

Outcomes of Multifetal Reduction: A Hospital-Based Study

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About the Author



Madhusudan Dey is an Associate professor in Obstetrics and Gynecology at Armed Forces Medical College, Pune. He is a trained Maternal and Fetal medicine specialist with keen interest in intra-uterine intervention and fetoscopic procedures, and he is also the member of Genetics and Fetal medicine committee, FOGSI. He has completed five research projects and published research papers in various journals. He is regularly delivers lectures in various conferences and he was resource person for various workshops and symposia. He is presently working on risk factors associated with umbilical artery Doppler abnormalities and first trimester biochemical markers for prediction of pre-eclampsia.

Abstract

Background Higher-order multiple (HOM) pregnancies are associated with increased incidences of pregnancy complications mainly abortions, pre-eclampsia, preterm delivery and fetal death. Multifetal reduction (MFR) during first trimester and subsequent delivery of twins can reduce pregnancy associated morbidities. This study was

conducted to evaluate the maternal and fetal outcomes of MFR procedure in patients with HOMs those managed in a tertiary care hospital.

Methods and Material It was a prospective observational study carried out in a tertiary care military hospital, India, and all women with higher-order multiples (triplets or more) conceived spontaneously or after infertility treatment (ovulation induction, intra-uterine insemination, or in vitro fertilization) during the 3-year period from Jan 2014 to Dec 2016 were included for MFR. Demographic and clinical data, and obstetric and neonatal outcomes were tabulated.

Results The study included 32 HOM pregnancies which underwent MFR. 16% patients had pre-eclampsia and 12% patients had gestational diabetes. The study had 2

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pregnancy losses before 24 weeks period of gestation (POG). 70% patients underwent cesarean delivery with mean gestational age of 35.5 weeks. Average birth weight of newborn was 1820 gm and 80% of them required NICU admission.

Conclusion Favorable pregnancy outcomes can be achieved after multifetal reductions during first trimester in higher-order multiples, but the procedure is not totally safe.

Keywords Infertility · Twin pregnancy · Fetal reduction · Pre-eclampsia · Abortion

Introduction

Multiple pregnancies and, in particular, higher-order multiple (HOM) pregnancies (triplets, quadruplets, quintuplets) are high-risk pregnancies with higher risks for the mother and babies. The spontaneous occurrence of higher-order gestations is rare. Spontaneous quadruplet pregnancy is very uncommon with an incidence rate of 1 in 512,000–1 in 677,000 births [1]. Ovulation induction with clomiphene citrate, FSH, and human menopausal gonadotropin (hMG) remarkably enhances the likelihood of multiple ovulations, thus increasing the chances of HOMs especially by timed intra-uterine insemination. The incidence of twin gestation with clomiphene citrate ranges from 6 to 8.4%, 0.55% for triplets and 0.3% for quadruplets but with hMG incidences are increased to 16–66% for twins, 3.5% for triplets and 1% for quadruplets [2]. In general with IVF, the risk of HOMs is related to the number of embryos transferred. Virtually, all of quadruplets are born preterm, 90% for triplets and 60% for twins [3]. Women with multiple pregnancies have an increased risk of miscarriage, anemia, hypertensive disorders, hemorrhage, operative delivery, and postnatal illness. In general, maternal mortality associated with multiple births is 2.5 times that for singleton births. The overall stillbirth rate in multiple pregnancies is higher than in singleton pregnancies, and it can be as high as 12.3 per 1000 twin births and 31.1 per 1000 triplet and higher-order multiple births, compared with 5 per 1000 singleton births [4]. In addition to these adverse outcomes, there is increased risk of congenital malformations in higher-order multiples, and this increased risk is for each fetus not because there are more fetuses per pregnancy. The risk of peripartum hysterectomy is also increased 24-fold for triplets or quadruplets as compared to threefold for twins [5].

Multifetal reduction (MFR) is the termination in the first trimester or early second trimester of one or more fetuses in a multiple pregnancy, performed to increase the chances of survival of the remaining fetuses and to decrease long-term morbidity of the remaining fetuses. Selective reduction implies early pregnancy intervention, whereas selective

termination is performed later. Multifetal reduction has been shown to decrease the incidence of abortion, preterm delivery and low-birth-weight babies, but it is also associated with fetal loss. This study was conducted to evaluate the maternal and fetal outcomes of MFR procedure in patients with HOMs those managed in a tertiary care hospital.

