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Review

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

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KEY MESSAGE

Multifetal pregnancy reduction of triplets to twins is associated with a better pregnancy outcome compared with that of non-reduced triplets. Should primary prevention strategies for high order multiple pregnancies fail, multifetal pregnancy reduction may be the appropriate alternative to reduce perinatal morbidity and mortality in trichorionic triplet pregnancies.

A B S T R A C T

The current systematic review and meta-analysis evaluate the perinatal outcomes in twin pregnancies following multifetal pregnancy reduction (MPR) compared with non-reduced triplet pregnancies. All studies comparing perinatal outcome of twin pregnancies following MPR to non-reduced triplet pregnancies were considered. MEDLINE, non-indexed MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science were searched for relevant published articles up to August 2016. The search yielded 653 publications of which 92 were assessed for eligibility. A total of 24 studies met the inclusion criteria. Overall, the outcomes of pregnancies following MPR were better compared with expectantly managed triplets. The MPR group delivered at a later gestational age and was less likely to be delivered before 32 or 28 weeks' gestation. Newborns in the MPR group had significantly higher birthweight at delivery (mean difference 500 g [95% CI 439.95, 560.04]). Rates of pregnancy loss before 24 weeks' gestation and overall infant survival were comparable between the groups. This meta-analysis suggests that MPR of triplet pregnancies to twins is associated with improved perinatal outcome compared with non-reduced triplets. Should primary prevention of high order multiple pregnancy fail, MPR is an appropriate alternative to minimize the perinatal morbidity and mortality of triplet pregnancies.

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Introduction

There is a growing trend in recent years for shifting childbirth to a later time in women's lives (Royal College of Obstetricians and Gynaecologists [RCOG] statement on later maternal age, 2009; Hamilton et al., 2015). Consequently, delayed childbearing is associated with increased likelihood of infertility and the need for assisted reproductive technology use which constitutes a major risk factor for the development of high order multiple pregnancies (Braude, 2006; European IVF-Monitoring Consortium (EIM) et al, 2016). The occurrence of high order multiple pregnancies, whether achieved spontaneously or with assisted reproductive technology, pose serious medical and ethical dilemmas to couples (Bergh et al., 1999; Chaabane et al., 2015; Evans and Britt, 2010; Practice Committee of American Society for Reproductive Medicine, 2013).

Preterm delivery is the most common cause of morbidity and mortality in triplet pregnancies. Recent data suggests that 41% of the triplets are delivered prior to 32 weeks' gestation, 37% are very low birthweight under 1500 g and that nearly 75% are admitted to the neonatal intensive care unit (NICU) (Drugan and Weissman, 2017; Hamilton et al., 2015). Nevertheless, the tremendous advances in neo-natal intensive care in recent years have led to improved survival of preterm neo-nates, including of extremely premature newborns at the threshold of viability (Horbar et al., 2012). In addition, it is accepted that the risks associated with multifetal pregnancy reduction (MPR) can be substantially reduced with increasing experience (Evans et al., 2001; Stone et al., 2002). With that in mind, prospective parents of triplet pregnancies are facing nowadays even greater decision challenges than in the past, that is: 'to reduce or not to reduce' triplet pregnancies.

The decision between expectant management and multifetal pregnancy reduction (MPR) is an uneasy one, as both involve risks that cannot be accurately predicted (Practice Committee of American Society for Reproductive Medicine, 2012). While expectant management carries a higher risk of adverse perinatal outcomes, mainly attributed to significant complications of prematurity (Garg et al., 2010; Salihu et al., 2003; Wen et al., 2004), the interventional step of MPR is associated with a potential risk of procedure-related pregnancy loss. Two earlier meta-analyses of smaller magnitude and with some methodological differences, reported contradictory results. While one study concluded that MPR carries a significant, nearly double (8.1%), higher risk of procedure related pregnancy loss before 24 weeks' gestation compared with expectant management of triplet pregnancies (4.4%, $P = 0.036$) (Papageorghiou et al., 2006), a second meta-analysis found no difference in the pregnancy loss rate <24 weeks' gestation for triplet pregnancies reduced to twins (7%) compared with that of non-reduced triplets (7.4%) (Wimalasundera, 2010). The prematurity rates under 28 and 32 weeks, however, were significantly lower for the reduced group in both studies.

Therefore, information regarding the outcome of twin pregnancies following MPR compared with non-reduced triplets is based on limited and conflicting data. To address this inconsistency in knowledge, this updated meta-analysis aimed to evaluate the perinatal outcomes in twin pregnancies resulting from MPR compared with expectantly managed triplet pregnancies.

Materials and methods

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

Data sources and search strategy

A search was conducted by an experienced librarian for possibly relevant published articles up to August 2016. Electronic databases that were used in this research included; MEDLINE, non-indexed MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science. The search strategy is detailed in Supplementary **Tables S1–S6**. Reference lists from retrieved citations were screened for other possibly relevant literature.

Study selection and data abstraction

All studies reporting data that compared multifetal pregnancy reduction of triplet pregnancies with non-reduced triplet pregnancies, were considered. 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 triplets; known method of reduction; and reported perinatal/neo-natal outcomes. Review articles, case reports, case series and studies reporting chorionicity other than trichorionic-triamniotic were excluded. 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's Review Manager 5.3 software (Review Manager [RevMan]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Pooled odds ratio for dichotomous outcomes or mean difference for continuous outcomes were calculated using a random effects model. 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 653 records were identified through searching the electronic database. (Supplementary **Figure S1**). After removal of duplicates, 389 records were screened by title and abstract, and of them 92 full text records were found to be relevant and assessed for possible inclusion. Sixty-six full-text articles were excluded for the following reasons: no control group ($n = 35$); comparison group of non-reduced twins ($n = 22$), and chorionicity other than trichorionic-triamniotic ($n = 9$). Among the accepted 26 articles two studies were found (Papageorghiou et al., 2002; Sebire et al., 1997) reporting data that were included in a more

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