East African Medical Journal Vol. 78 No. 2 February 2001
RISK FACTORS FOR PRETERM PREMATURE RUPTURE OF MEMBRANES AT MULAGO HOSPITAL, KAMPALA
D. Kaye, MBChB, MMed (Obs/Gyn), Lecturer,Department of Obstetrics and Gynaecology, Makerere University Medical School, P.O. Box 7072, Kampala, Uganda.

RISK FACTORS FOR PRETERM PREMATURE RUPTURE OF MEMBRANES AT MULAGO HOSPITAL, KAMPALA

D. KAYE

ABSTRACT

Objective: **To evaluate the epidemiological risk factors in patients admitted at Mulago Hospital with preterm premature rupture of the membranes from their socio-demographic characteristics and reproductive history.**
Design: **Cross-sectional case control study.**
Setting: **Labour ward, Mulago Hospital, Kampala, Uganda.**
Methods: **Cases were enrolled at admission while controls were enrolled after a term delivery not preceded by pre-mature rupture of the membrane (PROM). Controls were matched for age range (age $\pm$2 years) and parity with the cases. A detailed history of socio-demographic characteristics, past medical and surgical illness and past reproductive history were obtained and data entered into a coded questionnaire. Endocervical swabs and amniotic fluid samples were taken from the cases during labour. Validity was assessed using Chi-square with a p-value of less than 0.05 considered significant.**
Results: **Maternal socio-demographic characteristics were similar for cases and controls. A history of hypertension, abortion, prior PROM, Caesarean section, cervical cerclage, cervical incompetence or abnormal vaginal discharge were significant risk factors for preterm PROM ($p < 0.05$).**
Conclusion: **There are factors by which mothers at risk of preterm PROM can be identified before onset of rupture**

INTRODUCTION

Premature rupture of membranes (PROM) is the spontaneous occurrence of rupture of the foetal membranes before the onset of labour at term. If such rupture occurs before term (before 37 weeks of gestation) the condition is referred to as preterm PROM(1). The incidence of preterm PROM differs from community to community possibly due to population differences in contributory risk factors(1). Gunn *et al*(2) and Shubert *et al*(3), reported ranges of two to eighteen per cent and five to fifteen per cent, respectively. The significance of PROM depends on the gestation age at the time of occurrence(1). While most mothers at term go into labour and deliver spontaneously within 48 hours, those with preterm PROM have long and variable periods of latency whose length vary inversely with the gestation age(1). The incidence of preterm PROM increases with the gestation age(4). Preterm PROM is a major cause of perinatal morbidity and mortality. The main factors associated with these are prematurity, complications during labour and delivery, and perinatal infection(5). Preterm PROM precedes 40 to 60% of singleton preterm births(6) and is responsible, directly or indirectly, for ten per cent of perinatal deaths(7).

Maternal risks may be indirectly and inversely affected by the gestation age. Prolonged latency is associated with more risks to the mother than spontaneous labour, mainly from infectious and febrile morbidity, induction and Caesarean delivery(1).

Pathogenesis of preterm premature rupture of membranes: The foetal membranes are made of the outer thicker chorion, apposed to the maternal decidua, and the inner amnion. While the amnion is a single cell layer, the chorion is made of four to six layers attached to a collagen-rich connective tissue zone (at the basement membrane) and containing loose areolar tissue(1,5). Why do membranes rupture before onset of labour? How does this come about and what predisposes to it? The final unifying mechanism for premature rupture of membranes is a weakness in the chorioamnion membrane (relative or absolute, local or generalised)(1). This may be due to reduced size of the membrane at the rupture site(8), reduced collagen content(9), deficiency of type 3 collagen(10) or reduced elasticity(11). Proteolytic enzymes from cervico-vaginal flora or intra-amniotic infection may be the cause(1).

Several risk factors have been identified(12). Factors that antedate pregnancy include previous operations on the cervix, anatomical abnormalities of the cervix such as cervical incompetence, low socio-economic status and a history of preterm PROM or preterm labour. The factors in the index pregnancy that may predispose to rupture of

membranes include cervico-vaginal infections, anaemia, hypertensive disorders, coitus, vaginal examinations, maternal smoking, deficiency of some micronutrients, bleeding in the first, second or third trimesters and invasive procedures like amniocentesis or cervical cerclage.

