

## Premature rupture of the membranes at <26 weeks' gestation. Role of amnioinfusion in the management of oligohydramnios

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**Abstract.** *Objective:* We sought to evaluate whether serial amnioinfusions for persistent oligohydramnios can affect the perinatal and long-term outcomes in extreme cases of preterm premature rupture of membranes. *Study Design:* All singleton pregnancies with preterm premature rupture of membranes at <26 weeks' gestation and lasting >4 days between January 1991 and December 2001 were included. Amniotic fluid volume was assessed as the maximum cord-free pocket with serial ultrasonographic examinations. Consenting women with persistent (>4 days) oligohydramnios (amniotic fluid=2 cm) received serial transabdominal amnioinfusions to maintain an amniotic fluid pocket >2 cm. The pregnancy, neonatal, and long-term neurologic outcomes of the cases that spontaneously maintained a median amniotic fluid pocket >2 cm were compared with those of women with oligohydramnios who underwent amnioinfusion but continued to have persistent oligohydramnios and with those of women in whom oligohydramnios was alleviated. Statistical analysis included the Wilcoxon rank-sum test and the Fisher exact test with a 2-tailed  $P<0.05$  considered significant. Stepwise logistic regression analysis with the Nagelkerke adaptation of the Cox-Snell  $R^2$  was performed to assess prenatal predictors of survival in the persistent oligohydramnios group. *Results:* Among the 49 women included in the study, 13 (26.5%) did not have oligohydramnios, the neonatal survival rate was 92%, and normal fetal lung development and neurologic outcome were achieved in all survivors. The remaining 36 women had oligohydramnios, and all underwent serial amnioinfusions, which successfully restored a median amniotic fluid pocket >2 cm for =48 hours in 11 (30%) patients. This successful amnioinfusion group was comparable with the persistent oligohydramnios group ( $n=25$ ) in gestational age at first amnioinfusion (median, 20.2 weeks; range, 16-25.6 weeks; vs median, 20.3 weeks; range, 16.5-24.2 weeks;  $P=.4$ ), number of amnioinfusions (median, 3; range, 1-9; vs median, 3; range, 1-5;  $P=.4$ ), and interval between amnioinfusions (median, 6 days; range, 4-14 days; vs median, 8 days; range, 6-43 days;  $P=.1$ ). However, patients in the persistent oligohydramnios group had a significantly shorter interval to delivery, lower neonatal survival (20%), and higher rates of pulmonary hypoplasia (62%) and abnormal neurologic outcomes (60%) than the patients in the groups in which amnioinfusion was not necessary or was successful (all  $P=.01$ ). Logistic regression analysis demonstrated that after taking into consideration successful amnioinfusion ( $P=0.019$ ) and administration of steroids ( $P=0.022$ ), none of the other variables, including gestational age at delivery, contributed significantly to the prediction of perinatal survival in the persistent oligohydramnios group. *Conclusion:* Pregnancies with preterm premature rupture of membranes-related oligohydramnios at <26 weeks' gestation in which serial amnioinfusions successfully alleviate oligohydramnios have a perinatal outcome that is significantly better than the outcome in those with persistent oligohydramnios and is comparable with gestations with preterm premature rupture of membranes in which oligohydramnios never develops. In the persistent oligohydramnios group, successful procedures and prenatal administration of corticosteroids are the only independent predictors of perinatal survival.

