OBSTETRICS

Expectant management of severe preeclampsia remote from term: the MEXPRE Latin Study, a randomized, multicenter clinical trial

Paulino Vigil-De Gracia, MD; Osvaldo Reyes Tejada, MD; Andrés Calle Miñaca, MD; Gerardo Tellez, MD; Vicente Yuen Chon, MD; Edgar Herrarte, MD; Aurora Villar, MD; Jack Ludmir, MD

OBJECTIVE: The objective of the study was to determine whether expectant management of severe preeclampsia prior to 34 weeks of gestation results in improved neonatal outcome in countries with limited resources.

STUDY DESIGN: This was a randomized clinical trial performed in 8 tertiary hospitals in Latin America. Criteria of randomization included gestational age between 28 and 33 weeks' gestation and the presence of severe hypertensive disorders. Patients were randomized to steroids with prompt delivery (PD group) after 48 hours vs steroids and expectant management (EXM group). The primary outcome was perinatal mortality.

RESULTS: A total of 267 patients were randomized, 133 to the PD group and 134 to the EXM group. Pregnancy prolongation was 2.2 days for the PD group vs 10.3 days for the EXM group ($P = .0001$). The rate of perinatal mortality (9.4% vs 8.7%; $P = .81$; relative risk [RR], 0.91; 95% confidence interval [CI], 0.34–1.93) was not improved with expectant management, and neither was the composite of neonatal morbidities (56.4% vs 55.6%; $P = .89$; RR, 01.01; 95% CI, 0.81–1.26). There was no significant difference in maternal morbidity in the EXM group compared with the PD group (25.2% vs 20.3%; $P = .34$; RR, 1.24; 95% CI, 0.79–1.94). However, small gestational age (21.7% vs 9.4%; $P = .005$; RR, 2.27; 95% CI, 1.21–4.14) and abruption were more common with expectant management (RR, 5.07; 95% CI, 1.13–22.7; $P = .01$). There were no maternal deaths.

CONCLUSION: This study does not demonstrate neonatal benefit with expectant management of severe preeclampsia from 28 to 34 weeks. Additionally, a conservative approach may increase the risk of abruption and small for gestational age.

Key words: abruption placentae, expectant management, perinatal mortality and morbidity, severe preeclampsia

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From the Departments of Obstetrics and Gynecology, Complejo Hospitalario de la Caja de Seguro Social (Dr Vigil-De Gracia) and Hospital Santo Tomas (Dr Reyes Tejada), Panama City, Panama; Departments of Obstetrics and Gynecology, Hospital Carlos Andrade Marin, Quito (Dr Calle Miñaca), and Hospital Teodoro Maldonado Carbo, Guayaquil (Dr Chon), Ecuador; Department of Obstetrics and Gynecology, Hospital de Ginecología y Obstetricia del Instituto Materno Infantil, Toluca, México (Dr Tellez); Department of Obstetrics and Gynecology, Hospital de Ginecología y Obstetricia del Instituto Guatemalteco de Seguridad Social, Guatemala City, Guatemala (Dr Herrarte); Department of Obstetrics and Gynecology, Hospital Nacional Docente Madre Niño, San Bartolomé, Lima, Perú (Dr Villar); and Department of Obstetrics and Gynecology, Pennsylvania Hospital, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA (Dr Ludmir). The remaining MEXPRE Latin study investigators are listed in the Acknowledgments.

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Reprints: Paulino Vigil-De Gracia, MD, Complejo Hospitalario de la Caja de Seguro Social, Panama, Panama. pvigild@hotmail.com.

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Preeclampsia occurs in about 2-12% of all pregnancies, and severe preeclampsia remote from term accounts for approximately 25% of all cases.[1,2] The course of early severe preeclampsia is associated with progressive deterioration of maternal and fetal conditions, and the only known definitive treatment is delivery.[1] However, delivery at a gestational age remote from term (early preterm delivery) is associated with increased risk for adverse neonatal outcome.