MATERIALS AND METHODS

The study was a descriptive cross-sectional case-control study. Cases comprised mothers admitted in the labour ward with a diagnosis of ruptured membranes from the gestation age of 28 weeks onwards to 37. They included mothers of all ages and parities; those with singleton or multiple pregnancy; both booked and unbooked mothers, admitted to the labour ward between 1st February and 30th September 1996. Preterm PROM was defined as evidence of rupture of membranes before 37 weeks of gestation from history, clinical examination and speculum examination. Where the above were inconclusive, ultrasonographic demonstration of oligohydramnios was taken as evidence of membrane rupture. To be considered as booked, mothers had to provide documentary evidence of antenatal care attendance in a private clinic, maternity home, health centre or hospital on at least two occasions. Controls were matched for both and age parity with the cases. For both cases and controls, data regarding the maternal socio-demographic characteristics, gynaecological history, prior obstetric performance and events in index pregnancy were recorded on a coded questionnaire with the help of three assistants.

Maternal anaemia was defined as a level of less than 11g per 100mls (Sahli's method) or haematocrit less than 30% at admission or enrolment. Prior preterm delivery was defined as delivery before 37 weeks of gestation. Pyrexia was defined as a temperature of 38°C (axillary) or more measured using an electronic thermometer.

Vaginal discharge was considered abnormal if it fitted the criteria of the syndromic diagnosis of vaginal discharge and occurred within four weeks of rupture. Pre-eclampsia was defined according to the criteria of Davey and MacGillivray(13). For the cases, samples of amniotic fluid were taken from the vaginal pool using a pipette and cervical swabs taken. These were taken for culture and sensitivity tests. All the cases had antibiotics prescribed in labour. Overall, 186 cases and 180 controls were enrolled into the study. The data were analysed using the Epi Info-6 programme and tests for significance made using Chi-square, with a p value of < 0.05 considered significant.

RESULTS

During the study period, there were 6428 deliveries at Mulago Hospital labour ward. The prevalence of preterm PROM in this study was 2.89 per 100 births (2.89%).

Socio-demographic characteristics: The age distribution was similar for both cases and controls. The mean age of the cases was 23.188 (range 15-39 years) while that of the controls was 23.000 years (range 16-39 years). There were no significant differences in employment status, religion, marital status and educational level for the cases and their matched controls with a mean parity of 4 in both.

Table 1

Medical and surgical history of cases and controls

Risk factor		Cases n=186		Controls n=180		χ^2	P value	Sign
		Freq.	(%)	Freq.	(%)			
Abortion	Yes	58	(31.2)	39	(21.7)	425	0.03918	S
	No	128	(68.8)	141	(78.3)			
Preterm labour	Yes	24	(12.9)	21	(11.7)	0.13	0.71873	NS
	No	162	(87.1)	159	(88.3)			
Preterm PROM	Yes	58	(31.2)	13	(7.2)	33.59	<0.0001	S
	No	128	(68.8)	167	(92.8)			
Still birth	Yes	21	(11.3)	24	(13.3)	0.35	0.5518	NS
	No	165	(88.7)	156	(86.7)			
Caesarean section	Yes	22	(11.4)	10	(5.6)	3.88	0.04885	S
	No	164	(88.6)	169	(94.4)			
D and C	Yes	20	(10.9)	18	(10.1)	0.06	0.81422	NS
	No	164	(89.1)	160	(89.9)			
PPH	Yes	15	(8.1)	8	(4.4)	2.07	0.1498	NS
	No	170	(91.9)	172	(95.6)			
Cervical incompetence	Yes	15	(8.1)	2	(1.1)		0.0074	S
	No	171	(91.9)	178	(98.9)			
Hypertension	Yes	35	(18.8)	12	(6.6)			S
	No	151	(81.2)	166	(92.2)		0.00046	
Nature of abortion	SP	43	(74.1)	20	(51.3)		0.0489	S
	IN	15	(25.9)	19	(48.7)			

A history of abortion, premature rupture of membranes in a prior pregnancy, Caesarean section or cervical incompetence was highly significant as a risk factor for premature rupture of membranes. A history of preterm labour (without preterm PROM), postpartum haemorrhage, dilatation and curettage or still births was not significant ($p > 0.05$).

