Temporizing management vs immediate delivery in early-onset severe preeclampsia between 28 and 34 weeks of gestation (TOTEM study): An open-label randomized controlled trial

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Abstract

Introduction: There is little evidence to guide the timing of delivery of women with early-onset severe preeclampsia. We hypothesize that immediate delivery is not inferior for neonatal outcome but reduces maternal complications compared with temporizing management.

Material and methods: This Dutch multicenter open-label randomized clinical trial investigated non-inferiority for neonatal outcome of temporizing management as compared with immediate delivery (TOTEM NTR 2986) in women between 27+5 and 33+5 weeks of gestation admitted for early-onset severe preeclampsia with or without HELLP syndrome. In participants allocated to receive immediate delivery, either induction of labor or cesarean section was initiated at least 48 hours after admission. Primary outcomes were adverse perinatal outcome, defined as a composite of severe respiratory distress syndrome, bronchopulmonary dysplasia, culture proven sepsis, intraventricular hemorrhage grade 3 or worse, periventricular leukomalacia grade 2 or worse, necrotizing enterocolitis stage 2 or worse, and perinatal death. Major maternal complications were secondary outcomes. It was estimated 1130 women needed to be enrolled. Analysis was by intention-to-treat.

Results: The trial was halted after 35 months because of slow recruitment. Between February 2011 and December 2013, a total of 56 women were randomized to immediate delivery (n = 26) or temporizing management (n = 30). Median gestational age at randomization was 30 weeks. Median prolongation of pregnancy was 2 days (interquartile range 1-3 days) in the temporizing management group. Mean birthweight was 1435 g after immediate delivery vs 1294 g after temporizing management (P = .14).

Abbreviations: IQR, interquartile range; SGA, small-for-gestational-age.
INTRODUCTION

Preeclampsia is characterized by the clinical symptoms of hypertension arising after 20 weeks of gestation and involvement of one other organ system. Preeclampsia is associated with increased maternal and perinatal morbidity and mortality. The ultimate and only cure is delivery of the placenta, thus ending pregnancy. Late preeclampsia, usually defined as onset of the disease after 34 weeks of gestation, is less prone to complications, both because the disease in general tends to have a milder course and because pregnancies do not proceed until complications occur because labor is induced. Three trials have been published on temporizing management of preeclamptic pregnancies after 34 weeks. Between 34 and 37 weeks of gestation, temporizing management is associated with better perinatal outcome with an acceptable increase in maternal morbidity. However, after 37 weeks the advantages of immediate delivery are more evident, with reduction in hypertensive episodes and lower cesarean section rates. A recent British trial showed benefits of immediate delivery without compromising neonatal outcome.

In early-onset preeclamptic pregnancies, usually defined as onset of the disease before 34 weeks of gestation, there is a greater clinical dilemma, as iatrogenic preterm birth at very early gestational age can substantially contribute to severe adverse neonatal outcomes due to prematurity, and a temporizing management strategy may reduce that disease burden. In the Netherlands, temporizing management in early-onset severe preeclampsia has been standard care for decades. In the last decade

TABLE 1 Randomized controlled trials evaluating expectant or temporizing management compared with immediate delivery in early-onset severe preeclampsia

| First author | Year | n | GA at inclusion | Severe maternal morbidity (%) | Severe neonatal morbidity (%) | Prolongation of pregnancy (days) |
|--------------|------|---|----------------|-------------------------------|-----------------------------|---------------------------------|
| Odendaal10 | 1990 | 38 | 28-34          | 27                            | NA                          | 7.1                             |
| Sibai11 | 1994 | 95 | 28-32          | 4                             | NA                          | 15.4                            |
| Mesbah13 | 2003 | 30 | 28-33          | NA                            | NA                          | NA                              |
| Vigil-de Gracia12 | 2013 | 267 | 28-33 | 25 | 56 | 8.1 |

n, number of inclusions; NA, not available.

aPercentage of morbidity in the temporizing management group that was not statistically different from the immediate delivery group. In most studies it was not reported whether there was one or more morbidity.

bHELLP syndrome was excluded.
cMultiple pregnancies were excluded.
this policy has gradually been changing toward a more interventionist approach.9

