Birth outcomes of twins after multifetal pregnancy reduction compared with primary twins

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BIRTH OUTCOMES OF TWINS AFTER MULTIFETAL PREGNANCY REDUCTION COMPARED WITH PRIMARY TWINS

Condensation page

1) Short Title: Multifetal pregnancy reduction in trichorionic triplets to twins

2) AJOG at a Glance:

A. Why was this study conducted

- Trichorionic triplets reduced to dichorionic twins are compared with ongoing triplets and primary dichorionic twins.
- In the light of the improvement in neonatal care as well as in the multifetal pregnancy reduction procedure, an evaluation of the perinatal outcome of twins after multifetal pregnancy reduction was necessary.

B. What are the key findings?

- Multifetal pregnancy reduction from trichorionic triplets to dichorionic twins significantly improves birth outcomes (birth weight, gestational age) in comparison with ongoing triplets.

C. What does this study add to what is already known?

- The birth outcomes of primary twins before 32 weeks of gestation are still better in comparison with reduced triplets.
- A trend towards a lower risk of small for gestational age is observed

Conflict of interest:

No conflicts of interest to declare by the authors.

Keywords: Multifetal pregnancy reduction, birth weight, gestational age, small for gestational age, twins, triplets

Abstract

Background: The introduction of assisted reproductive technology and the trend of increasing maternal age at conception have been responsible for a significant rise in the incidence of multiple pregnancies. Multiple pregnancies bear several inherent risks for both mother and child. These risks increase with plurality and type of chorionicity. Multifetal pregnancy reduction is the selective abortion of one or more fetuses to improve the outcome of the remaining fetus(es) by decreasing the risk of premature birth and other complications.

Objective: This study compares the birth outcomes of trichorionic triplets reduced to twins with trichorionic triplets and primary dichorionic twins. The added value of this study is the comparison with an additional control group, namely primary dichorionic twins.

Study design: This is a retrospective cohort study. Data from January 1990 till November 2016 were collected from the East Flanders Prospective Twin Survey, one of the largest European multiple birth registries. Eigthy-five trichorionic triplet pregnancies (170 neonates) undergoing multifetal pregnancy reduction (MPR) to twins were compared to 5,093 primary dichorionic twin pregnancies (10,186 neonates) and 104 expectantly managed trichorionic triplet pregnancies (309 neonates). The outcomes are gestational age at delivery, birth weight, and small for gestational age.

Results: Pregnancy reduction from triplets to twins is associated with a higher birth weight (+365.44 g, 95%CI [222.75, 508.14 g], $p < .0001$) and longer gestational age (1.7 weeks, 95%CI [0.93, 2.46], $p< .0001$) compared to ongoing trichorionic triplets, adjusted for sex, parity, method of conception, birth year, and maternal age. A trend towards a lower risk of SGA is observed. Reduced triplets have, on average, a lower birth weight (-263.12 g, 95%CI [-371.80, -154.44 g], $p < .0001$), and a shorter gestational age (-1.13 weeks, 95%CI [-1.70, -0.56], p=0.0001) compared to primary twins. No statistically significant difference between primary twins and reduced triplets that reach 32 weeks of gestation is observed.

Conclusion: Multifetal pregnancy reduction from trichorionic triplets to twins significantly improves birth outcomes. This suggests that MPR of trichorionic triplets to twins is medically justifiable. However, the birth outcomes of primary twins before 32 weeks of gestation are still better in comparison with reduced triplets. The process of MPR includes at least one fetal death by definition, therefore prevention of higher-order pregnancies is preferred.

Introduction

The introduction of assisted reproductive technology (ART) and the trend of increasing maternal age at conception have been responsible for a significant rise in the incidence of multiple pregnancies [1,2]. In 1990, the incidence of twin and triplet pregnancies in the United States (US) was respectively 2.25% and 0.068%[3]. In 2016, the incidence of twin and triplet pregnancy in the US increased to respectively 3.34% and 0.095%[4]. In 2021, the incidence of twin pregnancies in Flanders (Belgium) was 2.9%, and the incidence of triplet pregnancies was 0.003%. Of these multiple pregnancies, 27% were conceived by ART. In other words, 8.2% of ART treatments in 2021 resulted in a multiple pregnancies [5].

