

Embryo Reduction to Twins (ERTT) Versus Cerclage in Triplets in Women with Normal Cervical Parameters: A Retrospective Study

Original
Article

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ABSTRACT

Objective: To compare the efficacy and safety of ERTT to cerclage in triplet pregnancy.

Material and Methods: In this retrospective study, files of 266 patients were examined. Eligible patients managed by ERTT (n=120) were allocated into study group while patients managed by cerclage (n=121) were allocated into control group. Embryo reduction was done by oocyte aspiration needle before 10th week. Cerclage was done at 14-16 weeks. Obstetrical and neonatal adverse outcomes were assessed in both groups.

Results: One hundred and twenty cases were allocated in cerclage (control) group, 121 cases were allocated in ERTT (study) group. There was significant difference between both groups regarding abortion rate (*P*-value=0.002), delivery time (*P*-value=0.0001), gestational age at time of delivery (*P*-value=0.0001) and mode of delivery (*P*-value=0.0002). There was significant difference between both groups regarding fetal birth weight (*P*-value=0.0002), overall neonatal complications (*P* value 0.009) and need of NICU (*P*=value 0.0003).

Conclusion: Embryo reduction to twins (ERTT) procedures improved obstetrical and neonatal outcomes in triplet pregnancies compared to conservative management with cerclage procedure.

Key Words: Cerclage, embryo reduction, preterm labour, progesterone, triplets.

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INTRODUCTION

Advances in the field of management of infertility especially different ART techniques are considered the main cause of increasing incidence of multiple pregnancy. ART techniques causing increase rate of multiple pregnancy due to use of Controlled ovarian stimulation together with Transfer of more than one embryo. The rate of twin pregnancy in USA increased from 18.9 to 33.3 per 1,000 births between 1980 and 2009 and declined to 32.6 twins per 1,000 in the period from 2014 to 2018. Regarding triplet and higher-order gestations, the rate also increased more than 400% during the 1980s and 1990s with a rate of 193.5 per 100,000 births in 1998 then declined to 153.4 per 100,000 births by 2009. Nowadays triplet and higher-order multiple birth rates were 93.0 per 100,000 births for 2018^[1].

The concern now worldwide is how to reduce multiple pregnancies rate as the risk of multiple pregnancy outweigh its benefits especially with the high incidence of complications including preterm birth, preeclampsia, Diabetes and placental problems, and the strategies are directed to both primary and secondary prevention^[2].

Controlling and limiting the number of embryos transferred in ART is the cornerstone in the primary prevention strategies as it lead to prevention of occurrence of multiple pregnancy, even some countries limited embryo transfer to maximum 2 embryos. However, the best practice is to include the couples in decision regarding number of embryos transferred as practiced in USA^[2].

On the other hand, some researchers advised single embryo transfer and reported good pregnancy rate if selection of suitable couples were done. In addition, prevention of multiple pregnancies in patients taking ovulation induction drugs is done by prevention of fertilization when multifollicular growth was noted^[3].

There are many lines of management could be used in secondary prevention of multiple pregnancy to prevent complications especially preterm labour such as cerclage, cervical ring, and progesterone. Fetal reduction is one of the most studied procedure and there is some sort of debate about its significance in the maternal and fetal outcome^[4]. As some studies reported that reduction of triplets to twin pregnancy was related to obstetrical and neonatal outcomes improvement, while others reported that fetal reduction did not improve these outcomes^[5-8].

This concurrent debate, to do fetal reduction in triplets or not to do triggered the conduction of this study to assess the effect of embryo reduction to twins in triplet pregnancies compared to conservative treatment by cerclage and no reduction.

MATERIAL AND METHODS

Study design and settings

This study is a multicenter case control study conducted in the period from June 1, 2016 to March 31, 2022. The study was conducted at Tanta University hospitals, Egyptian consultant's fertility center, Al-Yasmin fertility center, and Qurret-Ein fertility center.

