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PRE-TERM PRE-LABOUR RUPTURE OF MEMBRANES AND THE ROLE OF AMNIOCENTESIS

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INTRODUCTION

Pre-labour premature rupture of membranes (PPROM) is defined as rupture of membranes more than 1 hour prior to the onset of labour at <37 weeks gestation. PPROM occurs in approximately 3% of pregnancies and is responsible for a third of all preterm births.[1] Once membranes are ruptured prolonging the pregnancy has no maternal physical advantage but fetal morbidity and mortality are improved daily at early gestations: 19% of those infants born <25 weeks develop cerebral palsy (CP) and 28% have severe motor disability.[2] Those infants born extremely pre term (<28 weeks) cost the public sector £75835 (95% CI £27906–145508) per live birth[3] not to mention the emotional cost to the family. To prolong gestation is therefore the suggested goal: however how and why might we delay birth in those at risk?

PPROM is one scenario associated with preterm birth and here we discuss the causative mechanisms, sequelae, latency, strategies to prolong gestation (antibiotics) and consider the role of amniocentesis. We will also discuss novel therapies.

PATHOPHYSIOLOGY OF MEMBRANE RUPTURE

The membranes, which act to protect and isolate the fetus, are composed of two layers. The inner layer (amnion) which connects after fusion in the late first trimester, to the outer layer (chorion leave) through a collagen-rich vascular zone. These membranes are directly apposed to the maternal decidua.

The high resilience of the preterm fetal membranes makes them strong enough to withstand strong non-penetrating forces.[4] The supra-cervical portion of the membranes has been proposed as the site where the process of weakening and rupture through collagen remodelling[5] may be initiated.[6] Collagen remodelling is executed through the activation of the collagen specific matrix metalloproteinases (MMPs)

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in the extracellular matrix of the amniochorionic membrane. This remodelling may be due in large part to inflammation which may be infection related.[7,8] The supracervical location (i.e. close to the vaginal flora) of the structural changes observed in membranes prior and after rupture has supported the proposition that even in term pregnancies infection is implicated. Microbial invasion of the amniotic cavity is seen in 18% of term labours and 30% of term rupture of the membranes (ROM).[9] However, pre-labour ROM (as distinct from labour with intact membranes) has a greater association with infection.

Consequences of membrane rupture

In comparison to term ROM the rate of positive bacterial culture at the time of PPROM in the absence of labour is approximately 25–40%.[1] One–2% of pregnancies with PPROM have clinical chorioamnionitis at presentation with 3–8% developing subsequent chorioamnionitis.[1] Maternal infection increases the risk of neonatal infection[9] and the risk of infection clinically detectable in either mother or baby increases with duration of PPROM. A Nigerian study in 2007 of 356 women attending a University hospital with PPROM <36 weeks (1994–2003) reported 20% of patients delivered within 24 hours with 71% delivered between the 2nd and 10th day. The majority of women (29.7%) were 28–30 weeks gestation. All women received prophylactic antibiotics and steroids if <34 weeks gestation. Twenty nine per cent had evidence of chorioamnionitis of whom 70% had had multiple vaginal examinations (a known risk factor for infection). Thirty eight per cent of those with chorioamnionitis had received antibiotics within 24 hours of membrane rupture. Those delivering within 48 hours were least likely to have chorioamnionitis.[11] While this study was at an institution within a developing nation with higher perinatal morbidity and mortality than western studies the report demonstrates clearly the risk of infection over time in the context of PPROM using current management strategies. When considering management of PPROM risk of infection is thus the single most important determinant of maternal and fetal morbidity and mortality and increases with duration of ROM.

LATENCY IN PPROM

Pasquier et al[12] reviewed all cases of PPROM at 24–33+6 weeks gestation (542 women) at their French institution between April 1999–2001 and reported that 60% will deliver spontaneously during the first week of PPROM, with 80% delivering within 3 weeks. Cotton et al[13] reported a latency of 3.6 ± 2 days (range 0.5–9 days) in 19 women with PPROM with 52.6% delivering within 72 hours of admission. Manuck et al[14] confirmed that latency following PPROM at 22–33.9 weeks gestation was 8 days (interquartile range 3–15 days).

