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# The Outcome of Fetal Reduction in High Order Multiple Pregnancy

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## ABSTRACT

***Background:*** *High-order multiple pregnancies, is rising in incidence owing to rising incidence of assisted reproduction -conceived pregnancies, thus, start to emerge as a not infrequently seen challenge in our daily gyn/ob- daily clinical practice. The term of high order multifetal pregnancy is applied to gestation involving three or more fetuses, and is associated with significant maternal and neonatal complications, largely due to increased rates of preterm birth and low birth weight. Multifetal pregnancy reduction has been proposed as a strategy to improve perinatal outcomes, the technique was introduced in our middle Euphrates governorates (including Annajaf AlAshraf) relatively only recently, and its acceptance is still questionable among ART physicians. In this paper we try to show our patients series outcomes for all procedure done in our private center since it was first introduced in 2021 till the time we accomplished this paper.* ***Objective:*** *the aim of the study is to express maternal and neonatal outcomes of all high-order multiple pregnancies underwent multifetal reduction management to twin pregnancies, including our own figure of procedure- related pregnancy loss rate.* ***Methods:*** *This retrospective cohort study included 15 women with triplet or quadruplet pregnancies diagnosed before 10 weeks of gestation and managed at Al –Ameer assisted reproduction center in Annajaf Al-Ashraf province in Iraq managed with fetoreduction at 9-10 weeks of gestation having their pregnancies followed in collaboration with Al-Zahraa Maternity and Children's Teaching Hospital a teaching center affiliated to medical school of Kufa university, from January 2021 to September 2024. Maternal and neonatal outcomes, including gestational age at delivery, perinatal complications, birth weight, Apgar scores, maternal complications, and our own figure of intervention- associated pregnancy loss rate were all assessed in numbers and percentages.* ***Results:*** *of 15 collected sample studied 8 women were of the age group(25.1–30years), all the 15 were in their 1$^{st}$ pregnancy( primigravidae), 13 were with triplets and two of 15 with quadruplets, all of them were already diagnosed and are treated by fetoreduction 9-10 weeks, 11/15(73.3%) delivered at term, 13.3 % delivered at late preterm gestational age(35-36 weeks), 6.6% delivered at very preterm (29 weeks), 6.6% aborted at 18 weeks due to covid infection, there was no perinatal deaths of those reached potential viable pregnancy stage(14/14) with all live births had survived, with their Apgar Scores; 6.70 ± 1.77& 8.00 ± 3.97 at 1&5 minutes respectively, 21.4%(3/14) of reduced pregnancies developed preterm birth with or without prelabour rupture of fetal membranes all survived, our own procedure- related pregnancy loss rate is 0%.* ***Conclusion:*** *Fetoreduction in high-order multiple pregnancies appears to improve neonatal outcomes and reduce maternal complications, particularly preterm delivery and perinatal death. The study shows that fetoreduction is an effective management option in high-order multiple pregnancies even though it leads to more cesarean deliveries. To confirm these findings and improve clinical practices, more prospective studies across multiple centers are needed.*

**Keywords: Fetal Reduction, High Order Multiple Pregnancy.**

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## INTRODUCTION

High-order multiple pregnancies(HOM) are defined as pregnancies in which there are three or more fetuses, not just two. [1]They are differentiated from lower-order multiples such as twins, primarily due to their reduced incidence and greater associated complications such as prematurity and perinatal death .[2] The increasing use of fertility treatments worldwide has driven the rise in the rates of twin and high-order multiple pregnancies[3]. Indeed, over the 15 years between 2003 and 2018, alongside increases in expected rates of perinatal mortality from 4.9 per 1,000 live births in singletons to 9.3 in twins and 40.1 in triplets and more, the proportion of live births that were multiples also decreased in England and Wales from 3.7% in 2003 to 3.1% in 2018. The distinction between these two categories supports our focus and any resultant public and health policy implications on current and future maternity care provision.[4]