**Key words:** Premature rupture of membranes, oligohydramnios, amnioinfusion, pulmonary hypoplasia, pregnancy outcome

## Introduction

Perinatal survival after premature rupture of membranes during the early second trimester is primarily related to the gestational age at delivery. Two variables that are available at the time of membrane rupture have major prognostic implications: gestational age at rupture and residual amount of amniotic fluid. Oligohydramnios is associated with a shorter interval from preterm premature rupture of membranes to delivery and greater perinatal mortality (1), and it is the most important independent predictor of the occurrence of pulmonary hypoplasia (2), a complication that carries a risk of perinatal mortality as high as 80% (3). Moreover, oligohydramnios at the last ultrasonographic examination is associated with a higher risk of chorioamnionitis and infectious neonatal outcome (4, 5). Conversely, adequate residual amniotic fluid volume identifies patients with better odds of good perinatal and neurologic outcome (5). Recently, strategies for treatment and reparation membrane rupture have been devised to offer alternatives to standard approaches of termination and expectant management. Such therapies include serial amnioinfusions, intracervical tissue sealants, gelatin sponge embolization, and amniopatch. Because of the critical role played by amniotic fluid volume in pregnancy outcome, we have investigated the possibility of restoring amniotic fluid with amnioinfusions. A pilot study suggested that restoration of amniotic fluid with transabdominal amnioinfusions is associated with a significant decrease in the rate of pulmonary hypoplasia (6). To evaluate whether amnioinfusion also has an effect on the latency period and perinatal and long-term neurologic outcomes, we reviewed our series of second-trimester preterm premature rupture of membranes at <26 weeks' gestation, in which amnioinfusion was offered in the presence of persistent oligohydramnios. We introduce besides the result of the logistic regression analysis to evaluate the predictors of perinatal survival in a cohort of cases with persistent oligohydramnios managed with serial amnioinfusions.

## Methods

Included in the study were all singleton pregnancies with PROM at < 26 weeks and lasting 4 days or

longer admitted to the Division of Obstetric and Gynecology, University of Milan - Bicocca, S. Gerardo Hospital, Monza, Italy, during the period January 1991 - December 2001. Diagnosis of rupture of the membranes made by observation of persistent vaginal pooling and a positive Nitrazine test on sterile speculum examination. Gestational age was established by menstrual history and confirmed by ultrasonographic examination before 20 weeks. All patients were placed on hospital bed rest during the first week and received an initial 7-day course of antibiotic prophylaxis. Digital examination was avoided until active labor.

Thereafter before 25 weeks the patient was then discharged home on bed rest; vaginal cultures were obtained every two weeks, and positive results for potentially pathogenic bacteria were treated. From 25 weeks' gestation on women were admitted to the hospital and received at least one course of corticosteroid therapy. In the presence of preterm labor, tocolytic treatment was administered in the absence of clinical signs of chorioamnionitis or abruptio placentae. Fetal heart rate monitoring was obtained daily, and biophysical profile twice a week. Amniotic fluid (AF) volume was assessed sonographically weekly on the outpatients, and daily from admission until delivery. Consenting women with persistent (>4 days) oligohydramnios (maximum cord-free pocket of AF  $\leq 2$  cm) received serial amnioinfusions to maintain AF volume above 2 cm. Under sonographic guidance a 20 gauge needle was inserted transabdominally into the amniotic cavity. Transplacental passage was avoided whenever possible. We targeted either a small pocket of residual fluid, or loops of cord between the fetal limbs, using color flow mapping to avoid puncturing the umbilical cord. The correct positioning of the needle was checked either by aspiration of a little amount of amniotic fluid or by ultrasonographic visualization of a free dispersion of normal saline solution within the amniotic cavity. The volume infused of normal saline solution was aimed at restoring a normal amount of amniotic fluid; we noted that infusion of 10 cc per week of gestational age was usually sufficient for this purpose. If oligohydramnios recurred and persisted for >4 days, the procedure was repeated. Amnioinfusion was deemed successful if the median deepest pocket of fluid during the latency period was >2 cm.

Delivery was expedited in the presence of clinical chorioamnionitis; fetal tachycardia with diminished variability, recurrent late or severe variable decelerations, or a biophysical profile score <6; abruptio placentae; or gestational age >34 weeks.

Pulmonary hypoplasia was diagnosed based on strict clinical, radiological (including small, well-aerated lung fields with elevated diaphragms up the seventh rib, and bell-shaped chest), and pathology criteria (lung/body ratio <0.018 and/or evidence of abnormal low radial alveolar counts adjusted for gestational age). Neurologic, ophthalmologic and audiometric examinations were performed serially in all survivors. Abnormal neurologic outcome was defined as any of following conditions: cerebral palsy, spastic diplegia or tetraplegia, unilateral or bilateral deafness, or blindness.