Methodology

This was a prospective observational study conducted in the fetal medicine division at a tertiary care teaching hospital, Pune, India. Institute ethical committee approved the study protocol. The study population included all women with higher-order multiples (triplets or more) conceived spontaneously or after infertility treatment (ovulation induction, intra-uterine insemination, or in vitro fertilization) during the 3-year period from Jan 2014 to Dec 2016. Women included in this study were followed up till 1 month post-delivery. Last MFR was carried out in the month of May 2016.

Prior to the MFR procedure patient counseling, all possible risks were explained to them and a written informed consent was taken. An ultrasound examination was performed prior to the procedure to know the number of fetus, cardiac activity, to determine the chorionicity, to establish the relationship of the gestational sacs to each other and also to determine which of the fetuses were most accessible to needle insertion. MFR procedure was carried out between 11- to 14-week period of gestation. All the pregnancies underwent nuchal translucency and nasal bone scan (NT/NB scan) and determination of chorionicity prior to the procedure. In case of any abnormality, the anomalous fetus was chosen for reduction; otherwise, the fetus which was easily accessible to the needle in trans-abdominal approach usually that closest to the anterior uterine wall and/or the fundus was reduced while that near the cervix was avoided. Pre-procedure single dose of cefotaxime and single dose of progesterone 100 mg were given to all the patients.

Under ultrasound guidance, using 21-gauge spinal needle, the procedure was performed trans-abdominal (TA) by injection of 2–3 ml of potassium chloride (2 meq/ml) into the fetal thorax. Potassium chloride was injected slowly so as not to dislodge the needle tip. The cardiac activity is carefully observed for at least 2 min, and if cardiac activity persists, more potassium chloride is injected. Asystole was seen within 1–2 min of injection of potassium chloride, and total procedure was complete within 5 min. Reduction of second fetus was carried out with a separate needle prick. Out of the four quadruple pregnancies, two of them were reduced to twins in the same sitting and two of them were

reduced on next day. After the procedure, the patients were observed for 1 h for pain, leaking, bleeding, or any other complications related to the procedure. A repeat ultrasound was performed 1 h after the procedure to confirm asystole in the reduced fetus (es) and cardiac activity in the non-reduced fetus (es). All patients were scheduled for ultrasound examination after 1 week of procedure for fetal well-being and cervical length assessment. Patients were followed up regularly in fetal medicine division till delivery. During the follow-up period at 28-week period of gestation, all of them received two doses of Inj Betamethasone 12 mg, 24 h apart for fetal lung maturity as per institute protocol of management of multiple pregnancies. Maternal data, sonographic findings, and MFR procedure details were noted down. Sociodemographic data, maternal characteristics, number of fetuses, chorionicity, duration of pregnancy, mode of delivery, and neonatal outcomes were collected and analyzed by using Epi-info 2008 software.

Result

Thirty-two HOMs were included during the study period, and most of them were diagnosed by 11-week POG. Three of them were diagnosed at 12-week POG. Total number of deliveries in the same study period was 10,664 making the incidence of HOMs is about 0.3%. Among the HOMs, triplet pregnancies were more and quadruple pregnancies account for about 12%. All the 32 patients were followed up in our center till 28-week period of gestation and nine of them delivered in a different center for which data were collected post delivery follow-up period. Maternal demographic factors are shown in Table 1. Most of our patients were below the age of 30 years with middle socioeconomic status. 69% of our patients were delivered for the first time, and 72% of the patients were having normal BMI.

HOMs resulted from ovulation induction and timed intercourse were 66% of total cases followed by ovulation induction and intra-uterine insemination (16%) and in vitro fertilization (12%). Among the maternal co-morbidities, 18% of our patients had anemia (Hb less than 11 gm%), 16% developed pre-eclampsia, and 12% of them had gestational diabetes (Table 1).

Fetal characteristics and details of MFR procedure are shown in Table 2. Out of 32 HOMs, four were quadruples. All the fetuses had their own placenta. During the NT/NB scan, one of the fetuses of triplet pregnancy had anencephaly, and as per protocol, this fetus was reduced leading to delivery of healthy twins. Most of the cases (75%) of MFR were carried out by single pricks, but four triplet pregnancies required an additional needle insertion. Two

patients had slight bleeding and history of watery discharge following the procedure.

Pregnancy outcomes of MFR procedure are tabulated in Table 3. Out of 32 MFR carried out during the study period had two abortions. One abortion was at 13 weeks and another was at 19 weeks 3 days period of gestation. The pregnancy which was aborted at 13-week period of gestation was a quadruple pregnancy. Sixty-seven percent of patients had preterm delivery with median period of gestation of delivery was 35.5 weeks. Seventy percent of patients underwent cesarean delivery. Average birth weight of newborn was 1820 gm, and 80% of them required NICU admission mainly due to prematurity, low birth weight, and hypoglycemia.

