

# Multifetal pregnancy reduction: modification of the technique and analysis of the outcome

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**Objective:** To modify the technique of multifetal pregnancy reduction and to study the outcome of reduced twins in comparison with nonreduced twins and high-order multiple gestations.

**Design:** Prospective controlled study.

**Setting:** The Egyptian IVF-ET Center, Cairo.

**Patient(s):** Seventy-five patients with high-order multiple pregnancies resulting from assisted reproduction. Controls were 40 nonreduced twin pregnancies and 22 high-order multiple gestations.

**Intervention(s):** Transvaginal ultrasonically guided multifetal pregnancy reduction was performed. The first 30 cases were done using KCl as a cardiotoxic agent. The modified technique was used for the last 45 cases at an earlier gestational age (approximately 7 weeks) by eliminating the use of KCl and by aspirating the embryonic parts.

**Main Outcome Measure(s):** Miscarriage rate, gestational age at delivery, birth weight, and pregnancy complications.

**Result(s):** Using the modified technique, the miscarriage rate was 8.8% and 41 patients delivered between 32 and 39 weeks of gestation (mean  $\pm$  SD, 36.9  $\pm$  2.45 weeks). The mean ( $\pm$  SD) birth weight was 2,450.51  $\pm$  235.44 g. The miscarriage rate, fetal wastage rate, mean gestational age, and mean birth weight were similar in reduced and nonreduced twins and were significantly better than in nonreduced triplets and quadruplets.

**Conclusion(s):** The modified technique of multifetal pregnancy reduction significantly improved outcomes, which were similar to those of nonreduced twins resulting from assisted reproduction and significantly better than those of nonreduced triplets and quadruplets. (*Fertil Steril*® 1999;71:380–4. ©1999 by American Society for Reproductive Medicine.)

**Key Words:** Multifetal embryo reduction, reduced twins, multiple pregnancy, triplets, quadruplets, twins, embryo selection, selective embryo reduction

During the past 20 years, the use of ovulation-induction drugs for various assisted reproduction techniques has increased significantly. This practice has led to a marked increase in the multiple pregnancy rate, with all of its complications. To reduce the incidence of multiple gestations, most IVF centers reduce the dose of ovulation induction drugs and limit the number of embryos per transfer. However, multiple pregnancy is still unavoidable.

Multifetal pregnancy reduction was introduced to avoid the increased incidence of abortion and premature labor associated with multiple pregnancies (1). Since the beginning of our IVF program in 1986, multifetal pregnancies have been a problem. Multiple

gestation is a high-risk condition because of the marked increase in maternal complications and perinatal mortality and morbidity. Faced with potentially tragic situations such as the agony of infertile couples who lose their premature infants, we introduced multifetal pregnancy reduction in our center in 1990 after obtaining institutional review board approval.

We report our experience in performing 75 cases of multifetal pregnancy reduction for high-order multifetal pregnancies with special emphasis on our technique, which is a modification of previously described techniques. We also analyzed the obstetric outcomes to see whether this technical improvement has made

Received June 16, 1998;  
revised and accepted  
September 23, 1998.

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0015-0282/99/\$20.00  
PII S0015-0282(98)00461-0

this method a better approach for high-order multifetal pregnancies. A control group consisted of 40 nonreduced twin pregnancies resulting from assisted reproduction. Pregnancy outcomes were also compared with a group of 22 patients with high-order multiple gestations that did not undergo reduction.

## MATERIALS AND METHODS

From January 1990 to December 1997, we counseled 94 patients with high-order multiple gestations for embryo reduction after obtaining institutional review board approval. Seventy-five women underwent the procedure. Sixty-eight patients were from our center and 7 patients were referred to us from other doctors. Forty-five gestations were triplets, 27 were quadruplets, and three were quintuplets. All the patients were counseled to reduce the number of sacs to two. Two patients requested the reduction to a single sac, but we convinced them to leave two viable fetuses.

Embryo reduction was done as an outpatient procedure under IV general anesthesia using propofol 10% (Diprivan; Zeneca Limited, Macclesfield, Cheshire, United Kingdom). The vagina was prepared with 10% providone iodine and was then thoroughly rinsed with sterile saline solution and drying to remove any traces of povidone iodine. Transvaginal ultrasound was used (Bruel and Kaejer model 3536 with transvaginal transducer model 8538; Naerum, Denmark). The number of gestational sacs with pulsating echoes was confirmed.

