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Comparison of "growth promoted" and "normally grown" dichorionic–diamniotic twins: A population-based study

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ABSTRACT

Objectives: Macrosomia in singleton pregnancies and associated risks have been well characterized. Less is known about the outcomes of macrosomic newborns in twin pregnancy.Objective of this study was to compare maternal characteristics and perinatal outcomes of "growth promoted twins" (twin pairs with a total twin birth weight above 90th percentile) to "normally grown twins" (twin pairs with a total twin birth weight between 50th and 90th percentile).

Methods: We evaluated data (maternal characteristics and perinatal outcomes) of dichorionic–diamniotic twins born at 34 weeks of gestational age or later over a sixteen-year period (2002–2018) in two birth weight groups. We excluded twin pairs born before 34th week of gestation and discordant twin pairs. We used data from the Slovenian National Perinatal Information System.To define the percentiles, twin-specific growth curves have been used.

Results: Our study population consisted of 390 twin pregnancies with a twin total birth weight over 90th percentile and 1618 pregnancies with a total twin birth weight between 50th and 90th percentile for gestational age. Women in "growth promoted" twin group were significantly taller, heavier and more often multiparous. There was a higher incidence of gestational diabetes (10.8% vs 7.3%, OR 1.53 95% CI 1.06 – 2.22), a lower rate of caesarean births (48.2% vs 53.9%, OR 0.80 CI 0.64 – 0.99) and lower rate of assisted reproduction (21.0% vs 27.1%, OR 0.71 CI 0.55 – 0.93) in women in "growth promoted" twin group. There were no statistically significant differences in neonatal outcomes in both groups.

Conclusion: In contrast to macrosomia in singletons, macrosomia in twins does not appear to increase the risk for adverse perinatal outcomes.

Introduction

Macrosomia in singleton pregnancies and associated risks have been well characterized [1]. No general consensus on definition has been established, however American College of Obstetricians and Gynaecologists suggests a threshold of 4500 g for macrosomia [2]. Risk factors for development of macrosomia include pre-existing and uncontrolled gestational diabetes mellitus (GDM), pregestational obesity, excessive maternal weight gain, a prior macrosomic infant, post term pregnancy and maternal non-smoking status [3,4]. Data from the National Health Statistics report show that 9.5% of infants in Slovenia weigh 4000 g or more [5]. Risks associated with macrosomia can have important effect both on the mother and fetus. Maternal risks include prolonged labour, perineal lacerations, uterine atony, abnormal haemorrhage and increased rate of Caesarean section. Fetus risk include a higher risk of shoulder dystocia, hypoxia, plexus injuries, hypoglycaemia, congenital anomalies and need for intensive care [3,6].

Twin pregnancies are high risk pregnancies and require additional care. Initial studies on twin pregnancies showed, that twin pregnancy is more likely in mothers, which are taller, multiparous and come from higher income social groups [7]. In the age of assisted reproduction, approximately 30–40% of twin pregnancies are associated with assisted reproduction [8], which is also related to higher age [9].

Twin pregnancies have an increased risk of perinatal morbidity and mortality, mainly due to the increased rate of prematurity and growth abnormalities [10]. There are many reports on how fetal growth

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restriction (as a common complication of twin pregnancy) is connected to increased rates of perinatal morbidity and mortality [11].

Less is known about the outcome of macrosomic new-borns in twin pregnancy. *Blickstein and Weismann* were the first who evaluated the outcomes of "growth promoted twins" in 1990. In a comparison between 10th and 9th decile no increased fetal or maternal risk was noted in the growth promoted group with excellent perinatal results. Additionally data suggested that GDM is not a growth-promoting factor in twins [12]. Further studies that evaluated effects of GDM on twin pregnancies confirmed its low effect on growth promotion [13]. This could be related to glucose uptake by a higher fetal mass, which in contrast balances the diabetogenic effects of increased placentation in twin pregnancy [14].

Total twin birth weight represents uterine capacity for carrying and nurturing twins. Due to the mutual influence of twins on growth, the total weight is a better indicator of the placental function than the weight of an individual fetus [15].