So far, four randomized controlled trials have addressed the clinical dilemma of timing of delivery in women with severe preeclampsia between 28 and 34 weeks of gestation (Table 1).10-13 Study populations were too small, ranging from 30 to 267 women, and at least three studies did not include preeclamptic women with HELLP syndrome.10-12 All studies planned delivery in the active management arm 48 hours after administration of corticosteroid medication. Expectant management leads to a prolongation of pregnancy of 5.8-12.8 days in these studies. The two oldest studies, with a similar prolongation of pregnancy as in the two more recent studies, found stronger effects on adverse perinatal outcomes because composite neonatal outcome decreased from 75% to 25%. The most recent and largest study could not confirm this effect despite a prolongation in the expectant management group of 8.1 days. This may be due to the concomitant effects of continuously ameliorating neonatal care for preterm babies.14

The objective of this randomized controlled open-label non-inferiority study was to compare temporizing management with immediate delivery in pregnant women with severe early-onset preeclampsia. We hypothesized that immediate delivery would not be inferior regarding neonatal morbidity and mortality but might reduce maternal morbidity.

2 | MATERIAL AND METHODS

The TOTEM study (TempOrize or TErMinate pregnancy in women with severe preeclampsia) was an open-label, multicenter randomized controlled trial performed within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology. Nine of the 10 Dutch perinatal centers participated.

2.1 | Participants

Women with severe early-onset preeclampsia with a gestational age between 27+5 and 33+5 weeks were eligible for inclusion. Preeclampsia was diagnosed according to the contemporary definition of the International Society for the Study of Hypertension (ISSHP): hypertension (≥140/90 mm Hg) with proteinuria (≥0.3 g/24 hours).13 Severe preeclampsia was modified from the ACOG criteria for severe preeclampsia and defined as preeclampsia in combination with one or more of the following criteria9:

1. Clinical symptoms such as cerebral or visual disturbances (eg, headache) and/or right upper quadrant or epigastric pain.
2. Laboratory abnormalities: thrombocytopenia (<100 × 10^9/L) and/or impaired liver function tests aspartate transaminase/alanine transaminase (ASAT/ALAT) ≥40 U/L and lactate dehydrogenase (LDH) ≥600 U/L and/or haptoglobin <0.2 g/L.
3. Severe hypertension (systolic ≥160 mm Hg and/or diastolic ≥110 mm Hg).

Women had to be ≥18 years and have a working knowledge of the Dutch language, and the fetus had to have an estimated fetal weight ≥500 g.

Exclusion criteria were fetal distress, clinically relevant pulmonary edema, suspected placental abruption, eclampsia, major fetal congenital anomalies, fetal death, therapy-resistant hypertension, (sub)capsular liver hematoma, acute fatty liver of pregnancy, renal failure (creatinine clearance <40 mL/min), cerebrovascular incident, a thromboembolic event or other severe maternal complications.

All eligible women were treated with intravenous magnesium sulfate for at least 24 hours after admission; if necessary, antihypertensive medication to stabilize blood pressure and one course of corticosteroid therapy were given. Laboratory tests were routinely performed. In case of abnormalities, laboratory tests were repeated daily. Finally, fetal heart rate monitoring was performed at least twice a day during admission. Participants were treated according to the guideline on hypertensive disorders in pregnancy of the Dutch Society for Obstetrics and Gynecology.16

2.2 | Interventions

Eligible women were counseled on the day of admission by dedicated research nurses or by accredited clinical staff. A neonatologist also consulted every woman and her partner within 24 hours after admission. At admission, women had an abdominal ultrasound performed to rule out fetal congenital anomalies and to estimate fetal weight. Participating women signed a written consent the day after admission and randomization took place, and were allocated to immediate delivery or to temporizing management. After enrollment, demographic characteristics, medical history and all other data were recorded in case report forms by research nurses.

2.2.1 | Immediate delivery

At least 24 hours after randomization in the immediate delivery group, labor induction was started or an elective cesarean section was performed. Labor induction was performed according to local protocol by either mechanical or medical methods.

2.2.2 | Temporizing management

In the temporizing management group, the following strict criteria for intervention were used:

1. signs of fetal distress (defined as spontaneous, repeated, persistent unprovoked decelerations on the cardiotocogram),
2. no improvement within 3 days of the initial HELLP syndrome or recurrence,
3. clinical maternal deterioration and complications as per the earlier mentioned exclusion criteria.

In all women in the temporizing management arm, pregnancy was terminated if the patient reached a gestational age of 34 weeks, independent of complications.

After delivery, in both groups, all neonates were assessed by a neonatologist and, if necessary, admitted to the neonatal intensive care unit.

In the postpartum period, high blood pressure was treated with antihypertensive medication to attain systolic values of $\leq 140$ mm Hg and diastolic values of $\leq 90$ mm Hg.

