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Short title: Multifetal reduction of triplets to twins

Multifetal reduction of triplets to twins compared with non-reduced twins: a meta-analysis

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Key message

The current systematic review and meta-analysis combined data from 22 studies evaluating the perinatal outcomes in twin pregnancies following multifetal pregnancy reduction compared with non-reduced twins. Fetal reduction of triplets to twins was found to be associated with comparable perinatal outcomes to that of non-reduced twins.

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Abstract

The current systematic review and meta-analysis evaluates the perinatal outcomes in twin pregnancies following multifetal pregnancy reduction (MPR) compared with non-reduced twins. We considered all studies comparing perinatal outcomes of twin pregnancies following MPR to non-reduced twin pregnancies. Our search yielded 639 publications, of which 91 were assessed for eligibility. A total of 22 studies met our inclusion criteria. Overall, fetal reduction of triplets to twins resulted in comparable perinatal outcomes to non-reduced twins with regards to gestational age and birthweight at delivery, pregnancy loss prior to 24 weeks, as well as the development of gestational diabetes and hypertensive disorders of pregnancy. Of all outcomes, only the Caesarean section rate was significantly higher in the MPR group compared with the non-reduced twins group with an odds ratio of 1.95 (95% confidence interval 1.33–2.87). This meta-analysis suggests that MPR of triplet pregnancies to twins is associated with comparable perinatal outcomes to that of non-reduced twins. This information can further help in guiding, and probably reassuring, clinician and patient decision-making when faced with high-order multifetal pregnancies.

Keywords: meta-analysis, multifetal pregnancy reduction, non-reduced twins, perinatal outcome, triplets

Introduction

Triplet pregnancies are considered undesired sequelae of assisted reproductive technologies as they are associated with increased risk of perinatal morbidity and mortality (Garg *et al.*, 2010; Salihu *et al.*, 2003; Wen *et al.*, 2004).

The ongoing worldwide efforts to minimize the occurrence of high-order multiple pregnancies is encouraging. While some reduction can be achieved through single-embryo transfer following IVF, a substantial proportion of these pregnancies are the product of ovulation induction and superovulation methods, in which multifetal pregnancies are not as preventable (Braude, 2006; Clua *et al.*, 2012; Practice Committee of American Society for Reproductive Medicine, 2012). Nevertheless, if preventative measures fail, the option of multifetal pregnancy reduction (MPR) is a reasonable interventional step to be considered in order to improve the pregnancy outcome.

The literature on the risks and benefits of MPR is limited by a lack of randomized trials assessing safety and efficacy (Dodd *et al.*, 2015). Earlier data from a meta-analysis concluded that MPR carries a significantly higher risk of procedure-related pregnancy loss before 24 weeks' gestation compared with the expectant management of triplet pregnancies (Papageorghiou *et al.*, 2006). A more recent meta-analysis, based on a MEDLINE database search, found no difference in the pregnancy loss rate at <24 weeks for triplets reduced to twins compared with that of non-reduced triplets. However, the prematurity rate under 32 and 28 weeks was significantly lower for the reduced group (Wimalasundera, 2010).

When counselling prior to MPR, a major difficulty is the lack of clarity with regards to the outcome of twin pregnancies following reduction compared with that of non-reduced twin pregnancies. While some studies found no difference in either gestational age or mean birthweight between the groups (Haas *et al.*, 2014; Hershko-Klement *et al.*, 2013; Okyay *et al.*, 2014), others did find a benefit for the non-reduced twins (Cheang *et al.*, 2007; van de Mheen *et al.*, 2014). One study even reported an advantage for the MPR group over the non-reduced twins with regards to gestational age and birthweight at delivery (Yaron *et al.*, 1999). Thus, information regarding the outcome of twin pregnancies following MPR compared with non-reduced twins is based on limited and conflicting data. To address this gap in knowledge, the objective of this meta-analysis is to analyse the current literature regarding perinatal outcomes in twin pregnancies resulting from MPR compared with non-reduced twins.