In severe hypertensive disorders of pregnancy at gestational ages before 34 weeks, several management options can be considered including immediate delivery after maternal stabilization, prompt delivery after corticosteroid therapy for fetal maturation and expectant management if maternal and fetal condition are stable, and delaying delivery until signs of maternal or fetal compromise or reaching 34 weeks of gestation.[3]

Two randomized studies of women with severe preeclampsia remote from term investigated the maternal and neonatal complications after conservative management.[4,5] In both trials, expectant management consisted of hospitalization, bed rest, oral antihypertensives and intensive antenatal fetal monitoring with delivery when reaching 34 weeks' gestation, or earlier delivery if maternal or fetal condition worsened. The outcome of the studies demonstrated a reduction of neonatal pulmonary complications; necrotizing enterocolitis; and days in intensive care nursery without statistically significant difference in rates of stillbirth, neonatal death, and maternal complications.[4,5]

These studies are limited by the few number of enrolled patients (only 133); however, the Society of Maternal-Fetal Medicine based on these 2 studies, and additional observational studies recently stated that expectant management of a select group of women with severe preeclampsia occurring less than 34 weeks' gestation may improve newborn outcomes but requires careful in-hospital maternal and fetal surveillance.[6] Despite this statement, we believe that there are insufficient data to make recommendations about the most adequate care for patients with severe preeclampsia remote from term, in particular in developing countries with limited health resources.

★ EDITORS' CHOICE ★

The purpose of this study was to determine whether expectant management of severe preeclampsia prior to 34 weeks' gestation results in better perinatal outcome compared with prompt delivery after steroid administration in Latin American countries.

Materials and Methods

Participants and trial design

A randomized, multicenter, parallel, open-label clinical trial was undertaken between August 2010 and August 2012 in 8 tertiary teaching hospitals in Latin America with experience in the management of severe preeclampsia. The hospitals were selected among 21 others because of their ability to immediately respond to obstetric emergencies and the presence of neonatal specialized care 24 hours a day. These hospitals also had a track record of conducting clinical studies.

Pregnant women with singleton or twin pregnancy and severe hypertensive disorders at 28-33 weeks of gestation were invited to take part in the Expectant Management of Preeclampsia, or MEXPRE (Manejo Expectante de Preeclampsia) Latin study. Pregnancies less than 28 weeks were excluded because the neonatal mortality for those babies in the intensive care units of the hospitals involved is high and subject to limited resources.

Severe preeclampsia was diagnosed if there was presence of blood pressure of 140/90 mm Hg or greater on 2 occasions at least 4 hours apart and 0.3 g or greater of protein in a 24 hour urine specimen with 1 or more of the following additional criteria: blood pressure greater than 160 mm Hg systolic or greater than 110 mm Hg diastolic; proteinuria of at least 5 g per 24 hours; or symptoms suggesting significant end-organ involvement, such as headache, visual disturbances, epigastric pain, or tinnitus.

A diagnosis of severe gestational hypertension was made with a presence of blood pressure of 140/90 mm Hg or greater on 2 occasions at least 4 hours apart and less than 0.3 g of protein in a 24 hour urine specimen with 1 or more of the following additional criteria: blood pressure greater than 160 mm Hg systolic greater than 110 mm Hg diastolic; or symptoms suggesting significant end-organ involvement, such as headache, visual disturbances, epigastric pain, or tinnitus.

Chronic hypertension was defined as hypertension present before pregnancy or before the 20th week of gestation. Superimposed preeclampsia in women with chronic hypertension was defined as the development of new-onset proteinuria (excretion of greater than 300 mg of protein over 24 hours), with 1 or more of the following criteria: blood pressure greater than 160 mm Hg systolic or greater than 110 mm Hg diastolic; or symptoms suggesting significant end-organ involvement, such as headache, visual disturbances, epigastric pain, or tinnitus.

Exclusion criteria were eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), preeclampsia with renal failure or pulmonary edema, active vaginal bleeding, ruptured membranes, placenta previa, diabetes mellitus or gestational diabetes, preexisting renal disease, or autoimmune disease. In addition, major fetal abnormalities, fetal growth restriction (fetal estimated weight below the 10th percentile for gestational age determined by ultrasound), oligohydramnios, and reverse umbilical artery Doppler flow. All patients had an ultrasound before enrollment to rule out fetal growth restriction.

Eclampsia was defined as generalized convulsions in pregnancy not caused by epilepsy or other causes and HELLP syndrome as platelet count of 150,000 or less and aspartate aminotransferase of 70 units/L or greater, alanine aminotransferase of 40 units/L or greater, and lactate dehydrogenase of 600 units/L or greater.

