ORIGINAL RESEARCH PAPER

Obstetrics & Gynaecology

INTERLEUKIN 10 ANALOGUE AS A PROMISING ALTERNATIVE, IN THE MANAGEMENT OF PRETERM PREMATURE RUPTURE OF MEMBRANES – A COMPARATIVE STUDY.

KEY WORDS: Preterm Premature rupture of membranes (PPROM), Interleukin 10 analogue (IL10), Amnioseal.

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ABSTRACT

Preterm Premature rupture of membranes (PPROM) is one of the most important dilemmas in current obstetric practice. IL10 is a natural immunoregulatory cytokine required for preventing preterm labour induced by inflammatory cytokine. In this study, pregnant women in the study group were given Interleukin 10 analogue (Amnioseal), tocolytic, antibiotics and corticosteroids and control group received tocolytic, antibiotics and corticosteroids. Significant increase in the period of latency, period for which patient remains undelivered, was seen in the study group (28.36±8.76 days) than in the control group (10.28±5.13 days). The perinatal morbidity and mortality was significantly less in patients receiving Amnioseal, owing to increased gestational age and the favorable milieu externa of amniotic fluid which enables better survival prospects for baby as well as higher birth weight. Interleukin 10 analogue is a promising alternative to conventional therapeutic regimen for management of PPROM.

Background:
Preterm Premature rupture of membranes (PPROM) is a significant obstetric problem and one of the most important dilemmas in current obstetric practice. PPROM occurs in 3 % of pregnancies and is the cause of approximately one third of preterm deliveries. Choriodecidual infection or inflammation appears to play an important role in etiology of PPROM, especially at early gestational ages.[1] Preterm birth is responsible for approximately 75% of all neonatal deaths and 50% of childhood neurological morbidities.[2,3] it is also associated with high immediate and long-term costs after discharge from the hospital.[4]

The management of patients with PPROM has changed markedly in the past several years. Management of PPROM requires an accurate diagnosis as well as evaluation of the risks and benefits of continued pregnancy or expeditious delivery. Corticosteroids, tocolysis and antibiotics have been used for a long time. More recent treatment has included amnioinfusion and fibrin sealing. Comprehending the basic pathology at the molecular level, use of anti-inflammatory cytokines to modify the physiologically protective mechanisms or defenses may be the most effective method of preventing the onset of spontaneous preterm labor in premature rupture of membranes.

Hence, we have studied an interleukin 10 analogue -Amnioseal (a combination containing cytosine IL-10 enhancer, antimicrobial peptides, proapoptotic bax gene P53 inhibitor with other supportive factors like tocopherol, glutathione, biotin, folic acid, vitamins B1, B2, B6, B12 and arginine) for managing PPROM. IL10 is a cytokine produced primarily by monocytes and by lymphocytes. This is a natural immunoregulatory cytokine required for preventing PTL induced by inflammatory cytokines.[5] IL-10 could play a role in modulating or promoting resolution of the inflammatory processes associated with labour at term and with intrauterine infection-associated preterm labour. Amnioseal improves viscoelastic properties of chorioamniotic membrane, enhances anti apoptotic protein and encourages resealing.

Materials and Method:
It is hospital based comparative study carried out over a period of two year after approval from institutional ethical committee. The study group comprised of 50 pregnant women with singleton pregnancy with preterm premature rupture of membranes, those were given Amnioseal, tocolytic, antibiotics and corticosteroids. Another 50 pregnant women of preterm premature rupture of membranes were taken as controls and given tocolytics, antibiotics and corticosteroids.

Inclusion criteria: Women who were sure of date of the last menstrual period with gestational age more than 24 weeks & less than 36 weeks, history of leaking per vaginum with Cervical dilatation less than 3 cm, absence of active uterine contractions with demonstration of leaking per vaginum on speculum examination & membranes should be present with no additional obstetric complications & no symptoms and signs of chorioamnionitis.

Exclusion criteria: Gestational age less than 24 wks and more than 36 wks, pregnant women in active labour, multiple pregnancy, features of chorioamnionitis, profuse dribbling, pregnant women with medical disorders like hepatic, renal, cardio-respiratory, etc., fetuses with diagnosed congenital anomaly.

All pregnant women in control group were put on antibiotics, corticosteroids and tocolytics after sending a high vaginal swab for culture sensitivity. However, patients in study group were in addition given capsule Amnioseal. Dosage schedule was two capsules stat, two capsules after 3 hours followed by two capsules 8 hourly for upto 72 hours. Maintenance dose was one capsule twice daily for 15 days. Specific antibiotics were given according to the reports of culture and sensitivity.

Pregnant women were followed up daily monitoring of pulse, temperature, uterine tenderness and contractions, nature of discharge, leukocytosis, fetal heart rate, daily fetal movement count and cardiotocography and weekly ultrasounds for amniotic fluid index. The outcome of each pregnancy was documented in detail. Mode of delivery or any obstetric complications were noted. Time interval between the rupture of membranes and delivery of foetus and induction delivery interval in hours was noted.

