



Risk of premature delivery and fetal loss in trichorionic triplet pregnancies: multicenter study on fetal reduction versus expectant management

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ABSTRACT

Objective: to assess the impact of embryo-reduction (ER) in reducing the risk of miscarriage and premature birth in trichorionic triplet pregnancies. Short term outcome, incidence of cerebral palsy and periventricular leukomalacia were evaluated for each neonate of both groups.

Materials and methods: pregnancies enrolled for this study were recruited in the Unit of Prenatal Diagnosis of Piero Palagi Hospital, USL Centro Toscana, Florence and Unit of Fetal Medicine of Careggi Hospital, University of Florence. This was a multicentric retrospective study on trichorionic triamniotic triplet pregnancies with three live fetuses at 10–13 +6 weeks of gestation managed expectantly or by ER. The two groups were compared for the rates of miscarriage, defined as pregnancy loss before 24 weeks, early preterm birth before 32 weeks, birth weight and early neonatal outcome. Short term outcome, incidence of cerebral palsy and periventricular leukomalacia were evaluated for each neonate of both groups.

Results: 86 trichorionic triamniotic pregnancies met our inclusion criteria. 60 (69,8 %) opted for expectant management (group 1); 26 (30,2%) had ER in the first trimester (10–13 +6 weeks) (group 2). The percentage of miscarriage were not significantly different between the two groups ($p=0,688$), otherwise the percentage of early preterm delivery before 32 weeks was higher in those managed expectantly (20/60, 33,3%) group 1, 1/26 (3,8%) group 2 ($p < 0,006$). The incidence of cerebral palsy and periventricular leukomalacia were not significantly different between the two groups.

Discussion: results of our study are consistent with international literature confirming that ER is associated with an increased gestational age at birth and mean birth weight, without any difference in terms of early neonatal outcome; however the ER procedure does not seem to increase the rate of miscarriage. Our data are not sufficient to recommend a policy of pregnancy reduction to women with trichorionic triplet pregnancies.

Keywords: trichorionic pregnancy, premature birth, cerebral palsy, periventricular leukomalacia, miscarriage, embrioreduction

SOMMARIO

Obiettivo: valutare l'impatto della embrioreduzione nel ridurre il rischio di perdita dell'intera gravidanza, di parto prematuro e di outcome a breve termine in termini di incidenza di paralisi cerebrale e di leucomalacia periventricolare nella gravidanza tricolore triamniotica.

Materiali e metodi: i casi entrati nello studio sono stati reclutati presso l'Unità di Diagnosi prenatale del Presidio Ospedaliero Piero Palagi, USL Centro Toscana, Firenze e presso l'Unità di Medicina Fetale dell'Azienda ospedaliero Universitaria di Careggi, Firenze. Lo studio multicentrico retrospettivo riguarda gravidanza tricolore triamniotiche con tre feti vivi tra 10 e 13 settimane più 6 giorni che sono state sottoposte ad intervento di embrioreduzione o ad un trattamento di semplice attesa.

I due gruppi sono stati paragonati per incidenza di aborto, definito come perdita di tutta la gravidanza entro 24 settimane di amenorrea, parto prematuro entro 32 settimane, peso medio alla nascita e outcome neonatale a breve termine, inteso come incidenza di paralisi cerebrale e/o leucomalacia periventricolare.

Risultati: sono state ammesse allo studio 86 gravidanze tricolori triamniotiche. In 60 (69,8 %) le donne hanno optato per un trattamento di attesa (gruppo 1); 26 (30,2%) si sono sottoposte ad embrioreduzione nel primo trimestre di gravidanza (10–13 +6 settimane) (gruppo 2). La percentuale di aborto spontaneo non è stata significativa nei due diversi gruppi ($p=0,688$), mentre la percentuale di parto prematuro prima di 32 settimane è stata significativamente più elevata nel gruppo sottoposto al trattamento di attesa (20/60, 33,3%) gruppo 1, 1/26 (3,8%) gruppo 2 ($p < 0,006$). L'incidenza di paralisi cerebrale e di leucomalacia periventricolare non ha presentato differenze significative nei due gruppi esaminati.

Discussione: i risultati del nostro studio sono conformi a quelli emergenti dalla letteratura per quanto riguarda l'associazione del procedimento di embrioreduzione nelle gravidanze tricolori triamniotiche con un aumento della durata della gravidanza e del peso medio neonatale, mentre non sono state evidenziate differenze in termini di outcome neonatale precoce. D'altra parte la procedura di embrioreduzione non ha comportato una percentuale di perdita dell'intera gravidanza entro le 24 settimane superiore al gruppo non trattato. I nostri dati pertanto non confermano che ci siano motivi sufficienti a raccomandare una politica di embrioreduzione sistematica nelle donne con gravidanza tricolore triamniotica.

