th percentile for singletons; the area under the standard Gaussian curve up to -1. As shown in Appendix S1, the percentiles for EFW in twins can be derived from the fitted models for singleton z scores in twins and the singleton model[6]. Graphical and tabular summaries were produced for 50th, 10th and 90th percentiles in DC and MCDA twin fetuses; results were produced for EFW and singleton percentiles. The way in which these were obtained is explained and illustrated with an example in Appendix S1. For comparison with previous publications, we derived the singleton percentiles from the published twin EFW percentiles.

Hierarchical Gaussian models with three levels, pregnancy, fetus, and visit, were fitted to the distribution of singleton z-scores over scheduled visits, separately to DC and MCDA twins. The means, common to both twins in each pregnancy, were assumed to depend on gestational age according to a quartic polynomial for DC twins and a cubic polynomial for MCDA twins. Random effects were included for pregnancies, fetuses, and visits. The sample correlations of measurements between fetuses from the same pregnancy and within fetuses over different visits were examined. These decreased as the separation between visits increased. To account for this, first-order autoregressive (Markov) processes were included for pregnancy and fetuses' random effects. A Bayesian approach to modelling implemented using Markov Chain Monte Carlo method (MCMC)[8] was adopted. This is a computationally intensive and flexible methodology that is relatively easy to implement with the unbalanced data and complicated correlation structure.

Diagnostics were produced to assess the adequacy of the models in terms of the choice of functional form for the mean and the model for the correlation structure. This included summary statistics and Gaussian probability plots of EFW z-scores in MC and DC twins.

Distributions of z-scores were produced for scheduled and non-scheduled visits according to gestational age at delivery.

The statistical software R was used for data analyses[9]. The R package mvtnorm[10] was used for multivariate Gaussian quantiles. Model fitting was done using WinBugs[11].

RESULTS

The study population comprised 4,391 twin pregnancies, including 3,323 (75.7%) DC and 1,068 (24.3%) MCDA. From these, the model was fitted to EFW measurements of all DC pregnancies (56.2%) delivered at ≥37 weeks and all MCDA pregnancies (56.3%) delivered at ≥36 weeks. From DC pregnancies, 7,762 scans were included, with a mean of 0.83 measurements per pregnancy at each of the four scheduled visits. A total of 5,381 scans from MCDA pregnancies were included, with a mean of 0.81 per pregnancy at each of the eleven scheduled visits.

Figure 1 shows medians, 10th and 90th percentiles for EFW, and singleton percentiles for DC and MCDA twins compared to singletons. Tables 1 and 2 show 3rd, 10th, 50th, 90th, and 97th percentiles for DC and MCDA twins, respectively. Both DC and MCDA twins show a tendency for twins to be smaller than singletons at the earliest gestations; 16 weeks for MCDA and 20 weeks for DC twins. This is followed by a period of catch-up growth to around 24 weeks. After that, both DC and MCDA twins show reduced growth. The fitted model coefficients are shown in Table S1 and S2. The fitted mean singleton z-scores for DC and MCDA twins are shown in Figure S1.

Figure 2 shows the auto-correlation and cross-correlations, showing the correlation between z-scores within and between twins from the fitted model. These are shown with the sample auto-correlations and cross-correlations in Figure S2. Auto-correlations and cross-correlations are very similar in DC and MCDA twins.

Histograms of the z-scores from the model for DC twins are shown in Figure 3. The smooth curve represents the standard Gaussian distribution (mean = 0, standard deviation = 1) corresponding to perfect conformity with the modelled reference distribution. Panel (a) shows the distribution of z-scores for scheduled visits with births at 37 weeks' gestation or later; these data were used for model fitting and are in good agreement with the model. Panel (b) shows z-scores for non-scheduled visits of babies born at 37 weeks or later. These data show relatively more z-scores in the lower tail of the distribution. This tendency is more strongly pronounced in those pregnancies delivered before 37 weeks, as shown in panels (c) and (d). Figure 4 shows distributions of z-scores for MCDA twins. Scheduled visits with births at 36 weeks gestation or later, panel (a), are consistent with the Gaussian model. Non-scheduled visits for babies born before 36 weeks show a relatively higher proportion of lower z-scores, most strongly pronounced with the non-scheduled visits, panel (d). Distributions by individual weeks at scheduled visits with births at 37 weeks or later for DCDA twins and 36 weeks or later for MCDA twins are shown in Figures S3 and S4.

