Journal of Medical Sciences

ISSN 1682-4474

science alert

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Research Paper

J. Med. Sci., 7 (2): 203-209
15th February, 2007

Pulmonary Maturation in Preterm Rupture of Membranes with Oligohydramnios

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The cross-sectional comparative study performed over pregnant women with PPROM and gestational age of 28-34 weeks to assess the effects of mild and severe oligohydramnios on the fetal lung maturation in preterm pregnancies with preterm PROM. In this study, average gestational ages and birth weight were not significantly different between the 2 groups with mild and severe oligohydramnios. The average duration of PPROM was more in patients with severe oligohydramnios than those with mild oligohydramnios. Also, the newborns of patients with mild oligohydramnios were at higher risk of Hyaline Membrane Disease (HMD) or Respiratory Distress Syndrome (RDS) in comparison with the newborns of women with severe disease. In both groups the highest incidence of HMD is belonging to newborns of women with PROM occurred in lower gestational age. The neonates' mortality was not significantly different in 2 groups. Also, the relation of PROM-labour interval with incidence of HMD was not significant.

Key words: Pulmonary maturation, respiratory distress syndrome, oligohydramnios

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

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INTRODUCTION

Premature Rupture of Chorioamniotic Membranes (PROM) is the rupture of the fetal membranes before the onset of labour. In most cases, this occurs near term, but when membrane rupture occurs before 37 weeks gestation, it is known as Preterm PROM (PPROM) (Tanya *et al*., 2006). Preterm PROM is one of the most common complications of the pregnancy (Borna *et al*., 2004). This condition complicates approximately 3 percent of pregnancies and leads to one third of preterm births. It increases the risk of prematurity and leads to a number of other perinatal and neonatal complications, including a 1 to 2 percent risk of fetal death (Tanya *et al*., 2006).

One of the most common complications of preterm PROM is early delivery. The latent period, which is the time from membrane rupture until delivery, generally is inversely proportional to the gestational age at which PROM occurs. When PROM occurs too early, surviving neonates may develop sequelae such as malpresentation, cord compression, oligohydramnios, necrotizing enterocolitis, neurologic impairment, intraventricular hemorrhage and Respiratory Distress Syndrome (RDS) (Tanya *et al*., 2006).

The risk factors of preterm PROM include black race, having lower socioeconomic status (Tucker and McGuire, 2004), smoking, history of sexually transmitted infections or preterm delivery (Tucker and McGuire, 2004), having vaginal bleeding, or uterine distension (e.g., polyhydramnios, multifetal pregnancy) (Slattery and Morrison, 2002), procedures such as cerclage and amniocentesis and choriodecidual infection or inflammation (Bendon *et al*., 1999).

The diagnosis of PROM requires a thorough history, physical examination and selected labouratory studies. Patients often report a sudden gush of fluid with continued leakage. Physicians should not perform digital cervical examinations on patients with preterm PROM because they decrease the latent period. Shortening of the latent period may lead to increased infectious morbidity and sequelae from preterm labour. Speculum examination is preferred (Tanya *et al*., 2006).

Diagnostic methods using nitrazine paper and determination of ferning have sensitivities approaching 90%. The normal vaginal pH is between 4.5 and 6.0, whereas amniotic fluid is more alkaline, with a pH of 7.1 to 7.3. Nitrazine paper will turn blue` when the pH is above 6.0.

In unusual cases in which the patient's history suggests preterm PROM, but physical examination findings fail to confirm the diagnosis, ultrasonography may be helpful. When ultrasonography is inconclusive or the clinical situation depends on a precise diagnosis, intra-amniotic injection of dyes may help to confirm the diagnosis (Tanya *et al*., 2006).

The management of patients with PROM is controversial (Ananth *et al*., 2004); however, the management is usually based on Gestational Age: When preterm PROM occurs at 34 to 36 weeks gestation, physicians should avoid the urge to prolong pregnancy. Labour induction clearly is beneficial at or after 34 weeks gestation. For patients with preterm PROM at 32 or 33 weeks gestation with documented pulmonary maturity, induction of labour and transportation to a facility that can perform amniocentesis and care for premature neonates should be considered (Mercer, 2003). Delivery before 32 weeks gestation may lead to severe neonatal morbidity and mortality (Mercer, 2004; Yang *et al*., 2004).

