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ORIGINAL RESEARCH

# Selective Fetal Reduction in Triplet Pregnancy: Indian Experience—A Retrospective Review of 32 Cases

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## ABSTRACT

**Aim:** To review the effects of selective fetal reduction in trichorionic triplet pregnancy with focus on risk of miscarriage and preterm delivery in Indian women and thus provide local data for counseling the prospective parents in similar situation.

**Materials and methods:** This retrospective study reviewed the pregnancy outcome of 32 sets of triplet pregnancies following fetal reduction. All mothers had trichorionic triplet pregnancy with three live fetuses at 10 to 11 weeks of gestation. One to two milliliter ml of 10% potassium chloride (KCl) was injected into the heart of the target fetus to achieve asystole.

**Results:** The miscarriage (pregnancy loss before 24 completed weeks) rate in our study was 3.12%. The delivery in our study at ≤32 and ≤35 weeks were 6.45 and 51.61% respectively. The mean gestational age (mean ± SD) of the mothers was 242.58 ± 12.93 days. Regarding the birthweight of neonates, 5.08% babies were <1500 gm, 89.83% were between 1500 and ≤2500 gm and 5.08% were > 2500 gm. The mean birth weight (mean ± SD) of the babies was 1921.18 ± 339.78 gm. There was no neonatal death in this cohort.

**Conclusion:** Our study results, when compared with 'expectant management' group of two European studies as there was no control in our study, appeared significantly better in terms of gestational age at delivery and neonatal birth weight.

Selective fetal reduction remains an effective option to Indian women with trichorionic triplet pregnancy.


**Keywords:** Selective fetal reduction, Trichorionic triplet pregnancy, Preterm labor, Neonatal birth weight.

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## INTRODUCTION

In the United States (US), triplets and higher order multiple birth rates increased from 37.0 to 184.0 per 100,000 live births between 1980 and 2002,[1] a reflection of similar worldwide trend.

There are two major reasons for high incidence of multiple pregnancies. First, the trend for childbearing at an older age, which in itself is associated with increased risk of multiple births and, secondly, the increased availability and use of assisted reproduction technology.[2,3]

The earlier notion that there is a direct correlation between number of embryos transferred, and higher-order pregnancy rate is now attested by ample evidences. A single embryo transfer policy in UK has resulted in a decline of multiple pregnancy rate from 26.6% overall in 2008 to 20.1% overall in 2011.[4] Similarly, American Society of Reproductive Medicine's (ASRM) guidelines for the number of embryos to be transferred for *in vitro* fertilization were revised.[5] However, in a country like India where three embryo transfer is widely practised for higher success, incidence of triplet pregnancy remains significant.

The high incidence of triplet births is of concern as severe prematurity occurred in as many as 25% of triplet pregnancies.[6] In triplet pregnancy, there are reports of an increased rate of varieties of neonatal morbidity including 47 times higher risk of cerebral palsy.[7,8] Slow language development even when the babies are healthy and 6 times higher perinatal mortality when compared to singleton pregnancy.[9,10]

Selective fetal reduction, a procedure that reduces the number of fetuses, has been widely employed over more than 20 years to reduce the risk of complications related to multiple gestation and improve pregnancy outcome.[11]

There is ample evidence that fetal reduction reduces the risk of preterm labor in European women.[12,13] However, to our knowledge, there is not enough data about the effects of fetal reduction in triplet pregnancies In Indian women except a study of 12 cases of triplet pregnancy.[14]

The aim of this study is to review the effects of fetal reduction in triplet pregnancies with focus on risk of miscarriage and preterm delivery in Indian women and thus provide the local data for counseling the prospective parents.

## MATERIALS AND METHODS

This retrospective study reviewed the pregnancy outcome of 32 mothers with triplet pregnancies. All the mothers underwent fetal reduction to twins at a private diagnostic clinic in Kolkata between April 2010 and November 2013. Local ethics committee approval was obtained, and all mothers had given informed consent.

