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Incidence of neonatal morbidity in small-for-gestational age twins based on singleton and twin charts

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Running head: Neonatal intensive care in twin pregnancies

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CONTRIBUTION

What are the novel findings of this work?

In this study of 1,150 twins and 29,035 singletons that were scanned at 36 weeks' gestation, the overall proportions of neonates entering the neonatal intensive care unit (NICU) were similar (7.3% for twins and 7.4% for singletons), but twins tended to have longer lengths of stay in NICU (≥7 days 2.4% of twins vs. 0.8% of singletons). Using singleton charts to define small for gestational age (SGA), a much higher proportion of twins were classified as SGA than singletons (37.2% vs. 7.0%), but the proportion of SGA neonates entering NICU was similar (10.3% vs 10.1%) and the proportion of SGA neonates spending ≥7 days in NICU was substantially higher for twins than for singletons (3.7% vs. 1.4%, risk ratio 2.6, 95% CI: 1.1 – 4.7).

What are the clinical implications of this work?

When singleton charts are used to define SGA in twins and in singletons, there is a greater degree of growth-related neonatal morbidity amongst SGA twins than in SGA singletons. Consequently, use of singleton charts in twins does not inappropriately over diagnose fetal growth restriction and they should be used for monitoring fetal growth both in twins and in singletons.

ABSTRACT

Objective: Using lengths of stay in neonatal intensive care unit (NICU) as a measure of morbidity, the objective is to compare twins and singletons according to classification of small for gestational age (SGA) using the 10th percentile for twins or the 10th percentile for singletons.

Methods: NICU lengths of stay were compared in 1,150 twins neonates and 29,035 singleton neonates all scanned at between 35+0 and 36+6 weeks' gestation. Estimated fetal weights were obtained from measurements of head circumference, abdominal circumference and femur length using the Hadlock formula. Gestational ages were obtained from first trimester crown rump length measurements using the larger of the two twins. Singletons and twins were compared for NICU lengths of stay according to classification as small relative to the Fetal Medicine Foundation singleton and twin reference distributions.

Results: The overall proportions of neonates entering NICU for twins and singletons were similar (7.3% vs, 7.4%), but twins tended to have longer lengths of stay in NICU (≥7 days: 2.4% of twins vs. 0.8% of singletons, relative risk 3.0, 95% CI: 1.6 – 4.4). Using singleton charts, a much higher proportion of twins were classified as SGA than singletons (37.2% vs. 7.0%). However, the proportion of SGA neonates entering NICU was similar (10.3% for twins and 10.1% for singletons) and the proportions of SGA neonates spending ≥7 days in NICU was substantially higher for twins than for singletons (3.7% vs. 1.4%, risk ratio 2.6, 95% CI: 1.1 – 4.7).

Conclusions: When singleton charts are used to define SGA in twins and in singletons, there is a greater degree of growth-related neonatal morbidity amongst SGA twins than in SGA singletons. Consequently, use of singleton charts in twins does not inappropriately over diagnose fetal growth restriction and they should be used for monitoring fetal growth both in twins and in singletons.

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 the Fetal Medicine Foundation fetal and neonatal population weight charts, derived from singleton pregnancies[6], and charts for monitoring fetal growth in twins[7]. This paper focuses on the question of whether twin fetuses should be classified as small for gestational age (SGA) using twin specific charts or singleton charts. Some authors have advocated the use of twin, rather than singleton, charts to define SGA is twins[8,9]. The argument of such choice is that growth restriction in twins is a benign adaption to their intrauterine environment and the use of singleton charts overdiagnoses growth restriction in twins with little or no prognostic benefit. Evidence that, SGA defined using twin charts has better diagnostic accuracy (higher incidence of adverse outcome in the screen positive group) than SGA defined by singleton charts has been used to support this argument[8,9].