Discussion

As it is a well-known fact that assisted reproductive technology (ART) is one of the main reasons for increasing number of HOMs. In our study also shown that out of 32 HOMs, 30 of them were due to some form of infertility treatment. In two cases, we were unable to extract any history of infertility treatment as both of them were pregnant for the first time and within 1 year of cohabitation, and one of the patients had history of triplet pregnancy delivered in their family. Parity, maternal age, race, heredity, nutrition, pituitary gonadotropin, and body mass index all have been identified as risk factors for multiple gestations, but because of insufficient numbers of HOMs, most studies have only compared twins with singletons. In our study, most of the patients were below 30 years of age, and they are from middle to high socioeconomic status. 72% of the patients had normal BMI. After the recent revision of The American Society for reproductive Medicine (2013) guidelines on cleavage stage embryos or blastocyst transfer to reduce the incidence of HOMs, for example, women with younger than 35 years with favorable prognosis should have no more than two embryos transferred have effectively lowered rates of HOMs [6]. In this study, 12% cases were the result of IVF, but 82% HOMs were resulted from ovulation induction with timed intercourse/intra-uterine insemination showing that it is the main reason for occurrence of HOMs.

Chromosomal as well as congenital abnormalities are increased in cases of multiple gestations. Importantly, the increased risk is for each fetus and is not simply because there are more fetuses per pregnancy. Malformation rate in monochorionic gestation is almost twice than dichorionic gestation. With increased availability of ART, the risk of birth defects in dizygotic gestation also increased over a period of time [7]. Every pregnancy in our study underwent NT/NB scan, and one of the fetuses was detected to have

Table 1 Demographic factors of patients underwent multifetal reduction

Factors	Number (N)	Percentage (%)
<i>Age (years)</i>		
18–25	10	31.2
26–30	17	53.1
≥31	5	15.6
<i>Socioeconomic status</i>		
Low	3	9.3
Middle	24	75
High	5	15.6
<i>BMI (kg/m²)</i>		
18–24.9	23	71.8
25–29.9	4	12.5
≥30	5	15.6
<i>Parity</i>		
Primipara	22	68.8
Multipara	10	31.2
<i>Conception</i>		
Spontaneous	2	6.2
Ovulation induction + timed intercourse	21	65.6
Ovulation induction + intra-uterine insemination	5	15.6
In vitro fertilization	4	12.5
<i>Maternal co-morbidities</i>		
Pre-eclampsia	5	15.6
Gestational diabetes	4	12.5
Hypothyroidism	5	6.2
Anemia	6	18.7

anencephaly, and this fetus was reduced leading to delivery of healthy twins.

Multiple gestations are associated with higher incidences of maternal morbidities and mortality especially with hypertensive disorders of pregnancy. According to Luke and associates [8], the risk of pregnancy associated hypertension was significantly increased for triplets and quadruplets (11 and 12%, respectively) as compared to twins (8%). When pre-eclampsia occurs in HOMs, it more often occurs earlier, is more severe, and is atypical. As per NICE guidelines 2011, advise women with twin and triplet pregnancies that they should take 75 mg of aspirin daily from 12 weeks until the birth of the babies if they have one or more of the following risk factors for hypertension [4]:

- First pregnancy.
- Age 40 years or older.
- Pregnancy interval of more than 10 years.
- BMI of 35 kg/m² or more at first visit.
- Family history of pre-eclampsia.

Table 2 Fetal characteristics and MFR procedure

Factors	Number (N)	Percentage (%)
<i>Gestation sac</i>		
3	28	87.5
4	4	12.5
<i>Chorionicity</i>		
Trichorionic	28	87.5
Quadruchorionic	4	12.5
Anomalies detected at NT/NB scan (anencephaly)	1	3.1
Mean gestational age at presentation (weeks)	11 ± 2.5	
Mean gestational age at MFR done (weeks)	13 ± 1	
<i>No of attempts (pricks)</i>		
1	24	75
2	7 (includes 3 quadruples)	21.8
3	1 (includes 1 quadruple)	3.1
Average time taken for procedure (min)	4 ± 1.5	
Average volume of KCL used per reduction (ml)	2 ± 1.2	
<i>Maternal side effects</i>		
Pain after 6 h	3	9.3
Leaking	2	6.2
Bleeding	2	6.2

In our study, 16% patients had developed pre-eclampsia, and we did not start daily aspirin for the patients who were pregnant for the first time. Everyone received steroids at 28 weeks of gestation for fetal lung maturity as per institutional protocol for management of multiple pregnancies. The next common co-morbidity was gestational diabetes which affected about 12% patients.