DISCUSSION

Main findings

Fetuses from twin pregnancies tend to be smaller than singletons at 16 weeks for MCDA and 20 weeks for DC twins. This is followed by a period of catch-up growth to around 24 weeks. After that, both DC and MCDA twins show an increasing level of growth restriction.

Comparison with findings of previous studies

To compare the FMF twin growth models presented in this study, we collected details from nine previous models, which in total were based on 6,152 DC twin pregnancies (range 136 to 1,802), 1,920 MCDA twin pregnancies (range 32 to 688) and 884 twin pregnancies without distinguished details of chorionicity (see Figure 5)[12-20].

The pattern of growth, relative to the FMF singleton growth charts, in three of the nine published models, was similar to that of our model.[15,16,20] Twins were found to be smaller than singletons at earlier gestations with some degree of catch-up growth until around 20-24 weeks followed by an increasing degree of growth restriction relative to singletons. MCDA twins were generally smaller than DC twins. All models in Figure 5 show a period of deceleration in growth relative to the FMF reference early in the third trimester. However, in contrast to our model, five of them showed catch-up growth from around the middle of the third trimester.

Clinical implications

Using growth curves from singleton pregnancies, allows fetal size to be classified in a consistent way regardless of the fetal origin, be it from a singleton or twin gestation. Using a singleton percentile scale, rather than an EFW scale, allows growth to be monitored across the full gestational age range with no loss of resolution. Superimposing percentiles for twins allows growth trajectories to be assessed relative to the expected patterns of growth in twins allowing comparison of a given case with both singletons and other twins.

Strengths and limitations

Strengths of our study include, first, a large cohort of women with twin pregnancies undergoing routine ultrasound examinations in different countries. Therefore, the results are generalizable to different populations. Second, pregnancy dating based on fetal crown-rump length, trained sonographers that carried out fetal biometry according to a standardized protocol, and the use of a widely used model for calculation of EFW[7], which has been shown to be the most accurate one among 70 previously reported models[23]. Third, pregnancies selected for the model development resulted in two liveborn children delivered at ≥ 37 weeks for DC twins and at ≥ 36 weeks in MCDA twins, and scans used were from the scheduled visits, by which the reference cohort consisted of uncomplicated pregnancies and scans. Fourth, the model design using auto-correlations and cross-correlations in and between twins is a strength and a novelty of the study.

The distributional characteristics of twins relative to singletons were derived from the model for the distribution of EFW in singleton pregnancies[6]. This was fitted using measurements in singletons taken between 20+0 and 36+6 weeks. For MCDA twins, the results between 16 and 20 weeks were obtained by extrapolation of the fitted model for singletons; consequently, the results are less reliable at the lower end of this range. This problem applies to the singleton percentiles but not the EFW percentiles. The retrospective nature of the study design may introduce inherent limitations, such as reliance on existing data sources and potential incomplete documentation. Additionally, the study's generalizability might be constrained by the specific demographic characteristics of the study populations. It is also essential to consider that inherent measurement variability in ultrasound examinations and fetal biometry may introduce a degree of imprecision.

Conclusions

Our findings elucidate that fetal growth is reduced compared to singleton pregnancies in DC and, to a more pronounced degree, MCDA twin pregnancies. Moreover, with progressing gestational age, the divergence in growth trajectories between fetuses from twin and singleton pregnancies progressively increases, suggesting a greater influence of the twin intrauterine environment on fetal growth over time.

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FIGURE LEGENDS

Figure 1: Percentile charts for dichorionic and monochorionic diamniotic twins. The solid black line is the median, and the broken black lines are the 10th and 90th percentiles for singletons. The solid grey line is the median for twins. The grey shaded area covers the region between the 10th and 90th percentiles for twins.

Figure 2: Auto-correlations (same twin) and cross-correlations (between twin) for EFW z-scores

Figure 3: Distribution of estimated fetal weight z-scores for dichorionic twins according to gestational age at delivery and whether or not the visits were classed as scheduled (every four weeks from 20 to 36 weeks).

Figure 4: Distribution of estimated fetal weight z-scores for monochorionic diamniotic twins according to gestational age at delivery and whether or not the visits were classed as scheduled (every two weeks from 16 to 36 weeks).

