



Original Article

Pregnancy and birth outcomes of multiple gestations with PPROM occurred within 24 h after fetal reduction: A case series

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ABSTRACT

Objective: The study aims to analyze the pregnancy outcomes of multiple gestations with preterm premature rupture of membranes (PPROM) that occurred within 24 h after fetal reduction with potassium chloride (KCL).**Materials and methods:** We identified and evaluated the outcomes of 16 retrospectively recorded multigestational pregnancies that met the inclusion criteria between 2006 and 2016, from the Obstetrics Department of Shandong Provincial Hospital. A total of 16 patients carrying twins or higher order multiple gestations experienced PPROM within 24 h after fetal reduction, and all of them received expectant management after understanding the relevant risks. The maternal and neonatal records were retrospectively collected and reviewed. Every surviving child was followed up to at least 2 years old.**Result:** Of the 16 cases, 12 cases (75%) ended in successful pregnancy, resulting in the delivery of at least 1 child surviving from a multiple gestational pregnancy. All cases of successful pregnancies were either term (≥ 37 weeks) or near-term (36^{+5} weeks) at delivery. And of those 20 infants delivered, only 3 were low birth weight infants (< 2500 g) (15%). None of the 16 women had fever, or other clinical symptoms and signs of chorioamnionitis during hospital stay. Postnatal follow-up of the surviving babies showed no obvious sequelae thus far. No newborn baby had neonatal complications, or needed to be transferred to neonatal intensive care unit.**Conclusion:** Overall, our data demonstrate that dichorionic diamniotic (DCDA) twins or higher-order gestations who experienced PPROM of the reduced fetus within 24 h after selective reduction with KCL had relatively good outcomes with expectant management alone.© 2020 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The incidence of multiple gestations or high-order pregnancies has risen drastically over the past few decades, due to the advancement and increased availability and popularity of assisted

reproductive technologies [1–3]. Triplets or higher-order multiple gestations pose considerably greater risks for both the women and the fetuses compared to twins or singleton pregnancies [4]. According to past literature, there is a direct correlation between starting number of multiple gestation and pregnancy loss rate. Aside from pregnancy loss, other adverse pregnancy outcomes including premature birth, fetal growth restriction, and neonatal morbidity and mortality are all significantly reduced in multiple pregnancies after fetal reduction [5,6]. Consequently, the number of fetal reductions performed on multiple gestation also increased, as there appears to be dramatic survival benefit noted in reduction from higher initial starting number of fetuses in multigestational pregnancies [7]. The pregnancy loss rate for triplet-to-twin reductions is about 4.4%, and the pregnancy loss rate for quadruplet-to-twin reductions is about 6.6%. With increasing experience and improved quality of ultrasonography, some data suggest that the

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outcome of these reduced pregnancies have now improved even further [5]. The pregnancy loss rates of triplet-to-twin reduction have become closer to those of unreduced twin gestations, at about 3.6% [5]. However, there is little literature focusing on the pregnancy outcome of multiple gestations experiencing PROM within 24 h following reduction. It has been reported more than once that PPROM in the second trimester can associate with severe perinatal and neonatal morbidity such as fetal death, preterm birth and complications related to prematurity i.e. hypoplastic lungs, and infection [8–12]. Neonatal outcomes of multifetal gestations with early PPROM (<26 weeks) are largely unsatisfactory [13]. Several studies suggest that therapeutic selective fetocide of the dichorionic twin fetus with spontaneous PROM in second trimester may help stop amniotic leakage, facilitate cervical closure, and significantly increase the gestational age at delivery and the outcome of its co-twin [4,14–16]. However, few studies focus on iatrogenic cause of PPROM, or PPROM as a main complication of fetal reduction and its optimal management. This study aims to analyze the pregnancy outcomes of multiple gestational pregnancies that received fetal reduction, with a focus on the outcome of PPROM cases under expectant management.

Materials and methods

Data were collected retrospectively from the Obstetrics Department of Shandong Provincial Hospital from 2006 to 2016. Information regarding postnatal outcomes were obtained from the neonatal and pediatrics database. All cases included for the study met all of the following inclusion criteria: 1) patients carrying DCDA twins or higher-order gestations who received selective fetal reduction with KCL in Obstetrics of Shandong Provincial Hospital from 2006 to 2016; 2) PROM occurred to the reduced sac(s) within 24 h following fetal reduction. Of 517 cases that received fetal reduction with KCL during this study period, 16 cases met the above criteria. The gestational age of these patients when receiving reduction ranged from 11⁺⁶ to 16⁺⁵ weeks, and the mean gestational age was 13.7 weeks. Gestational age was calculated based on the first day of last menstrual period for spontaneous pregnancies, as well as days from corrected ovulation day for ovulation induction and in vitro fertilization. The baseline characteristics of these patients are shown in Table 1. The majority, 14 women conceived

under ovulation induction treatment and in vitro fertilization, while 2 women conceived spontaneously. As for indications for fetal reduction, one case was found to have fetal lymphatic cyst (Table 1, case n. 16), and the remaining 15 cases received the procedure in order to lower their obstetrical risks.