The objective of this study is to compare the morbidity in SGA singletons and twins when defined using twin and singleton charts[6,7]. The primary purpose of the analysis is to compare neonatal intensive care (NICU) admission rates and lengths of stay when classified as SGA using singleton and twin charts for estimated fetal weight (EFW) from ultrasound scans taken at 36-weeks' gestation. The gestational age of 36 weeks for the ultrasound scan is the latest gestation for which routine ultrasound scan findings in twins and singletons are available. This was chosen firstly, because the later the gestational age the greater the separation between singleton and twin charts, and second, because complicated twin pregnancies that inevitably deliver before 36 weeks are excluded.

METHODS

Study population

In this study we examined populations in twin and singleton pregnancies from two previously published studies. Data on twins were obtained from the EVENTS trial, in which 1,194 women with twin pregnancies were randomized to treatment with progesterone or placebo.[10] The primary outcome was the incidence of spontaneous birth before 34 weeks' gestation. There was no evidence of a treatment effect (P = 0.17). Apart from the trial treatment, women received standard care, including a routine ultrasound scan at 36 weeks' gestation.

Data on singletons were obtained from prospective non-intervention observational study in women with singleton pregnancies attending a routine hospital visit at 35+0 to 36+6 weeks' gestation at King's College Hospital, London, and Medway Maritime Hospital, Gillingham, United Kingdom, between October 2016 and September 2021[11].

Statistical methods

Singletons and twins were compared for admission to NICU and NICU lengths of stay according to classification as small relative to the Fetal Medicine Foundation singleton and twin reference distributions. Defining SGA according to singleton and twin charts NICU length of stay of the proportions of SGA neonates and non-SGA neonates spending 1, 2, 3, 4, 5, 6 and ≥7 days in NICU were obtained for neonates classified as SGA and non-SGA. The association between SGA and length of stay was quantified by the odds ratios (SGA / non-SGA). To account for correlations between twin fetuses, confidence intervals were obtained from bootstrap samples of pregnancies for both singletons and twins.

The statistical software R was used for data analyses[12]. The R package boot was used for bootstrap confidence intervals[13,14].

RESULTS

Characteristics of the study populations are shown in Table 1. The original EVENTS[10] data set included 1169 pregnancies; 902 (77%) were DC and 267 (23%) were MCDA. Ultrasound scans at 36 weeks' gestation were undertaken on 510/902 (57%) of the DC twins and 65/267 (24%) of MCDA twins. The small proportion of MC twins scanned at 36 weeks reflects the higher frequency of births occurring before 36 weeks in MCDA twins. For comparison, data were available on 29,035 singletons[11]. The median maternal age in DC twins is older than that in singletons and MCDA twins reflecting the relatively high proportion of IVF pregnancies in the DC twin population.

Length of stay in NICU for SGA neonates

Table 2 shows the proportions of SGA singleton and twin neonates spending 1 to ≥7 days in NICU when classified by singleton charts. The proportions for twins are also given using twin charts to define SGA. Risks ratios are given for twins relative to singletons.

Figure 1 (panel a) shows the proportions of SGA neonates spending 1 to ≥7 days in NICU when classified as SGA using the singleton chart. The proportion of twins entering NICU (d =1) is very similar to that in singletons; around 10%. However, as the number of days in NICU increases, the proportions of twins spending d or more days in NICU increases relative to the proportions of singletons. This is illustrated in panel b of Figure 1, which shows the relative risks of lengths of stay of d or more days (twins / singletons). Amongst twins classified as SGA using a singleton chart, there is more morbidity than in singletons. Panel c of Figure 1 shows the proportions spending d or more days in NICU when twin specific charts are used for twins and panel d shows the relative risks with twins classified as SGA using twin charts. The relatively high levels of morbidity in twins when compared to SGA singletons is much more extreme when twin charts are used to define SGA in twins. Figure S1 shows the results using singleton charts separately for DC and MCDA twins.

