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Risk Factors Associated with Early Preterm Premature Rupture of Membranes in Women with and without Early Preterm Premature Rupture of Membranes in Cameroon

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ABSTRACT

Background: *Preterm premature rupture of the membrane is an important cause of preterm birth. It often results in high perinatal morbidity and mortality in low-income nations. This study evaluated the risk factors associated with early PPROM among participants in Cameroon.*

Methods: *This multi-centric case-control study was conducted in Douala and Yaoundé. We enrolled 125 participants with (cases) and 125 others without (controls) Preterm premature rupture of membrane. Consented participants were asked to fill in a structured questionnaire and data on their socio-demographic, physical, and clinical variables were collected. Descriptive statistic was carried out on SPSS version 23 to provide frequencies and percentages of respective parameters; also the Logistic regression was computerized to identify independent associations between participant's characteristics, risk factors, and PPROM (Odds ratio at 95% CI, p< 0.05).*

Results: *There were similarities in the characteristics of participants except for their profession whereby, the unemployed were more likely to be cases than controls [OR= 1.99; 95%CI: 1.20- 3.31; p= 0.007]. Among participants with PPROM, cases were more likely to have had a previous PPROM than controls [OR= 4.74 CI 95%: 1.08-20.79; p= 0.001]. Regarding their infection status, cases were more likely to have had Chlamydia Trachomatis infection [OR= 16.58; CI 95%: 3.08- 89.32; p= 0.001), or Bacterial vaginosis infection [OR= 16.58; CI 95%: 1.18-232.31; p= 0.001] than controls.*

Conclusion: *Participants with the history of PPROM, Chlamydia Trachomatis infections and Bacterial vaginosis were more likely to have PPROM. As part of the preventive measure for a healthy pregnancy, pregnant women are advised to attend the antenatal clinic.*

Keywords
Preterm Premature Rupture of Membranes, Risk Factors.

Introduction
The World Health Organization defines preterm birth (PTB) before 37 weeks gestation with subcategories including extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), and moderate to late preterm (32 to 37 weeks) [1]. PTB is usually caused by Preterm premature rupture of membrane (PPROM). The incidence of PPROM ranges from 3.0-10.0% of all deliveries worldwide [2]. In low-income countries it is responsible for about 40-75% of cases of neonatal deaths [3]. The prevalence of PPROM varies across countries. A high prevalence of 16.9% was found in Nigeria [4] compared to a lower prevalence of 4.91% in Bamenda (Cameroon) where it accounted for one-third of all preterm births [5].

PPROM often results from the action of inflammatory cells produced by genital infections, which causes weakening of the foetal membranes among pregnant women thus causing PRROM [6]. PPROM is one of the important causes of PTB that can result in high perinatal morbidity and mortality along with maternal morbidity. PPROM complicates approximately 3% of pregnancies and leads to one-third of PTB. PTB are of different types. In Ethiopia, 66.1% of PTBs were spontaneous and 33.9% were induced PTBs [7]. Spontaneous PTB occurred in approximately 57% of PTB while provider-initiated births occurred in 43% [4]. There are numerous risk factors for PPROM, such as intrauterine and genital infections at early gestational age [8]. There are other risk factors like genitourinary tract infection, lower socioeconomic status of pregnant women, inadequate prenatal care and inadequate nutrition during pregnancy, sexually transmitted infections, vaginal bleeding, and smoking during pregnancy [9].

Both mother and foetus are at greater risk of infection after PPROM. The foetal and neonatal morbidity and mortality risks are significantly affected by the severity of oligohydramnios, duration of latency, and gestation at PROM [10]. The primary complication for the mother is the risk of infection such as chorioamnionitis [11]. Complications of PROM for the foetus and new-born consist of prematurity, foetal distress, cord compression, deformation and altered pulmonary development to pulmonary hypoplasia and pulmonary hypertension, necrotizing enterocolitis, and neurologic disorder. Infectious morbidities in the mother, foetus and new-born have been related to both PROM and prolonged rupture of membranes [12].