Comprehensive consultations were provided to all patients before the reduction procedure, including intraoperative risks, such as amniotic fluid embolism, placental abruption, and puncture failure, and postoperative risks, such as miscarriage, premature delivery, PROM, and chorioamnionitis.

The reduction procedure was performed via transabdominal ultrasound-guided intracardiac injection of 2–5 ml 10% KCL using a 23G PTC needle.

The diagnosis of PROM was confirmed by several methods. 1) Clear visualization of clear fluid in the vaginal vault or a steady outflow of fluid noted from the cervical canal. 2) A significant decrease in amniotic fluid index measured by ultrasound in one sac. The subsidiary confirmation methods used included a positive pH dipstick test for vaginal fluid that turned alkaline, or the detection of fern crystallization from the fluid in posterior vaginal fornix.

When the diagnosis of PPROM was confirmed, we explained the possible benefits and potential risks of conservative or expectant management. The choice of termination of pregnancy is also provided as alternative option to the patients. All 16 patients and their families expressed their desires to continue pregnancies. Clinical observation such as uterine contraction and vaginal bleeding was performed by hospital staffs. Maternal body temperature, white blood cell count, neutrophil count and c-reactive protein (CRP), procalcitonin (PCT) were also monitored for signs of chorioamnionitis during the hospitalization period. Oral antibiotics and intramuscular progesterone injection (≤ 12 weeks, 40 mg IM QD) were administered for 3 days. The patients were typically hospitalized for 3 days after PPROM occurred, and would not be discharged until amniotic fluid ceased to flow out of vagina, and there were no signs of infection. Serial ultrasound scans were arranged to assess fetal growth and amniotic fluid index of remaining fetuses. Fetal anomalies, if any, were detected during routine prenatal visits. The placenta from all of the 16 cases were sent for pathological examination.

The surviving children were followed up to at least 2 years old, and their neonatal records retrospectively collected. Data collected

Table 1
Clinical characteristics of 16 cases complicated by PROM after fetal reduction.

Case no.	Mater-nal age	No. of fetuses prior to reduction	No. of fetuses after reduction	Gest. age at reduction	No. of needles punctured	No. of kids survived	Leukocyte (*10 ⁹ /l) before/after ^a	Neutrophil (*10 ⁹ /l) before/after ^a	ROM of upper/lower fetus	Gest. age at delivery
1'	34	QCQA	DCDA	15 ⁺³	1/1	2	8.1/9.2	65.4/71.3	upper	37 ⁺³
2	27	TCTA	DCDA	11 ⁺⁶	3	2	6.8/7.3	70.2/74.8	upper	37 ⁺²
3'	27	QCQA	DCDA	13 ⁺⁵	3/2	0	7.4/7.5	74.2/73.5	upper	18 ⁺³
4	31	TCTA	DCDA	13	1	2	8.5/9.7	76/78.3	lower	37 ⁺⁴
5	22	TCTA	DCDA	16 ⁺⁵	2	0	10.3/11.2	71.2/75.6	upper	24 ⁺⁶
6	32	TCTA	DCDA	13	3	2	9.7/8.4	70.2/74.6	upper	37
7'	33	DCTA	singleton	12 ⁺¹	3	1	8.4/8.7	68.4/73.9	upper	38 ⁺⁶
8	32	TCTA	DCDA	12	2	2	9.1/9.3	69.8/73.8	upper	37 ⁺⁵
9'	29	TCQA	DCDA	12 ⁺⁵	1	2	9.3/10.1	74.8/81.3	lower	36 ⁺⁵
10	31	TCTA	DCDA	14 ⁺⁴	1	2	8.0/6.6	78/80.1	upper	38 ⁺⁴
11	26	TCTA	DCDA	13 ⁺¹	3	0	9.4/8.8	71.3/76.8	lower	23 ⁺³
12'	37	DCTA	singleton	12 ⁺⁶	2	1	8.5/7.5	80/83	upper	40 ⁺²
13	27	TCTA	singleton	15 ⁺¹	1	2	12.3/12.9	69.9/79.6	upper	37 ⁺⁶
14	41	DCDA	singleton	13 ⁺⁴	1	1	6.3/8.1	77.0/83.4	lower	38 ⁺⁴
15	38	DCDA	singleton	13 ⁺⁶	2	1	11.9/13.2	73.4/80.1	lower	38 ⁺⁵
16	26	DCDA	singleton	15 ⁺¹	3	0	8.8/8.6	71.3/70.5	lower	18 ⁺²

