

Preterm delivery at low gestational age: risk factors for short latency. A multivariate analysis

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Summary

Objective. The aim of this study is to identify the risk factors for a short latency in preterm delivery at low gestational ages (GA).

Study design. A retrospective analysis involving, between January 2004 and May 2006, 204 singleton pregnancies with admission diagnosis of preterm labor and, in particular, 91 pregnant women admitted between 24+0 and 31+6 weeks' gestation.

Results. In pregnant women with a diagnosis of preterm labor at 24-31+6 weeks' gestation, at ROC curve, a value of considering WBC and cervical dilatation, combined in the following formula $(75.237 - (2.290 * \text{"WBC"}) - (10.787 * \text{"cervical dilatation"})) \leq 33.101$ has a 74.2% Sensitivity and a 78.3% Specificity in predicting a latency ≤ 4 days (+LR 3.42 and -LR 0.33) and a 70% Sensitivity and a 84.3% Specificity in predicting GA at delivery at 24-31 weeks' gestation (+LR 4.46 and -LR 0.36).

Conclusion. We suggest a more strictly monitoring and a more aggressive therapy in presence of prognostic parameters of shorter latency.

KEY WORDS: preterm labor, preterm delivery, latency.

Introduction

Preterm labor has been defined as the presence of uterine contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix prior to term gestation (1, 2).

Preterm birth occurs in approximately 10% of pregnancies and accounts for 75% of neonatal morbidity, mortality, and health care spent (3). Despite advances in neonatal care have led to increased survival and reduced short- and long-term morbidity for preterm infants, the rate of low-birth-weight deliveries has actually

increased. Whilst some preterm births are iatrogenic and associated with severe complications during pregnancy (e.g. hypertensive disorders, antepartum haemorrhage, infection), or they can be the result of multiple pregnancies following assisted reproduction, a high proportion of preterm births occurs after spontaneous preterm labour of unknown origin (3).

To date three levels of intervention are applied to reduce morbidity and mortality of preterm birth. Primary intervention is directed to all women. Secondary intervention is aimed at eliminating or reducing existing risk factors; examples are screening for preterm birth risk, early diagnosis and patient education programs, lifestyle changes. Tertiary intervention is intended to improve outcome for preterm infants, e.g. corticosteroids or tocolytic treatment. Tertiary interventions are most commonly used and have been effective in reducing perinatal morbidity and mortality, even though the incidence of preterm birth is still increasing (4).

Optimal reduction of perinatal morbidity and mortality and of the costs associated with prematurity, will require an improved understanding of the etiology and the mechanisms of preterm labor, together with the development of adequate programs for an accurate identification of pregnant women at risk for premature labor and delivery, in order to offer subspecialized obstetrical care. The exact mechanism(s) leading to preterm labor is(are) largely unknown. One of the highest risk factor for preterm delivery is a previous delivery of a preterm infant; the molecular mechanisms involved in preterm delivery have become of great interest in research (5). Recent works suggest that parturition is an inflammatory process, and further understanding of this event will contribute to direct intervention programs in order to prevent preterm birth (6).

Although the causes of preterm labor are multifactorial, infection appears to have a primary role. An initial microbial invasion of the amniotic cavity could transform into fetal invasion, and microorganisms and their products, such as proinflammatory cytokines, could provoke a systemic fetal inflammatory response syndrome (FIRS), characterized by a systemic activation of the fetal innate immune system (7). Affected fetuses show multiorgan involvement with increased probability of a subsequent spontaneous preterm delivery (8, 9).

Secondary agents involved in preterm labor and delivery include: cervical incompetence (eg, trauma, cone biopsy), uterine distortion (eg, müllerian duct abnormalities, fibroid uterus), maternal inflammation (eg, urinary tract infection), decidual hemorrhage (eg, abruption, mechanical factors such as uterine overdistension from multiple gestation or polyhydramnios), hormonal changes (eg, mediated by maternal or fetal stress), uteroplacental insufficiency (eg, hypertension, insulin-dependent diabetes, drug abuse, smoking). A variety of

maternal and obstetric characteristics are known to increase the risk, presumably via one of the above mentioned mechanisms.

The purpose of this study was to demonstrate the hypothesis of a relationship between maternal and/or obstetric characteristics in women with preterm labor, and a short latency. A possible correlation will enable to offer to selected patients subspecialized obstetrical care and reducing morbidity, mortality, and costs associated with prematurity.

Materials and methods

A retrospective analysis on singleton pregnancies with a diagnosis of preterm labor was performed.