High-order multiple pregnancies, (HOM) include triplets, quadruplets, quintuplets, sextuplets, and other pregnancies that have multiples of at least one fetus greater than twins[5]. They can be broadly categorized into those that are naturally occurring and those that are the result of assisted reproductive technology. Physiologic restraint exists with regard to multiple ovulation and pregnancies, and thus, naturally occurring HOM is uncommon. They represent an emergency type of situation with which many clinicians have little experience. The majority of HOM, however, are the result of the induction of multiple ovulations and/or the transfer of multiple embryos during assisted reproductive technology cycles, thus subsequent pregnancies often have components, such as maternal age and gravidity[6]. while there are similarities among types of HOM, there are also significant differences in the incidence of maternal and fetal outcomes. There are unique characteristics that are representative of each type of high-order multiple pregnancy as well, which result from the mechanism by which the pregnancy occurred.[7] The higher the order of the multiple gestation, the higher the complications a mother is at an increased risk for the development of preeclampsia, gestational hypertension, gestational diabetes, and concomitant polyhydraminios, the presence of these complications in high-order multiple pregnancies was seen to be associated with increased maternal morbidity [8]added to it a low-birth-weight baby is another potent source of maternal stress, and the mothers of high-order multiples are at increased risk of anxiety and postpartum depression, especially when they migrate prematurely or have a baby with a difficult course in the nursery[9].

These fore mentioned possible complications contribute to increased mortality and morbidity observed in multifetal pregnancy births compared to singleton births [10].Preterm birth is leading cause for neonatal complications of multiple gestations [11]owing to increased risk of infant death and early and late prematurity-induced complications [10], represented by cardio -respiratory, neurological, infectious, gastrointestinal, and ophthalmological complications of prematurity that increase with the number of multiples [12]. There is a higher rates of retarded fetal growth in higher order multiples compared with singleton births, which may further compromise neonatal outcomes [13]. Greater degrees of growth discordance are associated with higher risk of neonatal morbidity and mortality [14].

Complications for survivor twin after spontaneous death of co-twin in utero; particularly with monochorionic multiple gestations, that are tend to occur towards the second half of pregnancy, thus; increasing morbidity and mortality of the co-twin. The following complications have been observed in infants who survived after the fetal

 

death of a co-twin: higher risk of preterm birth and fetal growth restriction, brain injury including cerebral palsy (CP), renal failure due to renal cortical necrosis, small bowel atresia, gastroschisis, limb amputation, infant mortality rates in the neonatal period (birth through 28 days) and during infancy (birth to one year of age) are higher among infants of twin and HOMPs compared with individuals from singleton births [15].

**Multifetal Pregnancy Reduction( MPR):** is defined as the intervention by which one or more embryos is killed by installing an embryocidal substance into thoracic region of the selected embryo (usually most accessible ones) with all the procedure being guided by ultrasound through either abdominal or vaginal approach according to operator preference and training, hopping to decrease.

The morbidity and mortality of MFPs by reducing numbers of fetuses to either twin or singleton by prevention of preterm birth and increasing the gestational age at birth [16] [17]. Minor and major maternal peripartum complications, such as anemia, preeclampsia, thrumboembolism, and operative delivery, are also reduced. The financial and psychological sequels of multiple gestation on families are also ameliorated by MPR. The caring and rearing for multiple newborns, especially those with special needs, is both emotionally and economically demanding , it was stated that over 25 percent of parents of multiples would suffer depression -anxiety disorders in the perinatal period[18]. American College of Obstetricians and Gynecologists (ACOG) Committee Opinion on multifetal pregnancy reduction recommended that " in charged obstetrician-gynecologists should respect patients' choice whether to continue or to reduce a multifetal pregnancy with only the patient can weigh the relative importance of the medical, ethical, religious, and socioeconomic factors and determine the best course of action for her unique situation" [19]. Those who are selected for MFR are trichorionic triplets or higher order multiples with good evidence based on meta-analyses of observational studies that it improves gestational age of newborns and neonatal outcomes [20,21].