All the patients, in this study, were referred to the clinic after ultrasonic diagnosis of triplet pregnancy. A detailed ultrasonography was then performed by the operator to confirm that all mothers had trichorionic triplet pregnancy with three live fetuses at 10 to 11 weeks of gestation. Nuchal translucency was noted along with any obvious fetal anomalies.

Mothers were counseled on options of fetal reduction vis a vis expectant management. All mothers opted for fetal reduction. Fetal reduction, following informed consent, was done within 3 days of scan in the clinic as described below:

While selecting the fetus to be reduced attention was paid to the lowest crown-rump length, highest nuchal translucency and operator's ease of access. Wherever possible, the lowest fetus was avoided to reduce the chance of infection. It is thought that necrotic materials close to the internal os could enhance the chance of post-reduction infection. Once the target fetus was selected, mother's abdominal wall was cleaned with antiseptics. A small area of skin and subcutaneous tissue was anesthetized with 5 ml of 2% xylocaine infiltration. Size 20 gauge spinal needle was advanced under direct ultrasonic guidance into the fetal heart. One to two milliliter of 10% potassium chloride (KCl) was injected into the fetal heart to stop the cardiac activity completely for all cases.

Mothers were allowed to rest in the clinic for about 2 hours. A repeat ultrasonography was done before discharge on that day. All were reviewed the next day to recheck fetal activity on the survivors. All cases were done as outpatient procedures. None in our series needed hospital admission.

All fetal reductions were done by a single operator (KM) trained in fetal medicine. Maternal details and ultrasound findings were recorded at the time of ultrasound scan in the clinic. Pregnancy outcome data were entered into the same database as it became available from the patients themselves during their follow-up.

The miscarriage is defined here as pregnancy loss before 24 completed weeks of gestation. Early preterm delivery is defined as delivery prior to 32 completed weeks of gestation.

The results in our study is compared with 'expectant management' arm of two other European studies by Antsaklis et al[12] and Boulot et al.[13] Our study result is also compared with 'embryo reduction' arm of these two European studies. The significance of the difference between these data is assessed by Chi-square test and Z-test. Hereafter, these two European studies[12,13] would be referred as 'Study A' and 'Study B' respectively. It is relevant to mention here that the terms 'fetal reduction' and 'embryo reduction' are interchangeable and both terms have been used in the literature.

## RESULTS

This retrospective study reviewed the outcome of 32 trichorionic triplet pregnancies reduced to twins by fetal reduction at 10 to 11 weeks of gestation. Seven triplet pregnancies during the study period, who had fetal reduction to singleton, were not included in this study to avoid confounding data. None of the mothers, after counseling, opted for expectant management and, hence, there was no control arm.

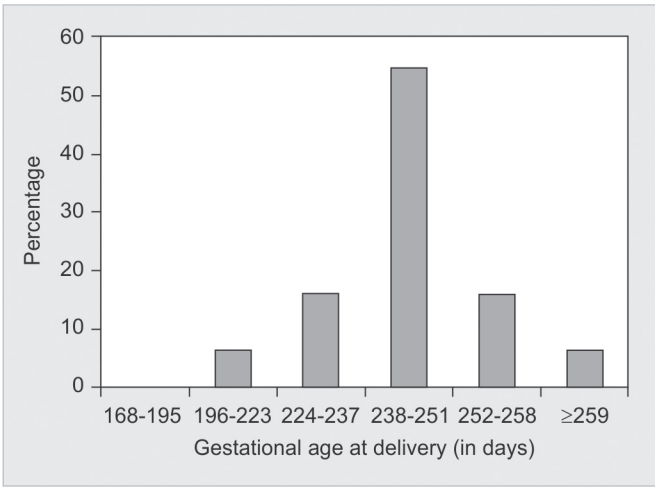
The mean (±SD) age of the mothers was 31.90 ± 4.11 years, and the median age was 32.0 years (26-39 years) respectively.

Around 34.37% of triplet pregnancies had ovulation induction and 65.63% of triplet pregnancies were pregnancies by *in vitro* fertilization (IVF). No patient in this study had conceived triplet pregnancies naturally. In fact, all the mothers were referred from fertility clinics.