Antibiotics should be administered to patients with preterm PROM because they prolong the latent period and improve outcomes. Corticosteroids should be given to patients with preterm PROM between 24 and 32 weeks gestation to decrease the risk of intraventricular hemorrhage, respiratory distress syndrome and necrotizing enterocolitis (Tanya *et al*., 2006).

A study showed deterioration in fetal pulmonary artery blood flow in pregnancies complicated by severe oligohydramnios (Blaszczyk *et al*., 2003). Also, the fall in intrauterine volume affects lung growth and maturation. The duration and severity of oligohydramnios are important elements in predicting the risk of pulmonary hypoplasia and neonatal morbidity (Aspillaga and Vial, 1995). Early and prolonged decreased amount of amniotic fluid determines deformities and impairment of fetal lung development (Aspillaga and Vial, 1995).

Hyaline Membrane Disease (HMD), also called Respiratory Distress Syndrome (RDS), is one of the most common problems of premature babies. It can cause babies to need extra oxygen and help breathing. The course of illness with hyaline membrane disease depends on the size and gestational age of the baby, the severity of the disease, the presence of infection, whether or not a baby has a patent ductus arteriosus (a heart condition) and whether or not the baby needs mechanical help to breathe. Gestational age, birth weight and maternal age are risk factors for RDS (Dani *et al*., 1999).

Neonatal morbidity from preterm prelabour rupture of the membranes is mainly related to oligohydramnios and pulmonary hypoplasia (Lamont, 2003).

The lungs of preterm infants with Respiratory Distress Syndrome (RDS) are deficient in pulmonary surfactant and the administration of exogenous surfactants improves oxygenation and reduces neonatal mortality rates among affected newborn infants (Moya *et al*., 2005; Sinha *et al*., 2005).

We performed this study to assess the effects of mild and severe oligohydramnios on the fetal lung maturation in preterm pregnancies with preterm PROM.

MATERIALS AND METHODS

This cross-sectional comparative study performed over pregnant women with gestational age of 28-34 weeks with Premature Rupture of Chorioamniotic Membranes (PPROM) attending consecutively to Tabriz Al-Zahra hospital since Jun 2003 to Jun 2006.

All of over mentioned women were enrolled initially. The data was collected by questionnaire filling via question from mothers and review of newborns hospital records. The questionnaire had questions including gravidity, parity, the number of alive children, the history of preterm labour with or without PROM, duration of PROM, the volume of amniotic fluid and information about newborn including birth weight, presence of HMD and status in discharge.

Initially, each patient was admitted to a labour and delivery suite for maternal and fetal assessment. After maternal condition was stabilized and there was no evidence of fetal distress, ultrasound evaluation was performed to assess fetal presentation, growth, anatomy and the Amniotic Fluid Index (AFI).

During admission period, repeated ultrasonography was performed every 48 h for determination of amniotic fluid index; and if there was continuous mild or severe oligohydramnios, the patient was selected and enrolled in one of two study groups. The patients who their amniotic fluid volume became normal, or had intermittent mild and severe oligohydramnios, were excluded from the study.

Gestational age was estimated using the date of the patient's Last Menstrual Period (LMP) and ultrasound dating and the cases with disagreement between their LMP and US results for gestational age, were excluded from the study. Also, the women whose pregnancy complicated by preeclampsia, hypertension, fetal IUGR, diabetes mellitus, uterine malformation, multiple pregnancy or fetal abnormality, were excluded.

The total of 172 patients was selected. Ultrasonography showed that 88 of them had mild oligohydramnios and 84 of them had severe oligohydramnios. All of selected patients were hospitalized and underwent fetal monitoring and daily Non-stress Tests (NST) during PROM period.

The patients were classified in two groups according to the amniotic fluid volume measured by US:

- Patients with AFI $\leq$ 5 cm of measurable pockets of amniotic fluid (free of umbilical cord) which considered as severe oligohydramnios and
- Patients with AFI>5 cm (but less than normal level) which considered as mild oligohydramnios.

Pelvic examination using a sterile speculum was performed. Digital examination was avoided unless the patient was committed to delivery. Diagnosis of preterm PROM was based on history and confirmed by the presence of pooled amniotic fluid on a sterile speculum, positive results from a ferning test, Nitrazine paper and transvaginal ultrasonographic evaluation that demonstrated oligohydramnios.

Pregnant patients who had PROM were given antenatal corticosteroids, fetal monitoring and prophylactic antibiotics.

