

Comparative analysis of perinatal outcome of spontaneous pregnancy reduction and multifetal pregnancy reduction in triplet pregnancies conceived after assisted reproductive technique

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ABSTRACT

INTRODUCTION: With the advent of assisted reproductive treatment options, the incidence of multiple pregnancies has increased. Although the need for elective single embryo transfer is emphasized time and again, its uniform applicability in practice is yet a distant goal. In view of the fact that triplet and higher order pregnancies are associated with significant fetomaternal complications, the fetal reduction is a commonly used option in such cases. This retrospective study aims to compare the perinatal outcome in patients with triplet gestation who have undergone spontaneous fetal reduction (SFR) as against those in whom multifetal pregnancy reduction (MFPR) was done. **MATERIALS AND METHODS:** In the present study, eighty patients with triplet gestation at 6 weeks were considered. The patients underwent SFR or MFPR at or before 12–13 weeks and were divided into two groups (34 and 46), respectively. **RESULTS:** Our study found no statistical difference in perinatal outcome between the SFR and MFPR groups in terms of average gestational age at delivery, abortion rate, preterm delivery rate, and birth weight. The study shows that the risk of aborting all fetuses after SFR is three times (odds ratio [OR] = 3.600, 95% confidence interval [CI] = 0.2794–46.388) that of MFPR in subsequent 2 weeks. There were more chances of loss of extra fetus in SFR (23.5%) group than MFPR group (8.7%) (OR = 3.889, 95% CI = 1.030–14.680). As neither group offers any significant benefit from preterm delivery, multiple pregnancies continue to be responsible for preterm delivery despite fetal reduction. **CONCLUSION:** There appears to be some advantages of MFPR in perinatal outcome when compared to SFR, especially if the latter happens at advanced gestation. Therefore, although it is advisable to wait for SFR to occur, in patients with triplet gestation at 11–12 weeks, MFPR is a viable option to be considered.

KEY WORDS: Fetal reduction, multiple pregnancies, triplet gestation

INTRODUCTION

The last decade has seen an exponential rise in the availability and accessibility of assisted reproductive treatment opportunities in the Indian subcontinent. Couple's desires to achieve maximum chances of conceiving as well as the option of fetal reduction are important reasons for multiple embryo transfer in an assisted reproductive technique (ART) cycle. Balancing benefit (increased pregnancy rate) against the disadvantage of multiple embryo transfer is not easy as both the clinician and the couple very

easily appreciate the benefit, whereas the disadvantages (pregnancy loss, preterm

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delivery, maternal and/or neonatal morbidity/mortality) are more distant consequences.

Therefore, in the absence of any standardized legislature to guide the number of embryos transferred after an ART procedure, multiple pregnancies have become one of the most important outcomes to be considered in an ART conception. The incidence of multiple gestation following ART ranges from 20 to 30%.^[1]

The risk of pregnancy loss and preterm delivery leading to neonatal morbidity and mortality increases in the presence of multiple pregnancy, especially higher order gestation like triplet or more.^[2,3] The length of gestation is inversely proportional to the number of intrauterine fetuses.^[4] Maternal complications for women carrying high-order multiple gestations include increased incidence of preeclampsia, cesarean delivery, postpartum hemorrhage, and fatty liver.^[3,5]

Many studies in the past have evaluated the risk of continuation of triplet conception versus reduction to twin or singleton pregnancy to improve perinatal outcomes. While some studies^[6,7] have found an increase in gestational age at delivery in triplet pregnancy after fetal reduction, some have not found any significant advantage.^[8] The impact on neonatal survival in these studies is even more variable. The role of multifetal pregnancy reduction (MFPR) is more clearly advantageous in quadruplets or higher order gestation.^[9]

Fetal reduction in itself is not without implications. A fetal loss of 8%–16% has been reported in literature after MFPR^[9,10] although this incidence depends not only on operator's experience but also on gestational age at reduction, number of fetuses reduced, patient factors, etc.

