

RESEARCH ARTICLE

Perinatal Outcome after Multifetal Pregnancy Reduction: A Retrospective Analysis of 1-year Data in a Referral Fetal Medicine Center

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ABSTRACT

Aims: Multiple pregnancies are associated with higher maternal and perinatal morbidity and mortality. Multifetal pregnancy reduction is an accepted method to reduce the morbidity associated with higher order multiples. The present study describes the perinatal outcome of 336 pregnancies which underwent multifetal reduction in our center.

Materials and methods: This is a retrospective descriptive study of all patients who underwent multifetal pregnancy reduction during the period from September 1, 2010 to August 31, 2011. The demographic details of the patients were extracted from the Sonocare software database. Fetal reductions were performed using standard protocols after a detailed structural evaluation including nuchal translucency. The perinatal outcome was obtained from hospital records or from patients over telephone.

Results: Of the total 336 pregnancies, 21% were lost to follow-up. The remaining 265 were analyzed for the perinatal outcome. The take home baby rate was 80.2%. Total fetal loss rate was 11.6% and partial pregnancy loss rate was 3.8%. Mean gestational age at delivery was 34.7 weeks. A total of 22.1% of women delivered at term. A total of 34.5% of the patients had late preterm delivery (35–37 weeks). The mean birth weight was 2002 gm.

Conclusion: The data shows that the outcomes of multifetal pregnancy reduction in India are similar to published data from other countries, with a good perinatal outcome in over 80% cases. However, the data also points to the urgent need for stringent guidelines for ovulation induction and embryo transfer to reduce the requirement for and number of these procedures in the future.

Keywords: Fetal reduction, Higher order multiple, Infertility, Multiple pregnancy, Potassium chloride.

How to cite this article: Latha PM, Andrew C, Suresh I, Seshadri S. Perinatal Outcome after Multifetal Pregnancy Reduction: A Retrospective Analysis of 1-year Data in a Referral Fetal Medicine Center. *J South Asian Feder Obst Gynae* 2016;8(4):266-270.

Source of support: Nil

Conflict of interest: None

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Date of received: 13 June 2016

Date of acceptance: 17 September 2016

Date of publication: October 2016

INTRODUCTION

There is an increased incidence of multiple pregnancies worldwide due to increased infertility rates and the various ART modalities. In India, approximately 13 to 19 million couples are likely to be infertile at any given time and all of them approach infertility centers. The increasing demand for ART has resulted in mushrooming of infertility clinics.¹ There is no reliable information on the number of ART clinics in India in the absence of a national registry of ART clinics.² According to Pai's studies, India has more than 550 registered IVF centers and a new clinic opens every 15 days.³ In most countries, including India, non-IVF ovarian stimulation treatments are done by general physicians.¹

Maternal and perinatal complications like preterm deliveries and low birth weight babies^{4,5} associated with multiple pregnancies increase proportionately with increase in the number of fetuses as seen in higher order multiple pregnancies (triplets or more).^{6,7} In the present day practice where fetal reduction has become an acceptable procedure to improve the maternal and perinatal outcome, it is essential to review the results of the procedure on a regular basis in order to lay emphasis on single embryo transfer.

The aim of our study is to analyze the perinatal outcome after fetal reduction performed in our institution, which is the largest referral center for fetal invasive procedures in South India, over a period of 1 year.

MATERIALS AND METHODS

Three hundred and thirty-six pregnant women were referred for multifetal pregnancy reduction (MFPR) from various centers during the study period from September 2010 to August 2011. All triplets and higher order multiple pregnancies, twin pregnancy with one abnormal fetus at gestational age > 10 weeks were included in the study. Women with history of active bleeding per vaginum and associated medical complications were excluded from the study. Prior to the procedure, detailed ultrasound

was performed to confirm the chorionicity, amnionicity and to rule out anomalies. The couples were counseled regarding the nature, technique, benefits, and risks. A written informed consent was then obtained from the couples prior to the procedure.

The fetuses were evaluated by a set protocol prior to the decision of fetus reduction. This protocol included crown rump length, nuchal translucency (NT) measurements, and anatomical screening. If all the fetuses appeared normal, the fetuses near the fundus and technically easy to approach were chosen. However, if any fetus appeared abnormal or had an increased NT, this was chosen irrespective of geographic location.