An International Federation of Gynecology and Obstetrics (FIGO) Committee recommends that "multiple pregnancy of an order of magnitude higher than twins involves great danger for the woman's health and also for her fetuses, which are likely to be delivered prematurely with a high risk of either dying or suffering damage" and "where such pregnancies arise, it may be considered ethically preferable to reduce the number of fetuses rather than to do nothing" [22] in Dichorionic diamniotic twin pregnancies, MPR may be indicated for maternal medical or obstetric comorbidities like maternal chronic heart disease, respiratory, or renal diseases, or for having prior history of cervical incompitance.[22] fetoreduction to a singleton can also be considered in women of very advanced maternal age (≥45 years old), to prevent augmented risks anticipated for this age like, low birth weight ( for either prematurity or fetal growth restriction), preeclampsia, and gestational diabetes that are more likely to accompany twin pregnancies compared to a singleton gestation[23].

The injection techniques discussed above for MPR are intended for multichorionic fetuses or for reduction of all of the fetuses in a monochorionic gestation (such as a monochorionic pair of a triplet or higher order gestation). Reduction of a single fetus in a monochorionic gestation requires specialized cord occlusion techniques to avoid death or neurologic harm to the co-twin from effects resulting from placental vascular anastomoses of monochorionicity. These cord occlusion techniques are associated with a higher risk of pregnancy loss than the injection technique

 

described above and, therefore, are rarely performed for MPR. [25]

**Procedure and Pre-procedure:** patient consent and counseling about risks benefits and risks of MPR, the cnters own figures for the procedure- linked risk of pregnancy loss, what alternatives, risk of fetal loss of expectant management of multiple higher order gestations, as the risk of miscarriage after MPR is lower than that for spontaneous loss of unreduced triplets or higher order multiples, and their increased risks of extreme preterm births [26].

Regional regulations and medicolegal issues; MPR differs from termination of pregnancy by the act of abortion, and is performed to save a pregnancy with another wise a high chance to be lost. Legal considerations do vary among countries, it is important to be familiar with them [27] Timing of the procedure–patients are scheduled for elective MFR at a gestational age raging between 10+0 and 13+6 weeks of gestation, as the risk of procedure-related pregnancy loss is thought to be low at this time although; however: in other centers it still be performed up to 16 and 18 weeks of gestation, but this may increase the rate of pregnancy loss [27] [28]most higher order multifetal pregnancies are reduced usually to twins not to singleton as families with long history of infertility afforded an expensive service of assisted reproduction desire a twin rather than a singleton birth [29].

However, still reduction of triplet and quadruplets to a singleton is an option associated with favored outcomes. [30] procedure; the fetus(es) targeted for termination is/are generally that which are nearest to uterine wall/ cervix, and vagina(or fundus for transabdominal approach), thus choosing the most accessible fetuses and minimizing unnecessary intrauterine coursing of the needle [31].

**Role of antibiotic prophylaxis:** We do not routinely use antibiotic prophylaxis as no benefit has been established. However, we recognize that practice varies. At least one group gives patients ampicillin 500 mg orally every eight hours for a total of five days .

Injection ; the procedure is most commonly performed by injecting approximately 2 to 3 mL of potassium chloride (concentration 2 mEq KCl/mL) into the fetal thoracic cavity or fetal heart using a 22-gauge spinal needle under ultrasound guidance. Asystole is usually seen within one minute of injection, and total procedural time is typically less than five minutes.

Additional fetuses can be reduced through same puncture or, morefrequently through a separate needle puncture. Another fetocidal liquids like lidocaine, digoxin, hyperosmolar urea, and cardiac tamponade with saline have also be used successfully for same purpose, although they are usually kept to be used for reduction at a later gestational ages [32]. Rescan typically is performed an hour after the procedure to ensure death of targeted embryo/s and to confirm viability in the adjacent sacs. [32]

### Aim of the study

This study aims to follow maternal and fetal outcomes for women with high-order multiples conceived by intracytoplasic sperm injection (ICSI) after fetal reduction to twins pregnancy. To calculate our own figure of procedure –related pregnancy loss rate which was a secondary outcome to measure.

