Review paper (After Acceptance of EiC)

Outcome-dependent twin growth curves for the bigger and smaller neonate within a Polish population – The best clinical support.

Keywords
pregnant woman, fetus, intrauterine growth restriction, intrauterine growth curve, percentile, obstetric ultrasound, the twins, a woman

Abstract
We searched for the best clinical support for daily practice with twin pregnancies. This retrospective study aim was to determine fetal growth standards separately for the bigger and smaller twin based on the group of potentially healthy neonates.
Data of the live-born twin neonates born between the 25th and 40th week of gestation were collected. When comparing 50th percentiles for the same gestational period between bigger and smaller twins, the split is always close to 240 grams. The biggest split of the growth curves appears between weeks 31–35. The minimum weight gain for both twins was shown to be similar with ≥120g at weeks 27–24, and ≥140 at weeks 34–37. As compared, the medium fetal mass for summarized 50th centiles of the bigger vs smaller neonates were 2019.5g vs 1858.8g.
Twin growth curves, especially for the bigger and smaller baby should be mandatory for daily clinical use.

Explanation letter
Manuscript AMS – 13848-2021-01
Response to the Reviewers

Dear Prof. Banach
Thank you for giving us the opportunity to submit a revised draft of the manuscript "Outcome-dependent twin growth curves for the bigger and smaller neonate within a Polish population – The best clinical support" for publication in the Archives of Medical Science. We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper. We have incorporated most of the suggestions made by the reviewers. Those changes are highlighted within the manuscript. Please see below, in red, for a point-by-point response to the reviewers' comments and concerns.
Reviewers' Comments to the Authors: Reviewer 1
Thank you for appreciating the large group of patients on whom the research was conducted. According to the suggestion of the reviewer, we have outlined the summary of fetal weight in the results section. We have summarized the mean fetal masses for the 50th centiles in the group of the bigger neonates, small neonates, the boys and girls and presented the results in the result section. This change led to interesting results which led to the creation of another table (table 5). We have also indicated the sample size in lowest and highest percentiles. We have specified the weighing equipment in the method section. We have moved some of the most valuable data from the discussion section in the result section. The review has enriched the study so much, highlighting the real value customized curves.
Reviewers' Comments to the Authors: Reviewer 2
Thank you!
Reviewers' Comments to the Authors: Reviewer 3
Thank you for pointing out the aspect of comparing different races. As suggested by the reviewer, in the discussion section we have added references, results of other study from country which represent Caucasian race as well as two interesting studies from India and China.

Reviewers' Comments to the Authors: Reviewer 4
Thank you for pointing this out. We have attached Figure 2 since it was not seen by the reviewer. We also mention the importance of Doppler examination in diagnosing of FGR, presenting three studies which in detail present the criteria and follow up.
Reviewers' Comments to the Authors: Reviewer 5
Thank you!
Reviewers' Comments to the Authors: Reviewer 6
As suggested by the reviewer, we have changed the abstract according to the journal writing rules. We have added up to date informations to the introduction sections by adding new publications on the topic, improving the result section, emphasizing the importance of such study and stating the aim of the study and the end of introduction section.
In the method section we have underlined that this is a retrospective study and added content to make it more detailed. We have also removed a sentence from the method section according to the reviewer suggestions.
We have rewrite and enriched the discussion according to the reviewer suggestions. We have added new literature which gave opportunity to compare the results with others.

Thank you very much for insightful review and suggestions that allowed us to expand and enrich the paper.

Response to the Reviewers AMS.docx

Outcome-dependent twin growth curves for the bigger and smaller neonate within a Polish population – The best clinical support.

