Improving Number of Antepartum Computerized Fetal Heart Monitoring Testing in Women with Preeclampsia with Severe Features does not Improve Maternal or Perinatal Outcome but Improve the Incidence of Caesarean Delivery

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Abstract

Objective: To evaluate if computerized cardiotocography (cCTG) twice a day improved maternal or perinatal outcome compared to daily cCTG in women with severe preeclampsia remote from term.

Study design: This is a 5 year population-based observational study. Women with severe preeclampsia remote from term (<34 weeks) monitored with cCTG twice a day were compared to women with severe preeclampsia remote from term monitored with daily cCTG. Algorism for cCTG were based on Dawes/Redman antepartum CTG analysis by using Sonicaid (Sonicaid Obstetric Solutions, Huntleigh). The primary outcome of this study was the incidence of indicated preterm birth (PTB)<34 weeks.

Results: 989 women with severe preeclampsia remote from term managed with expectant management (i.e., prolonging pregnancy beyond 48 h) were included in the analysis. 401 were monitored with daily cCTG and 588 were monitored with cCTG twice a day until delivery. After adjusting for confounders, we found that women with severe preeclampsia monitored with computerized CTG twice a day had a similar risk of indicated PTB<34 weeks, HELLP, DIC, pulmonary edema, abruption placentae, renal failure, eclampsia, cerebral hemorrhage, liver hemorrhage, maternal death, perinatal death and stillbirth compared to controls. Women monitored with cCTG twice a day had a significantly higher risk of cesarean delivery compared to those who were monitored with daily cCTG.

Conclusion: Improving number of antepartum computerized fetal heart monitoring testing in women with preeclampsia with severe features remote from term does not improve maternal or perinatal outcome but improve the incidence of cesarean delivery. Therefore, we recommend daily antepartum cCTG in women with severe preeclampsia managed expectantly.

Introduction

Fetal heart rate (FHR) testing, also called non-stress test (NST) or cardiotocography (CTG) is a widely used form of antenatal monitoring [1]. Although entrenched in high-risk pregnancy management, most antenatal testing schemes are not supported by high-level evidence and therefore recommendations regarding which pregnancies to test, for how many times and at what gestational age testing should start cannot be made given lack of sufficient evidence [2]. Computerized interpretation of FHR monitoring has evolved as a more specific, objective means of maximizing the information obtained from the CTG and may have significant benefit over standard NST in high-risk cases, including preeclampsia [1-3].

Preeclampsia is a pregnancy-related condition which affects approximately 3-7% of all pregnancies [4]. It is a major cause of maternal and perinatal morbidity and mortality [4]. Prior preeclampsia is one of the most important risk factors for preeclampsia [5]. In case of severe preeclampsia the management options are expeditious delivery or expectant management [6,7]. Expectant management of severe preeclampsia remote from term (<34 weeks) warrants hospitalization at a tertiary facility, daily antenatal testing, including computerized CTG, and laboratory studies at frequent intervals with the decision to prolong pregnancy determined day to day [6,7].

The aim of this study was to evaluate if antepartum computerized CTG twice a day improved maternal or perinatal outcome compared to daily computerized CTG in women with severe preeclampsia remote from term.

Materials and Methods

This is a 5 year population-based observational study using data collected prospectively in a dedicate database from clinical records of preeclamptic women who were referred to the Division of Maternal-Fetal Medicine and to Division of Reproductive Medicine, University of Naples Federico II (Naples, Italy) from January, 2010 to August, 2015. The study was approved by the local institutional review board for each Division. Data were anonymized before analysis. We aimed to compare management of the Division of Maternal-Fetal Medicine (daily antepartum computerized CTG) with the management of the Division of Reproductive Medicine (twice a day antepartum computerized CTG)

In both divisions, expectant management of severe preeclampsia (i.e., prolonging pregnancy beyond 48 h) included hospitalization,

daily laboratory studies and antepartum computerized CTG (i.e., computerized acquisition of the monitoring and computerized interpretation of the CTG) daily or twice a day until delivery.

Algorism for computerized CTG were based on Dawes/Redman antepartum CTG analysis by using Sonicaid (Sonicaid Obstetric Solutions, Huntleigh).

