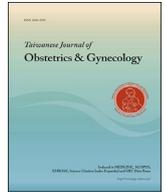




Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Early fetal reduction to twin versus prophylactic cervical cerclage for triplet pregnancies conceived with assisted reproductive techniques

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ARTICLE INFO

Article history:
Accepted 6 June 2017

Keywords:
Fetal reduction
Cervical cerclage
Triplet
Preterm labor
Prematurity

ABSTRACT

Objective: To compare the obstetric outcomes of triplet gestations managed by early fetal reduction to twins with those managed by prophylactic cervical cerclage in women conceived with assisted reproductive techniques (ART).

Materials and methods: Retrospective study of the pregnancy and neonatal outcomes of trichorionic triplet gestations achieved by ART and managed either by early transvaginal fetal reduction to twins (n = 53) or by prophylactic placement of cervical cerclage (n = 65).

Results: The pregnancy duration was significantly longer with fetal reduction and the incidences of delivery before 34 and 32 weeks gestational age were significantly lower with fetal reduction. Both miscarriage and live birth rates were comparable in the two groups. The incidences of very low birth weight (VLBW), neonatal respiratory distress syndrome (RDS), admission to neonatal intensive care unit (NICU) and early neonatal death (END) were significantly lower with fetal reduction.

Conclusion: Early transvaginal reduction of triplets to twins leads to improved obstetric outcomes as it decreases prematurity and its related neonatal morbidities and mortality without increase in the miscarriage rate. Early fetal reduction seems to be better than continuation of triplet pregnancies with prophylactic placement of cervical cerclage.

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Introduction

Iatrogenic multifetal pregnancies have been increased due to increased use of assisted reproductive techniques (ART) [1]. These pregnancies have a higher incidence of fetal and neonatal complications including, spontaneous miscarriage, intrauterine growth restriction (IUGR), preterm labor, low birth weight (LBW) and perinatal morbidities and mortality [2].

Limiting the number of transferred embryos or the use elective single embryo transfer policy has been advocated to avoid iatrogenic multifetal pregnancy [3]. Fetal reduction and prophylactic placement of cervical cerclage have been used as secondary options for management of multifetal pregnancies aiming at reducing the complications related to this problem [4,5].

When compared to expectant management, reduction of triplets to twins decreased the fetal and neonatal morbidities and mortality in many reports [6–8]. However, the results of prophylactic placement

of cervical cerclage in triplet gestations are still controversial. Some studies found no benefit of this management option over the expectant management [9–12].

To our knowledge, all studies considering fetal reduction or prophylactic placement of cervical cerclage as management options for triplet pregnancies have compared either of these two options to the expectant management but not to each other. Therefore, we aimed in this study to compare the obstetric outcomes of triplet gestations managed by early fetal reduction to twins with those managed by prophylactic cervical cerclage in women conceived with ART.

Materials and methods

Study design

This was a retrospective study conducted during the period from January 2011 to December 2016 in Mansoura University Hospital and private practice settings in Mansoura, Egypt. The study was approved by the Mansoura Faculty of Medicine Institutional Research Board (Code No. R/15.08.37). The main inclusion

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criterion was trichorionic triplet pregnancies achieved by ART. For all women, transvaginal sonography (TVS) scan was performed at 6–7 weeks of gestation to confirm presence of three intrauterine gestational sacs with presence of only one living embryo in each sac. Parents were then counseled regarding the options of early fetal reduction, prophylactic placement of cervical cerclage or expectant management. The decision of management option depended essentially on the choice of the parents because there was no conclusive evidence of an advantage of any option over the others.

Women included in the study were those who had opted for either early fetal reduction or prophylactic cervical cerclage. Before performing any procedure (fetal reduction or cervical cerclage), parents were informed about the procedure, the potential risks and the chance of success and a written consent was obtained. Also, a written permission was obtained from each woman to use her data for research purposes. Maternal demographic characteristics, ultrasound findings and the details of the procedure performed were recorded in a database. When the pregnancy and neonatal outcomes became available, they were collected into the same database. Women excluded from study were those who were diagnosed to have cervical insufficiency in the index pregnancy or a previous pregnancy and those who were diagnosed to have congenital uterine malformation. Women were also excluded from analysis if the pregnancy outcome or neonatal outcome data were unavailable.