The burden of PTB is particularly heavy in low resources settings of Sub-Saharan African countries including Cameroon where the main causes of neonatal admissions and neonatal hospital mortality remain the complications of PTB [13]. Neonatal mortality due to PRROM remains a preventable public health problem in Cameroon. But, a sustainable effort still needs to be made if the Cameroon government wants to reduce the current neonatal mortality rate from 21 deaths per 1000 live births to the global target of fewer than ten deaths per 1000 live births by 2035 [13]. PPROM is a common preventable reproductive health issue in Cameroon. However, its prevention remains challenging in Cameroon because of inadequate antenatal care services and few available data on perinatal care. This study compared the risk factors of PPROM, and the odds of PPROM in participants presenting with and without PPROM attending 6 referral hospitals in Cameroon.

Materials and Methods

Study Area

The study was implemented in Yaoundé in the centre Region and in Douala in the Littoral Region of Cameroon. Yaoundé is the political capital while Douala is the economic capital of the country. Both cities are cosmopolitan with inhabitants coming from different ethnic groups of the country.

Study Sites

Of the 7 referral hospitals offering the gynaecology and obstetrics services in these two cities, 6 were randomly selected for the study namely: the Douala General Hospital, Douala and Yaoundé Gynaeco-Obstetric and Paediatric Hospitals, the Yaoundé University Teaching Hospital, the Yaoundé Central Hospital, and the Laquintinie Hospital of Douala. These hospitals had the advantage of their accessibility and the availability of facilities for the management of gynaecology and obstetrics cases

Study Design

This multicentric case-control study was conducted from the 1^{rst} of January to the 31^{rst} of March 2019. This method was chosen because it will permit a quantitative comparison of the risk of PPROM between cases and controls.

Inclusion Criteria

Eligible participants were pregnant women presenting with (cases) and without (controls) PPROM from 24 weeks to 31 completed weeks of gestation. Participants with gestational age ranging from 24 to 31 completed weeks of gestation and clinically confirmed as cases of PPROM at least 12 hours before the onset of labour were included in the case group. But, those presenting with gestational age ranging as from 24 to 31 completed weeks of gestation and without PPROM during their latent phase of labour were named the control groups.

Exclusion Criteria

We excluded from the study, participants who were in labour before the rupture of the membrane (for the case group), those with unconfirmed cases of PPROM, those with any other medical complications occurring during pregnancy like Diabetes, Hypertensive disorders in pregnancy, and twin's pregnancy.

Sample Size Calculation

The minimum sample size (214) for this study was computed using the ratio of 1:1 and the values of prematurity reported in Yaoundé [8]. When considering the non-respondent rate of 10%, we finally obtained a minimum sample size of 236 participants for the study. We finally recruited 250 participants who were proportionally grouped into 125 for the case and 125 for the control groups. All eligible participants admitted at the selected hospitals were recruited. They were proportionally distributed on the basis of the average frequentation of each hospital. As such, we recruited 46 (18.4%) from the Douala General Hospital, 30 (12%) from the Gynaeco-Obstetric and Paediatric Hospital of Douala, 32 (12.8%) from the Gynaeco-Obstetric and Paediatric Hospital of Yaoundé, 14 (5.6%) from the Yaoundé University Teaching Hospital, 78 (31.2%) from the Yaoundé Central Hospital, and 50 (20%) from the Laquintinie Hospital in Douala.

Data Collection

The study took place at the Gynaecology and obstetrics units of each selected hospital. A structured questionnaire was used to obtain participant's socio-demographic characteristics (age,

occupation, level of education, marital status, residence, monthly income), obstetric and gynaecologic parameters [gestational age, parity, vaginal discharge, history of PPROM], and the medical history [a previous STIs, chronic diseases, and historical trauma before PPROM]. The diagnosis of the PPROM was later done using the "Vasalva maneuver" which consisted of using a sterile speculum examination to observe a gush of fluid from the perineal os through the vagina.

Data Collection Methods

The principal investigator was aided by an experience nurse (assistant researcher) on data collection. She underwent a three (3) days training before the study began. Her main duty was to take down data on a structured questionnaire written in French, translated in English and back into French.