Materials and methods

We conducted a systematic review of the available published data in accordance with the MOOSE recommendations (Stroup *et al.*, 2000).

Data sources and search strategy

A search was conducted by an experienced librarian for possibly relevant published articles up to February 2016. Electronic databases that were used in our search included MEDLINE, non-indexed MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science. The search strategy is detailed in **Supplementary Tables 1–6**. Reference lists from retrieved citations were screened for other possibly relevant literature.

Study selection and data abstraction

We considered all studies reporting data that compared multifetal pregnancy reduction of triplet pregnancies to non-reduced twin pregnancies. No publishing date, language or location limitations were imposed. Initially, all records were screened by title and abstract. Full-text articles from the relevant references were retrieved and evaluated for possible inclusion by two independent reviewers. Inclusion criteria were: triplet pregnancies that were reduced to twins; a comparison group of non-reduced twins; known method of reduction; and reported perinatal/neonatal outcomes. Review articles, case reports, case series and studies reporting chorionicity other than trichorionic–triamniotic were excluded. Primary outcomes were pre-specified as gestational age and birthweight at delivery, as well as pregnancy loss before 24 weeks' gestation. Secondary outcomes were defined as premature delivery prior to 28, 32 or 36 weeks' gestation, development of gestational diabetes or hypertensive disorders of pregnancy, and the rate of Caesarean section. The degree of agreement between the reviewers was assessed using a Kappa test and a value of 0.8 or more was considered to represent good agreement. Discrepancies between the reviewers were resolved by a third reviewer. Authors of the accepted studies were contacted for missing data. Duplicate publications of data were identified and excluded from data synthesis.

Data synthesis

Data analysis was performed using the Cochrane Review Manager 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark). Pooled odds ratios (ORs) for dichotomous outcomes or mean difference for continuous outcomes were calculated using a fixed-effects model. The I^2 test was performed to assess heterogeneity and a value of less than 50% was considered to represent low heterogeneity.

Assessment of study quality

The quality of each accepted article was assessed using the Newcastle–Ottawa Scale (NOS), which has been validated for use in non-randomized studies (Wells *et al.*, 2015). Quality assessment was performed by two independent reviewers.

Results

Search results

A total of 639 records were identified through the electronic database search (**Supplementary Figure 1**). After removal of duplicates, 375 records were screened by title and abstract, and of them 91 full-text records were found to be relevant and assessed for possible inclusion. Sixty-nine full-text articles were excluded for the following reasons: no control group (n = 43); comparison group other than non-reduced twins (n = 19); reported chorionicity other than trichorionic–triamniotic (n = 7). Twenty-two cohort studies (**Table 1**) met the final inclusion criteria (Alexander *et al.*, 1995; Angel *et al.*, 1999; Antsaklis *et al.*, 1999; Ata *et al.*, 2011; Brambati *et al.*, 2004; Cheang *et al.*, 2007; Depp *et al.*, 1996; Donner *et al.*, 1992; Groutz *et al.*, 1996; Haas *et al.*, 2014; Hershko-Klement *et al.*, 2013; Iberico *et al.*, 2000; Lipitz *et al.*, 1996; Macones *et al.*, 1993; Mansour *et al.*, 1999; Nevo *et al.*, 2003; Okyay *et al.*, 2014; Selam *et al.*, 1999; Smith-Levitin *et al.*, 1996; Torok *et al.*, 1998; Van de Mheen *et al.*, 2014; Yaron *et al.*, 1999). We could not identify any overlapping databases among the accepted articles. The agreement between the independent reviewers on study inclusion was considered good (Kappa = 0.88). Of the 22 studies that met our inclusion criteria, six could not be included in the quantitative synthesis. Four of these studies included in their study group higher-order multifetal pregnancies and did not report data separately on triplet pregnancies (Antsaklis *et al.*, 1999; Donner *et al.*, 1992; Iberico *et al.*, 2000; Nevo *et al.*, 2003) and two studies did not have the appropriate data on the outcomes of interest (Alexander *et al.*, 1995; Depp *et al.*, 1996).