INTRODUCTION

The incidence of multiple pregnancies has substantially increased in the last years, mainly due to the widespread of assisted reproduction techniques. Approximately two thirds of the increase is due to in-vitro fertilization (IVF) and ovulation induction⁽¹⁾. Multiple pregnancies are associated with a higher frequency of maternal and neonatal complications compared with single and twin pregnancies, most related to the increased risk of premature delivery and low birth weight⁽²⁾. Hypertensive disorders, elective caesarean section rate and post partum haemorrhage are the most recurring maternal morbidity; congenital malformations, prolonged hospitalization and neurodevelopment impairment related to prematurity are the most frequent neonatal morbidity^(3,4). As recommended by the American Society for Reproductive Medicine (ARSM)⁽⁵⁾ and the Society for Assisted Reproductive Technology (SART), in many countries the number of embryos transferred has been limited in order to decrease the triplet and higher order pregnancies⁽⁶⁾.

Many authors agree that in multiple pregnancies the embryo-reduction (ER) is performed in order to decrease the risk of preterm delivery and neonatal neurological impairment⁽⁷⁾. The decision whether carry out ER is still controversial^(8,9); many studies comparing triplet pregnancies embryo-reduced with those with an

expectant management, report a neonatal survival rate similar in both groups⁽¹⁰⁾, with an increase risk of miscarriage within a few weeks after the procedure. The aim of our study was to compare the risk of early premature delivery before 32 weeks and the rate of miscarriage before 24 weeks in triplet trichorionic triamniotic pregnancies managed with ER or expectantly.

MATERIAL AND METHODS

Pregnancies enrolled for this retrospective study were recruited in the Unit of Prenatal Diagnosis of Piero Palagi Hospital, USL Centro Toscana, Florence and Unit of Fetal Medicine of Careggi Hospital, University of Florence.

We reviewed our database for triplet pregnancies between January 2007 and December 2013. All triplet pregnancies with 3 fetuses alive at the 11-13+6 weeks ultrasound scan were enrolled. Maternal and pregnancy characteristics are reported in **Table 1**.

In all enrolled pregnancies, an ultrasound examination at 11-13+6 weeks was performed. Chorionicity and amnioticity, placental position, detection of any malformations and nuchal translucency were assessed for each fetus. Gestational age was calculated by crown-rump

Table 1.

Maternal and pregnancy characteristics of trichorionic triplet pregnancies managed expectantly or reduced to twins at 12 (10–14) weeks

	Expectant (60) n (%)	Embrioreduction(26) n (%)	p	OR
Maternal age, years (median, IQR)	35 (32-37)	37 (31-40)	0.182	-
Conception-ART	56 (93.3%)	25 (96.2%)	0.3014	-
Conception-non ART	4 (6.7%)	1 (3.8%)	1	-
Gestational Age at Delivery (weeks+days) (median, IQR)	32+2 (30+0-34+0)	35+6 (34+0-37+6)	0.000	-
Average Birthweight (grams) (median, IQR)	1566 (1175-1846)	2260 (1845-2605)	0.000	-
Delivery < 24 weeks	3 (5)	1 (3.8)	0.688	0.992
Delivery between 24+0 and 28+6 weeks	6 (10)	1 (3.8)	0.362	0.939
Delivery between 29+0 and 31+6 weeks	14 (23.3)	0	0.006	0.076
Delivery after 32 weeks	36 (60)	21 (80.7)	0.006	4.483
Pregnancies with no survivors	4 (2.4)	3 (11.5)	0.356	1.055
Pregnancies with 1 survivors	0	4 (15.4)	0.007	1.182
Pregnancies with 2 survivors	4 (2.4)	19 (73)	0.000	3.467
Pregnancies with 3 survivors	52 (86.7)	0	na	-
Pregnancies with at least 1 survivor	56 (93.3)	23 (88.5)	0.356	0.587

length of the largest fetus. Dichorionic triamniotic and monochorionic triamniotic pregnancies were excluded from the study. Parents were counselled by an obstetric specialized in Fetal Medicine regarding the opportunity to keep expectant management or to ER. Due to the lack of scientific evidence, the decision depended on parents' choice. All patients signed out an informed consent procedure. All ER procedures were performed transabdominally; an ultrasound scan was performed before the procedure. Fetus position, chorionicity, measurement of nuchal translucency (NT), placental position and its proximity to the cervix were evaluated in order to find the best fetus to achieve. Intracardiac injection of potassium chloride was done under ultrasound guide⁽¹¹⁾. Maternal and neonatal outcomes were collected in a database. Outcomes considered have been: rate of miscarriage before 24 weeks of gestational age, early preterm delivery, defined as birth between 24 and 32 weeks of gestation. Preterm delivery and mean gestational age at birth were calculated for both groups. The number of survivors fetuses in each group was calculated.