Predictive factors within the PPROM group to determine which cases have the shortest latency have been reported. Fisher et al[15] suggested that cervical length when measured translabially is not predictive of latency, chorioamnionitis or postpartum endometritis. However a Korean prospective study performed transabdominal amniocentesis, sampled maternal blood for white cell count (WCC) and C reactive protein (CRP) and measured cervical length in 50 singleton pregnancies < 36 weeks with PPROM. Patients with positive amniotic fluid cultures had significantly shorter cervical length and higher WCC and CRP than those with negative cultures. The prevalence of positive culture was 26% (13/50) and the mean gestational age at amniocentesis was 31.4 weeks. Using a ROC curve the best cut off value of cervical length for identification of microbial invasion of the amniotic cavity was 28 mm with a sensitivity of 85% and a specificity of 65%.[16] The latency from PPROM to delivery is not reported but the authors cite several other studies with microbial invasion and shorter latency from ROM to delivery in PPROM and infer that a short cervix would therefore be associated with an earlier delivery. The quantity of remaining fluid may be predictive of latency. Parks et al[17] studied 129 women with spontaneous PPROM at < 35 weeks in whom 29% had an AFI < 5 cm. This level of fluid was associated with higher rates of positive fluid cultures and a shorter PPROM to delivery interval. Both cervical length and anhydramnios may be surrogate markers; of infection, with infection being the main determinant of latency. A recent study by Manuck et al[14] has suggested that latency per se is not a risk factor for adverse perinatal outcome but congenital sepsis is (OR 13.2 95% CI 3.9–44.5).[14] Thus with expectant management the data suggest that a high proportion of women will deliver spontaneously within a week but the risk of infection increases with duration of PPROM and it is the presence of infection that is clinically important with respect to outcome.

ANTIBIOTICS IN PPROM

Antibiotic use has been shown to prolong pregnancy in the context of ROM.[18] However, increasing gestation with antibiotics does not translate into long-term benefits for the offspring. The ORACLE I trial[19] assessed the benefit of erythromycin and or amoxicillin/clavulinate and placebo for women with PPROM and no signs of infection. While erythromycin was associated with prolongation of pregnancy and reductions in neonatal morbidity, by the age of 7 years there was no difference in the degree of functional impairment amongst children who received antibiotics compared to those who did not.[19]

In the context of intact membranes and no signs of infection, antibiotics may increase neonatal mortality when used in women in preterm labour.[20] Most recently this was reported in the second ORACLE 7 year follow up study. Women with pre-term labour and intact membranes were randomised to the use of erythromycin and/or amoxicillin/clavulinate or placebo. Eythromycin use was associated with an increase in functional impairment in the offspring compared to those not receiving

erythromycin. Either antibiotic was associated with more cerebral palsy than in women receiving no antibiotics. The number needed to harm in the erythromycin group was 64 (95% CI 37–209) and in the co-amoxiclav group 79 (42–591).[21] These studies highlight that in women at significant risk of preterm birth use of antibiotics has not been shown to have benefit[21] though they may prolong pregnancy. In the context of PPROM therefore, measures to prolong pregnancy must be considered not only in terms of increasing gestation but must translate into measurable long term improvements in outcome for the neonate. Once evidence of clinical infection is apparent delivery should be expedited and should be treated with antibiotics because clinical chorioamnionitis remains an important cause of maternal, fetal and neonatal death.[19]

ROLE OF AMNIOCENTESIS IN PPROM

Amniocentesis to detect fetal lung maturity

Given the delicate balance between risks of infection to mother and baby in PPROM with expectant management and the benefit of increasing gestation in the absence of infection (particularly at early gestations), one role of amniocentesis in PPROM would be to determine fetal lung maturity. If confirmed, delivery could be expedited rather than waiting for clinical infection to develop. In 1979, the previously cited Garite study also used their amniotic fluid samples, obtained by amniocentesis in 69 patients with PPROM at 28 to 35 weeks of gestation, to test for lung maturity using the lecithin sphingomyelin LS ratio.[22]

