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Keywords
reduction, triplet pregnancy, expectant

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Material and methods

Clinical data from 24 women with triplet pregnancies were retrospectively collected and analyzed. Twelve women underwent fetal reduction (fetal reduction group) and 12 women continued triplet pregnancy (non-fetal reduction group). In the fetal reduction group, four dichorionic triamniotic triplets were reduced to dichorionic diamniotic twins (with a reduction of one of the monochorionic diamniotic fetuses); six trichorionic triamniotic triplets were reduced to dichorionic diamniotic twins (with a reduction of one monochorionic monoamniotic fetus).

Results

There were significant differences in the incidence of premature rupture of membranes and neonatal hypoglycemia between the reduction and non-reduction groups. The average birth weight was significantly different between the reduction group and non-reduction group. The Apgar score was significantly different between the monochorionic monoamniotic reduction group and monochorionic diamniotic reduction group.

Conclusions

Triplet pregnancy should be closely monitored throughout pregnancy and the perinatal period, regardless of fetal reduction. The chorionicity should be considered with fetal reduction. Compared with the mother, the remaining fetuses may benefit more from fetal reduction, especially in terms of neonatal weight.

Maternal and fetal benefits of fetal reduction in triplet pregnancies

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Disclosure of conflict of interest

None.

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Introduction

The incidence of triplet pregnancy is increasing, partially due to the development of assisted reproductive technology (ART). Compared with singleton pregnancy, multiple pregnancy is associated with higher risks of complications, including gestational hypertension, intrahepatic cholestasis of pregnancy, and preterm birth [1, 2]. Triplet pregnancies are associated with more complications than singleton pregnancies, including low birth weight [2-4]. Although fetal reduction (FR) has been widely recommended as it improves maternal and neonatal outcomes [1], some triplet pregnancies proceed without reduction due to a variety of factors, including late diagnosed pregnancies or the patient's wishes. One unresolved issue is how to optimize the triplet pregnancy outcome with or without fetal reduction. Therefore, this study was conducted to examine the prognosis of triplet pregnancy and reduction. The study population consisted of 24 women with triplet pregnancies who were divided into fetal reduction and non-fetal reduction groups. The objective was to explore the specific benefits and risks of fetal reduction and the possible adverse effects of continued triplet pregnancies.

Materials and methods

A retrospective analysis was performed using clinical data on pregnant woman treated at our hospital between January 2012 and June 2022. Ultrasound

signs were used as the diagnostic criteria for triplet pregnancy in the first trimester; a triplet pregnancy was diagnosed in cases with three individual fetal heartbeats in the uterus. The fetal reduction group consisted of 12 women who underwent fetal reduction, while the non-fetal reduction group consisted of 12 women who did not undergo fetal reduction due to their personal wishes. The reduction methods were potassium chloride injection into the fetal heart, radiofrequency ablation, ultrasound-guided embryo aspiration ultrasound, and transcranial fetal destruction. The study protocol was approved by the Medical Ethics Committee of the hospital. Informed consent was obtained from all patients before data collection. All procedures in studies involving human participants were performed in accordance with the ethical standards of the Institutional Research Committee, and with the Helsinki Declaration and its later amendments or comparable ethical standard.

Triplets can be classified according to chorionicity as monochorionic triamniotic triplets, dichorionic triamniotic triplets, and trichorionic triamniotictriplets. In the fetal reduction group, four cases of dichorionic triamniotic triplets (Figure 1) were reduced to dichorionic diamniotic twins (Figure 2) and included monochorionic diamniotic reduction. Six cases of trichorionic triamniotic triplets were reduced to dichorionic diamniotic twins and included monochorionic monoamniotic reduction. Two cases of dichorionic triamniotic triplets were reduced to singleton pregnancies.

The statistical analysis was performed by SPSS 22.0 software, the measurement data were expressed as χ±s (rank sum test), and the count data were expressed as n (χ^2 test or Fisher's exact probability test). Statistical methods are listed after tables. $P < 0.05$ was considered as a statistically significant difference.

Results

First, general characteristics were compared between the fetal reduction group and the non-fetal reduction group. There were no statistically significant differences in age, mode of conception, parity, or chorionic maternal diseases between the two groups (Table 1).