2.3 | Objectives

The study was designed as a noninferiority effectiveness trial with a neonatal safety outcome and a secondary maternal outcome. We postulated that immediate delivery would be noninferior to expectant management for the risk of neonatal morbidity as defined by a composite outcome measure of neonatal morbidity and perinatal mortality.

2.4 | Outcomes

The primary endpoint was adverse perinatal outcome, defined as a composite of neonatal morbidity and mortality: with at least one or more of the following neonatal complications: severe respiratory distress syndrome, chronic pulmonary disease (oxygen therapy beyond 36 weeks' postconceptual age), intraventricular hemorrhage grade 3 or more, periventricular leukomalacia grade 2 or more, proven sepsis or necrotizing enterocolitis stage 2 or worse and perinatal mortality.

Secondary neonatal endpoints were perinatal death, each of the components of the primary endpoint, birthweight, Apgar scores, arterial umbilical pH, number of days on additional oxygen, days on supported ventilation, use of surfactant, number of days in intensive care, total days in hospital. Bailey-3 assessments were performed at 2 years corrected age.

Secondary maternal outcomes were adverse composite maternal outcome and its individual components pulmonary edema, eclampsia, adult respiratory distress syndrome, cerebrovascular accident, placental abruption, liver hematoma or rupture, acute fatty liver of pregnancy, renal insufficiency, thromboembolism or maternal death.

2.5 | Sample size

Assuming an incidence of the primary composite outcome of neonatal morbidity and mortality of 12% and using a noninferiority margin of 5%, we needed to recruit two groups of 523 women (1046 women in total) to achieve 80% power at 95% significance. This percentage was based on the results of a previous study in the Netherlands.17

For the secondary aim to show that delivery 48 hours after admission would reduce the maternal complications from 20% to 10%, two groups of 215 women (430 women in total) were needed for a power of 80% and 95% significance.

Therefore, the sample size to be achieved was chosen as 1046 patients. To allow for losses to follow-up, the sample size was rounded up to 1130 patients.

Interim analyses were scheduled after every 150 randomizations.

2.6 | Randomization

Randomization was done using an online randomization system, with randomly permuted blocks, stratification by gestational age (lower or higher than 31 weeks) and by center.

2.7 | Statistical analyses

Analysis was planned to be done on the intention-to-treat and per-protocol populations. After the trial had been stopped, the final analyses were only conducted on the intention-to-treat population because of the small numbers.

For all outcomes we estimated relative risks (RR) or mean, median or differences, with 95% confidence (CI) intervals. Descriptive statistics were used to describe baseline measures. Significance was tested using chi-square tests (based on maximum likelihood), Fisher’s exact tests, $t$-test, or Mann-Whitney $U$ tests as appropriate. An alpha of 0.05 was used for statistical significance. For neonatal outcomes in multiple pregnancies, the outcome was assessed per pregnancy, and thus deemed present if at least one neonate was affected. No imputation was done for missing data. Given the size of the trial at time of stopping, it was not possible to account for the stratification factors from randomization in the analyses. Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

2.8 | Ethical approval

The study is registered under TOTEM NTR 2986 and approved by the Institutional Review Board of the Erasmus MC (MEC-2008-151, 8 April 2010) and the board of directors of the participating centers. The study complies with the Declaration of Helsinki.

3 | RESULTS

From February 2011 until December 2013, 56 women were included in the trial. Because of the slow recruitment rate, the trial was halted in December 2013. At that time, 26 women had been
randomized for immediate delivery and 30 women for temporizing management. There were several reasons for the slow recruitment rate. Most importantly, the number of eligible women was not as high as expected. In the largest center, 73 women were eligible during the study period. Extrapolating this number to the remaining part of the Netherlands, 350-370 women were eligible in the whole country (110-120 women per year). Almost half of the women refused to participate, which is a number that can be expected in trials with this format. Forty-three women refused to participate but 27 of those women gave permission to use their data. Some women refused to participate because there was a possibility that they would be randomized to an unwanted treatment. About half of the women who refused wanted to be delivered immediately because of their fear of complications. The other half of the women wanted to wait to improve the condition of their babies. Two women did not want to participate in a study at all. Also, especially at the start of the trial, obstetricians were reluctant to participate and to change their normal treatment. In nine women, the trial was not discussed and were missed for randomization. Finally, 21 women were randomized in this center, about one-third of all eligible women. This was a relative large number of inclusions, which is usually seen in multicenter trials in the center of the principal investigator. Thirty-eight women delivered within 24 hours after admission and could not be recruited. Most of these women were delivered because of suspected fetal distress after maternal stabilization.