Figure 5: Percentile charts for dichorionic and monochorionic diamniotic twins, based on previous twin-specific growth chart. The solid black line is the median, and the broken black lines are the 10th and 90th percentiles for singletons. The solid purple, orange, and green line is the median for dichorionic, monochorionic diamniotic, and unspecified chorionicities, respectively.

Table 1: Dichorionic twins: estimated fetal weight (EFW) in grams and corresponding percentile in the Fetal Medicine Foundation growth chart for singletons[6].

Weeks	Days	3rd percentile		10th percentile		50th percentile		90th percentile		97th percentile		EFW <10th percentile of singletons
		EFW	%	EFW	%	EFW	%	EFW	%	EFW	%	
20	143	294	1.5	309	6.5	343.7	46.2	382	90.7	402	97.7	14.2
21	150	351	1.7	370	7.2	411.8	48.3	459	91.6	483	97.9	13.1
22	157	417	1.8	439	7.6	490.2	49.5	547	92.0	576	98.1	12.6
23	164	493	1.9	519	7.8	579.8	50.0	648	92.2	682	98.1	12.4
24	171	578	1.8	609	7.7	681.3	49.8	762	92.1	803	98.1	12.5
25	178	673	1.7	710	7.4	795.2	48.9	891	91.8	939	98.0	12.9
26	185	779	1.6	822	6.9	921.7	47.6	1,034	91.3	1,090	97.8	13.5
27	192	895	1.4	945	6.3	1,061	45.7	1,191	90.5	1,257	97.6	14.5
28	199	1,020	1.2	1,077	5.6	1,211	43.4	1,362	89.5	1,439	97.2	15.7
29	206	1,154	1.0	1,220	4.9	1,373	40.7	1,546	88.2	1,634	96.8	17.3
30	213	1,295	0.8	1,370	4.2	1,544	37.7	1,741	86.6	1,841	96.2	19.1
31	220	1,443	0.7	1,527	3.5	1,723	34.6	1,945	84.7	2,058	95.4	21.2

32	227	1,594	0.5	1,688	2.9	1,908	31.5	2,156	82.6	2,283	94.5	23.5
33	234	1,748	0.4	1,852	2.4	2,095	28.6	2,371	80.4	2,512	93.6	25.9
34	241	1,901	0.3	2,015	2.0	2,283	26.0	2,587	78.1	2,742	92.5	28.3
35	248	2,051	0.3	2,175	1.6	2,468	23.6	2,800	75.8	2,970	91.4	30.5
36	255	2,195	0.2	2,330	1.4	2,647	21.7	3,006	73.8	3,191	90.3	32.6
37	262	2,330	0.2	2,475	1.2	2,815	20.1	3,202	72.0	3,400	89.3	34.4

Table 2: Monochorionic diamniotic twins: estimated fetal weight (EFW) in grams and corresponding percentile in the Fetal Medicine Foundation growth chart for singletons[6].

Weeks	Days	3rd percentile		10th percentile		50th percentile		90th percentile		97th percentile		EFW <10th percentile of singletons
		EFW	%	EFW	%	EFW	%	EFW	%	EFW	%	
16	115	127	<0.1	134	0.2	149.4	9.7	167	60.6	176	84.1	50.5
17	122	156	<0.1	164	0.5	184.1	14.7	206	69.7	218	89.4	42.4
18	129	191	0.1	201	0.8	225.6	19.9	253	76.4	267	92.7	36.0
19	136	231	0.2	244	1.2	274.6	24.8	308	81.2	326	94.7	31.1
20	143	279	0.2	295	1.7	332.0	28.9	374	84.4	395	95.9	27.6
21	150	335	0.3	354	2.1	398.7	32.1	449	86.4	475	96.7	25.2
22	157	398	0.4	421	2.4	475.5	34.3	536	87.7	568	97.1	23.6
23	164	471	0.4	498	2.6	563.1	35.4	636	88.3	674	97.3	22.9
24	171	552	0.4	585	2.7	662.0	35.6	749	88.4	794	97.3	22.8
25	178	643	0.4	682	2.6	772.6	34.9	875	88.0	928	97.2	23.2
26	185	744	0.3	789	2.3	895.0	33.5	1,015	87.3	1,077	96.9	24.1
27	192	853	0.3	906	2.1	1,029	31.6	1,169	86.1	1,241	96.5	25.5