Statistical Analysis

Data obtained from participants were processed into Census and Survey Processing System software, version 7.2, and later transferred into Statistical Packages for Social Sciences version 23 for analysis. Participants with missing information were excluded from the analysis. Descriptive statistic was used to computerise the mean and standard deviation for continuous variables (age). Also, their socio-demographic characteristics, obstetrical and gynaecological parameters, and the medical history were grouped into categories and the frequencies and percentages were calculated using descriptive statistics. Chi-square was also calculated to assess the relationship between categorical variables. The regression logistic analysis was later conducted to assess the odds of independent risk factors in the prediction of PPROM (Odds ratio at 95% CI and p< 0.005).

Results

Age Distribution of Cases and Controls

Participants recruited for this study were aged between 13-42 years. The mean age of cases (26.80 ± 6.23 years) was almost similar to that of controls (27.21 ± 6.96 years). However, PPROM was most frequent in 38 (57.6%) participants aged between 26-30 years (Figure 1).

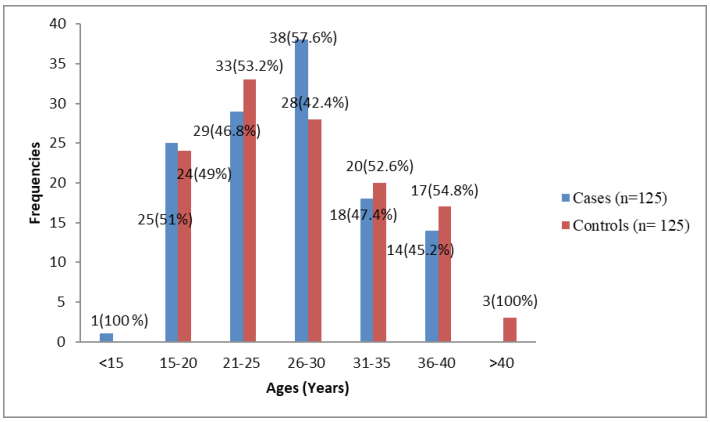

Figure 1: Age distribution of cases and controls.

Socio-Demographic Characteristics of Cases and Controls

Our data in Table 1 shows that 81 (57.4%) cases compared to 60 (42.6%) controls were unemployed. Unemployed participants were about 2 times more likely to be cases than controls [OR= 1.99; 95%CI: 1.20- 3.31; (p= 0.007)]. The majority of participants were single: 78 (49.7%) for cases and 79 (50.3%) for controls. There was a similarity in the place of residence of participants. We noted 121 (50 %) cases and 121 (50%) controls living in the urban area. Regarding their level of education, 58 (52.7%) cases compared to 52 (47.3%) controls had attended the secondary school [OR= 1.22, 95% CI: 0.74- 2.00; p= 0.445]. Table 1 further shows that 65 (56%) of cases compared to 51 (44 %) had no monthly income.

Obstetric and Gynaecologic History of Participants

There was no statistically significant difference in the parity of cases and controls. Table 2 shows that 53 (44.5%) cases compared to 66 (55.5%) were Multipara (G2-4) representing the highest proportion. Participants' gestational age was from 24 weeks to 31 completed weeks. However, 70 (51.5%) of them were between the gestation age of 30-31 weeks 6 days as compared to 66 (48.5%) in those without PPROM. Out of those affected with PPROM, 61 (75.3%) had a history of previous PROM as compared to 20 (24.7%) in the control group [AOR= 4.74; 95%CI: (1.08- 20.79); p=0.039]. Vaginal discharge was more likely to be seen in cases than in controls [AOR= 4.21; 95%CI: 3.58 (0.71- 18.13); p= 0.124] with 96 (63.6%) cases compared to 55 (36.4%) controls recorded with the history of abnormal vaginal discharge (Table 2).

Risk of STIs among cases and controls

The most common sexually transmitted infection associated with PPROM was *Chlamydia trachomatis* infection [36 (72.0%) cases compared to 14 (28.0%) controls]. Cases were 16 times more likely to be infected than controls [AOR= 16.58; 95%CI: (3.08- 89.32); p= 0.001].

Table 3 also shows that, 66 (63.5%) cases compared to 38 (36.5%) controls had vaginal candidiasis (p= 0.001), that 34 (70.8%) cases compared to 14 (29.2%) controls had *Trichomonas Vaginitis* (p= 0.001), and that 30 (73.2%) cases compared to 11 (26.8%) controls had bacterial vaginosis (p= 0.001).