Cotton et al[13] studied 61 patients with PPROM at 27–36 week's gestation. Liquor was sampled transvaginally if seen to be pooling or by transabdominal amniocentesis. Specimens were then sent for LS ratio and the presence of phosphatidyl glycerol, gram stain and culture were also performed. Delivery was expedited if the LS ratio was mature, or if bacteria were identified on gram stain. Antibiotics were only given in cases of chorioamnionitis. Forty two amniocenteses were performed of which 7 also had vaginally acquired samples. Although the abdominal samples were of greater volume, the results from the two sampling methods were not different. All patients with bacteria on gram stain or culture subsequently developed chorioamnionitis. Twenty six patients had a mature LS ratio (greater than or equal to 1.8). The mean gestational age estimated by the obstetric team in these women was 32.3 ± 2 weeks. Subsequent paediatric assessment suggested a mean gestational age of 33.2 ± 2.2 weeks. Three of 26 were believed to be 33 weeks by the obstetrician and 36 weeks by the paediatrician. Where the LS ratio was mature, 23/26 women were delivered within 48 hours and the remaining women were delivered by 96 hours. Four infants delivered <32 weeks had a mature LS ratios and their neonatal stays were 23, 29, 46 and 83 days. The authors concluded that at less than 32 weeks gestation amniocentesis need not be employed because the overall neonatal morbidity is sufficiently high in

this group, even in the presence of a mature LS ratio, that management should be conservative. At 34 weeks neonatal morbidity is sufficiently reduced that delivery should be considered. Thus between 32–34 weeks amniocentesis to assess fetal lung maturity may have a role.[13] Of note, in this study, corticosteroid administration for fetal lung maturity was at the discretion of the attending physician. The discussion explains that steroids were not given in sufficient numbers to determine their efficacy. Whether the increased neonatal morbidity at <32 would have been reduced by routine administration of steroids remains to be determined.

Several different methods have since been reported for assessing fetal lung maturity eg TDx FLM II, phosphatidyl glycerol (PG) and lamellar body count (LBC).[23] These methods are comprehensively reviewed by Grenache and Gronowksi.[23] LS ratio while still performed by many laboratories has a good sensitivity but lacks specificity. Phosphatidyl glycerol is a late marker of fetal lung maturity. TDx FLM II is a commercially available assay measuring the surfactant to albumin ratio by fluorescence polarization. The test is the most commonly used quantitative method for determining fetal lung maturity and has good sensitivities (95.7–100%) with specificities of 70–84%.[23] Lamellar body count also functions well as a test of fetal lung maturity with sensitivities approaching 100% and specificities 54–100%.[23] The authors conclude that while these tests perform well to determine maturity they are poor predictors of immaturity and that given the increasing prevalence of respiratory distress with reducing gestational age, risk stratified with regard to gestational age might be a more useful tool.[23] Thus in the context of PPROM a mature result using a rapid test (TDx FLM II or LBC) is strongly predictive of the absence of RDS. Inconclusive results may require additional testing.

Amniocentesis to identify bacterial infection

The overall rate of positive amniotic fluid culture in patients with PPROM ranges from 25–40%.[24] Averbach et al[24] performed an amniocentesis in 90 consecutive patients with PPROM at 23–36 weeks gestation for microbial culture, gram stain and white cell count. Thirty six percent had positive cultures (e.g. ureaplasma urealyticum, escherichia coli, proteus mirabilis and coagulase negative staphylococcus) but in total 66% had evidence of infection (culture, gram stain and/or elevated WCC). The clinical characteristics of the women were not different. The mean gestational age at delivery in patients with intra-uterine infection was 31.0 ± 3.8 weeks, compared to 33.0 ± 3.6 weeks in patients without intra-uterine infection. Birth weight and Apgar score at 1 minute were significantly lower in neonates born to mothers with intra-uterine infection when compared to those without infection.[24] In 1979, Garite and colleagues[22] obtained amniotic fluid samples by amniocentesis in 69 patients with PPROM at 28 to 35 weeks and tested lung maturity and screened for evidence of intra-amniotic infection using gram stain, WCC, and culture for aerobic and anaerobic bacteria.[22] Nine cases had a positive amniotic fluid culture, of which seven developed clinically significant amnionitis, a significant neonatal infection,

post-partum endometritis or a combination of these.[22] The other two patients delivered within 24 hours. Of the 21 patients with negative amniotic fluid culture only one developed chorioamnionitis. This study provided preliminary evidence that the presence of intra-amniotic infection defines a subgroup of patients at a higher risk for perinatal complications.