28	199	971	0.2	1,032	1.7	1,174	29.3	1,336	84.6	1,419	96.0	27.3
29	206	1,098	0.2	1,167	1.4	1,329	26.7	1,515	82.7	1,610	95.3	29.5
30	213	1,231	0.1	1,309	1.2	1,494	23.9	1,704	80.4	1,813	94.4	31.9
31	220	1,369	0.1	1,457	0.9	1,665	21.3	1,903	77.9	2,025	93.3	34.6
32	227	1,511	0.1	1,610	0.7	1,842	18.7	2,108	75.1	2,245	92.1	37.3
33	234	1,655	0.1	1,764	0.6	2,022	16.5	2,317	72.2	2,469	90.7	40.1
34	241	1,798	0.1	1,918	0.4	2,201	14.5	2,526	69.3	2,694	89.2	42.8
35	248	1,939	0.1	2,069	0.4	2,378	12.8	2,733	66.6	2,917	87.7	45.2
36	255	2,074	0.1	2,215	0.3	2,549	11.5	2,934	64.2	3,133	86.4	47.3
37	262	2,201	0.1	2,353	0.2	2,711	10.6	3,125	62.3	3,339	85.2	49.0

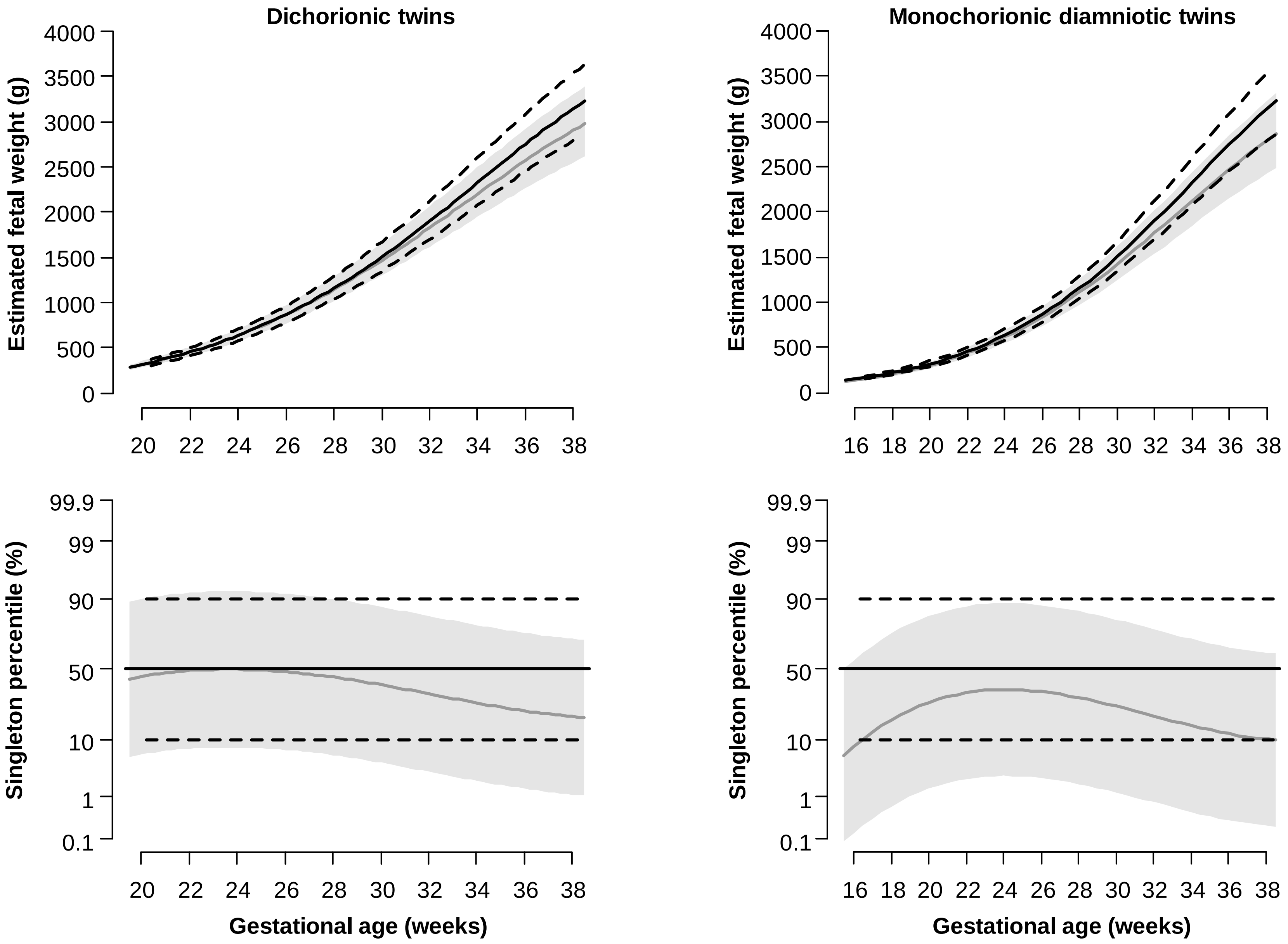

Dichorionic twins
Monochorionic diamniotic twins
Estimated fetal weight (g)
0
500
1000
1500
2000
2500
3000
3500
4000
20
22
24
26
28
30
32
34
36
38
16
18
Singleton percentile (%)
0.1
1
10
50
90
99
99.9
Gestational age (weeks)

Figure 1.

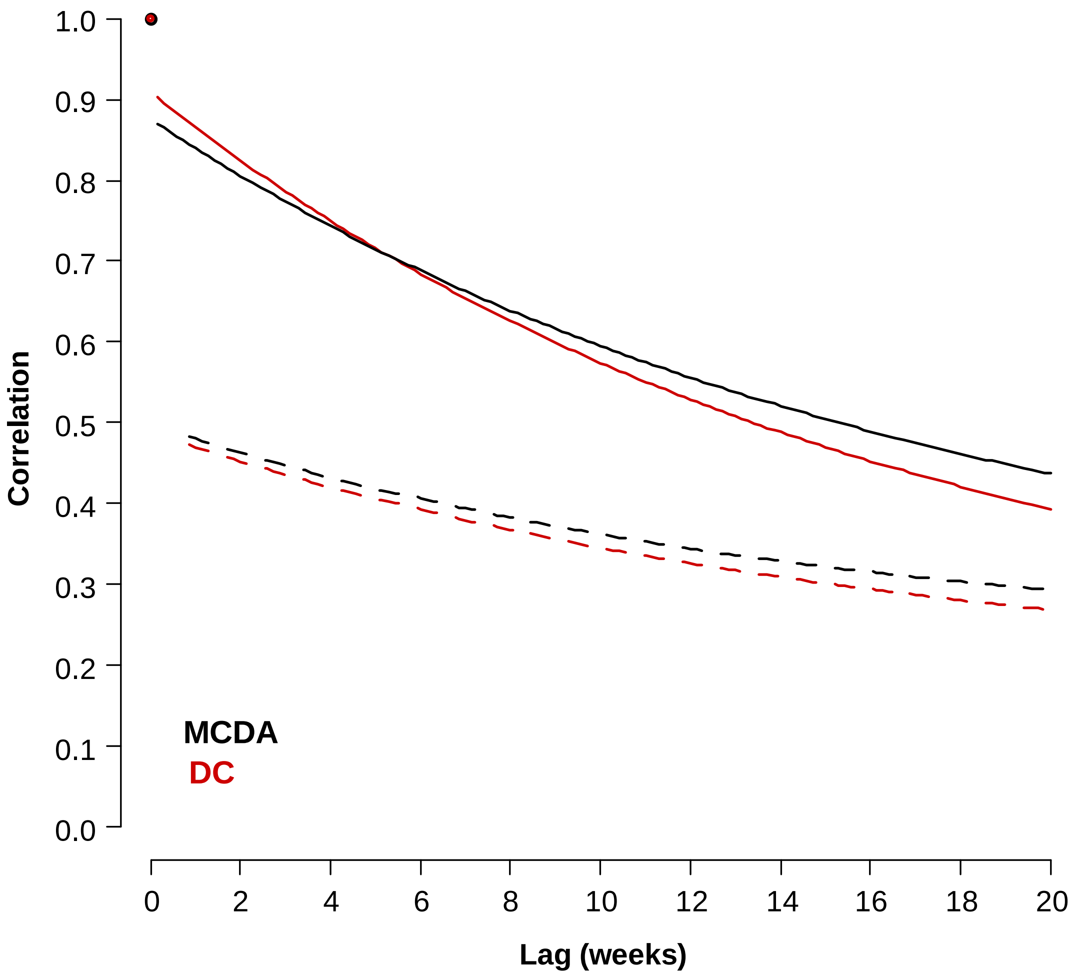

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Correlation
MCDA
DC
0
2
4
6
8
10
12
14
16
18
20
Lag (weeks)