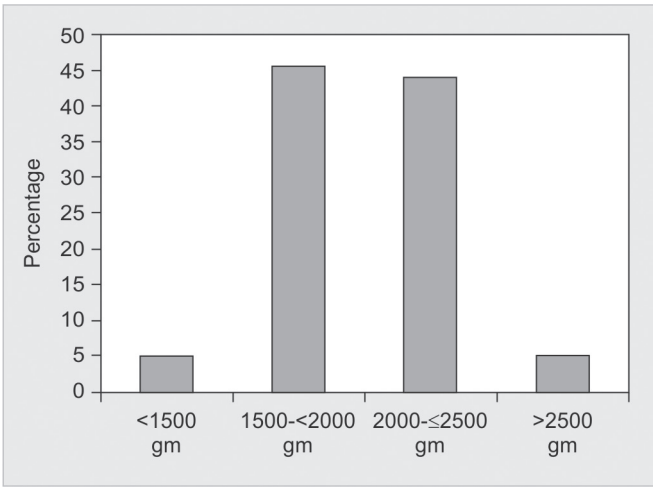
The mean gestational age (mean ± SD) of the mothers was 242.58 ± 12.93 days with range 197 to 262 days, and the median was 244.0 days.

The miscarriage (pregnancy loss before 24 completed weeks) rate in our study was 3.12%. The delivery in our study at ≤32 and ≤35 weeks were 6.45, 51.61 and 48.39% at >35 weeks. Frequency distribution of gestational age of the thirty one mothers is presented in Table 1 and Graph 1. Maternal characteristics and delivery data presented in Table 1.

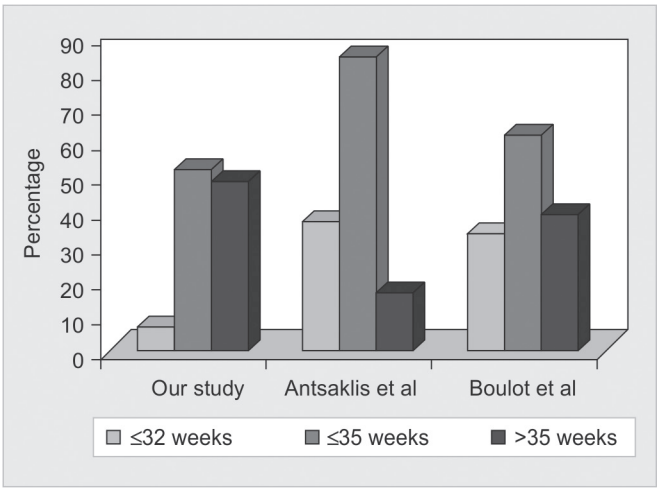
The mean birth weight (mean ± SD) of the babies was 1921.18 ± 339.78 gm with range 810 to 2700 gm, and the median was 2000.0 gm. Regarding the birth weight of neonates in our study, 5.08% babies were <1500 gm, 89.83% were between 1500 and ≤ 2500 gm, and 5.08% were >2500 gm. Frequency distribution of the birthweight of the neonates is presented in Table 2 and Graph 2. There was no congenital anomaly in any of the newborns. There was no necrotizing enterocolitis, congenital lung disease or advanced retinopathy of prematurity in any of the babies in this study. There was no neonatal mortality. Perinatal mortality was 5.08%. Neonatal data are presented in Table 2. However, it is relevant to mention that seven mothers with triplet pregnancies



