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Research Article

Early Multifetal Pregnancy Reduction Outcomes: Non-Chemical-Based Method Yield Improved Pregnancy Rates and Minimized Risks

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Abstract

Objectives: Multifetal pregnancies increase the risk of maternal and perinatal mortality and reducing to a lower-order pregnancy attenuates this risk. We assessed a non-chemical-based procedure for multifetal pregnancy reduction.

Methods: A single-arm prospective study was conducted between December 2013 and September 2018 on patients with trichorionic triamniotic pregnancies (n=296). Multifetal pregnancy reduction was performed between gestational weeks 5 and 10. Using the same equipment for transvaginal ultrasound-guided oocyte recovery, an echo-tipped needle (17 Cook medical ovum aspiration needle) was inserted into the embryo's cardiac area until the absence of fetal heartbeat. Afterward, the needle was extracted, and the hemostasis/vitality of the remaining embryos was verified. Patients were followed until delivery, where the birth weight was recorded as well as any complications.

Results: None of the women presented or indicated any surgical-related complications. Three patients lost their pregnancies (1.0%); however, 89.9% maintained the remaining two gestational sacs and 9.1% retained one gestational sac. The live birth rates were 95.1% for the two gestational sacs (birth weight: 2135±586 grams) and 96.3% for one gestational sac (birth weight: 2546±636 grams). The birth weight was significantly better in pregnancies that resulted in one gestational sac (p=0.001). There was a significant difference in the low birth weight rate (two sacs: 26.9% v one sac: 58.4%) but not with the very low birth weight rate (two sacs: 9.1% v one sac: 7.7%).

Conclusions: Here, we demonstrate that a non-chemical method can successfully reduce the number of embryos avoiding complications and allowing pregnancy.

Keywords: Embryo reduction; High-order multiple pregnancies; Pregnancy outcomes; Selective termination; Trichorionic triplet pregnancy

Introduction

Procedures to increase the success of achieving a clinical pregnancy include implanting multiple embryos; however, this has had many unforeseen risks [1]. The risk of spontaneous pregnancy loss is 25% for quadruplets, 15% for triplets, and 8% for twins [2]. Moreover, multifetal pregnancies increase maternal and perinatal morbidity and mortality [3]. Maternal risks of multifetal pregnancies include hypertension, preeclampsia, gestational diabetes, and postpartum hemorrhage [4,5]. Implementing multifetal pregnancy reduction during assisted reproduction technologies when three or more fetuses are present has become a common practice.

According to Liu, et al. the optimal strategy for multifetal pregnancy reduction has not been elucidated [6]. Multifetal pregnancy reduction is typically scheduled between 11 and 14 weeks of gestation, known as late reduction, with most common

procedures requiring the use of chemical substances, such as potassium chloride (KCl), as an adjuvant or gestational sac aspiration to improve the embryo reduction success rate [7]. Even though these procedures have improved assisted reproduction technology outcomes, under certain circumstances, these procedures present with significant complications, ranging from increased miscarriage rates to abdominal pain to maternal distress [8-10]. The proposed mechanisms postulated for these effects include procedure-related trauma, infection, over-activation of the maternal immune system due to the resorbing of dead fetoplacental tissue, feticide-promoted hemorrhage leading to the death or impaired development of the remaining fetus(es), or that the KCl from the injection transfers to another fetus via the intertwine placental vascular anastomoses [11,12,9,13]. Lastly, when late reduction could be or is not possible, alternative techniques, such as early reductions, should be considered. Certain circumstances include but are not limited to cervical ectopic pregnancy, placental complications, compromised embryo development, in which all implantations may suffer from prolonged intervention. With more unsatisfactory results associated with early reductions compared to late reductions concerning procedure-related fetal or pregnancy loss, augmented miscarriage rates, preterm delivery, and birth weight [14,15], the early reduction techniques need improvement. Therefore, we present a non-chemical-based method for fetal reduction, performed during early gestation.

Materials and Methods

Patients and study approval

Between December 2013 and September 2018, patients with trichorionic triamniotic triplets were asked to participate in this single-arm prospective study. To be included in the study, women had to be attending the Ingenes Institute for advanced maternal age without any other cause of female infertility and underwent a standardized in vitro fertilization (IVF) protocol. Exclusion criteria were an ectopic pregnancy, not willing to accept the procedure, or monetary issues. Options were explained to the patients and presented with embryo reduction as an alternative. They were explained the potential problems with the procedure.