Figure 2

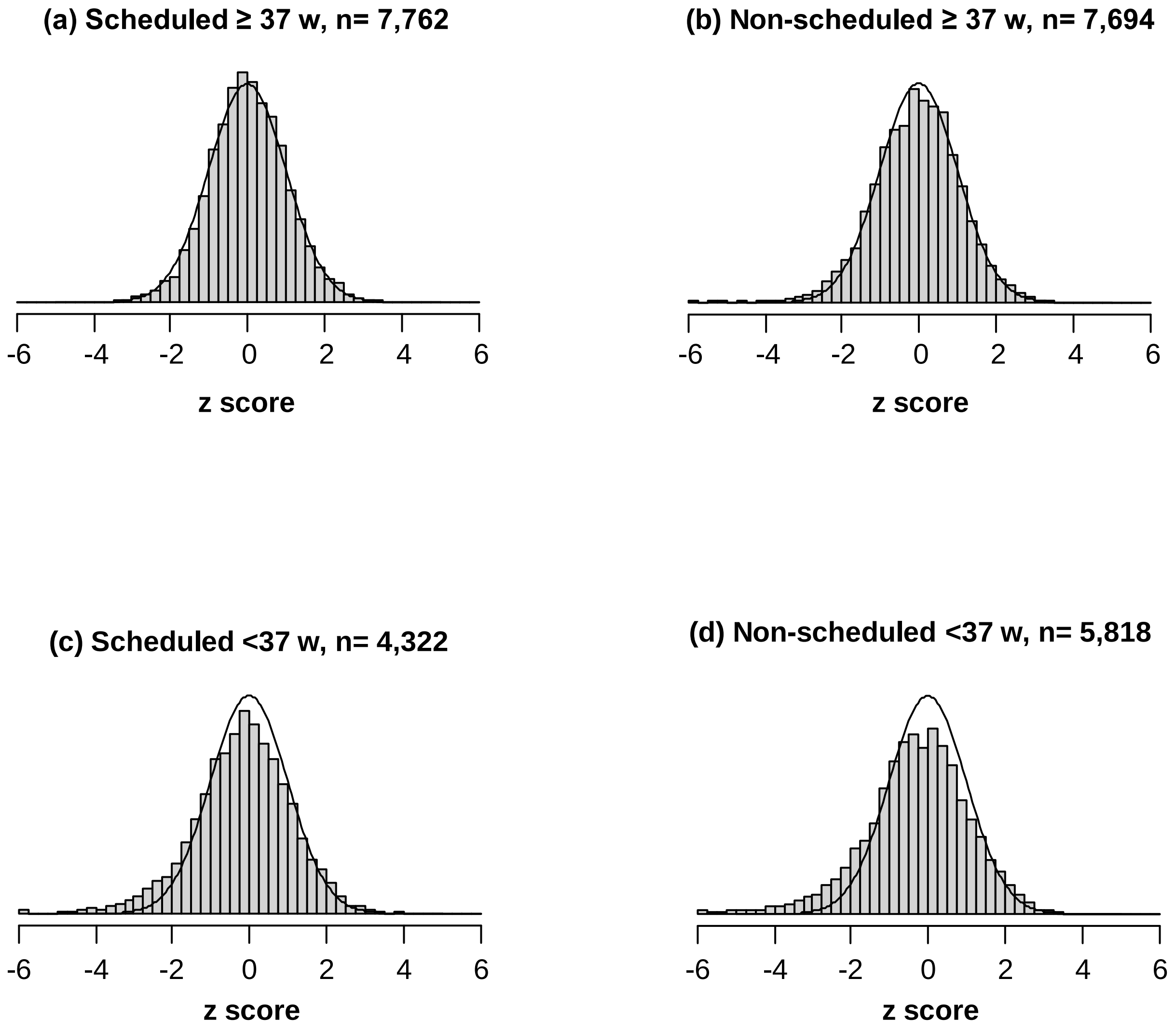
