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Birth Weight Reference Percentiles by Gestational Age for Turkish Twin Neonates

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What is already known on this topic?

- *Birth weight references for twins have been constructed and updated in many countries. However, Turkey still lacks these references for twin neonates.*

What this study adds on this topic?

- *We created gestational age-specific birth weight references for female and male Turkish twins.*

ABSTRACT

Aims: In clinical practice, birth weight reference percentiles for singletons are used to evaluate twin births. The utilization of singleton reference percentiles for twins is not appropriate as they experience different growth trajectories. However, Turkey still lacks such references. Our aim was to create gestational age-specific birth weight references for female and male Turkish twins.

Materials and Methods: This is a hospital-based, multi-centered, retrospective study. In total, 2544 live-born twins between 2010 and 2019 were included in the study. Gestational age, birth weight, mode of delivery, gender, birth order, chorionicity, maternal age, pregnancy resulting from assisted reproduction techniques, APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score at 5 minutes, admission to the neonatal intensive care unit (NICU), length of stay in NICU, and death during the NICU stay were recorded.

Results: Smoothed reference curves for birth weight by gestational age and separate tables for female and male twin neonates for the 3rd, 10th, 50th, 90th, and 97th percentiles from 26 to 39 weeks of gestational age were constructed. Overall neonatal and infant mortality rates during NICU stay in our twin cohort were 12/1000 and 16/1000, respectively.

Conclusion: Twin-specific birth weight nomograms could be helpful as a reference for clinicians to identify high-risk neonates and fetuses who need specialized care. However, further studies with larger series are urgently needed for validation and use of these nomograms in clinical practice.

Keywords: twin, birth weight, percentile, reference, neonate.

INTRODUCTION

Twin births comprise 2-4% of all births worldwide.[1-3] Twin pregnancies are more prone to perinatal and neonatal mortality than singletons, which can be mainly attributed to the high proportion of preterm delivery, being small for gestational age (SGA), low birth weight, and intrauterine growth restriction (IUGR).[4-6]

Birth weight remains the most commonly used indication of fetal growth.[7] Currently, in clinical practice, birth weight reference percentiles for singletons are used to evaluate twin births. However, it is reported that the use of singleton reference percentiles on twins is not appropriate as twins experience different growth trajectories than singletons.[8] Twins' intrauterine growth pattern diverges from that of singletons in the third trimester and further varies across racial groups.[6,9-11] Therefore, the correct classification of twin birth weights as

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appropriate for gestational age (AGA), SGA, and large for gestational age (LGA) by using the right references is very important for a more accurate risk prediction and more effective postnatal health care.

Until now, birth weight references for twin neonates have been constructed and updated for many countries.[12-16] However, Turkey still lacks such references, and singletons' birth weight nomograms are used to assess the birth weights of Turkish twin neonates. In this study, we aimed to create up-to-date, gestational age-specific birth weight references for female and male Turkish twins.

MATERIALS AND METHODS

All medical records of twin births between January 2010 and December 2019 from 5 referral hospitals in Istanbul, Turkey, were retrospectively reviewed.

Subjects

The data for twin pregnancies were paired, so our database contained information about both twins of each delivery. Turkish live-born twins, with a gestational age equal to, or more than, 23 weeks, with documented birth weights and genders, were included into the study. The gestational week was determined by first trimester ultrasonography, last menstrual period, or best obstetric estimate (a combination of clinical and ultrasonographic estimates). Birth weights were measured and recorded by a midwife or nurse trained on standardized anthropometric measurements within 1 hour after birth. Neonates of foreign origin, neonates with congenital anomalies, and stillbirths were excluded from the study. Inclusion of only live twins (exclusion of stillbirths) to the study was justified by the fact that the birth weight measured at death is known to be inaccurate.[17] Lastly, we excluded extreme birth weight outliers from the sample.

The database included gestational age, birth weight, mode of delivery, gender, birth order, chorionicity, maternal age, pregnancy resulting from assisted reproduction techniques, APGAR score at 5 minutes, admission to the neonatal intensive care unit (NICU), length of stay in NICU, and death during the NICU stay.

The Research Ethics Committee of Koc University Medical Faculty approved the study protocol (2018.243.IRB2.041) and informed consent was obtained in accordance with the Declaration of Helsinki.