TECHNIQUE OF FETAL REDUCTION

Transabdominal route is preferred in our center. A 22 g 7" spinal needle is introduced into the thorax of the fetus to be reduced, with aseptic precautions under continuous ultrasound guidance and strict aseptic precautions. After confirming intra-thoracic or intracardiac location of the needle, 0.3 to 0.6 mL of undiluted potassium chloride (KCl) is injected. Blood in the needle indicates preferred site of injection, the fetal heart.⁸ No aspirate in the syringe indicates that the needle is intrathoracic. Cessation of fetal heart beat usually occurred within a few minutes. Further instillation of KCl was required in few cases.⁸ After ensuring cardiac asystole for at least 1 minute, the needle was withdrawn. Different puncture site was chosen to reduce the second and third fetus in cases of quadruplets and higher order multiples. Amount of KCl used ranged between 0.3 and 0.8 mL, majority requiring 0.3 to 0.6 mL of KCl.

The outcome of the pregnancy was obtained by contacting the referral doctor or the patients. The outcome parameters assessed were pregnancy loss rate, premature delivery rate, and mean birth weight. Pregnancy loss at <24 weeks of gestation was classified as miscarriage⁹ and deaths that occurred after 24 weeks were classified as late fetal death. Fetal loss rate was defined as the sum of both miscarriage and late fetal losses. Deliveries between 35 and 37 weeks of gestation were considered as late preterm. Full term was defined as delivery at greater than 37 weeks of gestation.

Descriptive statistical methods were used for analyzing the data by Microsoft Excel.

RESULTS

Out of the 336 women referred for MFPR during the study period, 71 (21%) were lost to follow-up. Data was collected for 265 cases. Fifteen of them were spontaneously conceived, and the remaining cases were conceived after ovulation induction or ART (Table 1). There were 203 (71.7%) triplet pregnancies and 16 (6%) twins. The

Table 1: Distribution of patients according to mode of conception

Mode of conception	No. of patients	Percentage
Spontaneous	15	5.7
Induced ovulation/IUI	69	26.0
IVF ET	152	57.4
ICSI	29	10.9
Total	265	100

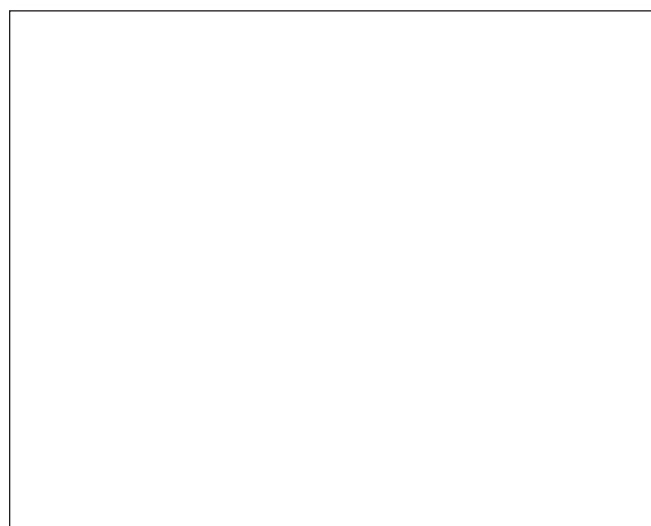
Table 2: Frequency of conceived and reduced fetuses among categories of multiple pregnancies

Number conceived	n	Reduced to	
		Singleton n (%)	Twins n (%)
Twins	16	16 (6)	0
Triplets	203	13 (4.9)	190 (71.7)
Quadruplets	30	0	30 (11.3)
Quintuplets	15	0	15 (5.7)
Sextuplets	1	0	1 (0.4)
Total	265	29 (10.9)	236 (89.1)

cohort included one sextuplet and the remaining 17% were quadruplets and quintuplets. After reduction, there were 29 singletons and 236 twins (Table 2).

The mean maternal age of the referred women was 31 years. Fifty six (21%) subjects were more than 35 years old. 62% of patients were in the age group of 26 to 35 years with the mean age of 31 years. The median gestational age at reduction was 11.4 weeks, of which 6 (2.3%) underwent the procedure at greater than 14 weeks of gestation (Graph 1).

Thirty-one pregnancies underwent complete fetal loss. Of these, 28 were miscarriage (10.5%) and three (1.1%) were late fetal losses. Two pregnancies were terminated at 22 weeks in view of severe preeclampsia. Twenty-nine pregnancies were ongoing at the time of analysis. Hence the gestational age at delivery and perinatal outcome was studied in 203 subjects. Partial fetal loss rate was seen in 10 (3.8%) pregnancies.



Graph 1: Distribution of gestational age at delivery in relation to starting number of fetuses

Five (16%) of the complete fetal losses were seen within 1 week of the procedure. Majority (48.3%) of these losses occurred 8 weeks after the procedure. There were no losses seen between 2 to 4 weeks and after 15 weeks from the time of procedure. Partial losses were seen in 10 patients and vanishing twins in three cases. There were seven patients who underwent intrauterine fetal demise (IUFD) of one twin. Demise of one of the twins occurred at 26 weeks in one patient and at 32 weeks in other. Gestational age at the time of one twin IUD is not available in the remaining five cases.