## PATIENTS AND METHODS

### Study Design and Setting

This was a retrospective observation of a cohort of high order multiples (HOMPs) all were conceived by intracytoplasmic sperm injection(ICSI), ICSI procedures were done either in our center or who were referred to our centre for fetoreduction after having pregnancy conceived in another centre inside

 

or outside of Iraq. All fetoreduction procedure was done at a private Al Ameer international assisted reproduction centre in Annjaf Al ashraf governorate of Iraq by single operator dr. Batool A. Al Khalidi( the author). The goal of the study was to look at maternal and newborn outcomes after the procedure. Study Population; 15 patients (13 with triplets all were trichorionic triaminiotic) and (2 with quadruplets one of them quadrichorionic quadriaminiotic and the other trichorionic quadriaminiotic and reduction of two embryos sharing same chorion was chosen for termination) underwent a planned fetal reduction procedure during the first trimester at 9-10 weeks.

**Inclusion Criteria**

Women who have been ICSI -conceived and diagnosed with triplet or quadruplet pregnancies before 10 weeks of pregnancy, who were followed by access to medical, birth, and newborn information.

**Exclusion Criteria**

Multifetal pregnancies, which are diagnosed after 13 weeks of gestation, data about the mother or baby that is not complete, and women who refused to do fetoreduction.

**Fetoreduction Procedure**

According to institutional and ethical requirements, all ladies who were pregnant with triplets or quadruplets were provided fetoreduction after both parents had receive a comprehensive counseling about the risks, possible advantage, and post-operative patients' self-care. The reduction was done between 9 and 10 weeks of pregnancy utilizing the following steps:

- A well-trained physician MD certified with over five years of experience uses transcervical approach guided by transvaginal ultrasound probe while the patient is positioned in lithotomy. Strict aseptic techniques are adhered to throughout the procdures which all were preceded by single prophylactic parenteral antibiotics.
- After accurate mapping the gestational sacs, identifying chorionicities and aminionicities of all embryos, ascertaining the viability ofall embryos, and determining the most accessible fetus, one or more were selected for fetocide injection.
- The selected fetus had its heartbeat stopped by the injection of potassium chloride (KCl) into its heart, and the fetal thoracic region was left only after confirming asystoles. All patients got single antibiotics prophylaxis to prevent infections, and an ultrasound done after the procedure to make sure the remaining fetuses were still alive and there were no problem.

**Data Collection**

We reviewed maternal records, ultrasound reports, and followed for neonatal outcomes to gather the data. The following items were looked for to fill the data collection forms: Mother's age, gravidity, and parity, number of gestational sacs (triplets or quadruplets) , fetus's age at diagnosis, delivery method, fetal outcomes (neonatal death/ complications, birth weight, Apgar scores at 1 and 5 minutes).

**Outcome Measured**

Primary outcomes include ● Gestational age ● Perinatal mortality ● Birth weight ● Need for special care neonate unit admission ● Apgar scores.Other secondary outcome included that we were able to calculate our own figure of procedure related pregnancy loss rate.

## STATISTICAL ANALYSIS

With IBM SPSS Statistics for Windows, Version 24, for all statistical analyses,we employed the Pearson Chi-Square test or Fisher's Exact test to compare categorical variables when appropriate. We applied the independent samples t-test to compare the

 

means of continuous variables. A p-value below 0.05 was considered statistically significant.

**Ethical Consideration**

The University of Al-Kufa College of Medicine approved this study at Al Zahra Teaching Hospital for Children and Maternity. All patients signed a written consent form agreeing to the fetal reduction procedures. For retrospective data analysis, patient confidentiality was maintained by anonymizing records and using a unique identifier.