Statistical Analysis

The fractions of gestational weeks were computed to the nearest week, with fractions of $\leq$ 4 days and $\geq$ 5 days assigned to the lower and higher weeks, respectively. The IBM Statistical Package for the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analyses. The variables were analyzed using visual and analytical methods to evaluate whether or not they were normally distributed. Non-normally distributed variables were presented as medians (25-75%) and categorical variables were presented as percentages. Non-parametric variables were compared by the Mann–Whitney *U*-test. Mortality rates between 2 groups (AGA vs. SGA and AGA vs. LGA) were compared by χ^2test. A *P* value < .05 was considered statistically significant.

Birth weight discordance was calculated by subtracting the weight of the smaller twin from the larger twin and dividing by that of the larger twin.

Birth weight nomograms by gestational age for twins were created by regression analysis. Gestational age-related reference intervals were obtained by modeling the mean and the standard deviation (SD) for birth weight as a function of gestational age (Royston–Wright method).[18] We used Stata®software Version 13 (Stata Corp, College Station, TX, USA) for the analyses. Separately for each gender, by using the Stata® xrigls function, the appropriate powers for the fractional polynomials to model the mean and SD were determined from the data, where the best model (fractional polynomial, constant, and linear fits) for both mean and SD was chosen.[19]

We then constructed separate tables for female and male twin neonates for the 3rd, 10th, 50th, 90th, and 97th percentiles from 26 to 39 weeks of gestational age. It is reported that 300 subjects or more are adequate to establish reliable limits.[19,20]

Birth weight data of singletons from the same database between 2010 and 2019 were used as reference for this study. Since our singleton data were limited in number, 288 Turkish, live-born singleton neonates between 26-39 weeks could be included. We plotted the median 50th percentile values of birth weights by gestational age for twins and singletons. Median test was used to estimate the significance of differences between the 50th percentile values.

RESULTS

A total of 2544 live-born twin neonates (1272 records of twin pregnancies) with a male/female ratio of 0.91 were included. Demographic characteristics of the study subjects are presented in Tables 1 and 2. Male twins, twins delivered by Cesarean section (C/S), first-born twins, and dichorionic twins were found to have heavier birth weights. Female twins, twins delivered by C/S, and dichorionic twins had longer median gestational ages.

Twin Birth Weight Reference Percentiles

Figure 1 presents smoothed reference curves for birth weight by gestational age for female and male live-born twins. The curve fitting for birth weight (BW) as a function of gestational age (GA) for mean and standard deviation, modeled through the coefficient of variation that is the preferred method for data where the standard deviation increases by increasing mean, produced the following regression equations (CV denotes coefficient of variation, i.e., SD divided by the mean):

$$BW_{girls} = 12650.83 + \frac{58815.63}{\left(\frac{GA}{10}\right)^2} - \frac{53361.09}{\frac{GA}{10}};$$

$$CV_{girls} : 0.369889 - 0.006325 \times GA$$

$$BW_{boys} = 8648.53 + \frac{26090.67}{\left(\frac{GA}{10}\right)^2} - \frac{82635.04}{\left(\frac{GA}{10}\right)^2} \times \ln\frac{GA}{10};$$

$$CV_{boys} : 0.267201 - 0.003618 \times GA$$

Table 1. Maternal and Neonatal Characteristics of Live-Born Twins, Turkey, 2010-2019

Characteristics	*n* (%)
Total of twin births	2544
Maternal age (years)	
<20	36 (1.4)
20-34	1671 (65.7)
≥35 (advanced maternal age)	837 (32.9)
Infertility treatment	997 (40.2)
Gestational age (weeks)	
23-27	80 (3.1)
28-31	306 (12)
32-36	1458 (57.3)
37-41	700 (27.5)
Birth weight (g)	
<1000	88 (3.5)
1000-1499	215 (8.5)
1500-2499	1304 (51.3)
>2500	937 (36.8)
Birth weight discordance (>18%)	291 (22.8)
APGAR score at 5 minutes	
0-3	13 (0.5)
4-6	89 (3.6)
7-10	2344 (95.8)
Admission to NICU	1303 (51.2)
Lenght of stay in NICU (days)	
Less than 1 day	30 (2.3)
1	80 (6.1)
2	70 (5.3)
3	60 (4.6)
4	38 (2.9)
5	62 (4.7)
6	55 (4.2)
7-13	333 (25.5)
14-20	200 (15.3)
21-27	99 (7.5)
28 days or more	276 (21.1)
Neonatal mortality	31 (12/1000)
Early (0-7 days)	23 (9/1000)
Late (7-28 days)	8 (3/1000)
Infant mortality during NICU stay	41 (16/1000)

NICU, neonatal intensive care unit.