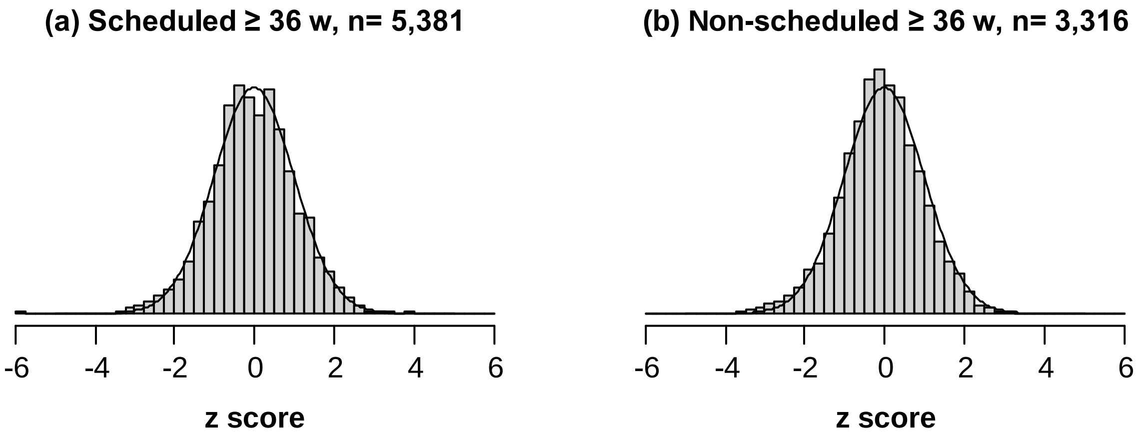
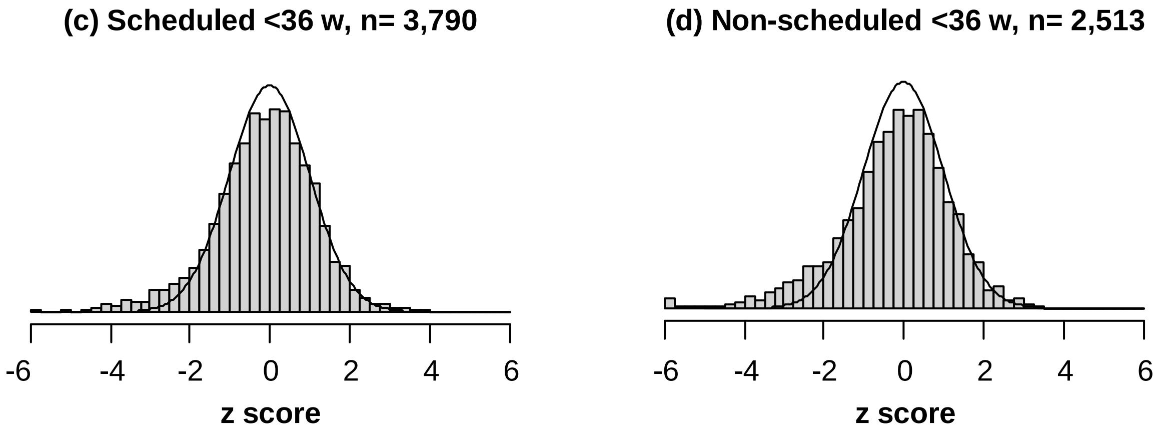