Patients with no spontaneous preterm labour and no evidence of infection were treated with parentral prophylactic antibiotics: Intramuscular ampicillin 1g (every 6 h) and gentamicin 80 mg (every 8 h) for 2 days and then oral ampicillin 500 mg (QTD) for 5 days.

Patients received two intramuscular injections of antenatal corticosteroids (12 mg of betamethasone every 24 h).

Clinical chorioamnionitis was diagnosed if two or more of the following symptoms were present: maternal pyrexia (>38°C [>100.4°F]) in conjunction with uterine tenderness, purulent vaginal discharge, or fetal tachycardia.

Indications for delivery included clinical chorioamnionitis, non-reassuring assessment for fetal well-being, fetal death and advanced labour. If infection was identified, delivery was expedited and the use of broad-spectrum antibiotics was initiated.

Following delivery, all newborns were admitted to the neonatal intensive care unit and antibiotic therapy with ampicillin and gentamicin sulfate were initiated while the results of the septic work up were prepared.

Diagnosis of hyaline membrane disease (respiratory distress syndrome) was based on clinical and physical signs of respiratory distress (tachypnea, grunting, subcostal and intercostals retraction and hypotension), labouratory findings (hypoxia, metabolic acidosis) and radiographic characteristics of the chest (diffused reticuloendothelial infiltration and inflated tracheobronchial system).

Also, for assessment of the relation between duration of PROM and incidence of HMD, the patients were classified in 4 groups according to the duration of PROM: 1)<24 h, 2) 24-72 h, 3) 72-168 h and 4)>168 h.

Finally the collected data were analyzed by SPSS-12 statistical software and chi-square, one way ANOVA and independent sample t-test. The p-value less than 0.05 were considered significant.

RESULTS

Of 172 studied patients 88 (51.2%) had mild and 84 (48.8%) had severe oligohydramnios. As showed in Table 1, PROM and subsequently oligohydramnios is the most frequent in gravida 1 women. However, the difference of gravidity between 2 groups of patients with mild and severe oligohydramnios was not significant (PV = 0.90).

Of all patients with mild or severe oligohydramnios, 108 (62%) had not alive child. 41 (23.6%) had one, 14 (8%) had two, 4 (2.3%) had 3 and 6 (3.4%) had >3 alive children.

Of all patients, 142 (81.6%) had not the history of abortion. 26 (14.9%) had the history of one abortion; 3 (1.7%) had the history of two abortions and 2 (1.2%) had the history of 3 or 4 abortions.

There were 3 cases with history of preterm labour in severe oligohydramnios group, of which 2 cases were due to PROM; these figures in mild oligohydramnios group were 4 and 3, respectively.

According to the Table 1 the direct relation between duration of PROM and severity of oligohydramnios was significant (PV = 0.012).

According to the Fig. 1, in patients with severe oligohydramnios the average duration of PROM in gestational age of 33-34 was less prolonged than it in gestational age of 30-32.

The duration in patients with mild oligohydramnios is the same in gestational ages of 30-32 and 33-34, but is shorter in gestational ages of 28-29. However, the relation of PROM duration and gestational age in both mild and severe oligohydramnios groups was not significant (PV = 0.675).

According to the Table 1 the incidence of HMD in patients with mild oligohydramnios was higher and this difference is significant (PV = 0.005).

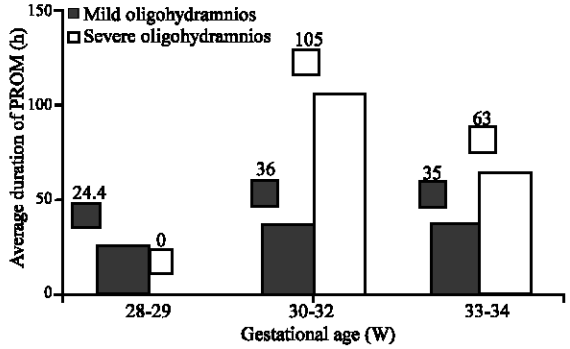

Fig. 1: Gestastional age and saverity of oligohydramnios

Table 2 shows that there was not significant relation between duration of PROM and incidence of HMD (PV = 0.15).

Also, Table 2 show that in patients with PROM duration of 24-72 h, the relation of oligohydramnios severity and incidence of HMD is significant (PV = 0.003). So, among patients belonging to this group, those with mild oligohydramnios were in higher risk of having newborn with HMD.