Short term outcome, incidence of cerebral palsy and periventricular leukomalacia were evaluated for each neonate of both groups.

Statistical analysis was performed with Student's T-Test, statistical significance was assumed for p-value <0.05.

Maternal characteristics and ultrasound findings were archived using View-Point (GE Medical Systems, Milwaukee, USA) and Astraia (Astraia Software GmbH, Munich, Germany) and data were recorded prospectively in a database Excel (Word, Office, Microsoft, USA).

RESULTS

Finally 86 triplet pregnancies met our inclusion criteria. Among these patients 60/86 (69.8 %) opted for expectant management (group 1) and 26/86 (30,2 %) chose to undergo ER.

According to the evidence that no difference was reported in literature in terms of obstetric outcome in case of spontaneous or elective embryo-reduction, we combined the data of these two pregnancies in group 2⁽¹²⁾.

Maternal and obstetric characteristics of both two groups of trichorionic triplet pregnancies and statistical analysis of the data, are shown in Table 1. Among the expectant management (group 1) 3/60 (5%) achieved pregnancy spontaneously, and

57/60 (95%) following ART techniques.

In the group 2, pregnancies ER, only one (1/26, 3.8%) spontaneous triplet trichorionic pregnancy was reported; the remaining 96,2 % pregnancies were obtained with ART techniques.

There was no statistical difference between the two groups.

The mean age at conception was 35 (32-37) years in group 1 and 37 (31-40) years in group 2 (p = 0.182). The percentage of abortions in our population was 3/60 (5%) in group 1 and 1/26 (3.8%) in group 2 (p = 0,688). The rate of preterm delivery was 20/60 (33.3%) in group 1 and 1/26 (3.8%) in group 2 (p < 0.006). The mean gestational age at delivery was 32.2 (30-30+4) weeks in group 1 and 35.6 (34-37+6) weeks in group 2 (p = 0.000). The average birthweight was 1566 grams in group 1 and 2260 grams in group 2 (p=000). No case of cerebral palsy and periventricular leukomalacia was reported in our neonatal population in both groups.

DISCUSSION

The data of our observational study, suggests that ER is associated with a risk of miscarriage not significantly greater than the expectant management (p = 0,688), although literature reports a risk of 4% risk increased miscarriage in the group of pregnancies reduced to twins⁽¹³⁾.

No case of cerebral palsy and periventricular leukomalacia was reported in our neonatal population in both groups.

Embryo-reduced pregnancies have not a significant reduction in terms of premature births under 29 weeks (10 % vs. 3.8%, p = 0.362); this gestational age is associated with an increased neonatal morbidity.

Otherwise we observed a decrease of preterm delivery between 29 and 32 weeks in the ER group (23.3 % vs 0%, p=0,006), and it explains the absence of cerebral palsy and periventricular leukomalacia in our neonatal population. In this study, ER is associated with a reduction of 28.9% of preterm deliveries (p <0.001). The average gestational age at delivery was higher in the group of reduced pregnancies on average of 29 days (p = 0.533), in agreement with data reported in the literature⁽¹³⁾.

In the group of embryo-reduced pregnancies (group 2) there is also a significant difference between the mean birth weight of 694 grams higher than in the group with the expectant management (p <0.001).

Due to the lack of randomized clinical trials, the choice to make an embryo-reduction is given by the will of the woman and the couple, supported by health care professionals that are able to offer an accurate counselling regarding maternal and perinatal morbidity and mortality risks.

Our study confirms the fact that embrioreduction procedure does not increase the risk of miscarriage before 24 weeks, but improves the gestational age at birth and the neonatal weight, without any difference in terms of early neonatal outcome.

In conclusion, the data of this study are consistent with the international literature on the

fact that the embryo-reduction is associated with prolongation of pregnancy and the increase in mean birth weight, which does not seem to have substantial clinical implications. Otherwise we have insufficient information about the long term outcome and on the well being of survivors . Our data are not sufficient to recommend a policy of pregnancy reduction to women with trichorionic triplet pregnancies. The most important factor in decreasing the incidence of multifetal pregnancies reductions is prevention⁽¹⁴⁾. Parents should be counselled that ER reduces the risk of early preterm delivery , without any difference in terms of early neonatal outcome.

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