BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.14512
www.bjog.org

Case report

Maternal and neonatal outcomes in women with severe early onset pre-eclampsia before 26 weeks of gestation, a case series

MF van Oostwaard,[a] L van Eerden,[b] MW de Laat,[c] JJ Duvekot,[d] JJHM Erwich,[e] KWM Bloemenkamp,[f] AC Bolte,[g] JPF Bosma,[h] SV Koenen,[i] RF Kornelisse,[j] B Rethans,[c] P van Runnard Heimel,[k] HCJ Scheepers,[l] W Ganzevoort,[c] BWJ Mol,[m] CJ de Groot,[n] IPM Gaugler-Senden[o]

[a] Department of Obstetrics and Gynaecology, IJsselland Ziekenhuis, Capelle aan den Ijssel, the Netherlands [b] Department of Obstetrics and Gynaecology, Maasstad Ziekenhuis, Rotterdam, the Netherlands [c] Department of Obstetrics and Gynaecology, Academisch Medisch Centrum, Amsterdam, the Netherlands [d] Department of Obstetrics and Gynaecology, Erasmus Medisch Centrum, Rotterdam, the Netherlands [e] Department of Obstetrics and Gynaecology, Universitair Medisch Centrum Groningen, Groningen, the Netherlands [f] Department of Obstetrics and Gynaecology, Leids Universitair Medisch Centrum, Leiden, the Netherlands [g] Department of Obstetrics and Gynaecology, Radboud Universitair Medisch Centrum, Nijmegen, the Netherlands [h] Department of Obstetrics and Gynaecology, Isala Ziekenhuis, Zwolle, the Netherlands [i] Department of Obstetrics and Gynaecology, Universitair Medisch Centrum Utrecht, Utrecht, the Netherlands [j] Department of Paediatrics, Erasmus Medisch Centrum, Rotterdam, the Netherlands [k] Department of Obstetrics and Gynaecology, Maxima Medisch Centrum, Veldhoven, the Netherlands [l] Department of Obstetrics and Gynaecology, Maastricht Universitair Medisch Centrum, Maastricht, the Netherlands [m] School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, SA, Australia [n] Department of Obstetrics and Gynaecology, VU Universitair Medisch Centrum, Amsterdam, the Netherlands [o] Department of Obstetrics and Gynaecology, Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, the Netherlands

Correspondence: MF van Oostwaard, Department of Obstetrics and Gynecology, IJsselland Ziekenhuis, PO Box 690, 2900 AR Capelle aan den IJssel, The Netherlands. Email miriamvanoostwaard@gmail.com

Accepted 30 November 2016. Published online 27 January 2017.

Objective To describe the maternal and neonatal outcomes and prolongation of pregnancies with severe early onset pre-eclampsia before 26 weeks of gestation.

Design Nationwide case series.

Setting All Dutch tertiary perinatal care centres.

Population All women diagnosed with severe pre-eclampsia who delivered between 22 and 26 weeks of gestation in a tertiary perinatal care centre in the Netherlands, between 2008 and 2014.

Methods Women were identified through computerised hospital databases. Data were collected from medical records.

Main outcome measures Maternal complications [HELLP (haemolysis, elevated liver enzyme levels, and low platelet levels) syndrome, eclampsia, pulmonary oedema, cerebrovascular incidents, hepatic capsular rupture, placenta abruption, renal failure, and maternal death], neonatal survival and complications (intraventricular haemorrhage, retinopathy of prematurity, necrotising enterocolitis, bronchopulmonary dysplasia, and sepsis), and outcome of subsequent pregnancies (recurrent pre-eclampsia, premature delivery, and neonatal survival).

Results We studied 133 women, delivering 140 children. Maternal complications occurred frequently (54%). Deterioration of HELLP syndrome during expectant care occurred in 48%, after 4 days. Median prolongation was 5 days (range: 0–25 days). Neonatal survival was poor (19%), and was worse (6.6%) if the mother was admitted before 24 weeks of gestation. Complications occurred frequently among survivors (84%). After active support, neonatal survival was comparable with the survival of spontaneous premature neonates (54%). Pre-eclampsia recurred in 31%, at a mean gestational age of 32 weeks and 6 days.

Conclusions Considering the limits of prolongation, women need to be counselled carefully, weighing the high risk for maternal complications versus limited neonatal survival and/or extreme prematurity and its sequelae. The positive prospects regarding maternal and neonatal outcome in future pregnancies can supplement counselling.