The aim of this study was to compare maternal characteristics and perinatal outcomes in two groups of dichorionic–diamniotic twins born at 34 weeks or later, "growth promoted twins" - twin pairs with a total twin birth weight above 90th percentile to " "normally grown twins" - twin pairs with a total twin birth weight between 50th and 90th percentile.

Materials and methods

We used the Slovenian National Perinatal Information System (NPIS), a population registry which registers all births at ≥22 weeks' gestation or birth weight ≥ 500 g. Registration is mandatory by law, and more than 140 variables are entered immediately postpartum into a computerized database, which is regularly validated for accuracy.

Our study included all consecutive dichorionic–diamniotic twin pregnancies in Slovenia between 2002 and 2018, where twins were born at ≥ 22 weeks' or with birth weights ≥ 500 g (n = 5006). We excluded twin pairs born before 34th week of gestation (n = 918) and discordant twin pairs (weight discordance > 25%) (n = 302). The twin pairs were divided according to the total twin weight (birth weight of fetus A + birth weight of fetus B) in percentiles. We excluded twin pairs with the total twin weight bellow the 50th percentile (n = 1778). 2008 twin pairs were finally included in the study (Fig. 1).

We compared data in two birth weight groups. We defined "growth promoted" twin group where total birth weight of both twins was above 90th percentile for gestational age. We compared them with "normally grown" twin group which was defined as total twin weight between 50th and 90th percentile for gestational age. To define the percentiles we used twin-specific growth curves, developed by Bricelj et al. [16].

We analyzed the following maternal characteristics: parity, age,

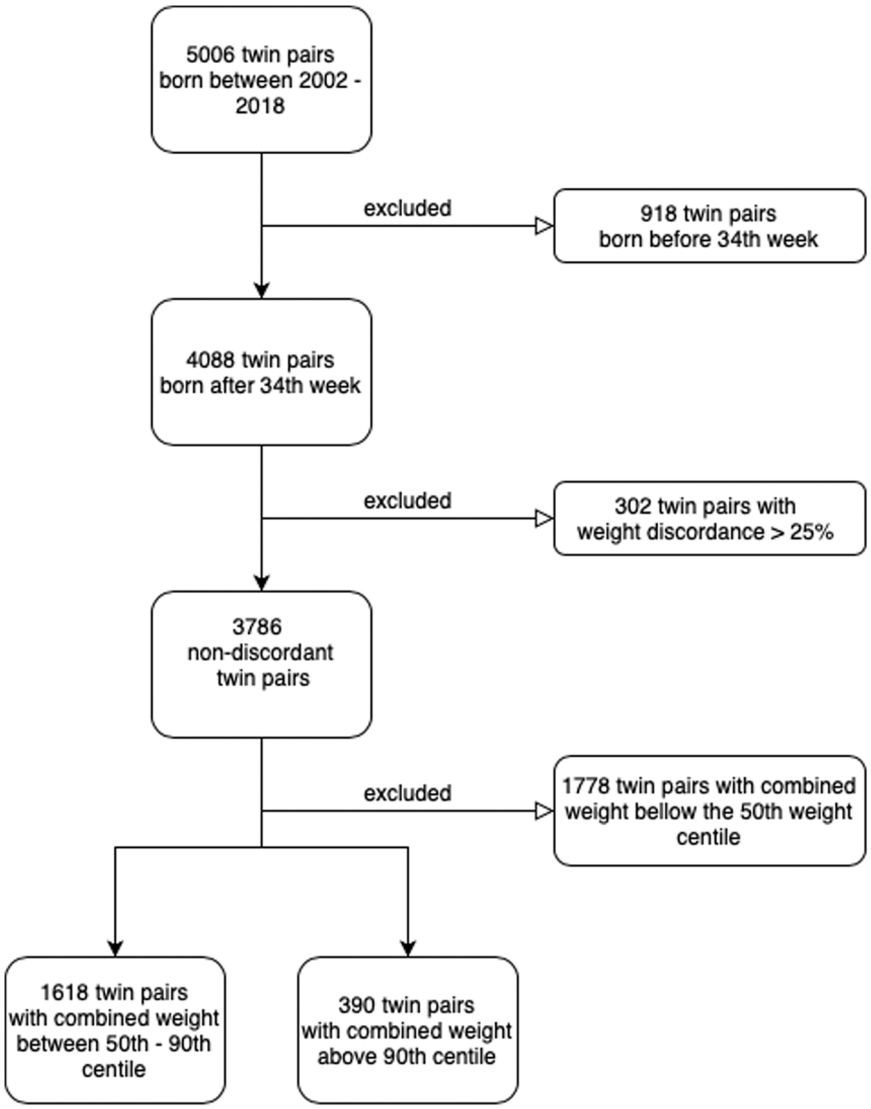

Fig. 1. The study population.