Next, maternal outcomes were compared. There was a significant difference in the incidence of premature rupture of membranes, but no significant differences in the occurrence of preterm rate, gestational diabetes mellitus, left-sided heart failure, pulmonary edema, gestational hypertension, or thyroid dysfunction between the two groups (Table 2). There were no significant differences in the rate of pregnancy termination, incidence of intrauterine packing, transabdominal cervical cerclage, or postpartum hemorrhage between the two groups (Table 2).

The newborns in the two groups were compared. There were significant differences in birth weight, gestational age, and the incidence of neonatal

hypoglycemia between the two groups. There were no significant differences in the rates of thyroid dysfunction, premature anemia, or respiratory disease, or in Apgar score between the two groups (Table 3).

We compared maternal complications and neonatal conditions under different chorionic and amniotic conditions. The fetal reduction group consisted of dichorionic triamniotic triplet pregnancies and trichorionic triamniotic triplet pregnancies. Four dichorionic triamniotic triplet pregnancies were reduced to dichorionic diamniotic twins. One of the parturients underwent reduction of one of the twins at delivery. One of the four parturients did not deliver any live infants. Two cases of dichorionic triamniotic triplets were reduced to singletons. Six trichorionic triamniotic triplet pregnancies were reduced to dichorionic diamniotic twins. One of the six parturients did not deliver any live infants. There were significant differences in the Apgar score at 1 min, incidence of thyroid dysfunction, and neurological conditions between cases with monochorionic diamniotic reduction and monochorionic monoamniotic reduction (Table 4). There was a significant difference in the incidence of fetal malformation but no significant difference in the rate of perioperative complications between the two groups (Table 5). In the fetal reduction group, the reduction was performed from 9 to 17 weeks, and reduction was performed at delivery in one case.

Discussion

This study shows that fetal reduction in triplet pregnancy can improve both maternal and neonatal outcomes, especially with regard to gestational age and birth weight. However, it may lead to premature rupture of membranes. It is necessary to carefully balance the benefits and risks of reducing one of the monochorionic diamniotic fetuses. Reduction can eliminate twin-specific complications, but it may affect the co-twin's nervous system and thyroid function.

With the exception of premature rupture of membranes, there were no significant differences in other pregnancy complications between the fetal reduction group and non-fetal reduction group. This may have been related to the inflammation caused by retention of the dead fetus in the amniotic cavity and the invasive nature of the procedure. Similarly, previous studies have shown that radiofrequency ablation cannot reduce the rate of premature delivery and premature rupture of membranes in complicated monochorionic pregnancies [5-7]. These side effects are concerning. Premature rupture of the membranes is the main cause of premature delivery in multiple pregnancies. The risk of premature rupture of the membranes is directly related to the number of interventions, as well as advanced fetal surgery type and uterine incision size[8-10]. Obstetricians should choose appropriate instruments and be familiar with the procedure to reduce the operating time. It was reported that

multiple pregnancy is a risk factor for gestational diabetes mellitus and hypertension [1, 11, 12]. A meta-analysis [11] showed that 7.3–12.4% of pregnant women with triplets had gestational diabetes mellitus. Although gestational diabetes mellitus is associated with multiple pregnancy, it does not affect short-term pregnancy outcomes with appropriate treatment. It is necessary to be alert to the occurrence of gestational hypertension and gestational diabetes mellitus in triplet pregnancies. The incidence of thyroid dysfunction was also higher in triplet pregnancy, especially in the non-reduction group [13, 14]. Early detection of thyroid dysfunction and supplementation with levothyroxine in a timely manner are necessary for women at high risk to improve the fetal prognosis [14]. The incidence of fetal growth restriction was also higher in triplets, and there was no significant difference between the two groups in the present study. Severe fetal growth restriction may lead to preterm birth, neonatal mortality, and increased neonatal morbidity (including hypoglycemia, hyperbilirubinemia, hypothermia, neonatal necrotizing colitis, respiratory diseases, and cerebral hemorrhage)[7, 15]. Two women in the reduction group did not have live births. The miscarriage rate in our study was higher than that in a previous study of 124 mothers [16], which reported a surgery-related abortion rate of 0.8% and a neonatal mortality rate of 0.8%.