According to the Table 3, in patients with severe oligohydramnios, the relation between gestational age and incidence of HMD is not significant (0.587) and in patients with mild oligohydramnios is significant (PV = 0.022) and the incidence of HMD become lower in higher gestational ages.

However, it is concluded from comparison of Table 3 that in gestational ages of 32-34 weeks, the incidence of HMD in newborns of mothers with mild oligohydramnios is significantly more than newborns of mothers with severe oligohydramnios (PV = 0.04).

The average birth weight of newborns in both groups was not significantly different (PV = 0.32) (Table 1).

Table 1: The characteristics of patients and their differences in both groups

Characteristics	Severe oligohydramnios	Mild oligohydramnios	p-value
Gravida 1	43 (51.1%)	40 (46%)	
Gravida 2 and 3	34 (40.5%)	38 (43.7%)	
Gravida 4-8	7 (9.4%)	9 (10.3%)	
Average Gravidity	1.94±1.40	1.99±1.22	0.90
Parity 0	47 (57.3%)	49 (56.3%)	
Parity 1and 2	30 (37.6%)	31 (35.6%)	
Parity 3-7	5 (5.1%)	7 (8.1%)	
Average Parity	0.74±1.25	0.83±1.22	0.661
Duration of PROM (h)			
Minimum	2	1	
Maximum	720	480	
Average	138.4±79.4	67.99±38	
Median	24	24	0.012
Incidence of HMD	57	38	0.005
Birth weight (g)			
Minimum	1200	920	
Maximum	2900	3000	
Average	2008.4±345.4	2067.7±441.6	0.32
New born mortality due to HMD	6 (6.8%)	5 (6%)	1

Table 2: Relation of duration of PROM with HMD in severe and mild oligohydramnios

Duration of PROM	Total number	Cases with HMD	p-value
Severe			
<24	38	17 (44.7%)	0.19
24-72	20	6 (30.0%)	
72-168	13	6 (46.2%)	
>168	8	6 (75.0%)	
Mild			
<24	44	25 (56.8%)	0.15
24-72	19	15 (78.9%)	
72-168	9	7 (77.8%)	
>168	8	7 (87.5%)	

Table 3: Relation of gestational age with HMD in severe oligohydramnios

Gestational age (weeks)	Total number	Cases with HMD	p-value
Severe			
28-31	3	2 (66.7%)	0.587
32-34	81	36 (44.2%)	
Mild			
28-31	19	17 (89.5%)	0.022
32-34	65	40 (61.5%)	

Also, the mortality of newborns due to HMD in each groups was not different (PV = 1) (Table 1).

DISCUSSION

In late gestation, the fetal lung undergoes marked changes in preparation for the transition to extrauterine life. These changes include growth, enlargement of distal potential air spaces, thinning of the septa, maturation of the surfactant system and differentiation of distal pulmonary epithelium into mature alveolar type I and type II cells. Several studies have shown that fetal lung growth is controlled primarily by mechanical factors, especially distension of the lung (Kitterman *et al*., 2002; Kitterman, 1996). Oligohydramnios, a deficiency of amniotic fluid, when prolonged, results in pulmonary hypoplasia in human fetuses (Kitterman *et al*., 2002).

Investigators have reported that oligohydramnios retards growth of both the fetal body and lungs. The probable explanation for the retarded lung growth with oligohydramnios is less distension of the fetal lung due to a smaller volume of fluid in the potential airways and air spaces. This decrease in fluid volume is relatively rapid and persists during oligohydramnios (Kitterman *et al*., 2002). Harding and Liggins have shown that oligohydramnios causes changes in thoracic dimensions of fetal sheep that are consistent with decreased thoracic volume (Harding and Liggins, 1991).

After adjusting for confounding variables, neonates with oligohydramnios are twice as likely to develop pulmonary hypoplasia (20 vs. 10%) and more likely to experience neonatal death (30 vs. 20%) when compared to those with adequate fluid (Shumway *et al*., 1999).

In the study of Khashoggi (2004) neonatal outcomes of pregnancies with preterm premature rupture of membranes included neonatal mortality (5.5%), respiratory distress (15.9%), sepsis (7.7%) and necrotizing enterocolitis (3.1%).