Keywords: intrauterine growth curve, intrauterine growth restriction, pregnant woman, percentile, fetus, obstetric ultrasound, the twins, a woman

Abstract

Introduction. We searched for the best clinical support for daily practice with twin pregnancies. This retrospective study aim was to determine fetal growth standards separately for the bigger and smaller twin based on the group of potentially healthy neonates.
Materials and methods. Data of the live-born twin neonates born between the 25th and 40th week of gestation were collected. Only data of the babies with a "good" neonatal status and without detectable serious congenital anomalies were included. The final sample included 2634 neonates. We analyzed the differences between curves.
Results. When comparing 50th percentiles for the same gestational period between bigger and smaller twins, the split is always close to 240 grams. The biggest split of the growth curves appears between weeks 31–35. The minimum weight gain for both twins was shown to be similar with ≥120g at weeks 27–24, and ≥140 at weeks 34–37. As compared, the medium fetal mass for summarized 50th centiles of the bigger vs smaller neonates were 2019.5g vs 1858.8g. While the same comparison for boys vs girls was 1964.1g vs 1908g, respectively.
Conclusions. Creation of the separate curves for the bigger and smaller baby seems much more clinically important than standards based on the other factors such as fetal sex or chorionicity. Twin growth curves, especially for the bigger and smaller baby should be mandatory for daily clinical use.

Introduction

It is common practice to assess the growth of twins *in utero* using the fetal growth standard for the assessment of singleton pregnancies. Whilst twin and singleton fetuses may follow a similar growth pattern during the first and second trimester (1,2), customized or adjusted fetal weight standards have been shown to be more accurate (3,4,5). Further, it is mandatory to create separate, customized curves for varying populations that take into account differences between twins and singletons, racial/ethnic spread as well as the large influence of the methodology applied to standard construction. Moreover, every 2–3 decades these standards should be made *de novo*, according to the current changes in living standards and habits of a specific population (6). Except for specific pathologies observed in twin pregnancies i.e., twin-to-twin transfusion syndrome (TTTS), anemia-polycythemia sequence (TAPS), or twin reversed arterial perfusion (TRAP), the surveillance of both singletons and twins is generally similar (7). Importantly, sonographic examinations of singletons, dichorionic, and monochorionic twins are completely different. Whilst limited, this difference can introduce a risk of misdiagnosis of developmental or growth defects of the fetus or fetuses. Additionally, the number of amnions is crucial for fetal monitoring frequency. However, by doing the scan, in absence of specific pathologies, the potential presence of malformations and signs of abnormal fetal growth is always assessed. In the case of fetal growth restriction, both for twins and singletons, further surveillance has been described in many studies or published recommendations like the PORTO Study, Delfi procedure on FGR, or Gratacos et al. (2007) (8,9,10). It is important to be conscious of the different growth curves in twins, even if twins are generally not listed between risk factors for small for gestational age/fetal growth restriction (SGA/FGR) (11,12). Despite data that shows that majority of infants born below the 10th percentile are not at risk for adverse outcomes (13), the endangered group should be defined as accurately as possible. Development of the new measurement methods does not cause substantial progress (13). For twins with different growth potentials, the 10th percentile is probably distinct for each fetus. The 10th percentile of one twin may be 3rd for the other. According to PORTO Study where the authors sonographically estimated fetal weight (EFW), fetuses whose weight fell below the 3rd percentile were consistently associated with adverse outcomes. All mortalities observed in that study had an EFW< the 3rd percentile (8). Regardless of the methods used, the correct estimation of the pregnancy age and fetal mass of the baby/babies is crucial. In this retrospective study, we report two outcome-dependent growth curves and birth weight standards for smaller and bigger Polish twins. The main goal was to find out the best tool for the daily clinical practice with twin pregnancies, thus trying to reduce the number of unnecessary interventions.

Materials and methods

The data used in the current study were retrieved from the database of a tertiary care woman hospital in western Poland. The study cohort was comprised of patients that delivered twin pregnancies between 1st of January 2005 and 31st March 2018. Both the patients, that electively chose our center as first-line care as well as the patients that transferred from other hospitals, including primary and secondary care, were included in the study (2). The database included: date of birth, gestational age (completed weeks of pregnancy), sex, birth weight (rounded to 10 grams; measured with OHIO neonatal stations), mother's parity and age, mode of delivery, and Apgar scores at 1, 3, 5, and 10 minutes. The database did not include information on chronicity, pre- and post-natal care (except serious congenital malformations), maternal health condition, or whether the pregnancy resulted from assisted reproduction techniques. The gestational age was based on the last menstrual period (LMP) and was confirmed via ultrasound examination at the first trimester of pregnancy. The weight of the fetus was determined by trained personnel using an electronic scale.