Table 2

Significance of operations on the cervix

Risk factor		Cases n= 186 Freq. (%)	Controls n = 180 Freq. (%)	$\chi 2$	P value	Sign.
Cervical Cerclage	Yes	11 (5.9)	1 (0.6)	10.91	0.0009	
	No	175 (94.1)	179 (94.4)			S
Operations on cervix	Yes	15 (8.1)	9 (5.0)			
	No	171 (91.9)	170 (95.0)	1.37	0.2419	NS

infection) within the previous one month was highly significant ($p = 0.00000061$), a history of bleeding in any trimester was not significant ($p = 0.74392$). Similarly, non-treatment of infection was significant.

Gestation age at which membranes ruptured: The lowest and highest gestation ages at which membranes ruptured were 26 and 36 weeks of gestation, respectively (mean 33 weeks, standard deviation 11.19). The gestation age was not specified in seventeen cases (9.1%). Where the gestation age was not specified, the fundal height and ultrasonographic gestation age estimation were used.

Time interval before presentation to hospital: The time interval prior to presentation ranged from 0 to 77 hours (mean 10.96 hours; standard deviation 11.65 hours; median 6.5 hours).

Antenatal care attendance: There was no significant difference in the time (gestation age) at booking antenatal

Table 3

Pregnancy complication and risk of preterm PROM

Risk factor		Cases n = 186 Freq.	%	Controls n = 180 Freq.	%	χ^2	P value	Sign
Haemorrhage	Yes	27	(14.5)	24	(13.3)	0.11	0-74392	
	No	159	(85.5)	156	(86.7)			
Abnormal discharge	Yes	114	(61.3)	63	(35 2)	24 87	<0.001	S
	No	72	(38.7)	116	(64 8)			
Smoking	Yes	6	(3.2)	5	(2.8)	0.06		0.8018
	No	180	(96.6)	175	(97.2)			
Alcohol intake	Yes	40	(21.5)	27	(15.0)	2.59	0.1076	NS
	No	146	(78.5)	153	(85.0)			
Hypertension	Yes	56	(30.2)	40	(22.2)	4.12	0.04723	S
	No	130	(69.8)	140	(77.7)			
Anaemia	Yes	16	(8.8)	4	(2.2)	3.72	0.4962	S
	No	170	(91.2)	176	(97.8)			
Antenatal care	Yes	154	(82.8)	119	(66.1)	13.44	0.00024	S
	No	32	(17.2)	61	(33.9)			
**Treatment of vaginal discharge	Yes	46	(40.4	21	(33.3)	0.85	0.3567	NS
	No	68	(59.5)	42	(66.7)			
Duration of treatment	<1 week	24	(21.1)	2	(0.6)			S
	>1 week	90	(78.9)	19	(90.4)			

** Cases n = 144; controls n =63
S = Significance; $\chi 2$ = Chi-square

A history of cervical cerclage in index or prior pregnancy was a significant risk factor for premature rupture of membranes ($p = 0.00095$). Stress incontinence and a history of operations on the cervix other than dilatation and curettage were not significant ($p > 0.05$). While a history of abnormal vaginal discharge (due to

care between the cases and the controls. Among the cases, 154 (82.8%) attended antenatal care at least twice compared to 119 (66.1%) among the controls. The number of times attended did not differ significantly between the cases and the controls. It ranged from two to eight times in the cases (mode 4) and two to twelve in the controls (mode 4).

DISCUSSION

Whereas no single factor singularly maintains a prominent role in the aetiology of premature rupture of membranes, several factors have been found to predispose to premature rupture of the membranes. Such factors constitute the risk factors for premature rupture of membranes.