IVF and pregnancy evaluation

All patients underwent a 10-day controlled ovarian stimulation with gonadotropin-releasing hormone agonists and antagonists. Ovarian response was assessed by monitoring follicular development by ultrasound examination and measuring serum estradiol levels. Oocyte retrieval was conducted 36 h after human chorionic gonadotropin (hCG) administration (10,000 IU Choragon Ferring Laboratories or 6500 IU Ovidrel, Merck Laboratories, Naucalpan de Juárez, Estado de México, México). At the end of hormonal stimulation, oocyte collection was performed under general anesthesia. To follow and locate mature follicles, transvaginal ultrasound was used. Ovulation was induced with hCG. Using a specialized suction system, 3–5 ml of follicular fluid containing the oocytes was extracted.

Samples were analyzed using a stereoscopic microscope to locate the oocytes, which were kept at 37.5 °C in an 8.3% CO_2 atmosphere until fertilization. Only the highest quality embryos were transferred, and pregnancy was diagnosed by β-hCG values >10 mUI/ml (Day 14) as well the presence of a fetal heartbeat, confirmed by ultrasound at 6–8 weeks. An embryologist monitored and recorded information about embryo development, embryo morphology, transfer, and pregnancy. Low birth weight was defined as a delivery weight below 2,500 grams and very low birth weight below 1,500 grams. Using the World Health Organization criteria, preterm births were categorized as either extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), moderate to late preterm (33 to 37 weeks)[16]. Birth weight discordance was calculated using the formula: (birth weight of the larger twin – birth weight of the smaller twin)/birth weight of the larger twin [17]. Pregnancy loss due to the procedure was defined as a loss of pregnancy within three weeks of the procedure as indicated by Evans, et al. [18] and Timor- Tritsch, et al. [19], whereas miscarriages were defined as a pregnancy loss before 24 weeks and abortion was defined as a pregnancy loss after 24 weeks.

Embryo reduction

Patients without spontaneous pregnancy reduction were counseled about multifetal pregnancy reduction at our facilities. The probable complications of multiple fetal pregnancies and the risks and benefits of multifetal pregnancy reduction were explained. The doctors gave advice about which embryo should be reduced according to the embryos' condition and position. Final decisions about whether to undergo multifetal pregnancy reduction and retained embryos were made by the patients, depending on their religious beliefs and personal preference.

Before the procedure, an ultrasound scan was performed using a 5.0 MHz transducer (Panavista-VA GM-2600A, Matsushita, Japan) to determine the location of the pregnancy and the size of the fetus and gestational sac. The embryos were observed, and an embryo was chosen for reduction based on its proximity to the cervix as well as the presence of an unfavorable prognosis. Fetal heartbeats were confirmed for each fetus before starting the procedure. Under general anesthesia, after patients had been placed into the lithotomy position, the vagina was prepared with 10% povidone-iodine and thoroughly rinsed with sterile saline solution. Prophylactic antibiotic (2.0g Cefalotin, intravenous injection) was administered one h before the procedure. Under on-screen sonographer guidance, the fetus was approached transvaginal through the anterior fornix with a 17-gauge COOK needle (COOK Medical, Bloomington, IN, USA) for embryo reduction. A cardiac puncture was performed. The transuterine puncture was carried out until reaching the fetus's heart. From there, a direct intracardiac puncture was performed, where the needle was repeatedly rotated 90 degrees or by making continuous punctures in the cardiac area until evidence of cessation of the cardiac activity. After ensuring that no fetal heartbeat occurred, the needle was withdrawn. There was no need for suction. Ultrasonic graphic presentation of the procedure is presented in Figure 1. Following the procedure, vaginal hemostasis revision was performed. Patients were followed until delivery and the birth weight was recorded as well as any complications.

Statistical analysis

The Shapiro-Wilk test was used to determine if the data were normally distributed. Either the Chi2 test, Mann–Whitney U test, or Student's t-test was used to examining differences between groups. P-values <0.05 (two-tailed) were considered significant. All analyses were carried out with the Statistical Package for the Social Sciences software v26.0 (IBM Corp., Armonk, NY, USA).