MPR versus non-reduced twins: perinatal outcomes

The quantitative forest plot summaries regarding the primary outcomes are presented in **Figures 1–3**. Briefly, fetal reduction of triplets to twins by transabdominal KCl injection or by other methods, namely earlier transvaginal MPR either through injection of KCl, 0.9% NaCl solution or aspiration, was associated with a comparable outcome to non-reduced twins in relation to gestational age at delivery [mean difference −0.16 weeks (95% confidence interval (CI) −0.12 to 0.44), I^2 = 67%] (**Figure 1**), birthweight at delivery [mean difference −33.67 g (95% CI −78.33 to 10.99), I^2 = 80%) (**Figure 2**) and pregnancy loss before 24 weeks' gestation (OR 1.27, 95% CI 0.83–1.96, I^2 = 34%; **Figure 3**).

Table 2 provides detailed additional information with regards to the secondary outcomes among the two groups of interest. Their individual forest plots are given in **Supplementary Figures 2A–F**. Similarly, no differences were seen between the groups with respect to the rate of premature delivery prior to 36 (OR 1.29, 95% CI 1.01–1.65, I^2 = 0%), 32 (OR 1.09, 95% CI 0.80–1.47, I^2 = 32%) or 28 weeks' gestation (OR 0.93, 95% CI 0.59–1.47, I^2 = 0%), development of gestational diabetes (OR 0.87, 95% CI 0.46–1.61, I^2 = 0%) and hypertensive disorders of pregnancy (OR 1.23, 95% CI 0.82–1.84, I^2 = 16%). The above results were comparable even when analysis was limited to transabdominal KCl injection only (**Table 2**).

The only notable finding in our meta-analysis was the rate of Caesarean section, which was significantly higher in the MPR group (n = 165) compared with the non-reduced twins (n = 537), with an OR of 1.95 (95% CI 1.33–2.87, I^2 = 29%). This difference was also apparent when analysis was limited to studies reporting fetal reduction via transabdominal KCl injection, with an OR of 2.16 (95% CI 1.42–3.28, I^2 = 22%).

Publication bias

Publication bias was only assessed for gestational age and birthweight at delivery due to the small number of studies included in the analysis of the other outcomes. The funnel plots depicted in **Supplementary Figures 3A, B** were not suggestive of publication bias.

Discussion

It is generally accepted that MPR of triplet pregnancies to twins results in improved pregnancy outcomes when compared with non-reduced triplets (Practice Committee of American Society for Reproductive Medicine, 2012; Wimalasundera, 2010). In this meta-analysis we endeavoured to assess whether the outcome of pregnancies following MPR of triplets to twins is comparable to pregnancies of non-reduced twins.

Overall, our meta-analysis resulted in a comparable perinatal outcome between the MPR group and the non-reduced twins group with regards to the rate of prematurity prior to 28, 32 or 36 weeks, birthweight at delivery, pregnancy loss prior to 24 weeks, as well as the development of gestational diabetes and hypertension disorders of pregnancy. The only difference in our analysis was the Caesarean section rate, which was significantly higher in the MPR group compared with the non-reduced twins group.

When patients face the difficult decision of whether or not to undergo MPR, they have to consider not only the medical risks and benefits that are linked to the procedure. MPR poses a serious ethical dilemma as well as a psychological burden to couples who in most cases have previously struggled with a prolonged history of infertility (Bergh *et al.*, 1999; Collopy, 2004; Evans and Britt, 2010). Moreover, it is estimated that over 10% of all women who are seeking MPR are over 40 years of age, further adding to the complexity of the decision process, as advanced maternal age is associated with an increased risk of other pregnancy complications (Gilbert *et al.*, 1999; Reefhuis and Honein, 2004; Seoud *et al.*, 2002). In that respect, our findings might further help alleviate the apprehensiveness of patients prior to the MPR procedure.