Microorganisms can gain access to the uterine cavity ascending through the vagina and cervix, by haematogenous dissemination through the placenta, by accidental introduction at the time of invasive procedures or retrograde spread through the fallopian tubes. Microorganisms are recognised by pattern recognition receptors e.g. toll like receptors which release inflammatory cytokines and chemokines (e.g. interleukin (IL) 8, IL-1beta and tumour necrosis factor alpha (TNF-α). Microbial endotoxins and proinflammatory cytokines stimulate prostaglandins (PG) other inflammatory mediators and matrix degrading enzymes. Prostaglandins stimulate uterine contractility whereas degradation of extracellular matrix in the fetal membranes leads to PPROM.[25] Infection then results in a fetal inflammatory response syndrome (FIRS), which may or may not be associated with a maternal inflammatory response. Once bacterial colonisation and maternal systemic response is established fetal and maternal outcomes are much worse. Therefore to identify intramniotic inflammation and/or infection prior to the onset of maternal symptoms of sepsis may be beneficial in terms of neonatal outcome.

Pathologic examination has been the gold standard for the diagnosis of inflammation. However, chemotactic signals must be present for the white blood cells to migrate to the site of injury or infection. Thus, there is a window of time in which a "molecular signature of inflammation" is present before histological evidence is observed.[9] Thus inflammation is a spectrum and the absence of a maternal fever, chills, rigors and leucocytosis does not exclude a bacterial insult and inflammation.[9] Romero et al[26] have shown that exposure to intra-amniotic inflammation and evidence of a systemic fetal inflammatory response (funisitis) are strong and independent risk factors for the subsequent development of cerebral palsy.

It has therefore been suggested that amniocenteses following membrane rupture may allow early identification of colonisation of the amniotic cavity with bacteria and fetal inflammation and thus provide a window prior to clinically detectable sepsis or bacterial culture when intervention may be beneficial.

Amniocentesis to detect novel markers of inflammation in the amniotic fluid

Cytokines

In 1993, Romero and colleagues[27] assessed the performance of amniotic fluid gram stain, WCC, the inflammatory cytokine IL-6, and glucose levels in detecting the presence of microbial invasion of the amniotic cavity as defined by a positive bacterial culture.[27] In this study, the prevalence of positive amniotic fluid cultures in 110

a

Group	*Depiction of group*	*No. of patients*	*Procedure-to-delivery interval (median and range, days)*	*Prevalence of positive amniotic fluid culture (%)*	*Maternal plasma IL-6 (median and range, pg/mL)*
Group A Amniotic fluid IL-6 ≤7.9 ng/mL Fetal plasma IL-6 ≤11 pg/mL		14 (46.6%)	5 (0.2-33.6)	4/14 (29%)	4.8 (3.8-16.8)
Group B Amniotic fluid IL-6 >7.9 ng/mL Fetal plasma IL-6 ≤11 pg/mL		5 (16.7%)	7 (1.5-32)	3/5 (60%)	7.5 (4.2-12.2)
Group C Amniotic fluid IL-6 >7.9 ng/mL Fetal plasma IL-6 >11 pg/mL		6 (20%)	1.2 (0.25-2)	6/6 (100%)	4.4 (3.4-45.2)
Group D Amniotic fluid IL-6 ≤7.9 ng/mL Fetal plasma IL-6 >11 pg/mL		5 (16.7%)	0.75 (0.13-1)	4/5 (80%)	4.8 (3.2-18.3)

b

Group	*Depiction of group*	*No.*	*Severe neonatal morbidity (%)*	*Gestational age at delivery (wk, mean ± SD)*	*Amniotic fluid IL-6 (ng/mL, median, range) (n = 59)*
Group 1 Negative amniotic fluid culture Fetal plasma IL-6 ≤11 pg/mL		27	7 (25.9%)	32.1 ± 3.1	1.2 (0.1-60.7)
Group 2 Positive amniotic fluid culture Fetal plasma IL-6 ≤11 pg/mL		10	4 (40%)	31.9 ± 2.3	2.0 (0.08-19.8)
Group 3 Negative amniotic fluid culture Fetal plasma IL-6 >11 pg/mL		10	6 (60%)	30.1 ± 4.9	22.0 (0.5-99.5)
Group 4 Positive amniotic fluid culture Fetal plasma IL-6 >11 pg/mL		26	22 (84.6%)	29.3 ± 2.9	36.7 (0.5-92.8)

