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Outcome of early transvaginal ultrasound-guided embryo reduction for high-order multiple gestations – A report and review of literature

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ABSTRACT

Objective: *To analyze the experiences of performing multifetal pregnancy reduction (MFPR) by early transvaginal ultrasound-guided embryo punctures at an ART centre in China.*
Design: *A retrospective clinical study.*
Setting: *Women's Hospital, Zhejiang, China.*
Patient(s): *Sixty-five multiple gestations following the assisted reproductive technology – use subject to MFPR.*
Intervention(s): *Multifetal gestations were diagnosed in the first trimester. MFPR was performed between 49-79 days using the transvaginal ultrasound-guided technique. All patients were prospectively followed up and delivered in a single perinatal department.*
Main Outcome Measure: *Clinical outcome after MFPR.*
Results: *MFPR was performed with a 96.9% success rate with no evidence of organ injury, massive hemorrhage and infection. A 96.4% reduction from triplets or quadruplets to twins was carried out successfully. No miscarriage occurred within the first 4 weeks after the reduction. The risk of fetal loss was 12.3% at 15-27 weeks; 96.3% of cases delivered potientially viable fetuses; 58.2% underwent term delivery while 41.8% had preterm delivery. There was no appreciable increase in congential malformations of the fetus.*
Conclusion: *The present study clearly shows that early transvaginal ultrasound-guided embryo puncture is an effective, simple and safe technique for improving outcome in multifetal pregnancies. The method can be used as routine therapy after infertility treatments. This procedure has increased options for Chinese couples, reducing obstetric and prenatal risks associated with high-order multiple pregnancies.*

Key words: *Multifetal pregnancy reduction, multiple pregnancies, transvaginal ultrasound. and infertility therapies.*

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INTRODUCTION

Multiple pregnancy constitutes a common iatrogenic outcome of ovarian stimulation with fertility drugs and assisted reproductive technology (ART)[1]. The prevalence of multiple pregnancy in these situations has shown an exponential increase during the past two decades[2–3]. Moreover, this increased incidence following assisted reproduction is also directly related to the number of transferred embryos[4].

A report from the Centers for Disease Control and Prevention, USA in 1997 indicated that there were 6737 triplet and higher order multiple births in USA[5]. Of this number 43% were the result of ART including in-vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT), 38% were attributed to ovulation-inducing drugs without ART and 18% occurred spontaneously[6].

Multifetal pregnancies are associated with increased prematurity and increased morbidity and mortality for both the mother and the infant. Maternal complications for women carrying high order multiple gestation include increased incidence of preeclampsia, cesarean delivery, postpartum hemorrhage, and fatty liver[7]. Multifetal pregnancy reduction (MFPR) from quadruplet and higher order gestations to twin gestation significantly decreases the risk of delivery before 28 weeks and associated neonatal and development morbidity, as well as risk to the mother[8,9]. However, twins resulting from reduction of quadruplet and higher order gestations may deliver earlier[10–13] and may be more likely than unreduced twins to have restricted fetal growth (RFG) or intrauterine growth retardation (IUGR)[14.15]. There is an 8% to 16% loss rate before viability after MFPR, although this incidence may decrease with physician experience[5]. Whether triplet gestations benefit from MFPR to twin gestation is less certain[8,9,16]. Most triplet pregnancies deliver after 32 weeks[17–19]. Overall, short-term and long-term outcomes for triplets do not differ significantly from gestational-matched singletons and twins[18,20]. Most studies have found that after MFPR, triplet gestations that reduced to twins delivered at a later gestational age or had higher birth weights than unreduced triplets[10,11,21–24], while others have found no significant difference in the length of gestation[8,9,17]. Some studies have noted that triplet gestations reduced to twins are delivered earlier and had lower birth weights than unreduced twins[11,21,25]. However, others found no differences in the length of gestation[22,23,26]. One study found that the incidence of RFG/IUGR in at least 1 fetus was doubled in triplet gestations reduced to twins compared with non-reduced twins[14,27,28] but 2 studies found no increase in RFG/IUGR after MFPR from triplet or quadruplet gestations to twins[21,22]. Another study found an increase only after MFPR from quintuplets or higher order gestations[15].