Fetal reduction

Fetal reduction procedure was performed between 7 and 8 weeks of gestation by ultrasound guided transvaginal embryo puncture and aspiration without injecting any substance. A preliminary TVS scan was performed to confirm viability, measure the crown-rump length (CRL) and determine the position of the three fetuses. The procedure was performed in the operative theatre under full aseptic conditions and light general anesthesia. The patient received intravenous antibiotic prophylaxis (Cefoperazone 1 gm) and the vagina was cleaned with an antiseptic solution.

A sterile single lumen, 18–20 gauge, 30 cm suction needle was connected to a vacuum pump that makes a negative pressure adjusted to a maximum 200 mmHg. The uterus was scanned to identify the configuration of each gestational sac and determine the position of each sac in the uterine cavity and location of each sac relative to each other. The embryo with the smaller CRL was selected for termination; however, when all embryos had normal CRL, the most easily accessible embryo was selected for termination, based on easy access to transvaginal needle insertion. The transducer was then rotated and manipulated until the selected embryo appears aligned with the needle guiding line on the screen of the ultrasound machine. The needle was then pushed through the vaginal fornix and then through the uterine wall to the selected gestational sac. The tip of the needle was then placed into the fetal echoes and suction was applied repeatedly till aspiration of as much as possible of the embryonic parts and amniotic fluid and disappearance of fetal cardiac pulsation. While the needle in place, absence of pulsation in any remaining fetal echo was confirmed again then the needle was withdrawn.

Before removal of the transducer from the vagina, the uterus was scanned to confirm again that there is no pulsation in any remaining parts of the reduced fetus and ensure that the other two gestational sacs are intact with presence of fetal poles and cardiac pulsations. If pulsation was still observed in the remaining echo of the reduced fetus, a second puncture was performed in the same setting and suction was repeated till disappearance of this pulsation.

The patient was monitored for 6 h after the procedure then discharged on prophylactic oral antibiotic therapy (Amoxicillin 250 mg + Flucloxacillin 250 mg every 8 h) for 7 days and oral analgesic (Paracetamol 500 mg) if needed. An ultrasound scan was performed one week after the procedure to confirm presence of only two intact gestational sacs with fetal poles and cardiac pulsations. All women received the routine antenatal care and regular pregnancy follow up.

Cervical cerclage

The prophylactic cervical cerclage was performed between 12 and 14 weeks of gestation by transvaginal placement of purse-string suture at the cervicovaginal junction, without mobilization of the urinary bladder (McDonald cervical cerclage) [13].

Outcome measures

The main outcome measures of the study were delivery before 34 and 32 weeks gestational age, miscarriage rate, live birth rate, very LBW (VLBW), neonatal respiratory distress syndrome (RDS), admission to neonatal intensive care unit (NICU) and early neonatal death (END). Miscarriage was defined as spontaneous pregnancy loss before completing 24 weeks gestational age. Live birth was defined as birth of a living fetus after 24 weeks of gestation regardless of gestational age. The LBW was defined as a birth weight of a living neonate of <2500 gm regardless of gestational age while the VLBW was defined as a birth weight of a living neonate of <1500 gm regardless of gestational age.

Statistical analysis

The analysis of data was done using the IBM® SPSS® Statistics, version 20.0 for Windows. The categorical variables were presented as frequencies and percentages and the Fisher's exact probability test was used to compare the differences between percentages. The continuous variables were presented as mean \pm standard deviation (SD) and the Shapiro–Wilk and Kolmogorov–Smirnov tests were used to test the normality distribution of the continuous variables. The *t*-test was used to compare the differences among the normally distributed continuous variables while the differences among continuous variables without normal distribution were compared with the Mann–Whitney U-test. Statistical significance was determined at a *P* value of <0.05. The probability of an event to occur between the two groups was compared with the relative risk (RR) and the odds ratio (OR).

Results

The population of this study consisted of 118 women with triplet pregnancies achieved by ART. Fifty three women were managed by early fetal reduction to twins (fetal reduction group) while 65 women had been managed by prophylactic placement of cervical cerclage (cervical cerclage group).

The mean maternal age was comparable in both fetal reduction and cervical cerclage groups (29.09 \pm 3.63 years vs 28.89 \pm 4.10 years, respectively). About 13.2% of women in the fetal reduction group conceived with intrauterine insemination (IUI) and 86.8% conceived with IVF/ICSI while in the cervical cerclage group, 9.2% of women conceived with IUI and 90.8% conceived with IVF/ICSI (Table 1).

