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Safety Of Multi Foetal Pregnancy Reduction : A Tertiary Care Centre Based Prospective Cohort Study

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KEYWORDS
foetal reduction, Kcl, 11to12 weeks, complications and safety, multiple pregnancies

ABSTRACT:
Introduction: The incidence of multifoetal pregnancies has increased significantly in the recent years due to increased use of artificial reproductive technique (ART). Higher-order multiple pregnancies are associated with increased incidences of pregnancy complications mainly abortions, pre-eclampsia, preterm delivery, and foetal death. Multifoetal reduction (MFR) during first trimester and subsequent delivery of twins or singleton can reduce pregnancy associated morbidities. This study was conducted to evaluate the complications and pregnancy outcomes of transabdominal ultrasound guided foetal reduction technique.
Material & Method: It was a prospective cohort study of the past 3 years i.e., from May 2019 to May 2022.Multifoetal pregnancy reduction was carried out in107 patients, at 11 to 12 weeks of gestational age after assessment of NT/NB and chorioniciy. Foetal reduction(FR) was done using 2mEq/mL of KCl, 0.5 – 2 ml solution was injected intracardiac/Intra thoracic into foetus under the guidance of trans abdominal ultrasound and the pregnancies were followed till delivery to observe for complications .
Results: The study included 107 multi foetal pregnancies which underwent MFR. 93.4% of reduction were done due to higher order pregnancy. Among them 53.3% were reduced from triplet to twin. 6.54% patients underwent foetal reduction for anomaly in co-foetus. 81.40% of patient were primigravida and 68.22 % of patients conceived through IVF. More than half of the patients were above the age of 30 years. The average time required for the foetal reduction was 4 to 5 minutes. The most common complication related to the procedure was leakage of amniotic fluid from the reduced sac which occurred in 8.40% of cases. 1.86% of cases had abortion within 2 weeks of procedure. Regarding pregnancy outcomes, the study had 4.6% (n=5) delayed abortions before 20 weeks period of gestation. 82.40% patients underwent caesarean delivery, With a mean gestational age of 35.1 weeks at the time of delivery. The average new-born weighed 1860 g, the live birth-rate was 91.76% ,78.2% of them needed to be admitted to the NICU and most of them made successful recovery.
Conclusions: Transabdominal ultrasound guided foetal reduction is an effective technique in preventing maternal and foetal complications of higher order pregnancy but with a 1-2 % risk of procedure related abortion.

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SIGNIFICANCE: Parents must make a very difficult choice regarding foetal reduction. Parents need to know all of the potential outcomes. Making an informed decision is more difficult in the absence of studies demonstrating whether or not foetal reduction is likely to benefit the remaining foetus or foetuses and outlining potential dangers.
Primary prevention strategies to limit multifoetal pregnancies, especially higher-order multifoetal pregnancies, can help to minimize the need for multifoetal pregnancy reduction and should be practiced by all obstetrician and gynaecologists who treat women for infertility. These strategies include cancelling an ovulation induction cycle when it places the patient at high risk of a multifoetal gestation, limiting the number of embryos transferred during IVF, the new ART regulation act introduced in India limiting the number of embryo transferred during IVF is a good initiative in this direction

INTRODUCTION: The incidence of multifoetal pregnancies has increased significantly in the recent years due to increased use of ART. Higher order multiple pregnancies are associated with increased incidences of pregnancy complications mainly abortions, pre-eclampsia, preterm delivery, and foetal death. Couples with higher-order multiple pregnancy have three options.
Reduction in the number of foetus: Foetal Reduction
Attempting to continue with all the foetuses: This is associated with inherent problems of preterm birth, poor survival, long-term morbidity, and maternal morbidity
Termination of the entire pregnancy: But this generally not acceptable to women, especially for those with a past history of infertility.