Participant's selection

Patients' files were reviewed in enrolled centers according to inclusion and exclusion criteria. The inclusion criteria are: (a) age from 20-40years, (b) triplet pregnancy (c) normal cervical measurements. The exclusion criteria were (a) patients with short cervix, or prior cervical conization (b) associated gynecological lesions as myoma or ovarian cyst, (c) associated diseases as diabetes or hypertension, (d) refusal to participate in the study.

Allocation: Patients were allocated into two groups

Study group who were managed by ERTT procedure, control group who were managed by cerclage procedure.

Interventions

- 1. Embryo reduction technique:** was done under general anesthesia using ovum pickup needle either by aspiration of embryo till 7 weeks or puncture of fetal heart from 8-12 weeks.
- 2. Cerclage operation:** was done under general anesthesia using McDonald's procedure applying 4 bites to cervix with knot applied posteriorly. The thread used was either Silk 1/0 or double needle Mersilene 1/0.
- 3. Progesterone supplementation:** Weekly IM injection of hydroxyprogesterone caproate (Cidolut Depot® CID pharmaceutical, Egypt). Progesterone supplementations started immediately after procedure and continued until delivery.

Methods

Demographic data of enrolled patients, origin of triplets, adverse pregnancy outcomes eg. abortion, preterm birth, PROM, gestational age at delivery, birth weight, neonatal morbidity and mortality.

Study outcomes

Primary outcome was continuation of pregnancy beyond 34 weeks while secondary outcomes were adverse maternal or neonatal outcomes like procedure related complications as bleeding, abortion or trauma, premature rupture of membranes, neonatal outcomes.

Study registration and ethical issues

This study was approved by the ethical committee of Tanta University with the following code: 34695/5/21 Privacy of participants and confidentiality of their data were maintained all through the study.

Statistical analysis

All analyses were performed using STATA 16.1 (Stata Corp- College Station- TX- USA). We tested the normality of the continuous variables using the Shapiro Wilk test and normal data were presented as mean and standard deviation and compared with the student t-test. Non-normal data were presented as median (Q1- Q3) and compared with the Mann-Whitney test. Categorical data were expressed as frequencies and percentages and compared with the Chi-square or Fisher exact test when appropriate. A *P-value* of less than 0.05 was considered statistically significant.

RESULTS

The examined file were 276 files in the four centers of recruitment. Exclusion of 35 files (25 cases were not meeting inclusion criteria and 10 cases lost follow up). The remaining 241 cases were allocated into cerclage (control) group (n=120) and into ERTT (study) group (n=121).

There was no significant difference in age ($P= 0.396$), infertility type ($P= 0.099$) or duration ($P= 0.213$), origin of triplets ($P = 0.426$) and gestational age at the time of the procedure ($P= 0.172$) between both groups as shown in (Table 1).

There was non-significant difference between both group regarding procedure related complications, mode of abortion and maternal adverse outcome. There was significant difference between both groups regarding abortion rate ($P\text{-value}=0.002$), the highest number of abortion was noticed in second trimester in cerclage group (33 cases), the number of cases complicated by abortion due to the procedure was very low (1 case and 3 cases in cerclage and ERTT groups respectively as shown in (Table 2).

Also there was significant difference between both groups regarding delivery time ($P\text{ value}=0.0001$) as where the number of cases who delivered after 34 weeks

was 34 cases and 86 cases in cerclage and ERTT groups respectively as shown in table 2. Consequently, there was significant difference between both groups regarding gestational age at time of delivery (P -value=0.0001) as show in (Table 2).

Regarding mode of delivery, there was significant difference between both groups (P -value=0.0002), where the number of cases who delivered by vaginal route

Table 1: Comparison of the baseline data between both groups

	Cerclage (n= 120)	ERTT (n= 121)	P -value
Age (yrs)**	30.77 (23- 39) SD = 4.018	30.91 (20- 39) SD = 4.32	0.396
Infertility type*			
Primary	83 (69.17%)	95 (78.51%)	0.099
Secondary	37 (30.83%)	26 (21.49%)	
Duration of infertility (yrs)**	5.47 (2-9) SD (1.505)	5.31 (2-9) SD (1.449)	0.213
Origin of triplets*			
ICSI	98 (81.67%)	105 (86.78%)	0.426
Spontaneous	3 (2.5%)	1 (0.8%)	
Ovulation induced	19 (15.83%)	15 (12.4%)	
Gestational age at time of procedure (weeks)**	7.4 (7-9) SD = 0.624	7.48 (7-9) SD = 0.669	0.172