Pregnancy and neonatal outcomes of the patients in whom a median amniotic fluid pocket was maintained spontaneously after preterm premature rupture of membranes >2 cm (group in whom amnioinfusion was not necessary) were compared with those of women with preterm premature rupture of membranes and persistent oligohydramnios despite amnioinfusion (persistent oligohydramnios group), as well as with those in women in whom amnioinfusion successfully alleviated the oligohydramnios (ie, median amniotic fluid pocket >2 cm; successful amnioinfusion group) with the Wilcoxon rank-sum test for continuous variables and the Fisher exact test for dichotomous variables. A 2-tailed  $P < .05$  was considered statistically significant. Prenatal predictors of outcome in the persistent oligohydramnios group were compared between

cases who survived the perinatal period and those who did not using stepwise logistic regression analysis with the Nagelkerke adaptation of the Cox-Snell  $R^2$ .

## Results

Fifty-one patients experienced preterm premature rupture of membranes at <26 weeks' gestation and remained undelivered for >4 days. Two patients with severe oligohydramnios opted for termination of pregnancy. Among the remaining 49 women who desired continuation of pregnancy, mean gestational age at preterm premature rupture of membranes was 19.2 weeks (range, 14-26.6 weeks). In 13 patients the deepest pocket of amniotic fluid remained >2 cm or it decreased to  $\leq 2$  cm for <4 consecutive days, thus never fulfilling the criteria for amnioinfusion. Oligohydramnios ensued in 36 patients, all of whom were offered amnioinfusion and consented to the procedure. Amnioinfusion was uncomplicated and replenished the amniotic fluid volume in all 36 women. However, 48 hours later, the infused fluid was retained (ie, the deepest pocket was >2 cm) in only 30% (11/36) of patients, whereas in the remaining 70% (25/36) oligohydramnios recurred within a range of 1 to 48 hours of the procedure.

Table 1 shows the demographic and obstetric characteristics of the 3 study groups. Of interest, all cases of chorioamnionitis occurred in the persistent oligohydramnios group.

Table 2 displays the perinatal and neurologic outcomes. The group with successful amnioinfusion and

**Table 1.** Demographic and obstetric characteristics [median (range) or No. (%)]

	Persistent Oligohydramnios (n=25)	P value	Amnioinfusion Not necessary (n=13)	P value	Successful Amnioinfusion (n=11)
Maternal age (years)	30 (20-39)	0.9	32 (20-40)	0.09	29 (24-35)
Nulliparity	13 (52%)	1	6 (46%)	0.5	7 (64%)
Gestational age at PROM	19.3 (14.0-25.2)	0.1	21.0 (16.0-26.6)	0.002	16.5 (14.0-21.0)
Caucasian ethnicity	23 (92%)	0.5	13 (100%)	0.5	10 (91%)
Chorioamnionitis	8 (32%)	0.03	0	1	0
Abruptio placentae	4 (16%)	0.6	3 (23%)	0.2	0
PROM-to-delivery interval	22 (9-105)	0.02	64 (7-119)	0.4	89 (48-139)
Cesarean delivery	9/15 (60%)	0.2	10/12 (83%)	0.2	5/10 (50%)

**Table 2.** Perinatal and neurologic outcome [median (range) or No. (%)]

	Persistent Oligohydramnios (n=25)	P value	Amnioinfusion Not necessary (n=13)	P value	Successful Amnioinfusion (n=11)
Gestational age at delivery	24.4 (17.0-29.0)	<0.001	28.5 (20.4-35.0)	0.8	29.4 (22.0-35.3)
Birth weight < 10th centile	2 (8%)	0.5	0	0.4	1 (9%)
Pulmonary hypoplasia*	13/21 (62%)	<0.001	0/12	0.4	1/10 (10%)
Postural deformities	4 (16%)	0.1	0	0.2	2 (18%)
Neonatal survival	5 (20%)	<0.001	12 (92%)	0.2	8 (73%)
Neonatal follow-up (months)	56 (12-96)	0.4	53 (16-108)	0.6	45 (12-106)
Abnormal neurologic outcome	3/5 (60%)	0.015	0/12	0.4	0/8

\* included cases in which pathological examination was diagnostic

the group in which amnioinfusion was not necessary had comparable outcomes, whereas the persistent oligohydramnios group showed a significantly worse perinatal outcome in terms of lower gestational age at delivery and poorer neonatal survival, higher rates of pulmonary hypoplasia, and abnormal neurologic outcome. The gestational age at delivery was significantly lower in the persistent oligohydramnios group compared with the successful amnioinfusion group ( $P < .001$ ).