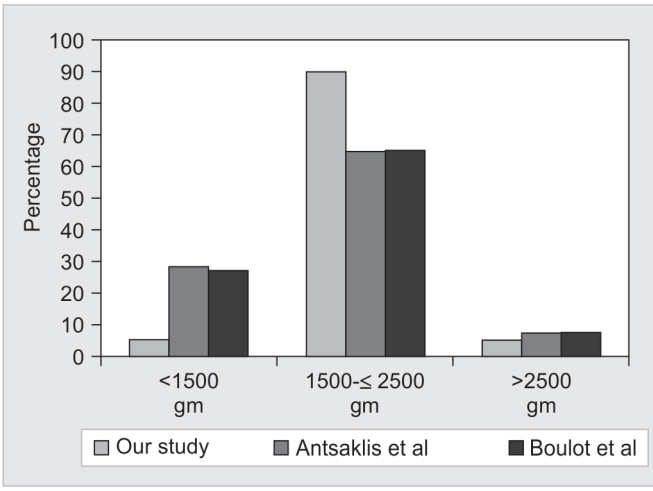

**Graph 1:** Gestational age at delivery (in days) in our study




**Graph 2:** Birth weight of the neonates in our study




**Graph 3:** Comparison of gestational age at delivery in our study with that in 'expectant management' group of Antsaklis et al's study and Boulot et al's study




**Graph 4:** Comparison of birth weight of the neonates in our study with that in 'expectant management' group of Antsaklis et al's study and Boulot et al's study

were excluded from this study to avoid bias because they had fetal reduction to singleton pregnancy. Two of these mothers had fetus with congenital anomalies (one mother had a fetus with spina bifida and other mother had a fetus with anencephaly).

It is already explained why this study had no control arm. In these circumstances, our results should be compared with the triplet pregnancy mothers from the same population treated expectantly. Even after a thorough search, we could not find adequate data on the outcome of triplet pregnancy in Indian women in literature. Hence, we had compared three most important parameters as miscarriage rate, gestational age at delivery and birthweight of the babies in our study results with the corresponding data of 'expectant management' arm of two European studies, Study A and Study B[12,13] in the description below as well as in Table 3 and Graphs 3 and 4.

This study result shows a miscarriage (fetal loss before 24 weeks) rate of 3.12%. The miscarriage occurred 11 days following the procedure. The miscarriage rate in 'expectant management' arm of Study A and Study B were 2.8 and 6% respectively. The difference in miscarriage rate between our study and the other two studies is not statistically significant.

The delivery in our study at ≤32 and ≤35 weeks were 6.45 and 51.61% whereas the delivery at ≤32 and ≤35 weeks in 'expectant management' arm of study A were 36.7% and 83.8%. In 'expectant management' arm of study B, the delivery at ≤32 and ≤35 weeks were 33.3 and 61.5% respectively. The difference between our study result and these two study results is highly significant ($p < 0.01$) regarding delivery at ≤32 weeks of gestation. Regarding delivery at ≤35 weeks of gestation our study result, though significantly different ($p < 0.01$) from study A, is not significantly different ($p > 0.05$) from study B.

Regarding the birth weight of neonates in our study, 5.08% babies were <1500 gm, 89.82% were between 1500 and ≤2500 gm whereas the 'expectant management' arm of study A and study B noted neonatal birthweight of 28.4 and 27.4 in <1500 gm category, 64.5 and 65% in 1500 to

**Table 1:** Maternal characteristics and delivery data in our study

| | *Fetal reduction (n = 32*)* |
|---|---|
| Maternal age in years (mean ± SD) | 31.90 ± 4.11 |
| Mode of conception | |
| • Ovulation induction | 11 (11/32, i.e. 34.37%) |
| • IVF | 21 (21/32, i.e. 65.63%) |
| Miscarriage (<24 weeks) | 1 (1/32, i.e. 3.12%) |
| Gestational age at delivery in days (mean ± SD) | 242.58 ± 12.93 |
| Frequency distribution of gestational age at delivery (in completed weeks)* | |
| • 24-<28 weeks | 0 |
| • 28-<32 weeks | 2 (2/31, i.e. 6.45%) |
| • 32-<34 weeks | 5 (5/31, i.e. 16.12%) |
| • 34-<36 weeks | 17 (17/31, i.e. 54.83%) |
| • 36-<37 weeks | 5 (5/31, i.e. 16.12%) |
| • ≥37 weeks | 2 (2/31, i.e. 6.45%) |

*In calculating the percentage of gestational age at delivery, the miscarriages are excluded from the denominator

