

Original Research

Amnioinfusion for the Management of Severe Oligohydramnios during the Second Trimester: A Retrospective Observational Study

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Abstract

Background: To evaluate the safety profiles and role of antepartum transabdominal amnioinfusion (TA) in detecting fetal anomalies in pregnant women with oligohydramnios during the second trimester. **Methods:** Pregnant women with a diagnosis of oligohydramnios at 16 0/7 to 27 0/7 weeks of gestation were evaluated at our center between June 2014 and April 2020. Data collected included maternal and fetal clinical characteristics, ultrasonographic or magnetic resonance imaging findings, chromosomal results, and perinatal mortality. Pregnancy outcomes and procedure-related complications were then analyzed. **Results:** The study analyzed 106 pregnant women with severe oligohydramnios, at a mean gestational age of 22⁺³ weeks. Out of these, 71 women received TA while the remaining 35 did not. Only two patients (2.82%) suffered adverse events of chorioamnionitis post-TA. Nineteen additional cases of fetal anomalies were detected following TA, leading to a significantly increased detection rate (24/71 vs 43/71, $p = 0.001$). Among the TA group, eight pregnancies without obvious fetal pathologies were delivered alive, and all newborns were discharged in good condition. **Conclusions:** TA is a safe and valuable procedure for pregnant women with severe oligohydramnios in the second trimester that improved the detection rate of fetal structural anomalies. TA may lead to favorable outcomes in pregnancies without obvious fetal pathologies.

Keywords: amnioinfusion; cordocentesis; oligohydramnios; prenatal diagnosis

1. Introduction

Oligohydramnios is a debilitating condition characterized by an amniotic fluid index of ≤ 5 cm or the deepest vertical pocket of ≤ 2 cm. It has been shown to be correlated with a series of perinatal morbidities at after 34 weeks of gestation, including low birth weight, fetal acidosis, limb deformities, pulmonary hypoplasia and respiratory distress syndrome [1]. The reported overall newborn survival rate was only 10.2% in those with severe oligohydramnios during the second trimester [2]. Oligohydramnios can be caused by a wide variety of etiologies, including preterm premature rupture of the membranes (PPROM) and conditions with reduced secretion of the amniotic fluid.

Managing oligohydramnios in the second trimester is often challenging. Previous reports have shown that antepartum transabdominal amnioinfusion (TA) may be of potential therapeutic utility for oligohydramnios by re-expanding the amniotic fluid volume [3]. Moreover, TA can enhance the quality of ultrasonographic images, leading to an increased diagnostic yield. Conversely, studies, predominantly in cases with PPRM, have reported that TA does not appear to improve neonatal outcomes and may be linked to potential complications, such as chorioamnionitis and placental abruption [4,5].

Accordingly, we present our experience with TA in managing patients with oligohydramnios in the second trimester for heterogeneous etiologies. The aim of the current study is to (1) evaluate the safety profiles of TA, (2) assess whether TA improves the detection rate of fetal anomalies.

2. Materials and Methods

2.1 Patients

Electronic medical records were retrospectively searched for cases of pregnant women with severe oligohydramnios in the second trimester seeking medical attention from June 2014 to April 2020 at the International Peace Maternity & Child Health Hospital (Shanghai, China). The protocol of this study was approved by the Ethics Committee of International Peace Maternity & Child Health Hospital. Informed consents were waived due to the retrospective nature of this analysis. Nonetheless, all patients were fully informed of the benefits and risks of the TA procedure (whether or not they received TA) and signed the informed consent form.

2.2 Inclusion and Exclusion Criteria

The study included adult pregnant women with severe oligohydramnios at 16 0/7 to 27 0/7 weeks of gesta-



tion as indicated by an amniotic fluid index ≤ 5 cm or deepest vertical pocket ≤ 2 cm. Patients with multiple pregnancies or those complicated by placental abruption or maternal fever were excluded from analysis. The diagnosis of PPRM was rendered by observation of vaginal pooling in conjunction with a positive insulin-like growth factor binding protein-1 test.