body mass index (BMI), height, weight, weight gain during pregnancy, GDM (in two different time periods- before and after adopted recommendations criteria for screening of gestational diabetes by IADPSG in 2010), mode of conception, mode of delivery (vaginal or caesarean), postpartum haemorrhage > 500 ml and neonatal outcomes: 5-min Apgar score, admission to neonatal intensive care unit (NICU), perinatal morbidity, neonatal morbidity, frequency of mild or severe asphyxia.

Results are presented as means with standard deviation when a normal (Gaussian) distribution had been ascertained. For categorical variables, the two groups were compared using the chi-square test or Fisher's exact test, as appropriate. Analysis of covariance (ANCOVA) and linear regression modelling was used to elucidate the most significant factors that affect the outcome. Odds ratios and their 95% confidence intervals (CI) were computed. $P < 0.05$ was considered statistically significant.

This retrospective study of anonymous entries was exempt of approval by the Local Ethics Committee. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Results

From January 2002 until December 2018, 5006 dichorionic–diamniotic twin pairs were born in Slovenia. After exclusion criteria, our study population consisted of 390 "growth promoted" twin pregnancies with a mean twin total birth weight over 90th percentile for gestational age and 1618 "normally grown" twin pregnancies with a mean total twin birth weight between 50th and 90th percentile for gestational age (Fig. 1). Maternal characteristic are presented in Table 1. While the mean age at delivery was not significantly different the data indicate that mothers with growth promoted twins were more often multiparous, taller, heavier, gained more weight during pregnancies and were more likely to have GDM. Analyzing incidence of GDM in two different time periods (before and after adopted recommendations criteria for screening of gestational diabetes by IADPSG in 2010) [17], we noticed an obvious increase in incidence in the second period, mainly in the group of "growth promoted" twins (Table 2). Women with ""growth promoted" twins were more likely to conceive spontaneously (21.0% vs 27.1%; OR 0.715; 95% Cl 0.547, 0.934). There was no difference in the incidence of preeclampsia between both groups.

Regarding obstetric outcomes, there was a statistically significant lower rate of Caesarean sections in "growth promoted" twin versus "normally grown" twin group (48.2% vs 53.9%; OR 0.80; 95% CI 0.64, 0.99), however there was no statistically significant difference in postpartum haemorrhage (>500 ml) (10.3% vs 8.5%) and rate of transfusion (5.6% vs 3.9%) in both groups. When comparing the proportion of prelabour and intrapartum cesarean section, there was no difference in any of both groups. There were no maternal deaths in the cohort.

Linear regression analysis and the odds ratios between "growth promoted" twin and "normally grown" twin groups for obstetric complications and maternal characteristics are summarized in Table 3.

Neonatal outcomes and odds ratios between both groups are presented in Table 4. There were no statistically significant differences in all of the observed outcomes (NICU admission, Apgar score bellow 7 at 5 min, stillbirth, neonatal mortality, mild or severe asphyxia). The heaviest twin in our study weighted 4000 g, whereas 57 (0.8%) of the newborn twins were heavier than 3500 g.

Table 1
Baseline characteristics of women with dichorionic–diamniotic twin pregnancies in two different total birth weight groups. Data are shown as mean ± SD, or as n (%). SD – standard deviation.