Keywords Maternal and neonatal outcome, preterm birth, prolongation, severe pre-eclampsia.

Tweetable abstract Severe early onset pre-eclampsia comes with high maternal complication rates and poor neonatal survival.

Linked article This article is commented on by OA Ashimi and SP Chauhan, p. 1448 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.14612.

Please cite this paper as: van Oostwaard MF, van Eerden L, de Laat MW, Duvekot JJ, Erwich JJHM, Bloemenkamp KWM, Bolte AC, Bosma JPF, Koenen SV, Kornelisse RF, Rethans B, van Runnard Heimel P, Scheepers HCJ, Ganzevoort W, Mol BWJ, de Groot CJ, Gaugler-Senden IPM. Maternal and neonatal outcomes in women with severe early onset pre-eclampsia before 26 weeks of gestation, a case series. BJOG 2017;124:1440–1447.

Introduction

Pre-eclampsia remains a common pregnancy disorder, with high maternal and neonatal mortality and morbidity. It affects 2–5% of pregnancies,[1] and occurs most commonly at term. At extremely premature gestational ages, severe pre-eclampsia and HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome are rare. At present, delivery of the fetus is the only curative treatment of hypertensive pregnancy complications, but for women with early pre-eclampsia this inevitably leads to extreme prematurity, with a high risk of neonatal mortality and morbidity. Conversely, the prolongation of pregnancy with severe early onset pre-eclampsia may increase the risk of maternal morbidity,[2–7] but may improve fetal prognosis. These conflicting interests between mother and fetus raise a dilemma in clinical decision making. This discussion is even more pressing as fetuses in early pre-eclampsia are also often severely growth restricted, further limiting their chances for (healthy) survival, both intrauterine and extrauterine, and increasing the risks of associated adverse long-term outcomes.

In 2006, Gaugler-Senden et al.[4] described high rates of major maternal complications (65%) and perinatal mortality (82%) after the expectant management of pregnancies complicated by severe, very early onset pre-eclampsia. In line with these findings, there is consensus that the prolongation of pregnancy should not be offered as a routine treatment option in women with severe pre-eclampsia with onset <24 weeks of gestation.[4–8] This subject is debated in the literature for a select group of patients, however, and this group is yet to be defined adequately.[9,10]

Neonatal care and resuscitation have improved, leading to a higher survival rate,[11] which may make management decisions even more difficult in the time frame at the limit of neonatal viability. Improved care and survival rates resulted in a new Dutch guideline regarding active neonatal resuscitation in *spontaneously* born premature neonates at a gestational age beyond 24 completed weeks in September 2010.[12] Before the introduction of the guideline, active neonatal resuscitation was not generally performed before 25 weeks of gestation, unless active resuscitation seemed justified. Expectant care for extreme early onset pre-eclampsia may seem defendable at an earlier gestational age in the hopes of neonatal survival. Iatrogenic prematurity in pre-eclampsia does not resemble spontaneous premature delivery, however.

In this nationwide case series we aimed to display the maternal and neonatal outcomes and prolongation of pregnancies with severe early onset pre-eclampsia and delivery before 26 weeks of gestation. Secondly, we analysed trends in management and maternal and neonatal outcomes over the years, and analysed the recurrence of pre-eclampsia in a subsequent pregnancy.

Methods

Study population

This study was performed in all ten tertiary care centres in the Netherlands. We included consecutive women who delivered between 22 and 26 weeks of gestation, between January 2008 and January 2014, and were diagnosed with severe pre-eclampsia. In each perinatal centre we identified women from electronic hospital health records and subsequently extracted data from their medical files. Women with a pregnancy complicated by fetal abnormalities or an intrauterine fetal death (IUFD) at admission were excluded. First-trimester ultrasound dating was standard practice for the determination of gestational age. The acknowledged ethical advisory board of the Academic Medical Centre, Amsterdam, approved the study (W13_106 # 13.17.0123).

Severe pre-eclampsia was defined as hypertension (diastolic blood pressure ≥110 mmHg or systolic blood pressure ≥160 mmHg on two occasions) in combination with proteinuria (defined as a protein/creatinine ratio of ≥30 mg/mmol in a random sample or a urine protein excretion of ≥300 mg per 24 hours), with oliguria, cerebral or visual disturbances, pulmonary oedema, epigastric or upper-quadrant pain, impaired liver function, thrombocytopenia, after 20 weeks of gestation.[13] Chronic hypertension was defined as pre-existing hypertension or hypertension before 20 weeks of gestation. Superimposed pre-eclampsia includes new proteinuria or a sudden increase in proteinuria, if already present, in a woman with chronic hypertension.[13] HELLP syndrome was defined by haemolysis [elevated lactate dehydrogenase (LDH) levels ≥600 U/l], elevated liver enzymes [measured by levels of aspartate transaminase (ASAT) or alanine transferase (ALAT) ≥70 U/l], and low platelets (<100 000/ml).[14] The deterioration of HELLP syndrome was defined as a new rise in laboratory findings after initial recovery. Small for gestational age (SGA) was defined as a birthweight below the fifth percentile.