The most serious intrapartum complication, threatened uterine rupture, occurred in the non-reduction group in a patient with a previous cesarean delivery. Multiple pregnancy is a risk factor for postpartum bleeding, as it can lead to uterine inertia [17]. For this, transabdominal cervical cerclage and uterine tamponade were used in most patients, and no postpartum hemorrhage occurred in our cohort. Multiple pregnancies could benefit from positive hemostasis.

There were significant differences in birth weight, and no neonates were below 1000g in the fetal reduction group. The improvement in neonatal weight appeared to be one of the benefits of reduction for the fetus, consistent with the literature [18].The incidence of neonatal hypoglycemia was significantly different between the two groups. Twin pregnancy is a risk factor for neonatal hypoglycemia [19]. This study suggests that the incidence of neonatal hypoglycemia is higher in triplet pregnancy than in twin pregnancy. Glucose should be closely monitored in triplet pregnancies. There was a significant difference in gestational age between the two groups, suggesting that fetal reduction could prolong the gestational age and is also related to increased fetal weight. Some studies showed that fetal reduction can effectively prolong gestation and reduce the incidence of extreme preterm birth [20]. The surgery was an effective means to improve neonatal outcomes. The incidence of respiratory diseases in triplets is high regardless of fetal reduction. Although

the use of glucocorticoids in singleton pregnancy is well established, more evidence is needed to determine whether triplets can benefit from glucocorticoids [20, 21].

One study reported that early fetal reduction is better than late reduction [22]. In our study, a miscarriage occurred 14 weeks after reduction, suggesting that reduction is suitable in the early gestational stage. In another woman, a miscarriage followed vaginal bleeding that occurred after fetal reduction at 9 weeks. This may have been related to a deficiency of the embryo.

The effect of the reduction was closely associated with the surgical program. Chorionicity was an important factor. The Apgar score of neonates in the monochorionic monoamniotic reduction group were higher than those in the monochorionic diamniotic reduction group, and the incidences of neurological conditions and thyroid dysfunction were lower in the monochorionic monoamniotic reduction group. The prognosis was better in the monochorionic monoamniotic reduction group than in the monochorionic diamniotic reduction group, and monochorionic monoamniotic reduction was recommended [23]. As two fetuses share a placenta in monochorionic multiple pregnancies, the co-twin may bleed into the stillbirth after reduction[24] resulting in higher rates of co-twin loss and neurological disease[25]. In addition to these risks, this study shows that twin fetuses may suffer from abnormal thyroid function. To improve the prognosis of such neonates, it is necessary to pay more attention

to therapy and postoperative evaluation. An ultrasound examination should be performed to evaluate fetal hemodynamics and fetal magnetic resonance imaging[26] should be used to evaluate the nervous system if necessary after fetal reduction. Care is also required regarding thyroid function. The pediatrician should evaluate the baby immediately after birth in cases of abnormal thyroid function. It appears that obstetricians can more easily reduce a monochorionic monoamniotic fetus. However, in complex clinical practice, reducing one of the monochorionic diamniotic twins should be considered. Monochorionic diamniotic pregnancy is a high-risk type of pregnancy due to the incidence of twin transfusion syndrome, twin anemic polycythemia sequence, and other specific complications[27]. Such complications could be effectively avoided by reduction of one of the twins. As fetal reduction is mostly performed in the first trimester, the choice of the reduced fetus was made blindly. The genetic material of the remaining twins differs in the case of reduction of one of the monochorionic diamniotic twins, which is more likely to result in at least one healthy fetus. In addition to chorionicity, the number of remaining fetuses has an impact on the effect of surgery. Compared with reduction to twins, a singleton pregnancy has a better survival rate[18, 28]. Decision making should take into account the greatest benefit for patients by comprehensively evaluating the risks of reduction and condition of obstetrics and neonatology, as well as the skill of the surgical team [29].

This study had some limitations. The number of cases was too small to obtain definitive results. Additional studies with larger sample sizes and multicenter research are required. Due to the limitation of the case number, no definitive conclusions could be drawn regarding the influence of fetal reduction methods and timing, which require further analysis in larger samples. Recall bias represents an additional limitation of the study, which must be addressed for generalization of the results.