(ICSI: Intra-cytoplasmic sperm injection; ERTT: Embryo reduction to twins)

* Categorical data as numbers and percentages and analyzed by chi-square test. ** Continuous data were presented as mean and SD or median (Q1- Q3) and analyzed by t-test.

Table 2: Comparison of the obstetrics outcomes between both groups

	Cerclage (n= 120)	ERTT (n= 121)	P -value
Procedure related complications*			
No	97 (80.83%)	98 (80.99%)	0.268
Spotting	11 (9.17%)	7 (5.65%)	
Vaginal bleeding	11 (9.17%)	5 (5.79%)	
Subchorionic hematoma	0	6 (4.96%)	
Abortion	1 (0.83%)	3 (2.48%)	
Bladder injury	0	2 (1.65%)	
Abortion timing*			
Procedure related	1 (0.83%)	3 (2.48%)	0.002
First trimester	10 (8.33%)	8 (6.61%)	
Second trimester	33 (27.5%)	4 (3.31%)	
Mode of abortion*			
Vaginal	38 (31.67%)	10 (8.06%)	0.204
Hysterotomy	4(3.33%)	4 (3.31%)	
CS	2 (1.65%)	1 (0.8%)	
Maternal adverse outcomes*			
No	41 (34.17%)	77 (63.64%)	0.043
Preeclampsia	12 (10%)	6 (4.96%)	
PROM	15 (12.5%)	11 (9.09%)	
Accidental hemorrhage	6 (5%)	8 (6.61%)	
IUFD	2 (1.65%)	4 (3.31%)	
Delivery time*			
<34	42 (35%)	20 (16.25%)	0.0001
≥34	34 (28.33%)	86 (71.07%)	
Gestational age at elivery (weeks)**	33.11(29-36) SD = 1.483	34.48 (28-37) SD = 1.792	0.0001
Mode of delivery*			
Vaginal	2 (1.67%)	23 (19.01%)	0.0002
CS	74 (61.67%)	83 (68.5%)	

(CS: cesarean section; ERTT: Embryo reduction to twins; IUFD: intrauterine fetal death; PROM: premature rupture of the membranes)

* categorical data as numbers and percentages and analyzed by chi-square test.

** Continuous data were presented as mean and SD or median (Q1- Q3) and analyzed by t-test.

Table 3: Comparison of the neonatal outcomes between both groups

	Cerclage (n= 120)	ERTT (n= 121)	P-value
Birth weight (Kg)**	1714.47 (600- 2310) SD =444.049	1985.8(680-2600) SD =492.21	0.0009
Neonatal complications*			
No	28 (23.33%)	62 (51.24%)	0.009
RDS	46 (38.33%)	40 (33.06%)	
IUFD	2 (1.67%)	4 (3.31%)	
NICU*			
Yes	50 (41.67%)	41 (33.89%)	0.0003
No	24 (20%)	61 (50.41%)	
Neonatal mortality*			
No	47 (39.17%)	84 (69.42%)	0.021
1	19 (15.83%)	11 (9.09%)	
2	6 (5%)	7 (5.79%)	
3	2 (1.67%)	0	

ERTT: Embryo reduction to twins; IUFD: intrauterine fetal death; NICU: neonatal ICU; RDS: respiratory distress syndrome

* categorical data as numbers and percentages and analyzed by chi-square test.

** Continuous data were presented as mean and SD or median (Q1- Q3) and analyzed by t-test.

DISCUSSION

High order pregnancy especially triplet pregnancy had been increased in the last two decades due to the increased medical management of infertile cases either with induction of ovulation or ART protocols, and this put an extra hazard to those high risk group and expose them to many obstetric complications like preterm labour, abortion or poor fetal outcome^[9].

