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Summary

Premature rupture of the membranes (PROM) constitute one of the most important dilemmas in current obstetric practice. The term is applied when there is leakage of amniotic fluid in the absence of labour irrespective of gestational age. If this happens before the 37th gestational week the correct term is premature PROM (PPROM). There is further subdivision of PPROM into previable and viable.
PPROM is the classic case when a normal pregnancy suddenly becomes a high risk one for mother and the fetus or the neonate. This complication has been and is still considered as one of the most serious events.

Overall, about 10% of all gestations are complicated by PROM. Approximately 70% of PROM occurs at term, the remaining 30% at preterm.

Nearly all women with PROM will eventually deliver before term, and the majority of these women will deliver within one week of rupture regardless of their gestational age at the time of membrane rupture. PROM is an important cause for preterm delivery, an estimated 30% of these births are associated with PPROM.

Understanding and appreciating the mechanisms lying behind PROM and PPROM are of great importance, since it is associated with preterm delivery which is a major cause for neonatal morbidity and mortality. I have gathered information and research done in this field in recent time, and I try to present it in a comprehensible manner.

Introduction

Premature rupture of the membranes is defined as the rupture of the fetal membranes before the onset of labour, abbreviated PROM.
Preterm PROM is PROM before 37 gestational week, PPROM.
Prolonged PROM is PROM of longer than 24 hours duration.
Latent period refers to the time between rupture of membranes up to delivery.
Latent interval refers to period of time from rupture of membranes to the beginning of active phase of labour (4).

PROM and Delivery

PROM is the single most common diagnosis associated with preterm delivery, i.e. delivery before 37th gestational week. As mentioned above it is associated with 30% of preterm deliveries.

Labour usually follows shortly after the occurrence of PROM. 90% of term patients and 50% of preterm patients go into labour within 24 hours after rupture. Patients who don't go into labour immediately are at increasing risk of infection as the duration of rupture increases, chorioamnionitis, endometritis, sepsis, and neonatal infections (4, 5, 8, 20).

Perinatal risks with preterm PROM are primarily complications from immaturity, including respiratory distress syndrome, intraventricular hemorrhage, patent ductus arteriosus and necrotizing enterocolitis. Premature gestational age is a more significant cause of neonatal morbidity than is the duration of the membrane rupture. (20)

Etiology of PROM

The chorioamniotic membranes possess properties which are characteristic of a viscoelastic material. The membranes consist of multiple layers, amniotic epithelium, which is a monocellular layer approximately 0.02 to 0.05 mm thick and not vascularized, basement membrane, connective tissue which consists of dense filaments of collagen, and chorion. Chorion is a 2 to 10 mm layer of cuboid cells, adherent to the decidua and perfused by dense vascularisation. This special structure makes the membranes more resistent to damage. If they are locally damaged by any factor which disappears later on, it could be possible that the membranes will probably restore their integrity (2, 4, 8, 10, 15, 20).

Under normal circumstances the rupture of the fetal membranes at term is an event integral to the onset and development of labor at birth. Under term and normal contractions rupture of fetal membranes can precede onset of uterine contractions. Physiology behind this rupture remain unclear, but be a combination of apoptosis, extracellular matrix remodelling and stretch induced physical weakness of fetal membranes. There has been documented a zone of weakness in part of membranes overlying the cervix. The choriodecidual layer has been shown in studies done in vitro to be the first layer to rupture, before the amnion layer. The sequence of rupture of the membranes in normal term pregnancy is fetal membranes distention, separation of the amnion and choriodecidua, rupture of the choriodecidua, nonelastic further distention of the amnion, and amnion rutpure. The amnion is stronger than the choriodecidua. The strength of the intact fetal membranes is equal to the sum of the strength of its individual components, however it takes greater work to rupture the two than one layer individually. Studies in the normal physiology could possibly give further clues to as what goes wrong in cases of PROM and PPROM (2).

The membranes may resist to a pressure higher than the intrauterine one. They rupture if submitted to acute increases in pressure and or damaged by any risk factors. If

pressure increases this leads to reduced utero decidual perfusion of the membranes (2).

The membranes are not damaged uniformly. The common place of rupture is the lower pocket because this is the locus where ascending infections attack (20).

However, there is evidence that suggest that when the membranes are stressed, either by internal pressure due to labour or by infection, they are weakened and have an increased susceptibility to premature rupture. With advancing gestational age the stretching of the membranes and strains due to uterine activity, leads to decreased tensile strength. There is also possible that developmental weak spots in the membranes could exist (4).

Several studies have shown that both the cytoarchitecture of the amniotic membrane and the quality and the quantity of membrane collagen are altered in the patient with PROM. Specifically it appears that collagen type 3 may be reduced. There is additionally enhanced collagenolytic activity has been found in premturely ruptured amniotic membranes. Regardless of this, in a normal pregnancy towards the end of gestation there is decreased content of collagen in the membranes (4).