Case 1', 3', 7', 9', 12' were reduced 2 fetuses. Among them, case 7', 9', 12' were reduced monochorionic twin pair.

Case 3, 5, 11, 16 ended in failed pregnancies: PROM occurred to the retained fetus in case 3, 5, 16; placental abruption occurred to the retained fetus in case n.11.

For case 1 and case 3, there were two fetuses that were injected with KCL for each case, so each case had two numbers of needles punctured.

^a Before: one day before reduction; after: several hours after the PROM.

from the pregnancies included parity, chorionicity, mode of pregnancy, gestational age at reduction, ultrasound assessment, gestational age at delivery, neonatal birth weight and other neonatal outcomes.

Results

In this study, a total of 16 cases were included, whose reduced fetuses experienced PPROM within 24 h after selective reduction. There were 3 cases of DCDA twins, 8 cases of trichorionic triamniotic (TCTA) triplets, 2 cases of dichorionic triamniotic (DCTA) triplets, 2 cases of quadrichorionic quadriamniotic (QCQA) quadruplets, and 1 case of trichorionic quadriamniotic (TCQA) quadruplets. There were 5 cases (case 1, 3, 7, 9, 12) that were reduced 2 fetuses. Among them, 3 cases (case 7, 9, 12) were reduced monochorionic twin pair. The other cases were reduced one fetus. So, 11 cases (case 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 13) became DCDA twins after reduction, and 5 cases (case 7, 12, 14, 15, 16) became singletons after reduction. All of the 16 patients chose expectant management after understanding the relevant risks.

Twelve out of 16 cases (75%) ended in successful pregnancies, delivered at full-term or near-term (36^{+5} weeks, 1 case). The mean gestational age at delivery was 38.1w (SD, 1.0w) for the 12 cases. And of the 20 newborns, only 3 (18.9%) were deemed low birth weight infants (<2500 g) (15%). None of the newborns was considered to be very low birth weight (<1500 g). The live birth rate, or take-home baby rate was 20 out of 27, or 74.5%. The mean neonatal birth weight was 2739.5g (SD, 382.4g) for these 12 cases. The 20 surviving babies from the 16 women had fair neonatal outcomes, showing no signs of respiratory distress at birth. None of the babies required to be transferred to neonatal intensive care unit. Every surviving child was followed up at least two years after birth, with no obvious sequelae noted.

The pregnancy loss rate for these 16 cases was 25%. As for the cases of miscarriage, 1 case (case 16) accepted DCDA-to-singleton reduction; 2 cases (case 5, 11) accepted TCTA-to-DCDA reduction; 1 case (case 3) accepted QCQA-to-DCDA reduction.

The failed pregnancies included one DCDA twins (case 16), two TCTA triplets (case 5, 11), and one QCQA quadruplets (case 3). The gestational age for cases of failed pregnancies at delivery ranged from 18^{+2} to 24^{+6} weeks. In case n.11, aside from PROM, placental abruption also occurred to the retained fetus at 23^{+3} weeks. None of the 16 cases had fever or other clinical symptoms signs of chorioamnionitis during the observation period at the hospital. In all cases, the amniotic fluid leakage gradually ceased after PPROM, and the infection markers did not rise after PPROM. None of the pregnancies were complicated with hypertensive disorder, preeclampsia, gestational diabetes, or cervical insufficiency. The pathological examination of placenta showed no signs of inflammation.