Since the 1990's assisted reproduction techniques including ovarian stimulation and in vitro fertilization were widely used in China, resulting in a marked increase in multiple pregnancy rates. Our hospital being the largest women's hospital in China, have observed that pregnancies quadrupled since the advent of assisted reproduction techniques which were introduced in 1994. The occurrence of multiple pregnancies showed a similar trend to that reported previously[29]. Multifetal pregnancy reduction (MFPR) was introduced to avoid perinatal mortality and morbidity and maternal complications associated with multiple pregnancies[24,30.31]. Since it has been shown that MFPR significantly improved the outcome of multiple pregnancies[9,32], an effort to ensure a successful outcome for both the fetus(es) and the mother, MFPR is usually medically recommended.

In this report, we analyzed 65 cases of multiple pregnancies treated with MFPR in our hospital in China between 1996 and 2001, in order to delineate causes of multiple pregnancies, the techniques employed, timing of MFPR, and influences of maternal and neonatal conditions following the MFPR procedure.

MATERIALS AND METHODS

Subjects. 65 cases of multifetal pregnancy reduction were performed in the Women's Hospital, Zhejiang University School of Medicine from March 1996 to April 2001. The age of patients were from 24–35 years (mean ± SEM: 28.4 ± 2.3). Thirty-eight women underwent ovarian hyperstimulation and intrauterine insemination (IUI), and twenty-seven underwent in vitro fertilization and embryo transfer (IVF-ET). In all cases 39 gestations were triplets, 18 were quadruplets, 7 were quintuplets, and 1 was septuplet.

Method of MFPR. MFPR was performed under the guidance of transvaginal ultrasound. The procedure was performed between 49–79 days of gestation. Embryo reduction was performed in lithotomy position with epidural anesthesia. Transvaginal transducer of 7.5MHZ was used to confirm the alignment of gestational sacs and fetal heart in the sacs. An oocyte retrieval needle of 17–16G or special embryo reduction needle (Cook, Australia) was used. The most accessible gestational sac was chosen, and the needle was advanced sharply toward the fetal heart. After the disappearance of pulsating echoes, we applied suction repeatly until all or most of the embryonic parts and amniotic fluid were aspirated. If needed, we withdrew the needle and punctured toward a second embryo. In principle, we reduced the number of sacs to two. In one operation, the number of sacs to be reduced was no more than three. We did the embryo reduction in two separate attempts if the gestational sacs numbered five or more. The patient was given

Salbutamol for 2 days before the procedure. After the operation, Magnesium Sulfate and antibiotics were used to prevent uterine contraction and infection.

Follow up. The symptoms of threatened abortions such as abdominal pain and vaginal bleeding were monitored. Ultrasound examination was performed for 2 days following the procedure to observe the effect of reduction operation and the pulsating echoes, size of gestational sacs, and placenta attachment site of the remaining embryos. Ultrasound examination was repeated after 2 weeks and all patients received routine antenatal care and follow-up of the pregnancy until delivery. The patient would be admitted if there was any prevalent symptoms of threatened abortion or premature delivery. The new born babies were subjected to routine physical examination after delivery.

RESULTS

Outcome of fetal reduction. Fetal reduction was successful in 63/65 cases (96.9%). The number of gestational sacs was reduced to two in 60 cases, 3 quintuplets were reduced to triplets. One case with 7 sacs was reduced to triplet by two procedures, while the two failed cases were quadruplets. Miscarriage occurred in both of them due to successful fetal reduction. In 5 cases, delivery of a single fetus resulted by the natural loss of the other fetus. Gestational age at procedure: Gestational age of 49 to 56 days, 34 cases, 1 case failed; at gestational age of 57 to 63 days, 22 fetal reductions were performed resulting in the procedures; however all cases at gestational age of 77 and 79 days were successful (Table 1).