The pregnancy duration (gestational age at birth) was significantly longer in women who underwent fetal reduction than in those who received cervical cerclage (33.47 \pm 2.82 weeks vs 31.63 \pm 2.90 weeks; *P* < 0.001). The incidence of delivery before 34

Table 1
Demographic characteristics of the study groups.

	Fetal reduction group (n = 53)	Cervical cerclage group (n = 65)	P value
Maternal age (years)^a	29.09 ± 3.63	28.89 ± 4.10	0.771
Occupation^b			
House wife	26/53 (49.1%)	40/65 (61.5%)	0.196
Employee	27/53 (50.9%)	25/65 (38.5%)	
Primigravida^b	33/53 (62.3%)	45/65 (69.2%)	0.442
Nulliparous^b	46/53 (86.8%)	60/65 (92.3%)	0.370
Mode of conception^b			
IUI	7/53 (13.2%)	6/65 (9.2%)	0.562
IVF/ICSI	46/53 (86.8%)	59/65 (90.8%)	

^a Expressed as mean ± SD and P value was calculated by the Mann–Whitney U-test.

^b Expressed as frequency and percentage and P value was calculated by the Fisher's exact test. ICSI, intracytoplasmic sperm injection. IUI, intrauterine insemination. IVF, in vitro fertilization.

weeks gestational age was significantly lower in women who underwent fetal reduction than in those who received cervical cerclage (44.9% vs 80.3%; RR = 0.448; 95% CI = 0.289–0.671; $P < 0.001$) and also, the incidence of delivery before 32 weeks gestational age was significantly lower in the fetal reduction group than in the cervical cerclage group (24.5% vs 49.2%; RR = 0.525; 95% CI = 0.311–0.888; $P = 0.010$) but the incidence of delivery before 28 weeks of gestation and the miscarriage rate were not significantly different in both groups (Table 2).

The live birth rate was comparable in both groups (92.9% in the fetal reduction group vs 88.5% in the cervical cerclage group); however; the neonatal morbidities and mortality related to preterm birth were significantly lower in women who underwent fetal reduction than in those who received cervical cerclage as revealed by lower incidence of VLBW (19.8% vs 43.8%; RR = 0.454; 95% CI = 0.291–0.710; $P < 0.001$), lower occurrence of neonatal RDS (35.2% vs 70.4%; RR = 0.397; 95% CI = 0.280–0.564; $P < 0.001$), lower rate of admission to NICU (44.0% vs 72.8%; RR = 0.472; 95% CI = 0.340–0.654; $P < 0.001$) and lower END rate (18.7% vs 49.4%; RR = 0.369; 95% CI = 0.233–0.587; $P < 0.001$) in the fetal reduction group (Table 3).

Discussion

About 80% of high-order multifetal pregnancies (more than two fetuses) results from infertility therapy, of them up to 44% may result from ART [14]. In IVF/ICSI, although the policy of limiting the number of transferred embryos to two has led to a decrease in the rate of trichorionic triplets [15], the incidence of triplets with mixed chorionicity still occurs and may be explained by cleavage of one of the two transferred embryos [16]. High-order multifetal gestations are associated with increase in the perinatal morbidity and mortality

that are directly related to the consequences of preterm labor [14]. Fetal reduction and prophylactic cervical cerclage have been proposed to prolong pregnancy and subsequently reduce the fetal and neonatal risks associated with high-order multifetal gestations [4,5].

The present study is a retrospective one that compared the pregnancy and neonatal outcomes of triplet gestations managed by early fetal reduction to twins with those managed by prophylactic cervical cerclage among 118 women conceived with ART. To best of our knowledge, our study is the first one that compared both of these management options of triplet pregnancies. All previous studies compared either fetal reduction or prophylactic cervical cerclage with the expectant management.

This study demonstrated that early reduction of triplets to twins is associated with improved all perinatal aspects when compared with prophylactic placement of cervical cerclage. In the fetal reduction group, the mean gestational age at birth was two weeks longer with significant decrease in the risk of preterm delivery before 34 weeks (from 80% to 45%) and subsequent significant reduction in the rate of LBW (<2500 gm) and VLBW (<1500 gm).

