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Risk factors for spontaneous preterm deliveries above twenty-eight complete weeks of gestation

Abstract

Purpose: To identify risk factors for spontaneous preterm delivery (SPD) given that it is associated with high neonatal morbidity and mortality.

Material and methods: This case-control study was carried out between 1st February and 31st July 2021. Women who delivered spontaneously between 28 and <37 weeks (cases) or at ≥37 weeks (controls) were recruited. The main variables recorded included maternal age and parity, inter-pregnancy interval, if the pregnancy was intended, medical, obstetrical and family past-histories, gestational age at delivery, number of gestation and pathologies during current gestation. Fisher exact test, t-test and logistic regression were used for comparison. P<0.05 was considered statistically significant.

Results: Our frequency of preterm delivery was 15.3% (116/759 births), with 9.9% (75/759) being SPD. Significant risk factors for SPD were premature rupture of membranes (aOR 19.96, 95%CI 11.04-45.82), inter-pregnancy interval >60 months (aOR 13.02, 95%CI 6.11-33.01), Nulliparity (aOR 10.21, 95%CI 5.72-21.31), 1st degree family history of SPD (aOR 7.73, 95%CI 1.54-11.39), malaria in the 3rd trimester (aOR 6.89, 95%CI 2.15-8.63), multiple pregnancies (aOR 6.43, 95%CI 3.21-9.79), severe anemia (Hb <6g/dl) in the 3rd trimester (aOR 5.73, 95%CI 2.04-10.60) and unintended pregnancies (aOR 2.44, 95%CI 1.98-7.88).

Conclusion: Women with multiple or unintended pregnancies and those with the pre-gestational risk factors identified above should be well followed up during pregnancy to allow prevention, if not, early diagnosis of SPD. Moreover, prevention of the above-identified pathologies in pregnancy is mandatory if we want to reverse the rate of SPD.

Keywords: spontaneous preterm delivery, risk factors, premature rupture of membranes, nulliparity, multiple pregnancies

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Elie Nkwabong,[1] Yasmine Anique Mayo,[2] Felicité Nguefack,[3] Florent Fouelifack[4]

[1]MD, Department of Obstetrics and Gynecology; Faculty of Medicine and Biomedical Sciences & University Teaching Hospital, University of Yaoundé I, Cameroon
[2]MD; General Practitioner, Department of Surgery; Higher Institute of Medical Technology, University of Douala, Cameroon
[3]MD; Department of Pediatrics; Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Cameroon
[4]MD; Obstetrician & Gynecologist, Department of Surgery; Higher Institute of Medical Technology, University of Douala, Cameroon

Correspondence: E Nkwabong, MD, Obstetrician & Gynecologist, Department of Obstetrics and Gynecology; Faculty of Medicine and Biomedical Sciences & University Teaching Hospital, University of Yaoundé I, Yaoundé P.O. Box 1364 CHU Yaoundé, Cameroon, Tel (237) 699663843, Fax (237) 222312567, Email enkwabon@yahoo.fr

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Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; GA, gestational age; HIV, human immunodeficiency virus; OR, odds ratio; PD, preterm delivery; PROM, premature rupture of membranes; SD, standard deviation; SPD, spontaneous preterm delivery; SPSS, statistical package for social sciences

Introduction

Preterm delivery (PD) is defined as the delivery of a baby before 37 complete weeks of gestation.[1] It can be either spontaneous (labor initiated without any intervention from physician) or induced (by physician to reduce the maternal or perinatal morbidities or mortalities). Preterm births have been categorized as extreme preterm (< 28 weeks), very preterm (28-<32 weeks), moderate preterm (32-<34 weeks) and late preterm (34-<37 weeks).[2]

Because of higher mortality associated with extreme preterm deliveries, the latter was considered as late abortion in some low-income countries, yet with advances in technology, corticosteroids, tocolytics and antibiotics, preterm babies can have improved survival rates after 24 weeks.[3] Each year, there are about 15 million premature births worldwide,[4] with 81.1% of them occurring in sub-Saharan Africa and South Asia.[5] PD rate has increased over the past 20 years and is still increasing. The estimated global PD rate in 2014 was 10.6%, with rates varying between 5-11% in Europe[6] and 15-38% in Sub-Saharan Africa.[7] The rate in sub-Saharan Africa would have been higher if the PD lower limit of 22 weeks was universally used in all countries. PD is associated with high neonatal complications. Early complications include respiratory distress syndrome, apnea, hypothermia, hypoglycemia, hyperbilirubinemia and eating difficulties. Even late preterm babies are at higher risks of respiratory distress and other complications than those born at term.[8] The economic cost of prematurity is very high, specifically in low-income countries, since most cases require neonatal intensive care and other advanced treatments.

