Research Article

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Determinants of Tocolysis Failure in Preterm Labor: A Case-Control Study in Two Hospital in Yaounde

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Abstract

Background: Tocolysis aims to prolong pregnancy by stopping labor to achieve lung maturation. Failure of tocolysis is a common situation in obstetrics with its share of risks and complications for the fetus.

Objective: To identify the determinants of tocolysis failure in two Hospitals in Yaounde.

Patients and methods: We carried out a case-control study over a 6 months period at Yaounde Gyneco-Obstetric and Pediatric Hospital (YGOPH) and Yaounde Central Hospital (YCH). We compared each case (patient with failure of tocolysis after 48 hours) with 3 controls (patients with successful tocolysis after 48 hours). The association degree between two variables was measured by calculating the odds ratio (OR) with their confidence interval. Multivariate analysis was performed to eliminate confounders.

Results: In this study, 238 women were included: 62 cases and 186 controls after multivariate analysis, predictive factors were: sexual activity during the last two month of pregnancy (AOR = 2.76; CI: 1.06-7.23, p = 0,038), prenatal follow-up by midwife or nurse (AOR = 8.96 CI: 2,05-39.22, p = 0,003), the persistence of the temperature $\geq$ to 38°C after 48 H (AOR = 3.89; CI: 1.36-11.6, p = 0,011), and the Bishop score $\geq$ 7 at admission (AOR = 12.50; CI: 4.30-36.27, p < 0,001).

Conclusion: The determinants of tocolysis failure in our study were sexual activity during the last two month of pregnancy, prenatal midwife/nurse follow-up, temperature persistence $\geq$ 38°C after 48 hours of tocolysis, Bishop's score $\geq$ 7 at admission.

Keywords: Preterm labor, Tocolysis, Determinants

Introduction

Preterm birth, defined as birth before 37 weeks of gestation, is the single most important determinant of adverse infant outcomes, in terms of survival and quality of life [1]. Globally, it is the leading cause of perinatal and neonatal mortality and morbidity [2]; and Cameroon is not an exception to that [3].

Tocolysis aims to prolong pregnancy. The acute use of tocolytic drugs up to 48 hours can be considered to provide

a window for administration of antenatal corticosteroid and/or in-utero fetal transfer to an appropriate neonatal healthcare setting, although there is currently no direct evidence to show that this measure improves neonatal outcomes [4]. In women with acute preterm labor, a 2009 meta-analysis of randomized trials found that these drugs were more effective than placebo/control for delaying delivery for 48 hours (75 to 93 percent versus 53 percent for placebo/control) and for seven days (61 to 78 percent versus 39 percent for placebo/control), but not for delaying delivery to 37 weeks [4].

Tocolytic drugs have been available for several decades but their actions are directed toward the effects and not the causes of preterm labor. Their efficacy depends on an early and accurate diagnosis of the condition, the fetal fibronectin, and cervical length at ultrasonography [5]. But what about the factors determining the failure of tocolysis in preterm labor? No studies found in the literature mention it to our knowledge.

Hence, we sought to identify those factors in a case-control study in two Hospitals in Yaounde city in Cameroon.

Patients and Methods

Methods

We carried out a case-control study over a 6 months period (from the 5th October 2017 to the 31 March 2016) at Yaoundé Gyneco-Obstetric and Pediatric Hospital (YGOPH) and at Yaounde Central Hospital (YCH). Our study population consisted in women with preterm labor without premature rupture of the membranes. We compared one case (patient with failure of tocolysis after 48 hours) with 3 controls (patients with successful tocolysis after 48 hours).

Data (sociodemographic characteristics, obstetrical history, toxicologic history, admission parameters, type of tocolysis and neonatal outcomes) were collected thanks to a pre-tested survey form in patients admitted to the delivery room after obtaining their informed consent. An authorization was obtained beforehand from YGOPH and the YCH ethics committees.