**Table 2:** Birth and neonatal data in our study

| | *Fetal reduction (n = 31*)* |
|---|---|
| Total no. of infants | 62 |
| IUD | 3 |
| Live infants born | 59 |
| Birth weight in gm (mean ± SD) | 1921.18 ± 339.78 |
| Frequency distribution of birth weights: | |
| • <1000 gm | 2 (2/59, i.e. 3.38%) |
| • 1000-<1500 | 1 (1/59, i.e. 1.69%) |
| • 1500-<2000 | 27 (27/59, i.e. 45.76%) |
| • 2000-≤2500 | 26 (26/59, i.e. 44.06%) |
| • >2500 | 3 (3/59, i.e. 5.08%) |
| Neonatal mortality | 0 |
| Perinatal mortality | 3 (3/59, i.e. 5.08%) |

*One mother who had a complete miscarriage was excluded

≤ 2500 gm category respectively. The difference between our study result and these other two studies is highly significant ($p < 0.01$). As far as the neonatal birthweight is concerned, the result in the 'expectant management' arm of study A is remarkably similar to that in study B.

Also, as adequate data on fetal reduction on Indian women in the literature could not be found, we estimated our results vis a vis the 'embryo reduction' arm of the study A and B as well. To this end, we had compared these parameters as miscarriage rate, gestational age at delivery and birth weight of the babies in our study results with the corresponding data of 'embryo reduetion' arm of the study A and B. This comparison had been described below as well as presented in Table 4.

The miscarriage rate in our study was 3.12%, whereas the miscarriage rate in 'embryo reduction' arm of study A and B were 8.11 and 5.4% respectively. The difference between our result and the other two studies is not significant ($p > 0.05$).

The delivery in our study at ≤32 and ≤35 weeks were 6.45 and 51.61%, whereas the 'embryo reduction' arm of study A and B noted a delivery of 11.17 and 14.3% at ≤32 weeks and of 40.58 and 25.4% at ≤35 weeks respectively. The difference with study A is not significant (> 0.05). The difference with study B, though not significant at ≤32 weeks ($p > 0.05$), is significant at ≤ 35 weeks ($p < 0.01$).

Regarding the birth weight of neonates, 5.08% babies were <1500 gm and 89.82% were between 1500 and ≤2500 gm in our study, whereas 'embryo reduction' arm of study A and B noted 10.98 and 6.9% babies in <1500 gm category, 57.57 and 50.8% babies in 1500 to ≤2500 gm category respectively. The difference between our study and 'embryo reduction' arm of these two studies in < 1500 gm category is not significant (> 0.05) whereas the difference in 1500 to ≤ 2500 gm is significant ($p < 0.01$).

## DISCUSSION

There is not much information on fetal reduction in triplet pregnancy in Indian women in the literature. Hence, it was decided to conduct this retrospective study. This

**Table 3:** Our results vis a vis 'expectant management' (referred as EM in the table below) group of Antsaklis et al's study (study A) and Boulot et al's study (study B)

| | *Our study fetal reduction (n = 32)* | *Antsaklis et al EM group (n = 70)* | *p-value* | *Boulot et al EM group (n = 78)* | *p-value* |
|---|---|---|---|---|---|
| Miscarriage rate (<24 weeks) | 3.12% (1 in 32) | 2.8% | >0.05 | 6.0% | >0.05 |
| *Gestational age at delivery* | | | | | |
| ≤32 weeks | 6.45% (2 in 31) | 36.7% | <0.01 | 33.3% | <0.01 |
| ≤35 weeks | 51.61% (16 in 31) | 83.8% | <0.01 | 61.5% | >0.05 |
| >35 weeks | 48.38% (15 in 31) | 16.2% | <0.01 | 38.5% | >0.05 |
| *Baby's birth weight* | | | | | |
| <1500 gm | 5.08% (3 in 59) | 28.4% | <0.01 | 27.4% | <0.01 |
| 1500-≤2500 gm | 89.8% (53 in 59) | 64.5% | <0.01 | 65.0% | <0.01 |
| >2500 gm | 5.08% (3 in 59) | 7.1% | >0.05 | 7.6% | >0.05 |