Pulmonary edema was defined as tachypnea greater than 40 per minute,

gas diffusion deficit, and compatible chest X-ray and renal insufficiency as urine output less than 500 mL/d, serum creatinine greater than 1.2 mg/dL, and creatinine clearance less than 20 mL/min.

Disseminated intravascular coagulation was defined as the presence of 3 or more of the following criteria: low platelet count (<100,000 cells/mL), low fibrinogen concentration (<300 mg/dL), presence of D-dimers (≥40 mg/dL), or prolonged prothrombin time (≥14 seconds), and partial thromboplastin time (≥40 seconds). Oliguria was defined as the urine output less than less than 0.5 mL (kilograms per hour) or less than 100 mL per 4 hours. Gestational age was judged from the menstrual history and confirmed by measurement of fetal crown-rump length at first-trimester scan.

The diagnosis of small for gestational age (SGA) was defined as birthweight less than the 10th percentile for gestational age. Abruptio placentae was defined as clinical/pathology diagnosis of retroplacental hematoma at delivery.

Stillbirth or fetal death was defined as death in utero and neonatal death as death from birth to 28 days after birth. Perinatal death was defined as fetal plus neonatal deaths.

The ethics committees or institutional boards for all participating hospitals approved the protocol. Trial coordinators regularly undertook quality control of screening data handling and verification of adherence to the protocols at the different hospitals.

Randomization and masking

After written informed consent was obtained from women, they were randomly allocated to the prompt delivery group (PD) or expectant management group (EXM) in a 1:1 ratio.

All patients were extensively counseled regarding the maternal and perinatal risks of expectant or early delivery management. The principal investigator made the assignment centrally for each hospital by using a computer-generated code with variable block size of 4 and 6, with concealment of allocation by sealed envelopes. The trial coordinator or recruiters in each hospital did not have access to the randomization sequence. This study was open label because of the nature of the intervention.

Interventions

In the PD group, the patients received glucocorticoid therapy followed by delivery in 24-72 hours; in the EXM group, the women were treated expectantly (glucocorticoid therapy followed by delivery only for specific maternal/fetal indications or reaching 34 weeks of gestation).

Antepartum management included bed rest; to prevent and control seizure, all women initially received magnesium sulfate as a 4 g intravenous loading dose followed by 1 g intravenous per hour for 24-48 hours. In the PD group, magnesium sulfate was continued until 24 hours after delivery. Bolus doses of hydralazine, labetalol, or oral nifedipine were administered to control severe hypertension (≥160/110 mm Hg). Four doses of 6 mg of dexamethasone intramuscularly given 12 hours apart were administered or 2 doses of 12 mg of betamethasone intramuscularly given 24 hours apart. Maternal evaluation included frequent blood pressure measurements along with questioning for symptoms of worsening preeclampsia.

Oral antihypertensive medications were used only in some hospitals, in those women with severe hypertension to maintain systolic blood pressure (BP) below 160 mm Hg and diastolic BP less than 110 mm Hg, after use of intravenous bolus doses of hydralazine, labetalol, or oral nifedipine to control severe hypertension. The oral antihypertensive drugs used were α-methyl dopa, nifedipine, or hidralazine. The administration of oral antihypertensives after the acute treatment of severe hypertension was at the discretion of the treating physician and varied between hospitals.

Laboratory evaluation included serial measurement of liver function tests, complete blood cell count, coagulation profile, and renal function tests at admission and each day for 48 ± 72 hours in both groups; in the expectant group, the laboratory evaluation continued twice per week.

Fetal status was assessed with a non-stress test each day and ultrasound to rule out fetal growth and restriction, and assessment of amniotic fluid was performed at admission prior to randomization and then serially. Ultrasounds to evaluate fetal growth were performed every 1-2 weeks according to findings as long as the patient remained pregnant in the expectant group.

Specific indications for delivery in the expectant group were uncontrollable blood pressure, nonreassuring fetal heart rate tracing, abnormal fetal testing, fetal growth restriction (fetal weight below the 10th percentile for gestational age determined by ultrasound), abruption placentae, decline in renal function, the HELLP syndrome, persistent severe headache or visual changes, or epigastric pain and 34 weeks of gestation. Magnesium sulfate was restarted when delivery was indicated and continued for 24 hours after delivery.