In general, fetal reduction may reduce the risk of maternal complications, such as gestational diabetes mellitus and gestational hypertension; it may prolong gestational age and increase fetal weight. However, the risk mainly includes the occurrence of premature rupture of the membranes and its possible effects on the nervous system and thyroid functioning; further research is needed to explore this risk.

Conclusion

Fetal reduction can improve both the maternal prognosis and fetal prognosis. The risk of monochorionic diamniotic fetus reduction is higher, so it is necessary to carefully balance the risks and benefits of reduction in triplet pregnancies and perform careful monitoring throughout pregnancy.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Table 1 General information

	Non-fetal reduction group (N=12)	Fetal reduction group (N=12)	P
Age (years)	31.17±5.83	30.42±6.08	0.761
Gravida	1.91±0.94	1.75±1.21	0.731
Parity	1.18±0.40	1.33±0.65	0.515
Chorionicity			0.640
Monochorionic	1 (8.3%)	0	
Dichorionic	9 (75.0%)	8 (66.7%)	
Trichorionic	2 (16.7%)	4 (33.3%)	
Education level (higher than junior high or middle school)	7 (58.3%)	10 (83.3%)	0.155*
Polycystic ovary syndrome	2 (16.7%)	4 (33.3%)	0.640*
Assisted reproductive technology	8 (66.7%)	8 (66.7%)	1.000*

*Fisher's exact probability test

Table 2. Pregnancy Complications and perioperative situation

	Non-fetal reduction group (N=12)	Fetal reduction group (N=12)	P*
Preterm (<32weeks)	2 (16.7%)	3 (25.0%)	0.611
Preterm (<34weeks)	7 (58.3%)	3 (25.0%)	0.387
Preterm (<37weeks)	12 (100.0%)	9 (75.0%)	0.217
Gestational diabetes mellitus	3 (25.0%)	3 (25.0%)	1.000
Gestational hypertension	4 (33.3%)	2 (16.7%)	0.640
Left-sided heart failure	1 (8.3%)	1 (8.3%)	1.000
Pulmonary edema	1 (8.3%)	1 (8.3%)	1.000
Hyperlipidemia	1 (8.3%)	2 (16.7%)	1.000
Intrauterine fetal distress	2 (16.7%)	0	0.478
Fetal growth restriction	3 (25.0%)	2 (16.7%)	1.000
Thyroid dysfunction	5 (41.6%)	2 (16.7%)	0.155
Abnormal fetal umbilical blood flow	1 (8.3%)	0	1.000
Fetal malformation	1 (8.3%)	3 (25.0%)	0.595
Anemia	3 (25.0%)	2 (16.7%)	1.000
Threatened uterine rupture	1 (8.3%)	0	1.000
Transabdominal cervical ring binding	5 (41.7%)	2 (16.7%)	0.155
Uterine tamponade	7 (58.3%)	4 (33.3%)	0.214
Premature rupture of membranes	0	6 (50.0%)	0.014
Sepsis	0	1 (8.3%)	1.000
Live-born infant	12 (100.0%)	10 (83.3%)	0.478
Postpartum hemorrhage	0	0	1.000

*Fisher's exact probability test

Table 3. Newborn complications

	Non-fetal reduction group (N=36)	Fetal reduction group (N=17)	P*
Neonatal hypoglycemia	11 (30.6%)	0	0.010
Neonatal hyperglycemia	0	1 (8.3%)	0.320
Birth weight (g)	1596.11±491.24	2204.41±745.88	0.014
Gestational age (d)	229.50±20.44	243.41±20.65	0.030
Apgar score at 1 min	8.67±2.01	8.76±2.28	0.875
Apgar score at 5 min	9.67±0.53	9.35±1.41	0.387
Apgar score at 10 min	9.72±0.45	9.82±0.39	0.433
Congenital heart disease	1 (2.7%)	2 (11.8%)	0.238
Separation of duplicated collecting system	0	2 (11.8%)	0.099
Thyroid dysfunction	7 (19.4%)	3 (17.6%)	1.000
Rickets	3(8.3%)	0	0.543
Premature anemia	2 (5.6%)	2 (11.8%)	0.585
Myocardial ischemia	1 (2.8%)	0	1.000
Neonatal hemolysis	5 (13.9%)	1 (5.9%)	0.651
Retinopathy of premature infants	1 (2.8%)	0	1.000
Preterm severe metabolic bone disease	3 (8.3%)	0	0.543
Neonatal hemolyticdisease	4 (11.1%)	10 (58.8%)	< 0.005
Respiratory disease (neonatal respiratory distress syndrome, neonatal wet lung, assisted ventilation, neonatal asphyxia, bronchial pulmonary hypoplasia)	15 (41.6%)	6 (35.3%)	0.768
Digestive disease (gastrointestinal bleeding, neonatal necrotizing enterocolitis, allergic microenteritis)	1 (2.8%)	2 (11.8%)	0.238
Neurological conditions (abnormal electroencephalogram, neonatal intracranial hemorrhage, subependymal cyst)	3 (5.6%)	3 (17.6%)	0.372