Diagnostic accuracy

Twin charts have been advocated on the basis that SGA is more strongly associated with poor outcomes when twin charts, rather than singleton charts are used to define SGA[8,9]. Table 3 and Figure 2 show diagnostic odds ratios for NICU lengths of stay of 1 to ≥7 days in singletons and in twins defining SGA using twin and singleton charts. For singletons (panel a) and twins (panel b), the twin charts have greater diagnostic accuracy. This happens because SGA defined by twin charts is more extreme than that defined by singleton charts and morbidly is relatively more frequent the more extreme the SGA. The argument that twin charts should be used to define SGA because of the stronger association with adverse outcome would imply that twin charts should be used for singletons as well as twins. A notable feature of Figure 2 and Table 3 is that the association between SGA and NICU outcomes is stronger in twins than in singletons.

DISCUSSION

Main findings

Using measurements of EFW taken from ultrasound scans at 36 weeks' gestation we examined outcomes for SGA defined by the 10^{th} percentile in populations of twins and singletons. Although, using singleton charts, a much higher proportion of twins were classified as SGA than singletons (37.2% vs. 7.0%), the proportion of SGA neonates entering NICU was similar (10.3% for twins and 10.1% for singletons). The proportions of SGA neonates spending ≥7 days in NICU was substantially higher for twins than for singletons (3.7% vs. 1.4%). As expected, twins delivered at earlier gestations than singletons with median gestational ages at birth of 37.3 weeks for DC twins and 36.7 weeks for MCDA twins, compared to 40.0 weeks for singletons.

It has been argued that twin charts should be preferred because when using twin charts, rather than singleton charts, the association between SGA and morbidity is stronger. In this study, we have shown that this applies to both singletons and twins. This happens because SGA defined by twin charts is more extreme than that defined by singleton charts. Therefore, choice of charts should not be based on this alone.

As we have proposed previously, using singleton charts and singleton percentiles for twins, rather than an EFW scale, allows fetal size to be classified in a consistent way regardless of fetal origin, be it from a singleton or a twin pregnancy[5,6]. Plotting singleton percentiles, enables growth to be monitored with high resolution across the full gestational age range. Superimposing percentiles of the distribution of twins indicate to what extent growth seen in twins is unusual. This gives a more nuanced and precise understanding of growth trajectories and potential growth anomalies endemic to twin pregnancies.

Comparison with findings of previous studies

Our results confirm previous findings that, first, when SGA in twins is defined on the basis of singleton charts the incidence of SGA in twins is higher than in singletons, and second, the association between SGA and morbidity is stronger when twin specific charts are used for twins[8,9]. Additionally, we showed that this also applies to singletons and that it is explained by the way in which SGA defined by twin charts is more extreme than it is when defined by singleton charts. For example, at 37 weeks' gestation, the 10th percentile for DC and MCDA twin pregnancies are equivalent to the 1.4th and 0.3rd percentiles for singletons respectively.

It has been suggested that the smallness of twins relative to singletons results from adaptation that also involves promotion of maturity[15]. This has been used to support the use of twin-based charts, designed to adjust for this physiological adaptation and avoid overdiagnosis of intrauterine growth restriction in twins. We have shown that, when defined in terms of a singleton chart, SGA twins have a higher degree of morbidity than singletons and that SGA is more strongly associated with morbidity in twins than in singletons. This applies to both DC and MCDA twins, but it is more pronounced in MCDA twins (Figure S1). This does not preclude the possibility of adaptive mechanisms in the growth of twins but, given any such adaption, SGA twins defined in terms of singleton charts, have a higher degree of morbidity than singletons.

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. Although a relatively large proportion of twin fetuses are classified as SGA when this is done, there is a greater degree of morbidity in SGA twins than in SGA singletons. This runs contrary to the view that using singleton charts leads to overdiagnosis of fetal growth restriction in twin pregnancies.