Patients

In this study, 238 women were included: 62 cases and 186 controls. Inclusions criteria were patient in preterm labor with failure of tocolysis after 48 hours (case) and patients in preterm labor with successful tocolysis after 48 hours (control) with a gestational age between 28 and 36 weeks. Patients with premature rupture of membranes and those who didn't consent to participate were excluded. Patients admitted to the delivery room or hospital was recruited thanks to a pre-tested survey form after obtaining their informed consent. Additional data were collected in the patients' medical record.

Statistical analysis

Statistical analysis was done using Epi info 3.5.4. The chi-square statistical test and Fisher's exact test were used to verify the association between two categorical

variables. Values of $p < 0.05$ were considered statistically significant. The association degree was measured by calculating the odds ratio (OR) with their confidence interval. Multivariate analysis was performed to eliminate confounders.

Results

Patient's age

Patients aged between 20 to 30 years were the most represented in both groups. Age ≥ 30 years appears as a risk factor (OR = 2.75, CI=1.51-4.98, $P = 0.001$), while age between 20 and 30 was protective (OR = 0.42, CI= 0.23-0.75, $P = 0.001$) (Table 1).

Association between tocolytic drugs and tocolysis failure

There were no significant associations between tocolytic drugs and tocolysis failure (Table 2).

Summary of significant predictors of tocolysis failure after univariate analysis

Significant predictors of tocolysis failure in univariate analysis were maternal age ≥ 30 years (OR = 2.75, CI: 1.51-4.98, $p < 0.001$), sexual activity during the last two month of pregnancy (OR = 2.61, CI: 1.29-5.55, $p < 0.001$), antenatal visits < 4 (OR = 1.84, CI = 1-3.49 , $P = 0.030$), midwife/nurse follow-up (OR = 4.22, CI: 1.75-10.19 , $P < 0.001$), notion of referral (OR = 2.91, CI: 1.56-5.37, $p < 0.001$), history of preterm labor (OR = 6.54, CI: 1.56-32.50, $p = 0.010$), Bishop score $\geq$ to 7 at admission (OR = 5.47, CI: 2.63-11.32, $p < 0.001$), twin pregnancy (OR = 2.42, CI: 1.11-5.15, $p < 0.001$) Management with blood derivatives (OR = 1.98; CI: 1.03 to 3.77; $P = 0.030$), and the persistence of the temperature $\geq$ to 38°C after 48 H. (OR = 2.26, CI: 1.07-4.677, $p = 0.020$) after 48 hours of tocolysis (Table 3).

Summary of significant predictors of tocolysis failure after multivariate analysis

After multivariate analysis, predictive factors were: sexual activity during the last two month of pregnancy (AOR = 2.76; CI: 1.06-7.23, $p = 0.038$), prenatal follow-up by midwife or nurse (AOR = 8.96 CI: 2.05-39.22, $p = 0.003$), the persistence of the temperature $\geq$ to 38° C (AOR = 3.89; CI: 1.36-11.6, $p = 0.011$), the Bishop score ≥ 7 at admission (AOR = 12.50; CI: 4.30-36.27, $p < 0.001$) (Table 4).

Table 1: Distribution of cases (n = 62) and controls (n = 186) by age group.

Drug	Case n (%)	Control n (%)	OR (CI 95%)	p
Nicardipine	14 (22,6)	42 (22,6)	1 (0,49-1,97)	0,560
Nifedipine	17 (27,4)	52 (28)	0,97 (0,5-1,84)	0,540
Salbutamol	33 (53,2)	96 (51,6)	1,07 (0,6-1,91)	0,470
Terbutaline	2 (3,2)	6 (3,2)	1 (0,14-4,86)	0,640

Table 2: Association between tocolysis failure and tocolytic drugs in cases and controls.

Age	Case n (%)	Control n (%)	OR (IC 95%)	p
<20	5 (8,1)	17 (9,1)	0,87 (0,28-2,39)	0,510
[20-30]	25 (40,3)	115 (61,8)	0,42 (0,23-0,75)	0,001
≥ 30	32 (51,6)	52 (28)	2,75 (1,51-4,98)	0,001

Table 3: Summary of statistically significant predictors of tocolysis failure after univariate analysis.