Inclusion criteria for the study were as follows:

i. Twin pregnancies born at least in 23rd gestational week without regard to the way of delivery (natural vs. c-section)
ii. No known congenital anomalies
iii. The inclusion of only live twins in the study was justified by the fact that the birth weight measured at death is known to be inaccurate (2).

Because this study was intended to be outcome-dependent and the database did not yield any information about the post-natal course, all neonates that might have had a high risk of an unfavorable outcome had to be identified.

Thus, the following exclusion criteria were as follows:

i. A birth weight discordance greater than 18% (14,15).
ii. An Apgar scored in the 1st minute less than 7 or deteriorating in consecutive measurements (16,17).
iii. Extreme outliers were identified and excluded from the sample set. Because fetal mass within each gestational age did not have a normal distribution, we chose to identify the outliers without any method referring to a standard deviation. Further, as all the data were acquired by trained personnel and after applying all criteria, we decided to remove only extreme outliers within each gestational week. All fetuses within a gestational week that had a mass below the 3rd or above the 97th percentile were identified as extreme outliers and were removed. This accounted for 0.5% of the cases.
iv. All records with missing data of any of the twins, as well as all the twin data that met exclusion criteria were removed from the study. The removal of the data from the database was done in pairs, so if any information about one of the twins was missing or if at least one of the twins did not qualify for the study, the corresponding record related to the other twin from the same delivery was also removed.

After applying the above criteria, 591 out of 1908 paired records were excluded. The final sample was comprised of 1317 records of twin pregnancies referring to 2634 children. These 2634 children were used to generate size-dependent growth curves for the twin fetuses. Growth curves of singletons from the same database were used as a reference for this study. The same inclusion and exclusion criteria except for birth weight discordance were applied for the singletons. There were 42182 cases of which 3995 were excluded, creating a final sample of 38197 singleton cases.

All the statistical analyses were conducted as in previous studies (2,6). The Shaphiro-Wilk test revealed a non-normal distribution weight and sex with regard to the week of gestation in twins. To alleviate this, we used the Generalized Additive Model for Location Scale and Shape (GAMLSS) which has been applied for data that has lost normality, for example when the distributions are skewed or curtotic. This non-linear model was used to create growth curves by the WHO (18,19). Prior to using GAMLSS, the distribution and smoothing method for the tested groups were applied by fitting all relevant distributions and choosing the one, which fitted the best. Correctness was checked by visual inspection of theoretical and calculated percentiles as well as worm plots with regard to gestational age. The percentile curves were calculated in the same manner for both the twin and the singleton sample sets. To compare the mean data for bigger and smaller twin as well as boys or girls we created theoretical fetuses for each week on the basis of all neonates born between 45th and 55th centile. Creating in the same manner individual groups, we compared them with Mann-Whitney U-test. All the calculations were performed in Microsoft Windows, with GAMLSS package ver. 5.0-6 for R ver. 3.4.3 in RStudio ver. 1.1.419 framework.

Results

Twins born between the 25th and 40th week of gestation were included in this study. Subsequently, the final study sample had 1317 records of twin pregnancies (resulting in 2634 children). Several cases across each gestational age as well as a histogram of the group relating to the sex of the babies were previously presented (2). Centile curves separately for the bigger and smaller twin as well as for the boys and girls were presented in Figures 1 and 2, respectively. Percentiles of the fetal birth weight with regard to the week of gestation for the bigger twin and smaller twin were presented in Tables 1 and 2, for the girls and boys in Tables 3 and 4, respectively.