*Fisher's exact probability test or rank sum test

Table 4 Chorionicity and neonatal complications

	Monochorionic monoamniotic reduction group (N=10)	Monochorionic diamniotic reduction group** (N=5)	P***
Neonatal hyperglycemia	0	1 (20.0%)	0.333
Neonate birth weight (g)	2106.00±458.09	1783.00±530.40	0.206
Gestation age (d)	246.40±14.49	225.00±17.13	0.075
Apgar score at 1 min	9.90±0.37	6.00±2.64	0.013
Apgar score at 5 min	10.00*	7.80±1.92	-
Apgar score at 10 min	10.00*	9.40±0.55	-
Congenital heart disease	2 (20.0%)	0	0.429
Separation of duplicated collecting system	2 (20.0%)	0	0.429
Thyroid dysfunction	0	3 (60.0%)	0.022
Sepsis	2	2 (40.0%)	0.560
Neonatal hemolysis	0	1 (20.0%)	0.333
Neonatal hemolytic disease	5 (50.0%)	4 (80.0%)	1.000
Respiratory disease (neonatal respiratory distress syndrome, neonatal wet lung, assisted ventilation, neonatal asphyxia, bronchial pulmonary hypoplasia)	2 (20.0%)	4 (80.0%)	0.089
Digestive disease (gastrointestinal bleeding, neonatal necrotizing enterocolitis, allergic microenteritis)	0	2 (40.0%)	0.095
Neurological conditions (abnormal electroencephalogram, neonatal intracranial hemorrhage, subependymal cyst)	0	3 (60.0%)	0.022

* The Apgar scores were 10 in all cases.

** One of the parturients underwent reduction of one of the twins at delivery.

***Fisher's exact probability test or rank sum test

Table 5. Chorionicity and pregnancy complications

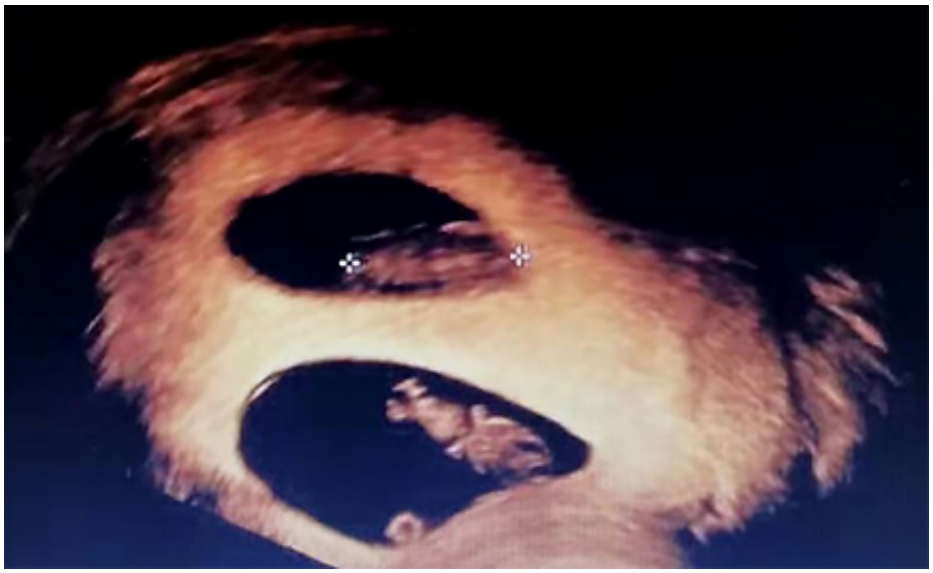
	Monochorionic monoamniotic reduction group (N=6)	Monochorionic diamniotic reduction group (N=4)	P*
Gestational diabetes mellitus	1 (16.7%)	1 (25.0%)	1.000
Pregnancy-induced hypertension	2 (33.3%)	0	0.467
Left-sided heart failure	0	1 (25.0%)	0.400
Pulmonary edema	0	1 (25.0%)	0.400
Hyperlipidemia	1	1 (25.0%)	1.000
Fetal growth restriction	2 (33.3%)	0	0.467
Thyroid dysfunction	1 (16.7%)	1 (25.0%)	1.000
Sepsis	1 (16.7%)	0	1.000
Fetal malformation	0	3 (75.0%)	0.033
Anemia	2 (33.3%)	1 (25.0%)	1.000
Premature rupture of membranes	4 (66.7%)	2 (50.0%)	1.000
Transabdominal cervical cerclage	0	2 (50.0%)	0.133
Uterine tamponade	1 (16.7%)	3 (75.0%)	0.190
Live-born infant	5 (83.3%)	3 (75.0%)	1.000