After admission, women were stabilised by the administration of antihypertensive therapy, and in the case of severe hypertension by magnesium sulphate for the prevention of eclampsia. Fetal growth and condition was determined

by ultrasound measurement and Doppler studies. Cardiotocography was performed when considered appropriate, depending on ultrasound findings and gestational age. The parents were then counselled by experienced obstetric and neonatology staff, and depending on the clinical condition of both mother and fetus, the obstetric management was determined. If active neonatal support was pursued, a course of 12 mg intramuscular betamethasone was given and repeated after 24 hours to accelerate fetal lung maturation. Initiating delivery, depending on maternal and fetal condition, was performed by induction of labour or caesarean section. Induction of labour was started in the case of good fetal condition (based on cardiotocography and ultrasound findings), or when the management was not aimed at the survival of the fetus (termination of pregnancy). A caesarean section was reserved for cases where it was considered to improve the chances of survival in compromised fetuses, or when normal delivery was not feasible (transverse position, maternal condition).

Neonates born before the implementation of the new Dutch guideline regarding active neonatal resuscitation, in 2010,[12] were in general not offered active support before 25^{+0} weeks of gestation. After the new guideline, active support from a gestational age of 24^{+0} weeks of gestation was optional, but could be refrained from in the case of poor fetal prognosis. The counselling of future parents on maternal and neonatal management was performed by gynaecologists and neonatologists. We will evaluate differences in prolongation before and after 2010, and trends in maternal and neonatal outcomes.

Maternal data included: maternal age at delivery; parity; medical and obstetric history; and cardiovascular risk factors, such as smoking, body mass index (BMI) before pregnancy, chronic hypertension diagnosed before pregnancy, and thrombophilia. We recorded pregnancy data (e.g. maximal blood pressures, proteinuria, maximal laboratory abnormalities, use of medication, HELLP syndrome at admission, mode of delivery, and complications). Maternal complications were defined as: HELLP syndrome (appearing or deteriorating after admission), eclampsia, pulmonary oedema (clinical and radiographic diagnosis), cerebrovascular incidents, hepatic capsular rupture, placental abruption, renal failure (with need for dialysis), and maternal death. We documented the interval between admission and delivery, and the indication for delivery. Neonatal data included: gestational age at birth, birthweight, sex, perinatal death, and complications. Neonatal complications if admitted to a Neonatal Intensive Care Unit (NICU) were defined as: intraventricular haemorrhage (IVH; defined as ≥grade 3, according to Papile et al.[15]), retinopathy of prematurity (ROP; defined as ≥grade 3 in accordance with the International Classification for ROP[16]), necrotising enterocolitis (NEC; defined as ≥stage 2 in accordance with the staging by Bell et al.[17]), bronchopulmonary dysplasia [BPD; classified according to the consensus BPD definition as moderate if the oxygen need (FiO_2) at 36 weeks postmenstrual age is between 0.21 and 0.30, and severe in the case of an $FiO_2 > 0.30$ and/or receiving continuous positive airway pressure (CPAP) or mechanical ventilation[18]] and sepsis (defined as the presence of clinical symptoms and a positive blood culture).

If information on a subsequent pregnancy was available, these data were also documented.

Statistical analysis

Statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means with standard deviations (SDs) or medians with interquartile ranges (IQRs).

Results

During the study period a total of 1 044 287 women delivered in the Netherlands, 114 868 of whom delivered in one of the ten tertiary care centres. During the study period, 133 women fulfilled the inclusion criteria, including eight multiple pregnancies, delivering 140 neonates. The incidence of severe premature pre-eclampsia between 22 and 26 weeks of gestation was 0.0127% nationally and 0.116% in the tertiary care setting. In one woman with a multiple pregnancy, an IUFD was discovered in one of the fetuses at 16 weeks of gestation, and was considered a singleton pregnancy in the neonatal analyses. Baseline characteristics are shown in Table 1. Most women were nulliparous (64%). At admittance the median gestational age was 24^{+0} weeks (IQR: 23^{+1}–24^{+5} weeks), and 61 women (46%) had a gestational age of less than 24 weeks. HELLP syndrome was present in 42 women (32%) at the time of admission.