We summarized the mean fetal masses for the 50th centiles in the group of the bigger neonates, smaller neonates, the boys and girls, irrespective of the possibility of the statistical correctness. The mean mass was 2019.5 for the bigger baby, 1858.8 for the smaller one, and 1964.1 and 1908 for the boys and girls, respectively.

The sample size for the 5th centile vs. 95th centile for the bigger baby were 65 vs. 64, respectively. As compared separately for the boys and girls the 5th centile samples were 83 and 57, and for the 95th centile 73 and 67, respectively.

Our study has shown that a weight gain equal to or higher than 120 g at weeks 27-34 and 140 g between weeks 34-37 is a good predictor of a favorable outcome.

As compared the hypothetical fetal mean masses of boys vs. girls, bigger twin vs. smaller twin as well as the boys, or girls, or bigger, or smaller twin vs. mean value of the whole group we acquired statistical differences in all analyzed group. The p-values are presented in table 5. The highest statistical power was found between the bigger and smaller twins, and both for the bigger vs. mean values and smaller vs. mean values, where for the weeks 34-37 the p-value has at least 15 zeros after the decimal point.

Discussion

Commonly used diagnostic processes for the surveillance of twins *in utero* should be supported by accurate and clinically relevant growth curves. Further, it is commonplace for the growth curves constructed from singleton pregnancies to be applied to twin pregnancies. The use of such curves may introduce misinformation that can lead to incorrect diagnoses. This results in excessive cesarean sections and iatrogenic prematurity. In this study, we aimed to fill this knowledge gap using data from Polish patients pregnant with twins. Our database was constructed using potentially healthy neonates who were also premature. Neonates, which were born with diagnosed pathologies or developmental defects, were excluded. Similarly, only paired twins, with an absence of detectable pathology or developmental defects, were taken into consideration. Moreover, extreme outliers, where the fetal mass difference was over 18%, were excluded (2,6). These strategies were implemented to augment the search for morphologically healthy neonates born before term. Current research confirms 18% discordance to be important criterion, while regardless of chorionicity, even twins without fetal growth restriction are nearly twice as likely to deliver earlier in gestation and experience greater neonatal morbidity (respiratory distress syndrome, NICU admissions) (20). Despite all these selection criteria, the difference in size between bigger and smaller neonates was significant enough to be a more valuable developmental marker than sex or chronicity. Comparing the last 4 weeks of gestation analyzed within our study group, the ratio for 50^{th} centiles for smaller-bigger twins is approximately 0.92. Crude centiles would differ more, however were not calculated. Poland, according to the Eurostat statistics, is the most racially uniform nation in Europe with Caucasians making up the majority (97%) of the population (21). Thus, for a Caucasian population, the size-dependent growth curves detailed in this study are appropriate when assessing the development of twins. However, for different racial/ethnic groups, the curves should be adjusted using Gardosi's proportionality notion (22), but with a shift to the 37^{th} week, as proposed by Zhang J, et al. (3). The data acquired in the last decades, confirm that the neonatal mass differs substantially between races and countries. Comparing our results with recent Chinese twin growth standards and growth curves for twins from Slovenia we find our 50^{th} centile for the smaller neonate very close to the whole group 50^{th} centile of the populations cited above (4,23). There are few possible causes. First of all, creation of the growth curves if frequently based on the serial (every 2-3 weeks) measurements of the same fetuses. If we multiply 100 fetuses by 10 ultrasound estimations, we acquire 1000 possible fetal masses (24). We may expect similar deviations between USG estimations and real fetal mass, multiplied by number of visits. We need to be aware of the rotation of the examining personnel either. Contrary, the neonatal mass is accurate when taken by trained person, just after birth. Moreover, inclusion criteria are often completely different, so the analyzed material cannot be compared. As an example, we may quote results obtained by Premkumar et al, on the population of south India (25). Comparing to our results the