The most accessible gestational sac was chosen, and the fetal heart was visualized and aligned with the puncture guideline on the screen. An oocyte retrieval needle (Labotect cat. no. 322109; Gottingen, Germany), was advanced sharply toward the fetal heart. For successful puncture of the fetal heart, the ultrasound transducer should be introduced deeply inside the vagina so as to firmly stretch the vaginal vault before introducing the needle. It is sometimes helpful to support the uterus lightly in the suprapubic region.

In the first 30 patients in this series, we injected 0.5–3 mL of KCl (15%) according to a previously described technique (2). We modified this technique by eliminating the use of KCl completely. After introduction of the needle into the fetal echoes, we applied suction (using a 20-mL syringe) repeatedly until all or most of the embryonic parts were aspirated. We did not aspirate any amniotic fluid. In most cases, the fetal echoes disappeared completely and the sac remained of the same size or slightly smaller, but empty of fetal parts. After making sure that the fetus was aspirated, or, if not completely aspirated, that there were no more pulsations, we withdrew the needle.

The procedure was repeated for another gestational sac (or two) in the case of quadruplet or quintuplet pregnancies. The patients were given 1 g of IV cefotaxime (Claforan;

Hoechst Orient SAE, Cairo, Egypt) before the procedure and were discharged after 3 hours. Follow-up ultrasound examination was done 1 week after the procedure. All patients received routine antenatal care and follow-up of the pregnancy except for those who traveled abroad. Outcome data was obtained for all pregnancies.

An age-matched group of 40 patients with nonreduced twin pregnancies resulting from assisted reproductive techniques was chosen as a control. In addition, we compared outcomes between the study group and 22 high-order multiple pregnancies that did not undergo fetal reduction.

Student's *t*-test was used to compare the mean gestational ages and birth weights. Fisher's exact test was used to compare the miscarriage rates.

## RESULTS

The gestational age at reduction ranged between 6 and 9 weeks (mean  $\pm$  SD of  $7.2 \pm 0.1$  weeks). At first the procedure lasted 5–10 minutes per gestational sac, but after the clinician gained more experience, the procedure took only 1–5 minutes per sac. In addition, in the beginning 0.5 to 3 mL of KCl was injected ( $n = 30$  cases), but the procedure was later done without use of KCl ( $n = 45$ ). No immediate complications of the procedure (e.g., vaginal bleeding) occurred, and all the cases were technically successful. No chorioamnionitis or septic abortion occurred.

We analyzed the 45 cases using the modified technique. First-trimester miscarriage occurred in one patient and second-trimester miscarriage occurred in three patients (miscarriage rate of 8.8%). Forty-one patients delivered 73 infants (nine deliveries were singletons). The mean ( $\pm$  SD) gestational age was  $36.9 \pm 2.45$  weeks, and the mean ( $\pm$  SD) birth weight was  $2,450.51 \pm 235.44$  g. One stillbirth and one neonatal death occurred.

The first group of patients ( $n = 30$ ) that had the procedure with KCl had nine miscarriages (30%), three stillbirths, and two neonatal deaths. Twenty-one patients delivered 41 infants (3 singletons, 2 triplets, and 16 twins). The mean ( $\pm$  SD) gestational age was  $36.3 \pm 1.64$  weeks, and the mean ( $\pm$  SD) birth weight was  $2,198.06 \pm 656.3$  g.

The outcome of an age-matched group of nonreduced twin pregnancies resulting from medically assisted reproduction was compared with our study group in which we did not use KCl (Table 1). The study and control groups were similar in maternal age (32.6 versus 33.4 years, respectively) and duration of infertility (5.4 versus 6.1 years, respectively). There were no statistically significant differences in the abortion rate, mean gestational age, mean birth weight, and fetal wastage between the groups.

The outcomes of high-order multiple pregnancies that did not undergo reduction were compared with the outcomes after multifetal reduction with the modified technique (Table

TABLE 1

Analysis of the results of reduced and nonreduced twins.

| Group            | No. of cases   | Miscarriage |        |          | No. of deliveries | No. of live-born infants | Mean gestational age (wk) | Mean birth weight (g)          | No. of stillborn infants | No. of neonatal deaths |
|------------------|--|-------------|--------|----------|-------------------|--------------------------|---------------------------|--------------------------------|--------------------------|------------------------|
|                  |  | <12 wk      | >12 wk | Rate (%) |                   |                          |                           |                                |                          |                        |
| Reduced twins    | 26 triplets<br>17 quadruplets<br>2 quintuplets<br>45 total | 1           | 3      | 8.8*     | 41                | 72 (9 singletons)        | 36.9 ± 2.45 <sup>†</sup>  | 2,450.51 ± 235.44 <sup>‡</sup> | 1                        | 1                      |
| Nonreduced twins | 40   | 1           | 3      | 10*      | 36                | 62 (5 singletons)        | 36.5 ± 2.58 <sup>†</sup>  | 2,316.04 ± 603.09 <sup>‡</sup> | 1                        | 1                      |

Note: Data are expressed as *n*, %, or mean ± SD.