The investigators and the neonatologist who followed up the infants prospectively collected data on the pregnant women and their newborns on a standardized form. Outcome data included maternal demographics and maternal and neonatal outcomes. Demographic data included maternal age, gestational age at diagnosis, days of expectant management, gestational age at delivery, the indication for delivery, and the mode of delivery. An attempt was made to blind the treatment allocation to the data abstracter, especially to the neonatologist.

Maternal morbidities included placental abruption, pulmonary edema, the HELLP syndrome, renal insufficiency, eclampsia, disseminated intravascular coagulation, and death.

Neonatal data included fetal or neonatal death (perinatal death), birthweight, Apgar scores, neonatal intensive care unit admissions and length of stay, composite neonatal morbidities (respiratory distress syndrome [RDS], intraventricular hemorrhage [IVH] grade III and IV, necrotizing enterocolitis, neonatal sepsis).

Statistical analysis

The primary outcome was perinatal mortality (fetal and neonatal death). Secondary outcomes were composite

neonatal morbidities (RDS, IVH, necrotizing enterocolitis, neonatal sepsis), neonatal data (birthweight, SGA, Apgar scores, neonatal intensive care unit admissions and length of stay), and maternal morbidities (placental abruption, pulmonary edema, the HELLP syndrome, renal insufficiency, eclampsia, disseminated intravascular coagulation) and death.

The sample size was calculated, assuming a 15% rate of perinatal mortality (fetal death and neonatal death at ≤28 days) in the prompt delivery group,[4] a 2-sided α error of 5%, and 80% power to detect a reduction of 30% in the rate of perinatal mortality with the expectant management. The high rate of perinatal mortality assumed in the study reflects the reality in Latin American countries. To detect that difference, 260 patients with 130 in each group needed to be recruited.

The baseline characteristics of the participants in each group were compared with a Student *t* test for continuous variables with normal distribution and a Mann-Whitney *U* test for discrete and ordinal variables or those with nonnormal distribution. Univariate comparisons of dichotomous data were done with a Fisher exact test. The *P* values for all hypotheses were 2 sided, and values of $P < .05$ were judged to be significant. Statistical analysis was performed with Epi Info software version 7 (Centers for Disease Control and Prevention, Atlanta, GA), under the intention-to-treat principle. The trial is registered (ClinicalTrials.gov no. NCT01164852).

RESULTS

During 25 months, 267 women gave informed consent to the MEXPRE Latin study. Two patients did not complete the study (refusal to continue in the hospital), and 1 patient did not receive the correct management because of the physician's error, all in the EXM group. The data for these 3 women were not available and were excluded. The remaining 264 women were eligible for analysis. A total of 131 women were randomized to the EXM group and 133 to the PD group. The Figure outlines the study profile.