The values of cutoffs for the 3rd, 10th, 50th, 90th, and 97th BW percentiles by GA between 26 and 39 weeks for female and male twins are shown in Table 3. The median BW of male twins was higher than that of female twins at all GAs except at 26 weeks of gestation.

Twin Versus Singleton Birth Weight Reference Percentiles

The comparison of the median 50th percentile values of BW by GA between twins and singletons is shown in Figure 2. The median 50th percentile values were similar between 26 and 34 weeks. Beginning from 35 weeks (P = .041), a trend of a significantly lower average BW for twins was observed. The maximum difference of BW between singletons and twins was 870 grams at 39 weeks.

Table 2. Birth Weight and Gestational Age of Live-Born Twins According to Variables, Turkey, 2010-2019

Variables	*n* (%)	Birth Weight (g)	Gestational Age (weeks)
Gender			
Male twin	1213 (47.7)	2370 [1900-2717]*	35.5 [33.1-37]¥
Female twin	1331 (52.3)	2273 [1880-2590]*	35.8 [33.7-37]¥
Mode of delivery			
Cesarean section	2331 (91.6)	2330 [1910-2650]δ	35.8 [33.7-37]†
Vaginal	213 (8.4)	2155 [1400-2537]δ	33.8 [30-36.7]†
Birth order			
First	1272 (50)	2360 [1928-2680]ɣ	-
Second	1272 (50)	2280 [1840-2612]ɣ	-
Chorionicity			
Monochorionic	150 (6.9)	2195 [1845-2471]§	35.2 [33.1-36.7]¶
Dichorionic	2031 (93.1)	2430 [2040-2710]§	36 [34.2-37]¶
Preterm birth (<37 weeks)			
Yes	1844 (72.5)	2145 [1720-2490]a	34.8 [32.4-36]c
No	700 (27.5)	2670 [2460-2903]a	37.4 [37-38]c
Low birth weight (<2500 g)			
Yes	1607 (63.2)	2020 [1650-2280]e	34.2 [32-36]l
No	937 (36.8)	2750 [2610-2920]e	37 [36-37.4]l

*P < .001; ¥P = .044; δP < .001; †P < .001; ɣP = .01; §P < .001; ¶P = .004; aP < .001; cP < .001; eP < .001; lP < .001.

Twin Mortality

Overall neonatal and infant mortality rates during NICU stay in our twin cohort were 12/1000 and 16/1000, respectively (Table 1). Most of the neonatal deaths occurred in the first week of life. Finally, we analyzed the neonatal and infant mortality in twins categorized by current reference percentiles (Table 4). Both neonatal and infant mortality rates were found to be higher in SGA twins when compared to AGA twins. SGA twins showed nearly seven-fold greater mortality rate than AGA twins. However, AGA and LGA twins had similar neonatal and infant mortality rates.

DISCUSSION

This paper presents gender-specific twin BW percentiles between GAs of 26 and 39 weeks, based on multi-centered hospital data in Istanbul, Turkey between 2010 and 2019. To our knowledge, this is the first study providing BW reference percentiles by GA for Turkish twin neonates.

Similar to other studies, we found that growth in twins differs from growth in singletons (Figure 2).[21-23] The GA at which twin and singleton growth curves start to diverge ranges from

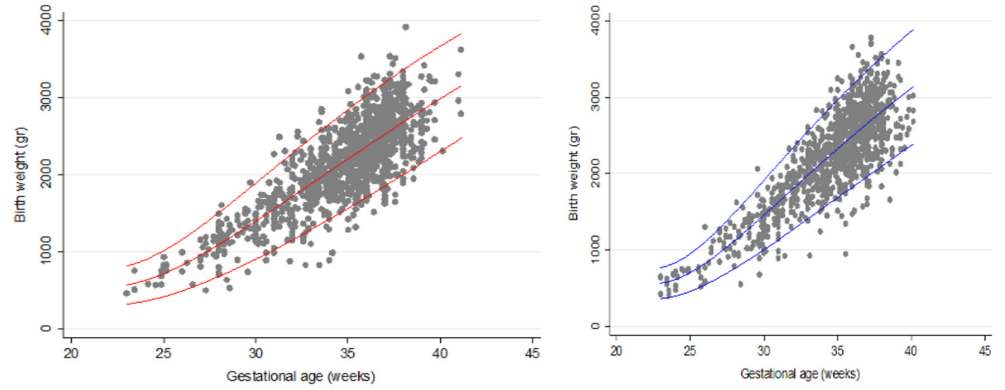

Figure 1. Birth weight nomograms by gestational age for female (left) and male (right) live-born twins Turkey, 2010-2019. Lines correspond to 3rd, 50th, and 97th percentiles.