Placental abruption is a strong predictor of PPROM. The occurrence of decidual hemorrhage as manifest by vaginal bleeding in the first trimester doubles the adjusted relative risk for preterm delivery. The risk of PPROM increases spceficially if there is bleeding in the later trimesters of pregnancy. Thrombin production is associated with abruption initiated PPROM. Human decidua contains excessively high levels of tissue factor, the primary cellular initiator of hemostasis. Once thrombin is formed this cleaves fibrinogen into generating the fibrin clot. Thrombin is able to bind to protease activated membrane receptors in several cell systems, e.g. in decidual cells, to initiate an array of biological actions including the synthesis and secretion of matrix metalloproteinases (MMPs). Among the classes of MMPs, there are some that can degrade broad arrays of extracellular matrix components. In addition, MMPs also have an autoactivating ability, activating and recruiting higher numbers of MMPs (17).

In more than 50% of the cases, PPROM occurs when the woman is at physical rest. Physical activity doesn't seem to be of importance (4).

There is now compelling evidence that infection is a major etiologic factor in a significant proportion of preterm labour and preterm premature rupture of fetal membranes. Chorioamnionitis is associated with preterm PROM (21).

The most commonly associated organisms found were those causing bacterial vaginosis, Trichomonas vaginalis, mycoplasmae, chlamydia trachomatis, Neisseria gonorrheae, group B Streptococci. In addition, Bacteroides fragilis, peptostreptococci, and Fusobacterium, bacteria commonly isolated from the amniotic fluid in the presence of preterm labour, and other common vaginal bacteria including lactobacilli and staphylococcus epidermidis may release inflammatory mediators which may cause uterine contractions.

Ureaplasma urealyticum was found in amniotic fluid of women who had adverse outcome of pregnancy (25). Presence of this bacteria was associated with increased rupture of the membranes, postcaesarean endometritis, development of chronic lung diseases in the offspring. It was found also, in the same study, that colonization of amniotic fluid occurs early in pregnancy. Bacterias present may produce proteases and phospholipases initiating digestion and breakdown of the membranes. This leads to cervical change, separation of the chorion from the amnion, and the premature rupture of the membranes. The pathogens mentioned above are also associated with preterm labour, where membranes are intact.
It has been found in a postnatal study, that only 50% of those women who were found to have microbial invasion of the chorioamnion also had the microbial colonization of the amniotic fluid (21).

The woman might even under occult infection have a response to the pathogens present. Leukocyte activation and cytokine release are further methods of how membrane weakness could arise (8).

The possibility of a direct membrane trauma underlying the rupture, should not be forgotten. It could also be due to iatrogenic causes such as cerclage placement, amniocentesis.

Maternal and fetal stress may also lead to the release of stress mediators via the hypothalamic pituitary adrenal axis leading to enhanced production of placental corticotrophin releasing hormone. The latter acts as a paracrine effector, enhancing the release of enzymes and compounds which may lead to PPROM. This state of infection is best treated with complete avoidance, since treating it after it has begun is often too late since it already might have caused irreversible damage to the membranes. Attempts at turning the process could be damaging themselves. The earlier in pregnancy at which abnormal genital tract flora was detected, the greater was the risk of PROM. A positive screening test at 26 to 32 weeks was associated with statistically significant 1.4 to 1.9 fold increased risk of PROM. A similar finding in the second trimester was associated with 2.6 to 6.9 fold increased risk of late miscarriage or PROM. It was found that antibiotics used against this pathogens in first trimester was much more helpful and reduced the risk much more than if given during second trimester, when damage to the membranes might already have taken place. Antibiotics helped most of the women revert to normal vaginal flora. Even though normal flora was restored outcome of pregnancies were shown to be adverse, e.g. PROM. The damage done by these pathogens even in early pregnancy could cause problems even months after. The integrity of the menbranes could be somewhat compromised, leaving them weaker, On a more positive note, one could focus upon the fact that due to this there is actually a vaginal marker that could be somewhat predictive in the outcome of given pregnancies (1, 4, 8, 10, 12, 15, 19, 21, 24).

Smoking constitutes a risk factor for PROM (14). The risk of preterm birth with or without PROM is shown to be increased with smoking. Among women with two

successive births, those who stop smoking from one pregnancy to the next, reduce their risk of preterm birth in their second pregnancy to that of non smokers in both pregnancies. These findings suggest a direct effect of smoking during pregnancy on risk of preterm birth. Smoking related causes of preterm birth may include spontaneous preterm labour , preterm PROM and antepartal bleedings, as recently reported from a French case control study, using retrospectively collected information on smoking exposure during pregnancy. It was found in the study that there is a dose dependent association between smoking and risk of very preterm birth. Heavy smokers, i.e. more than 10 cigarettes every day, had a three fold increased risk compared to nonsmokers. The mechanims underlying preterm birth are associated with PPROM, idiopathic spontaneous labour and pregnancy bleedings

Poor nutritional status constitutes a risk factor for PROM and preterm labour (4)

Certain factors are called not remediable factors. These constitute PROM in a previous pregnancy, Ehler Danlos syndrome, placenta previa, placental abruption, marginal insertion of the umbillical cord, battledore placenta, multiple gestation, polyhydramnios, uterine anomalies and incompetent cervix. Recurrence risk for PROM is estimated to be 20 to 30% (4).