FIGURE
Patient flow diagram of the clinical trial

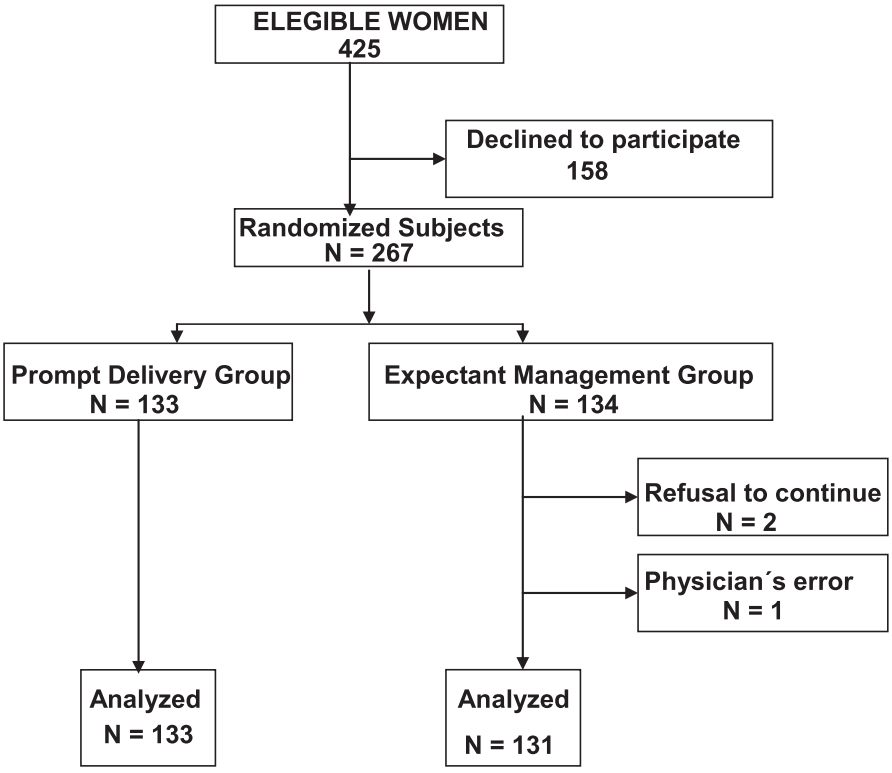

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Table 1 shows the baseline characteristics. There were no significant differences between groups in baseline characteristics. Eleven patients with twin gestations were included in the study, 4 in the PD group and 7 in the EXM group. A total of 138 births were analyzed in the EXM group and 137 in the PD group. One fetal death occurred in each group.

Oral antihypertensive medications to maintain systolic BP below 160 mm Hg and diastolic BP below 110 mm Hg (after control of severe hypertension) in women randomized to EXM only was used in 61 women (46.5%). There were no significant differences in perinatal mortality between women with oral antihypertensive medications and women without oral antihypertensive medications: 7 (11.48%) vs 5 (7.14%) ($P = .29$). The incidence of severe blood pressure in the oral antihypertensive group was similar to the group on no oral antihypertensives (41% vs 38.6%, $P = .81$). Abruptio placentae was found in 5 women with oral antihypertensive medications (8.20%) and 5 women without oral antihypertensive medications (7.14%). However, there was a significant difference in higher maternal morbidity (37.7% vs 14.3%, $P = .02$) in the EXM group receiving oral antihypertensive medications to maintain systolic BP below 160 mm Hg and diastolic BP below 110 mm Hg.

There were no significant differences between groups in corticosteroids used: betamethasone (58.6%) and dexamethasone (41.4%) ($P = .31$).

Reasons for delivery in the EXM group were the following: uncontrollable blood pressure (40.4%); fetal compromise (29%) (fetal growth restriction [10%], oligohydramnios [2%], abnormal fetal heart rate [12%], abnormal Dopplers of fetal vessel [5%]); persistent symptoms (severe headache, visual changes, or epigastric pain [28.2%]); attainment of 34 weeks of gestation (26.0%); and maternal complications (eclampsia, the HELLP

TABLE 1
Patient characteristics at randomization

Variable	Prompt delivery (n = 133)	Expectant management (n = 131)
Hypertensive disorder		
Severe preeclampsia	107 (80.4)	100 (76.3)
Superimposed preeclampsia	19 (14.2)	19 (14.5)
Severe gestational hypertension	7 (5.4)	12 (9.2)
Age, y	27.9 ± 6.6	28.4 ± 6.7
Nulliparous	55.0 (41.3)	53.0 (39.8)
Mean gestational age, wks	30.8 (1.6)	30.7 (1.5)
Median urinary protein, 24 h	2.2 (2.8)	2.2 (2.4)
SBP, mm Hg	161.6 ± 15.5	161.3 ± 14.9
DBP, mm Hg	105.9 ± 9.9	105 4 ± 8.6
SBP ≥160 mm Hg	83 (62.4)	85 (64.9)
DBP ≥110 mm Hg	68 (51.1)	65 (49.6)
BP ≥160/110 mm Hg	60 (45.1)	57 (43.5)
Symptoms	107 (80.4)	103 (78.6)
Twins pregnancy	4 (3)	7 (5.2)

Data are number (percentage) or mean (SD), unless otherwise indicated.

BP, blood pressure; *DBP*, diastolic BP; *SBP*, systolic BP.

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syndrome, pulmonary edema, oliguria, abruption placentae, or renal insufficiency [21.3%]). Many patients had more than 1 indication for earlier delivery.

There were no significant differences between groups in the primary outcome (perinatal mortality): 9.4% in the PD group vs 8.7% in the EXM group (Table 2). There were no cases of perinatal death in twin pregnancies. Composite neonatal morbidities were similar in both groups: 56.4% in the PD group vs 55.6% in the EXP group ($P = .89$).