Contribution of PD to early neonatal death is about 35% worldwide.[5] In 2015, there were an estimated 1 million deaths in children under age 5 years globally attributed to prematurity.[9] Respiratory distress is the main cause of death. Also, 50% of perinatal and long-term morbidities are associated with PDs[10] Short and long term complications are respiratory illness, cerebral palsy, neurodevelopmental impairment, mental retardation, visual and hearing impairments, learning difficulties.[11] The risk factors for PD include multiple pregnancies, preterm rupture of membranes, malaria or urinary tract infection in pregnancy, past history of preterm birth and the presence of chronic illnesses.[12,13] Some other risk factors might exist in our environment given the high incidence in Africa. Identifying the risk factors can help in the prevention of some cases of PD. To the best of our knowledge, no recent study has evaluated the risk factors for PD, hence this study aimed at seeking for this risk factors.

Methods

This case-control study was carried out between 1st February and 31st July 2021 in a University Teaching Hospital. Women who delivered spontaneously before 37 complete weeks of gestation were recruited as cases (group A) and those who delivered at or after 37

complete weeks of gestation were recruited as controls (group B). For each case, three controls who delivered just after each case were recruited. Women with incomplete files, undated pregnancies and those who refused to participate were excluded. A written informed consent was obtained from each woman or from their relatives. This study was approved by the institutional ethics committee. The variables recorded on a pre-established questionnaire in both groups included maternal age at delivery, educational level, parity, occupation, family and personal past-histories, inter-pregnancy interval, HIV status, pre-gestational body mass index, if this current pregnancy was unintended, gestational age (GA) at booking and at delivery (confirmed by an ultrasound scan performed before 20 weeks' gestation), number of antenatal visits done, number of gestation, diseases that occurred during pregnancy and birth weight.

The necessary minimum sample size was calculated as needing at least 56 cases of PD, using the following formula: $N=2\times(Z\alpha+Z\beta/P0-P1)^2\times P\times(1-P)$,[14] where $Z\alpha=1.65$ corresponds to a type I error of 5%, $Z\beta=1.03$ corresponds to a power of 85%, P0 the percentage of preterm rupture of membranes (PROM) amongst women with PD (29.8%),[15] P1 the percentage of PROM amongst women with term delivery (8.5%)[15] and P is (P0+P1)/2. To increase the power of our study, we decided to recruit three controls for each case. Data were analyzed using SPSS 26.0. Data of cases were compared to those of controls. Fisher's exact test was used to compare categorical variables and t-test to compare continuous variables. We used odds ratios (ORs) with their 95% confidence intervals (CIs) to present the comparison between the two groups. Logistic regression was used to control for confounders. P<0.05 was considered statistically significant.

Results

During the study period, we had a total of 116 PDs out of 759 deliveries performed, giving a PD rate of 15.3%, 75 (9.9%) were spontaneous preterm delivery (SPD). A total of 10 cases of SPD (13.3%) were excluded, four (5.3%) for incomplete files and four (5.3%) because the pregnancy was undated. Furthermore, two women (2.7%) refused to participate. The 65 women with SPD remaining and 195 controls took part to this survey. Some sociodemographic variables are given in Table 1. SPD occurred before 32 weeks of gestation in 15.4% (10/65) and between 32 and <34 weeks in 23 cases (35.4%). In 32 cases (49.2%) it occurred at ≥34 weeks of gestation.

We found no difference between the two groups as concerns educational level, pre-gestational body mass index, number of antenatal visits and gestational age at booking. Some obstetrical variables are given in Table 2.

There was also no association between SPD and rural residency (4 or 6.1% vs. 9 or 4.6%, OR 1.36, 95%CI 0.40-4.56, P=0.416) or (passive) tobacco consumption (3 or 4.6% vs. 5 or 2.6%, OR 1.84, 95%CI 0.43-7.92, P=0.320).