Table 3. Birth Weight Percentiles by Gestational Age for Female and Male Live-Born Twins, Turkey, 2010-2019

Gestational Age (weeks)	Percentiles (Females)					Percentiles (Males)				
	3	10	50	90	97	3	10	50	90	97
26	509	609	827	1045	1147	558	644	827	1011	1097
27	597	711	955	1199	1313	660	758	968	1178	1277
28	698	824	1095	1365	1492	773	885	1124	1362	1474
29	807	946	1244	1541	1680	896	1021	1289	1557	1682
30	925	1076	1398	1721	1872	1025	1163	1460	1757	1895
31	1048	1210	1557	1904	2067	1158	1310	1634	1959	2110
32	1177	1350	1719	2088	2260	1295	1459	1810	2160	2324
33	1311	1493	1881	2270	2452	1433	1609	1984	2360	2535
34	1449	1638	2044	2449	2639	1573	1759	2157	2555	2741
35	1589	1786	2206	2626	2822	1713	1908	2327	2746	2942
36	1733	1935	2366	2797	2999	1852	2057	2494	2931	3135
37	1879	2085	2525	2964	3170	1991	2203	2657	3110	3322
38	2028	2236	2681	3126	3334	2129	2348	2815	3283	3501
39	2178	2387	2835	3283	3492	2266	2490	2969	3449	3673

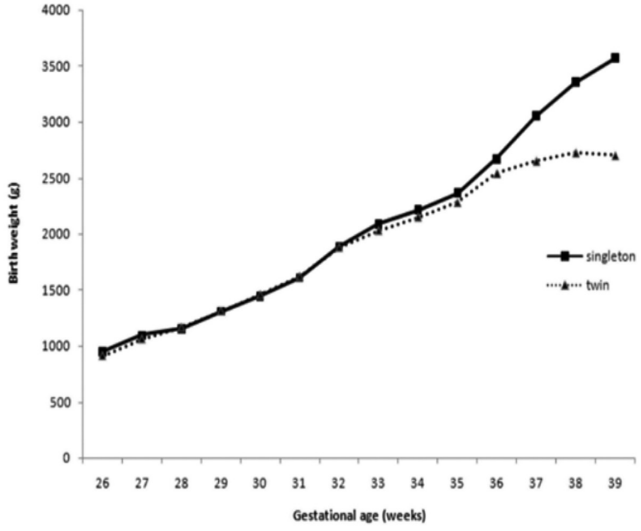

Figure 2. Comparison of the 50th percentiles of BW by gestational age for twins (dashed line) and singletons (continuous line).

Table 4. Neonatal Mortality and Infant Mortality During NICU Stay by Reference Birth Weight Percentiles for Gestational Age in Twins

	AGA, *n* (‰)	SGA, *n* (‰)	LGA, *n* (‰)	*P*
Number of twins (*n*: 2500)	1959	208	333	
Neonatal mortality	15 (8)[*†]	11 (53)[*]	5 (15)[†]	[*]*P* < .01; [†]*P*: NS
Infant mortality	21 (11)[δ¶]	15 (72)[δ]	5 (15)[¶]	*P* < .01; [¶]*P*: NS

Mortality rate was defined as the number of deaths per 1000 live births. NICU, neonatal intensive care unit; AGA, appropriate for gestational age; SGA, small for gestational age; LGA, large for gestational age.

24 weeks to 36 weeks of gestation.[6,9,12,24] In our sample, the 50th percentiles of growth curves for twins and singletons remained similar until 35 weeks of gestation and started to differ thereafter. The 50th percentile for twins peaked early at about 38 weeks and then declined. It was reported that the discrepancy of BW for singletons and twins after a certain gestational week might be a reflection of placental insufficiency and/or intrauterine constraint, which further resulted in accelerated growth.[25] However, Hiersch et al.[26] reported that the slower growth of twins during the third trimester may reflect a state of relative growth restriction that is not related to placental insufficiency. Moreover, in ewes, both placental weight and fetal body weight in late gestation in twins reduced to singletons at early gestation were lower than naturally conceived singletons, suggesting that placental size and fetal growth may be predetermined, partly, by processes in early gestation.[27,28] There might be different mechanisms of intrauterine growth for twins and singletons. Therefore, it could be better to use twin-specific growth curves for monitoring of growth in this population.