	Total birthweight > 90th percentile, (± SD) N = 390	Total birthweight 50–90th percentile, (± SD) N = 1618	p value
Maternal age (years)	31.28 ± 3.99	31.53 ± 4.57	0.545
Height (cm)	169.55 ± 5.60	167.80 ± 5.84	< 0.001[a]
Weight before pregnancy (kg)	72.75 ± 14.65	67.85 ± 13.12	< 0.001[a]
Weight gain (kg)	18.47 ± 6.37	17.21 ± 6.60	0.001[a]
BMI[b] (%)			
Underweight < 18.5	8 (2.1%)	58 (3.6%)	< 0.001[a]
Normal 18.5–24.9	214 (54.9%)	1050 (64.9%)	< 0.001[a]
Overweight 25–29.9	108 (27.7%)	332 (20.5%)	< 0.001[a]
Obese ≥ 30	60 (15.3%)	176 (10.9%)	< 0.001[a]

[a] p value < 0.05 was considered statistically significant.
[b] BMI – Body mass index.

Table 2
Incidence of GDM in dichorionic–diamniotic twin pregnancies in two different total birth weight groups and two time periods (2002–2010 and 2011–208). Data are shown as n (%). OR - odds ratio. CI - confidence interval.

	Total birthweight 50–90th percentile N = 3236	Total birthweight > 90th percentile N = 780	OR	95% CI
2002–2010	28 (4.0%)	7 (4.0%)	0.993	0.426–2.311
2011–2018	90 (9.8%)	35 (16.4%)	1.801	1.180–2.748

Table 3
Characteristics and obstetric outcomes of women with dichorionic–diamniotic twin pregnancies in two different total birth weight groups. Data are shown as n (%). OR - odds ratio. CI - confidence interval.

	Total birthweight > 90th percentile N = 390	Total birthweight 50–90th percentile N = 1618	OR	95% CI	p value
Primipara	130 (33.3%)	754 (46.6%)	0.57	0.45 – 0.72	< 0.001[a]
Gestational diabetes mellitus	42 (10.8%)	118 (7.3%)	1.53	1.06 – 2.22	0.028[a]
Rate of IVF[b]	82 (21.0%)	439 (27.1%)	0.72	0.55 – 0.93	0.014[a]
Preeclampsia	16 (4.1%)	78 (4.8%)	0.84	0.48 – 1.46	0.327
Caesarean section	188 (48.2%)	872 (53.9%)	0.80	0.64 – 0.99	0.043[a]
Pre-labour	103 (26.4%)	465 (28.7%)	0.82	0.63 – 1.06	0.136
Intrapartum	85 (21.8%)	407 (25.2%)	0.77	0.58 – 1.03	0.069
Postpartum haemorrhage > 500 ml	40 (10.3%)	137 (8.5%)	1.25	0.85 – 1.79	0.263
Rate of transfusion	22 (5.6%)	63 (3.9%)	1.50	0.90 – 2.43	0.124

[a] p value < 0.05 was considered statistically significant.
[b] IVF – in vitro fertilisation.

Discussion

Our findings suggest that women with "growth promoted twins" (where total birth weight of both twins was above 90th percentile for gestational age) are not at increased risk for maternal and fetal adverse outcomes as it was shown in singleton pregnancies [3,4,6]. Moreover,

Table 4
Neonatal outcomes in dichorionic–diamniotic twin pregnancies in two different total birth weight groups. Data are shown as n (%). OR - odds ratio. CI - confidence interval. p value < 0.05 was considered statistically significant.

	Total birthweight > 90th percentile N = 780	Total birthweight 50–90th percentile N = 3236	OR	95% CI	p value
5′ Apgar < 7	11 (1.4%)	55 (1.7%)	0.83	0.43 – 1.59	0.568
NICU[a] admission	76 (9.7%)	359 (11.1%)	0.86	0.67 – 1.12	0.276
Stillbirth	3 (0.4%)	9 (0.3%)	1.38	0.37 – 5.13	0.625
Neonatal mortality	0	5 (0.2%)	0.998	0.997 – 1.000	0.272
Mild asphyxia	4 (0.5%)	38 (1.2%)	0.43	0.16 – 1.22	0.103
Severe asphyxia	2 (0.5%)	10 (0.3%)	0.83	0.18 – 3.79	0.809

[a] NICU – neonatal intensive care unit.

the rate of caesarean sections was statistically significantly lower in the ”growth promoted” twin group than in “normally grown” twin group, although comparing two subgroups (pre- and intrapartum) there was no difference between ”growth promoted twins” and ”normally grown twins”.