Social class: The results showed no significant differences in the socio-demographic characteristics between the cases and the controls. Our findings, using the employment status and the education level of the patient and spouse as indicators of social class, agree with those of Harger *et al*(14) that social class is not a significant risk factor for preterm PROM. This finding is probably not true since the two are non-specific indicators of social class. Spinillo *et al*(15) found maternal social class to be a strong independent predictor of preterm PROM. Social class may reflect inequalities in access to health care services, nutritional status or different sexual and hygiene habits(16), or difference in health seeking behaviour.

Hypertension and haemorrhage in pregnancy: History of both anaemia and hypertension in the index pregnancy were significant risk factors for preterm PROM. However, contrary to previous findings(14,17,18), bleeding in pregnancy was not a significant risk factor for preterm PROM. Though there were more mothers with third trimester haemorrhage (6%) in the cases, this was not statistically significant (4.2%) in the controls. First trimester bleeding is associated with preterm PROM, the cause being chronic abruption with ischaemic damage to the decidua(1). In the latter half of pregnancy, chronic abruption placenta may cause decidual necrosis, which weakens membranes or predisposes to intramniotic infection eventually leading to membrane rupture(19). The present study did not investigate incidence of bleeding due to cervical polyps, cervical ectropion and placental abnormalities; or incidence of foetal congenital anomalies. These have been found to be associated with preterm PROM (1,3,15).

Cervical incompetence: Both a history suggestive of cervical incompetence and of cervical cerclage were significant risk factors for premature rupture of membranes in the study. Spinillo *et al*(15), found that cervical incompetence might predispose membranes to trauma and rupture through effacement and dilatation of the cervix. Similarly, such membranes exposed to the cervico-vaginal flora are at a higher risk of infection from without than in the normal cervix(2). One of the consequences of cervical cerclage, especially using the Shrodikar method, is damage to the cervix, especially after multiple cerclage operations. Such defects may later predispose the membranes to rupture as they affect the sphincteric action of the cervix.

Abortions: A history of abortion was found to be a significant risk factor independent of the number or nature of abortions (spontaneous or induced). Whereas there was no significant difference in the number of first trimester abortions between the cases and the controls, there were more second and third trimester abortions in cases compared with controls. Two or more induced-abortions more than double the risk of preterm PROM, which risk is independent of an increased risk for incompetent cervix(23).

Preterm labour: Though preterm labour (without PROM) was not a significant risk factor for preterm PROM in this study, others(14) found it to be significant. Uterine anatomical abnormalities such as double uterus may predispose to both preterm labour and preterm PROM. Intra-amniotic infection may initiate either preterm labour or preterm PROM(25).

Caesarean section: This was a significant risk factor for preterm PROM. There is a higher incidence of placental abnormalities such as praevia and adherent placenta in patients with previous Caesarean section than in other multigravidae. There may be associated foetal membrane structural abnormalities which predispose to rupture in such cases(14,17).

Operations on the cervix: Though dilatation and curettage to induce abortion was found by Linn *et al*(20) to be associated with subsequent preterm PROM, it was not a significant risk factor in this study. Similarly, operations on the cervix other than dilatation and curettage were not a risk factor for PROM.

Smoking: This leads to changes in blood levels of micronutrients such as ascorbic acid, vitamin B_{12} and zinc. Evaldson *et al*(17) and Harger *et al* (14) found smoking to be significant as a risk factor for preterm PROM. Nicotine causes arteriolar constriction leading to uterine decidual ischaemia(3) so affecting the integrity of the membranes.

Antenatal care: In this study, antenatal care attendance was associated with preterm PROM. Probably other risk factors, such as anaemia, hypertension, cervical incompetence, vaginal discharge or previous Caesarean section led more to the cases to attend antenatal care compared of the controls.