Pregnancy outcome and delivery time. No miscarriage occurred in 4 weeks after fetal reduction. Miscarriage occurred in 8 patients at gestational age > 15 weeks and no malformation of the fetuses were observed. No intrapartum haemorrhage occurred in fifty-five patients who delivered normal infants. Preterm deliveries were noted in 23 cases (41.8%, 2 cases of triplet, 20 cases of twins, 1 case of singleton). Of the 23 patients, 7 patients had vaginal delivery and 16 patients underwent Caesarean section. Total 43 infants was alive in preterm delivery. Thirty-two patients underwent term delivery (58.2%), with 8 cases of vaginal delivery and 24 cases of Caesarean section. A total of 63 infants were alive following term delivery. (Table 2).

Maternal and neonatal health condition. No signs of pelvic infection were noted following fetal reduction procedures. Slight vaginal bleeding occurred between 1 and 3 days following the procedure in 24 cases (43.6%). Eight patients complained of slight abdominal pain 1–2 days after fetal reduction. Severe pregnancy-induced hypertension syndrome (PIH) occurred in 1 patient and slight to moderate PIH occurred in 12 patients. No severe anaemia or other medical complications were observed. One hundred and ten infants were delivered, including 4 stillborn infants who were delivered at gestational age of 28 weeks of neonatal respiratory distress syndrome. No malformations were recorded in all these cases. Of the 106 live infants, there was 1 case of Hexadactyly and 1 case of arterial septal defect, all other infants were healthy. Their body weight, height and intellect were not different from the infants who were delivered normally at term pregnancy.

TABLE 1
Multifetal pregnancies and outcome of reduction

Cases (n) (weeks)	After reduction				2 weeks after reduction			
	Singleton	Twin	Triplet	Quadruplet	Singleton	Twin	Triplet	Quadruplet
39 (Triplets)	0	39	0	0	3	36	0	0
18* (Quadruplets)	0	17	0	0	0	15	0	1
7 (Quintuplets)	0	4	3	0	2	3	2	0
1 (Septuplet)	0	0	1	0	0	0	1	0

*Total fetal loss occurred in 1 case, failed in 1 case.

TABLE 2
Pregnancy outcome of 63 cases subjected to MFPR

Age of Gestation (weeks)	Number of cases	Vaginal delivery	Caesarean section	Live infants	Stillborn infants
15 – 27	8	8			
28 – 36	23	7	16	43	4
≥ 37	32	8	24	63	0

DISCUSSION

Significance of performing MFPR. The multifetal pregnancy rate in normal pregnancy rarely exceeds 3%. From 1990's; there has been a dramatic increase in multifetal pregnancies in China due to the wide use of ovulation induction and in vitro fertilization. In the United States, 43% of multifetal gestations were the result of in vitro fertilization (IVF) and gamete intrafallopin transfer (GIFT), 38% were attributed to ovulation inducing drugs[33,34]. Multifetal gestations increase morbidity and mortality for both mother and infants. Maternal complications include increased incidence of pregnancy-induced hypertension (PIH), gestational diabetes, and hemorrhage during pregnancy, malnutrition, postpartum hemorrhage and high-Caesarean section rate. Neonatal outcome of multifetal pregnancy is generally believed to be associated with an increased risk of premature delivery, low birthweight neonates, and neonatal mortality and morbidity[35,36]. All these factors contribute to the financial burden of family and society. In our series of patients, all the 65 cases of MFPR performed in our hospital were secondary to asissted reproductive treatments. Among them thirty-eight women underwent ovarian hyperstimulation and intrauterine insemination (IUI) and twenty-seven underwent in vitro fertilization and embryo transfer (IVF-ET). Of all the patients undergoing MFPR, one had severe pregnancy-induced hypertension syndrome (PIH) and twelve had mild to moderate PIH. No other pregnancy complications were recorded. From the analysis of data above, it could be inferred that multifetal pregnancy reduction is an effective technique to treat multifetal pregnancy. In this context, this technique is praticed in China to deal with the clinical sequelae of high-order multifetal gestations resulting from infertility therapy. However, it may be neccessary to issue guidelines in China to decrease the incidence of multifetal gestations including measures to control the number of follicles following ovulation induction regimes and also to diminish the number of embryos transfered in such patients subjected to assisted reproductive techniques.