*Fisher's exact probability test

Figure Legends

Figure 1. A patient from the fetal reduction group before fetal reduction. Dichorionic triamniotic triplet pregnancy.

Figure 2. A patient from the fetal reduction group after fetal reduction. Dichorionic diamniotic twin pregnancy. ARSA, vagus right subclavian artery; LSA, left subclavian artery; DAO, descending aorta.



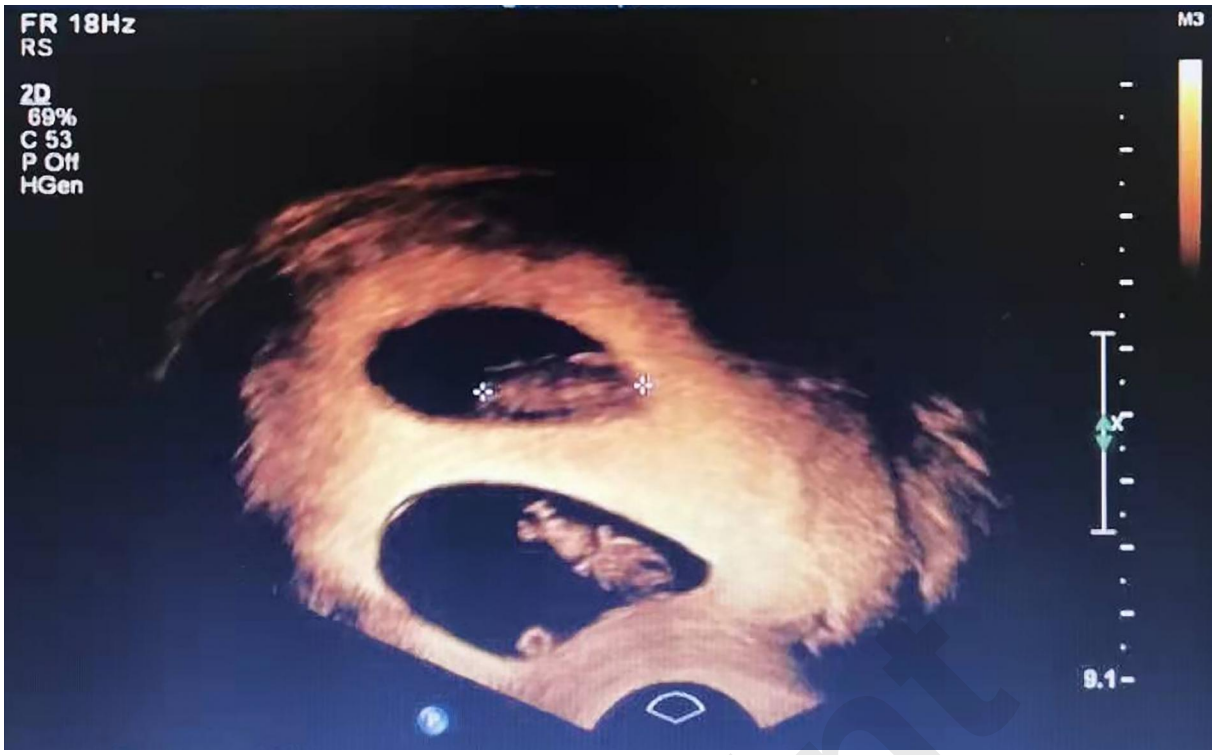


Figure 1. A patient from the fetal reduction group before fetal reduction. Dichorionic triamniotic triplet pregnancy