Medical, Surgical, and Social Histories of Cases and Controls

Statistically, there was no significant difference in the HIV status of participants. We noted that 9 (69.2%) cases compared to 4 (30.8%) controls were HIV positive (p= 0.154). A history of trauma before PPROM was significantly (p < 0.005) associated with the risk of having premature rupture of membranes (Table 4).

Discussion

Characteristics of Participants

This case-control study compared the risk factors associated with PPROM in participants attending 6 referral hospitals in Douala and Yaoundé. In this study, the characteristics of cases and controls were similar, except for their occupation. We noted that unemployed participants were about 2 times more likely to be cases

Table 1: Socio-demographic characteristics of cases and controls

Characteristics	Cases N=125 (%)	Controls N=125(%)	OR (CI 95%)	p-value
Occupation				
Unemployed	81 (57.4)	60 (42.6)	1.99 (1.20- 3.31)	0.007
Students	26 (46.4)	30 (53.6)	0.83 (0.46- 1.51)	0.544
Employed (Other than health Personnel)	11 (35.5)	20 (64.5)	0.51 (0.23- 1.11)	0.084
Health Personnel	4 (44.4)	5 (55.6)	0.79 (0.21- 3.03)	1.000
Others	3 (23.1)	10 (76.9)	0.28 (0.08- 1.05)	0.084
Marital Status				
Single	78 (49.7)	79 (50.3)	0.97 (0.58- 1.61)	0.896
Married:Monogamous	43 (49.4)	44 (50.6)	0.96 (0.57- 1.63)	0.894
Married: Polygamous	1 (33.3)	2 (66.7)	0.49 (0.04- 5.54)	1.000
Divorced	3 (100)	0 (0.0)	/	/
Residence				
Urban	121 (50)	121 (50)	/	/
Rural	4 (50.0)	4 (50.0)	/	/
Educational Level				
Uneducated	1 (50)	1 (50)	/	/
Primary	24 (52.2)	22 (47.8)	1.11 (0.57- 2.11)	0.744
Secondary	58 (52.7)	52 (47.3)	1.22 (0.74- 2.00)	0.445
University	42 (45.7)	50 (54.3)	0.76 (0.45-1.27)	0.294
Monthly income				
< 50000	39 (48.1)	42 (51.9)	/	
50000 - 100000	14 (45.2)	17 (54.8)	0.90 (0.53- 1.52)	0.685
100001 - 200000	7 (31.8)	15 (68.2)	0.80 (0.38- 1.70)	0.565
>2000000	0 (0.0)	0 (0.0)	0.44 (0.17- 1.11)	0.074
None	65 (56.0)	51 (44.0)	/	/
Tobacco smoking	2 (66.7)	1 (33.3)	1.57 (0.95- 2.59)	0.076

Table 2: Obstetrical and gynaecological past history of participants.

Variables	Cases N (%)	Controls N (%)	OR (CI 95%)	p-value	Adjusted OR (CI 95%)	p-value
Parity						
Nulliparous	46 (52.3)	42 (47.7)	1.15 (0.68- 1.94)	0.596	/	/
Multipara (G_{2-4})	53 (44.5)	66 (55.5)	0.64 (0.39 -1,05)	0.077	/	/
Grand Multipara ($\geq G_5$)	26 (60.5)	17 (39.5)	1.67 (0.85 -3.26)	0.131	/	/
Gestational age						
24 -27weeks6days	10 (50)	10 (50)	1.00 (0.40 - 2.49)	1.000	/	/
28 -29weeks6days	45 (47.9)	49 (52.1)	0.87 (0.52 – 1.46)	0.601	/	/
30-31weeks6days	70 (51.5)	66 (48.5)	1.14 (0.69 – 1.87)	0.611	/	/
Previous PPROM	61 (75.3)	20 (24.7)	5.00 (2.76 – 9.05)	< 0.001	4.74 (1.08- 20.79)	0.039
Abnormal vaginal discharge	96 (63.6)	55 (36.4)	4.21 (2.44 – 7.23)	< 0.001	3.58 (0.71- 18.13)	0.124
Number sexual partner						
< 1	107 (48.6)	113 (51)	0.63 (0.29 – 1.37)	0.243	/	/
≥ 2	18 (60)	12 (40)	1.00	/	/	/

Table 3: Risk of STIs among cases and controls.