Strengths and limitations

Strengths of our study include, first, large cohorts of women undergoing routine ultrasound examinations at 36 weeks' gestation; second, pregnancy dating based on fetal crown-rump length, trained sonographers that carried out fetal biometry according to a standardized protocol, and use of a well validated model for calculation of EFW[16,17]; and third, availability of outcome data on lengths of stay in NICU.

We chose to compare outcomes after ultrasound scans taken at 36 weeks where smallness in twins is most pronounced and to minimize the contribution of complicated twin pregnancies, especially MC twins, many of which deliver before 36 weeks. Consequently, the extent to which the results apply to ultrasound scans at earlier gestational ages requires further investigation. It is likely that even after 36 weeks the increased morbidity in twins, compared to singletons, is due to a combination of them being small as well as being born earlier. This strengthens the case of using singleton, rather than twin charts, in the assessment and management of twins.

Conclusions

Using singleton charts does not inappropriately over diagnose fetal growth restriction. When singleton charts are used to define SGA in twins and in singletons, there is a greater degree of growth-related morbidity amongst SGA twins than in SGA singletons**.** Consequently, both in twins and in singletons, singleton charts should be used for classifying fetal growth and defining SGA. Viewing growth in terms of singleton and twin reference percentiles is the best way of monitoring growth in twins.

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FIGURES LEGENDS

Figure 1: Proportions of SGA neonates spending 1 to ≥7 days in NICU from singleton pregnancies (black) and twin pregnancies (red). The top left panel shows results when SGA is defined according to the 10th percentile for singletons. The top right panel shows the corresponding risk ratios. The bottom panels show the results when SGA in twins is defined by the 10th percentiles for twins.

Figure 2: Diagnostic odds ratios for prediction of lengths of stay in NICU by SGA defined by the 10th percentiles for singletons (black) and the 10th percentiles for twins. The left panel shows the results for singletons and the right panel shows the results for twins.

Table 1: Demographic and pregnancy characteristics.

Characteristic	Singletons (n = 29,035)	Dichorionic (n = 510)		Monochorionic diamniotic (n = 65)	
			P value		**P value**
Maternal age (years)	32.6 (28.7, 36)	34.8 (30.6, 38.2)	< 0.001	32.6 (29.8, 36.2)	0.382
Gestation at birth (weeks)	40 (39.1, 40.9)	37.3 (37.0, 37.9)	< 0.001	36.7 (36.1, 37.1)	<0.001
Body mass index (kg/m^2)	24.7 (22.1, 28.5)	24.8 (22.2, 28.5)	0.769	23.1 (21.1, 26.4)	0.020
Ultrasound scan					
Gestational age (weeks)	36.0 (35.6, 36.3)	36.0 (35.6, 36.3)	0.378	35.9 (35.4, 36.1)	0.006
Estimate fetal weight (g)	2774 (2613, 2940)	2531 (2346, 2717)	< 0.001	2431 (2197, 2605)	<0.001
Nulliparous	13,767 (47.4)	270 (52.9)	0.014	25 (38.5)	0.693
Ethnicity			0.004		0.404
White	23166 (79.8)	434 (85.1)		56 (86.2)	
Black	3076 (10.6)	51 (10.0)		7 (10.8)	
South Asian	1385 (4.8)	15 (2.9)		0 (0)	
East Asian	596 (2.1)	5 (1)		1 (1.5)	
Mixed	812 (2.8)	5 (1)		1 (1.5)	
Conception			< 0.001		0.052
Natural	27632 (95.2)	305 (59.8)		58 (89.2)	
In vitro fertilization	1231 (4.2)	162 (31.8)		6 (9.2)	
Ovulation drugs	172 (0.6)	43 (8.4)		1 (1.5)	
Smoker	1550 (5.3)	30 (5.9)	0.552	1 (1.5)	0.277

Values are given as mean (interquartile range) and n (%).