There is still no universal consensus about the management of triplet pregnancy aiming to decrease the risk of anticipated complications. Our study aimed at evaluation of the role of embryo reduction of triplet to twins pregnancy and compare it with cervical cerclage with continuation of the pregnancy to term is the main outcome.

In the current study, there was significant difference between both groups regarding the number of cases complicated by abortion (P -value 0.002), delivery time (P -value=0.0001), gestational age at time of delivery (P -value=0.0001) and mode of delivery (P -value=0.0002) also there was significant difference between both groups regarding fetal birth weight (P -value=0.0009), overall neonatal complication (P -value=0.009) and need of NICU (P -value= 0.0003).

In analysis of our results, embryo reduction in triplet pregnancy to twins pregnancy may lead to reduction of obstetric complications, and decrease number of cases who complicated by abortion and so increase gestational age at time of delivery. also the possibility of vaginal delivery will increase as the reduction to twins pregnancy decrease risk of miscarriage and allow the route for vaginal delivery, while in cerclage group, the increased tension inside the uterus may lead to increased risk of abortion, and the presence of triplet pregnancy will decrease gestational age at time of delivery and make the vaginal delivery not possible.

Of course increasing gestational age at time of delivery and reduction of number of feti to twins pregnancy allow to increase fetal weight at time of delivery and hence decrease need of NICU and decrease neonatal complications.

The benefits of fetal reduction to twins pregnancy in triplet pregnancy as shown in this study, also was proved by Shlomo *et al*, (1994) who compared the outcome of expectant management of triplet pregnancies and which managed by reduction to twins. They included 140 triplet pregnancies less than 9 weeks of gestation (34 women accepted the reduction, and 106 were managed expectantly) and they found that miscarriage before 25 weeks gestation occurred in 20.7% of cases managed expectantly and 8.7% in the patients who underwent reduction to twins. A successful pregnancy occurred in 88.2%, 74.5% in expectant management and fetal reduction respectively. A significantly lower incidence of prematurity ($p < 0.001$), and low-birth-weight ($p < 0.001$) was noticed in the group who were reduced to twins. They concluded that improved pregnancy outcome resulted from reduction of triplet pregnancies to twins^[10].

Shiva *et al*, (2014) conducted a retrospective study including 115 triplets pregnancies. They allocated 57 patients to reduction group versus 58 to conservative group. They compared pregnancy outcome in both groups. Their results agreed with ours as they found that embryo reduction group had better obstetrical outcomes and neonatal outcomes^[11].

Sebire *et al*, (1997) had studied the effect of embryo reduction to twins pregnancy in triplet pregnancy. They included 66 triplet pregnancies in the reduction to twins group and 47 triplet pregnancies were included in the non-reduction group. Their study disagree with ours as they showed that The miscarriage rate was higher than non-reduction (7.6% compared with 2.6%, in our study 34% in non-reduction and 12% in reduction group) and

also they found that the reduction did not decrease risk of prematurity, but in this study we found there was significant effect of embryo reduction in decreasing number and hazards of prematurity. The difference may be attributed to the technique they used in embryo reduction which may differ from ours^[12].

Abdelhafez *et al.*, (2018) conducted a retrospective study to assess the benefits of embryo reduction in triplet pregnancies compared to cerclage procedures. They allocated 53 triplet pregnancies into either reduction and 65 patients were allocated into cerclage group. Their study agreed to our study in many aspects as they found that the reduction groups had higher birth weight, increased gestational age at time of delivery with decreased preterm birth before 32 and 34 weeks. Miscarriage and live birth rate were comparable in their results. They concluded that better obstetrical and neonatal outcomes were found in reduction group and they advised to reduce triplet pregnancies rather than to continue pregnancy with triplets and cerclage^[13].

Our study agreed with Tse *et al.*, (2017) who studied obstetric outcome of fetal reduction in triplet pregnancies in Hong Kong. They conducted fetal reduction on 26 triplet pregnancies while the other 26 cases were managed conservatively. The mean gestational age at delivery was higher in reduction group than in non-reduced group (the mean gestations at delivery were 35.2 versus 32.6 weeks respectively). They concluded that significant reduction of extreme premature labour and its related morbidity and mortality were associate with fetal reduction^[14].