Fetal malformations and malpresentation are also risk factors for PROM (8).

Complications of PROM

The complications of PROM can be defined as fetal, neonatal or maternal.

The consequences of PROM for the neonate fall into 3 major overlapping categories.

The first is the significant neonatal morbidity and mortality associated with prematurity. If being born during 24 gestational week, survival rate is being assessed as being so low as 36%. Once reached week 28 or 29 survival rate becomes a whole better, as high as 85 to 90 %. Survival rates are dependent on many factors that could arise during the course of pregnancy and delivery (4, 8, 20).

Second are the complications during labour and delivery that increase the risk for neonatal resucitation. Due to changes in the volume of amniotic fluid, this could be frank oligohydramnios, that could accompany PROM there is an increased risk for cord prolapse which would compromise the fetal blood flow and hence oxygenation. Umbilical cord prolapse is an uncommon but potentially lethal obstetric emergency (10). The reported incidences vary from 0,14% to 0,62% with perinatal mortality rates ranging from 55 to 430 in 1000. Stillbirth occurs in 1 to 3 %. PROM is a very important risk factor, as is multiple gestation, low birthweight, fetal malpresentation, multiparity and obstetric manipulation. Prompt delivery is usually required for fetal survival, often by emergency caesarean section unless, vaginal birth is imminent. However there are report of pregnancy in 23 gestational week having being conservatively treated and observed for 3 weeks before CS was undertaken leading to the birth of a preterm but healthy baby boy (16). Delivery before 23 week would most likely have compromised this babys life, since lung maturity is not completed by that gestational age. Neonates down to gestational age of 24 week have been saved, since their lungs at this age actually has started the maturity process, and it is possible to medically induce further maturation by application of corticosteroids, see below.
A number of manouvres are described to reduce risk of cord compression including manual elevation of the presenting part off the cord, tocolysis, bladder filling, placing the patient in the knee chest position and funic reduction. One must keep in mind the risk of cord spasms upon manually reducing the cord prolapse outside the vagina (16).

The assessment of amniotic fluid is very important. This can be done by the use of ultrasound, as mentioned above. If the greatest pocket is more than 2 cm, the risk of harm for the fetus is low. But for better accuracy amniotic fluid index, AFI, should be calculated. If exposed for a long time to oligohydramnios, the fetus is at risk of developing non renal agenesia (Potter syndrome). The duration of exposure might be as little as six days (8).

Early PROM is associated with fetal deformations syndrome. Signs of this syndrome could be IUGR (intrauterine growth retardation), compression deformities and pulmonary hypoplasia.

Pulmonary hypoplasia is a condition that could compromise the neonate and the fetal life as mentioned above. Etiologies of this condition has been presumed to be due to compression of fetal chest, eg. In diaphragmatic hernia, increased outflow of lung fluid, and decreased fetal breathing movements. There are no one reliable diagnosis for this. Chest circumference, lung size, amniotic fluid volume, fetal breathing activity and doppler blood flow in ductus are all measures in current use (4).

Third are the infections. Preterm PROM is especially in risk of developing neonatal sepsis. This risk is further increased when there is maternal chorioamnionitis and

endomyometritis. The risk of sepsis itself is independent of duration of PROM, however prolonged PROM does increase the risk for maternal infection, and it is estimated that 20 to 25% of preterm PROM where there is maternal infection there will be neonatal sepsis. Neonatal sepsis occurs in as much as 40% of PROM before 20 week of gestation, and decreases drastically by 28th gestational week (9, 21).

Maternal infection is termed chorioamnionitis and fetal infection may occur as septicemia, pneumonia, urinary tract infection or local infections such as omphalitis or conjunctivitis.
The previous refers to infection of the umbillical cord. The incidence of chorioamnionitis, in association with PROM varies with the population studies. In prolonged rupture of the membranes, the incidence is 3 to 15 % and it appears to be more common in PPROM with a frequency of 15 to 25%. Major neonatal infections occur in about 15% of all cases of preterm PROM and in 15 to 20 % of those with chorioamnionitis (4).

Morbidity and mortality associated with PROM increases with decreasing gestational age (20).

Once the membranes rupture, the duration of the latency period varies inversely with the gestational age. When PROM occurs between 28 and 34 weeks, or , 50% are in labour within 24 hours and 70 to 80 % within 1 week. At term, 50% of the women have latency period lasting less than 6 hours. 95% in the same group have latency period lasting less than 72 hours (4, 21).