Results

For this proof of principle study, we only approached patients with three gestational sacs (trichorionic triamniotic), which were reduced down to two. Two hundred ninety-six patients agreed to participate out of 407. The characteristics of the participants are presented in Table 1. For the women who choose not to proceed, the top reasons were personal reasons/choices, religious beliefs, and economic causes. Embryo reduction typically took place during the 7th week (range: 5-10.5 weeks). The procedural time was 15 minutes. None of the women presented or indicated any complications due to the surgery.

After the procedure, three patients lost their pregnancy (1.0%) due to the procedure (within three weeks); however, 89.9% maintained the remaining two gestational sacs and 9.1% for one gestational sac. The live birth rates were 95.1% for the two gestational sacs and 96.3% for one gestational sac (Table 1). There was no difference in the live birth rate (p=0.784). Even though there was no difference in the gestational age at birth, the one gestational sac group had more full-term deliveries, and the two gestational sacs group had more moderate to late preterm deliveries. Interestingly, there was no difference between the groups with respect to preterm deliveries <33 weeks. For patients in which the reduction led to 1 gestational sac, there was a significant benefit concerning birth weight (p=0.001). When the birth weight was stratified into normal, low, and very low, there was a significant difference in the low birth rate but not the very low birth weight (Table 1). The most common fetal complication for the two gestational sacs group was the pregnancy that required neonatal intensive care unit intervention (4.5%), whereas for the one gestational sac group was the restriction of intrauterine growth (14.8%, Table 2).

Table 1: Characteristic of the participants separated by pregnancy outcome (Twin or Singleton).

Category	Twin	Singleton	p-value[a]
Sample (n)	266	27	N/A
Age (years)	37.2 ± 5.4	40.2 ± 4.6	0.007 *
Height (m)	1.59 ± 0.1	1.60 ± 0.1	0.45
Weight (kg)	65.5 ± 11.2	62.8 ± 7.2	0.095
Body-mass index (kg/m^2)	25.9 ± 4.3	24.8 ± 2.8	0.072
Donor (%)	57.5	70.4	0.196
Average week of reduction	7.3 ± 0.7	7.5 ± 0.7	0.183
Live birth rate (%)	94.5	96.3	0.694
Average gestation week at birth	34.6 ± 4.2	35.4 ± 5.6	0.376
Pre-term birth (%)	13.5	11.1	0.724
Birth Weight (g)	2135 ± 586	2546 ± 636	0.001*
Normal birth weight (%)	28.1	65.4*	<0.001*
Low birth weight (%)	58.4	26.9*	
Very low birth weight (%)	13.5	7.7	
Weight discordance (%)	10.7 ± 11.4	N/A	N/A

[a]Differences between the Twin and Singleton groups were determined using either Chi2 test or Student's t test. *indicates a significant value (<0.05, two-tailed).

Table 2: Complications presented during the study.

Category	Twins	Singleton
Fetal complication		
Intrauterine Growth Restriction	9	4
Edwards Syndrome	1	0
Down Syndrome	0	1
Neonatal Intensive Care Unit	24	0
Onfalocele	1	0
Maternal complication		
Pre-eclampsia	18	4
Premature Rupture of Membranes	2	0

Gestational Diabetes	2	0
Premature	16	0
Sepsis	0	0
Maternal Death	0	0
Obstetric Hemorrhage	1	0