## RESULTS

A total of 15 cases of high-order multiple pregnancies were included in this study. Various maternal and pregnancy-related factors.

**Table 1. Distribution of patients by Maternal Age.**

| Age of Mother | Fetoreduction |
|---|---|
| 20–25 years | 2(13.3%) |
| 25.1–30years | 8 (53.3%) |
| 30.1-35 | 1(6.6%) |
| 35.1-40 | 4(26.6%) |
| Total | 15(100%) |

**Table 2. Distribution of Management Approach by Gravidity.**

| Gravidity | Fetoreduction |
|---|---|
| 1 | 15(100%) |
| ≥1 | 0 |
| Total | 15(100%) |

**Table 3. Distribution of patients by number of High-Order Multiple Pregnancy.**

| Number of High-Order Multiples | Number |
|---|---|
| Triplets | 13(86.6%) |
| Quadruplets | 2(13.3%) |
| Total | 15(100%) |

**Table 4. Gestational Age at Diagnosis.**

| Gestational Age at Diagnosis | Fetoreduction number |
|---|---|
| ≤10 wk | 15 |
| >10 wk | 0 |
| Total | 15 |

**Table 5. Pregnancy outcome (Gestational Age at Delivery).**

| Gestational Age at Delivery | Fetoreduction number |
|---|---|
| Pregnancy loss less than 20 week | 1(at 18 wk covid infection diabetic mother) |
| Very preterm 28.0-32.0 week | 1(twins at 29 wk both alive) |
| Moderate to late preterm 32–37 weeks | 2 (35-36 wk)all survived |
| Term ≥37 weeks | 11 (all survived) |
| Total | 15 |

 

**Table 6. Perinatal death.**

| Perinatal death | Fetoreduction |
|---|---|
| Abortion | 1 |
| No perinatal deaths | 14 (100%)= 14/14 of those reached potential viable pregnancy stage |
| Total | 15 |

**Table 7. Birth Weight.**

| Preterm & at term | N | Mean(kg) | Std. Deviation |
|---|---|---|---|
| Fetal Reduction | 15 | 2.52 | 0.76 |

**Table 8: Apgar Scores for Fetal Reduction neonates at 1 & 5 minutes**

| Apgar Scores | Fetal Reduction (Mean ± SD) |
|---|---|
| 1 minute | 6.70 ± 1.77 |
| 5 minutes | 8.00 ± 3.97 |

**Table 9: Maternal Outcomes: antenatal, perinatal maternal complications.**

| Maternal complications | Fetoreduction (n = 10) |
|---|---|
| Gestational Hypertensive disorders | 0 |
| Diabetes Mellitus (GDM)-difficult to control with covid infection | 1 |
| Preterm Premature Rupture of Membranes (PPROM), preterm labour | 3(all survived) |
| Cesarean Section | 14/14 |
| Antepartum Hemorrhage | 0 |
| Thrumboemolism | 0 |
| Major fetal anomalies | 0 |

*Our own procedure- related pregnancy loss rate is 0%.*

## DISCUSSION

Our study examines the maternal and newborn outcomes in high-order multiple pregnancies managed with fetoreduction. Our data shows that procedure has favored outcomes like newborn survival rates, term pregnancies, and improved immediate post-birth conditions. These results have important implications for maternal-fetal medicine, indicating that fetoreduction might be a valuable management option for high-order multiple pregnancies, potentially enhancing both short and long-term outcomes. Unlike Riina Maria Jernman et al [33], who conducted 54 MFR procedures in her retrospective case series study over 13 years targeting an anomalous co-twin, in our centre, MFR is a routine care offered for HOMP resulted from ICSI after thorough councelling of both parents about possible adverse sequels of HOMP, for both the mother and neonates.