Moreover, all 5 cases of intrauterine death occurred in the oligohydramnios group. Pulmonary hypoplasia occurred in 30% of patients in the overall population (14/47); it was the primary cause of death in 7 neonates and was additionally present in 3 spontaneous abortuses and 4 infants born alive. Although 62% of patients in the persistent oligohydramnios group had pulmonary hypoplasia, so did 1 (10%) patient in the successful amnioinfusion group, that infant survived. Applying the logistic regression analysis to the cases with oligohydramnios we have found that the only independent predictors of perinatal survival were successful amnioinfusion and steroid administration (significantly added to the equation to explain perinatal survival); 22% of perinatal survival was predicted by successful amnioinfusion and an additional 17% (cumulative  $R^2 = 39\%$ ) was predicted by administration of steroids.

## Comment

Our findings suggest that in pregnancies with preterm premature rupture of membranes at <26 weeks' gestation, a median residual amniotic fluid

pocket persistently  $\leq 2$  cm identifies cases at highest risk of poor perinatal and long-term neurologic outcome. This bleak outlook can in part be prevented by transabdominal instillation of isotonic sodium chloride solution with restoration of an adequate amniotic fluid volume for >48 hours. Even though the procedure was completed successfully in all patients in our series, only 30% retained the infused solution and they benefitted the most from the procedure.

Prospective identification of the successful cases is difficult. Gestational age at occurrence of oligohydramnios does not seem to identify a subgroup less likely to benefit from amnioinfusion and thus have a worse prognosis. The analysis of our data was limited by the absence of a group of patients who, after experiencing oligohydramnios associated with preterm premature rupture of membranes, desired continuation of pregnancy while declining participation in the study. Our patients' decisions were probably justified by the poor prognostic significance of oligohydramnios during the early second trimester and the lack of alternative procedures to ameliorate the outlook. Indeed, in a series of patients with preterm premature rupture of membranes between 20 and 25 weeks' gestation, Hadi et al (5) reported a perinatal mortality rate of 90% (64/71) among those with an amniotic

fluid pocket <2 cm on admission. Our series confirms previous reports that oligohydramnios with persistent preterm premature rupture of membranes is associated with a significantly lower gestational age at delivery and higher rates of chorioamnionitis and pulmonary hypoplasia, which in turn result in a lower survival rate. Logistic regression analysis demonstrated that the only independent predictors of perinatal

survival were successful amnioinfusion and steroid administration. Conversely, a median amniotic fluid pocket >2 cm after preterm premature rupture of membranes, which was present in 27% (13/49) of our patients, is a reassuring predictor of perinatal survival (92%). Patients with a median pocket of amniotic fluid >2 cm, either spontaneously or after amnioinfusion, can also be reassured that the long-term neurologic outcome is good (20/20 patients in our series; 95% confidence interval, 84%-100%) and that the occurrence of pulmonary hypoplasia is negligible, independent of gestational age at preterm premature rupture of membranes.

In summary, our experience demonstrates that trans-abdominal isotonic sodium chloride amnioinfusion in cases of early second-trimester preterm premature rupture of membranes with oligohydramnios is feasible and carries minimal risk to the mother and the fetus. Pregnancies in which serial amnioinfusions successfully reverse oligohydramnios have a perinatal and long-term neurologic outcome similar to that of pregnancies in which oligohydramnios does not develop after preterm premature rupture of membranes and a much better outcome than that of gestations with persistent oligohydramnios. Research should continue to develop alternative strategies to restore amniotic fluid in extremely preterm PROM and to identify the optimal patient candidates for the individual types of procedures.

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