The rate of GDM was higher in ”growth promoted” twin group. Previous studies showed an incidence of GDM in twin pregnancies of about 8% [18,19]. Incidence in the ”normally grown” twin group coincides with the data in the literature, however the rate of 10.8% in the ”growth promoted” twin group is slightly higher than shown in the data. In our opinion it could be related to a greater placental mass and higher levels of diabetogenic human placental lactogen (hPL) in ”growth promoted twins” [20]. There are conflicting reports between the incidence of GDM in twin and singleton pregnancies, but latest and large studies [19] showed an increased rate of GDM in twin pregnancies.

Since the screening and diagnostic approach to gestational diabetes was changed in the middle of our study period (after the adopted recommendations criteria for screening of gestational diabetes by IADPSG in 2010) [17], we decided to analyze both time periods separately. Since there was no difference between both groups in first time period (4% in ”normally grown twins” and ”growth promoted twins”), the incidence in the ”growth promoted” twin group was much higher in second time period (9.8% in ”normally grown” and 16% in ”growth promoted” twin group). In contrast to singleton pregnancies, a higher incidence of GDM in ”growth promoted” twin group, did not show an increased risk for adverse maternal and neonatal outcomes, similarly to some other studies which failed to show an increased effects of GDM on adverse outcomes in twin pregnancy [13,21]. Moreover, in our case the neonatal results in ”growth promoted” twin group were even slightly better, however not significantly.

One of the reasons that we did not have many adverse outcomes in “growth promoted” twin group is that very few newborns (less than 1%) were heavier than 3500 g. This is mostly due to our induction policy because in dichorionic–diamniotic twin pregnancies we usually induce labour or decide for cesarean section around 38 weeks of gestation. If newborns were heavier, we would expect more adverse outcomes to be related to difficulties with labour and delivery.

Analyzing maternal characteristics, we noticed that taller, heavier women and multiparous are more likely to give birth to larger twins. All described characteristics were previously observed in women with “growth promoted” twins [7,15,22]. We also found a higher rate of spontaneous conceptions in the “growth promoted” twin group. Similarly, singleton conceives spontaneously, are heavier than those conceived by assisted reproduction procedures [23].

Excessive weight gain during singleton pregnancy is associated with significant adverse maternal and neonatal outcomes [3], however our study in twins showed that although women gained more weight and had higher BMI, it did not result in worse perinatal results.

To the best of our knowledge, there is only one old study, by *Blickstein and Weismann* from 1990, which studied macrosomic twins [12]. Results of our study are in concordance with most findings of their study.

One of notable strengths of our study was large cohort of twin pairs. Additionally, to get representative groups, we excluded all twin pairs with total twin birth weight below the 50th percentile and all discordant twins, since it has been shown that frequencies of divergent birth weight is higher up to the median total birth weight [15]. We also excluded all twins born before 34th week, to exclude prematurity as a cause of perinatal morbidity and mortality.

Studies of fetal growth in twins usually use absolute measures of birth weight, which are problematic because this measure cannot separate neonates, who are small due to preterm delivery, from those who are small due to intrauterine growth restriction. Therefore, we decided to use more appropriate twin-specific growth curves [16], where percentiles for each gestational age were calculated.

The main limitation of our study is its retrospective observational nature.

Additionally, while our sample size was large enough for us to analyze maternal characteristics and outcomes, we were unable to perform well the analyzes of neonatal outcomes. Due to the rareness of events our cohort failed to show statistically significant differences.

We believe that our observations add important information to the existing literature on growth promoted twins and perinatal outcomes of large twin pairs. Even though our results showed better results in ”growth promoted” twin group, we stress the importance of antenatal care in twin pregnancies, with dietary and life style counselling intended to achieve optimal body weight prior to conception and during pregnancy.

Further studies with a wider range of observed outcomes are needed to confirm our retrospective results.

Declaration of Competing Interest

All authors state that there are no conflicts of interest related to the results presented within the submitted paper. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. This retrospective study of anonymous entries was exempt of approval by the Local Ethics Committee.

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Declarations of interest

None.

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