Table 2: Risks of neonatal intensive care unit length of stay in singletons classified as small for gestational age (below the 10th percentile) using singleton and twin charts.

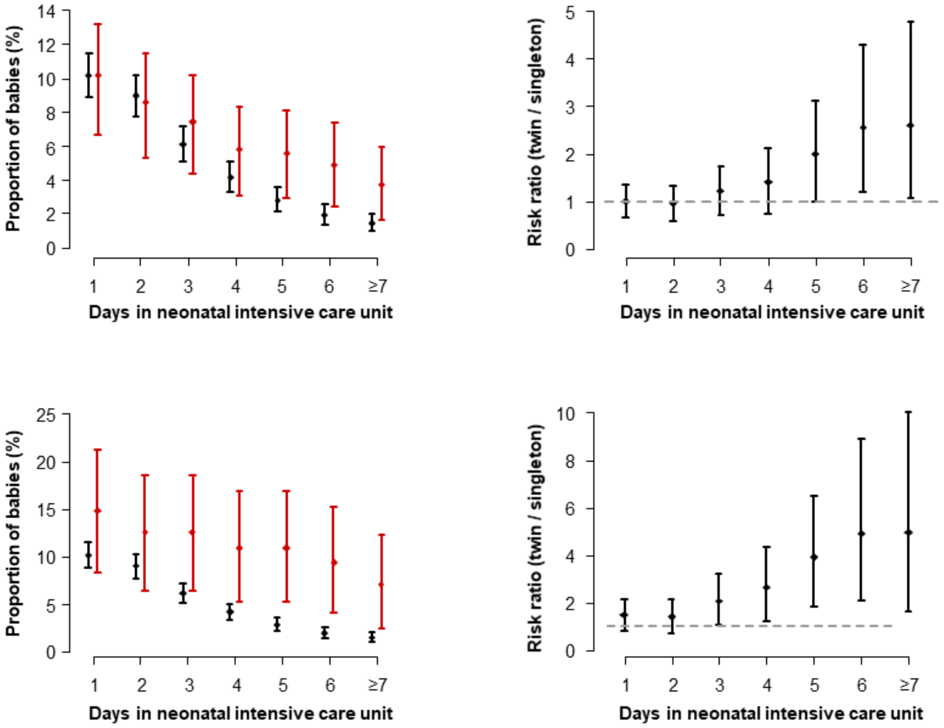
Length of stay (days)	Singletons (n = 29,035)		Twins (n = 1,150)					
	Singleton chart		Singleton chart			Twins chart		
	SGA: n = 2,040 (7.0%)		SGA: n = 432 (37.6%)			SGA: n = 128 (11.1%)		
	n	%	n	%	RR	n	%	RR
1	207	10.1 (8.9,11.5)	44	10.2 (7.1, 13.7)	1.0 (0.7, 1.4)	19	14.8 (8.9, 21.9)	1.5 (0.9, 2.2)
2	183	9.0 (7.8,10.3)	37	8.6 (5.7, 11.8)	1.0 (0.6, 1.4)	16	12.5 (7.0, 19.0)	1.4 (0.8, 2.2)
3	124	6.1 (5.1, 7.2)	32	7.4 (4.8, 10.4)	1.2 (0.8, 1.8)	16	12.5 (7.0, 19.0)	2.1 (1.1, 3.3)
4	84	4.1 (3.3, 5.1)	25	5.8 (3.5, 8.5)	1.4 (0.8, 2.2)	14	10.9 (5.8, 17.4)	2.7 (1.4, 4.5)
5	57	2.8 (2.1, 3.6)	24	5.6 (3.3, 8.2)	2.0 (1.1, 3.3)	14	10.9 (5.8, 17.4)	3.9 (2.0, 6.8)
6	39	1.9 (1.4, 2.6)	21	4.9 (2.7, 7.5)	2.5 (1.3, 4.5)	12	9.4 (4.6, 15.5)	4.9 (2.3, 9.1)
≥7	29	1.4 (1.0, 2.0)	16	3.7 (1.9, 6.1)	2.6 (1.2, 5)	9	7.0 (2.8, 12.7)	4.9 (1.8, 10.2)

SGA, small for gestational age.