In many cases, spontaneous fetal reduction (SFR) is seen, wherein one or several embryos naturally disappear. Pregnancies undergoing SFR have found to be at higher risk of preterm delivery and poorer neonatal outcomes, especially when they were reduced to singleton from twin and more so when reduced to a twin from triplets.^[11] Most of these SFRs occur within 12 weeks with an average incidence being 32%–40%.^[10,11] This study aims to compare the perinatal outcomes between patients with SFR and MFPR.

MATERIALS AND METHODS

This retrospective analysis was performed in the Department of Reproductive Medicine and Surgery from January 2012 to December 2015. Details of any pregnancy conceived after ART - *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) was recorded in the departmental record in

the form of an individual patient file which is periodically updated either at the time of patient follow-up visit or telephonic enquiry. Records of patients who had conceived triplet gestation after IVF/ICSI and had delivered were evaluated for the purpose of this study, and age, parity, number of embryo transferred, calculated last menstrual period, number of gestational sacs, antenatal course, pregnancy outcome, date of delivery, birth weight, and neonatal course were collected from them.

The patients with three gestational sacs (trichorionic triamniotic) with cardiac activity seen at 6 weeks of gestation on transvaginal scan were considered for the study. Patients, who were lost to follow-up, had heterotopic pregnancies, had previous pregnancy losses, or continued with triplet or higher order gestation beyond 12 weeks and/or whose records were incomplete were excluded from the study.

As per departmental protocol, ultrasonography (USG) was initially performed to determine the location and number of gestational sacs when quantitative beta-human chorionic gonadotropin levels were expected to be 2000 mIU/mL or more between 5.5 and 6.5 gestational weeks (3.5–4.5 weeks after embryo transfer). USG was repeated every 2 weeks until the 12th gestational week, transvaginally. Pregnant women were followed up in the department under a fetal medicine specialist until 12 weeks. Patients not under regular care were periodically followed contacted via telephone.

For the purpose of the study, SFR was defined as disappearance of gestational sac or loss of cardiac activity in one or two gestational sacs (after its identification) out of the triplet pregnancies. A single operator performed MFPR at 11–13 weeks in cases where cardiac activity was seen in all three gestational sacs between 10 and 12 weeks gestation. The reduction was done abdominally under ultrasound guidance with intracardiac KCl injection such that single fetus was reduced in triplet gestation. Fetuses were selected for reduction by: (1) Discordant fetal growth, (2) the presence of increased nuchal translucency, (3) distance of the amniotic sac from the internal os, and (4) accessibility to transabdominal reduction.

No cases of quadruplet or higher order gestation were noted/considered in the study population. In the MFPR group, all triplets were reduced to twin gestation only. Triplet gestation reduced to singleton was not considered for the study to reduce confounding factors.

Abortion was defined as disappearance of cardiac activity in utero after SFR/MFPR or delivery before 28 completed weeks of gestation. Preterm delivery was defined as the birth of a viable baby (after 28 weeks) at or before 37 completed

weeks of gestation. Neonatal death was defined as the death of a live baby within 4 weeks of delivery. Restricted fetal growth or intrauterine growth restriction (IUGR) was defined as a birth weight less than the 10th percentile for gestational age on the basis of national singleton birth weights.^[12]

Eighty pregnancies with triplet gestation at 6 weeks scan fulfilled the inclusion criteria and underwent spontaneous or MFPR before 12–13 weeks of gestation. The patients were divided into two groups – SFR and MFPR – according to the reduction method. Patients who had fetal losses after MFPR were considered in MFPR group. Patients who had SFR were not considered for MFPR as per protocol.

Primary outcome measures were abortion rate and average gestational age at delivery. Secondary outcome measures were live birth rate, average birth weight, and preterm birth rate. The outcome variables studied in the present study were pregnancy loss, weeks of gestation at delivery, birth weight of the baby, incidence of IUGR, incidence of preterm labor, and incidence of single and twin delivery.

Measurement data underwent normality test and were expressed as a mean \pm standard deviation. The maternal and fetal parameters of the two groups were compared using Chi-square test and *t*-test wherever applicable to determine statistical significance. Association of the type of fetal reduction with fetal outcome was evaluated using Chi-square test. Statistical significance was established at $P < 0.05$.