Significant differences were noted in secondary outcomes between the groups (Table 2). The PD group had lower birthweight at delivery; however, the EXM group experienced more cases of small for gestational age and abruption placentae in comparison. There was a nonsignificant trend in higher maternal morbidity (25.3% vs 20.3%, $P = .34$) and cesarean delivery (94.7% vs 88.7%, $P = .12$) in the EXM group. The average pregnancy prolongation in the EXM group was 10.3 ± 8 days, which was significantly higher than the average of 2.2 ± 0.8 days in the PD group ($P = .0001$) (Table 2). There were no cases of maternal death.

There were no differences between the 2 groups in perinatal mortality and neonatal morbidities, regardless of the hospital in which the study was performed.

Furthermore, there were no differences in perinatal mortality (9.9% vs 11.2%, $P = .53$) and neonatal morbidities (50.4% vs 52.3%, $P = .68$) between the PD and EXP groups, respectively, when the analysis was limited only to the patients with severe preeclampsia by strict definition (excluding the patients with chronic hypertension with superimposed preeclampsia and severe gestational hypertension in either group).

A stratified analysis to detect any differences in the total perinatal mortality and morbidity by gestational age (28-29, 30-31, and 32-33 weeks) was performed. The rates of total neonatal morbidity and mortality stratified by gestational age at randomization were as follows: 85% (63 of 75), 66.3% (65 of 98), and 36.2% (37 of 102), respectively, and there were no significant differences between the PD group and EXM groups (Table 3). Interestingly, 60% of the perinatal deaths (15 of 25) occurred in patients with a gestational age of 28-29 weeks and only 2 (8%) in the cohort with the gestational age of 32-33 weeks.

Comment

To date, when confronted with severe preeclampsia, the only curative treatment is interruption of gestation with delivery of the fetus.[1-3] At gestational ages remote from term, the consequences of prematurity for the neonate have to be balanced with the potential maternal morbidity by prolonging gestation. In Latin American countries in which the number one reason for maternal mortality continues to be preeclampsia-eclampsia[7] and with limited health resources for maternal and neonatal intensive care nurseries, the decision to prolong gestation under the circumstances mentioned previously can carry significant consequences.

Our randomized, multicenter, parallel trial conducted in Latin America demonstrates that the expectant management of women at 28-33 weeks of pregnancy with severe hypertensive disorder after treatment with corticosteroids is ineffective in reducing perinatal mortality and fails to reduce the incidence of various other complications of prematurity such as RDS, IVH, necrotizing enterocolitis, and neonatal sepsis.

Antenatal treatment with corticosteroids to accelerate fetal maturation has been used for more than 4 decades, and its effectiveness and safety is well established for pregnancies between 24 and 34 weeks.[8,9] A possible extension of the benefits of a single course of antenatal steroids for a period of 1-2 weeks has been widely considered,[10,11] but the exact duration of steroid benefit remains controversial.[12]

Our randomized, multicenter trial shows that despite prolongation of pregnancy by 10 days in women with severe hypertensive disorders, the neonatal outcomes are similar (perinatal mortality, RDS, IVH, necrotizing enterocolitis, and neonatal sepsis), that when