Figure 1. Tables reporting inflammation as measured by IL6 concentrations in amniotic fluid and fetal cord blood with respect to bacterial colonisation and neonatal morbidity (a) Classification and procedure-to-delivery interval of patients according to amniotic fluid and fetal plasma IL-6 concentrations. (Reproduced from Romero R, et al[28] with permission.) (b) Severe neonatal morbidity according to presence of microbial invasion of amniotic cavity and fetal plasma IL-6 concentration in 73 patients delivered within 7 days of amniocentesis or cordocentesis. (Reproduced from Gomez R, et al[29] with permission).

patients with preterm premature rupture of membranes was 38%. Amniotic fluid IL-6 levels were the most sensitive test (80.9%) for the detection of microbial invasion of the amniotic cavity while the most specific test was the Gram stain of amniotic fluid (98.5%). When cultures were positive the amniocentesis-to-delivery interval was shorter and the neonatal complication rate was higher. In 1998, the same group linked amniotic fluid inflammation to a fetal systemic inflammatory syndrome (FIRS). To do this, they performed concurrent amniocentesis and cordocentesis in 30 patients with PPROM at around 30 weeks of gestation.[28] Microbial invasion of the amniotic cavity was present in 58.5% of the patients. Fetuses with plasma IL-6 concentrations > 11 pg/mL had a significantly higher rate of spontaneous preterm delivery within 48 and 72 hours of the procedure than those with fetal plasma IL-6 levels < 11 pg/mL (Figure 1).

In addition, fetuses with plasma IL-6 concentrations > 11 pg/mL had a significantly higher rate of severe neonatal morbidity than did those with fetal plasma IL-6 levels <11 pg/mL as evidenced in an accompanying study (Figure 1b).[29]

The data presented in Figure 1a suggests that most of the complications occur in the subset of patients with evidence of an intra-amniotic infection/inflammation as defined by amniotic fluid IL-6 level >7.9 ng/ml or a positive amniotic fluid culture. There remains a subset of patients with FIRS (fetal plasma IL-6> 11 pg/ml) where amniotic fluid cultures are negative and amniotic fluid IL-6 levels are less than 7.9 ng/ml. This subset could represent early haematogenous infectious spread to the fetus or a false-negative amniotic fluid result. These fetuses remain at risk of imminent delivery and poor neonatal outcome but cannot (according to the above criteria) be identified without fetal blood sampling. For this reason, the authors, in subsequent publications, suggest a lower threshold for the definition of intra-amniotic inflammation. Using a threshold of 2.6 ng/ml for amniotic fluid IL-6, intra-amniotic inflammation was twice as common as intra-amniotic infection (defined by a positive culture) and could identify infection with a sensitivity of 90% and a specificity of around 75–80%.[30]

Buhimschi et al[31] have shown that proteomic mapping of the amniotic fluid reveals a profile, designated as the Mass Restricted score that is highly characteristic of intraamniotic inflammation. The authors have shown that the presence of four protein biomarkers (neutrophil defensins-2 and -1 and calgranulins C and A) is highly predictive of preterm birth, funisitis (a hallmark of fetal inflammatory syndrome) and early neonatal sepsis. Of 158 women having amniocentesis to exclude infection in the context of PPROM, histological chorioamnionitis was found in 64%. The Mass Restricted score significantly correlated with stages of histological chorioamnionitis ($r = 0.539$, $P<.001$), grades of choriodeciduitis ($r = 0.465$, $P<.001$), and amnionitis ($r = 0.536$, $P<.001$). The authors concluded that proteomic analysis of amniotic fluid may provide an opportunity for early recognition of histological chorioamnionitis and may in the future identify candidates for antenatal therapeutic interventions. Proteomic mapping of markers is still a research tool but may represent a useful and sensitive clinical adjunct in the future.[31]

Matrix Metalloproteinase Enzymes

As the matrix metalloproteinase (MMP) enzymes are involved in parturition, premature rupture of the membranes, and intra-amniotic infection,[32,34] these have also been used to diagnose intra-amniotic inflammation in PPROM cases. Of the various MMPs, MMP-8 has received most clinical attention. In a study assessing the ability of amniotic fluid MMP-8 to detect intra-amniotic infection and inflammation as defined by a positive amniotic fluid culture and amniotic fluid IL-6 levels greater than 2.6 ng/ml, a positive amniotic fluid MMP-8 test result (defined as greater than 20 ng/ml) had a sensitivity of 90%, specificity of 80%, positive predictive value of 77%, and negative predictive value of 92% in the identification of intra-amniotic