In a similar study by Borna *et al*. (2004) in Tehran University of Medical Sciences, 95 singleton pregnancies complicated by Preterm Premature Rupture of the Membranes (PPROM) with delivery between 26 and 34 weeks gestation were assessed.

Patients were categorized into 2 groups on the basis of the admission AFI measurement by US. Patients in Group 1 were those with an AFI<5 cm, whereas those in Group 2 had AFI $\geq$ 5 cm. The 2 groups were compared for gestation age at both rupture of the membranes and delivery, latency until delivery, mode of delivery, birth weight, the development of clinical chorioamnionitis, postpartum endometritis, early onset neonatal sepsis and respiratory distress syndrome. Gestational age at delivery and latency period until deliveryand birth weight were not significantly different between the 2 groups. The risk of Respiratory Distress Syndrome (RDS) was less in Group 2 than Group 1 (11.8 vs. 26.1%) (Borna *et al*., 2004).

In this study, average gestational ages and birth weight were not significantly different between the 2 groups with mild and severe oligohydramnios which is compatible with Borna *et al*. (2004) study.

The average duration of PPROM was more in patients with severe oligohydramnios than those with mild oligohydramnios.

Also, the newborns of patients with mild oligohydramnios were at higher risk of HMD or RDS in comparison with the newborns of women with severe disease.

In other study by Park *et al*. (2001) in Seoul National University College of Medicine, amniotic fluid index was determined in 129 patients with preterm PROM and gestational age $\leq$ 35 weeks.

Amniotic fluid index was $\leq$ 5 cm in 29% of patients (38/129). Spontaneous preterm delivery within 24 and 48 h was more frequent among patients with an amniotic fluid index of $\leq$ 5 cm than those with an amniotic fluid index of >5 cm (for 24 h, 29% vs. 12%; for 48 h, 42% vs. 21%). The latent phase was significantly shorter in patients with an amniotic fluid index of $\leq$ 5 cm than in patients with an amniotic fluid index of >5 cm (median, 38 h vs. median, 100 h) (Park *et al*., 2001).

In this study, the number of patients in both mild and severe oligohydramnios was the same [88(51.2%) vs. 84(48.8%)] but the average duration of PROM in group with AFI $\leq$ 5 cm (severe oligohydramnios) was more

(79.4 vs. 38 h). So, the latent phase in patients with AFI = 5cm was more prolonged but the median in both groups was 24 h.

Namavar Jahromi *et al.* (2000) performed a study on 159 cases of PPROM with gestational ages between 24 and 37 weeks to evaluate the relationship between duration PPROM and development of RDS.

They showed that there exists a reverse linear relationship between duration of ROM and RDS in the first 48 h. However, after 48 h, the risk of RDS increases, which may represent the effect of complications such as: chorioamnionitis; sepsis and pulmonary hypoplasia on RDS (Namavar *et al.*, 2000).

We categorized the patients into 4 groups on the basis of the duration of ROM for determination of relation between ROM duration and the risk of HMD; but there were not significant relation between incidence of HMD and ROM duration in any of mild or severe oligohydramnios groups. However, in patients with ROM duration of 24-72 h, the relation of oligohydramnios severity and the incidence of HMD was significant. So that, in group with mild oligohydramnios, the incidence of HMD was higher.

Smith *et al.* (2005) showed that the increased neonatal morbidity associated with PPROM appears to be inversely related to GA. Also, Bhutta and Yusuf, (1997) concluded that occurrence of RDS in women with PPROM is inversely related to GA.

These results are compatible with our study findings in which the highest incidence of HMD is belonging to newborns of women with PROM in lower gestational ages.

Yoon and Harper (1973) showed that prelabour PROM lasting more than 24 h decrease the rate of RDS.

In this study patients with PROM lasting 24-72 h and severe oligohydramnios, the risk of HMD decreases in the first 24 h but then increases. Also, in patients with mild oligohydramnios the risk of HMD increases after 24 h and is the same in 24-72 h, 72-168 hand after 168 h.

CONCLUSION

We concluded from this study that the newborns of patients with mild oligohydramnios were at higher risk of Hyaline Membrane Disease (HMD) or Respiratory Distress Syndrome (RDS) in comparison with the newborns of women with severe disease.

In both groups the highest incidence of HMD is belonging to newborns of women with PROM occurred in lower gestational age. The neonates' mortality was not significantly different in 2 groups. Also, the relation of PROM-labour interval with incidence of HMD was not significant.

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