Maternal complications include infection, increased risk of cesarean section, and placental abruption in as much as 8%. The maternal infection is increased in the cases where the PROM is preterm, before week 24 of gestation the risk is as high as 35 to 45%.
PROM is associated with an increased risk for caesarian section due to fetal distress due to maternal infection, higher incidence of malpresentation. Fetal monitoring is mandatory in these pregnancies, fetal distress shown by for instance deep variable decelarations on the cardiotocogram (CTG). Reliable factors one should look to for estimating fetal well being is result of non stress test (NST) and biophysical profile. Reactive NST is associated with 93% fetal survival within one week.Factors relying on one factor such as maternal fever and fetal tachycardia could of course reflect a true state of fetal compromise, but does have quite a high false positives.(4, 8).

Clinical signs of maternal infection are fever, above 38 degrees celsius of longer than 24 hour duration, tachycardia over 100 bpm, leukocytosis, uterine tenderness, foul vaginal discharge, fetal tachycardia, abnormal fetal testing, elevated CRP or ESR. If two or more of these signs are present, chorioamnionitis is considered to be present.

A number of studies have demonstrated that intrauterine infection may be associated with the subsequent development of adverse neonatal outcomes such as neonatal deaths, periventricular leukomalacia, intraventricular hemorrhage, cerebral palsy and bronchopulmonary dysplasia (10).

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The relative contibutions of prematurity and perinatal infections to perinatal mortality are responsible for most of the controversy surrounding the optimal management of PPROM (5). In most cases, perinatal mortality consequent upon PPROM arises from complications of prematurity such as respiratory distress syndrome, intraventicular hemorrhage, and necrotizing enterocolitis. Thus, in a 26 week gestation, the relative contribution of prematurity to the risks of perinatal morbidity and mortality far outweigh any risks from infection, and thus all efforts at prolonging pregnancy would seem reasonable. However, in a fetus at 34 week gestion, at which point perinatal mortality is not substantially different from that of a fetus at term, the relative contribution of infection becomes more important.

Diagnosing PROM

The diagnosis of rupture of the membranes is based on the logical sequence of history, physical examination and investigation. In many instances, it is clear from a history of sudden gush of fluid from the vagina and its continuing intermittent trickle. Even though there are no real prodromes of PROM or PPROM, there is found that amniorrhea are sometimes preceded by lower pelvic pain in approximately 35% of cases and in 30% of cases increased vaginal discharge.
Amniorrhea is the single most important sign. However, most fluid might have escaped and fluid may not be present in the vagina making it difficult to confirm or refute the diagnosis. Furthermore, fluid may be contaminated with urine, cervical mucus, bath water, vaginal discharge, blood or meconium. Because of these difficulties, even when fluid is available, the differentiation between amniotic fluid and urine, or vaginal secretions is essential. Indeed, Kragt and Keirse, found that 20% of women with preterm getations who came to a labour and delivery unit with a primary complaint of aqueous discharge, didn't have ruptured membranes. False positive signs of PROM could be fluid leakage from other sources than membrane rupture e.g. urine, advanced cervical dilation, membrane prolapse, cervicitis and bloody show (4).
The pH in vagina is usually between 4.5 to 6. Amniotic fluid usually has an alkaline pH lying approximately at 7.1 to 7.3. Other fluids that share this is blood, semen, alkaline urine and vaginal milieu in the case of bacterial vaginitis.

No one test has been found to be completely accurate, and diagnosis still requires an integration of the clinical history, physical examination and laboratory testing.
These tests are currently used for diagnosing ROM

- Ferning. Arborization or fern like patterns occurs in a number of body fluids when put onto a glass slide due to the presence of proteins and electrolytes. Positive ferning is considered to be a sign of ruptured membranes. In case there is blood, urine or meconium, the results could misleading.

- Nitrazine test. Probably the most widely used test in establishing the diagnosis of ruptured membranes. Nitrazine is an indicator paper with a narrow set point of PH 6.4 to 6.8. where it undergoes the characteristic colour change to blue in the presence of amniotic fluid.

- Pooling of fluid in the vagina
- Ultrasound, measuring the deepest pocket or calculating amniotic fluid index, amniorrhea could be diagnosed and the quantity of amniotic fluid could be followed throughout pregnancy, thus confirming if oligo hydramnios is still

present or recovered. The presence of an anterior pocket is a valuable prameter of the pregnancy outcome.

- Indigo carmine
- Fluorescein dye
- Fetal fibronectin
- Alpha fetoprotein
- Fetal cells
- Valsalva
- History, very important in the diagnosis

Overall, the combination of history, physical examination, nitrazine testing and microscopy for fern like patterns of amniotic fluid should lead to the correct diagnosis of up to 90% of cases of premature rupture of membranes. The question as to whether or not to perform vaginal examination in patients with PROM is a controversial area of practice. The most widely held opinion is that a visual speculum examination alone is sufficient to provide most of the necessary information required for management (4).