During perinatal period babies were followed up for fever, gastrointestinal disturbances and signs of infections such as skin infections, conjunctivitis, oral thrush, umbilical cord sepsis and respiratory infection, etc. Signs of infections in the mother were noted as rise in temperature, tachycardia, foul smelling vaginal discharge, wound infection, uterine tenderness, involution of uterus and parametritis.

Data analysis
Maternal and foetal outcome in both the groups were recorded. The variables were studied in each group separately and compared. The data was analyzed using chi-square test.

Observations and Discussion:
The present study was aimed to study the efficacy of interleukin 10 analogue (Amnioseal), in management of preterm premature

rupture of membrane. It is also aimed to study the maternal and neonatal outcome when Amnioseal is used in patients of preterm premature rupture of membrane. Following observations were noted.

Table 1: Distribution of pregnant women according to parity and gestational age

	Study Group		Control Group		Z value	P value
	N	Percentage	N	Percentage		
Parity						
Nullipara	27	54	30	60	-0.61	0.54
Para 1	13	26	15	30	-0.45	0.66
Para2	10	20	5	10	1.40	0.16
Total	50	100	50	100		
Gestational Age (weeks)						
24-28	21	42	24	48	-0.60	0.55
28-32	23	46	18	36	1.02	0.31
32 – 36	6	12	8	16	-0.58	0.56
TOTAL	50	100	50	100		

N = number of pregnant women

Primigravida comprised the major population; about 27 and 30 in study and control group respectively (57%), while multigravida comprised 23 in the study group and 20 in control group (43%). The above result is comparable to the study by Pandey S et al[6], in which Primigravida comprised 52% and multigravida 48%. (Table1)

In the study group, about 42% (21) pregnant women were from 24-28 wks, 46% (23) were from 28-32 wks and 12% (6) from 32-36 wks of gestational age. In the control group, 48% (24) pregnant women were from 24-28 wks, 36% (18) from 28-32 wks and 16% (8) belonged to 32-36wks of gestational age. The differences between the two groups were statistically not significant therefore the results were comparable between study and control group. (Table 1)

In the study group, labour was induced in 52% (26) of pregnant women and 48% delivered spontaneously. Whereas 72% pregnant women in control group underwent spontaneous labour and about 28% (14) required induction.

Table 2 : Distribution of pregnant women according to Leaking induction and leaking delivery interval.

Leaking induction interval (Weeks)	Study Group N/Percentage	Control group N/Percentage	Leaking delivery interval (Weeks)	Study Group N/Percentage	Control group N/Percentage
1-2	0/0	11/78.57	<1	2/4	15/30
2-4	15/57.69	3/21.43	1-2	1/2	25/50
4-6	8/30.76	0/0	2-4	22/44	10/20
6-8	3/11.53	0/0	4-6	21/42	0/0
>8	0/0	0/0	6-8	4/8	0/0
			>8	0/0	0/0
Total	26/100	14/100	Total	50/100	50/100

The major brunt of PPROM is due to prematurity and by any means if pregnancy could be prolonged till the period of viability, would become milestone in management of PPROM.

Labour induction was done in 26 women in study group and 14 in control group. Of these 26 women induction was done within 2-4 weeks in 57.69% (15), 4-6weeks in 30.76% (8) and after 6-8 weeks in 11.53% (3). On the contrary in control group none of the pregnancies could be extended beyond 4 weeks and had to be terminated within 1-2weeks in 78.57%(11) and in 2-4 weeks in 21.43%(3). The above results were significant (p values <0.05). (Table 2)

The period of latency i.e. the period for which pregnant women remain undelivered in patients of PPROM was >4 weeks (28.36 days ± 8.76) in the study group whereas in control group none of the pregnancies could be extended beyond 4 weeks(10.28 days ± 5.13). The average increase in period of latency i.e. the period for which patient remains undelivered was 28.36 days (SD± 8.76) in study group and 10.28 days (SD± 5.13) in control group. The difference in period of prolongation of pregnancy between the two groups was statistically significant (p value <0.05). (Table 2)

In study by Dam P et al[7] the mean prolongation of gestational age in study group was 6.16 ± 3.21 as against 2.66± 1.95 in control group with p <0.005 (significant) in pregnant women at 26-30 weeks of gestation and mean prolongation of pregnancy was 4.19 ± 1.42 in study group as against 3 ± 1.54 in control group with p<0.01 (significant) in pregnant women at 31-36 weeks of gestation. The results of the above two studies are comparable.

Chorioamnionitis was found only in 1 women (2%) of study group as compared to 10 women (20%) in control group which had a significant p value of 0.01.

In study carried out by Newton ER et al[8], the overall incidence of intra-amniotic infection was 4.3%.