Baseline characteristics were comparable between groups (Table 2 and Table S2). Chronic hypertension and multiple pregnancies were slightly more common in the immediate delivery group. Nulliparity was more prevalent in the temporizing management group. Six women had been diagnosed with preeclampsia before 28 weeks and were temporized until 28 weeks before they were randomized.

In all, 71 of all women had clinical symptoms: 38% with laboratory abnormalities and 62% with severe hypertension at inclusion.

We were unable to compare baseline characteristics for randomized and non-randomized women because data of non-randomized women were not reliably recorded.

Data on the course of pregnancy and delivery are specified in Table 3. There was a small difference in the randomization to delivery interval between both groups (median 2 days, interquartile range [IQR] 1-3 days).

In the temporizing management group, 11/30 pregnancies were terminated for fetal compromise and 19/30 for maternal condition. There were no cases of prespecified indications for delivery in this group. No deliveries took place during the first 24 hours after randomization in this group.

In the immediate delivery group, seven women delivered within 24 hours after randomization, four of whom also had suspected fetal distress. One patient delivered 4 weeks after randomization because the clinical situation improved after randomization to non-severe preeclampsia and it was decided not to follow the study protocol and to leave the study. The data of this patient were not used for the analysis. Twenty-one women were induced, resulting in vaginal delivery in seven women.

In the temporizing management group, significantly more women underwent an elective cesarean section. However, the overall cesarean section rate was equal and was in the whole group eventually 87.5%.

During admission, maximum mean arterial pressure was not significantly different between the two groups of patients with a median of 117 mm Hg (IQR 108-123). Mean birthweight was slightly higher in the immediate delivery group (1440 g vs 1295 g) but was not statistically significant. This was despite the fact that there were more multiples in the immediate delivery group. In the temporizing management group, more severe small-for-gestational-age (SGA) babies were born (71% vs 55%). In both groups together, 63% of all babies were SGA.

Table 4 describes the neonatal outcomes. Almost all neonates were admitted to the Neonatal Intensive Care Unit. In both groups, one neonate died postpartum. Severe neonatal complications occurred in more than half of the babies. Overall, adverse neonatal outcome in the whole group was 54%. After the study was halted, only a minority of the neonates still had Bailey-3 assessments performed at 2 years of corrected age. Neonates born after 30 weeks of gestation are not routinely assessed in the Netherlands. The remaining numbers were too small to analyze.

Maternal outcomes are presented in Table 5. None of the women died. In the temporizing management group, one woman developed a placental abruption and one a pulmonary edema. HELLP syndrome, as defined above, was present or developed during admission in 41% of the women.

Separate analyses were done on only the singleton pregnancies (Tables S2-S5). The results of these analyses did not show differences with the previously described data.

4 | DISCUSSION

This randomized controlled open-label trial was stopped after 35 months because of slow recruitment and long before reaching the intended number of participants. For several reasons, the reporting of the results from this trial has taken a prolonged period of time, but for ethical reasons we pursued publication.

The small number of inclusions makes it impossible to draw any conclusions. The only relevant findings were that participants who were randomized to temporizing management did not experience a clinically relevant prolongation of pregnancy, and that prespecified rules for termination of the pregnancy in the temporizing management group were not met. The two severe maternal complications occurred in the temporizing management group. Not very surprisingly, given this small and not relevant clinical difference in interval between randomization and delivery, neonatal complications were similar in both groups.

So far, four randomized controlled trials have been published in an identical population of patients (Table 1). Only the largest trial included multiple pregnancies. All these trials started
TABLE 2  Baseline characteristics. Data are presented as n (%), mean (SD) or median (range). If data are not available from all women, the denominator is noted separately