Premature delivery rate at less than 35 weeks was 43.3%. There were 70 (34.4%) late preterm deliveries. The median birth weight was 2002 gm (SD: 540; range 1730–2600 gm). There was a clinically significant difference in the mean birth weight between singletons [2580 gm and twins (1900 gm)]. Neonatal mortality rate was 5.1% (19 babies). Four women who lost both the babies had preterm deliveries of which three were extreme prematurity. Birth weight of all the babies was less than 1000 gm.

Out of 11 babies who had neonatal deaths, one neonate required surgery for intestinal obstruction and one had sepsis. The remainder of the neonatal deaths were due to complications associated with low birth weight (<1.5 kg) and prematurity. The take home baby rate was 80.2%.

DISCUSSION

As the incidence of multiple gestations increases with assisted reproductive techniques and the rate of maternal and perinatal complications is directly proportional to the number of fetuses conceived, American Society for Reproductive Medicine (ASRM) has laid strict guidelines regarding the number of embryos to be transferred based on the maternal age.¹⁰ Decreased multiple pregnancy rates from 29.5 to 9.1% were observed in Belgium after implementing a new embryo transfer policy since 2003.¹¹

In our institution the percentage of IVF conceptions referred for MFPR have increased significantly in the last 10 years from 23.9 to 68.3%.⁸ As this unit is not attached to a single infertility center, the increasing trend reflects both the increasing number of practitioners practicing multiple embryo transfer and the increasing awareness of MFPR in the country.⁸

Satya Balasubramanyam¹² found that Indian women are similar to their western counterparts in desiring multiple embryo transfers in order to maximize their chance of getting a positive pregnancy result. Fetal reductions did not pose any moral concerns to most women. The confidence of the treating physician to offer single embryo transfer also appears to affect the patients' choice on deciding for single embryo transfer.

Solutions to reduce the incidence of multiple pregnancies by infertility therapy are still under investigation and

implementation of these solutions in all the infertility centers in India may take some more time. Meanwhile, MFPR has become an accepted tool to improve the perinatal outcome.

Mean birth weight in our study was 2002 gm. Birth weight negatively correlated with the starting number of fetuses before the procedure. As observed by various authors, the starting number prior to reduction continued to influence outcome even after the procedure was performed. We found significant difference between starting number of five and starting number of three. This suggests the need to reduce the number of embryos transferred to one or two. As expected, there was statistically significant inverse correlation between finishing number of fetuses (2.58 kg in singletons and 1.99 in twins).

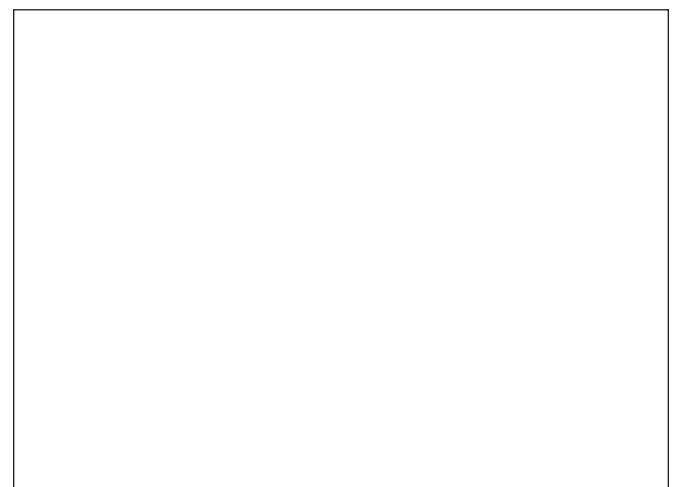
Mean gestational age at delivery in reduced triplets to twins was 35 weeks in our study which is similar to Papageorghiou (36 weeks),¹³ Lipitz (35.7 weeks),¹⁴ and Yaron (35.6 weeks).¹⁵

Mean gestational age at delivery was found to be inversely related to the starting and finishing number of fetuses in various studies.¹⁶⁻¹⁸

We found that there was statistically significant difference in the mean gestational age at delivery in relation to the finishing number (34.6 weeks in twins and 36.6 weeks in singleton). Though there was decreasing trend in the gestational age at delivery as the starting number of fetuses increased (36.7 weeks for twins to singleton, 34.6 for triplets to twins, 34.2 for quadruplets and quintuplets to twins), there was no statistically significant difference in the mean gestational age at delivery when the finishing number was kept constant at two.