50th centile of the smaller baby is definitely greater than 50th centile from Indian twins, regardless of chorionicity. The gap between centiles reach nearly 200 grams for most of the analyzed gestational weeks. We have to stress, that in their population they had 17% of women with preeclampsia. Here, we show that customized and based on the analyzed population curves are extremely important tool. Moreover, the sex of the fetus is less important relative to the size of the twin. For instance, between weeks 37-40 of gestation, the difference in weight observed in male and female neonates within the 50th percentile was 87, 77, 64, and 49 grams, respectively. In comparison, when assessing the changes in weight between the smaller and larger twin within 50th percentiles the weight change was approximately 240 grams. Regardless of the statistical correctness, we summarized all the neonatal masses for the bigger and smaller neonates as well as for the boys and girls and divided it by 16 analyzed weeks of delivery. This may indicate the extent of the differences. When analyzed the bigger and smaller babies the medium fetal masses were 2019.5g and 1858.8g, respectively. Much smaller difference was found between boys (1964,9g) and girls (1908g). The analysis of the statistical differences of the shift of the curves of the 50th centile is impossible, so to examine this, we created the subgroups covering the mean centiles (45-55) of the babies in each group. This comparison revealed huge differences between groups. We acquired confirmation of the highest significance for the creation of the separate growth curves for the bigger and smaller twin. The difference begins in week 28th, and for the weeks 34-37 the p-values reached the values with minimum 15 zeroes after the decimal point for. Thus, the observation of the fetal growth, using separate curves for the bigger and smaller fetus seems the most valuable, and we may recommend its application to be obligatory.

Interestingly, in a study that assessed 977 unselected twin pairs in which both fetuses were alive beyond week 24 of gestation, the authors found that perinatal mortality, individual morbidity, and composite perinatal morbidity increased with birth weight discordance (26). Morbidity and mortality exceeded 18% for dichorionic pairs (hazard ratio 2.2) and 18% for monochorionic twins without twin-to-twin transfusion syndrome (hazard ratio 2.6). However, a minimum two-fold increase in the risk of perinatal morbidity persisted even when both twin birth weights were appropriate for gestational age (5,26). This work supports our strategy to exclude the pair of fetuses that had weight discordance over 18%. Moreover, those authors recognized chorionicity as a less important diagnostic factor, except in serious, specific complications. Further within that study, material monochorionic twins were diagnosed in 19% and dichorionic in 81% of patients, respectively. It is worth emphasizing that even in a perfectly organized and supervised multicenter study, the percentage of the misdiagnosis of chorionicity was 1,7 (26). This supports our strategy for the construction of the most appropriate growth curves detailed in this study based on the separate curves for the bigger and smaller twin.

Comparing the size-specific outcome-dependent curves detailed in this study with general twin growth curves for the Polish population (2), important differences arise. Namely, within the 20-25 percentiles, the general twin curves are equal or similar to the 10th percentile of the smaller twin. Additionally, within the 10th percentile of the general twin population, the twin curve is close to the 5th percentile of the smaller twin, respectively. This observation is extremely important for clinical practice. Without the correct assessment of the growth of the fetus, based on the good, customized curves, the smaller twin may be erroneously diagnosed ill or iatrogenically premature. This risk is exacerbated using singleton fetus growth curves in the instances of twins.

In clinical practice, it is common to assess the week-to-week weight of both the smaller and bigger fetus. Our study has shown that a weight gain equal to or higher than 120 g at weeks 27-34 and 140 g between weeks 34-37 is a good predictor of a favorable outcome. Surely, the exclusion of the other pathologies in both twins is mandatory. An interesting observation from the current study shows that in the last weeks of the ongoing pregnancy, the weight gain, as observed in the 5^{th} and 10^{th} percentile relative to the 50^{th}, 90^{th}, and 95^{th} percentiles, is faster. This phenomenon was noted at week 36 of gestation for both the bigger and smaller twin. Probably, as in singletons hypotrophic fetuses tend to make up for the mass required during earlier delivery due to fetal growth restriction or other underlying pathologies (8). In some patients, an estimation of the real pregnancy week is not possible. Further, any subsequent adjustment is not accurate. Gestational age, as reported on the last menstrual period, must be confirmed by the first-trimester ultrasound examination. Clinical data indicates that 10.7% of the women may not indicate the first day of their last menstrual cycle, and that cause first trimester fetal sonographic measurements to show a difference of 2 weeks (3). However, by using separate size-dependent curves for twins, we may rely on the results of the last two estimations of the fetal mass. The spread of the centiles is important for the assessment of fetal growth restriction. The next steps, based on doppler examinations, are written in details in aforementioned studies presented by Unterscheider et al. Gordijn et al. or Gratacós et al. (8,9,10).