Table 3 shows significant independent risk factors for SPD.

Table 1 Characteristics of the population under study

Variables	Group A women (n=65)	Group B women (n=195)	OR	95% CI	P-value
	Mean ± SD (range)	Mean ± SD (range)			
Mother's age (y)	25.6 ± 6.1 (17-40)	28.5 ± 6.1 (16-41)	-	-	0.001
Parity	3.9 ± 1.9 (1-12)	3.8 ± 1.8 (1-9)	-	-	0.702
GA at delivery (w)	33.0 ± 2.1 (28-36)	39.0 ± 1.7 (37-42)	-	-	0.000
Birth weight (g)	2237 ± 541 (900-2650)	3173 ± 498 (2999-4500)	-	-	0.000
Jobless	8 (12.3)	4 (2.1)	6.70	1.95-23.07	0.002
Past history of infertility	17 (26.2)	10 (5.1)	6.55	2.82-15.23	<0.001
1st degree family SPD	24 (36.9)	10 (5.1)	10.83	4.81-24.38	<0.001
Positive HIV status	14 (21.5)	13 (6.7)	3.84	1.70-8.69	0.001
Primary school education	14 (21.5)	25 (12.8)	1.87	0.90-3.85	0.069
BMI ≥30kg/m^2	5 (7.7)	9 (4.6)	1.72	0.56-5.34	0.254

Number (percentage)

OR, odds ratio; CI, confidence interval; CI, confidence interval; GA, gestational age; SPD, spontaneous preterm deliveries; HIV, human immunodeficiency virus; BMI, body mass index

Table 2 Obstetrical characteristics in the population under study

	Group A women (n=65) N (%)	Group B women (n=195) N (%)	OR	95%CI	P-value
Unintended pregnancies	44 (67.7)	45 (23.1)	6.98	3.-12.95	<0.001
Inter-pregnancy interval >60 months	24 (36.9)	31 (15.9)	3.09	1.64-5.83	<0.001
Nullipara	18 (27.7)	29 (14.9)	2.19	1.12-4.29	0.018
Past history of late abortion	4 (6.2)	2 (1.0)	6.33	1.13-35.40	0.036
Past history of preterm delivery	4 (6.2)	3 (1.5)	4.20	0.91-19.27	0.068
Multiple pregnancies	26 (40.0)	11 (5.6)	11.15	5.09-24.45	<0.001
Booking >16 weeks	26 (40.0)	66 (33.9)	1.30	0.73-2.32	0.226
Malaria in 3rd trimester	32 (49.2)	27 (13.9)	6.03	3.20-11.37	<0.001
<4 antenatal visits	19 (29.2)	38 (19.5)	1.70	0.90-3.24	0.073
PROM	30 (46.2)	22 (11.3)	6.74	3.49-11.03	<0.001
Severe anemia (Hb <6g/dl) in pregnancy	13 (20.0)	9 (4.6)	5.17	2.09-12.75	<0.001
Urinary tract infection	9 (13.9)	27 (13.9)	1.00	0.44-2.25	0.591
Cervico-vaginitis	15 (23.1)	33 (16.9)	1.47	0.74-2.93	0.177

OR, odds ratio; CI, confidence interval. PROM, premature rupture of membranes

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Table 3 Independent risk factors for premature delivery

Variables	OR	95%CI	P-value	aOR	95%CI	P-value
PROM	6.74	3.49-11.03	<0.001	19.96	11.04-45.82	< 0.001
Inter-pregnancy interval >60 months	3.09	1.64-5.83	<0.001	13.02	6.11-33.01	0.002
Nullipara	2.19	1.12-4.29	0.018	10.21	5.72-21.31	0.003
1st degree family SPD	10.83	4.81-24.38	<0.001	7.73	1.54-11.39	0.001
Malaria in 3rd trimester	6.03	3.20-11.37	<0.001	6.89	2.15-8.63	0.001
Multiple pregnancies	11.15	5.09-24.45	<0.001	6.43	3.21-9.79	0.026
Severe anemia (Hb <6g/dl) in pregnancy	5.17	2.09-12.75	<0.001	5.73	2.04-10.60	0.002
Unintended pregnancies	6.98	3.-12.95	<0.001	2.44	1.98-7.88	0.001
Past history of late abortion	6.33	1.13-35.40	0.036	1.32	0.78-3.37	0.345
Jobless	6.70	1.95-23.07	0.002	0.88	0.46-5.44	0.467
Positive HIV status	3.84	1.70-8.69	0.001	0.55	0.35-1.77	0.139
Past history of infertility	6.55	2.82-15.23	<0.001	0.42	0.08-1.32	0.514

OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; SPD, spontaneous preterm delivery; HIV, human immunodeficiency virus; PROM, premature rupture of membranes

Discussion

Our rate of SPD was 9.9%. Risk factors for SPD were preterm rupture of membranes, inter-pregnancy interval >60 months, nulliparity, 1st degree family history of SPD, malaria in the 3rd trimester, multiple pregnancies, severe anemia (Hb <6g/dl) in the 3rd trimester and unintended pregnancies.

Our global PD rate of 15.3% is higher than the 8.6% rate found in India, but lower than the 21.8% noticed in Pakistan.[13] Our SPD rate (9.9%) is also within this range. PROM was a risk factor for SPD in our series, as noticed in South India.[16] Rupture of fetal membranes leads to the release of prostaglandins that initiate labor. Pregnant women carrying the risk of PROM should be well monitored during pregnancy.

An inter-pregnancy interval of >60 months was another risk factor for SPD. This could be attributed to secondary infertility. Infertility and the fertility treatments are associated with abnormal placentation leading to adverse pregnancy outcomes, including preterm birth.[17] This is in contrast with the findings in Ethiopia where short inter-pregnancy interval was found to be a risk factor for PD.[12] Nulliparity was also found to be a risk factor in our study, as observed in Pakistan.[13] It might be attributed to smaller uterine cavity and reduced uteroplacental blood flow of women who never gave birth.[18] Pregnant nulliparous women should be regularly follow up in order to diagnose early and treat preterm labor.

First degree family history of SPD was another risk factor identified in our study. No previous study reported this finding. It might be attributed to the presence of some hereditary connective tissue disorders, leading to cervical incompetence (with rapid shortening and dilatation), as reported in USA.[19] Pregnant women with family history of SPD should be closely followed up. Malaria in the 3rd trimester was also a risk factor for SPD, as already found in a previous study in our unit.[20] This has also been observed in Ethiopia.[12] Premature initiation of labor might be attributed to anemia and to high levels of pro-inflammatory cytokines such as interleukin-10 and placental tumor necrosis factor-alpha.[21] Women should be advised to sleep under insecticide treated nets always and to take intermittent preventive treatment against malaria regularly.

Multiple gestation was also found as a risk factor for SPD, as noticed in Ethiopia.[12] It is attributable to uterus over-distension with myometrium stretch leading to excitation of oxytocin receptors, and therefore preterm labor.[22] When multiple pregnancies are diagnosed, women should be regularly followed up. Severe anemia was another Risk factor for SPD, as observed in South India and in a previous survey in our unit.[16,23] Anemia with resulting hypoxia can induce maternal and fetal stress. This stress stimulates the synthesis of corticotropin-releasing hormone and of cortisol, which are major risk factors for preterm labor.[24] Efforts should be made to avoid anemia. This implies rapid treatment of malaria and regular consumption of hematinics during pregnancy.

Finally, an unintended pregnancy was a risk factor for SPD. This might be attributed to the non-observance of recommendation given. At booking, women with unintended pregnancies should be well counselled and also regularly followed up. We found no difference between the two groups concerning the number of antenatal visits, residency and tobacco use. This is in contrast with the findings in some low- and middle-income countries where few antenatal visits were associated with preterm delivery.[13] The lack of significance with residency or tobacco consumption might be attributable to our small sample size, since only few women were living in rural area or were smokers. Our limitations are our small sample size due to the short period of study and to the Covid-19 pandemic. Indeed, because of fear of being contaminated, only few women attended our hospitals. Therefore, similar studies with large sample sizes should be carried out to verify these findings.

Conclusion

Our study found some pre-gestational risk factors for SPD such as nulliparity, inter-pregnancy interval of >60 months and first degree family history of SPD. We also found gestational risk factors like multiple or unintended pregnancies, PROM, malaria and anemia in pregnancy. We should take into considerations these risk factors if we have to reduce the prevalence of SPD.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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