However the couple choice depends on their underlying beliefs and social background. Multifoetal reduction (MFR) during first trimester and subsequent delivery of twins or singleton can reduce pregnancy associated morbidities.This article mainly focused on reduction in the number of foetuses.
Multi-foetal reduction (MFR) is defined as a first-trimester or early second-trimester procedure for reducing the total number of foetuses in a multifoetal pregnancy by one or more [1]. The goal of this intervention is to prevent the preterm delivery and its neonatal complications.
Multiple pregnancies (triplets, quadruplets, quintuplets) are high-risk pregnancies with higher maternal and foetal complications. The spontaneous occurrence of multiple pregnancies is rare. Spontaneous quadruplet pregnancy is extremely rare, with an incidence rate of 1 in 512,000-1 in 677,000 births [2]. The wide spread use of infertility treatments has resulted in an increased incidence of multiple pregnancies. Ovulation induction with oral ovulogens and gonadotropin remarkably enhances the likelihood of multiple ovulation, thus increasing the chances of multiple pregnancies especially by ovulation induction with timed intra-uterine insemination. Multifollicular development is relatively common with clomiphene citrate and the total risk of multiple pregnancy is increased by nearly 7-10%[3,4,5] . The vast majority of multiple pregnancies conceived during clomiphene-induced cycles are twins. The risk for triplets is 0.3–0.5%, for quadruplets 0.3%, and for quintuplets 0.1%[6,7], but with gonadotropins incidences of multiple pregnancies are increased to 16-66% for twins, 3.5% for triplets and 1% for quadruplets [8].
In general, the number of embryos transferred (2 or more) during IVF significantly affects the likelihood of multiple pregnancies. The maternal mortality associated with multiple births is 2.5 times that for singleton births .Women with multiple pregnancies has an increased risk of miscarriage, anaemia, hypertensive disorders, haemorrhage, operative delivery, and postnatal illness. The risk of abruptio placenta is 4.7% in twins compared to 0.7% in singleton pregnancies.[9] For triplets or quadruplets, the risk of peripartum hysterectomy secondary to Postpartum haemorrhage is also 24 times higher than it is for twins [10].
In terms of foetal complications, all quadruplets , 90% of triplets and 60% of twin births are born premature respectively [11] .The rate of cerebral palsy is 28 per 1000 live births in triplets compared to 7 and 1.6 per 1000 live births in twins and singletons respectively.[12] In addition to these negative outcomes, multiple pregnancies have a higher risk of congenital abnormalities, and this risk is higher for each foetus, not because there are more foetuses per pregnancy. The total stillbirth rate in multiple pregnancies is greater 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 to 5 per 1000 singleton births [13].

Aim & objectives: The main objective of this study is to assess the immediate complications (within 2 weeks) that occur after foetal reduction procedure and assess the maternal and foetal outcomes of the procedure.
Primary outcomes: Immediate complications of the foetal reduction procedure
Secondary outcomes: Maternal and Foetal outcomes after the procedure.

Materials and methods:
Study design: This was a prospective cohort study. Patients who underwent foetal reduction for any indication between May 2019 to May 2022 over a period of 3 years were included in this study. This prospective cohort study included One hundred and seven patients

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(107) with higher order pregnancies, resulting from In vitro fertilization-embryo transfer 73patients (68.22 %), Ovulation induction + timed intercourse 14 patients (13.09 %), Ovulation induction + intrauterine insemination 14 patients (13.09 %) Spontaneous conception 06 patients (5.6 %) We reviewed medical records of the 107 patients retrospectively out of which 6.54% were twins (n=7), 63.5% were triplets (n=68), 26.16% were quadruplets (n=28), 3.7% were quintuplets (4). All cases of foetal reduction were performed for the purpose of reducing the foetal number or due to an anomaly in one foetus. Patients were counselled regarding the risk of miscarriage, preterm delivery and other morbidity associated with multiple pregnancies and was offered the option of foetal reduction. Potential complications of the procedure were explained to all the patients and informed consents were obtained and, if the patients selected the option of foetal reduction.

Inclusion Criteria: Maternal age ≥ 18 years, Dichorionic diamniotic/ trichorionic pregnancy

Minimum number of alive foetuses at the time of reduction ≥2, Multifoetal pregnancy with alive anomalous foetus.

Exclusion Criteria: Monochorionic multifetal pregnancy

Procedure: Ideal gestation age which was chosen for foetal reduction was12 weeks at which foetuses can be screened for NT/NB and anomaly. Other prerequisite for reduction was chorionicity. Only dichorionic foetuses were reduced. Monochorionic sacs were reduced as a whole if they were coupling with dichorionic foetus. Foetus which was most accessible to needle was reduced if all foetuses were normal in anomaly screen. If gestation age discrepancy was more than 1 week among foetuses than smaller foetus was chosen for reduction in view of high risk for aneuploidy and IUGR of that foetus. In multiple reductions (quadruplet/quintuplet gestation), in one sitting one or more foetuses were reduced if foetuses were easily accessible and operator was able to reduce with minimum stimulation. In difficult cases only one foetus was reduced in one sitting and procedure was postponed to one week for further reduction. Last gestation age which was taken for reduction in our study was 15-16 week. Antibiotic prophylaxis with tablet Amoxycillin and Potassium Clavulanate 625 mg single dose was given one hour prior to each procedure. Procedure was done in sonography room as day care procedure. Procedure was done with 5.0 MHz transducer (GE Voluson E6). After taking all aseptic precautions, local anaesthesia was given with 2% lignocaine injection, then under trans abdominal sonographic guidance a 22G amniocentesis needle was advanced into intracardiac space (or intrathoracic) through which 0.5 to 2ml of 2mEq/mL of KCl was given until foetal asystole was confirmed , then the needle was withdrawn. . When there were quadruplets or higher-order pregnancies, the aforementioned process was repeated for additional gestational sacs. After the procedure antibiotic coverage is continued by Tablet Amoxycillin and Potassium Clavulanate 625 mg twice a day for 3 days. Patients were discharged 3-4 hours after observation in hospital. After one week, a follow-up ultrasound examination was performed. All the patients were followed up till 2 weeks after the procedure. All of the patients then underwent a regular Antenatal follow-up and were delivered at our centre.