In the retrospective study by Antsaklis et al. [17], 185 trichorionic triplet gestations that have been reduced to twin were compared to 70 triplet pregnancies that were managed expectantly with significant lower preterm birth and LBW infants in the reduced group. Similar results were obtained by Papageorghiou et al. [18] who found reduced preterm birth (from 27% to 10%) with fetal reduction. More recently, Chaveeva et al. [19] compared the outcome of trichorionic and dichorionic triplet pregnancies managed expectantly and those reduced to twins or singletons and they found significant lower preterm birth in the fetal reduction group.

However, although fetal reduction of triplets to twins have been shown to decrease the incidence of preterm labor, twin pregnancies resulting from fetal reduction (reduced twins) may still have higher incidence of preterm birth and perinatal problems than primary twins (non-reduced twins). In the case–control study by Silver et al. [20], reduced twins were found to have higher incidence of preterm birth, IUGR and discordancy than non-reduced twins. More recently, Cheang et al. [21] conducted a retrospective study and found higher incidence of prematurity and LBW in the reduced twins than in the non-reduced twins. On the other hand, Ata et al. [6] have found that spontaneously or electively reduced twins do as well as non-reduced dichorionic twins.

In our study, the neonatal RDS and the admission to NICU were significantly lower in the reduced group and the END was nearly 2.5 times lower in the reduced group. The results of our study are comparable to Drugan et al. [7] who found significant increase in the neonatal RDS rate, the mean stay period in the NICU and the END rate in the non-reduced group. Our results agree also with that was reported by Shiva et al. [8] who have found significant more NICU admission in the non-reduced group.

Table 2
Pregnancy outcomes in the study groups.

	Fetal reduction group (n = 53)	Cervical cerclage group (n = 65)	Relative risk (95% CI)	Odds ratio (95% CI)	P value
Miscarriage (at < 24 weeks) ^a	4/53 (7.5%)	4/65 (6.2%)	1.122 (0.544–2.314)	1.245 (0.296–5.233)	1.000
Miscarriage at < 16 weeks ^a	1/53 (1.9%)	0/65 (0.0%)			0.449
Miscarriage at ≥ 16 weeks ^a	3/53 (5.7%)	4/65 (6.2%)	0.951 (0.395–2.293)	0.915 (0.196–4.281)	1.000
Delivery at < 28 weeks ^a	3/49 (6.1%)	8/61 (13.1%)	0.587 (0.219–1.576)	0.432 (0.108–1.725)	0.340
Delivery at < 32 weeks ^a	12/49 (24.5%)	30/61 (49.2%)	0.525 (0.311–0.888)	0.335 (0.147–0.763)	0.010
Delivery at < 34 weeks ^a	22/49 (44.9%)	49/61 (80.3%)	0.448 (0.298–0.671)	0.200 (0.086–0.465)	<0.001
Delivery at ≥ 34 weeks ^a	27/49 (55.1%)	12/61 (19.7%)			<0.001
Gestational age at delivery (weeks) ^b	33.47 ± 2.82	31.63 ± 2.90			<0.001

Bold P values are statistically significant.

^a Expressed as frequency and percentage and P value was calculated by the Fisher's exact test.

^b Expressed as mean ± SD and P value was calculated by the Mann–Whitney U-test.

Table 3
Neonatal outcomes in the study groups.

	Fetal reduction group (n = 98) ^a	Cervical cerclage group (n = 183) ^a	Relative risk (95% CI)	Odds ratio (95% CI)	P value
Live birth ^b	91/98 (92.9%)	162/183 (88.5%)			0.300
LBW ^b	65/91 (71.4%)	150/162 (92.6%)	0.442 (0.328–0.594)	0.200 (0.095–0.421)	<0.001
VLBW ^b	18/91 (19.8%)	71/162 (43.8%)	0.454 (0.291–0.710)	0.316 (0.173–0.577)	<0.001
Neonatal RDS ^b	32/91 (35.2%)	114/162 (70.4%)	0.397 (0.280–0.564)	0.228 (0.132–0.395)	<0.001
Admission to NICU ^b	40/91 (44.0%)	118/162 (72.8%)	0.472 (0.340–0.654)	0.292 (0.170–0.502)	<0.001
Mechanical ventilation ^b	20/91 (22.0%)	85/162 (52.5%)	0.397 (0.259–0.609)	0.255 (0.142–0.458)	<0.001
Early neonatal death (END ^b)	17/91 (18.7%)	80/162 (49.4%)	0.369 (0.233–0.587)	0.235 (0.128–0.434)	<0.001

Bold P values are statistically significant.