An overview of management is shown in Figure 1. After a median of 6 days from admittance, 22 (17%) intrauterine fetal deaths occurred, after which labour was induced. Delivery was indicated for maternal reasons in 85 women (64%) and for fetal indication in 26 women (20%). Maternal indication for delivery included the worsening of an existing maternal condition, based on: complications, deteriorating laboratory findings in HELLP syndrome, and uncontrollable blood pressures. Also, fetal condition played a role in the timing of delivery. Worsening fetal condition requiring immediate delivery or poor fetal prognosis encouraged more active management, whereas excellent fetal condition supported expectant management with fetal viability within reach. In 63 women this resulted in a termination of pregnancy and in 22 women active support was offered to the child(ren). In one case spontaneous preterm labour followed 5 days after admittance, which was classified as maternal indication.

Table 1. Baseline and clinical characteristics of the 133 women with severe early onset pre-eclampsia

	***n* = 133**
Demographic characteristics	
Maternal age at delivery (years)	31 (5.7)
Smoking	11 (8.3%)
Body mass index, BMI (kg/m^2)	28 (6.5)
Chronic hypertension before pregnancy	35 (26%)
History of disease	
Obesity (BMI > 30 kg/m^2)	34 (26%)
Pulmonary disease	6 (4.5%)
Thrombophilia	4 (3.0%)
Kidney disease	3 (2.3%)
Diabetes mellitus	2 (1.5%)
Coronary disease	2 (1.5%)
SLE	1 (0.8%)
Other*	12 (9.0%)
Obstetrical history	
Nulliparous	85 (64%)
Multiparous	48 (36%)
Pre-eclampsia in a former pregnancy	21 (44%)
Multiple pregnancy	3 (8.8%)
Clinical syndrome	
Pre-eclampsia	133 (100%)
HELLP syndrome at admittance	42 (32%)
Maximum blood pressure (mmHg)	
Systolic	179 (20)
Diastolic	111 (11)
Maximal laboratory abnormalities	
ASAT (IU/L)	193 (38–159)
Platelets (×10^9/l)	90 (57–157)
Proteinuria (mg/24 hours)	1028 (393–3790)
PCR**	195 (37–431)
Use of medication	
Oral antihypertensive	117 (88%)
iv antihypertensive	107 (81%)
iv anticonvulsive	120 (90%)
Gestational age at admittance (weeks^{+days})	24^{+0} (23^{+1}–24^{+5})
Gestational age <24 weeks of gestation	61 (46%)
Estimated fetal weight at admittance (g)	479 (125)
Abnormal umbilical artery Doppler flow	92 (72%)

*Other medical history: haemoglobinopathy (3), HIV, thrombotic thrombocytopenic purpura, hypothyroidism, Crohn's disease, sarcoidosis, mixed connective tissue disease, and cutaneous lupus erythematosus

**PCR: protein/creatinin ratio, registered if a 24-hours collection of urine was not performed (*n* = 17).

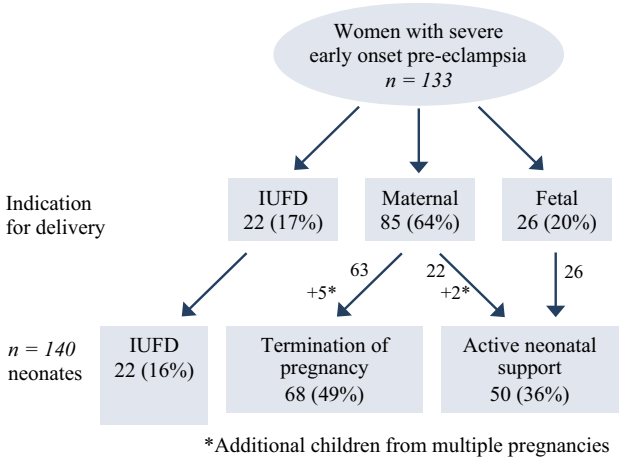

Figure 1. Overview of the management for 133 pregnancies with severe, early onset pre-eclampsia.