Despite the strengths of the size-specific outcome-dependent growth curves detailed in this study; it is important to be conscious of their limitations. Importantly, the lowest and the highest percentiles are always less numerous, so the statistical strength is poorer. In our study we summarized the 5^{th} and 95^{th} centiles for the bigger and smaller babies as well as the same centiles considering the sex of the neonates. The number did not differ substantially with minimum of 57 neonates and maximum of 83 neonates. Thus, we can accept the construction of our curves as appropriate. Additionally, the health and development of the neonates used in this study were only assessed in the first minutes after birth. Thus, the use of these curves does not correlate fetus growth to further developmental disturbances or less serious congenital anomalies, which may only be identified postpartum. However, by including only potentially healthy babies and using robust statistic methods to smooth kurtosis and skewness, we have attempted to mitigate these limitations as much as possible.

Together, these data indicate that, when customized for the proper population, separate growth curves for the bigger and smaller fetus are superior to previous clinical standards. Further, we have shown how the sex and chorionicity of the fetus are less important than their size. Moreover, the use of the growth curves detailed in this study allow for the robust assessment of fetal development independent of chorionicity and sex. Finally, separate cures for twins should be introduced as soon as possible for daily use.

Conclusions:

1. Creation of the separate curves for the bigger and smaller baby seems much more clinically important than standards based on the other factors as fetal sex or chorionicity.

2. Week-to-week weight gain equal to or higher than 120 g at weeks 27-34 and minimum 140 g between 34 and 37 weeks seems to be good predictor of favorable outcome in absence of the other pathologies for both twins.

Conflict of interest: The authors report no conflict of interest.

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Table 1: **Percentiles of fetal birth weight for the bigger twin vs. gestational age**.

percentile week of delivery	5	10	25	50	75	90	95
25	698	723	766	815	867	917	948
26	822	851	903	962	1025	1083	1119
27	946	980	1040	1110	1182	1248	1288
28	1073	1112	1179	1259	1341	1414	1457
29	1204	1247	1323	1413	1505	1584	1631
30	1339	1388	1473	1574	1677	1764	1814
31	1476	1531	1627	1743	1858	1954	2008
32	1612	1674	1784	1916	2047	2153	2212
33	1748	1818	1942	2093	2240	2357	2421
34	1881	1960	2100	2269	2433	2561	2629
35	2016	2102	2257	2445	2625	2761	2834
36	2159	2252	2417	2619	2809	2951	3026
37	2319	2413	2581	2787	2980	3122	3195
38	2494	2583	2747	2948	3136	3271	3340
39	2671	2756	2910	3103	3283	3411	3476
40	2845	2925	3071	3256	3428	3549	3609

Table 2: **Percentiles of fetal birth weight for the smaller twin vs. gestational age.**

percentile week of delivery	5	10	25	50	75	90	95
25	634	659	702	749	796	838	864
26	752	782	831	887	942	992	1022
27	868	903	961	1026	1090	1148	1183
28	986	1026	1093	1167	1241	1308	1348
29	1104	1150	1226	1311	1396	1473	1519
30	1221	1273	1361	1459	1557	1645	1697
31	1335	1395	1497	1610	1724	1825	1886
32	1446	1516	1634	1764	1895	2013	2083
33	1560	1640	1773	1921	2068	2201	2281
34	1682	1769	1915	2078	2240	2386	2474
35	1814	1907	2063	2235	2408	2564	2657
36	1961	2056	2216	2393	2571	2730	2826
37	2118	2214	2373	2551	2728	2887	2983
38	2284	2377	2534	2707	2881	3037	3131
39	2453	2544	2695	2863	3032	3183	3274
40	2621	2709	2856	3019	3182	3329	3416