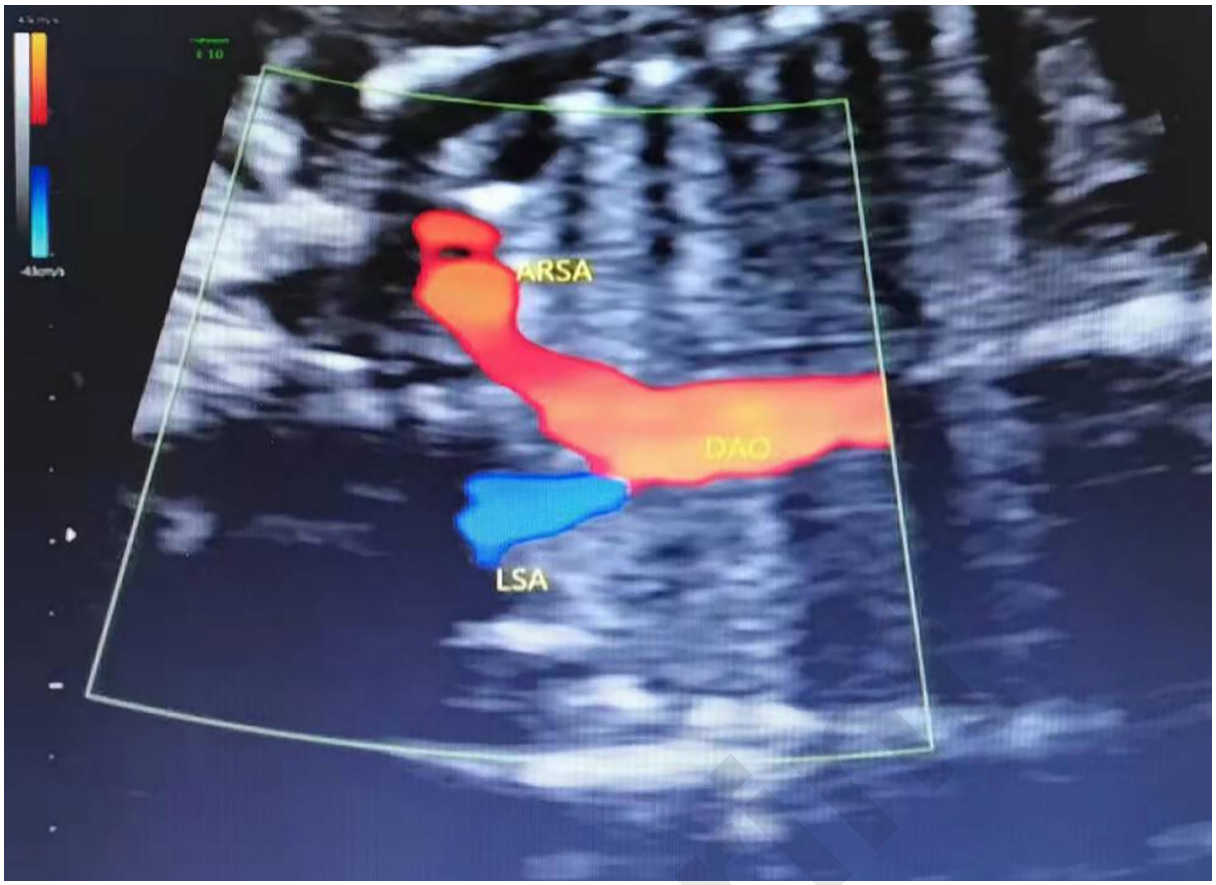


Figure 2. A patient from the fetal reduction group after fetal reduction. Dichorionic diamniotic twin pregnancy. ARSA, vagus right subclavian artery; LSA, left subclavian artery; DAO, descending aorta