^a The number of neonates in each group is higher than the number of women because there were 2 neonates in each pregnancy in the fetal reduction group and 3 neonates in each pregnancy in the cervical cerclage group.

^b Expressed as frequency and percentage and P value was calculated by the Fisher's exact test. LBW, low birth weight. NICU, neonatal intensive care unit. RDS, respiratory distress syndrome. VLBW, very low birth weight.

Six studies compared prophylactic cervical cerclage to expectant management in triplet pregnancies and the results were controversial. Two studies reported that prophylactic cervical cerclage in triplet pregnancies is beneficial [5,22]. Goldman et al. [5] have found significant improvement in the mean duration of pregnancy, mean birth weight, RDS and perinatal mortality with prophylactic cervical cerclage in triplet pregnancies. More recently, Elimian et al. [22] found that prophylactic cerclage in triplet gestations significantly increased the proportion of neonates delivered at 32 weeks of gestation or more and decreased the incidence of VLBW.

Four studies have found that cervical cerclage in triplet pregnancies is not better than expectant management [9–12]. The largest of these studies was conducted by Rebarber et al. [12] on 3278 triplet pregnancies of which 248 pregnancies received prophylactic cervical cerclage while the other 3030 pregnancies were managed expectantly. No significant differences were found in the incidence of preterm delivery before 32 weeks gestational age, mean gestational age at delivery, neonatal birth weight and NICU admission.

The miscarriage rate (fetal loss before 24 weeks of gestation) was not significantly different in both groups in our study. Our results agree with that was reported by Drugan et al. [7] and Shiva et al. [8] while contradict the results of Papageorgiou et al. [18] and Chaveeva et al. [19] who reported increased incidence of fetal loss before 24 weeks gestational age with fetal reduction. The increased incidence of fetal loss in these studies may be explained by the possibility of escape of the fetotoxic potassium chloride (KCl) into the liquor of the remaining gestational sacs [18]. Another explanation is the presence of retained fetoplacental tissue that may initiate an inflammatory reaction with release of prostaglandins which stimulate uterine contractions [23]. In our study, fetal reduction was done by early fetal aspiration without use of KCl thus avoiding the potential harmful effect of both KCl and retained fetoplacental tissue.

One disadvantage of early fetal reduction may be the early intervention before the possibility of occurrence of the phenomenon of spontaneous fetal reduction (vanishing twin phenomenon). However, it was reported that the rate of spontaneous reduction of triplet gestations is approximately 20% [6,24], and 85–90% of these reductions occur during the first 7–9 weeks of gestation [24,25]. No cases of vanishing twins were reported in our study. This could be explained by the fact that in most of cases, we have reduced the embryo having the smallest CRL. It was reported that 79% of embryos with decreased size for gestational age end in spontaneous loss while the incidence of spontaneous loss of embryos with an adequate size for their gestational age is only 8% [26].

The strength of our study is that it the first study that compared fetal reduction to cervical cerclage and no previous similar studies were published. Also, in our study, fetal reduction of triplets was done through early fetal aspiration without use of KCl while in all

previous studies considering triplet gestations, fetal reduction was done in the second trimester with use of KCl. A limitation of our study is the small number of participants which limits the strength of our results and another limitation lies in its retrospective nature which led to possible bias but the ethical view of the risk that would be imposed on the participants mandated the implemented design. Absence of no intervention group represents an important limitation as it is possible that cervical cerclage in multifetal pregnancies is associated with increased risk of adverse outcomes but we could not enroll women with conservative management as a third group (no intervention group) in our study because in our population, there is almost no women opting conservative management for triplet pregnancies achieved by ART.

In conclusion, early transvaginal reduction of triplets to twins leads to improved obstetric outcomes as it decreases prematurity and its related neonatal morbidities and mortality without increase in the miscarriage rate. Early fetal reduction seems to be better than continuation of triplet pregnancies with prophylactic placement of cervical cerclage. However, further studies among larger cohorts, randomized controlled when possible, are needed to confirm our results.

Conflicts of interest

The authors declare that they have no conflict of interest.

Acknowledgments

None.

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