In agreement with Steffen Ernesto Kristensen et al [34, 35] who accomplished his retrospective study on 172 dichorionic twin pregnancies which were reduced to singleton over 10 years (from 2008-2018)and he was stated that the later the gestational age the fetoreduction done at, the shorter gestational age to deliver; in his study the intervention was take place between 11-23 weeks, while, all our cohort had their procedure done at much earlier gestational age 9-10 weeks this gestational age appears to be more physiological and simulating natural age of autoreduction of genetically abnormal fetuses, in our practice we do not

 

reduce twins and this was also another difference between the two studies. Mi Sun Kim et al [36], in his report on 124 of transabdominal fetoreduction which was accomplished retrospectively to cover procedures done between 2006-2018 at mean gestational age 12+6 D on multifetal gestations(48/124) of their sample was twins also, aiming to prevent fetal loss, preterm birth and overall perinatal morbidities, in that study they calculated 0.8% procedure related pregnancy loss rate, our cohort we don't have procedure related loss; however: we have overall pregnancy loss rate 6.6% compared to their figure of 2.4% and this happened for triplet reduced to a twin in a diabetic 32 years old lady at GA 9 weeks, later on she developed high grade fever at 18 weeks of gestation for which she was hospitalized, diagnosed and treated as a covid infection at covid era, but unfortunately she aborted three days of her admission.

This high fetal loss rate in our study is explained by our much smaller sample size compared to them(15/124), we believe that fetoreduction in 1st trimester of high order multiples lowers but does not prevent preterm births(3/15 delivered prematurely, 2 of them were moderate preterm, fortunately all preterm infants survived in our case series, and is that the procedure can efficiently prolongs the gestational age for such high risk pregnancies for this complication which is for long time being regarded as key initiator for sequels of neonatal complications, thus improving overall perinatal outcome, an opinion that was also agreed by Miao Huang et al[37]and Hale Cetin Arslan et al [38], the latter study compared expectant vs fetoreduction of triplets retrospectively over 10 years (2014-2024) and total 187 triplets involved 47 of them reduced to twin and 140 managed expectantly, the observed significantly longer GA for the reduced group ((35.2 vs 32.2wk, P = .003)and that the expectant management of triplets was independent risk factor for giving birth<34 wk. The average birth weight (2.52 ± 0.76 kg) for our neonates in this case series, this supports the findings of Hasson et al.[39], who showed that easing the strain on the uterus enhances nutrient and blood flow to the placenta.

Allen et al. [40]emphasized that infants with low birth weight are at a greater risk of neurological issues. The positive effect of fetoreduction on birth weight highlights the potential advantages of the procedure, offering a sense of optimism. Owing to long history of infertility, advanced maternal age (in 4 cases) history of uterine surgery, myomectomy (1) or metroplasty(1), increased monitoring, planned delivery, and lastly, high cost of their management with ICSI with sometimes the need to adopt hard option of travel abroad for treatment, all of our patients preferred operative delivery over the unpredicted trial of vaginal birth.

***This study provides useful information, but also has particular issues that need to be acknowledged:***

1. Small Sample Size: Because of the limited number of participants in the study, the results are not as statistically robust or generalizable. We need to perform larger multicenter trials to verify that these results apply to a broader population.
2. This study was performed at one institution, which could introduce bias because of its specific practices, patient demographics, or counseling methods.
3. Retrospective Design: Since this is a retrospective observational study, we cannot confirm causality.
4. Patient Selection Bias: Unmeasured factors such as socioeconomic status, demographic, cultural or religious believes, or patient preferences/reluctance may have influenced maternofetal outcomes.
5. Limited Long-Term Follow-Up: The main goal of this study was to examine short-term outcomes for mothers and babies. We didn't

 

investigate the long-term effects on development, mental health, or reproduction.

## CONCLUSION

The findings indicate that fetoreduction results in improved outcomes for both mothers and babies and in summary, all patients had strict follow up visits resulting in early diagnosis and managing of high order multiples by fetoreduction with zero% procedure related pregnancy loss rate, with more babies reached full term, all of term and preterm survived, higher birth weights and improved Apgar score.

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