Variables	Case n (%)	Control n (%)	OR	IC (95%)	p-value
Age ≥ 30 ans	32 (51,6)	52 (28)	2,75	1,51-4,98	< 0,001
Unemployed	17 (27,4)	27 (14,5)	2,22	1,09-4,43	0,020
Referral by private health center	19 (30,6)	23 (12,4)	3,13	1,54-6,27	< 0,001
Sexualactivity in pregnancy	51 (82,3)	119 (64)	2,61	1,29-5,55	< 0,001
History of preterm labor	6 (9,7)	3 (1,6)	6,54	1,56-32,58	0,010
Midwife/Nurse	13 (21)	11 (5,9)	4,22	1,75-10,19	< 0,001
General practitioner	23 (37,1)	38 (20,4)	2,3	1,21-4,29	0,010
ANC < 4	44 (71)	106 (57)	1,84	1,00-3,49	0,030
Bishop score ≥ 7	22 (35,5)	17 (9,1)	5,47	2,63-11,32	< 0,001
Fetus =2	14 (22,6)	20 (10,8)	2,42	1,11-5,15	0,020
Temperature >= 38°C	15 (24,2)	23 (12,4)	2,26	1,07-4,67	0,020

Table 4: Summary of statistically significant predictors of tocolysis failure after multivariate analysis.

Variables	AOR	IC (95%)		P-value
Sexualactivity in pregnancy	2,7658	1,06	7,23	0,038
Midwife/Nurse	8,9621	2,05	39,22	0,003
Temperature ≥ 38°C	3,8937	1,36	11,16	0,011
Bishop Score ≥ 7	12,4973	4,30	36,27	0,000

Discussion

In our study, age ≥ 30 years was a predictive factor of tocolysis failure. Indeed, several studies refer to maternal age ≤ 18 or ≥ 40 years as a risk factor for preterm labor [6-8]. In a large cohort study with more than 165000 patients, Fuchs et al found that advanced maternal age (40 years and over) was associated with an increased risk of preterm birth even after adjustment for confounders [6].

The common hypothesis which state that the increased risk of preterm birth among aged mothers is largely explained by early labor induction for medical conditions as sustained by Khalil et al. [9] was not confirmed in their study and they showed that advanced maternal age was independently associated with spontaneous prematurity, as McIntyre et al. concluded in a population based cohort study [8]. This age was significantly associated with the failure of tocolysis in our study, because most

of these patients were primiparous; primiparity being associated with poor antenatal care (ANC) [10] and high susceptibility to malaria [11] as we are in an endemic zone, and therefore to preterm labor. Malaria being one of the leading cause of preterm labor in our setting [12].

We found that being unemployed increases the risk of tocolysis failure by two. Benoist et al. in France had similar results [13]. Indeed, the low socio-economic level is associated with poor antenatal care and therefore preterm labor. These women consult late and arrive in delivery room with an advanced stage of labor leading to a higher risk of tocolysis failure.

Sexual activity during the last two months of pregnancy appears as a risk factor of tocolysis failure in our study. Indeed, there are some theoretical mechanisms of induction of labor by sexual activity described such as nipple and genital stimulation that may induce oxytocin release from the posterior pituitary, causing uterine contractions; prostaglandins released from mechanical stimulation of the cervix may cause cervical ripening and prostaglandins in semen may cause cervical ripening [14]. A multicenter prospective study compared the rate of preterm delivery in women who had frequent intercourse (defined as once per week or more) with those who did not. Frequent intercourse was associated with an increased risk of preterm delivery only in the subset of women colonized with *Mycoplasma hominis* or *Trichomonas vaginalis* [15]. Yost and colleagues [16] studied the impact of sexual intercourse on recurrent preterm delivery in women with a previous spontaneous preterm birth at less than 32 weeks' gestation and found that, women with a higher number of lifetime sexual partners had an increased risk of preterm delivery. This may be because of an increased incidence of asymptomatic bacterial colonization of the genital tract in women who have had more sexual partners, leading to subclinical infection, which can induce preterm labor. Thus, could explain the higher rate of tocolysis failure among them. For this reason, the current guidelines from the Society of Obstetricians and Gynecologists of Canada recommend that women at increased risk for preterm labor receive screening and treatment for bacterial vaginosis [17].