RESULTS

The average age of patients in the present study was 32.76 years. Only 12 (15%) had a history of previous conception. Of 80 patients considered for the study, 34 had SFR, whereas 46 underwent MFPR as per protocol.

Of eighty triplet pregnancies considered in the present study, a total of 15 patients aborted before the period of viability (28 weeks). Therefore, the miscarriage rate was 18.75% (15/80). The difference in probability of abortion in both groups was not statistically significant ($P=0.3942$), even if only early abortions are considered (gestational age <14 weeks). The SFR group had higher risk (odds ratio [OR] = 3.600, 95% confidence interval [CI] = 0.2794–46.388) of loss of all the fetuses over the next 2 weeks (<14 weeks) than MFPR groups (37.5% vs. 14.3%, respectively). Twenty-six patients out of 34 (76.5%) in the SFR group had live births in comparison to 84.78% (39/46) in the MFPR group. Although the percentage of live birth was higher in patients who had MFPR, it was not statistically significant [Table 1].

Table 1: Perinatal outcome in two groups

	SFR (n=34)	MFPR (n=46)	Total (n=80)	P
Gestational age at abortion and live birth (weeks)				
<14	3	1	4	0.3942
15-20	4	2	6	
21-28	1	4	5	
Live birth (>28)	26	39	65	
Live births after 28 weeks				
Singleton delivery	8	4	12	0.0781
Twin delivery	18	35	53	
Gestational age at delivery (weeks)				
Very preterm (29-32)	5	6	11	0.297
Preterm (33-36)	7	18	25	
Term (>37)	14	15	29	
Pregnancy-induced hypertension	7	7	14	0.564
Summary of birth weight				
ELBW (<999 g)	1	1	2	0.364
VLBW (1.0-1.5 kg)	13	13	26	
LBW (1.6-2.5 kg)	24	52	76	
>2.6 kg	6	8	14	
Summary of neonatal outcome				
Average gestation at delivery	30.82	33.13	63.26	0.2025
Live birth	44	74	118	0.3942
Average live birth weight	1.98	2.03	2.01	0.6261
IUGR	14	25	39	0.9863
Congenital anomalies	1	2	3	0.8859
Neonatal deaths	2	8	10	0.4009

IUGR=Intrauterine growth retardation, VLBW=Very low birth weight, ELBW=Extremely low birth weight, LBW=Low birth weight, SFR=Spontaneous fetal reduction, MFPR=Multifetal pregnancy reduction

There were more chances of loss of extra fetus in SFR (23.5%) group than MFPR group (8.7%) (OR = 3.889, 95% CI = 1.030–14.680, $P = 0.0781$). The statistical probability of having a term delivery, preterm or very preterm delivery did not differ in both groups statistically ($P = 0.297$).

After SFR or MFPR, a total of 118 babies were born to eighty patients either as singleton^[12] or twins (106). 58.33% (7/12) singleton babies had a birth weight of more than 2.6 kg, while in twin gestation, only 6.6% (7/106) babies had a birth weight of more than 2.5 kg ($P < 0.0001$). However, no association of birth weight was observed with the type of fetal reduction (SFR and MFPR group) ($P = 0.364$) [Table 1].

The average gestational age in the SFR group was lower in comparison to the MFPR group, but this does not reach clinical significance ($P = 0.2025$) [Table 1]. The incidence of pregnancy-induced hypertension was more in SFR than MFPR group; however, the difference was statistically insignificant.

MFPR group had 74 babies with an average birth weight of 2.03 ± 0.49 kg. Although birth weight was higher than SFR group (1.98 ± 0.61 kg), the difference does not reach clinical significance. No significant difference was observed in terms of incidence of IUGR, congenital abnormalities, and neonatal death in two groups [Table 1].

Of the three congenital anomalies, there were two fetuses with cardiac anomalies (one in each group) and one fetus had an absence of bilateral toe in MFPR group. Of the ten neonatal deaths, seven were early neonatal death, one was late neonatal death, and two were immediate neonatal deaths.