Multiple pregnancies bear several inherent risks for both mother and child: lower birth weight, shorter gestational age, and higher morbidity and mortality rate for mother and child [6]. These risks increase with plurality and type of chorionicity[7–9]. The US National Vital Statistics Report from 2021 stated that 62.5% of twins were born preterm (<37 weeks) and over 55% had low birth weight (<2500 grams). Triplets had preterm birth rates of 98.6% and low birth weight rates of over 95.4% [2].

Multifetal pregnancy reduction (MPR) is a technique introduced in the 1980s. It is the selective abortion of one or more fetuses to improve the outcome of the remaining fetus(es) by decreasing the risk of premature birth[9,10]. Today, transabdominal injection of potassium chloride (KCl) into the fetal thorax between 11 and 14 weeks of gestation is the most common method. For the procedure, a transabdominal approach is preferred to a transvaginal approach because of a lower overall fetal loss (5.2% vs 13.3%). Other factors determining the chosen approach are accessibility of the gestational sac and gestational age at the time of the procedure[11,12]. The selection of the fetus to be reduced is in most countries based on technical considerations and ultrasound evaluation of the fetuses. Over time, the diagnostic capabilities (ultrasound devices), the experience of the obstetricians, and MPR procedure have evolved and improved[13–15]. Since the 1980s there has been the possibility of genetic testing using chorionic villus sampling (CVS) in pregnancy[16]. The use of genetic testing by CVS prior to MPR has been described as beneficial, to avoid reducing a normal fetus and is implemented in some countries as the standard of care[15,17,18]. However, genetic testing before MPR is not common practice in Flanders, Belgium.

It is a procedure that is considered in higher order multiple pregnancies as it is thought to reduce the above-mentioned obstetric risks and thus improve neonatal and long-term outcomes. By reducing a higher order pregnancy to a twin or singleton, studies have shown a lower risk of fetal loss, prematurity, infant mortality and morbidity of the remaining fetuses, and improvement in obstetrical outcomes[19–21]. However, the beneficial effect of MPR in a triplet pregnancy is now, more than ever, subject to debate because of the improvement in neonatal and obstetric care of the triplets and their mothers [22,23]. Apart from the consideration to perform MPR, there is ambiguity regarding the number of fetuses (twin or singleton) to reduce to.

There are possible adverse effects of MPR. The first is a risk of total pregnancy loss, which is defined as fetal loss before 24 weeks [19,24,25]. A study by Chaveeva *et al.* found a total pregnancy loss rate of 7.3% when reducing trichorionic (TC) triplets to twins as opposed to 3.1% for expectant management in TC triplets [24]. Zemet *et al.* found a total pregnancy loss rate of 1.3% in TC triplets reduced to twins and 4.8% in TC and dichorionic (DC) triplets reduced to singletons[26]. Secondly, the psychological and emotional burden of MPR should not be underestimated. Couples conceiving a multifetal pregnancy find themselves in a paradoxical situation. On one hand, their desire for a child is fulfilled. On the other hand, they are faced with the question of whether to give up one (or more) fetuses to improve the others' life chances. Garel *et al.* state that parents who had a proper medical explanation concerning MPR, based on scientific facts, could cope better with the feelings of anxiety and guilt that accompany MPR. Therefore, physicians must have good scientific evidence to build their advice on [27].

This study aims to contribute to the scientific evidence that helps parents and physicians go through the process of MPR. In light of the improvement in neonatal care as well as in the MPR procedure over the last 25 years, an evaluation of the perinatal outcome of twins after MPR was ought necessary. To this end, we compared perinatal outcomes (birth weight, gestational age at birth, and small for gestation age (SGA)) between TC triplets reduced to DC twins, TC triplets and primary DC twins. The added value of this study is the comparison with an additional control group, namely primary dichorionic twins. Data were collected from the East Flanders Prospective Twin Survey (EFPTS), a population-based registry of multiple births in the province of East-Flanders in Belgium[28].