In studies done on women with PPROM and preterm delivery there was found a correlation between elevated levels of C reactive protein (CRP) and CD63. (24). Increased serum levels of the latter, was associated with a ten fold increase in preterm delivery with or without PPROM. Macrophages with receptors to this inflammatory marker are abundant and predominant in the preterm placenta. Elevated CRP is associated with five fold increase in risk of preterm delivery. PROM and preterm delivery can be predicted by other biomarkers as well. I have touched on the subject of cytokines above. Il6, in addition Il 1, 8 and TNF have been associated with PPROM.
Fetal fibronectin is uniquely produced in the fetal tissues, as well as some malignant tumors (23). It is mainly in the amniotic fluid and placenta. It is thought to have the function of cellular glue in cementing the blastocyst into the endometrium. Its presence in vaginal fluids could indicate microruptures in the fetal membranes or disruption of the choriodecidual interface often caused by occult intrauterine infection. Positive test on its presence in the vagina even in early stages of pregnancy is associated with 15 fold increase of preterm delivery.
Cortocotrophin releasing hormone (CRH) is produced also during pregnancy by placenta and fetal membranes. It has been suggested that this hormone, which is particularly high in the later stages of pregnancy leading to increased cortisol levels, may be a placental clock, and that the timing of the rise of free CRH determines the onset of labour (23).

Microbial invasion of the amniotic cavity is frequently observed in patients with PPROM. It is a major risk factor for neonatal infection and adverse neonatal outcomes. Antenatal detection of neonatal infection would also make it possible to target more accurately the population of newborn infants who require antibiotic treatment (19, 21). PPROM and elevated levels of IL 6 in amniotic fluid are associated with microbial invasion, chorioamnionitis and preterm delivery. Il 6 has a better diagnostic value for these complications than other markers that are studied in

amniotic fluid, which include Gram stain, glucose levels, white blood cell count and leukocyte esterase. Methods for investigating amniotic fluid could be by obtaining amniotic fluid by amniocentesis or using sample of fluids pooled in the vagina after the rupture of the membranes. Detection and assay of IL 6 can be done by using qualitative immunochromatographic test that can even be performed at bedside (9, 16). The test is easy to perform, is cheap and is quicker than other possible tests such as ELIZA. Results in a correctly perfomed test is 15 minutes. It has been found that IL6 in vaginal fluid is better correlated with neonatal infection and outcome than maternal serum levels of CRP and CR63. On a more negative note, only 30% of those patients with a positive result, actually have elevated levels of IL6. This could lead to treatment of patients not needing treatment with antibiotics. However, maybe the value of the bedside test in an emergency lies in determining those who do have a negative result.

Management of PROM

Of primary importance is to verify the diagnosis. This can be done by methods mentioned above. One useful method is by using sterile speculum. Other very important matters to keep in mind during this examination is to estimate cervical dilation, if there is any sign of cord prolapse through the uterine cervix, or prolapse of any other fetal parts for that matter. One could use this opportunity to release cervical cerclage, and also obtain cultures of chlamydia, GBS and any other pathogens that could be source of infection (4, 5, 11, 20).
The fluid collected given it is amniotic fluid could be sampled and used to assess lung maturity. It was also once used to diagnose intra amniotic infection. The latter indication has been discarded. Calculation of fetal well being can be done by assessing biophysical profile.

Ultrasound is of vital importance in determining fetal presentation, gestational age, evaluate growth and estimate fetal weight, exclude fetal anomalies and also to measure amniotic fluid volume. Information obtained by ultrasound can be combined with CTG,,non stress test, manual examination and maternal sensation of fetal movements in assessing the fetal well being and in making a biophysical profile.

Pulmonary maturity must be determined. If gestational age is more than 32 weeks and there is evidence of pulmonary maturity labour can be induced and the baby delivered. This would decrease the risk of mother developing infection, and the fetus for that matter, and the fetal outcome would not be changed even if labour is postponed as long as is possible. In Norway, PROM in term pregnancies, are managed in such a way that mother is observed at home basis for signs of prolapse or infection, It is custom that the labour is given a chance to initiate on its own if there are no complications, without the use of intitating medical agents. If failure to progress to

labour within five days, depending on the patients profile, the delivery will be initiated.
Inducing agents could be prostaglandins followed by pitocin (5).

Fetus and mother should be monitored continuously for 24 to 48 hours while admitted on gynocological and obstetric ward immediately after conditon has been diagnosed or while being examined.

Transient contractions often follow PROM, in early pregnancy these might not be recorded on monitor, so it is vital that one listens to the patient and describtion of sensations. The finding of repetitive variables on a monitor strip should suggest labour. Digital examination should be avoided until labour in verified. One should keep in mind that labour could progress rapidly. Fetal acidosis for cord compression may occur quickly. A prophylactic amnioinfusion could be helpful.

If neither mother nor fetus are found to be compromised in well being, home management is one option. This could be done in the cases where the gestations are previable, i.e. older than 24 weeks and there is a resolution of leakage. The latter occurs in 10% of these cases.
Problems and risks of home management are quick labor, delayed diagnosis of infecton, sudden abruptions and unrecognized fetal distress. The mother should frequently be examined for signs of labor, chorioamnionitis, fetal or cord compromise and placental abruption. This means on a daily basis. One should look for ominous signs such as drop on non stress test or biophysical profile conversion or fetal tachycardia on top of this (4).