Infection types	Cases N (%)	Controls N (%)	OR (CI 95%)	p-value	Adjusted OR	P-value
Chlamydia trachomatis	36 (72.0)	14 (28.0)	3.21 (1.63 – 6.31)	0.001	16.58 (3.08- 89.32)	0.001
HBs Ag	10 (47.6)	11 (52.4)	0.90 (0.37 – 2.21)	0.820	/	/
HIV	9 (69.2)	4 (30.8)	2.34 (0.70 – 7.83)	0.154	/	/
Neisseria Gonorrhoea	9 (100)	0 (0.0)	2.08 (1.82 – 2.37)	0.003	/	/
Syphilis	9 (69.2)	4 (30.8)	2.35 (0.70 -7.83)	0.154	/	/
Trichomonas Vaginitis	34 (70.8)	14 (29.2)	2.96 (1.50 – 5.86)	0.001	0.19 (0.02- 1.75)	0.144
Bacterial vaginosis	30 (73.2)	11 (26.8)	3.27 (1.56 – 6.88)	0.001	16.6 (1.18-32.31)	0.037

Table 4: Medical, surgical and social histories of cases and controls.

Variables	Cases N (%)	Controls N (%)	OR (CI 95%)	p-value	Adjusted OR (CI 95%)	p-value
Diabetes	1 (50)	1 (50)	/	/	/	/
Hypertension	0 (0.0)	6 (100)	/	/	/	/
Surgical History	53 (55.8)	42 (44.2)	1.46 (0.87- 2.43)	0.152	/	/
History of trauma	48 (77.4)	14 (22.6)	4.94 (2.55 – 9.59)	< 0.005	2.59 (0.40 – 16.63)	0.317

than controls. Such findings were also reported in another study [14]. Such a finding might be an indicator to the decreasing job situation in Cameroon where the majority of the urban population is jobless a condition, which could explain why most participants had no monthly income.

Obstetric and Gynaecologic History of Participants

This study revealed that parity, gestational age, and the number of sex partners did not significantly increase the risk of PPROM among cases compared to controls. But in another study, mothers who had multiple gestations were about five times more likely to deliver preterm babies than those who had single pregnancy. The mechanism for that could be attributed to the over-distension of the uterus, which leads to a stretch of membranes with subsequent release of prostaglandins that initiate preterm labour leading to preterm delivery [15].

STI and PPROM

In the study of STIs, we noted that cases were more likely to have had respectively *Chlamydia trachomatis* infection, vaginal candidiasis, *Trichomonas vaginitis* infection and bacterial vaginosis than controls. These findings were also reported in previous studies [6,10,14,15]. There are disparities in the role played by the STI pathogens in the occurrence of PPROM according to studies, which could be unconnected from the study design, and the behavioural characteristics of the study population.

In this study, there was no significant difference in the occurrence of PPROM between HIV and Group B streptococcus infected cases and controls respectively. But early studies instead suggested a significant association between Group B streptococcus, HIV infection, and PPROM [9,16,17]. The lack of significant association between those STIs and PPROM might be attributed to the differences in the use of antibiotics between cases and controls (p= 0.001). Also, the lack of significant association between HIV infections and the occurrence of PPROM in this study might have occurred thanks to the Cameroon Ministry of Public health's efforts toward the reduction of the incidence of HIV infections among pregnant women through counselling and the routine screening during antenatal clinic.

Syphilis

This study revealed no increased risk of PPROM among cases compared to controls. That was in discordance with another study that reported syphilis to be the only STI found to increase the odds of any PTB [18]. The controversy between both findings might be due to the low prevalence of diagnosed cases of syphilis in this study.

Chlamydia Trachomatis Infections

Genital *Chlamydia trachomatis* infection is one of the most common sexually transmitted diseases throughout the world. It was reported in high prevalence in patients with imminent preterm delivery in Curaçao (2022) [19]. In this study, we found cases most at risk of *Chlamydia trachomatis* than the controls which was in line with the previous study [20]. That was in contradiction with other studies which reported no significant association between PROM and *Chlamydia trachomatis*. However, it was hypothesised that *Chlamydia trachomatis* infection in pregnancy caused the release of inflammatory mediators that are implicated in membrane rupture [6,18]. However, *Chlamydia trachomatis* infections are associated with several behavioural factors, which need effective and sustainable counselling during antenatal clinics.