Materials and methods

Data were collected from the East Flanders Prospective Twin Survey (EFPTS). The EFPTS is a population-based registry of multiple births in the province of East-Flanders in Belgium, that records perinatal data at birth [29]. Since only multiples are registered at birth, there are no singletons or multiples reduced to singletons included in the analyses. The study protocol was approved by the ethical committee of Ghent University Hospital, Belgium on 19th June 2017 (reference number: EC/2017/2714).

Study population

This study focuses on DC twins and TC triplets. Dichorionic triplets are reduced to monochorionic twins or singletons. Since monochorionic twins are not comparable to DC twins perinatally (lower birthweight and gestational age, higher morbidity and mortality), they were excluded from the analysis[33]. Singletons and triplets reduced to singletons were excluded, because the EFPTS dataset only registers multiples at birth.

The first twin born after MPR in East-Flanders was registered in 1990. Thus, only twins and triplets born between January 1990 and November 2016 were included in the analysis. In accordance with the WHO recommendations, only cases in which at least one of the children weighed 500 grams or more, or gestational age at delivery was at least 22 weeks were included (n twins =6,472; n triplets=141)[30]. Chorionicity of the triplets and twins was confirmed after birth, during the placenta examination. Only live births were taken into account.

Data collection

The following data were recorded by the obstetrician at birth: birth year, parity, gestational age at delivery, birth weight, fetal sex, perinatal mortality, maternal age, method of conception, and performance or absence of reduction. Gestational age was based on the last menstruation or a first trimester ultrasound investigation and was calculated both in days and in number of completed pregnancy weeks. Perinatal mortality was defined as antenatal death from 22 weeks of gestation onward, to 1 week after birth. The categories of method of conception are 'spontaneous', 'Artificial Induction of Ovulation (AIO) only' and 'Assisted Reproductive Technology (ART)'. Newborns were classified as SGA when birth weights were below the 10^{th} percentile for a given gestational age and sex according to cut-off values based on data from twin births in Flanders from the Study Centre for Perinatal Epidemiology (SPE) in the period 2001–2010 [31,32].

Statistical analysis

SAS software version 9.4 was used for the analyses. The normal distribution of all quantitative variables was visually inspected in QQ-plots. All reported p-values are two-sided and were considered statistically significant when $p<0.05$. For the association between gestational age and reduction, twins were studied as pairs with multiple linear regression analysis. The children were analysed as individuals and to account for dependence between twin/triplet members a random intercept was added to the model. Generalized linear mixed models were used to investigate the association between the binary outcome ‘small for gestational age’ and reduction. Mixed-effects modelling was used to investigate the association between birth weight and reduction and a sensitivity analysis with stratification for gestational age at birth was done (term (≥37), moderate to late preterm (32–36 weeks) and very preterm (<32 weeks) birth. Additional covariates used in all models were sex, parity, maternal age of mother (linear and quadratic), method of conception, and year of birth.

Results

Description of the study population

Eighty-five cases of triplets being reduced to twins (170 neonates) were compared to 5,093 primary DC twins (10,186 neonates) and 104 ongoing TC triplets (309 neonates). We excluded 187 twin pairs and 9 sets of triplets from our analysis based on missing data on age mother, parity, method of conception, sex or chorionicity. An overview is presented in Figure 1. The characteristics of the three groups are given in Table 1. Most of the mothers (52.7%) were primiparous and the average maternal age was 30 years. The average (±SD) birth year of triplets (1998 ± 7.4) was earlier than that of primary twins (2003 ± 7.4) and reduced triplets (2001 ± 6.9). There were more males in the group of reduced triplets (58.8%), which was coincidental. There was no selection based on sex, since the selection was only based on ultrasound and technical aspects.