| At start of pregnancy | Temporizing management (n = 30) | Immediate delivery (n = 26) |
|-----------------------|---------------------------------|----------------------------|
| Maternal age, yr (mean, SD) | 29.2 (4.6) | 28.7 (5.4) |
| Ethnicity | | |
| Caucasian | 21 (70%) | 15 (58%) |
| Other | 9 (30%) | 11 (42%) |
| Highest level of education | | |
| Primary or secondary school | 0 (0%) | 0 (0%) |
| Lower/medium professional education | 6 (20%) | 6 (21%) |
| Higher professional education/ university | 2 (7%) | 2 (8%) |
| Other/unknown | 22 (73%) | 16 (61%) |
| Current pregnancy: | | |
| Singleton | 29 (97%) | 22 (85%) |
| Twin | 1 (3%) | 3 (12%) |
| Triplet | 0 (0%) | 1 (4%) |
| Parity | | |
| Nulliparous | 22 (73%) | 12 (46%) |
| Primi- and multiparous | 8 (27%) | 14 (54%) |
| Preeclampsia in previous pregnancya | 5/8 (63%) | 9/14 (64%) |
| Blood pressure, at booking (mm Hg) | | |
| Systolic | 118 (9.6) | 135 (22.9) |
| Diastolic | 74 (8.1) | 80 (16.4) |
| BMI at booking >35 | 1 (3%) | 4 (15%) |
| At start study | | |
| Gestational age (days) | 214 (12.6) | 216 (10.7) |
| Inclusion for:b | | |
| Clinical symptoms | 23 (77%) | 17 (68%) |
| Laboratory abnormalities | 10 (33%) | 11 (42%) |
| Severe hypertension | 20 (67%) | 12 (46%) |
| Proteinuria (>300 mg/day) | 28 (100%) | 25 (100%) |
| Protein-to-creatinine ratio (mg/mmol) | 184 (93-460) | 73.5 (28-174) |
| Blood pressure, at inclusion (mm Hg) | | |
| Systolic | 154 (30.1) | 153 (17.0) |
| Diastolic | 99 (10.8) | 93 (10.6) |
| Smoking | | |
| No | 24 (80%) | 18 (69%) |
| Stopped in 1st or 2nd trimester | 4/29 (14%) | 4/25 (16%) |
| Unknown | 2 (7%) | 4 (15%) |
| Antihypertensive medication at study entry | | |
| Oral | 27/29 (93%) | 22 (85%) |
| Intravenous | 15/29 (52%) | 13/24 (54%) |
| Anticonvulsive medication (including magnesium sulfate) | 25/26 (96%) | 20 (77%) |

BMI, body mass index.

aNumerator: primi- and multiparous women.
bMultiple inclusion criteria possible.
similarly to our trial with inclusion at 28 weeks of gestation and continued until at least 32 weeks. Of the 56 included women, only six (11%) were randomized between 32 and 34 weeks of gestation in our trial. Maternal morbidity, HELLP syndrome, pulmonary edema and placental abruption occurred in our trial in 25 women of the 56 women (45%). This is in line with the maternal complication rate of the largest and most recent study by Vigil-de-Garcia;\textsuperscript{12} however, that trial did not include women with HELLP syndrome, in contrast to our study, and not all women in that study had severe pre-eclampsia. Also, the indications for delivery were different than in our trial. In particular, fetal growth restriction and the development of HELLP syndrome were not indications for delivery in our study. Since the inclusion criteria and rules for termination of pregnancy were clearly different from the previous trials, this trial contributes

| TABLE 3 Delivery outcomes Data are n (%), mean (SD) or median (IQR) |
|---------------------------------------------------------------|
| **Temporizing management** | **Immediate delivery** | **Relative risk (95% CI)** | **P value** |
| (n = 30) | (n = 25) | |
| Gestational age at delivery (weeks) | 31.1 (29.3-33.0) | 30.9 (30.1-32.3) | 0.14 (−1.00-1.29)\textsuperscript{a} | .93 |
| Time randomization to delivery (days) | 3 (2-6) | 1 (0-2) | −2 (1-10)\textsuperscript{c} | .0004 |
| Total number of children born | 31 | 31 | — | — |
| Stillbirth | 0/31 (0%) | 0/31 (0%) | — | — |
| Gender, girls | 19/31 (61%) | 13/31 (42%) | — | — |
| Onset of labor: | | | | |
| Spontaneous | 0 (0%) | 0 (0%) | — | — |
| Induction | 8 (27%) | 14 (56%) | 2.10 (1.06-4.18) | .03 |
| Elective cesarean section | 22 (73%) | 11 (44%) | 0.60 (0.37-0.98) | .03 |
| Indication for induction | | | | |
| Randomization | 0/8 (0%) | 1/13 (8%) | — | — |
| Fetal condition | 4/8 (50%) | 10/13(77%) | n/c | — |
| Maternal condition | 4/8 (50%) | 0/13 (0%) | n/c | — |
| Other | 0/8 (0.0%) | 2/13 (15%) | n/c | — |
| Indication for cesarean section | | | | |
| Randomization | 0/22 (0%) | 7/11 (78%) | n/c | — |
| Fetal condition | 7/22 (32%) | 1/11 (9%) | n/c | — |
| Maternal condition | 15/22 (68%) | 3/11 (27%) | n/c | — |
| Other | 0/22 (0%) | 0/11 (0%) | n/c | — |
| Mode of delivery | | | | |
| Vaginal delivery | 3 (10%) | 4 (15%) | 1.06 (0.87-1.30) | .69\textsuperscript{b} |
| OVD | 0 (0%) | 0 (0%) | — | — |
| Cesarean section (elective and emergency) | 27 (90%) | 22 (85%) | 0.94 (0.77-1.15) | .69 |
| Postpartum blood loss (mL) | 400 (300-500) | 400 (300-500) | 0 (−100-100)\textsuperscript{c} | .90 |
| Postpartum hemorrhage | 3 (10%) | 2 (8%) | — | — |
| Birthweight (g) | 1294 (386) | 1,440 (297) | 145 (−31.0-321.3)\textsuperscript{a} | .10 |
| Small for gestational age \textsuperscript{d} | | | | |
| <5th percentile | 19 | 10 | 0.53 (0.29-0.94) | .03 |
| <10th percentile | 22 | 17 | 0.77 (0.52-1.14) | .20 |
| Large for gestational age \textsuperscript{d} | | | | |
| >90th percentile | 2 | 4 | 2.00 (0.39-10.13) | .67\textsuperscript{b} |
| >95th percentile | 2 | 4 | 2.00 (0.39-10.13) | .67\textsuperscript{b} |