Maternal and neonatal outcome

Table 2 shows outcomes of women and neonates. The median interval between admittance and delivery was 5 days (IQR: 3–9 days), with a range of 0–25 days. In 107 women (80%) this prolongation was more than 2 days. The median gestational age at delivery was 25^{+0} weeks (IQR: 24^{+2}–25^{+4} weeks). Maternal complications occurred in 72 women (54%) and included: HELLP syndrome (new, deteriorating, or postpartum), eclampsia, lung oedema, placental abruption, hepatic capsular rupture, renal failure, and other (infection, cardiac decompensation, haemorrhagia postpartum). HELLP syndrome occurred in 83 women (62%). In 42 women (51%) HELLP was already present at the time of admittance, which deteriorated in 22 women (52%) during hospitalisation. In 38 women (46%) the HELLP syndrome appeared after admission. The appearance or deterioration of HELLP syndrome after admission (63 women) occurred after a median of 4 days from admittance, and in two women (2.4%) HELLP syndrome occurred postpartum. A completed course of betamethasone for fetal lung maturation was given in 52 women (58 neonates). An intended course could not be completed as a result of the deterioration of maternal or fetal condition in four women (7.7%). Active neonatal support was offered in 50 neonates (36%), 27 of whom (54%) survived (overall neonatal survival of was 19%). Only four (6.6%) neonates survived after admission before 24 weeks of gestation. Caesarean sections were performed in 48 women (36%); 24 caesarean sections (51%) were for fetal indication, after which 46 (96%) neonates were offered active support. Perinatal death occurred in 21 neonates (44%) after caesarean section.

The incidence of neonatal complications in the 27 surviving children is also shown in Table 2. Eighty-four percent of surviving neonates experience complications. Neonatal mortality was associated with NEC in five (19%), sepsis in 11 (41%), IVH in five (19%), and infant respiratory distress syndrome (IRDS) in five neonates (19%), mostly in combination. Other complications leading to neonatal death included: arrhythmia, intracardial thrombus, and multi-organ failure.

Table 2. Outcomes of the 133 women and 140 neonates after severe early onset pre-eclampsia

	***n* = 133**
Interval between admittance and delivery	5 (3–9)
Gestational age at delivery (weeks^{+days})	25^{+0} (24^{+2}–25^{+4})
Gestational age <24 weeks of gestation	20 (15%)
Caesarean section	48 (36%)
Hospitalisation (days)	10 (7–14)
Maternal complications	
HELLP syndrome appearing or deteriorating after admission	64 (48%)
Eclampsia	4 (3%)
Lung oedema	10 (7.5%)
CVA	0 (0%)
Placental abruption	5 (3.8%)
Hepatic capsular rupture	1 (0.8%)
Renal failure	1 (0.8%)
Maternal death	0 (0%)
Other*	7 (5.3%)
Any complication	72 (54%)
Any complication including HELLP at admission	91 (68%)
All neonates	***n* = 140**
Male—female	65—75 (46—54%)
Birthweight (g)	500 (127)
Small for gestational age	80 (57%)
Completed course lung maturation	58 (41%)
Active neonatal support	50 (36%)
IUFD	22 (16%)
Intrapartum death (termination of pregnancy)	68 (49%)
Neonatal death ≤7 days	13 (8.5%)
Perinatal death (all the above)	103 (74%)
Neonatal death >7 days	10 (7.9%)
Total mortality	113 (81%)
Total survival	27 (19%)
Active neonatal support	***n* = 50**
NICU admission	48 (96%)
Total mortality after active support	23 (46%)
Total survival after active support	27 (54%)
Neonatal complications	***n* = 27**
IVH ≥ grade 3	1 (4%)
ROP ≥ grade 3	4 (21%)
NEC ≥ stage 2	3 (12%)
BPD—moderate	13 (48%)
BPD—severe	7 (28%)
Sepsis	15 (56%)
Other**	16 (60%)
Any complication	22 (84%)

Continuous data are presented as means (SDs); interval between admittance and delivery, gestational ages, and hospitalisation are medians (IQRs).
*Other maternal complications: infection, cardiac decompensation, and haemorrhagia postpartum.
**Other neonatal complications: patent arterial duct, cerebellar haemorrhage, lung bleeding, and focal bowel perforation.

Maternal and neonatal outcome in relation to gestational age at admittance is presented in Table S1. From admission before 22^{+6} weeks of gestation to admission between 25 and 26 weeks of gestation, the median interval between admittance and delivery ranged from 9.5 to 3.5 days, caesarean section rates ranged from 12 to 75%, and total perinatal death (with or without active support) ranged from 96 to 52%. Maternal complications ranged from 38 to 58%. Neonatal complications ranged from 80 to 100%.