The distributions of the birth outcomes are summarized in Table 1 and depicted in Figure 2. Reduced triplets have an average gestational age at birth of 34.4 (± 3.7) weeks. The gestational age at birth of triplets is, on average, 32.8 (± 3.7) weeks, and for primary twins 35.8 (±2.6) weeks. The mean birth weights of primary twins, reduced triplets and triplets were 2,421 ± 556g, 2,142 ± 664g and 1,762 ± 575g respectively. Primary twins are less frequently born SGA compared to reduced triplets (10.6% vs 14.9%, p = .08). Reduced triplets, are, on average, less frequently born SGA compared to ongoing triplets (14.9% vs 23.8%, p = .02).

Gestational age (Figure 2, Table 2)

In reduced triplets, gestational age at birth is longer compared to triplets (+1.70 weeks, 95% CI [0.93 to 2.46], p<0.0001), and shorter compared to primary twins (-1.13 weeks, (95% CI [-1.70 to -0.56], p=0.0001) without (Figure 2) and with (Table 2) taking into account sex, parity, method of conception, birth year, age of mother (linear and quadratic).

Birth weight (Figure 2, Table 2&3)

Birth weight of reduced triplets is, on average, 365.44 g higher (95% CI [222.75 to 508.14 g]) than birth weight of triplets. Compared to primary twins, reduced triplets weigh, on average, 263.12 g less (95% CI [-371.80 to -154.44 g]). Stratified analysis (Table 3), shows that this difference in birth weight of reduced triplets compared to primary twins is observed only in very preterm born twins (<32 weeks of gestation).

Small for gestational age (SGA)(Table 2)

The adjusted odds ratio for SGA in reduced triplets is 1.55 (95% CI: 0.97 to 2.49) compared to primary twins, and 0.62 (95% CI [0.35 to 1.08]) compared to triplets.

Comment

Principal findings

The added value of this study is the comparison of reduced dichorionic twins to an additional control group, namely primary dichorionic twins. We observed that the birth weight of reduced triplets is still 263.12 g lower (95% CI [-371.80 to -154.44 g]) compared to primary twins. After a gestational age of 32 weeks, the difference in birth weight between reduced triplets and ongoing triplets remains. The difference in birth weight after 32 weeks of gestation between reduced and primary twins is not statistically significant, but shows the same trend namely a lower birth weight and gestational age for the reduced triplets compared to the primary twins.

Results in the context of what is known

In accordance with the majority of studies on this topic, our results show that DC reduced triplets generally fare better than ongoing TC triplets [22,34–39]. The results of this study show that MPR from TC triplets to twins is associated with a higher birth weight (+365.44 g, 95% CI [222.75 to 508.14 g]) and a longer gestational age (1.7 weeks, 95% CI [0.93 to 2.46]) compared to ongoing TC triplets. In addition, we also observed a trend towards a lower risk of SGA. The majority of studies agree on a positive correlation between MPR and birth weight and gestational age [15,21,33,37,38,40,41]. We suspect that this positive correlation can be attributed to the fact that birth weight and gestational age are both influenced by the order of the multiple pregnancy which is by definition reduced in MPR [19]. A same trend for SGA was found in an updated meta-analysis on MPR of triplet pregnancies to twins: Zipori *et al*. reported 19.7% SGA in the MPR group versus 22.8% in the triplet group (95% CI of the risk difference) [39]. Our findings are also in line with the study of Garite *et al.* suggesting that reduced triplets are not following the true growth curves of primary twins and retain their suboptimal growth potential as triplets[42]. This could be due to effects on early placentation or to retained fetoplacental material after MPR[26,39,42]. However, previously published data by Torok *et al.* and Belogolovkin *et al.* suggest that MPR does not increase the rate of fetal growth restriction[43,44]. We observed more preterm deliveries before 32 weeks of gestation in the group of reduced triplets (26.2%) in comparison with the primary twins (6.5%) and ongoing triplets (11.9%). This result is not statistically significant and could be coincidental due to the smaller cohort of reduced triplets. The reduction could have an influence on the preterm birth, but therefore a large cohort of reduced triplets should be analyzed.

Some authors reported that the difference between reduced triplets and triplets is too small to justify MPR. They conclude that MPR should be considered a malpractice as long as there is no randomized controlled trial exploring the causal effect of MPR on pregnancy outcomes. Ethical considerations also play a role in discouraging MPR[25,38,46]. The results of these studies show only a limited improvement in the group of reduced triplets compared with expectant management triplets, but the set-up is typically a multicentre study with multiple operators, which could influence the outcomes [33].