In case chorioamnionitis should arise, labour should be induced. If the indications are those for CS, preparation of the patient for this should be started promptly. Appropriate antibiotics, which ones could be given by culture result if time allowed this, or started empirically by assumption of underlying pathogens. Enhanced spectrum ATB that cover GBS, e.g. ampicillin, amoxicillin, clavulanic acid, and erythromycin. Treatment should be of minimally 7 to 10 days duration, and mostly until GBS culture is negative, could be also until delivery? Fetal outcome is better if atb is given as prophylaxis. It is not suitable to use bacteriolytic atb because of the toxins induction of preterm contractions.
Antibiotics unfortunately are associated with increased risk and frequency of necrotizing enterocolitis. One concern is that atb given to mother could lead to resistance in the neonate. Hyperthermia should be controlled and oxygen should be supplemented. During the whole process of chorioamnionitis being diagnosed until delivery of the baby, the fetus should be monitored, Amnioinfusion could be needed.

If labour and not CS is induced, one should be careful and observe carefully for any signs indicating that labour is progressing dysfunctionally (5, 20).

Inducing the labour in PROM at term could be done with various agents. Intravenous oxytocin relatively close timewise after the rupture, has shown to be associated with low incidence of infection. Other promising agents are misoprostol, an E1 analogue, was shown to reduce the latency period (8).

Management of preterm PROM

The major risks to the baby following PROM are related to the complications of prematurity. The neonatologist and obstetrician should work as a team to ensure that optimal care is provided for the mother and fetus. Several studies have shown that small changes in gestational age have significant impact on survival especially for neonates delivered between 24 and 26 weeks. Morbidity is also dependent on weight and decreases with increasing brithweight (8).

Since the goal of management in PPROM is prolongation of pregnancy, the most commonly accepted management scheme for the patient less than 36 weeks is expectant management in the hospital which consists of careful observation for signs of infection, labour or fetal distress in an effort to gain time for fetal growth and maturation. Although most patients comit themselves to delivery by going into labour, some do reach term and the timing of delivery must be decided. When the patient reaches 36 or 37 weeks, delivery may be accomplished but documented lung maturity may permit a somewhat earlier delivery.

This expectant approach is complicated by controversies surrounding the efficacy of tocolytic agents to stop uterine contractions, prophylactic antibiotics, corticosteroids to accelerate fetal lung maturation, and amniocentesis for diagnosis of occult infection and fetal lung maturity. In any event, where adequate facilities for intensive perinatal and neonatal care is lacking, it is prudent to refer the patient to a center where such facilities are available.

Prophylactic tocolysis could be beneficial also if labour is postponed for only a few days. This buys time to allow corticosteroid administration which is beneficial for pulmonary immature fetuses. One could administer corticosteroid such as dexamethasone. Corticosteroids are recommended if before 30 to 32 gestational week. Has demonstrated to also reduce the risk of respiratory distress syndrome. In a study dexamethasone had a clearly much lower incidence of RDS than the control study. However, on a more negative note, the incidence of maternal infections are increased with the use of corticosteroids. So ultimately, securing a more mature pulmonary profile could put the fetus in a situation of facing sepsis (3).

Approximately 24 hours is needed for administration and shown benefit for the fetus. It is confirmed that the best results are achieved after the first treatment, beginning after 24 hour up to one week after. The second cycle of treatment gives a lower rate of RDS prevention. As mentioned above intramuscular is preferred method to oral treatment. Steroids appear to be succesful to prevent RDS when administrered in pregnancies between week 27 to 30 with prevention rates of about 50%. The treatment with corticosteroids application started as trial in 1972 by Liggins and is

today one of mainstay treatment in PPROM. Fetuses are shown to have an effect of this. Neurological impairment were shown to be less frequent in those infants who were treated with CS. Pulmonary maturation also benefits from this. Pulmonary maturation are by reasons unknown accelerated in PPROM.
Tocolytics are contraindicated regardless fetal pulmonary status if there are signs of infection, abruption or fetal compromise (3).

PROM is associated with an increased frequency of maternal infection, neonatal infection and fetal distress during preterm and term labour. The main challenge therefore, it is how to recognize and detect intrauterine infection at its incipient stages. In the United States, analysis of amniotic fluid obtained by amniocentesis is currently the most widely practiced method to determine the presence or absence of bacteria in the amniotic cavity and to determine fetal pulmonary maturity. The most common tests for the detection of bacteria are Gram stain and cultures for aerobic and anaerobic bacteria including Mycoplasma species. In order to improve the efficacy of Gram staining, other markers of infection have been examined by different groups such as amniotic fluid white blood cell count, leukocyte esterase and glucose. Although there is currently inadequate evidence on the value of amniocentesis in PROM, it would appear that the routine use of transabdominal amniocentesis to detect silent intraamniotic infection, is justified.