Vaginal discharge and cervico-vaginal infection: Abnormal vaginal discharge was a significant risk factor for PROM. This finding was similar to those of previous studies(17,21). Intraamniotic infection may increase intrauterine activity leading to increased intrauterine pressure and so greater stress on the membranes, leading to their rupture. Bacterial proteolytic enzymes (proteases, collagenases or trypsin) from the cervico-vaginal flora can degrade foetal membranes(1). The micro-organisms implicated include *Chlamydia trachomatis, bacteriodes* species, *T. vaginalis, S. epidermidis, H. influenzae, Candida* species, *Mycoplasma* species, *E. coli* and bacterial vaginosis. Most of the above infections present with an abnormal vaginal discharge and can be diagnosed from their symptomatology (syndromic diagnosis of vaginal discharge). The presence of such a discharge especially was a significant risk factor for PROM in the study. The mechanism involved in the pathogenesis of PROM includes: (i) release of phospholipase A_2 (which leads to prostaglandin synthesis with effacement of the cervix and membrane exposure); (ii) raising of the pH of the vagina (thus favouring colonisation by other pathogenic

organisms); (iii) infection of the membranes with eventual damage (through ascending infection) and; (iv) the body cells that are involved in the inflammatory reaction may release elastases and other cytotoxic substances(22), eventually leading to membrane damage, weakness and subsequent rupture.

Prior PROM: A history of PROM in a prior pregnancy was a significant risk factor. This finding was similar to earlier reports(3,14). The cause may be cervical incompetence or untreated cervicovaginal infection by bacterial vaginosis or *Chlamydia*(25).

Overdistension of the uterus: There were only five cases with overdistension of the uterus (one mother with twins; four mothers with polyhydramnios). Three controls delivered twins.

Foetal sex: There were more male babies among the cases (57.0%) than in the controls (42.8%). Probably, PROM is associated with foetal gender and is commoner in the males. Jacobovitis *et al* (24) and MacGillivray *et al*(25) found more male babies among mothers with preterm PROM.

In conclusion, a history of hypertension, anaemia, PROM in a prior pregnancy, abortion, cervical incompetence and abnormal vaginal discharge are significant risk factors that can be detected either prior to conception or during antenatal period. Although most causes of PROM are unknown and non-remediable, antenatal care screening, treatment of cervicovaginal infections and cervical cerclage can reduce the incidence of PROM.

ADDENDUM

CULTURE OF AMNIOTIC FLUID AND ENDOCERVICAL SWABS

After Gram stain and wet preparation, each of the swabs and amniotic fluid samples in 180 patients with PROM was cultured on Blood Agar, Chocolate Agar and MacConkey Agar and later subcultured on Drug-sensitivity Agar. There were no organisms identified on Grain stain in 64 (35.6%) cases. In 14 (7.7%) of cases, *Trichomona vaginalis* was identified on wet preparation. On culture, organisms were identified in only 24 cases (13.3%). Organisms identified were *E.coli* 11, *Beta haemolytic Streptococcus* 8, *Proteus* 3, *Peptostreptococci* species 2.