Clinical implications

According to our data, MFPR is medically justifiable, since the birth outcomes (birth weight and gestational age) are better in the reduced TC triplets compared to the ongoing TC triplets. When comparing reduced triplets to primary twins, we observed no statistically significant difference in birth weight when twins were born after 32 weeks' gestation. When reaching this milestone of 32 weeks, birth weights in reduced triplets approximated those of primary twins rather than expectantly managed triplets. Ideally a multiple birth, and the associated pregnancy risks, can be avoided by e.g. performing a single embryo transfer (SET) instead of transferring multiple embryo's and by rigorously controlling ovulation induction. Not every country implemented SET as a recommendation and/or law, Belgium did in 2003. On the other hand, an increase of monochorionic twins is detected after SET which is correlated with more pregnancy complications [47,48].

Strengths and Limitations

The characteristics of the EFPTS database were to our advantage. Firstly, since the data is retrieved from all hospitals in East-Flanders, this is a population based multicentre study. Secondly, the fact that the data was retrieved over 26 years in the same way according to the predefined protocol in the entire province of East-Flanders, Belgium (i.e. not clinical-based) makes it a reliable source of perinatal outcomes. Another important analytical advantage of this study is the inclusion of chorionicity (namely only di-or trichorionicity) in the selection criteria, thus acknowledging the fact that chorionicity alters perinatal outcomes.

The available data only provides information up until birth. After that, contact with the families is often lost. Accordingly, it was not possible to check for long-term consequences of MPR or triplet pregnancy for the parents and surviving neonates. Unintentional fetal death after MPR with one fetus remaining was reported as a singleton and therefore not registered in the EFPTS dataset. Therefore, fetal death of one or both fetuses after MPR is not included in this study and could be a possible source of bias. In addition, a spontaneous reduction of a triplet to a twin before 22 weeks would be registered as a primary twin. The medical indication to perform MPR and type of MPR procedure was not registered in the database and thus was not taken into account in the analyses. Only reductions from trichorionic triplets to dichorionic twins were included in the trial. There is no comparison with singletons, since the EFPTS dataset only includes multiples at birth. Apart from birth weight, gestational age and congenital malformations no other neonatal outcomes are registered in the EFPTS database. Hence, outcomes such as Apgar, respiratory distress syndrome or infections were not explored.

Research implications

Recommendations for future research would be to create a prospective cohort study where women pregnant of triplets are included at the first ultrasound. To include a specific timeline for the interventions during pregnancy and two-year follow-up of all pregnancies that are diagnosed as triplets on the first ultrasound. Thus, spontaneous and elective reductions can be recorded, as well as fetal loss ensuing the MPR procedure. This would also allow for comparison of triplets to triplets reduced to twins and to singletons. Secondly, extending the follow-up period to two years would provide valuable information on long-term morbidity and mortality. Including this in the analysis might highlight the importance of prolonging gestational age and bring to light possible adverse effects of MPR for the surviving children. Studies have shown a great influence of the maternal socio-economic level on perinatal outcomes [49–51]. By including socio-economic factors in a future study, it would be possible to analyse the associations of these factors with the outcomes of MPR and on the decisionmaking process involving MPR. However, the feasibility and cost-efficiency of such a prospective cohort study could form a serious obstacle.

Conclusion

According to our data, MPR in trichorionic triplets to twins is associated with a higher birth weight and a longer gestational age at birth compared to expectantly managed trichorionic triplets. Primary twins, however, still fare better than reduced triplets, hereby stressing the importance of current guidelines and regulations of trying to prevent high-order pregnancies conceived with ART.

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Figure 1 Flowchart showing the final study population of 5178 dichorionic twin pairs (=10,356 neonates) and 104 sets of trichorionic triplets (=309 neonates) [a] We excluded 187 twin pairs and 9 sets of triplets from our analysis based on missing data on age mother, parity, method of conception, sex or chorionicity. MCDA = Monochorionic Diamniotic; MCMA = Monochorionic Monoamniotic; DCTA = Dichorionic Triamniotic; DCDA = Dichorionic Diamniotic; MCTA = Monochorionic Triamniotic; MCDA = Monochorionic Diamniotic.