Table 3: **Percentiles of fetal mass for male twins vs. gestational age.**

percentile week of delivery	5	10	25	50	75	90	95
25	689	715	755	797	842	892	927
26	806	836	885	937	992	1051	1091
27	921	957	1015	1077	1144	1212	1258
28	1039	1079	1147	1221	1300	1378	1428
29	1159	1205	1283	1371	1463	1550	1605
30	1284	1337	1426	1529	1635	1733	1793
31	1414	1473	1575	1695	1817	1925	1990
32	1546	1612	1728	1866	2005	2125	2194
33	1678	1752	1883	2039	2196	2326	2400
34	1810	1891	2036	2212	2385	2525	2601
35	1941	2029	2187	2382	2571	2718	2797
36	2070	2165	2336	2548	2752	2904	2985
37	2201	2300	2481	2708	2923	3080	3160
38	2334	2436	2625	2863	3087	3244	3323
39	2468	2572	2767	3015	3244	3402	3479
40	2602	2708	2908	3165	3400	3557	3633

Table 4: **Percentiles of fetal mass for female twins vs. gestational age.**

percentile week of delivery	5	10	25	50	75	90	95
25	623	653	704	761	818	869	900
26	745	780	839	905	971	1030	1066
27	866	906	974	1050	1125	1193	1234
28	988	1034	1111	1196	1282	1358	1404
29	1111	1163	1249	1345	1441	1527	1578
30	1234	1292	1389	1496	1604	1701	1759
31	1354	1420	1529	1651	1772	1882	1947
32	1472	1546	1670	1807	1945	2069	2143
33	1588	1672	1812	1967	2122	2261	2345
34	1708	1801	1956	2128	2300	2456	2548
35	1839	1939	2106	2291	2476	2643	2743
36	1993	2095	2266	2456	2646	2816	2919
37	2168	2268	2435	2621	2807	2974	3074
38	2362	2456	2612	2786	2960	3117	3211
39	2563	2649	2792	2951	3110	3254	3339
40	2763	2841	2971	3116	3261	3391	3469

Table 5: **Comparison of the medium percentiles (45-55) between boys, girls, bigger twin and smaller twin.**

Group / Week of delivery	Boys vs. MEAN	Girls vs. MEAN	Bigger twin vs. MEAN	Smaller twin vs. MEAN	Boys vs. Girls	Bigger twin vs. smaller twin
25	NS	NS	NS	NS	NS	NS
26	NS	NS	NS	NS	NS	NS
27	NS	NS	NS	NS	NS	NS
28	NS	NS	0.01	0.05	NS	0.05
29	NS	NS	0.01	0.01	NS	0.01
30	NS	NS	3-z3	4-z3	0.05	7-z3
31	NS	NS	3-z3	1-z3	NS	1-z2
32	NS	0.05	1-z5	2-z4	0.01	5-z6
33	NS	0.05	2-z7	2-z7	4-z3	2-z7
34	5-z6	0.01	2-z15	2-z14	3-z7	3-z15
35	4-z4	6-z7	1-z15	1-z15	1-z11	1-z15
36	9-z6	6-z5	1-z15	1-z15	2-z10	1-z15
37	0.001	1-z8	1-z15	1-z15	3-z11	1-z15
38	NS	2-z3	1-z11	1-z11	8-z4	3-z11
39	NS	NS	0.01	NS	NS	0.05
40	NED	NED	NED	NED	NED	NED

Legend: MEAN – the whole group, NED – not enough data, NS- not significant, p-value is expressed as $p<0.05$, $p<0.01$, $p<0.001$ or as a number of zeros that appear after the decimal point e.g. 1-z6 for 0.0000001