REFERENCES

1. Allen, R,S. The epidemiology of premature rupture of the foetal membranes. *Clin. Obstet. Gynaec.* 1991; **34**:685-93.
2. Gunn, G.C., Mishell, D.R. and Morton, D.G. Premature rupture of membranes, a review . *Amer. J. Obstet . Gynaec .* 1970; **106**:469-483.
3. Shubert, P.J., Diss E. and Iams, J.D. Aetiology of preterm premature rupture of membranes. *Obstet. Gynaec. Clin. N. Amer.* 1992; **19**:251-280.
4. Johnson, J.W.C, Daikoku, N.K. Niebyl, J. *et al.* Premature rupture of the membranes and prolonged latency. *Obstet . Gynaec. 1*987; **57**:547-56.
5. Kitzimiller, J.L. Preterm premature rupture of the membranes. In: Fuchs F., Stubble field P.G. (Eds) *Preterm birth: Cause, prevention and management.* 1st edition. MacMillan. 1984; pp 298-322
6. Keirse, M.J., Ohlsson, A. Treffers, P. *et al.* Prelabour rupture of membranes preterm. In: Chambers I., Enkin M., Keirse M.N.J.C. *Effective Care in Pregnancy and Childbirth.* (Eds) Oxford, 1984; 666-693.
7. Naeye, R.L. Causes of perinatal mortality in the US Collaborative Perinatal Project. *J. Amer. Med. Ass.* 1977; **238**: 228-231.
8. Lavery, J.P. and Miller, C.E. Deformation and creep in the human chorioamotic sac. *Amer. J. Obstet. Gynaec.* 1979; **134**: 366-375.
9. Skinner, S.J.M., Capos, G.A. and Liggins, E.L. Collagen content of human amniotic membranes. Effect of gestation lengths on premature rupture. *Obstet. Gynaec.* 1981; **57**:487-489.
10. Kanayama, N., Terao, T., Kawashima, Y. *et al.* Collagen types in normal and prematurely ruptured amniotic membranes. *Amer. J. Obstet. Gynaec.* 1985; **153**:899-903.
11. Artal, R., Sokol, R.J., Newman, M. *et al.* The mechanical properties of prematurely and non-prematurely ruptured membranes. *Amer. J. Obstet. Gynaec.* 1976; **125**:655-669.
12. Maxwell, G.L. Premature rupture of membranes: A review. *Obstet. Gynaec. Surv.* 1993; **48**:576-589.
13. Davey, D.A. and MacGillirray, J.M. The classification and definition of the hypertensive disorders of pregnancy. *Amer. J. Obstet. Gynaec.* 1988; **158**:892.
14. Harger, J.H., Hsing, A.W., Tuomala, R.E. *et al.* Risk factors for preterm premature rupture of the membranes, a multicentre case-control study. *Amer. J. Obstet. Gynaec.* 1990; **163**:130-133.
15. Spinillo, A., Nicola, S., Piazzi, K. *et al.* Epidemiological correlates of preterm premature rupture of the membranes. *Int. J. Gynaec. Obstet .* 1994; **47**:7-11.
16. Garcia, J., Blondel, B., Saurelo-Cubizolles, M.J. The needs of child bearing families, social policies and the organisation of health care. In: *Effective Care in pregnancy and childbirth;* (Eds), Chalmers, E.M. Enkin, MJNC Keirse) Oxford University Press, 1989; 205-212.
17. Evaldison, G., Lagrelius, A. and Winiarski, J. Premature rupture of membranes. *Acta. Obstet. Gynaec. Scand.* 1980; **59**:385-393.
18. Sipila, P., Martikainen-Sorli, Al. *et al.* Perinatal outcome of pregnancies complicated by vaginal bleeding. *Brit. J. Obstet. Gynaec.* 1992; **99**:959-962.
19. Darby, M.J., Caritis, S.N. and Shen-Swarz, S. Placental abruption in the preterm gestation: an association with chorioamnionitis. *Obstet. Gynaec.* 1989; **74**:88-90.
20. Linn, S., Schoenbaum, S.C., Monson, R.R. *et al.* The relationship between induced abortion and outcome of subsequent pregnancies. *Amer. J. Obstet. Gynaec.* 1983; **146**:136-140.
21. Creatsas, G., Pavlates, M. and Lolis, D. *et al.* Bacterial contamination of the cervix and premature rupture of membranes. *Amer. J. Obstet. Gynaec.* 1981; **139**:522-525.
22. Sbara, A.J., Selvaraj, R.J. Cetrulo, C.L. *et al.* Infection and phagocytosis as possible mechanisms of rupture in PROM. *Amer. J. Obstet. Gynec.* 1985; **153**:38-40.
23. Jacobovits, A.A. and Zubek, L. Premature rupture of membranes and foetal sex. *Amer. J. Obstet. Gynaec.* 1988; **159**:1307-1308.
24. MacGillivray, I. and Davey, D.A. The influence of foetal sex on rupture of the membranes and preterm labour. *Amer. J. Obstet. Gynaec.* 1985; **153**:814-815.
25. Minkoff, H., Grunebaum, A.N, Scwarz, R.H. *et al.* Risk factors for prematurity and premature rupture of membranes: A prospective study of vaginal flora in pregnancy. *Amer. J. Obstet. Gynaec.* 1984; **150**:965-967.