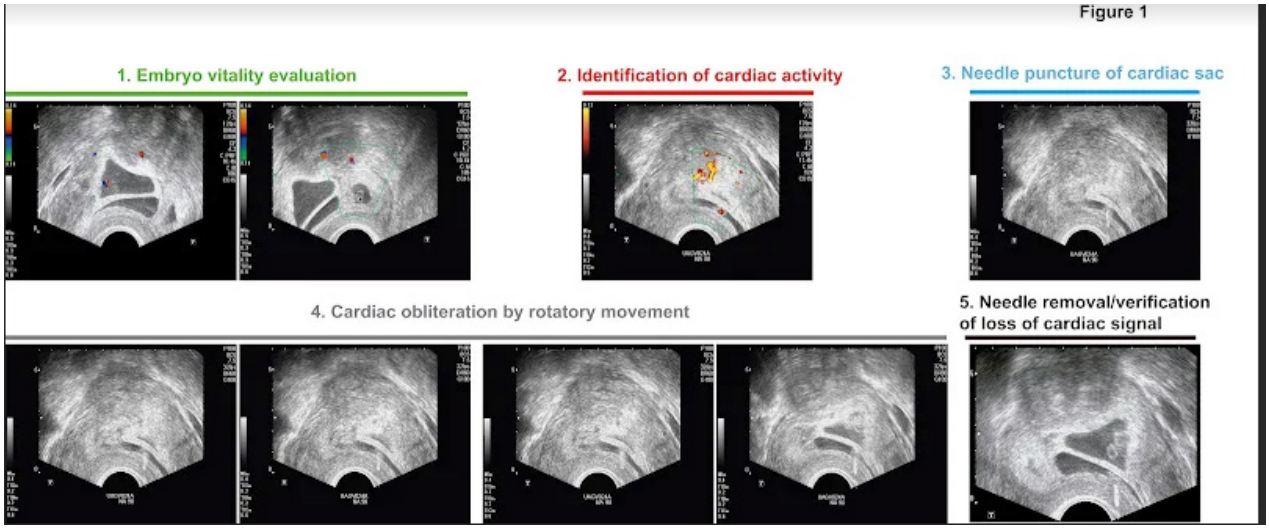

Figure 1: Ultrasonograms are showing multifetal embryo reduction. Multifetal embryo reduction occurred during the early stages of embryo development (gestational week 5 to 10). The intracardiac needle obliteration procedure method (non-chemical) was conducted, under general anesthesia, with the patients placed into the lithotomy position. Using on-screen sonographic guidance, the embryos were identified, and their vitality was assessed (top row, 1st and second image). Using cardiac imaging, the heart sac was located (top row, third image). Afterward, the fetus was approached transvaginal through the anterior fornix with a 17-gauge COOK needle (top row, fourth image). Embryo reduction occurred by cardiac puncture and rotatory movement (bottom row, 1st to fourth images). After ensuring that no fetal heartbeat occurred, the needle was withdrawn (bottom row, fifth image).

Discussion

When late reduction is unavailable, early reduction remains an option over expectant management but is associated with poorer efficiency when compared to late reduction. Here, we demonstrate that the use of intracardiac needle obliteration of the fetal heartbeat does present as an alternative to KCl injections or embryo aspiration with similar efficiencies to late reduction.

One main concern with multifetal pregnancies is as the number of embryos increases to greater than three embryos, the risk of spontaneous pregnancy loss concurrently increases with preterm birth [20]. The reduction to either twin or singleton pregnancies does relieve this risk but at the cost of the increased potential of miscarriage, preterm birth, and low birth weights. Here, our study presented with marked improvement of spontaneous pregnancy loss. Data suggests that under managed expectant conditions, on average, about 7% (ranging between 3 and 24%) of IVF cycles would result in complete pregnancy loss [3,21-24]; however, only 1.0% of our cohort lost the remaining two gestational sacs. For trichorionic triplet pregnancies that underwent early reduction, this rate is superior to reports by Abdelhafez. et al. (7.5%) and Liu et al. (5%), which was independent if the pregnancy was reduced to either twins or singleton [6,25,26]. Interestingly, 9.0% of the trichorionic triplet IVF cycles that were reduced to a dichorionic twin, further reduced to monochorionic (singleton) pregnancies. A similar result can be seen with other early reductions of trichorionic triplets in which 3.7% [26] to 7.3% [6] of their original cohort resulted in singleton pregnancies. The differences in these rates could be due to the technique as one method utilized embryo aspiration as well as KCl, whereas the other used KCl only. For late reductions of trichorionic triplet pregnancies, our rate for overall pregnancy loss is similar, if not superior, exhibited in reports by Okyay, et al. (1.2%), Zemet et al. (1.3%), Papageorghiou, et al. (9.0%), Chaveeva, et al. (8.3%), and Bhandari et al. (15.2%) [8, 22, 24, 27, 28]. With respect to spontaneous reduction to monochorionic pregnancies, the rates for late reduction were superior to the method proposed here, ranging between 2.8 and 5.8% [12,13,24,29]. Interestingly, all late reduction methods for trichorionic triplets reduced to dichorionic twins utilized KCl. This does suggest that our approach does improve IVF outcomes with respect to a live birth. Nevertheless, some studies have shown that the mother's age, the initial number of gestational sacs, chorionicity, polycystic ovarian syndrome, and other factors influence the spontaneous pregnancy loss rate [30,6], which we did not take into consideration.

Under managed expectant conditions, preterm births (<32 weeks to <37 weeks) typically occurs in 36.8-85.0% of trichorionic triplet cases [3, 6, 12, 22, 23], whereas, here, for <32 weeks, our rate was 9.1% and 7.7% for twins and for singleton reductions, respectively, and for <37 weeks was 71.9% and 42.3%, respectively.