Only women with severe preeclampsia managed with expectant management (i.e., prolonging pregnancy beyond 48 h) were included in this study. Women with severe preeclampsia remote from term (<34 weeks) managed with computerized CTG twice a day (i.e., intervention group) were compared to women with severe preeclampsia remote from term managed with daily computerized CTG (i.e., comparison group). Women with severe preeclampsia at or near term (>34 weeks) and women managed with aggressive management (delivery within 48 h after completion of corticosteroid administration) or with immediate delivery before 48 h (even before completion of steroids) were excluded from the study. Women with preeclampsia without severe features and women with severe preeclampsia <23 weeks were also excluded [6].

Primary and secondary outcomes were designed a priori. The primary outcome of this study was the incidence of indicated preterm birth (PTB)<34 weeks. Secondary outcome included incidence of cesarean delivery, incidence of HELLP syndrome, disseminated intravascular coagulation (DIC), pulmonary edema, abruption placentae, renal failure, seizure (eclampsia), cerebral hemorrhage, liver hemorrhage, maternal death and neonatal outcome including perinatal death (i.e., death of a live-born baby until before 28 days) and still-birth.

Diagnosis of preeclampsia and preeclampsia with severe features were based on ACOG guidelines [6]. Management were based on ACOG and SMFM guidelines [7]. Preeclampsia (i.e., preeclampsia without severe features) was defined as a blood pressure elevation (≥ 140/90 on two occasions four hours apart or ≥ 160/110 once), after 20 weeks of gestation, with proteinuria (≥ 300 mg on 24 h protein or >0.3 protein/creatinine ratio) or any of the following if proteinuria not presents: platelets<100,000; creatinine>1.1 (or doubling of creatinine in absence of other renal disease); doubling of AST or ALT. Preeclampsia with severe features (i.e., severe preeclampsia) was defined as preeclampsia with any of the following: blood pressure ≥ 160/110 four hours apart on bed rest (unless on antihypertensive); platelets<100,000; doubling of AST or ALT; creatinine>1.1 (or doubling of creatinine in absence of other renal disease); pulmonary edema; new cerebral or visual disturbances. Our data was collected

prospectively in a dedicate database from January 1989, but we retrospectively classified preeclampsia and preeclampsia with severe features based on the new ACOG guidelines [6]. In the presence of severe preeclampsia at ≥ 34 weeks, given the high maternal incidence of complications with expectant management, expeditious delivery was performed. In the presence of severe preeclampsia at <34 weeks, expectant management (i.e., prolonging pregnancy beyond 48 h) was performed in case of absent of the following: uncontrollable blood pressure in spite of continuing increase in antihypertensive drugs, persistent headache and/or visual/central nervous system symptoms, epigastric pain, vaginal bleeding, persistent oliguria, preterm labor, premature rupture of membranes, AST/ALT>70 UI/L, platelets<100,000 mm^3 (partial or complete HELLP syndrome), or reversed umbilical artery endodiastolic flow ≥ 32 weeks [6,7].

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA). Data were shown as means ± standard deviation or as number (percentage). Categorical variables were compared using the chi-square or Fisher exact test. Within-group comparison was undertaken using Wilcoxon and Mann-Whitney tests. P-value<0.05 was considered statistically significant. Planned primary and secondary outcomes were estimated with multivariate analyses through logistic regression models in both groups. Logistic regression, presented as adjusted odds ratio (aOR) with the 95% of confidence interval (CI), was performed to correct data for those variables significantly different between groups. The study was performed following the STROBE guidelines [8].

Results

3,360 women with preeclampsia with severe feature were referred to our Division, of whom 989 (0.6%) were women with severe preeclampsia remote from term (26-34 weeks) managed with expectant management (i.e., prolonging pregnancy beyond 48 h). Therefore, these 989 women met the inclusion criteria of this study and were included in the analysis. 401 (40.5%) were monitored with daily antepartum computerized CTG until delivery and 588 (59.5%) were monitored with computerized CTG twice a day until delivery.

Table 1 shows the characteristics of the included women. The two groups were similar in terms of maternal demographics except for the ethnicity. The percentage of smoking was 21.9% versus 24.0%. The mean gestational age at diagnosis of severe preeclampsia were 30.1 versus 30.6 weeks.