OVD, operative vaginal delivery.
\textsuperscript{a}Mean difference between groups with 95% CI (two-sample t-test).
\textsuperscript{b}Fisher’s exact test.
\textsuperscript{c}Hodges-Lehmann estimator and Mann-Whitney-Wilcoxon test.
\textsuperscript{d}Percentile groups are not mutually exclusive.
to the knowledge of the management of this category of patients. The prolongation of 2 days in our trial is not in line with the findings of the most recent and largest trial, which found a prolongation of 8.1 days. But, as already mentioned, the inclusion criteria of this trial were different from our trial. Differences in patient characteristics and severity of disease differed between our and prior studies and may account for the shorter randomization-to-delivery interval in our temporizing management group. Omitting the one patient in the immediate delivery group that left the study would have increased the randomization-delivery interval to almost 3 days. This is still shorter than any of the other studies but in at least three of those studies, HELLP syndrome was a contraindication for inclusion. Also, the development of HELLP syndrome was not a reason for termination of pregnancy in our study. The relative safety of this management was earlier described in a study comparing patients with severe preeclampsia with and without HELLP syndrome with an onset before 28 weeks. In our study, more than one-third of the women had laboratory abnormalities consistent with the features of HELLP syndrome. A subanalysis of women with HELLP syndrome was not possible because of the small numbers.

| TABLE 4 | Neonatal outcomes (intention-to-treat). Data are n (%) or mean (standard deviation). Confidence intervals are 95% |
|---------|---------------------------------------------------------------|
|         | Temporizing management | Immediate delivery | Relative risk (95% CI) | P value |
| n = 31  | (n = 30)             |                   |                         |
| Neonatal death | 1 (3%) | 1 (3%) | 0.97 (0.06-14.8) | .98a |
| Admission neonate to intensive care unit | 29 (94%) | 30 (100%) | 0.94 (0.085-1.02) | 1.00a |
| Indication for NICU admission: | | |
| Hypoglycemia | 2 (6%) | 0 (0%) | — | — |
| Respiratory distress syndrome | 13 (42%) | 9 (29%) | 0.69 (0.35-1.38) | .30 |
| Necrotizing enterocolitis (>stage 1) | 2 (6%) | 1 (3%) | 0.50 (0.05-5.23) | 1.00a |
| Neonatal infection/sepsis | 5 (16%) | 6 (19%) | 1.20 (0.41-3.52) | 1.00a |
| Intraventricular hemorrhage (>grade 2) | 1 (3%) | 1 (3%) | 1.00 (0.07-15.3) | 1.00a |
| Periventricular leukomalacia (>grade 1) | 1 (3%) | 3 (10%) | 3.00 (0.33-7.29) | .61a |
| Adverse perinatal outcome | 16 (52%) | 17 (55%) | 1.06 (0.67-1.70) | .80 |

NICU, Neonatal Intensive Care Unit.