Figure 2 Birth outcomes of reduced triplets compared to triplets and primary twins. a) Birth weight, b) gestational age, c) odds ratio small for gestational age.

* $p<0.05$ ** $p<0.001$

Table 1 Study population characteristics

	Primary twin	**Reduced triplets**	**Triplet**
Mothers	**n = 5093**	**n = 85**	**n = 104**
Age mother, years	30.09 ± 4.5	30.25 ± 4.0	29.51 ± 3.6
Parity			
1	2667 (52.4)	50 (58.8)	68 (65.4)
≥2	2426 (47.6)	35 (41.2)	36 (34.6)
Method of conception			
AIO only	924 (18.2)	36 (42.3)	54 (51.9)
IVF or ICSI or GIFT or ZIFT	1504 (29.4)	39 (45.9)	37 (34.6)
Spontaneous	2665 (52.3)	10 (11.8)	13 (12.5)
Newborns	**n = 10 186**	**n = 170**	**n = 309**
Sex			
Male	5098 (50.0)	100 (58.8)	160 (51.8)

Female	5088 (50.0)	70 (41.2)	149 (48.2)
Gestational age, weeks			
Mean ± SD	35.76 ± 2.6	34.44 ± 3.7	32.88 ± 3.7
Median	36.00	35.50	34.00
Missing	122	2	6
Classes of gestational age			
Term (>37 weeks)	4596 (45.7)	26 (15.5)	77 (25.4)
Moderate to late preterm (32-36)	4810 (47.8)	98 (58.3)	190 (62.7)
Very preterm (<32 weeks)	658 (6.5)	44 (26.2)	36 (11.9)
Birth weight,g			
Mean ± SD	2421 ± 556	2142 ± 664	1762 ± 575
Median	2470	2300	1855
Missing	28	0	1
Small for gestational age	1062 (10.6)	25 (14.9)	72 (23.8)
Missing	152	2	7
Birthyear	2003 ± 7.4	2001 ± 6.9	1998 ± 7.4

Data presented are means ± standard deviation (SD) or number (percentage). Abbreviations: AIO only: Artificial Induction of Ovulation only', IVF: 'In vitro fertilization', ICSI: 'Intracytoplasmic sperm injection', GIFT: 'Gamete intrafallopian transfer', ZIFT: 'Zygote intrafallopian transfer'

Table 2 Adjusted mean difference in birth weight and gestational age, adjusted odds ratio small for gestational age of reduced triplets compared to triplets and primary twins

	Compared to triplets			Compared to primary twins		
	Estimate	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
Birthweight, g	365.44	222.75 to 508.14	<.0001	-263.12	-371.80 to -154.44	<.0001
Gestational age, weeks	1.70	0.93 to 2.46	<.0001	-1.13	-1.70 to -0.56	.0001
Small for gestational age, odds ratio	0.62	0.35 to 1.08	.09	1.55	0.97 to 2.49	.07

Adjusted for fetal sex, parity, age of mother (linear and quadratic), method of conception, and year of birth

Table 3 Adjusted mean difference in birth weight of reduced triplets compared to triplets and primary twins in term, moderate to late preterm and very preterm twins.

	Compared to triplets			Compared to primary twins		
	Estimate	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
All	365.44	222.75 to 508.14	<0.0001	-263.12	-371.80 to -154.44	<0.0001
Term (>37 weeks)	295.38	75.41 to 515.35	0.0085	-81.22	-219.92 to 57.49	0.25
Moderate to late preterm (32-36 weeks)	248.16	118.19 to 378.14	0.0002	-82.06	-183.83 to 19.71	0.11
Very preterm (<32 weeks)	89.10	-272.32 to 450.51	0.63	-343.22	-646.85 to 39.60	0.03

Adjusted for fetal sex, parity, age of mother (linear and quadratic), method of conception and year of birth