DISCUSSION

In ART pregnancies, the first scan is done at around 6 weeks of gestation. On visualization of triplet sacs, the patient is counseled regarding the pros and cons of continuation of triplet pregnancies as against fetal reduction. However, at times before the reduction is scheduled (generally after 11–12 weeks), spontaneous loss of one or more fetuses is seen. This study aims to compare the perinatal outcome in cases where fetal reduction occurred spontaneously as against wherein MFPR was performed.

Most of the studies done in the past have compared the perinatal outcomes in reduced and nonreduced pregnancies.^[6–8] Studies which compare head-to-head SFR and MFPR are scant. This study is relevant not only to understand the implications of SFR for counseling patients but also to decide whether it is prudent to wait for 12 weeks or more before MFPR was done, so as to allow for SFR. This study is also needed because knowing the probability of preterm delivery or growth restriction will aid not only in counseling the couple but also in planning the place of delivery and measures thereof.

Spontaneous fetal reduction and multifetal pregnancy reduction

It is reported that SFR rate is 12%–30% in ART cycles and even as high as 50%–80% in triplet or higher order gestation.^[10,11,13,14] Association of SFR with increasing maternal age was found in these studies as well. In the present study, 34 out of eighty triplet pregnancies (42.5%) underwent SFR. Although the percentage of SFR in previous studies is similar to our own, we did not find any difference or association with maternal age in both groups because average maternal age in our study was less (32.76 years). In a large study by Zhang *et al.*,^[11] SFR rate was lesser in twin gestation in comparison to triplet gestation significantly. Therefore, it can be postulated that multiple gestational sacs in it predispose to the loss of one or more fetuses in utero. The possible reasons may be small uterine space and the

relative lack of blood supply of the gestation sac caused by multiple pregnancies.

Zhang *et al.*^[11] have found that SFR occurred within 8 weeks in 78.4% of cases. In patients who underwent SFR later in their gestation, they found an increasing trend of low birth weight and very low birth weight rates. Therefore, we believe that although our study does not show any significant difference in the perinatal outcome between SFR and MFPR groups, waiting for SFR in advanced gestation (>12 weeks) may not be beneficial to the patient because patients in MFPR group were selected for reduction by discordant growth, increased nuchal translucency as already mentioned in the materials and methods.

Risk of abortion after spontaneous fetal reduction and multifetal pregnancy reduction

In an observational study by Papageorghiou *et al.*,^[15] the rate of miscarriage (pregnancy loss before 24 weeks) was 8.3%, while the rate of early preterm delivery was 9.7%. The rate of abortion is lower to our own (15.2%) as the period of viability considered by us is 28 weeks as against 24 weeks in the above-mentioned study. Our percentage of abortion is higher than some previous studies as well.^[4] As ours is a retrospective analysis and the follow-up of patients beyond 12 weeks was not done at our own center in all cases, the reasons for such high abortion rates are not clear. It is possible that some of our patients were not under expert medical care after the second trimester and therefore were not as closely monitored as was required.

Chronology of abortion in spontaneous fetal reduction and multifetal pregnancy reduction

Our study shows that loss of fetus occurred after MFPR occurred in 1 patient within 2 weeks. However, in over 80% cases, interval between MFPR and miscarriage was more than 2 weeks. This finding is similar to that reported previously.^[4,15]

It is, therefore, important to counsel the couple who choose to have a fetal reduction that most of the excess loss with MFPR occurs several weeks after the procedure and is likely to be the consequence of the resorbing dead fetoplacental tissue, rather than the technique itself.

When we look into the pattern of miscarriage in the SFR group, we found that miscarriage of the remaining fetuses in 37.5% (3/8) occurred with 2 weeks of SFR. This is higher than the MFPR group (14.3%, 1/7). This shows that counseling needs to be done in weeks following SFR in comparison to those who have undergone MFPR.

In the MFPR group, only 2 (4.35%) patients out of 46 underwent loss of remaining fetuses within 2 weeks of

reduction as against 8.8% (3/34) in the SFR group. In the study by Zhang *et al.*,^[11] 14.4% (13/90) patients undergoing MFPR from triplet to twins had fetal losses within 1 week (7.7%) and rest within 4 weeks.