Along with the maternal morbidities, fetal morbidities are increased by many folds in cases of HOMS as compared to singletons as well as twin gestations. MFR should be considered for those pregnancies where three or more fetuses are present to reduce the fetal and maternal morbidity and mortality. The risk of entire pregnancy loss in case of quadruplets is 25, 15% for triplets, and 8% for twins [9]. Due to high maternal and fetal morbidities, it is ethically also preferable to reduce the number of fetus to have a favorable perinatal outcome. [10]. All our pregnancies were either trichorionic or quadruchorionic. Except for one case where anencephaly was diagnosed, all other cases fetal reduction was carried out in accessible fetus, usually closest to the fundus. All the cases were carried out transabdominally and Inj KCL was used for reduction.

Table 3 Pregnancy outcome

Factors	Number (N)	Percentage (%)
Miscarriage (one at 13 weeks and another at 19 weeks 3 days)	2	6.2
<i>Period of gestation at delivery (n = 30) (median POG = 35.5 weeks)</i>		
Term	10	33.3
Preterm	20	66.7
Early preterm	4	13.3
Late preterm	16	53.3
<i>Mode of delivery</i>		
Vaginal	9	30
Cesarean	21	70
<i>New born (n = 60)</i>		
Average birth weight (gm): 1820 ± 416		
IUGR	12	20
NICU admission	47	78.3
Hypoglycemia	13	21.6
Neonatal mortality	1	1.6

Maternal pain and anxiety were the immediate side effects of the procedure, but with proper counseling we could complete all the procedure in a single session. Three patients had persistent pain after 6 h, and two patients had slight amount of leaking and bleeding in the same day of the procedure. All the cases managed conservatively with bed rest, and paracetamol was prescribed for pain relief.

However, the abortion risk before 24 weeks POG following MFR has been a controversial issue. Earlier, it was reported that risk of abortion was increased after MFR, but recent review reported similar risk of pregnancy loss before 24 weeks of POG for reduced and non-reduced pregnancies [11, 12]. Coming to the procedure-related fetal complications, we had two abortions: one at 13-week period of gestation and one at 19 weeks 3 days POG. The pregnancy aborted at 13-week POG was a quadruple pregnancy, and two fetuses were reduced in a single session. One of the triplet pregnancies which was reduced to twins aborted at 19 weeks 3 days POG, and this one may not be related to the procedure as it was after 6 weeks after MFR.

Duration of gestation decreases with increasing fetal number, and prematurity is increased sixfold and tenfold in twins and triplets, respectively. The proportion of preterm birth associated with premature rupture membrane increased with gestational plurality from 13% with singletons to 20% with triplets or more [13]. Average gestational age at delivery in our study was 35.5 weeks with 33% had term deliveries. Even among the preterm deliveries, most of them had late preterm deliveries with excellent neonatal outcome. Till 28–30 weeks of gestation, birthweight of twin pregnancies are closely parallel to

singleton gestation and by 35–36 weeks twin birth weights clearly diverge from those of singletons [14]. Growth discordancy may affect earlier in cases of HOMs and incidence is about 17–24% in cases of triplets and quadruplets. Post reduction, in our study 20% fetuses had IUGR. Higher incidences of malposition, malpresentation, cord prolapse, and placental insufficiency following delivery of the first fetus leads to almost 100% cesarean delivery in cases of HOMs. In our study, though the cesarean rate (70%) was higher, 30% patients underwent vaginal delivery. High cesarean rates were due to malpresentation, prematurity, IUGR, and premature rupture of membrane with unfavorable cervix. We avoided induction of labor in our patients. A meta-analysis conducted by Zipori et al. shows that fetal reduction of triplets to twins resulted in comparable perinatal outcomes to non-reduced twins with regards to gestational age and birthweight at delivery, pregnancy loss prior to 24 weeks, as well as the development of gestational diabetes and hypertensive disorders of pregnancy. Cesarean section rate was significantly higher in the MFR group compared with the non-reduced twins group [15]. Prospective design and good number of cases were the strength of the study but we did not have any control group (either twin pregnancies or HOMs managed without reduction) to compare the results.

Conclusion

Favorable pregnancy outcomes can be achieved after multifetal reductions during first trimester in higher-order multiples, but the procedure is not totally safe.

Compliance with Ethical Standards

Conflict of interest Dey Madhusudan and Monica Saraswat declare that they have no conflict of interest.

Informed Consent Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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