2.3 TA Procedure

TA was performed predominantly for re-expanding the amniotic fluid volume and/or the detection of fetal structural anomalies missed by initial ultrasonography. Following ultrasonographic detection of the deepest pocket of the amnion, cordocentesis was performed for chromosomal karyotype and chromosome microarray analysis. A 22 G \times 200 mm needle (GALLINI, Mantova, Italy) was then inserted into the amniotic cavity directly without pre-procedural local anesthesia, followed by gravity-fed infusion of pre-warmed (37 °C) lactated Ringer's solution (300–500 mL) under ultrasonographic guidance. The injection was terminated either once a single vertical pocket of 3 to 5 cm was obtained or upon the appearance of any adverse events (such as frequent uterine contraction, abdominal pain or vaginal pooling), after which detailed ultrasound scans of the fetus were performed immediately. The patients were followed weekly at the outpatient clinic where the amniotic fluid volume was measured and fetal structural abnormalities were screened using Doppler ultrasonography. Amnioinfusion was considered successful if the amniotic fluid index > 5 cm or the deepest vertical pocket was maintained at > 2 cm for a minimum of 48 hours. Once oligohydramnios recurred or persisted for one week, the TA procedure was repeated weekly.

2.4 Patient Management

All cases were monitored during the pre- and postpartum periods. Magnetic resonance imaging was performed to help identify potential etiologies for oligohydramnios except for patients with PPRM. Any adverse obstetric events, including vaginal bleeding, hypertensive disorders, or fetal distress, were carefully monitored and treated. Termination of pregnancy was considered for the TA group in the event of obvious structural abnormalities, appearance of chorioamnionitis or personal wishes. In the third trimester of pregnancy, the delivery mode was determined by obstetric indications. A pediatrician was present at the delivery and was responsible for recording neonatal clinical data. All newborns were admitted to the neonatal intensive care unit and received outpatient follow-up after discharge.

2.5 Statistical Analysis

Software SPSS (statistical package version 26, SPSS, Chicago, IL, USA) was used for statistical analysis. Data that included maternal and neonatal clinical characteris-

tics and postnatal conditions were collected for descriptive statistics. The independent student *t*-test or Chi-Square test were applied to analyze variables, as appropriate. A two-sided $p < 0.05$ indicated statistical significance.

3. Results

3.1 Overall Patient Characteristics

Data from a total of 106 cases of severe oligohydramnios in the second trimester were analyzed, including 71 cases that received TA and 35 cases without TA. Patient demographics and characteristics are presented in Table 1.

3.2 Etiologies for Severe Oligohydramnios

Underlying etiologies for severe oligohydramnios in the TA group were abnormalities of the kidneys ($n = 33$), PPRM ($n = 12$), and unknown ($n = 26$), respectively. By comparison, underlying etiologies for severe oligohydramnios in the no-TA group were urogenital malformations ($n = 20$), PPRM ($n = 3$) and unknown ($n = 12$). Overall, the fetal structural malformation rate was 68.86% (73/106 cases).

3.3 Adverse Events Associated with TA

After TA, only two patients (2.82%) suffered adverse events of chorioamnionitis as confirmed by clinical symptoms and pathologic examination of the placenta. No case of placental abruption, bleeding or death occurred.

3.4 Fetal Anomaly Detection Rate

In the TA group, initial ultrasonography pre-TA detected 24 cases (33.80%) of fetal anomalies. Notably, 19 additional cases of fetal anomalies were detected through improved visualization after amnioinfusion (24/71 vs 43/71, $p = 0.001$), including 12 by ultrasonography and seven by magnetic resonance imaging.

3.5 Pregnancy Outcomes

All patients in the no-TA group decided to terminate pregnancy. However, among the 71 cases with TA, eight neonates were successfully delivered (six in our hospital and two in other hospitals) with pregnancies prolonged up to 63–119 days. A total of 63 pregnant women in the TA group elected to terminate pregnancy for fetal structural anomalies ($n = 43$), PPRM ($n = 12$), post-TA chorioamnionitis ($n = 2$) and personal wishes ($n = 6$). Among the six live births at our hospital, four were delivered vaginally and four by cesarean section between 32⁺⁶ and 37⁺⁵ weeks. Indications for cesarean section were preeclampsia and previous cesarean section, respectively. The average birth weight was 1943.3 g and the Apgar scores at 1 minute and 5 minutes were 10 and 10, respectively. All newborns were admitted to the neonatal intensive care unit with an average hospital stay of 29 days. All babies were evaluated and discharged in good condition. Notably, there were no cases of neurologic or respiratory abnormalities during

Table 1. Demographics and characteristics of patients with severe oligohydramnios treated with or without transabdominal amnioinfusion.

| Characteristics | TA group (n = 71) | No-TA group (n = 35) | p value |
|---------------------------------------|-------------------|----------------------|---------|
| Maternal age (years) | 30.03 ± 4.36 | 29.29 ± 4.15 | 0.40 |
| Primipara (n, %) | 48 (67.61) | 23 (65.71) | 0.85 |
| Deepest vertical pocket (mm) | 9.86 ± 5.93 | 8.69 ± 5.92 | 0.34 |
| Gestation at presentation (weeks) | 22.68 ± 2.48 | 21.71 ± 3.30 | 0.13 |
| Chromosomal abnormalities (n, %) | 5 (7.04) | / | / |
| Malformation (n, %) | 43 (60.26) | 30 (85.71) | 0.009 |
| Premature rupture of membranes (n, %) | 12 (16.90) | 3 (8.57) | 0.25 |
| Termination of pregnancy (n, %) | 63 (88.73) | 35 (100.00) | 0.04 |

TA, transabdominal amnioinfusion.