(a) Scheduled ≥ 37 w, n= 7,762
-6
-4
-2
0
2
4
6
z score
(b) Non-scheduled ≥ 37 w, n= 7,694
-6
-4
-2
0
2
4
6
z score
(c) Scheduled <37 w, n= 4,322
-6
-4
-2
0
2
4
6
z score
(d) Non-scheduled <37 w, n= 5,818
-6
-4
-2
0
2
4
6
z score

Figure 3.


(a) Scheduled ≥ 36 w, n= 5,381

(b) Non-scheduled ≥ 36 w, n= 3,316


(c) Scheduled <36 w, n= 3,790

(d) Non-scheduled <36 w, n= 2,513

Figure 4.

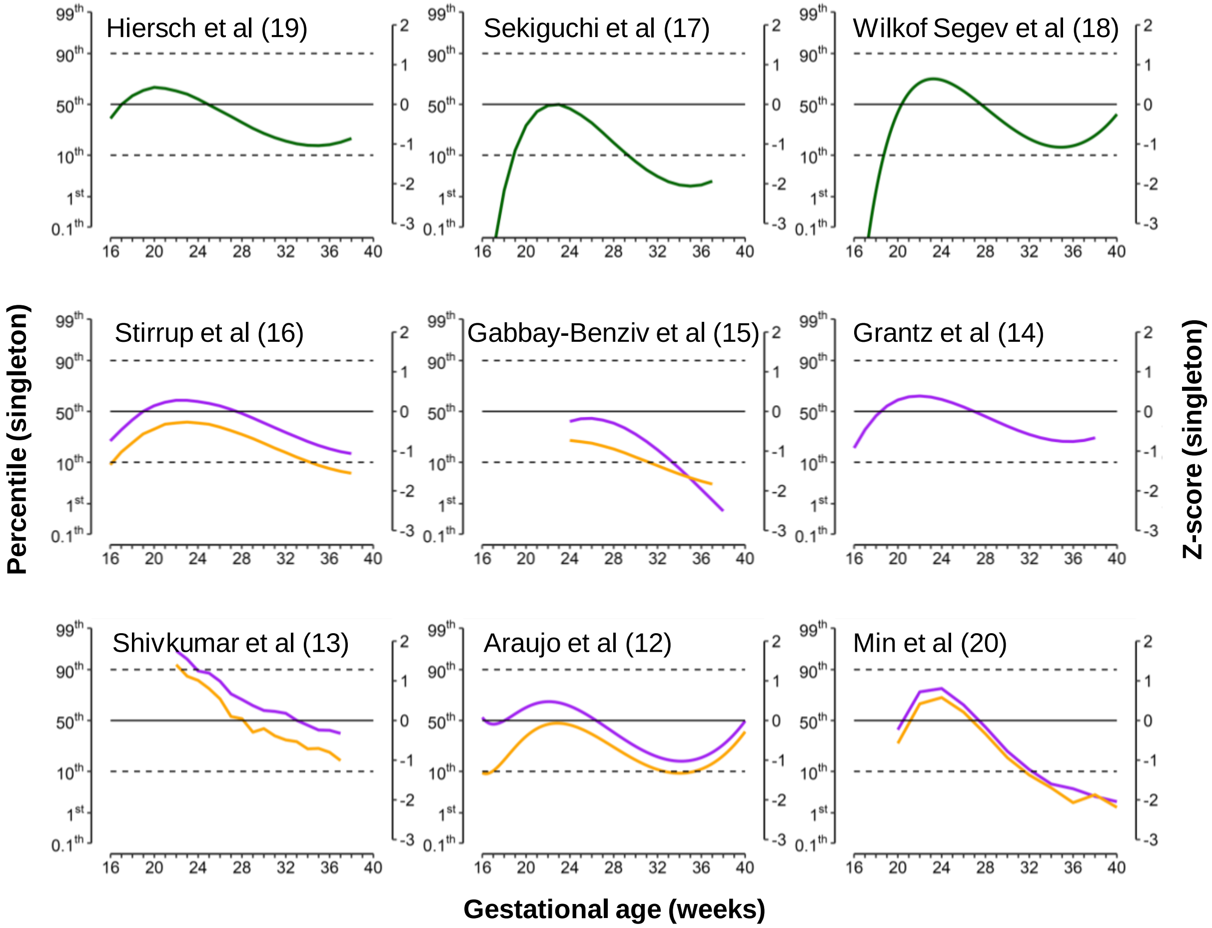

Hiersch et al (19)
Sekiguchi et al (17)
Wilkof Segev et al (18)
Stirrup et al (16)
Gabbay-Benziv et al (15)
Grantz et al (14)
Shivkumar et al (13)
Araujo et al (12)
Min et al (20)
99th
90th
50th
10th
1st
0.1th
2
1
0
-1
-2
-3
16
20
24
28
32
36
40
Percentile (singleton)
Z-score (singleton)
Gestational age (weeks)

Figure 5.