History of premature delivery in our study multiplied by six the risk of tocolysis failure thus going in straight line with the data found by Rundell et al. who showed that women with a prior preterm delivery have a 1.5 - to two-fold increased risk of a subsequent preterm

delivery [18]. In a study including 19,025 third births; the recurrence risk ranged from 42% (for women with 2 prior preterm deliveries), through 21% (term/preterm) and 13% (preterm/term), to 5% (term/term). The recurrence risk was highest (57%) for women with 2 prior very preterm deliveries (21-31 weeks) and lowest (33%) for those with 2 prior moderate preterm deliveries (32-36 weeks). The recurrence risk was less pronounced for women with 1 prior very or moderate preterm delivery [19]. The recurrence risk of preterm labor may be associated with other known risk factors for prematurity such as placenta previa, gestational diabetes, occurrence of an invasive procedure in aged mothers, past drug use and smoking [6]. Such conditions can hinder the outcomes of tocolysis among these patients.

Antenatal care by a general practitioner (GP) two-fold increase the risk of tocolysis failure, and when done by a midwife or a nurse the risk was 8-fold higher. Similarly, the number of prenatal consultations was significantly associated with tocolysis failure. Ratzon et al. [20] evaluating the role of prenatal care in recurrent preterm birth in 1470 women found that lack of prenatal care was significantly associated with adverse pregnancy outcomes such as very preterm labor and birth (odds ratio: 4.03; 95% confidence interval: 2.04-7.97). They conclude that prenatal care might reduce the risk for adverse pregnancy outcomes by providing close monitoring of the fetus, leading to timely interventions that can improve infant survival, such as prenatal corticosteroidal treatment. Another possible path-way is that the counseling and support in diverse topics, given by the staff, lead to healthier behavior which may improve pregnancy outcomes. On another hand, Beeckman et al. [21] evaluating the importance of the content of care in the relationship between antenatal care and preterm birth found a significant association between the content and timing of care and preterm birth. Compared with the CTP (Content and Timing of care in Pregnancy) lowest ('inadequate') category, women in the CTP 'sufficient' (OR 0.30; 95% CI 0.09-0.94) and CTP 'appropriate' (OR 0.21; 95% CI 0.06-0.68) category had a lower risk. Hence, they concluded that measurement of the content and timing of care of antenatal care using the new CTP tool is a better assessment of the risk of preterm birth than assessment of the number of antenatal visits alone. Thus, we can associate the low content and timing of care in pregnancy with the follow-up by GP, midwife or nurse in our study explaining failure in tocolysis among these women.

The Bishop score ≥ 7 would increase the tocolysis

failure risk by 5. This agrees with the results of Newman et al. who found that Bishop Score ≥ 4 at 22–24 weeks and ≥ 5 at 26–29 weeks were associated with spontaneous preterm delivery in a singleton population [22]. Although the Bishop score is a labor induction score, it nevertheless allows the assessment of the local cervical state in preterm labor and therefore it would be an excellent predictor of tocolysis failure.

We found that the persistence of the temperature $\geq 38^\circ\text{C}$ after 48 hours of tocolysis exposed as twice as high the risk of tocolysis failure corroborating the study by Chansamouth et al. who had similar results [23]. These results are super impossible with many series in Africa where malaria was the leading cause of fever during pregnancy [10]. Failure of tocolysis in patients with persistent fever for more than 48 hours is reported to be due to lack of etiological diagnosis or failure of etiological treatment.

Conclusion

The determinants of tocolysis failure in our study were sexual activity during the last two month of pregnancy, prenatal midwife/nurse follow-up, temperature persistence $\geq 38^\circ\text{C}$ after 48 hours of tocolysis, Bishop's score ≥ 7 at admission.

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