Overall complete fetal loss rate observed in our study (11.7%) (Graph 2) is similar to other studies, Antsaklis (10.6%, n=158)¹⁹ and Evan's et al (11.7%, n=1789).²⁰

Antsaklis et al compared the outcome of 158 sets of twins obtained by MFPR compared with 135 control twin



Graph 2: Comparison of fetal loss rates with other studies

pregnancies and found that the loss rate in non-reduced twins was 9.5%. This implies that twin pregnancies are at risk of miscarriage and all the fetal losses may not be procedure related.

In recent years, Stone et al¹⁶ and Timor-Tritsch et al²¹ have reported relatively less fetal loss rates of 4.7 and 3.5% respectively. Timor-Tritsch et al have compared the loss rates in transvaginal *vs* transabdominal route and found that the overall loss rate was 6.5% (3.5% for transabdominal and 13.3% for transvaginal).

Fetal loss rate in triplets reduced to twins in our study was 8.8%, which is similar to observations made by Boulot (5.4%),²² Hruby et al (6.6%),²³ and Papageorghiou (8.3%).²⁴

In our study, there were no fetal losses in triplets reduced to singletons as opposed to Papageorghiou et al's study where there was miscarriage rate of 13.6% in triplets reduced to singletons.

We observed that the loss rates were progressively increasing with the increase in the starting number of fetuses as described by various authors in the literature.^{19,21,25}

The interval between the time of procedure and the fetal loss rate was found to be similar to Stone et al¹⁶ who found that 46% of the losses occurred after 8 weeks which is similar to our study (48%).

Median interval between the reduction and the fetal loss was 4.4 weeks and 10.6% were lost <24 weeks of gestation. These findings are similar to Sebire et al's²⁶ study where the median interval was 5 weeks and loss rate for <24 weeks was 12.6%.

Yaron¹⁵ compared the outcomes of triplet pregnancies undergoing reduction to twins with outcomes of non-reduced twin pregnancies and expectantly managed triplet pregnancies. They found that the gestational age at delivery was similar in twins reduced from triplets and non-reduced twins. In addition, the outcomes were better in these groups when compared to expectantly managed triples.

In contrast to the above findings, Groutz et al²⁷ had reported that the mean gestational age at delivery and the mean birth weight in pregnancies who underwent MFPR to twin were significantly lower than the twins which did not undergo the procedure. In addition, Papageorghiou et al¹³ have recently reported that reduction of triplets to twins increases the risk of miscarriage but decreases the risk of early preterm rate. The lack of appropriate control group in the present study did not allow us to ascertain either of these findings.

Overall neonatal mortality rate in our study was 5.1%. Neonatal mortality in triplets reduced to twins was 2.9% which is very high when compared to Boulot et al²² (0.86%). This may be because of high number of

preterm and low birth weight babies in our study. In our study, 78.5% of babies had low birth weight (<2.5 kg) as compared to 58% and the prematurity rate was 78% as compared to 60% in Boulot's study. The percentage of preterm deliveries <32 weeks was 29% in our study as compared to 14.1% in Boulot's study.

Overall take home baby rate in our study was 80.2%. Take home baby rate was 97% in the group of triplets reduced to twins and 88% in the group of quadruplets to twins. These rates were similar to observed by Evan et al¹⁸: 95% in triplets to twins group and 92% in quadruplets to twins group. This again reflects the reduced take home baby rate with increasing higher order multiples in comparison with triplet reductions.

Although the survival rates increase with excellent NICU care, there is no convincing evidence on the long-term outcome of extreme prematurity. In view of this, emphasis should be laid on primary prevention of reducing the incidence of multiple pregnancies by modifying the infertility treatment strategies in India.

In our study, majority of transabdominal MFPR was done between 11 and 12 weeks of gestation. We found that there was no statistical difference in the birth weight between 11 to 12 weeks and 13 to 14 weeks group at the time of reduction, which was similar to Lipitz et al.¹⁴ But the mean gestational age at delivery was statistically different between 11 to 12 weeks group (34.5 weeks) and 13 to 14 weeks (36.3 weeks). And there were no fetal losses seen in 13 to 14 weeks group.

LIMITATIONS OF THE STUDY

Our institution is a tertiary care referral center with referrals from different regions. As the patients return to their obstetrician after reduction, the management protocols may vary between different units and thus alter the outcomes. We could not standardize these managements and therefore could not analyze the factors that may influence the pregnancy outcome in detail. Similarly, the neonatal care availability and the survival rates in various NICUs may differ which would also alter the outcome measures.

The outcomes of the study group could not be compared with a control group which did not undergo reduction. This comparison has been therefore done with published data from other studies which quote survival rates for triplet and higher order gestations.

The data shows that the outcomes of MFPR in India are similar to published data from other countries in the perinatal outcome. However, the data also points to the urgent need for stringent guidelines for ovulation induction and embryo transfer to reduce the requirement for and number of these procedures in the future.

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