**Table 4:** Our results vis a vis 'embryo reduction' (referred as ER in the table below) group of Antsaklis et al's study (study A) and Boulot et al's study (study B)

| | *Our study fetal reduction (n = 32)* | *Antsaklis et al ER group (n = 185)* | *p-value* | *Boulot et al ER group (n = 65)* | *p-value* |
|---|---|---|---|---|---|
| Miscarriage rate (<24 weeks) | 3.12% (1 in 32) | 8.11% | >0.05 | 5.4% | >0.05 |
| *Gestational age at delivery* | | | | | |
| ≤32 weeks | 6.45% (2 in 31) | 11.17% | >0.05 | 14.3% | >0.05 |
| ≤35 weeks | 51.61% (16 in 31) | 40.58% | >0.05 | 25.4% | <0.01 |
| >35 weeks | 48.38% (15 in 31) | 59.42% | >0.05 | 74.6% | <0.01 |
| *Baby's birth weight* | | | | | |
| <1500 gm | 5.08% (3 in 59) | 10.98% | >0.05 | 6.9% | >0.05 |
| 1500-≤2500 gm | 89.8% (53 in 59) | 57.57% | <0.01 | 50.8% | <0.01 |
| >2500 gm | 5.08% (3 in 59) | 31.45% | <0.01 | 42.3% | <0.01 |

data may be useful for counseling prospective parents and also for monitoring the impact of the more recent developments in the care of the triplet pregnancies.

All the mothers in this study, after ultrasonic diagnosis of triplet pregnancy, were referred to one of the authors (KM). All these mothers, after being counseled about the options of fetal reduction or expectant management, had opted for fetal reduction. Hence, this study had no control arm.

Ideally, our results should be compared with triplet pregnancy mothers from the same population treated expectantly. As there is inadequate data on triplet pregnancy and fetal reduction in Indian women in literature, we compared our study result with the corresponding data of expectantly treated mothers with triplet pregnancy in two European studies, study A and B. Also, we have compared our results with 'embryo reduction' arm of these two European studies.

The two worrisome complications in triplet pregnancies are miscarriage rate and early preterm delivery, i.e. before 32 completed weeks.[15]

There was one miscarriage in this study (3.12%) which occurred 11 days following the procedure. It is very unlikely that miscarriage is procedure related and is probably due to the resorbing dead feto-placental tissue of the reduced embryo.[15] We have already noted that the difference in miscarriage rate between our study result and 'expectant management' arm of both study A and B is not significant. This finding, though not consistent with study A who found a significant difference of miscarriage rate between the 'embryo reduction' arm and the 'expectant management' arm (8.11 *vs* 2.8%) in their study, agrees with the finding of study B who noted no significant difference of miscarriage rate between the 'embryo reduction' arm and the 'expectant management' arm (5.4 *vs* 6.0%) in their study.

The fact that the delivery rate at ≤32 weeks of gestation in our study (6.45%) is significantly lower than the 'expectant management' arm of study A and B, is consistent with the result found in the comparison between 'embryo reduction' arm *vs* 'expectant management' arm in study A (11.17 *vs* 36.7%) as well as study B (14.3 *vs* 33.3%).

It has been noted in the results that the delivery rate at ≤35 weeks of gestation in our study (51.61%) is significantly lower than the 'expectant management' arm of both study A as well as study B. This is consistent with the result found in the comparison between 'embryo reduction' arm *vs* 'expectant management' arm in study A (40.58 *vs* 83.8%) as well as study B (25.4 *vs* 61.5%).

It is found in our study result that the delivery rate at >35 weeks of gestation (48.38%) is significantly higher than that in the 'expectant management' arm of study A and B. This is consistent with the result found in the comparison between 'embryo reduction' arm *vs* 'expectant management' arm in study A (59.42 *vs* 16.2%) as well as study B (74.6 *vs* 38.5%).