\* *P* = .211 (not significant).

<sup>†</sup> *t* = 0 (not significant).

<sup>‡</sup> *t* = 0.75 (not significant).

2). There was a significantly higher abortion rate and fetal wastage rate and a significantly lower gestational age and birth weight when no fetal reduction was performed.

## DISCUSSION

In this study, we modified the technique of multifetal pregnancy reduction by avoiding completely the use of any cardiotoxic substance such as KCl. Our approach depends mainly on performing the procedure early (as soon as fetal pulsations are confirmed), usually between 6 and 8 weeks of gestation. At this stage, it is not difficult to aspirate all or most of the embryonic parts, leaving the gestational sac almost intact and full of amniotic fluid but empty of any embryonic tissues.

Itskovitz et al. (3) described two cases of multifetal reduction without the use of an embryotoxic substance. Their technique differed from ours in two respects. First, they applied suction only to stop fetal pulsations and not to aspirate the embryonic tissues. Second, they partially aspirated the amniotic fluid.

The rate of miscarriage in this study using the modified technique was 8.8%. This is less than the 12.6% loss rate reported by Sebire et al. (4) in their series of 127 multifetal pregnancies undergoing embryo reduction and also less than the 13.7% loss rate reported by Evans et al. (2) in a multicenter study of 380 multifetal embryo reductions.

In the first 30 cases when we used KCl as an embryotoxic substance, we had a high fetal wastage rate (30%). One explanation for the lower miscarriage rate using the modified technique is that we performed it after gaining more experience and at an earlier gestational age. It has been reported that it is feasible to complete the procedure as early as 6 weeks' gestation, although it might be preferable to wait until 8 weeks or later for fear of the natural phenomenon known as "vanishing twin." We recommend performing the procedure as early as possible without excessive concern about the phenomenon of vanishing twins because two gestational sacs will remain. Even if one sac vanishes, a singleton pregnancy will result. In this series of 75 fetal

TABLE 2

Analysis of the results of reduced twins and nonreduced triplets and quadruplets.

| Group                  | No. of cases   | Miscarriage |        |          | No. of deliveries | No. of live-born infants | Mean gestational age (wk) | Mean birth weight (g) | No. of stillborn infants | No. of neonatal deaths |
|------------------------|--|-------------|--------|----------|-------------------|--------------------------|---------------------------|-----------------------|--------------------------|------------------------|
|                        |  | <12 wk      | >12 wk | Rate (%) |                   |                          |                           |                       |                          |                        |
| Reduced twins          | 26 triplets<br>17 quadruplets<br>2 quintuplets<br>45 total | 1           | 3      | 8.8*     | 41                | 72 (9 singletons)        | 36.9 ± 2.45*              | 2,450.51 ± 235.44*    | 1                        | 1                      |
| Nonreduced triplets    | 16   | —           | 4      | 25*      | 12                | 29                       | 33.46 ± 2.787*            | 2,002.8 ± 500.5*      | 5                        | 5                      |
| Nonreduced quadruplets | 6  | —           | 3      | 50*      | 3                 | 10                       | 32.67 ± 2.31*             | 1,400 ± 316.2*        | 2                        | 2                      |

Note: Data are expressed as *n*, %, or mean ± SD.

\* *P* < .05.

reductions to twins, the pregnancies continued as a singleton in 12 cases (16%).

Another factor that may have played a role in reducing the miscarriage rate using the modified technique is that we aspirated most of the embryonic tissues at an earlier stage. Aspiration leaves a minimal amount of necrotic tissue, which may have detrimental effects on the remaining gestational sacs. In the beginning, it was difficult to imagine that it was possible to aspirate an embryo of 6–8 weeks with visible pulsations. However, the embryo at this stage is composed of three primary germ layers (ectoderm, endoderm, and mesoderm) folding to form the head, tail, and lateral body folds, and these soft tissues and membranes are easily removed with repeated suction.