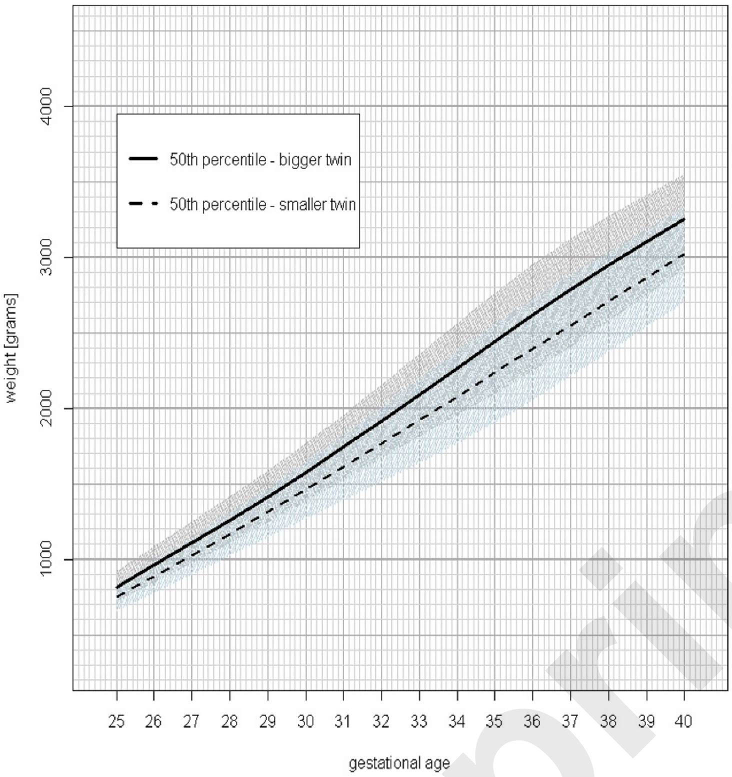

Figure 1: **Centile curves for the bigger and smaller twin vs. gestational age.**

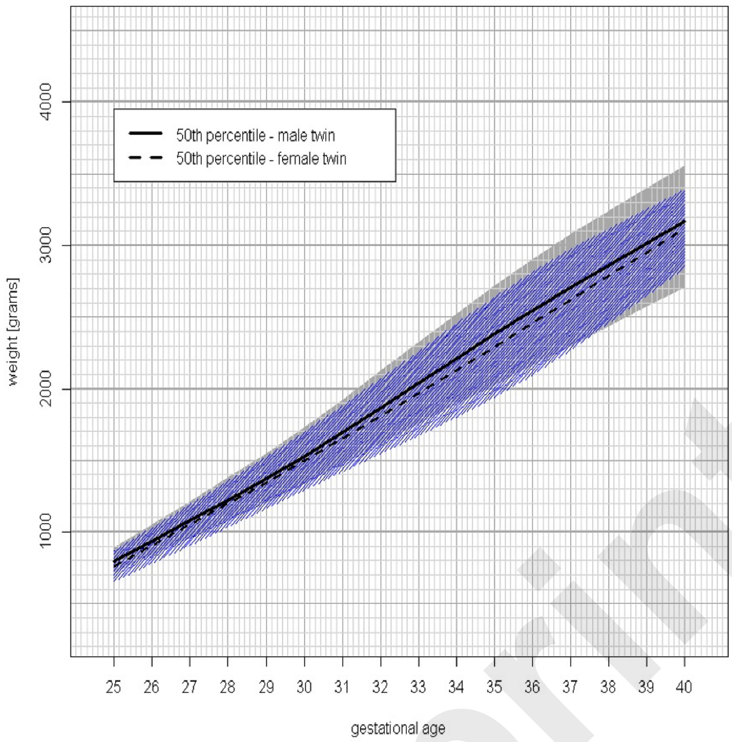

Figure 2: **Centile curve for the male and female twin vs. gestational age.**