Trichomonas Vaginalis Infections

Considering the strong association between *Trichomonas vaginalis* infection and PROM reported in a previous study [6], this study reported that it increased to about 3 times the risk of PPROM among cases than controls. But that association between both factors was not statistically significant following adjustment with other confounding factors. From that finding, it might be suggested that *Trichomonas vaginalis* is not an independent predictor of PPROM but might need the synergetic action with other cofactors for its occurrence.

Our finding was therefore in contradiction with the previous study, which reported that *Trichomonas vaginalis* increase the risk of PROM via the releases inflammatory cytokines and proteases [6]. It was also suggested that the independent role of *Trichomonas vaginalis* in the occurrence of PPROM should take into consideration a number of clinical variables [21]. Whatever the case, there is necessity to treat diagnosed cases of *Trichomonas vaginalis* infections such as to avoid their adverse effects on pregnancy.

Abnormal Vaginal Discharge

In this study, cases were about 4 times more likely to have abnormal vaginal discharge than the controls. Another study reported PPROM to be about 7 times more likely to occur in pregnant mothers who had a complaint of abnormal vaginal discharge compared to their counterparts [22]. Abnormal vaginal discharge is frequent among women in our country; often resulting from sexual transmission. Our findings thus, suggest abnormal vaginal discharge as an independent cause of PPROM

among our participants. Proper monitoring of vaginal discharge among pregnant women is possible during antennal clinic. Even though vaginal discharge is multifactional, primary and secondary preventive measures are needed to prevent for infectious causes of abnormal vaginal discharge, which might lead to negative outcome of pregnancy such as PTB, PPROM [23,24]. But clinical monitoring of vaginal discharge is challenging in Cameroon because most women especially those in the rural areas visit the health care centres only at the time of delivery.

Bacterial Vaginosis

Concerning bacterial vaginosis, cases were about 16 times more likely to have vaginal discharge than controls. That finding was in agreement with the result of another study in Vietnam (2021) which indicated that bacteria vaginosis increased the risk of preterm labour and PPROM to about 4 times [25]. Another study in Uganda (2015) also reported that women with bacterial vaginosis compared with women without bacterial vaginosis were more likely to develop PPROM [6]. Bacterial vaginosis is frequent during pregnancy [26]. Bacterial vaginosis in pregnancy often results from poor hygiene and the practice of vaginal douching which is a common practice among women in our setting. However, it can be prevented via sustainable health education for women during the prenatal consultation but also, via the use of antibiotics in early pregnancy [27].

History of PPROM

Regarding their Medical and surgical histories, this study showed that cases were about 5 times more likely to have a history of trauma before PPROM compared to controls. A similar case-control study in Ethiopia also reported that participants who had PPROM in previous pregnancies were 4.7 times more likely to develop PPROM as compared to their counterparts [28]. Finding a significant association between the histories of PROM with PPROM in this study was in disagreement with another study, which suggested no significant association between them [29]. Despite that controversy, a study in favour of the positive relationship between the history of PPROM and its subsequent occurrence suggested that the mechanism could be related to the abnormal formation of the uterus and the cervix [29,30]. Another mechanism explains that PPROM causes the release of inflammatory cytokines, which initiate contractions of the uterine smooth muscles hence leading to preterm birth [15].

Conclusion

PPROM is a frequent health emergency in Cameroon affecting most pregnant women in the age between 26-30 years. This study compared the risk factors among cases and controls. We found out that *Chlamydia trachomatis*, bacterial vaginosis infections, and a history of previous PPROM increased the risk of PPROM in cases than in controls. Proper management of PPROM in Cameroon is advocated by targeting those risk factors identified in this study. That could be achieved through regular antenatal clinic visitation during pregnancy.

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Ethical Considerations

The study was approved by the Institutional Review Board of the Faculty of Health Sciences, University of Buea (N°: 2019/881-01/UB/SG/IRB/FHS). Also, each hospital administration gave a written authorization permitting us to use their patients. Consented participants were informed of the benefits, clinical procedures used, and the confidentiality of our findings. Consented participants signed an informed consent form, while verbal and/or written assent was required from those aged less than 21 years.

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