Surviving neonates versus non surviving neonates

Gestational ages at delivery of the 27 pregnancies with surviving children were on average 7 days longer (24^{+6} versus 23^{+6} weeks of gestation; $P < 0.001$) than the non-surviving neonates ($n = 106$). Furthermore, the estimated fetal weight at admittance was higher (598 versus 454 g; $P < 0.001$), and children were less often SGA (30 versus 68%; $P < 0.001$) and less frequently presented abnormal umbilical artery Doppler flow (52 versus 78%; $P = 0.011$) than non-surviving neonates. Of the 27 surviving neonates, 26 were delivered by caesarean section. Neonatal sex did not affect survival (male, 37 versus 49%; $P = 0.264$). The clinical maternal syndrome was not significantly different regarding maximal blood pressures, maximal laboratory abnormalities, and medication.

Trends in prolongation

We investigated prolongation in more detail. Prolongation, presented as time between admittance and delivery in relation to gestational age at admittance, and survival of the neonate can be seen in Figure 2A. In the course of the study period the implementation of a new guideline for neonatal support allowed a shift in the minimal gestational age for active neonatal support from 25^{+0} to 24^{+0} weeks.[12] Disregarding the year 2010 as a year of transition, we compared the prolongation time from admittance to delivery between the years 2008–2009 and 2011–2013 in Figure 2B. The median prolongation after 2010 was 5 days, which equals the median prolongation before 2010.

Trends in maternal and neonatal outcome

Trends in maternal and neonatal outcomes over the course of the study period are shown in Figure S1. The occurrence of maternal complications decreased from 65–75 to 41% during the study period, and neonatal survival after active neonatal support fluctuated between 40 and 80%. Most surviving neonates (21 of 27) were born between 25 and 26 weeks of gestation. Only six neonates born between 24 and 25 weeks of gestation (after 2010) survived. The caesarean section rate peaked at 62% in 2011, whereas it ranges from 26 to 38% in the remaining years of the study

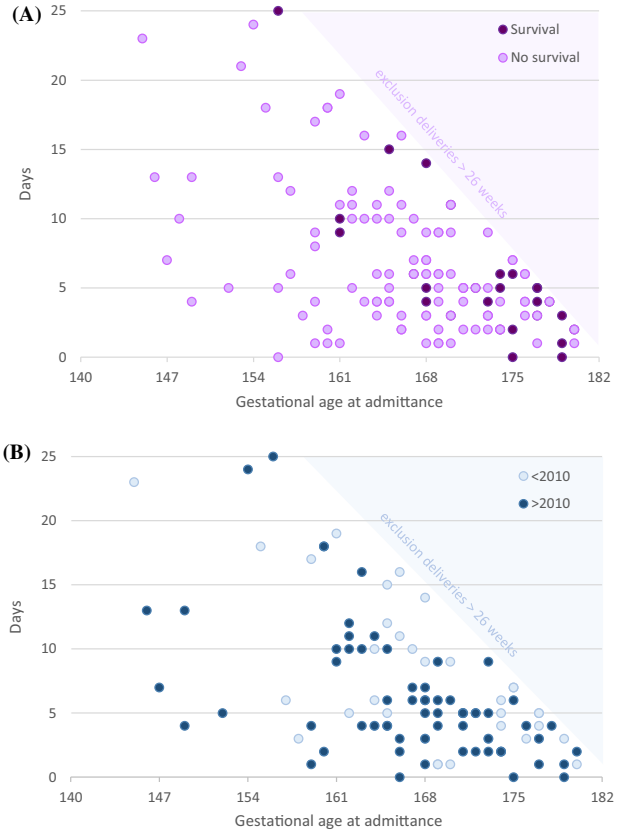

Figure 2. (A) Interval from admittance to delivery. (B) Interval from admittance to delivery before and after 2010.

period. Only one caesarean section (8.3%) was performed at a gestational age before 24 weeks (2013). In women with a gestation before 25 weeks (n = 41), nine caesarean sections (22%) were performed.

Subsequent pregnancies

Forty-two women (32%) of the 133 women were lost to follow-up and information on subsequent pregnancies could not be obtained. A subsequent pregnancy occurred in 61 women (67%), two of whom miscarried. We had complete data of 55 continuing pregnancies. They delivered again after a mean of 20 months (SD: 10 months) after the index delivery, at a mean gestational age of 35^{+4} weeks (SD: 36 days).