342 admissions for preterm labor, from January 2004 to May 2006, at Institute of Gynecology, Perinatology and Child Health-Department of Pediatrics of Rome, were considered. Gestational age ranged between 24+0 and 36+6 weeks.

Multiple admission patients were considered only at their first entry at the hospital. Twin pregnancies and presence of fetal malformations were not considered in the study.

So, former analysis were performed on 204 women whose GA at first admission ranged between 24 and 36+6 weeks and GA at preterm delivery was included between 24 and 36+6 weeks.

After general considerations about characteristic and obstetric outcome, we selected a subgroup of patients for further statistical analysis, a smaller group of 91 women whose first admission was between 24+0 and 31+6 weeks' gestation which were subsequently divided in two subgroups according to the gestational age at admission: between 24+0 and 27+6 weeks vs 28+0 and 31+6 weeks.

A status of preterm labor was diagnosed after regular objective contractions registered with a routine cardiotocograph: a minimum 1 every 10 minutes during a period of at least an hour and/or after referral by the woman of additional, often nonspecific symptoms e.g. pelvic pain or pressure, increased vaginal discharge, backache, menstrual-like cramps, vaginal spotting or bleeding.

After anamnesis, each patient underwent digital cervical examination i.e. evaluation of cervical change (dilatation and/or effacement of the cervix) and calculation of the Bishop score. In addition, every woman was monitored with nonstress test and the presence of uterine contractions was assessed.

In all cases in which data suggested the presence of PROM, sterile speculum examination (for visualization of fluid in the posterior vaginal fornix or passing from the cervical canal) and, sometimes, PROM-test, were performed.

Patients had an ultrasonographic examination to document cervical length and eventually oligohydramnios (suggestive of membrane rupture in the absence of fetal urinary tract malformations or significant growth-restricted fetus), using 4 quadrants AFI measurement (10), as described by Phelan et al., and to confirm gestational age and fetal health.

Each patient was investigated to assess the presence of risk factors for preterm labor: demographic characteris-

tics such as race, maternal age, weight gain in pregnancy, parity, aspects of obstetric history such as having undergone amniocentesis, previous preterm delivery, previous fetal demise, previous induced abortion, presence of uterine distortion (e.g. uterine fibroids or uterine malformations such as didelphys, bicornuate or septate uterus), incompetent cervix, complications in pregnancy (threatened abortion or vaginal bleeding in the first trimester of gestation, PROM, urinary tract infections, gestational diabetes, hypertension, placenta previa, fetal growth restriction, excessive or inadequate amniotic fluid volume, etc.).

Patients between 24 and 34 weeks' gestation were subjected to administration of antenatal corticosteroids to enhance lung maturity (12 mg of intramuscular betamethasone at admission and 24 hours thereafter) and tocolysis (usually various dosages of ritodrine or nifedipine, with a treatment period varying in accordance to the clinical status).

At last, birth weight, Apgar score at first and fifth minute were considered as neonatal outcome.

Statistical analysis

Statistical analysis was performed using SPSS v 15.0. In order to evaluate group differences, a T-test was performed. When the test for normality did not satisfy the criteria of Gaussian distribution, a nonparametric test was applied. For the evaluation of statistical correlations, the Pearson test was performed. When correlations were found significant, a linear regression was run, followed by a multiple linear regression to evaluate the predictability of one parameter with respect to the other parameters. In order to search for the optimal sensitivity and specificity, a receiver operator characteristic (ROC) analysis was performed. The conventional probability value $p < 0.05$ was considered as significant.

Results

The analysis was performed on 204 women with diagnosis at admission of preterm labor at a gestational age included between 24+0 and 36+6 weeks' gestation (mean 32 weeks).

GA at delivery was included between 24+3 and 42+5 weeks' gestation (mean 35+3 weeks), latency was included between 0 and 112 days (mean 24 days, median 14 days). The number of admissions for each patient was included between 1 and 10 (mean 2): 70% of admissions for preterm labor had as conclusion that patient returned pregnant at home. This result demonstrate the need for clinicians of clinical parameters, of easy use and available even in small centres, helpful to predict evolution of preterm labor, and latency.

For this reason we studied, in particular, 91 women admitted between 24±0 and 31±6 weeks' gestation (mean GA at admission 28.8 weeks; mean gestational age at delivery 33.7 weeks; median latency 22 days). Table I shows the description of the study group.

According to Pearson test, latency showed positive correlation coefficients and P values below 0.05 with: GA at delivery (0.901 $p = 4.277E-034$), birth weight (0.836

Table I - Description of the study group (N=91).