Feasibility analysis of MFPR. MFPR has been practised for about 15 years and a lot of modifications have been made. The main methods of MFPR are 1) at the beginning, applying suction toward the supposed fetus by transcervical procedure under the ultrasound guidance[37]; 2) puncturing and injecting KCl or other drugs into the fetal heart by transabdominal or transvaginal procedure under the ultrasound guidance[38]; 3) after introduction the needle into the sacs by transvaginal procedure under the ultrasound guidance, aspirating or puncturing repeatedly toward the fetus[39,40]. The first two methods which is performed after 9 weeks of gestation has a higher miscarriage rate, 24.8% and 16.7%, respectively[41]. The third method could be performed earlier at gestational age of 7–8 weeks and the miscarriage rate has been reported to be 7.3%–10.6%[40,42,43]. In this study we performed MFPR at gestational age of 46–79 days using the third method. In our opinion, it was easier to cause fetal demise at an early stage (gestational age 46–56 days) by advancing the needle toward the fetus and puncturing and aspirating repeatedly while it is difficult and unethical to aspirate the bigger fetus at gestational age of between 56 and 79 days. This procedure invloved advancing the needle sharply toward the fetus repeatedly until the disappearance of pulsating echoes. No infection or vaginal haemorrhage occurred in the 65 cases of selective reduction performed in this study group. Slight vaginal hemorrhage was noted at 1–3 days following the procedure in 24 cases (43.6%). Eight patients complained of slight abdominal pain at 1–2 days after fetal reduction. No miscarriage occurred before gestational age of 14 weeks (3 weeks after operation). These data suggest MFPR is safe, effective, simple with minimal side effects and this could be a recommended procedure. To avoid reduction failure, the alignment and numbers of gestational sacs should be scrutinized under ultrasound guidance to confirm the location and number of fetuses to be reduced.

Maternal neonatal influence of MFPR. MFPR may influence the viability of remaining fetus[44]. Our data showed that 4 cases resulted in failure in which natural loss of the other fetus occurred. We speculate that the cause of natural fetus loss might be due to injury at the site of placental attachment of the remaining fetus during the MFPR procedures.

In conclusion, since the majority of multifetal pregnancy cases were reduced to twins and triplets, the present data showed a high premature delivery rate of 41.8% (23/55). All the subjects were infertile patients and conceived following treatment with assisted reproductive technology. The fetus was cherished and Caesarean section rate was 72.7% (40/55). Therefore, MFPR could not decrease dystocia rate and premature delivery rate, but could reduce fetus loss and increase live born infant rate and neonatal survival rate. One hundred and six of the one hundred and ten infants born after MFPR survived. Except 1 case of Hexadactyly and 1 case of atrial septal defect, the other infants were healthy and their body weight, height and intellect were comparable to infants of the same age. Therefore, MFPR did not cause injury or malformation of the remaining infants. This study further highlights the fact that embryo reduction is an accepted alternative especially for quadruplets or higher-order pregnancies. Although, controversy remains in cases of triplet pregnancies with perinatal mortality rates of between 5 and 20%, we recommend MFPR because the obstetric risks and delivery of normal fetuses are

good and acceptable in our experience. Also embryo reduction should preferably be carried out between 8 and 10 weeks of pregnancy.

Importance of follow-up. The obstetric follow-up of the parents after embryo reduction performed is very essential for good final outcome[45]. The obstetric follow-up includes personal interviews and medical observation of any underlying symptoms or complications by the obstetrician. The early signs of threatened abortion such as vaginal hemorrhage, abdominal pain should dealt with immediately. It is also important to subject each patient to ultrasonography 3 days after MFPR. Because majority of multifetal pregnancy is usually reduced to twins, it is important to provide antenatal care routinely to prevent malnutrition, PIH and intrauterine growth retardation (IUGR) especially in the developing countries. Special attention is necessary in late pregnancy to observe and provide care in order to avoid premature delivery. Therefore, follow-up after reduction will decrease miscarriage rate, maternal neonatal morbidity and infant mortality.

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