Of the 55 subsequent pregnancies, 17 women (31%) had recurrent pre-eclampsia at a mean gestational age 32^{+6} weeks (SD: 38 days), of which three pregnancies were complicated by HELLP (18%). Four women (7.3%) delivered again before 28 weeks of gestation. Perinatal death occurred in five subsequent pregnancies (9.6%): two pregnancies were terminated (trisomy 18 and fetal intracerebral haemorrhage), in two other pregnancies IUFD occurred, and one neonatal death was associated with severe growth restriction. Eventually, 50 women (91%) had a living child from the subsequent pregnancy.

Discussion

Main findings

In the Netherlands, women with severe early onset pre-eclampsia are delivered mostly for maternal reasons after a median prolongation of 5 days, which was unaffected by the implementation of the new guideline for active neonatal support. Maternal complications occurred frequently (54%) and neonatal survival was limited (19%), and troubled by complications (85%). The recurrence rate of pre-eclampsia was 31%; however, at significant later gestational age (mean: 32^{+6} weeks of gestation) with 91% neonatal survival.

Strengths and limitations

This contemporary case series is unique, as all Dutch perinatal centres participated in this study, and we were therefore able to include all women who met the inclusion criteria. Data collection was complete because we collected information from the medical files.

Baseline characteristics show serious illness of the mother and compromised fetal condition, as expected. New development or deterioration of HELLP syndrome (63 women) contributed to the maternal reason to deliver after expectant management. With this study we are unable to answer the question of whether HELLP syndrome or a deterioration of HELLP syndrome could have been prevented by prompt delivery.

There are several sources of potential bias that hinder the drawing of too firm conclusions. First, the size of the study is rather small, in line with the rarity of this extreme condition and similar, even smaller, published cohorts.[4–7] Furthermore, the retrospective nature of this case series and the fact that we were unable to retrieve the reasons behind the different management regimes do not allow for a meaningful comparison of outcomes between groups of expectant care or immediate delivery. Finally, women were selected for gestational age at delivery rather than gestational age at decision for management regime, inducing an information gap for women who are admitted before, but delivered after 26 weeks of gestation.

Interpretation

The overall maternal complication rate of 68% (including HELLP syndrome at admittance) is comparable with rates reported in the literature.[4–7] In contrast to other literature, our study presents the appearance of or deterioration of HELLP syndrome after admittance, which can be regarded as a complication of expectant management. Although a decreasing trend may be seen in the occurrence of maternal

complications over the study period, it is too soon to draw any conclusions about the reasons for this decrease. Perinatal mortality and neonatal complications are also comparable with the literature on severe early onset pre-eclampsia;[4–7] however, compared with perinatal death rates of 45% in extremely premature neonates in a Swedish nationwide cohort without maternal pre-eclampsia,[11] the rate of perinatal death was much higher in our study. This concurs with the concept that neonates born from mothers with severe early onset pre-eclampsia are not comparable with spontaneous prematurely born children. On the other hand, the neonatal survival rate after active support (27/50, 54%) is comparable with the results of the Swedish study.[11] Neonatal survival after extreme premature pre-eclampsia in this case series does not seem to have improved over recent years. From 2010 active support has been offered at an earlier gestational age, which may have effected survival rates.

In 80% of the women included in this study, the prolongation was 3 days or more, despite the high maternal complication rate and perinatal mortality. The prolongation time between admittance and delivery was in general 5 days, which is comparable with the results of some studies.[5,6] Prolongation may be longer if we had been able to include women that delivered beyond 26 weeks of gestation. In other studies much longer prolongation times of up to 32 days have been reported.[4,7,10] In contrast to our case series, only women eligible for expectant care were selected in these studies. As can be seen in Table S1 and Figure 2A, survival is very limited when presenting before 24 weeks of gestation, despite prolongation. Ganzevoort and Sibai have both reviewed different management regimes described in the literature.[8,10] They conclude that before 24 weeks of gestation, because of the absence of perinatal benefits and high maternal complication rate, an expectant management approach should not be offered routinely. Our findings endorse this consensus. Prolongation should only be offered to a select group of women (that still needs to be defined), in whom it is believed to benefit the neonatal prognosis, preferably after 24 weeks of gestation at presentation. In our study, maternal complications, perinatal death, and neonatal complications after 24 weeks of gestation were still very high, and in 85 women (64%) active neonatal support was never offered (59 neonates) despite prolongation, as their fetus was not considered viable. In line with other studies, this study did not provide the selection criteria for women considered eligible for expectant care. The differences presented between pregnancies with and without surviving neonates could give guidance for counselling on this matter.