Discussion

PPROM, its cause and management

PPROM before or at the age of viability may occur spontaneously or during/after an invasive procedure such as amniocentesis, selective fetal reduction, or fetal surgery, when the fetal membranes need to be iatrogenically breached. Other risk factors for PPROM are similar to those of preterm labor, which include prior history of preterm labor, cervical insufficiency, antepartum hemorrhage or multiple gestations. Previous studies suggested that due to the avascular nature of fetal membranes, they may be particularly vulnerable to the local effects of inflammatory reactions or intrauterine infection [17]. However, none of the 16 cases had fever or other clinical symptoms and signs of chorioamnionitis during the

observation period after reduction. And the infection markers remained within normal range after PPROM. Although placental microbiology was not studied, pathological examination of the placenta did not show inflammation or aberrant trophoblastic development, a pathology suggestive of preeclampsia in the late first trimester [18]. On the other hand, an invasive procedure such as diagnostic amniocentesis is also known to be associated with PPROM, which complicates approximately 1–2% of the cases undergoing such procedures [19]. Previous literature also reported high rate of early PPROM following multifetal reduction procedure, especially in high order pregnancies (13.3% for triplet reducing to twins, and 19.3% for quadruplet reducing to twins) [20]. However, compared to the PROM rate, the reported pregnancy loss rate for multifetal reduction procedure is significantly lower, ranging from 3.2 to 6% [20]. Of the 517 cases of multiple gestational pregnancies that received fetal reduction during the study period at our hospital, only 16 patient (3%) experienced PPROM in the reduced fetuses. The pregnancy loss rate was low as 0.77% overall. The low PROM and pregnancy loss rate in our hospital could be due to improvement in ultrasonography image resolution in recent decades, as well as the procedure being performed by experienced practitioners. The cause of PROM in the reduced fetus after reduction might be largely procedure-related, as there were no evidence of infection or maternal vascular malperfusion lesions.

Past studies have shown that in contrast to spontaneous PROM before or at the limit of viability, amniotic fluid leakage shortly after amniocentesis or procedure-related PROM tend to result in significantly better perinatal outcomes with expectant management alone [19]. Cessation of leakage is thought to be associated with changes in the decidua and myometrium that block further leakage, creating a “resealing” effect [21]. The relatively small, focal nature of iatrogenic membrane disruption, usually distal to cervix, results in higher resealing or fluid reaccumulation rate within 1 week [21]. Expectant management is usually considered in such cases, with good pregnancy and prenatal outcome. The reported perinatal survival rate as high as 91% [19]. The conservative or expectant management is in agreement with our results, which showed take-home baby rate of 74.5% and good neonatal outcomes for multiple gestational pregnancies complicated with PPROM after fetal reduction.

Analysis of the cases that ended in failed pregnancies

We also suspect that the intrauterine location of the reduced fetus play a role in the outcomes of some of these cases. In our study, 10 of the cases had their reduced fetuses in the upper sacs, and 8 of them (80%) had successful pregnancies. In 6 cases, the reduced fetuses were in the lower sac, and only 4 (66.7%) of them had successful pregnancies. Although the number of failed pregnancies was higher in cases with reduced fetus in the lower sac, the case number is too few to discern any obvious trend.

Secondly, sometimes it may require more than one puncture per sac for each fetal reduction procedure. The number of puncture may play a role in the resultant PPROM in some of the cases. One of the failed pregnancies, a QCQA quadruplets (case n.3), had to have 3 puncture for one of the fetus, and 2 puncture for another fetus, before completion of reduction to twins. For these 16 PROM cases, 5 cases (31.2%) only required one needle puncture, 4 cases (25%) had to be punctured twice, and 5 cases (31.2%) had to be punctured three times (Table 1). Among patients of multiple pregnancies who did not experience PROM after KCL fetal reduction in our hospital, 345 out of 501 cases (68.8%) received only one needle puncture, 47 cases (9.3%) received two punctures, and 13 cases (2.6%) received three punctures. As the number of PROM cases was too small, we could not make a statistical analysis. However, the higher number of puncture may have contributed to PPROM in our study.

Strengths and limitations

There were several strengths to our study. Firstly, there were three operators for the fetal reduction with KCL, and no significant difference was found in the pregnancy outcomes of the cases operated by the three operators (data is not shown). Also, we were able to follow every surviving child for a minimum of two years. The main limitation of the study is the small sample size. The 16 PPROM cases included high order gestations of mixed parity and chorionicity, and the detailed baseline patient characteristics were not compared. Inherent to the retrospective cohort study design, there might be presence of confounding bias. As this is single-center finding, the result may not be generalizable to other populations. Large-scale studies with long-term follow-ups are essential to determine the best management of these cases.

Conclusion

Overall, our results support conservative expectant management for women carrying DCDA twins or high-order multiple gestations whose reduced fetuses had PPROM within 24 h after selective reduction with KCL. Although more cases are needed to establish a clinical practice guideline, these data could still provide a basis for counseling and management should early PROM occurs after fetal reduction.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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