Age	Intervention group* (n=588)	Comparison group** (n=401)	p value
Mean ± SD (years)	29.1 ± 5.7	29.5 ± 11.4	NS (0.14)
Ethnicity			
Caucasian n (%)	382 (65.0%)	320 (80.0%)	<0.0001
Non-Caucasian n (%)	206 (35.0%)	81 (20.0%)	
Gravidity			
mean ± SD	3.7 ± 1.5	3.2 ± 1.9	NS (0.44)
median (range)	5.1 (1-11)	5.5 (1-15)	-

Parity			
mean ± SD	1.3 ± 1.4	1.2 ± 1.0	NS (0.13)
median (range)	3.1 (1-6)	3.2 (1-7)	-
BMI			
mean ± SD (Kg/m2)	25.9 ± 14.9	25.8 ± 12.7	NS (0.89)
>30 n (%)	90 (15.3%)	70 (17.5%)	NS (0.30)
Smoking			
n (%)	129 (21.9%)	96 (24.0%)	NS (0.29)
Chronic hypertension			
n (%)	105 (17.9%)	84 (20.9%)	NS (0.10)
Diabetes mellitus (including GDM)			
n (%)	64 (10.9%)	49 (12.2%)	NS (0.68)
Family history of hypertension*			
n (%)	150 (25.5%)	118 (29.4%)	NS (0.17)
Prior preeclampsia			
n (%)	9 (1.5%)	6 (1.5%)	NS (0.86)
No. of fetuses			
Singleton n (%)	558 (94.9%)	380 (94.8%)	NS (0.89)
Multiple n (%)	30 (5.1%)	21 (5.2%)	
GA at diagnosis			
mean ± SD (weeks)	30.1 ± 2.2	30.6 ± 2.1	NS (0.12)
median (range)	28.5 (26–33)	29.2 (26–33)	-

Table 1: Characteristics of the included women (Data are presented as number (percentage) or as mean difference ± standard deviation or as median (range). Boldface data, statistically significant. *First-degree family history of hypertension GDM, gestational diabetes mellitus; SD, standard deviation; NS, non-significant; GA, gestational age; *Intervention group, women with severe preeclampsia remote from term (<34 weeks) managed with expectant management (i.e., prolonging pregnancy beyond 48 hours) including computerized CTG twice a day until delivery; **Comparison group, women with severe preeclampsia remote from term (<34 weeks) managed with expectant management (i.e., prolonging pregnancy beyond 48 h) including daily computerized CTG until delivery.

After adjusting for confounders statistically proven (i.e., ethnicity), we found that women with severe preeclampsia monitored with computerized CTG twice a day had a similar risk of PTB <34 weeks (80.0% vs. 78.6%; aOR 1.02, 95% CI 0.95 to 1.09), HELLP (17.9% vs. 20.9%; aOR 0.85, 95% CI 0.66 to 1.10), DIC (10.9% vs. 12.2%; aOR 0.89, 95% CI 0.63 to 1.26), pulmonary edema (5.1% vs. 5.2%; aOR 0.97, 95% CI 0.57 to 1.68), abruption placentae (1.5% vs. 1.2%; aOR 1.23, 95% CI 0.41 to 3.64), renal failure (1.3% vs. 1.5%; aOR 0.91, 95% CI 0.32 to 2.60), eclampsia (0.2% vs. 0.2%; aOR 0.68, 95% CI 0.04 to 10.87), cerebral hemorrhage (0% vs. 0.2%; aOR 0.23, 95% CI 0.01 to 5.57), liver hemorrhage (0% vs. 0.2%; aOR 0.23, 95% CI 0.01 to 5.57), maternal death (0% vs 0.2%; aOR 0.23, 95% CI 0.01 to 5.57), perinatal death (2.2% vs. 2.5%; aOR 0.89, 95% CI 0.39 to 2.00) and still-birth (1.2% vs. 1.5%; aOR 0.80, 95% CI 0.27 to 2.35) compared to controls. Women monitored with computerized CTG twice a day had a significantly higher risk of cesarean delivery compared to those who were monitored with daily computerized CTG (94.9% vs. 88.8%; aOR 1.27, 95% CI 1.13 to 1.33) (Table 2).