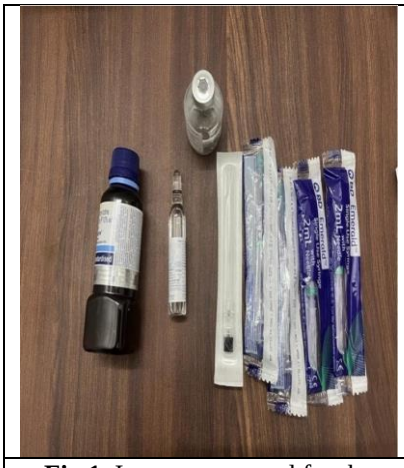

Fig 1. Instruments used for the procedure.

Fig 2. Insertion of the needle transabdominally.

Fig 3. USG image showing the needle insertion into fetal heart.

Results: 107 foetal reductions were performed in the study period. As our hospital is a tertiary care facility, after infertility treatment, majority of patients with multiple pregnancies are referred from outside facilities. Among 107 patients 33 patients were from our centre and 74 cases were referred from other centres. Among

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the 107 multiple pregnancies, 6.54% were twins (n=7), 63.5% were triplets (n=68), 26.16% were quadruplets (n=28), 3.7% were quintuplets (n= 4) . All the 107 patients were followed up in our centre till 2weeks after the procedure and 33 of them delivered at our centre and 74 patients delivered at other centres for which data were collected post-delivery.

Demographic information is displayed in Table. 1. Majority of women, 47.60% belonged to age group of > 31 year. As the multifoetal pregnancy is a side effect of infertility treatment in most of the cases, 81.4% of women were primigravida. Multiple pregnancies resulted from spontaneous conception in only 5.6% of cases. In rest of the cases ovulation induction with timed intercourse in13.09%, ovulation induction and intra-uterine insemination in 13.09% and in vitro fertilization in 68.22% cases respectively.

Table 1. Demographic factors of patients underwent multifoetal reduction

Demographic Factors	Number	Percentage
Age (years) (n=107)		
•18–25	16	14.90%
•26–30	40	37.50%
•>31	51	47.60%
Parity		
•Primipara	87	81.40%
•Multipara	20	18.60%
Conception		
•In vitro fertilization	73	68.22%
•Ovulation induction + timed intercourse	14	13.09%
•Ovulation induction + intra-uterine insemination	14	13.09%
•Spontaneous	6	5.60%

Foetal characteristics and details of foetal reduction procedure are shown in Table 2.

In 93.4% of patients, the procedure was performed primarily to lower the number of foetuses, in 6.54% of patients during the NT/NB scan one foetus showed anomaly ,and as per protocol, this foetus was reduced leading to delivery of healthy twins or singleton .The most common anomaly encountered was anencephaly in 3 foetuses, cystic hygroma in 2 foetuses, omphalocele in 1 foetus and early TTTS in a monochorionic sac of quadruplet pregnancy so the sac was reduced leaving healthy twins. The procedure typically took 4 +/- 1 minutes on an average . And 1.5 ml of KCL on average were utilised during the process.

Table 2. Foetal characteristics and foetal reduction procedure

Foetal characteristics	Number	Percentage
Foetal Reduction done to (n= 107)		
•4 & above to Triplets	1	0.93%
•4 & above to Twins	28	26.16%
•4 & above to Singleton	3	2.80%
•Triplets to twins	57	53.37%
•Triplets to singleton	11	10.20%
•Twins to singleton	7	6.54%
Anomalies detected at NT/NB scan	7	6.54%
Average time taken for procedure (in min)	4 +/- 1 min	
Average volume of KCL used per reduction (ml)	1.5 ml +/- 1 ml	

Complications of the foetal reduction procedure table 3: Leaking from the reduced sac was the most frequent complication, occurring in 8.4% (n=9) of patients. Following the procedure, there was minor bleeding episode in 1.86 % (n=2) individuals. In 3 patients 2.8%, the procedure was unsuccessful, necessitating a repeat procedure for the same sac, while in 1 (0.9%)patient unintentionally the adjacent sac was injured . Abortion within 2 weeks of procedure occurred in 1.86% (n= 2) patients.