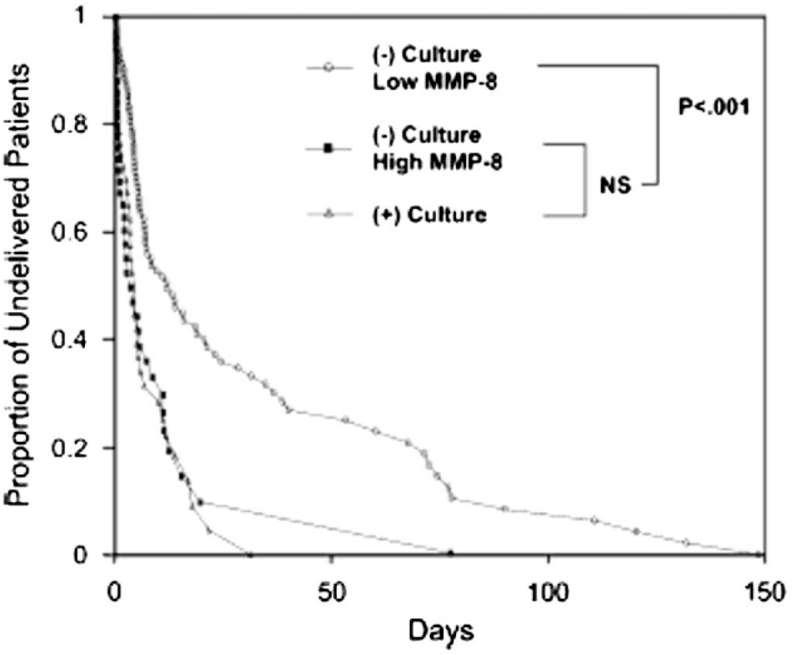

Figure 2. Amniocentesis-to-delivery interval, according to the results of amniotic fluid culture and amniotic fluid matrix metalloproteinase 8 (MMP-8) concentrations in 219 women with pre term premature rupture of membranes. (Reproduced from Shim SS et al[37] with permission).

infection.[35] In this study, a positive MMP-8 was also an independent predictor of interval to delivery and significant neonatal morbidity.[35]

The major advantage of MMP-8 testing is that it is available as a bedside test (MMP-8 PTD Check (SK Pharma, Kyunggi-do, Korea) requiring 20 ul of amniotic fluid and 15 minutes to obtain results without the need for laboratory equipment.[36] In contrast, amniotic fluid culture for microbiologic testing requires around 48 hours while the IL-6 assay uses a commercially available enzyme-linked immunosorbent assay (R and D systems, Minneapolis, USA) which, although much faster than culture, still needs to be performed in a laboratory setting.

In a more recent study, Shim et al[37] studied the clinical significance of positive amniotic fluid MMP-8 (intra-amniotic inflammation) as compared to amniotic fluid culture (intra-amniotic infection). Patients with intra-amniotic inflammation or infection had a shorter interval to delivery (figure 2) and more complications including higher rates of preterm delivery, histologic chorioamnionitis, funisitis, low Apgar scores and admission to neonatal intensive care unit as well as more significant neonatal morbidity and lower gestational age at birth and birth weight. These complications were still statistically significant after accounting for gestational age at amniocentesis.[37]

There were no differences in the interval to delivery (Figure 2) or rate of complications between patients with intra-amniotic inflammation and a negative amniotic fluid culture and patients with proven amniotic fluid infection.[37] These data indicate that intra-amniotic inflammation is a risk-factor for adverse neonatal and maternal outcome as well as for impending preterm delivery irrespective of amniotic fluid culture results. The proportion of amniotic fluid samples where inflammation is observed in the absence of positive culture results could be partially explained by the presence of atypical organisms such as Ureaplasma urealyticum since up to 40% of these infections are missed using conventional cultures.[38]

The thresholds and criteria used for the definition of intra-amniotic inflammation are variable despite most studies being performed by a limited number of associated researchers. The task of interpreting the results and applying them clinically is formidable.