In this study, the sample size is based on the hospital data with 1272 twin pairs and is smaller than that of population-based twin studies performed in other countries. It is known that hospital-based data also includes high-risk twins.[16] Therefore, the present data might not reflect the general characteristics of the twin population. This was a limitation of our study. However, especially for low GAs, quality of hospital-based data is higher. It is reported that BW nomograms should be updated every 10 years due to the secular trend.[15] Updating the charts will identify changes in BW distributions of twins over time and will determine whether the shift to higher BW seen among singleton infants has also occurred for twins.[14] In our study, birth years were distributed roughly over 10 years, between 2010 and 2019.

In all 5 referral hospitals included in the study, all measurements of BW for twin neonates were performed by trained nurses. Due to the retrospective nature of the study, the midwives or nurses did not have any specific education such as Intergrowth 21st course for a standardized measurement.

Our twin data was collected from only 5 referral hospitals in Istanbul and the rate of twin pregnancies conceived through assisted reproduction technologies was found to be 40.2%. Three of these referral hospitals were also in vitro fertilization centers. This could explain the high infertility treatment rate seen in our series. Therefore, as a limitation, the data herein could not reflect the whole population of twin births in our country.

Sezer et al.[29] reviewed 18 studies conducted in Turkey on twin pregnancies between 1991 and 2010. In that study, the neonatal mortality rate in twins was reported as 40-98/1000. A decade later, in our study, it was 12/1000, exhibiting a remarkably decreasing trend. Recent improvements in antenatal and postnatal care in Turkey might explain this rapid decline in mortality rates seen in twin neonates.

Mendez-Figuera et al.[30] demonstrated that use of twin-specific references is less likely to categorize twins as SGA and more likely to identify those at risk for adverse outcomes. Also, in that study, an increased rate of LGA among twins was observed. However, as reported in other studies, unlike LGA singletons, LGA twins did not have an increased rate of adverse outcomes.[15,31] In our cohort, rates of SGA, LGA, and AGA among twins were 8.4, 13.4, and 79.3%, respectively. Neonatal mortality rate was found to be dramatically increased in SGA twins when compared to AGA ones (53/1000 vs. 8/1000, *P* < .001). However, LGA twins had similar neonatal mortality rate compared to AGA ones (15/1000 vs. 8/1000, *P*: NS). In a Chinese population-based twin BW percentile study, neonatal mortality rates for SGA, LGA, and AGA twins were reported as 33.1/1000, 9.5/1000 and 10.4/1000, respectively.[32] The high mortality rates seen in SGA twins are quite alarming. Therefore, it could be better to use twin-specific BW nomograms to properly classify "real" SGA twins who need more intensive and specialized care.

Reduction in expected fetal growth pattern was observed in intrauterine growth restriction.[33] Unfortunately, due to both the retrospective nature of the study and lack of perinatal follow-up data about estimated fetal weight, the estimated fetal growth discordance and umbilical artery pulsatility index of the smaller twin, the rate of IUGR could not be presented in this study. Also, we could not collect the birth length data of the twins to calculate Ponderal Index (100 × birth weight(g)/birth length $(cm)^3$) for evaluation of IUGR postnatally. These were the other limitations of our study. Further anthropometric studies are needed to establish birth length and head circumference reference percentiles in Turkish twin neonates.

CONCLUSION

This is the first study to present BW percentiles by GA for contemporary Turkish twins, based on 10-year, multi-centered hospital data. Twin-specific BW nomograms could be helpful as a reference for clinicians to identify high-risk neonates and fetuses who need specialized care. However, further studies with larger series are urgently needed for validation and use of these nomograms in clinical practice.

TAKE-HOME MESSAGES

Twins have a different intrauterine growth pattern than singletons. Therefore, for neonatologists and pediatricians, it would be better to use twin-specific BW nomograms to accurately classify twin neonates as AGA, SGA, and LGA in clinical practice.

Ethical Committee Approval: Ethical committee aproval was received from the Koç University School of Medicine (2018.243.IRB2.041).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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