The risks associated with MPR can be considerably improved with increasing operator experience. The overall miscarriage rate of 6.5% (range 3.6–15.8%) in our meta-analysis is in agreement with previous reports that the MPR loss rate of triplets by an experienced operator should not be greater than 5% (Evans *et al.*, 2001; Stone *et al.*, 2002). It should be noted that the reported miscarriage rate was not limited to the immediate post-procedure period and can even occur several weeks after the procedure, i.e. in the mid second trimester. Late miscarriages, as well as differences in the operator’s experience, may explain the wide range of reported miscarriage rates. Angel *et al.* (1999) reported their three pregnancy losses at 18.6, 20.1 and 22.4 weeks’ gestation, whereas Hershko-Klement *et al.* (2013) described a mean gestational age of the pregnancy loss of 18.9 weeks’ gestation. This late occurrence of pregnancy loss was previously postulated to occur as a secondary response to the resorbing fetoplacental tissue rather than solely due to the reduction procedure itself (Ata *et al.*, 2011; Papageorghiou *et al.*, 2006).

The only significant difference in outcome in our meta-analysis was a higher rate of Caesarean section among the MPR group compared with the non-reduced twins group. A physiological hypothesis for this intriguing finding cannot be easily established. Nevertheless, due to the observational nature of these studies, the difference in Caesarean section rates may be attributed to confounding factors. The MPR groups will be expected to have a higher rate of pregnancies following assisted reproductive technologies and possibly a higher likelihood of advanced maternal age. Although the data are not sufficient to establish our hypothesis, such differences between the study and control populations can easily confound the results to reflect a higher rate of Caesarean section in the MPR group.

Strengths and limitations

This systematic review and meta-analysis is inherently limited, as are all meta-analyses of observational studies, by the quality of the included studies, and pooling of the results from multiple studies does not reduce the risk of bias. Thus the possibility of confounding factors must always be taken into account, as postulated above regarding the higher rate of Caesarean section in the MPR group. Overall, the studies included in this meta-analysis in most cases did not appropriately control for possible confounders such as maternal age, method of conception and socioeconomic status. Therefore, the risk of bias, mainly selection bias, is the main limitation of this meta-analysis. Another limitation of our study is the fact that for some of the outcomes assessed we have found a high I^2 value, indicating significant heterogeneity. The heterogeneity of the results may reflect varying levels of expertise in the MPR procedure and differences in patient population between the studies, as well as differences derived from the time-span of the studies that may reflect advances in perinatal and neonatal care.

Despite these limitations, in the absence of data from randomized controlled trials, the current meta-analysis summarizes the best available evidence with regards to perinatal outcomes after fetal reduction when compared with non-reduced twins. Although publication bias should always be considered in systematic reviews, our analysis suggests that publication bias is not a major concern in this case, thus lending support to the validity of the results.

In conclusion, this meta-analysis suggests that MPR of triplet pregnancies to twins is associated with comparable perinatal outcomes to that of non-reduced twins. However, as none of the included studies were randomized controlled trials, the results should be interpreted cautiously in this respect. Nevertheless, the information provided from this meta-analysis can further help in guiding clinician and patient decision-making when faced with high-order multifetal pregnancies.

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Figure 1 Forest plot of the included studies reporting data on gestational age at delivery.

Figure 2 Forest plot of the included studies reporting data on birthweight at delivery.

Figure 3 Forest plot of the included studies reporting data on pregnancy loss before 24 weeks.

Supplementary Figure 1 The systematic review flow chart of study selection.

Supplementary Figure 2A Forest plot of the included studies reporting data on preterm delivery <36 weeks.

Supplementary Figure 2B Forest plot of the included studies reporting data on preterm delivery <32 weeks.

Supplementary Figure 2C Forest plot of the included studies reporting data on preterm delivery <28 weeks.

Supplementary Figure 2D Forest plot of the included studies reporting data on gestational diabetes.

Supplementary Figure 2E Forest plot of the included studies reporting data on hypertension disorders of pregnancy (pregnancy-induced hypertension, pre-eclampsia).

Supplementary Figure 2F Forest plot of the included studies reporting data on the rate of Caesarean section.

Supplementary Figure 3A Funnel plot assessment for publication bias for gestational age at delivery.

Supplementary Figure 3B Funnel plot assessment for publication bias for birthweight at delivery.