RR, relative risk in SGA twins (twins / singleton

Table 3: Diagnostic odds ratios for prediction of length of stay in singletons and twins by SGA classified using singleton and twin charts.

Length of stay (days)	Singletons		Twins	
	Singleton chart	Twin chart	Singleton chart	Twin chart
1	1.46 (1.25, 1.69)	2.84 (2.25, 3.58)	1.95 (1.20, 3.15)	2.59 (1.42, 4.43)
2	1.52 (1.29, 1.78)	3.03 (2.38, 3.85)	2.53 (1.42, 4.57)	2.99 (1.50, 5.47)
3	1.5 (1.24, 1.81)	2.59 (1.93, 3.48)	2.83 (1.50, 5.67)	3.95 (1.94, 7.56)
4	1.61 (1.28, 2.03)	2.69 (1.88, 3.83)	2.92 (1.37, 6.94)	4.75 (2.18, 9.82)
5	1.59 (1.21, 2.11)	3.13 (2.11, 4.65)	2.79 (1.30, 6.68)	4.94 (2.25, 10.33)
6	1.65 (1.18, 2.3)	2.92 (1.79, 4.77)	3.04 (1.30, 8.32)	4.98 (2.13, 10.81)
≥7	1.88 (1.27, 2.77)	2.83 (1.55, 5.16)	2.29 (0.91, 6.43)	4.03 (1.42, 9.77)



Proportion of babies (%)
Days in neonatal intensive care unit
Risk ratio (twin / singleton)
Days in neonatal intensive care unit
Proportion of babies (%)
Days in neonatal intensive care unit
Risk ratio (twin / singleton)
Days in neonatal intensive care unit

FIGURE 1

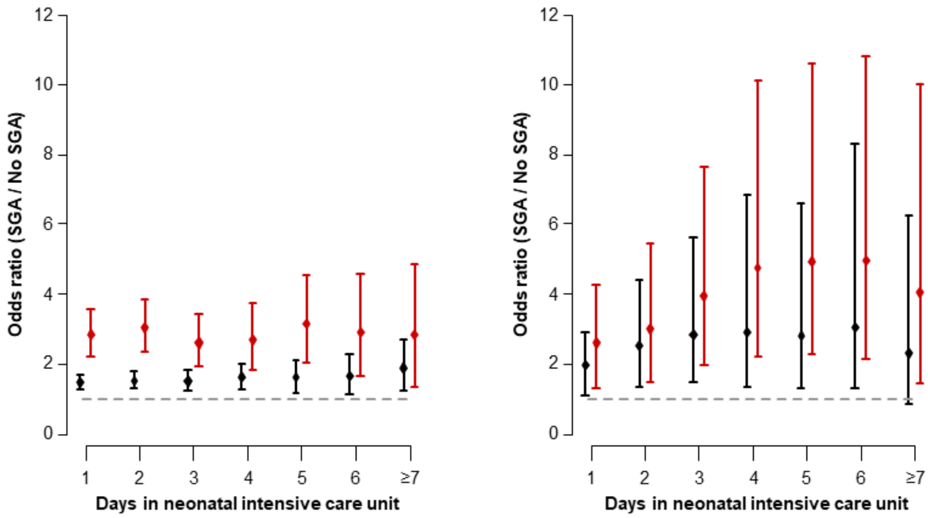

Odds ratio (SGA / No SGA)
12
10
8
6
4
2
0
1
2
3
4
5
6
≥7
Days in neonatal intensive care unit
Odds ratio (SGA / No SGA)
12
10
8
6
4
2
0
1
2
3
4
5
6
≥7
Days in neonatal intensive care unit

FIGURE 2