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Pregnancy outcomes of foetal reduction procedure table 4:

Out of 107 foetal reductions carried out during the study period 4.67% (n=5) had abortion, Maternal co-morbidities include preeclampsia in 10.2% (n=11) patients including 1 eclampsia , 1.80% (n=2) patients had GDM , 0.9% (n=1) patient had anaemia (haemoglobin less than 10 gm/dl)12.1% (n=13) patients had PROM, 58.8 % (n= 60) patients had preterm labour as complications out of which 37.25% (n=38) had late preterm deliveries (34 to 37 weeks), and 21.58% (n= 22) had early preterm (less than 34 weeks) deliveries. Majority 41.17% (N=42) of pregnancies ended in term deliveries (more than 37 weeks). Average gestational age at delivery was 35 weeks + 1 days. The live birth-rate was 91.76%, although 82.4% (n=84) of patients underwent caesarean delivery, the most common indication was an elective LSCS in view of precious pregnancy and ART conception. Average birth weight of new-born was 1860 gm, and 78.2 % (n= 142) of them required NICU admission due to prematurity, low birth weight, and hypoglycaemia; nevertheless, most of them made a full recovery and are now healthy. Neonatal mortality occurred in 8.24 % (n=15) of new born in early preterm cases.

Table 3. Complications due to foetal reduction procedure

Early complications (n= 107)	Number	Percentage
Early post procedure PROM (Leaking from reduced sac with in 2 week)	9	8.40%
Bleeding with in 2 week	2	1.86%
Spontaneous abortion with in 2 weeks	2	1.86%
Failure of procedure and need of 2nd procedure for same sac	3	2.80%
Accidental injury to other sac	1	0.93%

Table 4. Pregnancy Outcomes after foetal reduction procedure.

Factors	Number	Percentage
Maternal complications (n = 107)		
Preeclampsia	11	10.20%
Gestational Diabetes	2	1.80%
PROM	13	12.10%
Anaemia	1	0.90%
Period of gestation at delivery (n=102)		
Avg Gestational Age at Delivery	35w1D	
Term (> 37 weeks)	42	41.17%
Early pre term (< 34 weeks)	22	21.58%
Late pre term (34 to < 37 weeks)	38	37.25%
Abortion (< 20weeks)	5	4.67%
Mode of Delivery (n= 102)		
Vaginal	18	17.60%
LSCS	84	82.40%
New born (n=182)		
Average Birth weight	1.86	KG
NICU Admission	142	78.20%
Neo natal mortality	15	8.24%

Discussion: We observed that leakage of fluid from the sac of the reduced foetus is a common complication (8.4 %). This is similar to the observation of Shlomo lipitz, et al.[14] (13.3% to 19.3%). This leaking is not alarming and not related to premature contractions and miscarriage in both studies. We report two events (1.86%) of procedure-related pregnancy loss, within 2 weeks following foetal reduction. This loss rate is similar to Evans et al. 2014 [15] who published a 25 years overview of foetal reductions and reported 2.5% foetal loss rate following reductions from twins to singleton. In present study 4.6% patients had pregnancy losses before 20 weeks. The abortion risk before 24 weeks of gestation following foetal reduction has been a controversial issue. Earlier, it was reported that risk of abortion was increased after foetal reduction, but recent review reported similar risk of pregnancy loss before 24 weeks of gestation for reduced and non-reduced pregnancies [16,17]. The risk of entire pregnancy loss in case of quadruplets is 25%, for triplets 15%, and for twins 8% [18]. The risk of entire pregnancy loss after foetal reduction procedure is1.86% according to present study

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and many other studies, which is much less than the risk associated with continuing higher order pregnancies. As per ACOG PRACTICE BULLETIN VOL. 137, NO. 6, JUNE 2021 women who underwent pregnancy reduction from triplets to twins, as compared with those who continued with triplets, were observed to have lower frequencies of pregnancy loss, antenatal complications , preterm birth, low-birth-weight infants, caesarean delivery, neonatal deaths. With rates similar to those observed in women with spontaneously conceived twin gestations. (Level B Recommendation)

Conclusion: Transabdominal ultrasound guided foetal reduction is an effective technique in preventing maternal and foetal complications of higher order pregnancy but with a small risk of 1-2% procedure related abortions. It is a simple, affordable and convenient day care procedure which needs minimal post procedure monitoring.

SWOT Analysis:

STRENGTHS :- • Single skilled operator-based study with good patient compliance. • Large sample size with encouraging results. • Allows selective termination of abnormal fetus • Decreases the maternal and foetal morbidity & mortality. • Able to track the pregnancies until they resulted in delivery or ended otherwise and we recorded perinatal outcomes.	WEAKNESS :- • No universally agreed method or timing for procedure.
OPPORTUNITIES: - • More research can be conducted to select healthy foetus using noninvasive methods. • Ideal timing and agent to be used for the procedure can be further evaluated.	THREATS: - • Accidental injury of the adjacent non selected foetus. • There is a 1- 2 % chance that the woman will lose the entire pregnancy prior to 20 weeks of gestation.

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