	Mean±Std Dev	Median (Min-Max)
Age	31.4±5.710	32.0 (18-44)
GA at admission	28 + 6±2.155	29.2 (24+1-31+6)
Amniocentesis	20%±0.437	-
Weight gain (kg)	9.6±4.687	8.0 (0-30)
WBC (103/mm3)	13.1±4.344	11.8 (6.6-24.8)
Bishop score	3.5±1.953	3.0 (0-8)
PROM	30%±0.458	-
GA at delivery	33 + 5±4.874	32 + 4 (24+2-42+5)
Latency (days)	34.2±34.492	22.0 (0-112)
Birth weight (g)	2241±1025.161	2162 (450-4300)
Apgar 1'	6.5±2.270	7.0 (1-10)
Apgar 5'	8.5±1.378	9.0 (1-10)
Number of admissions for each patient	2±1.759	1.0 (1-10)

p=1.250E-023), Apgar 1° (0.518 p=0.0000135), Apgar 5° (0.499 p=0.0000321), total numbers of admissions (0.259 p=0.0371).

Negative correlation coefficients and P values below 0.05 were found between latency and: GA at admission (-0.228 p=0.0301), WBC (-0.376 p=0.000261), cervical dilatation (-0.431 p=0.0000226), Bishop score (-0.379 p=0.000274), PROM (-0.271 p=0.0293), corticosteroids (-0.306 p=0.00316).

A multiple linear regression analysis revealed the predictability of latency with WBC and cervical dilatation (cm), according to the following formula:

$$\text{LATENCY} = 75.237 - (2.290 * \text{WBC}) - (10.787 * \text{CERVICAL DILATATION}).$$

At ROC Curve: a value <=33.101 has a 74.2% Sensitivity and a 78.3% Specificity in predicting a latency <= 4 days (positive likelihood ratio (+LR) 3.42 and negative

likelihood ratio (-LR) 0.33) and a 70% Sensitivity and a 84.3% Specificity in predicting a GA at delivery at 24-31 weeks' gestation (positive likelihood ratio (+LR) 4.46 and negative likelihood ratio (-LR) 0.36).

As perinatal mortality rate is 216‰ at 24-31 weeks, 18‰ at 32-36 weeks, and 2‰ at 37-40 weeks' gestation (2), we have divided the study group of 91 women, admitted between 24 + 0 and 31 + 6 weeks' gestation, in 2 subgroups, according to gestational age at delivery: "24-31 weeks" (GROUP 1) vs ">32 weeks" (GROUP 2).

To reveal the differences among the 2 groups (latency 4 vs. 57.8 days), so to inquire about the factors that, at the same GA, can influence latency, a T-test was performed: GA at delivery: "24-31 weeks" vs ">32 weeks". See table II.

Finally, in order to better understand how to predict lower GA at delivery, we have divided the study group of 91 women, admitted between 24 + 0 and 31 + 6 weeks' gestation, in 2 subgroups, according to the gestational

Table II - T-test: GA at delivery: "24-31 weeks" (Group 1) vs ">32 weeks" (Group 2).

Parameter	GROUP	Mean± Std Dev	P value
Latency	1	4.025±4.817	= <0.001
	2	57.843±28.718	
Amniocentesis	1	0.150±0.362	= 0.046
	2	0.333±0.476	
WBC	1	15.143±4.763	= <0.001
	2	11.539±3.215	
Cervical dilatation	1	1.563±1.262	= <0.001
	2	0.620±0.842	
Bishop score	1	4.184±2.154	= 0.007
	2	3.060±1.646	
GA at delivery	1	29.038±1.986	= <0.001
	2	37.440±2.833	
Birth weight	1	1273.077±359.754	= <0.001
	2	3044.383±617.499	
APGAR1	1	5.564±2.174	= <0.001
	2	8.167±1.308	
APGAR5	1	7.974±1.442	= <0.001
	2	9.417±0.584	

age at admission: "24 – 27+6 weeks" (N=30) vs "28 – 31+6 weeks" (N=61).

T-test was performed, revealing no significant differences for the following parameters: age, parity, previous preterm delivery, amniocentesis, weight gain, WBC, leucorrhea, cervical dilatation, PROM, latency, number of admissions for each patient, Apgar 5°.

According to Pearson test, in the "GA admission 24 – 27+6 weeks", latency showed positive correlation coefficients and p values below 0.05 with: GA at delivery (0.981 p=1.588E-021), birth weight (0.909 p=8.613E-012), Apgar 1° (0.701 p=0.000138), Apgar 5° (0.797 p=0.00000318).