Patel *et al.*, (2021) conducted a retrospective analysis of multifetal pregnancy reduction (MFPR) over past 25 years comparing different routes. They assessed 975 cases with higher order pregnancies from January 1995 to December 2020. They reported 33 (3.28%) abortions related to procedure. In our study, we reported 3 (2.48%) abortions related to procedure. They concluded that fetal reduction lead to improvement in maternal, fetal and neonatal outcomes. They reported lower complications rate with trans-abdominal reduction approach^[15].

Papageorghiou *et al.*, (2006) had assessed the risk of miscarriage and preterm delivery in triplet pregnancy after embryo reduction as compared by expectant management. They studied the data from 365, and they agreed partially with our study as they found that reduction group had a lower risk of preterm delivery and decreased risk of all sequel of prematurity, but they disagree with our study as they found that there is increased risk of miscarriage in reduction group, this difference may be attributed to different technique and protocol in embryo reduction^[16].

Chaveeva *et al.*, (2013) had compared the outcome of triplet and twins pregnancy who managed by expectant

management and by embryo reduction at 10-14 weeks using a retrospective study and they found that embryo reduction had higher rate of miscarriage while our study showed decrease in number of miscarriage in embryo reduction group and this may be attributed to difference in embryo reduction technique, but they agreed with our study in the effect of embryo reduction in decreasing the risk of prematurity and its outcomes^[17].

Yaqiong *et al.*, (2018) had a retrospective study in which they observed the pregnancy and perinatal outcomes of fetal reduction in triplet and twins pregnancy. But unlike to our study they had three groups, group with fetal reduction into twins pregnancy, second group with fetal reduction into singleton pregnancy, and the last group with expectant management. They found that The groups with fetal reduction had the better pregnancy and perinatal outcomes including higher birth weight and elder gestational age. Our study agreed with their result as a whole, but the increased abortion rate with fetal reduction technique in their study may be attributed to they tried the reduction in triplet pregnancy into singleton pregnancy which may put an extra intervention with extra risk, also they studied the reduction into twins pregnancy which was out of scope of our study^[18].

Sheila *et al.*, (2012) disagreed with our results; they had a retrospective study to assess the selective reduction into twins in triplet pregnancies. They compared the study group with two groups, group of medical management of triplet pregnancy by progesterone and another group with placebo. They found that embryo reduction from triplet to twin did not prolong pregnancy duration (gestational age) nor improve neonatal outcome, these differences may be attributed to difference in the technique and settings of embryo reduction technique^[19].

Dawood *et al.*, (2021) had a retrospective study in which they assessed the obstetrical outcomes of ERTT in Egyptian IVF/ICSI centers. They studied the Data of 124 patients in five IVF/ICSI centers. They found 29.84% aborted following procedure at different gestational ages. They reported that 34.51 weeks was the mean gestational age at delivery and 41.93% of babies required incubator admission.. The overall postoperative complications were 9.68%. They concluded that ERTT was safe, feasible and was linked to better obstetrical and neonatal outcomes^[4].

Our study also agreed with Morlando *et al.* (2015), Abel *et al.* (2016), Cai *et al.* (2020) and Shaw *et al.* (2021) who compared embryo reduction to conservative approaches in triplets and they concluded that better maternal and neonatal outcomes were found in women underwent embryo reduction. Moreover, little or no risks were associated with these procedure^[20-24].

Our study had some limitations, for example the technique of embryo reduction was not assessed or

compared with other techniques and our study lack the long term follow up of the neonates.

CONCLUSION

Embryo reduction to twin pregnancy in triplet pregnancies had a favorable outcomes compared to cerclage without fetal reduction regarding to lower abortion rate, miscarriage, higher gestational age at time of delivery, higher birth weight and lower neonatal complications.

CONFLICTS OF INTERESTS

There are no conflicts of interest.

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