| TABLE 5 | (Adverse) maternal outcomes (intention-to-treat) |
|---------|------------------------------------------------|
|         | Temporizing management | Immediate delivery | Relative risk (95% CI) | P value |
| n = 30  | (n = 25)             |                   |                         |
| Eclampsia | 0 | 0 | n/a |
| Pulmonary edema | 1 (3%) | 0 | n/a |
| Liver hematoma | 0 | 0 | n/a |
| HELLP syndrome | 7 (23%) | 9 (35%) | 0.67 (0.29-1.56) | .35 |
| Hemolysis | 0 | 1 (4%) | n/a |
| Low plateletsb | 3 (10%) | 4 (16%) | 0.56 (0.16-2.64) | .69 |
| Abnormal liver function testsc | 7 (23%) | 7 (27%) | 0.87 (0.35-2.15) | .76 |
| Placental abruption | 1 (3%) | 0 | n/a |
| Maternal death | 0 | 0 | n/a |
| Women with maternal complications^a | 9 (30%) | 9 (36%) | 0.83 (0.39-1.78) | .64 |

|         | Multiple inclusion criteria possible. |
|         | ^b≤100.10³/mm³. |
|         | ^cALAT ≥70 or ASAT ≥70 U/L. |

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A recent Cochrane review and meta-analysis evaluated these four trials, the present trial (congress abstract) and a subset from the Growth Restriction Intervention Trial (GRIT).\textsuperscript{19,20} It was concluded that temporizing management under strict regulation is safe and may be associated with decreased morbidity for the neonate. The latter was suggested but is mainly based on the two oldest studies in this review. The most recent and largest study by Vigil-De Gracia did not find neonatal benefits with expectant management.\textsuperscript{12} Also, in this review, 262 women were included from GRIT trial.\textsuperscript{20} The women who were selected from this trial were included in the trial between 24 and 34 weeks of gestation but their clinical diagnosis did not meet the criteria for early-onset severe preeclampsia as used in our trial and the other four earlier mentioned trials. Because of this aberrant inclusion period and lack of severe preeclampsia criteria, the findings from this trial should not have been incorporated in this review.

A previous meta-analysis published in 2017 included seven trials including our trial (at that time a conference abstract).\textsuperscript{21} The subject of this meta-analysis was expectant management vs elective delivery in preeclamptic patients during several periods of pregnancy. The data of our study could be used in this meta-analysis only in the case of placental abruption. The authors concluded that the chance of placental abruption was halved by elective delivery in women with early-onset severe preeclampsia (RR 0.43; 95% CI 0.19-0.98).

The most important limitation of this study is that the goal of included patients was not reached. It proved to be very difficult to obtain informed consent from eligible patients. Preeclampsia and its management are linked to strong personal views, both for doctors and their patients. Also, many women could not be randomized because of the perceived necessity to deliver before randomization could take place. Although randomization was also stratified for a gestational age before or after 31 weeks, the numbers were too small for calculations and it was not possible to draw conclusions from these subgroups.

When designing this trial, adverse neonatal outcome in the surviving neonates was estimated to be 12%, which was based on a previous study.\textsuperscript{17} However, in our study, adverse neonatal outcome was more than 50% in both groups. The main difference with the previous study was that also respiratory distress syndrome, necrotizing enterocolitis and proven sepsis were incorporated under adverse neonatal outcomes in this trial. After removing these parameters, the percentages of adverse neonatal outcome in both groups were comparable to the previous study and no differences were seen between the groups. Nevertheless, adverse neonatal outcome was comparable to that in the MEXPRE Latin study.\textsuperscript{12} Recalculation of the number of participants that would have been required to obtain 80% power for a study with a composite neonatal morbidity of 50% resulted in a total of 2474 subjects. It is obvious that a randomized controlled trial on this subject of this magnitude will never be feasible. This would also be the case were such a trial be performed in an international setting because of the different management protocols. There also should be a larger commitment to the necessity of the trial, both in doctors and patients, to obtain a higher recruitment rate than 50%.

One strength of this trial is that temporizing management under observation with strict rules looks safe in this period of gestation in women with severe preeclampsia. Another strength of this trial are the strict inclusion criteria. Only women with severe preeclampsia were included. This may be the explanation for the large number of SGA cases. The largest other study found 21.7% and 9.4% of SGA babies.\textsuperscript{12} Our large percentage may have initiated the large percentage of cesarean sections on fetal indication.