For trichorionic pregnancies, these rates for very and extremely preterm (<32 weeks) were comparable to other studies for early reduction, independent if the reduction was from trichorionic triplets to either dichorionic twins or monochorionic singletons [25,26]. However, when considering just preterm (<37 weeks), our rates were higher than those reported by Liu et al. (53.0%) and Haas et al. (49.1%) [6,26]. Interestingly, with early reduction, reductions that lead to monochorionic pregnancies did result in a low number of preterm births [6,25,26]. With late reductions, our cohort reported rates lower for very and extremely preterm birth (<32 weeks) when compared to the rates observed by Papageorghiou, et al. (17.3% to 18.0%); nonetheless, our rates were similar to Bhandari et al. (68.5%) and Zemet, et al. (56.9%) for preterm birth <37 weeks [22,27]. These data suggest that early reduction has a better prognosis to avoid preterm birth without considering spontaneous pregnancy loss and birth weight.

Several meta-analyses and studies have shown that reducing to a lower-order pregnancy (triplet or quadruplet to twin) reduces the risk of medical complications associated with maintaining higher-order pregnancies [7,31], such as low birth weight. The low birth weight rate was 58.4% and 26.9% for two gestational sacs and one gestational sac, respectively. Concerning managed expectant conditions, the low birth rate for trichorionic triplet pregnancies ranges between 77.2% to 92.9% [6,22,23], in which our rates are well below the reported values for trichorionic triplet pregnancies. This could be due to conditions that resulted in retaining the remaining gestational sacs, such as the immune response, preterm delivery, and follow-up care, in naming a few. For the very low birth weight rate, the rates were 13.5% for two gestational sacs and 7.7% for one gestational sac, which were not significantly different. Independent if early or late reduction was used to reduce a trichorionic triplet pregnancy to dichorionic twins, the very low birth weight rate was around 71.4% [25] and between 68.5% to 89.1% [22,23,28] for early and late reductions, respectively. Moreover, the very low birth weight rates ranged between 18.9% and 26.5%, irrespective of the reduction method [22,23,25,28]. Our method does show marked improvement in the very low birth weight rate, independent if the reduction leads to either twins or singletons.

This study has a few limitations. First, we assessed trichorionic triplet pregnancies, and alternative formations of triplets or higher-order pregnancies still need to be evaluated. Removal of a monochorionic embryo in the presence of dichorionic embryos could yield similar result; however, Liu et al. demonstrated, using KCl as the method for multifetal pregnancy reduction, that reduction to singleton decreased the preterm delivery rate and the low birth rate with improvements in the average birth weight and gestation at delivery [6]. Second, this was a single-arm study in which no comparison to managed expectant treatment or KCl treatment was assessed; however, it is well documented the outcomes of these treatments with triplet pregnancies. Nevertheless, a well-designed randomized clinical trial would solidify any concerns about the result's overall benefit when considering standard options for multifetal pregnancies. Third, the results here focused on triplet pregnancies reduced to twin pregnancies. This method allows the reabsorption of a single non-viable embryo. During this process, the mother's immune system activates, promoting the loss of the pregnancy. The more embryos removed does increase the immune response. Here, we only removed one embryo; therefore, any reduction higher than triplets trichorionic to twins could have more detrimental results. Fourth, technical preferences could affect the efficiency of the procedure as well as the assessed IVF outcomes. For example, here, we used a 17-gauge needle that could be associated with vascular injury, even though no evidence was observed with our cohort. Other clinicians may prefer to use a thinner bore needle to minimize the trauma to the area as well as for easier manipulation. Another preference could be the use of general anesthesia, which does increase the cost of the procedure. Our reasons were to minimize the trauma and awareness of the procedure. Nevertheless, it is possible to perform this procedure under local anesthesia. Lastly, with any early reduction technique, the identification of structural malformations due to aneuploidies may be missed. However, implementing preimplantation genetic testing for aneuploidies would minimize this concern.

In conclusion, we demonstrated that an intracardiac needle obliteration procedure, a non-chemical-based method, can successfully reduce multifetal pregnancy to twins, allowing improved IVF outcomes. The technique is rapid and straightforward, with the retention of more than 95% of the pregnancies with minimal complications.

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Conflict of Interest

Authors declare no conflict of interest.

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