TABLE 2
Primary and secondary outcomes in the PD and EXM groups

Outcomes	PD group (n = 133)	EXM group (n = 131)	Relative risk (95% CI)	*P* value
Perinatal deaths	13 (9.4)	12 (8.7)	0.91 (0.34–1.93)	.81
Composite neonatal morbidity[a]	70 (56.4)	70 (55.6)	1.01 (0.81–1.26)	.89
RDS	65 (52.4)	58 (46.0)	1.13 (0.88–1.47)	.31
Necrotizing enterocolitis	1 (0.81)	2 (1.6)	1.96 (0.18–21.4)	1.00
Intraventricular hemorrhage	4 (3.2)	1 (0.79)	0.24 (0.02–2.17)	.21
Neonatal sepsis[b]	31 (25.0)	31 (24.6)	0.98 (0.63–1.51)	.94
Birthweight	1543 (438)	1659 (509)	—	.04
SGA	13 (9.4)	30 (21.7)	2.27 (1.21–4.14)	.005
Apgar score				
1 minute	7.49 (1.3)	7.50 (1.4)	—	.94
5 minutes	8.60 (0.7)	8.56 (1.0)	—	.80
NICU admission	95 (69.3)	102 (73.9)	1.05 (0.92–1.2)	.40
Length of NICU admission stay	13.8 (14)	13.4 (15)	—	.81
Sex female of baby	69 (50.3)	75 (54.3)	1.17 (0.73–1.88)	.50
Cesarean delivery	118 (88.7)	124 (94.7)	1.06 (0.99–1.14)	.08
Pregnancy prolongation, d	2.2 (0.8)	10.3 (8)	—	.0001
Maternal complications[c]	27 (20.3)	33 (25.2)	1.24 (0.79–1.94)	.34
Abruptio placentae	2 (1.5)	10 (7.6)	5.07 (1.13–22.7)	.01
Eclampsia	1 (0.75)	1 (0.76)	0.98 (0.06–15.91)	1.00
HELLP syndrome	21 (16.0)	18 (13.5)	0.87 (0.5–1.6)	.32
Pulmonary edema	1 (0.76)	2 (1.5)	1.98 (0.17–22.15)	1.00
Renal insufficiency	1 (0.76)	3 (2.26)	3.04 (0.32–29.2)	.28
Oliguria	6 (4.58)	6 (4.51)	0.98 (0.30–3.13)	1.00
DIC	0 (0)	2 (1.5)	—	.24

Data are number (percentage) or mean (SD), unless otherwise indicated.

CI, confidence interval; *DIC*, disseminated intravascular coagulation; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count; *NICU*, neonatal intensive care unit; *PD*, prompt delivery; *RDS*, respiratory distress syndrome; *SGA*, small for gestational age; *EXM*, expectant management.

[a] Some neonates had more than 1 complication. None includes cases with perinatal death; [b] Includes cases of proven or suspected neonatal sepsis (treatment for sepsis); [c] Maternal complications: during pregnancy, partum or postpartum, some women had more than 1 complication.

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glucocorticoid therapy is followed by delivery after 24-72 hours from initial injection. These findings suggest that the administration of steroids and the simultaneous prolongation of pregnancy between 28 and 33 weeks' gestation by 10 days produce no benefit to neonates.

Although the majority of the patients in our study had severe preeclampsia by strict definition (80.4% in the PD group and 76.3% in the EXM group), we decided to incorporate patients with chronic hypertension with superimposed preeclampsia and severe gestational hypertension patients in the study protocol because the morbidity for these 3 conditions are the same and their management is similar. Furthermore, the study reported by Sibai et al[5] included patients with chronic hypertension with superimposed preeclampsia, and the study reported by Odendaal et al[4] did not exclude women with chronic hypertension. Thus, the majority of the patients (94.6% in PD group and 90.8% in EXP group) in our study were similar to those included in the 2 previous randomized trials.[4,5]

Any management protocol of severe preeclampsia has to take into consideration that progressive deterioration of the maternal condition is a potential complication.[1,13,14] Our ability to predict maternal complications or perinatal morbidity and mortality at time of presentation is limited.[14,15] The current

TABLE 3
Stratified analysis

Variable	Total morbidities/mortality[a]	Relative risk (95% CI)	*P* value
All gestational ages			
EXM group (n = 138)	82 (59.4)	0.98 (0.80–1.19)	.84
PD group (n = 137)	83 (60.6)	1.00	
28-29^{+6} weeks			
EXM group (n = 40)	32 (80.0)	0.90 (0.74–1.09)	.24
PD group (n = 35)	31 (88.6)	1.00	
30-31^{+6} weeks			
EXM group (n = 52)	33 (63.46)	0.91 (0.68–1.2)	.52
PD group (n = 46)	32 (69.56)	1.00	
32-33^{+6} weeks			
EXM group (n = 46)	17 (36.9)	1.03 (0.61–1.7)	.90
PD group (n = 56)	20 (35.7)	1.00	

Risk of total morbidities and mortality according to gestational age at admission and allocation to early delivery or expectant management group. Data are number (percentage).

CI, confidence interval; *EXM*, expectant management; *PD*, prompt delivery.

[a] Some neonate had more than one complication.

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investigation demonstrates the same type of maternal complications reported in randomized trials,[4,5] observational studies/reviews,[3,13] and observational studies in Latin America.[16,17] Additionally, we did not observe higher maternal morbidity in those women who received glucocorticoid therapy and were managed expectantly with delivery approximately 10 days afterward, compared with those women who delivered 24-72 hours after glucocorticoid therapy.