Table 2. Detailed information of eight live births delivered from pregnant women with severe oligohydramnios treated with transabdominal amnioinfusion.

| Case No. | Number of TA | Gestational age at diagnosis (weeks) | Gestational age at delivery (weeks) | Birth weight (g) | Delivery indications | Delivery mode | Apgar score (1/5 minutes) | Hospital stay (days) |
|----------|--------------|--------------------------------------|-------------------------------------|------------------|----------------------|---------------|---------------------------|----------------------|
| 6 | 3 | 24 ⁺⁵ | 34 ⁺³ | 1400 | PPROM | VD | 10/10 | 58 |
| 14 | 1 | 24 | 37 ⁺⁵ | 2050 | PE | VD | 10/10 | 9 |
| 19 | 1 | 23 ⁺⁵ | 32 ⁺⁶ | 1310 | PPROM | VD | 10/10 | 44 |
| 20 | 1 | 23 ⁺⁶ | 38 | 2440 | / | VD | 10/10 | 5 |
| 26 | 2 | 24 | 37 ⁺⁵ | 2340 | PE | CS | 10/10 | 7 |
| 34 | 1 | 20 ⁺⁵ | 37 ⁺¹ | 2120 | PC | CS | 10/10 | 27 |

TA, transabdominal amnioinfusion; PPRM, preterm premature rupture of the membranes; PE, preeclampsia; PC, previous cesarean section; VD, vaginal delivery; CS, cesarean section. / indicates information unavailable.

Table 3. Detailed information for the five cases with abnormal karyotype and chromosomal microarray analysis results.

| Case No. | Imaging findings | Karyotype | Chromosomal microarray analysis |
|----------|---|-----------------------|---|
| 9 | Renal dysplasia; Aorta overriding; pulmonary stenosis | 46XN | 4p16.1(9,716,385–10,278,410) X3 VUS |
| 25 | Renal dysplasia | 46XN | 9p13.1p11.2(39,099,640–43,658,954) X3 VUS |
| 36 | Renal dysplasia | 46, XX(11)/46, XY(19) | 4p14(38,703,104–40,998,822) X3 VUS |
| 44 | Renal dysplasia | Not available | 8q13.3(71,947,511–72,220,009)*1 LP |
| 49 | None | 69, XXX | (1–22, X)*3 |

*denoted chromosome copy, (1–22, X)*3 means there are 3 copies of 1–22 and X chromosomes.

X, X chromosome; N, sex chromosome can be an X or Y; VUS, variant of uncertain significance; LP, likely pathogenic.

routine follow-up. The maternal and neonatal details are provided in Table 2.

3.6 Karyotype and Chromosomal Microarray Analysis Results

Of the 71 cases sampled from the TA group for karyotype and chromosomal microarray analysis, results were normal in 66 cases and abnormal in the remaining five. Table 3 provides a detailed description of the abnormal karyotype and chromosomal microarray analysis results for the five cases.

4. Discussion

Oligohydramnios can be found in idiopathic cases or in complicated pregnancies. Impaired regulatory mechanisms accompanied by fetal anomalies, PPRM, fetal

growth restriction and impaired placental function are the common etiologies for oligohydramnios [6]. Previous research has indicated that oligohydramnios complicates 32% of fetuses with severe urinary tract anomalies [7]. Similarly, the current study found that 68.87% of cases with severe oligohydramnios were complicated by fetal abnormalities. An additional 19 cases of fetal malformations were detected post-TA by ultrasonography or magnetic resonance imaging, suggesting that TA is a valuable procedure for severe oligohydramnios in the second trimester, enabling detection of fetal anomalies through detailed imaging examinations.

Our results support the notion that TA is a relatively safe procedure with limited complications, which is in line with the reports from Chhabra's [8] and Wenstrom's groups [9]. In a retrospective analysis of 313 TA procedures in 126

patients with oligohydramnios, Nagai *et al.* [10] found that fetal/maternal adverse events occurred in two cases and fetal adverse events requiring pregnancy termination in only seven cases. To minimize the risk of adverse events, all TA procedures should be performed by a multidisciplinary team of operators with extensive experience.