Table 1 Studies that met the inclusion criteria.

Author	Year	Reduction group (*n*)	Control group (*n*)	Gestational age at reduction (weeks)	Approach of reduction	Method of reduction	Years of reduction	Location
Alexander	1995	12	38	10	Mixed	KCl	1988–1993	Birmingham, AL, USA
Angel	1999	19	24	Not documented	Abdominal	KCl	1993–1998	Tampa, FL, USA
Antsaklis	1999	108	135	11	Abdominal	KCl	1992–1996	Athens, Greece
Ata	2011	26	483	12–14	Abdominal	KCl	1997–2009	Montreal, QC, Canada
Brambati	2004	155	147	11–13	Abdominal	KCl	1989–2002	Milan, Italy
Cheang	2007	176	389	10–14	Abdominal	KCl	1998–2004	Taipei, Taiwan
Depp	1996	113	61	9–12	Abdominal	KCl	Not documented	Philadelphia, PA, USA
Donner	1992	13	32	10	Abdominal	KCl	1985–1990	Brussels, Belgium
Groutz	1996	30	30	10	Vaginal	NaCl	1992–1994	Tel Aviv, Israel
Haas	2014	55	78	6–8	Vaginal	Aspiration	2005–2011	Tel Aviv, Israel
Hershko-Klement	2013	70	394	11–13	Abdominal	KCl	2004–2010	Ramat-Gan, Israel
Iberico	2000	98	134	7–9	Vaginal	Heart puncture	1996–1999	Pennsylvania, USA
Lipitz	1996	43	134	9	Abdominal	KCl	1989–1993	Ramat-Gan, Israel
Macones	1993	47	63	9–12	Abdominal	KCl	1988–1992	Philadelphia, PA, USA
Mansour	1999	26	40	6–9	Vaginal	Mixed (aspiration/KCl)	1990–1997	Cairo, Egypt
Nevo	2003	64	64	7–11	Vaginal	Mixed (aspiration/KCl)	1989–1997	Haifa, Israel
Okyay	2014	43	233	11–14	Abdominal	KCl	2003–2012	Izmir, Turkey
Selam	1999	49	140	10–13	Abdominal	KCl	1986–1997	New York, NY, USA
Smith-Levitin	1996	59	88	10–12	Abdominal	KCl	1990–1994	New York, NY, USA
Torok	1998	223	136	10–13	Abdominal	KCl	1986–1996	New York, NY, USA

Van de Mheen	2014	86	824	10–15	Abdominal	KCl	2000–2010	Amsterdam, Netherland
Yaron	1999	143	812	9–15	Abdominal	KCl	1987–1996	Detroit, MI, USA and Tel Aviv, Israel

Table 2 MPR versus non-reduced twins: other perinatal outcomes

	Studies reporting transabdominal KCl injection only				Studies including other methods of reduction (if available)			
Outcome	Studies	Cases (MPR/control)	OR (95% CI)	I^2	Studies	Cases (MPR/control)	OR (95% CI)	I^2
Preterm delivery <36 weeks	4	501/747	1.29 (1.01, 1.65)	0%				
Preterm delivery <32 weeks	7	689/2454	1.13 (0.83, 1.53)	30 %	8	744/2532	1.09 (0.80, 1.47)	32%
Preterm delivery <28 weeks	8	789/2675	0.93 (0.59, 1.47)	0%				
Gestational diabetes	4	168/408	0.77 (0.34, 1.73)	0%	5	223/486	0.87 (0.46, 1.61)	0%
Hypertension disorders[a]	7	290/712	1 (0.63, 1.58)	0%	8	345/790	1.23 (0.82, 1.84)	16%
Rate of Caesarean section[b]	3	135/507	2.16 (1.42, 3.28)	22 %	4	165/537	1.95 (1.33, 2.87)	29%

CI = confidence interval; MPR = multifetal pregnancy reduction.
[a] Pregnancy-induced hypertension or pre-eclampsia.
[b] Significantly more Caesarean deliveries in the MPR group.