It is important to note that the rate of placental abruption was 5 times (7.6%) more frequent in those patients having expectant management vs those deliveries promptly after steroid injection. This finding underscores the importance of intensive maternal and fetal monitoring during expectant management of severe preeclampsia remote from term and the need for tertiary hospital care with the ability to perform immediate delivery 24 hours a day. The fact that the rate of stillbirth was the same in both groups despite the increased rate of abruptions in the expectant group credits the tertiary-level hospitals involved in the study.

Despite a significantly higher birthweight in the EXM group, the neonates in this group showed 2.6 times higher rates of SGA infants compared with the PD group. These findings are similar to the ones reported by Sibai et al.[5] Our study and the study by Sibai et al[5] found a rate of approximately 10% for SGA infants in the PD group. The expectant management group of Sibai et al[5] gained 5 more days of gestation compared with our gain of approximately 10 days; however, these extra 5 days resulted in a 10% higher rate of SGA infants compared with our study, suggesting a possible correlation between the prolongation of days of pregnancy and the risk for SGA infants. However, this difference will be explained because we used a fetal weight with less than the 10th percentile as exclusion criteria, and Sibai et al[5] used the less than the fifth percentile; however, the definition of small for gestational age at delivery was similar; as a result, this difference in exclusion criteria could be seen as a weakness of our study.

It is well established that the frequency and severity of neonatal complications vary with the gestational at which delivery occurs, and the use of corticosteroids decreases these complications according to gestational age.[18] This study demonstrates the same neonatal findings. It is important to note that in this study the total perinatal mortality was 5% in a pregnancy of 30 weeks or longer of gestation and only 1.9% in a pregnancy of 32 weeks or longer of gestation; however, at the gestational age of 28-29 weeks of gestation, the perinatal mortality was 20%. This perinatal mortality did not change with expectant management. Equally, the rate of composite neonatal morbidity decreased with increasing gestational age in the PD and EXM groups.

We believe that intensive maternal-fetal monitoring on admission and continuing for 24-72 hours, the use of corticosteroid therapy, the constant presence of experienced personnel, and good neonatal intensive care are responsible for the improved neonatal outcome observed in the study. We speculate that these outcomes could be different for patients cared for in low-resource settings, either in developed or developing countries.

Although the 2 randomized trials,[4,5] the observational studies,[2,15,16,19,20] the reviews,[3,13,17] and the recent Committee Opinion of the Society of Maternal-Fetal Medicine[6] suggests a reduction in the risk of neonatal complications with expectant management of severe preeclampsia remote from term, in our opinion the best management protocol remains controversial.

Our study is a randomized, multicenter, parallel, open-label clinical trial made in 8 tertiary teaching hospitals in Latin America, with adequate power to detect differences in perinatal mortality and including double the number of patients reported in previous randomized trails.[4,5] All patients included had the same diagnostic criteria and were managed by the same protocol.

To date, this study is the largest randomized trial comparing prompt delivery management with expectant management of severe hypertensive disorder of

pregnancy between 28 and 33 weeks' gestation. This study does not demonstrate neonatal benefit with prolongation of pregnancy in women with severe preeclampsia prior to 34 weeks and suggests that corticosteroid therapy with prompt delivery results in similar neonatal outcomes for the prolongation of pregnancy for 10 additional days. Furthermore, a conservative approach may increase the risk of placental abruption and the risk for an SGA infant requiring acute interventions and putting babies at risk for ill-defined long-term sequelae.

In our study, small for gestational age at the time of admission was an exclusion criteria. Other studies have not excluded growth restriction from conservative management, and this could be seen as a weakness of the study; however, this investigation reflects the management of severe preeclampsia in Latin America.

Another weaknesses of this study is the lack of long-term follow-up in the babies beyond 28 days of life and the few number of twin gestations involved in the study to be able to make any recommendations specific to this type of gestation.

In our opinion, severe hypertensive disorders prior to 34 weeks' gestation should be managed in a tertiary care hospital with adequate personnel in obstetrics and neonatology. The most important factors for improved neonatal outcome are gestational age on presentation, the use of corticosteroids, and the ability to provide intensive neonatal care. Our data suggest that severe preeclampsia prior to 34 weeks should be managed with prompt delivery after corticoid administration. ■

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