The frequency of babies with birth weight <1500 gm in our study (5.08%) is significantly lower than the 'expectant management' arm of study A and B. This is consistent with the result found in the comparison between 'embryo reduction' arm *vs* 'expectant management' arm in study A (10.98 *vs* 28.4%) as well as study B (6.9 *vs* 27.4%).

The frequency of babies with birth weight of 1500 to ≤2500 gm in our study (89.82%) is significantly higher than the 'expectant management' arm of study A and B. This is not consistent with the corresponding result found in the comparison between 'embryo reduction' arm *vs* 'expectant management' arm in study A (57.57 *vs* 64.5%) as well as study B (50.8 *vs* 65.0%).

The frequency of babies with birth weight of >2500 gm in our study (5.08%) is not significantly different from the 'expectant management' arm of study A and B. This is not consistent with the corresponding result found in the comparison between 'embryo reduction' arm *vs* 'expectant management' arm in study A (31.45 *vs* 7.1%) as well as study B (42.3 *vs* 7.6%).

Summarily, in our study, only a few women (6.45%) had delivered ≥37 weeks. So, few babies were >2500 gm. Also, few women (22.58%) had delivered before 34 weeks resulting in fewer babies with birth weight <1500 gm. Many mothers (48.38%) had delivered at >35 weeks of gestation. So, the majority of babies (89.83%) were in between 1500 and ≤2500 gm. This study result is significantly better in terms of gestational age at delivery and neonatal birth weight than the 'expectant management' arm of the two European studies, study A and B.

In the 'embryo reduction arm' of the European studies, majority (60-70%) of women were beyond 35 weeks, and many (39% in study B) of them were at >37 weeks of gestation at the time of delivery. Only few were in the early gestational age and few babies were <1500 gm. The fact, that Asian mothers had shorter gestational lengths[16] and lighter babies compared to European counterparts,[17] could be a reason why most of the mothers in our study could not attain a gestational age of 36 weeks at delivery and most of the babies did not have a birthweight of 2500 gm even after fetal reduction.

In the 'expectant management', arm of the European studies, most of the women delivered in the early third trimester, followed by those who went beyond 34 weeks and very few at term. Thus, most babies were <1500 gm, others were in 1500 to ≤2500 gm range and only few were >2500 gm.

The conclusion in our study is that though the fetal reduction had not enabled majority of the Indian women to reach term pregnancy and good neonatal birth weight, i.e. >2500 gm, in most of the mothers (54.83%) pregnancy had progressed beyond critical stage, i.e. 34, completed weeks of gestation and most of the babies were beyond the threshold birthweight, i.e. >1500 gm, which is another prognostic indicator of the ability to survive.

However, this comparison has so far remained limited to the medical aspect of the effects of fetal reduction. The statement does not intend to show the value of the medical data in a reductive way as that is of enormous importance for counseling of prospective mothers with triplet pregnancy.

Beside medical reasons, fetal reduction brings an enormous relief to a mother who is very distressed at the daunting prospect of rearing up three children, managing her home as well as job and the intimidating financial task of providing for three children in a way she prefers. All these apart from the physical and other inconveniences of a triplet pregnancy. The issue of an individual mother's concern should not be diluted in terms of percentage and statistical jargon. This is what we realized while dealing with two of the mothers who were excluded from this study. These two individuals were hell-bent on reducing the triplets down to singleton even after incurring the burdensome expenditure of ART. Fetal reduction is a valuable option and particularly an important adjunct to ART treatment in countries like India, where three embryo transfers is still a common practice.

It will be ideal to conduct a prospective randomized study on triplet pregnancy comparing a group with fetal reduction to twins with another group managed expectantly, both group being from the same population. One such study will require an enrolment of 320 mothers with triplet pregnancies to detect an 18% difference in the rate of early preterm delivery (90% power and significance level of 0.05).[15] Besides these mothers need to be unbiased regarding the options, i.e. fetal reduction or expectant management. It might be difficult to conduct such a study as we came across a large number of mothers who already had their strong personal choice.

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## AUTHOR CONTRIBUTIONS

Both authors contributed equally during the preparation of this manuscript.

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