Ultrasonography has become an essential part of the evaluation of patients with PPROM. The evaluation includes assessment of dates and size, exclusion of fetal anomalies, and determination of fetal behavior.

The use of prophylactic antibiotics in PPROM could reduce maternal and perinatal risks of infection and secondly, the interval from PROM to delivery might be prolonged, since occult infection is a probable cause of PPROM and preterm labour. In a metaanalysis of antimicrobial therapy in PPROM, Mercer and Arheat showed that antimicrobial treatment offered significant benefit in pregnancy prolongation and fewer women delivered by 24 hours with antimicrobial therapy and at 48 hours. There was also a decrease in the incidence of chorioamniotitis as well as infectious maternal and infant morbidity including sepsis and pneumonia. However, many questions remain to be answered including whether or not these findings are applicable to all populations, what is the best antibiotic including route and duration of therapy, and whether or not a selective approach is feasible reserving antibiotic therapy for a specific group of patients at higher risk. Until these issues are addressed, the use of antibiotic prophylaxis in PPROM should be individualized and blanket use should not yet be regarded as standard of care as it may increase iatrogenic morbidity from superinfection due to resistant bacterial species (4, 19).

The benefit of antenatal corticosteroid therapy has been demonstrated in several randomized controlled trials. The overall reduction in the odds of neonatal RDS is about 50%. This beneficial effect on RDS is thought to have a domino effect on other

forms of neonatal morbidity including a 10% and 80% reduction in the odds of periventricular hemorrhage and necrotizing enterocolitis respectively (3).

In the light of available evidence, corticosteroid therapy should be initiated as soon as possible in all cases of PPROM from 24 to 34 weeks unless immediate delivery is indicated for chorioamnionitis, antepartum hemorrhage, cord prolapse or fetal distress. Treatment should consist of dexamethasone by intramuscular injection in two doses at 12 hour intervals. If the patient remains undelivered after 1 week, an attempt should be made to assess lung maturity and to repeat the corticosteroid regime if necessary (3, 20).

Several prospective randomized controlled trials of tocolytic agents, i.e. agents that reduce uterine contractions, in patients with PPROM have been conducted. Overall, there was no difference in pregnancy prolongation beyond 24 hours or any difference in any index of perinatal mortality or morbidity measured. Two randomized trials of prophylactic oral tocolytics also failed to show pregnancy prolongation. These data offer no support for suggestions that prophylactic oral tocolysis before the onset of uterine contractions is worthwhile. A possible but unproven advantage of tocolysis lie in the postponement of labour in order to facilitate in utero transfer in PPROM and the time granted to administer corticosteroids. No great side effects of the cortic osteroids administered have been documented. Examples of tocolytic agents are oxytocin, barusiban, atosiban. Unfortunately the tocolytics are reported to have some cardiovascular side effects.

In cases of PROM very early in pregnancy, survival after delivery at or less than 23 weeks is limited, and neonatal morbidity and mortality after delivery at 24 to 26 weeks are high. If labour or clinical infection is present at initial evaluation of these patients, delivery is indicated. For the remainder of patients, there are two options, expectant management or termination. It is extremely important that the patient be involved in the decision process. On going counselling and psychological support are essential in the management of this morbid pregnancy complication (4, 5).

Timing of delivery depends on the previable status of the fetus. This is set at approximately 24 gestational week. At this gestational age, termination versus conservative management should be assessed. Only 20 to 25% of these pregnancies will continue for 30 days until a time when fetal maturity is improved. All along one has to calculate and bear in mind maternal and fetal risks. Number one risk is actually chorioamnionitis.

Should one initiate labour induction or expectant management in PROM at term? The question as to whether to induce labour immediately or not when PROM occurs at term is a vexed issue. Reports on the widespread practice of immediate induction of labour showed that the policy resulted in high ceasarean section rates which were

thought to be due to the fact that the cervix was unripe in many cases. However, a recent careful large randomized controlled trial that includes 5041 women with PROM at term showed that induction of labour with intravenous oxytocin, induction of labour with vaginal prostaglandin E2 gel, and expectant management are all reasonable options for women and their babies if membranes rupture before the start of labour at term, since they result in similar rates of neonatal infection and ceasarean delivery. However, induction of labour with intravenous oxytocin resulted in a lower risk maternal infection and women viewed induction of labour more positively than expectant management. (4).

Progesterone supplementation for women with PPROM has been documented to have a promising effect, prolonging the pregnancy and hence improving fetal outcome. However, the optimal doses and intervals of administration of progesterone are not clear presently.

In the recent Centers for Disease Control and Prevention recommendations for preventing early onset neonatal group B Streptococci, prolonged rupture of membrane for more than 18 hours was classified asa risk factor for GBS infection and antibiotic chemoprohylaxis with penicillin or ampicillin was recommended in this setting. For women allergic to penicillin, clindamycin or erythromycin would be suitable alternatives.
Antimicrobial treatment against bacterial vaginosis in asymptomatic women do not seem to have any effect in preventing PROM. One study, however, found that women with pathogens in vaginal flora and positive fetal fibronectin in vaginal fluid had effect of administration of metronidazole (22).