Technique of amniocentesis in PPROM

Amniocentesis in PPROM should be done by an experienced operator. In many cases, the reduced amount of amniotic fluid means that access to a fluid pocket is limited to a narrow window. Garite et al[22] suggested it might be only technically successful in 51% of the cases. A 22 gauge needle is most appropriate and the use of a small volume syringe may help prevent blockage due to suction of the nearby the membranes. A trans-amniotic approach is preferable but a trans-placental approach could be used as long as the target pocket does not lie under the central portion of an anterior placenta.[39] In cases where no intra-amniotic infection or inflammation is evident at amniotic fluid analysis and the decision is made to continue with the pregnancy, repeat amniocentesis in 1–2 weeks may be useful. This is justified by certain authors, as there is evidence that in PPROM the incidence of intra-amniotic infection increases with longer latency periods.[40]

Complications with late amniocentesis are rare. In 137 patients with PPROM examined at 28–34 weeks of gestation, Yeast et al[41] reported that amniocentesis was successful in 66.4%. They could not attribute any maternal or neonatal morbidity to the amniocentesis itself and the amniocentesis-delivery analysis suggested that the amniocentesis did not accelerate delivery.[41] The volume of fluid available for sampling is a consideration. Cotton et al[13] performed the procedure only in those with a pool of at least 1×1 cm.[13] Frequently only 1–2 ml of fluid were sampled[13] but this was sufficient for gram stain, culture and LS ratio. Of note Gramellini et al[42] showed that after genetic amniocentesis the amniotic fluid index decreases by about 1 cm. The amount of amniotic fluid needed for inflammation/infection studies depends on the studies being performed but in general just a few millilitres.

Patient acceptability of amniocentesis in PPROM

There remains the issue of patient acceptability. It should be made clear to the parents that there remains a lot of uncertainty especially regarding long-term outcomes. Despite these difficulties, it is exciting to know that 70% of patients with PPROM between 28 and 34 weeks would agree to participate in a randomized study comparing expectant management with amniocentesis-based management.[43] More importantly, those who responded that they would not participate related their refusal to concerns about the complications of amniocentesis such as fetal trauma, iatrogenic preterm labour, infection or pain.

POTENTIAL ADJUNCTIVE THERAPIES IN PPROM: IMMUNOMODULATORS

In cases of intra-uterine inflammation or infection, the relatively mature fetus may be best delivered. Conversely those fetuses below 32 weeks of gestation may be candidates for in utero treatment. Intra-amniotic infection is rarely eradicated using antibiotics.[44] Antibiotics with adjunctive therapy might be best studied in those cases where there is intra-amniotic inflammation in the absence of a positive culture or gram stain. Porecco et al[39] retrospectively evaluated a policy of induction of labour where intra-amniotic inflammation or infection was evident on amniocentesis, the group managed according to amniocentesis results fared better than the conventionally managed group in regard to composite neonatal morbidity with an average latency period of around 1 week in both groups.[39] However, the optimal timing of delivery in the presence of intra-amniotic infection or inflammation is still unknown.

Since most of the damage in intra-uterine infection is caused by inflammation mediated by cytokines[45] a combination of antibiotic and anti-inflammatory/immunomodulatory agents may prove to be effective in preventing fetal injury and prolonging gestation. In a primate model of intra-uterine infection using group B streptococci, the addition of indomethacin and dexamethasone to the antibiotic regimen was effective in eradicating the infection, suppressing the inflammatory response and prolonging gestation.[46] In human neonatal sepsis, use of steroids,[47] intravenous immunoglobulins,[48] and colony stimulating factors[49] were not effective in improving outcomes. Pentoxyphylline, which inhibits the production of TNF-α, was effective in reducing the levels of the pro-inflammatory cytokines TNF-α and IL-6 in premature infants with sepsis. Most importantly it reduced the mortality rate in these infants by about 80%.[50,51]

CONCLUSION

There is a need for a randomised controlled trial of amniocentesis-guided management (for the presence of bacteria and lung maturity) versus standard conservative management of PPROM. Until this data is available there may be a role for

amniocentesis in PPROM at early gestations e.g. <32 weeks in selected cases when the risk of delivery may outweigh the risks of remaining in utero. This is particularly pertinent following the ORACLE trial when the benefits of antibiotics to prolong gestation has been called into question. However, antibiotics clearly have an important role in those with clinical signs of infection and delivery should not be delayed in these women. Detection of inflammation and potential therapies to modify the inflammatory response are currently only in the research stage but in the future may play a role in combination with amniocentesis to detect those pregnancies which may be compromised. As we have learnt from the ORACLE studies,[52] any trial addressing outcome in pre-term birth must include robust long-term follow up of infants. Perceived short-term benefits in prolonging gestation may not translate to long-term benefit to children born as a result.

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