One of the causes of pregnancy loss in reduced twins is the development of an inflammatory response to the resorbing necrotic fetoplacental tissues, with the resulting release of cytokines and prostaglandins (4). High concentrations of  $\alpha$ -fetoprotein (AFP) are found in the amniotic fluid of twin pregnancies after spontaneous death of one of the fetuses, as reported by Bass et al. (5) and in reduced twins.

Abbas et al. (6) reported that after reduction of multifetal pregnancies, the maternal serum AFP concentration increases in proportion to the amount of dead fetoplacental tissue, and this increase persists for several months after the procedure. We believe that performing multifetal reduction at an earlier stage (i.e., before 8 weeks of gestation) probably decreases the concentration of AFP remaining after the reduction. This has yet to be confirmed.

Another reason for the lower miscarriage rate is that the injection of KCl is not strictly limited to the fetal heart. During injection, the fetus is sometimes pushed away from the needle and KCl diffuses into the amniotic sac; consequently it may diffuse to the adjacent gestational sacs. Toxic effects of KCl on the remaining fetuses have been reported by Tabsh et al. (7) and Wapner et al. (8).

In comparison with the nonreduced twins, the outcome of the twins resulting from the modified reduction technique was not significantly different with regard to the miscarriage rate, fetal wastage rate, mean gestational age, and birth weight. Nonreduced twins that were chosen as a control in this study resulted from IVF or intracytoplasmic sperm injection. It has been shown that twin pregnancies conceived by assisted reproductive techniques resulted in more frequently discordant birth weight and low birth weight compared with those conceived spontaneously. In 1996, Smith-Levitin et al. (9) demonstrated that reduced twins were similar to nonreduced twins conceived with assisted reproduction in all variables studied.

It was also noted in this series that the early (<12 weeks) miscarriage rate was only 2.6%, which is similar to that of early amniocentesis in singleton pregnancies (2.2%). This leads to the assumption that most miscarriages associated

with multifetal reduction are not the consequence of spontaneous loss, nor are they directly due to the procedure and the use of needles in the reduction.

The mean gestational age at delivery ( $36.9 \pm 2.45$  weeks) of the twins resulting from the modified technique was similar to that of the nonreduced twins conceived by assisted reproduction ( $36.5 \pm 2.58$  weeks). This finding is probably due to the minimal amount of necrotic tissues remaining after reduction and thus the smaller likelihood that their resorption could trigger labor.

Compared with the outcome of high-order multiple pregnancies, our results indicate that the gestational age at birth and mean birth weight increased after multifetal reduction. The miscarriage rate and perinatal mortality also decreased significantly with fetal reduction. Among six cases of quadruplets that were managed without embryo reduction, three (50%) resulted in late miscarriage. At delivery, the mean ( $\pm$  SD) birth weight was  $1,400 \pm 316$  g and the mean ( $\pm$  SD) gestational age was  $32.67 \pm 2.31$  weeks. The fetal wastage rate (miscarriage, stillbirth, and neonatal death) was 66.6%.

The control group also included 16 cases of nonreduced triplets. Miscarriage occurred in four cases (25%). At delivery, the mean ( $\pm$  SD) birth weight was  $2,042.8 \pm 500.5$  g and the mean ( $\pm$  SD) gestational age was  $34.46 \pm 2.787$  weeks, which were significantly lower than those of the reduced twins. Five infants were stillborn and five died in the neonatal period (45.8% fetal wastage). This very high fetal wastage rate in triplets and quadruplets used as a control group in this study was mainly due to prematurity and low birth weight.

Bollen et al. (10) and Smith-Levitin et al. (9) demonstrated that multifetal pregnancy reduction gave better outcomes than expectant management of triplets. In a large British study by Botting et al. (11), the perinatal mortality rate was 41.6% in sextuplets, 21.9% in quintuplets, 20% in quadruplets, and 16.4% in triplets.

Multifetal pregnancy reduction raises considerable ethical and religious debates. It is a difficult situation for both the physician and the patient. Our study was approved by our institution's ethics committee, but it was difficult to counsel patients because of the lack of sufficient data about the procedure. We did not know initially what the chances would be of successfully performing the procedure or the risks of long-term effects of the procedure on the remaining pregnancy. The emphasis was placed on the incidence of early pregnancy loss and the perinatal complications of prematurity. We also emphasized that the procedure could result in total loss of the pregnancy and that the future risks were still unknown.

Our approach to counseling has evolved over the years. At present, we inform patients that the chance of successfully performing the procedure with minimal risk is very

high and that the outcome of reduced twins is significantly better than for nonreduced high-order multiple pregnancies. However, the long-term complications and potential risks of the procedure are still uncertain.

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