Table 3: Neonatal morbidity

Neonatal morbidity	Study Group		Control Group		Z-value	P-value
	N	%	N	%		
No morbidity	5	10.0	2	4.0	1.18	0.24
Prematurity	8	16.0	13	26.0	-1.23	0.22
Low birth weight	12	24.0	11	22.0	0.24	0.81
Birth Asphyxia	4	8.0	4	8.0	0.00	1.00
Fever convulsion	4	8.0	1	2.0	1.37	0.17
Septicemia	11	22.0	11	22.0	0.00	1.00
Pneumonia	3	6.0	4	8.0	-0.39	0.69
Jaundice	2	4.0	1	2.0	0.59	0.56
Respiratory Distress Syndrome	5	10.0	4	8.0	0.35	0.73
Congenital anomalies	1	2.0	0	0.0	1.00	0.31
Mortality	6	12.0	13	26.0	-1.78	0.07
Cerebral palsy	1	2.0	0	0.0	1.01	0.31
Hypothermia	2	4.0	3	6.0	-0.46	0.65

PPROM is a grave syndrome that may result in significant neonatal morbidity and mortality. In our study, low birth weight was major neonatal morbidity affecting 12 (24 %) in the study and 11 (22%) in the control group followed by septicemia affecting 11 (22%) each in study and the control group. Prematurity was found in 8 (16%) neonates and 13 (26%) neonates in study and control group respectively. 5 (10%) neonates in study group and 4 (8%) in control group suffered from respiratory distress syndrome. The neonatal mortality rate in our study, was 6 (12%) in study group and 13(26%) in the control group with p value of 0.07. There were also some other complication observed like birth asphyxia, pneumonia, cerebral palsy, fever and convulsions.

In study by Pandey S et al[6] prematurity was the most common offending factor (41.6%) responsible for all perinatal mortalities followed by neonatal sepsis, perinatal asphyxia and respiratory distress syndrome affecting 25% each. Devi A et al[9] found 29.8% of birth asphyxia in study group vs. 10.5% in control group. Prematurity was the most common neonatal morbidity. Kodkany BS et al[10] found birth asphyxia as the most common morbidity (29.5% cases) followed by respiratory distress syndrome (27.5% cases). Singh D et al[11] found neonatal mortality in 6.7%, purulent meningitis in 3% and pneumonia in 4.8% cases.

Conclusion:

Preterm premature rupture of membranes is an obstetrical complication which is associated with significant maternal and perinatal morbidity. Interleukin 10 analogue (Amnioseal) was found to increase the period of latency i.e. the period for which pregnant women remains undelivered, when given in combination with conventional therapy viz. tocolytics, antibiotics and corticosteroids (28.36 days±8.76). Amnioseal suppresses the inflammatory process which is involved in pathogenesis of preterm premature rupture of membranes.

Also, the perinatal morbidity and mortality was significantly less in pregnant womens receiving Amnioseal, interleukin10 analogue owing to increased gestational age and the favorable milieu externa of amniotic fluid around baby which enables better survival prospects for baby as well as higher birth weight.

Thus, we conclude that Interleukin 10 analogue (Amnioseal) is a promising alternative to conventional therapeutic regimen for management of Preterm premature rupture of membrane.

References:

1. Bendon RW, Faye-Petersen O, Pavlova Z, QureshiF,Mercer B, Miodovnik M, Et Al. Fetal Membrane Histology in Preterm Premature Rupture Of Membranes: Comparison to controls, and between antibiotic and placebo treatment. The national institute of child health and human development maternal fetal medicine unit network. Pediatr Dev Pathol 1999;2: 552–8.
2. Maymon E, Romero R, Pacora P, Gomez R, Athayde N, Edwin S. Human neutrophil collagenase (matrix metalloproteinase 8) in parturition, premature rupture of the membranes and intrauterine infection. Am J Obstet Gynecol 2000;183:94–9
3. Lewis DF, Major CA, Towers CV, Asrat T, Harding JA, Garite TJ. Effects Of Digital Vaginal Examinations On Latency Period In Preterm Premature Rupture Of Membranes. Obstet Gynecol 1992;80:630–4.
4. Alexander JM, Mercer BM, Miodovnik M, Thurnau GR, Goldenberg RL, Das AF. The Impact Of Digital Cervical Examination On Expectantly Managed Preterm Rupture Of Membranes. Am J Obstet Gynecol 2000;183:1003–7.
5. Oberg LJ, Garite TJ, Freeman RK. Fetal Heart Rate Patterns And Fetal Distress In Pregnant womens With Premature Rupture Of Membrarnes.1984; 60-64.
6. Pandey Swati, Dave Anupama, Bandi S. Maternal and fetal outcome in cases of preterm premature rupture of membranes. Journal of obstetrics and Gynaecology of India. 2000;50:63-65.
7. Dam Purvita,Laha Somnath,Bhattacharya Parnamita,Daga Pallavi.Role of Amnioseal in Premature Rupture of Membranes.The journal of obstetrics and gynaecology of India May/June 2011;61:296-300.
8. Newton ER, Prihoda TJ, Gibbs RS. Logistic regression analysis of risk factors for intraamniotic infection. Obstet Gynecol 1989;73(4):571-5
9. Devi Anjana and Rani Reddi. Premature rupture of membrane: A clinical study. J Obst Gynecol India 1996; 46: 63-76
10. Kodkany BS, Telang MA. Premature rupture of membranes: A study of 100 cases. J Obstet Gynecol Ind 1991; 41: 492-6
11. Singh D, Verma M, Simn M et al. Neonatal infections following premature rupture of membranes. J Obstet Gynecol. 1990;40:232-5.