5 | CONCLUSION

Because of lack of power and lack of difference in treatment between immediate delivery vs temporizing management in this study among women with early-onset severe preeclampsia, no conclusions can be drawn as to which management provides a better balance of maternal complications vs infant outcome. This topic warrants further research, but any new study should address the issue of treatment preference among clinicians and their patients. New treatment options for preeclampsia currently under investigation may lead to new insights into prolongation of pregnancy in this category of women.\textsuperscript{22}

REFERENCES

1. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet. 2016;387:999-1011.
2. Harem K, Svendsen E, Alligdaard U. The HELLP syndrome: clinical issues and management. A review. BMJ Pregnancy Childbirth. 2009;9:8.
3. Bernardes TP, Zwartbroek EF, Broekhuijsen K, et al. Delivery or expectant management for prevention of adverse maternal and neonatal outcomes in hypertensive disorders of pregnancy: an individual participant data meta-analysis. Ultrasound Obstet Gynecol. 2019;53:443-453.
4. Broekhuijsen K, van Baaren GJ, van Pampus MG, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomized controlled trial. Lancet. 2015;385:2492-2501.
5. Chappell LC, Brocklehurst P, Green ME, et al. Planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial. Lancet. 2019;394:1181-1190.
6. Magee LA, Yong PJ, Espinosa V, Cote AM, Chen I, von Dadelszen P. Expectant management of severe preeclampsia remote from term: a structured systematic review. Hypertens Pregnancy. 2009;28:312-347.
7. Visser W, Wallenburg HC. Maternal and perinatal outcome of temporizing management in 254 consecutive patients with severe
pre-eclampsia remote from term. Eur J Obstet Gynecol Reprod Biol. 1995;63:147-154.
8. Visser W, Wallenburg HC. Temporising management of severe pre-eclampsia with and without the HELLP syndrome. Br J Obstet Gynaecol. 1995;102:111-117.
9. ACOG Committee on Practice Bulletins – Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol. 2002;99:159-167.
10. Odendaal HJ, Pattinson RC, Bar M, Grove D, Kotze TJ. Aggressive or expectant management for patients with severe preeclampsia between 28–34 weeks’ gestation: a randomized controlled trial. Obstet Gynecol. 1990;76:1070-1075.
11. Sibai BM, Mercer BM, Schiff E, Friedman SA. Aggressive versus expectant management of severe preeclampsia at 28 to 32 weeks’ gestation: a randomized controlled trial. Am J Obstet Gynecol. 1994;171:818-822.
12. Vigil-De Gracia P, Reyes Tejada O, Calle Miñaca A, et al. Expectant management of severe preeclampsia remote from term: the MEXPRE Latin Study, a randomized, multicenter clinical trial. Am J Obstet Gynecol. 2013;209(5):425.e1-425.e8.
13. Mesbah EMM. Severe pre-term preeclampsia: aggressive or expectant management. Med J Cairo Univ. 2003;71:175-182.
14. Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA. 2015;314:1039-1051.
15. Brown MA, Lindheimer MD, De Swiet M, van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy. 2001;20(1):1X-XIV.
16. Dutch Society of Obstetrics and Gynaecology (NVOG). Hypertensive disease during pregnancy by the Dutch Society of Obstetrics and Gynaecology (NVOG). 2011.
17. Ganzevoort W, Rep A, de Vries JI, Bonsel GJ, Wolf H; PETRA-Investigators. Prediction of maternal complications and adverse infant outcome at admission for temporizing management of early-onset severe hypertensive disorders of pregnancy. Am J Obstet Gynecol. 2006;195:495-503.
18. Haddad B, Barton JR, Livingston JC, Chahine R, Sibai BM. HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome versus severe preeclampsia: onset at < or = 28.0 weeks’ gestation. Am J Obstet Gynecol. 2000;183:1475-1479.
19. Churchill D, Duley L, Thornton JG, Moussa M, Ali HS, Walker KF. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks’ gestation. Cochrane Database Syst Rev. 2018;(10):CD003106.
20. Thornton JG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M. GRIT study group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. Lancet. 2004;364:513-520.
21. Wang Y, Hao M, Sampson S, Xia J. Elective delivery versus expectant management for pre-eclampsia: a meta-analysis of RCTs. Arch Gynecol Obstet. 2017;295:607-622.
22. Cluver C, Walker SP, Mol BW, et al. A double blind, randomised, placebo-controlled trial to evaluate the efficacy of metformin to treat preterm pre-eclampsia (PI2 Trial): study protocol. BMJ Open. 2019;9:e025809.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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