Negative correlation coefficients and p values below 0.05 were found between latency and: body temperature (-0.402 p=0.0341), WBC (-0.654 p=0.0000899), cervical dilatation (-0.442 p=0.0144).

A multiple linear regression analysis revealed the predictability of latency with WBC, according to the following formula:

$$\text{LATENCY}=116.512-(5.279 \times \text{WBC}).$$

At ROC curve, in women with GA at admission between 24 and 27+6 weeks, a value ≤ 51.0524 has 82.4% Sensibility and 84.6% Specificity (+LR 5.35 and -LR 0.21) in predicting preterm delivery at 24-31 weeks. Furthermore a value ≤ 41.5502 predicts a latency ≤ 4 days with 90% Sensibility and 80% Specificity (+LR 4.50 and -LR 0.12).

Discussion

Preterm labor is a relevant complication in pregnancy especially at low gestational ages. Because of the relevant changes in perinatal mortality at different GA, the clinical conduct is to preserve pregnancy as it is possible, considering that one more day in utero reduces perinatal mortality of 1%, knowing that maternal environment could represent a serious danger for the fetus itself. So it should be possible to choose the best compromise between elective preterm delivery and continuing pregnancy until signs of fetal demise appear. In order to better evaluate what could be possible risk factors involved in preterm delivery at low gestational ages, we have performed a multivariate analysis on a population of women admitted for preterm labor between 24 and 31+6 weeks.

The analysis demonstrates that longer latency is correlated with a better neonatal outcome (birth weight, Apgar score at 1° and 5° minute) for every GA at admission and reveal the important role of WBC, cervical dilatation and Bishop score at admission in predicting latency.

However it should be noted that no role was established for medical history's aspects that are commonly considered as risk factors for preterm delivery, such as: demographic characteristics (race, maternal age), weight gain in pregnancy, parity, aspects of obstetric history such as having undergone amniocentesis, previous preterm delivery, presence of uterine distortion, complications in pregnancy (in particular threatened abortion or vaginal bleeding in the first trimester of gestation), and presence of nonspecific symptoms at admission (e.g. pelvic pain or pressure, increased vaginal discharge, backache, menstrual-like cramps, vaginal spotting or bleeding).

In conclusion, we suggest a more strictly monitoring and a more aggressive therapy in presence of prognostic parameters of shorter latency.

References

1. Jain S, Earhart A, Ruddock N, Wen T, Hankins GDV, Saade GR. The validity of cervical dilatation as an indication of true labor between 32 and 36 weeks 6 days of gestation. *AJOG* 2007 Oct;431.e1-3.
2. Pates JA, McIntire DD, Leveno KJ. Uterine Contractions Preceding Labor. *Obstetrics & Gynecology*. Sept 2007; 110(3):566-9.
3. Andrés López Bernal. Preterm labour: mechanisms and management. Overview. *BMC Pregnancy and Childbirth* 2007;7(Suppl 1):S2 doi:10.1186/1471-2393-7-S1-S2.
4. Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. *Lancet*. 2008 Jan 12;371(9607):164-75.
5. Wilcox AJ, Skjærven R, Lie RT. Familial Patterns of Preterm Delivery: Maternal and Fetal Contributions. *Am J Epidemiol*. 2007 Nov 28.
6. Norman JE, Bollapragada S, Yuan M, Nelson SM. Inflammatory pathways in the mechanism of parturition. *Pregnancy Childbirth*. 2007 Jun 1;7 Suppl 1:S7.
7. Gomez R, Romero R, Ghezzi F, et al. The fetal inflammatory response syndrome. *Am J Obstet Gynecol*. 1998;179:194-202.
8. Gotsch F, Romero R, Kusanovic PJ, Mazakitov S, Pineles BL, Erez O, Espinoza J, Hassan SS. The Fetal Inflammatory Response Syndrome. *Clinical Obstetrics and Gynecology* Sept 2007;50(3):652-683.
9. Yoon BH, Kim YA, Romero R, Kim JC, Park KH, et al. Association of oligohydramnios in women with preterm premature rupture of membranes with an inflammatory response in fetal, amniotic and maternal compartments. *Am J Obstet Gynecol* 1999;181:784-8.
10. Phelan JP, Smith CV, Broussard P, Smal IM. Amniotic fluid volume assessment with four-quadrant technique at 12-36 week's gestation. *J Reprod Med* 1987;32:540-2.