	Intervention group* (n=588)	Comparison group** (n=401)	aOR (95% CI)
PTB<34 weeks	470 (80.0%)	315 (78.6%)	1.02 (0.95 to 1.09)
CD	558 (94.9%)	356 (88.8%)	1.27 (1.13 to 1.33)

HELLP	105 (17.9%)	84 (20.9%)	0.85 (0.66 to 1.10)
DIC	64 (10.9%)	49 (12.2%)	0.89 (0.63 to 1.26)
Pulmonary edema	30 (5.1%)	21 (5.2%)	0.97 (0.57 to 1.68)
Abruption placentae	9 (1.5%)	5 (1.2%)	1.23 (0.41 to 3.64)
Renal failure	8 (1.3%)	6 (1.5%)	0.91 (0.32 to 2.60)
Seizure (Eclampsia)	1 (0.2%)	1 (0.2%)	0.68 (0.04 to 10.87)
Cerebral hemorrhage	0	1 (0.2%)	0.23 (0.01 to 5.57)
Liver hemorrhage	0	1 (0.2%)	0.23 (0.01 to 5.57)
Maternal death	0	1 (0.2%)	0.23 (0.01 to 5.57)
Perinatal death	13 (2.2%)	10 (2.5%)	0.89 (0.39 to 2.00)
Stillbirth	7 (1.2%)	6 (1.5%)	0.80 (0.27 to 2.35)

Table 2: Primary and secondary outcomes.

Discussion

This population-based study showed that antepartum computerized CTG twice a day did not improve maternal or perinatal outcome compared to daily computerized CTG in women with severe preeclampsia remote from term managed expectantly while improve the incidence of cesarean delivery.

Our study has several strengths. We used the same algorism and the same software (Dawes/Redman criteria, Sonicaid Obstetric Solutions, Huntleigh), for the computerized CTG during this 5 years. This is a large 5 year population-based study. The number of the included women was very high. The two groups were similar in terms of maternal demographics. Primary and secondary outcomes and subgroup analyses were established a priori. These are key elements that are needed to evaluate the reliability of a study [9]. This may be the first study in the literature evaluating the number of antepartum computerized fetal heart monitoring testing in women with preeclampsia with severe features. No similar publication was found by a systematic review: searches were performed in MEDLINE, OVID, Scopus, Sciencedirect.com, ClinicalTrials.gov and EMBASE with the use of the following key words: "nonstress test," "cardiotocography," "preeclampsia," "hypertension," "guidelines," "heart rate," "surveillance," "antenatal testing" and "neonatal"

The most important limitation of our study is that this is a retrospective, non-randomized comparison. Management of women (i.e., daily vs. twice a day CTG) were according to the Divisions' guideline. A priori power analysis could not be assessed due to its retrospective nature [9]. However, the confidence intervals of odds ratio for the overall analysis are quite narrow, indicating low variability and high sample size [10]. The confidence intervals are more statistically useful than post-hoc power calculations [10]. We do acknowledge that many outcomes, including eclampsia, cerebral and liver hemorrhage and maternal death, were underpowered; however these are indeed uncommon outcomes with an overall incidence less than 1%. We were not able to collect data on neonatal outcomes including hypoxemia-neurologic injury, respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, admission to neonatal intensive care unit. This study spans over 5 years and this

rise the question of practice changes, including interpretation of the computerized monitoring, over the past decades. Even if we attempted to answer an important question (i.e., the frequency of testing in women with preeclampsia remote from term), our study was limited by the study design in which management were based on attendings' discretion. Women with severe preeclampsia are at risk for indicated PTB, and therefore it is unclear if PTB<34 weeks is a good (i.e., prevention of still-birth) or a bad outcome (i.e., result of a false positive antenatal testing). Fetal monitoring is designed to improve neonatal outcomes, but the vast majority of the outcomes assessed were maternal. Since that our Division is a referral center for high risk pregnancies, the rates of severe preeclampsia remote from term and adverse maternal outcome in the study group are high. We did not look at indication for PTB and indication of cesarean delivery.

In summary, improving number of antepartum computerized fetal heart monitoring testing in women with preeclampsia with severe features does not improve maternal or perinatal outcome but improve the incidence of cesarean delivery. Therefore, we recommend daily antepartum computerized CTG in women with severe preeclampsia managed expectantly.

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