The following scheme is generally recommended (4).

20 to 24 weeks of pregnancy, the survival rate is very low, less than 20 to 25%, with a vey accurate expectant management of the pregnancy. Infection risk is very high and the long term complications are very common and need an expensive follow up. Therefore, termination of pregnancy is more offered to the parents.

24 to 26 weeks of pregnancy, most of the studies suggest active management, checking for infection or fetal distress. In case of clinically apparent symptoms and positive laboratory results for choriomanionitis, it is advisable to interrupt the pregnancy by induction of the labour. Caesarean section should be avoided if possible, being associated with a high rate of puerperal infection.

26 to 30 weeks of pregnancy, observation and folllow up are advisable. Antibiotic prophylaxis and steroids are considered to be of benefit. The risk of prematurity is higher than the risk of fetal and neonatal infection. This age group has the highest benefits from the steroids treatment. Tocolysis is indicated if transfer to another health care unit is needed.

30 to 36 weeks of pregnancy, survival rate is high in this group. Lung maturity is achieved in more than 50% of cases, thus one has to check if steroids are needed. Antibiotics are advisable if the latent period is rather long. Interruption of pregnancy, once the diagnosis of intra amniotic infection is confirmed, has no better outcome than using antibiotics before induction is commenced. In this age group induction failure rate is low and the need of CS and its puerperal complications are rare.

Prognosis

The neonatal outcome in PROM could be divided into short term and long term prognosis. Short term prognosis depends upon factors such as gestational age and weight at delivery, gestational age at rupture and if there is infection present.

Long term prognosis depends on gestational age at delivery and if there is infection present.

PROM is associated with 66% neonatal deaths if gestational age is less 20 weeks, decreasing to approximately 7% if gestational age reaches 27 to 28 week. Approximately half of neonatal deaths in gestional age before week 20 was associated with pulmonary hypoplasia, decreasing to 3% if gestation reaches 25 to 28 week.

Interruption of pregnancy is considered when the risk of infection overcomes the risk of prematurity. There are three major indications, which obviously suggest the interruption of pregnancy

- fetal lung maturation
- fetal distress
- maternal and, or infection.

Many studies advice decision making according to the gestational age. Before week 24 rate of survival is very low, 36%. Gestational age higher than 25 th week, 50% of neonate survive.

Abruption of placenta and vaginal bleeding occur in 4 to 12% in patients with PPROM. These cases are further associated with short latency periods, and hence also more grave fetal outcome, compared to women with PROM who didn't have this. It has been found that neonates born to women with PPROM and vaginal bleeding wew more likely to have RDS than neonates to mothers with PPROM but without vaginal bleeding (4, 7, 10, 15, 17).

Conclusion

Premature rupture of the fetal membranes is an obstetric enigma and several aspects of management of PPROM and PROM at term remain controversial. Although clinical judgement, physician experience and careful individualization of management will often come into play, certain principles are widely accepted as being essential.The issues to be addressed by the obstetrician caring for the patient presenting with PROM

- Are the membranes indeed ruptured?
- What is the gestational age?
- Should the cervix be examined?
- Should labour be suppressed or induced?
- Should the mother be transported?
- Is there any reason to administer glucocorticoids?
- How and when should labour be accomplished?

These questions are best anwered based on the best available evidence. Future studies are warranted in PROM to identify the optimal methods prolongation of the latency period while avoiding compression deformities and pulmonary hypoplasia in cases where membrane rupture occur very early in pregnancy as well as the optimal mode surveillance in these pregnancies.

A healthy vagina and a competent cervix are defined as god barriers to ascending infections. Cervical mucus plays also an important anti bacterial role as well as the pH of the healthy vagina itself.

One important aspect in this field is to prevent PROM. This could be done by identifying high risk patients and the specific risks that put them in this category, and try to alleviate this factors before they instigate a cascade of events leading to PROM. The value of treating cervicitis and vaginitis is of great importance since infection, as mentioned above, is one major risk factor for PROM. Patients should be encouraged to report symptoms early, and they should also be taught and told what signs to look and feel for, even this might of course increase false positives. Cerclage should be placed when indicated, and preterm labour should be treated early.
In vitro studies conducted showed that antioxidants, e.g. vitamins C and E protect the chorion and amnion from damage due to reactive oxygen species produced in the presence of pathogens and infection of the genital tract (18). Vitamin C is required to scavenge oxygen species in the amniotic fluid and vitamin E prevents lipid peroxidation within the membranes. In addition, vitamin C is involved in collagen synthesis, an important constituent of the fetal membrane. Inadequate intake of these vitamins have been associated with PPROM and PROM. In vivo studies have unfortunately not been able to reproduce the in vitro results.

There are many studies dealing with this complication and yet there is no final agreement on the assessment of fetal well being, management and follow up of the pregnancy up to the decision when to interrupt it.

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