Amnioinfusion can be performed intrapartum or antepartum, as well as for diagnostic or therapeutic purposes [11]. In recent years, antepartum TA has been used primarily for prenatal diagnosis. Based on our analysis, we suggest that TA can enhance the detection of fetal anomalies through an ultrasonographic scan. Earlier studies demonstrated that diagnostic amnioinfusion helped improve the visualization rate of fetal structures from 51% to 77% [12]. Similarly, the detection rate of fetal anomalies significantly increased from 33.80% pre-TA to 60.56% post-TA in the current study. Moreover, magnetic resonance imaging has been demonstrated to improve diagnostic accuracy in certain abnormalities that are otherwise difficult to diagnose due to fetal position and oligohydramnios [13]. Of note, TA ensures better perinatal outcome by prolonging the duration of pregnancy. Several studies have been conducted where women who underwent a subsequent series of TA reached a higher gestational week with a lower rate of perinatal mortality [14,15].

Whether TA improves perinatal outcomes remains an open question as previous studies report conflicting results. For instance, Turhan *et al.* [16] and van Kempen *et al.* [17] both reported that TA in patients with oligohydramnios showed similar perinatal outcomes as those managed expectantly, whereas significant effects of TA on latency period and neonatal outcomes in pregnant women complicated with PPRM have also been reported [18,19]. In the present study, eight neonates were successfully delivered with pregnancies prolonged up to 63–119 days. In the eight cases of severe oligohydramnios with no obvious associated fetal anomalies, adequate amniotic fluid volume was achieved by repeated TA, thus reducing the incidence of pulmonary hypoplasia and increasing the latency of pregnancy. However, it should be noted that all the women in the no-TA group opted for pregnancy termination. Ideally, a control group of pregnant women with severe oligohydramnios who were managed conservatively would have provided the best comparison. However, due to the tolerability for abortion in China, obtaining such control group would be extremely difficult. Therefore, we believe that TA may be most effective in neonates without fetal structural anomalies.

We acknowledge that most previous studies examining the effectiveness of TA have been conducted in patients with oligohydramnios caused by PPRM. Porat *et al.* [20] suggest that the latency period from PROM to delivery increased, and the rate of pulmonary hypoplasia and neonatal death decreased after TA. Conversely, in a study with 58 cases of PROM, some researchers found no statistically

significant differences between weekly serial TA and no intervention [5]. The etiologies for oligohydramnios in the present study were heterogeneous and thus probably more representative. Nonetheless, the number of PPRM cases in the current study was small and all cases opted for pregnancy termination.

Pulmonary hypoplasia can be secondary to oligohydramnios in PPRM, in which the normal development of lungs is hindered by the lack of amniotic fluid and chronic compression. Moreover, the severity of pulmonary hypoplasia has been observed to be intimately associated with the timing of occurrence of oligohydramnios [21]. Several prior studies [22,23] reported that fetoscopic endoluminal tracheal occlusion, an experimental prenatal procedure that reversibly block the trachea of the fetus, may improve lung development and increased neonatal outcomes in PPRM before 22 weeks of gestation. Regrettably, this procedure is still in its infancy in China and it requires stringent protocols and extensive experience.

Undoubtedly, additional large, randomized controlled trials are necessary to investigate the benefits of therapeutic TA. However, there are inherent difficulties in designing such studies predominantly due to the ethical and practical difficulties in obtaining the control group. Despite all these, our preliminary experience demonstrates that TA is technically feasible and safe. We believe that more informative decisions could be made following TA that provides enhanced visualization of fetal structures. In the future, such large-scale studies may help establish guidelines for managing oligohydramnios in the second trimester.

5. Conclusions

In summary, this study showed that TA demonstrates promise in increasing the diagnostic efficiency and enhancing the probability of fetal survival. Given the retrospective nature of this analysis, larger prospective multi-center studies are necessary to conclusively determine the safety and efficacy of TA for severe oligohydramnios.

Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Conception and design: YLW; Administrative support: YLW; Provision of study materials or patients: YLW, WG; Collection and assembly of data: WG; Data analysis and interpretation: XZ, YW, RH, LG; Manuscript writing: All authors. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was approved by institutional ethics board of Ethics Committee of International Peace Maternity & Child Health Hospital (approval number: GKLW2019-72). Written informed consents were waived due to the retrospective nature of this study.

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Conflict of Interest

The authors declare no conflict of interest.

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