Gestational age at delivery

In the study by Dickey *et al.*,^[10] the average gestation of patients with SFR was shortened by 4 days in comparison to unreduced twin gestation. Although the comparison of gestational age of delivery of reduced and unreduced pregnancies is beyond the scope of the present study, it is expected that in twin gestations delivered after SFR, the patients delivered earlier than unreduced twin pregnancies. The average gestational age at delivery in our study is about 30 weeks, which is much lower than that of Dickey *et al.* (35 weeks).^[10] This may be secondary to patient factors and lower degree of maternal care in some of our cases who did not have access to higher centers.

Preterm delivery in spontaneous fetal reduction and multifetal pregnancy reduction

Dickey *et al.*,^[10] in their study, showed that triplet gestation undergoing SFR in the first trimester had more propensity of delivering earlier than their twin or singleton counterparts. Our study has compared the risk of preterm birth in spontaneous versus reduced multifetal gestation. This study shows that in comparison to SFR, MFPR offers a higher chance of delivering at later gestation. It is important to point out that the average gestation in both cases remains in the preterm range and therefore practically neither of the two procedures offers a chance to prevent preterm birth. The SFR group had earlier delivery probably because the SFR occurred due to certain maternal and/or uterine factors, which eventually led to preterm delivery too. However, determination of the reason for lower average gestation in SFR group in comparison to MFPR requires further studies.

Term delivery in spontaneous fetal reduction and multifetal pregnancy reduction

In an Indian prospective study,^[4] 45% patients (5/12) carried the pregnancy to term. This is very similar to our own study, wherein 44.2 (29/65) patients delivered at term even though the average gestational age of the entire cohort was 32.14 weeks. Of the two groups even though the average gestational age of SFR group at delivery is lesser, 53.84% (14/26) delivered at or after 37 weeks in comparison to 38.46% (14/39) in the MFPR group. However, this difference in the term delivery rate in the two groups is not statistically different. In the above-mentioned study, the mean gestational age at delivery was 35.4 weeks which is a little higher than our own (32 weeks). The sample size in the former is much lesser^[12] than our own and could lead to a difference in the result.

Effect of fetal reduction on neonatal outcomes

Some studies^[10,13] have reported that SFR improved neonatal prognosis while others^[16] have found conflicting results. In these studies, the authors have compared the perinatal outcomes after reduction with pregnancies where no reduction was required (singleton) or was not done (twins). The effect of fetal reduction on the perinatal and neonatal outcome is multifactorial. It depends on the gestational age of fetal reduction, maternal factors influencing pregnancy, as well as number of gestational sacs, to begin with. Our study shows that while these factors indeed may alter neonatal prognosis, effect of nature of fetal reduction (SFR or MFPR) is not a clinically significant factor, especially if triplet to twin reduction is considered.

Can multifetal pregnancy reduction be avoided in favor of spontaneous fetal reduction?

In our study, triplets' pregnancy underwent MFPR to twins if SFR did not occur by 12 weeks. Therefore, the two groups formed (SFR and MFPR) were mutually exclusive. In the study by Zhang *et al.*,^[11] patients in SFR group had undergone MFPR in the same gestation. This study shows that in patients with only MFPR, the perinatal outcome was significantly better than those in SFR group. This may be because loss of fetuses in SFR group was secondary to MFPR itself or some other confounding factor in this group. These results may be difficult to compare with our own study due to the difference in design; however, as neonatal prognosis is inversely related to gestational age at reduction, waiting for SFR in advanced gestation (>12 weeks) may not be beneficial to the patient. At the same time, as most SFR occurred within 8–10 weeks of gestation, it is appropriate to wait for SFR before planning for MFPR for the patient.

CONCLUSION

Fetal reduction is a viable option for patients with multiple gestations. Fetal reduction of triplet to twin pregnancy improves perinatal morbidity and mortality. MFPR have a better prognosis than SFR in terms of gestational age at delivery, fetal birth weight as well as abortion rates although the differences are not clinically significant. As neither strategy offers a benefit when compared to singleton pregnancies or unreduced pregnancies as per previous studies, the primary aim of any ART should be to reduce multiple embryo transfer in the first place.

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Conflicts of interest

There are no conflicts of interest.

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