Although we must keep in mind that because of the rareness of this clinical dilemma the number of patients does not warrant making too firm conclusions, trend analyses show a peak caesarean section rate in 2011. These findings could suggest a subtle influence of this guideline, with presumed improved neonatal survival chances after 25 weeks of gestation and after caesarean section.

In general, women need to be counselled carefully, weighing the risk for maternal complications against high perinatal mortality.

Conclusion

Severe pre-eclampsia at extreme premature gestational age is a rare but serious condition with high rates of maternal and neonatal complications and perinatal death. Prolongation of more than 2 days was often applied in the Netherlands, despite the consensus in international literature that prolongation of pregnancy should not be offered as a routine treatment option. Prolongation does not necessarily lead to fetal viability. Considering the limits of prolongation, women need to be counselled carefully, weighing the high risk for maternal complications against limited neonatal survival and/or extreme prematurity, and its sequelae. Estimated fetal weight, growth restriction, and Doppler abnormalities should be taken into account. Furthermore, we should also provide information on the positive prospects regarding maternal and neonatal outcome in a future pregnancy.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

MvO is the primary author, created the database, performed part of the data collection, and did most of the writing of the article. LvE helped design the study, performed data collection, and reviewed the article. MdL helped to design the study, performed data collection, and reviewed the article. JD, JJE, KB, AB, JB, SK, BR, PvRH, and HS performed data collection and reviewed the article. RK reviewed the article from a neonatologist's perspective. WG, BWM, and CdG contributed to the design of the study, supervised the data collection, and reviewed the article. IG-S initiated and designed the study, supervised the data collection, and reviewed the article.

Details of ethics approval

The ethical advisory board of the Academic Medical Centre, Amsterdam, considered this study not to be subject to the Medical Research Involving Human Subjects Act (WMO). This decision was based on the fact that retrospective data were used and that the women in this case series were not submitted to any examinations or hospital visits; therefore, the board approved the study (W13_106 # 13.17.0123) on 29 May 2013.

Funding
No funding was received for the study.

Acknowledgements
None.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Trends in maternal complications, neonatal survival, and caesarean sections.

Table S1. Prolongation and maternal and neonatal outcome in relation to gestational age at admission. ■

References

1 Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet* 2005;365:785–99.
2 Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 2010;376:631–44.
3 Sibai BM, Akl S, Fairlie F, Moretti M. A protocol for managing severe preeclampsia in the second trimester. *Am J Obstet Gynecol* 1990;163:733–8.
4 Gaugler-Senden IP, Huijssoon AG, Visser W, Steegers EA, de Groot CJ. Maternal and perinatal outcome of preeclampsia with an onset before 24 weeks' gestation. Audit in a tertiary referral center. *Eur J Obstet Gynecol Reprod Biol* 2006;128:216–21.
5 Belghiti J, Kayem G, Tsatsaris V, Goffinet F, Sibai BM, Haddad B. Benefits and risks of expectant management of severe preeclampsia at less than 26 weeks gestation: the impact of gestational age and severe fetal growth restriction. *Am J Obstet Gynecol* 2011;205:465.e1–6.
6 Bombrys AE, Barton JR, Nowacki EA, Habli M, Pinder L, How H, et al. Expectant management of severe preeclampsia at less than 27 weeks of gestation: maternal and perinatal outcomes according to gestational age by weeks at onset of expectant management. *Am J Obstet Gynecol* 2008;199:247.e1–6.
7 Budden A, Wilkinson L, Buksh MJ, Mc Cowan L. Pregnancy outcome in women presenting with pre-eclampsia at less than 25 weeks gestation. *Aust N Z J Obstet Gynaecol* 2006;46:407–12.
8 Ganzevoort W, Sibai BM. Temporising versus interventionist management (preterm and at term). *Best Pract Res Clin Obstet Gynaecol* 2011;25:463–76.
9 Hall DR, Odendaal HJ, Steyn DW, Grové D. Expectant management of early onset, severe pre-eclampsia: maternal outcome. *BJOG* 2000;107:1252–7.
10 Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. *Am J Obstet Gynecol* 2007;196:514.e1–9.
11 EXPRESS Group, Fellman V, Hellström-Westas L, Norman M, Westgren M, Källén K, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA* 2009;301:2225–33.
12 NVOG Guideline: 'Perinatal policy in extreme premature birth' [www.nvog.nl]. Accessed 15 September 2010.
13 ACOG Practice Bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet* 2002;77:67–75.
14 Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? *Am J Obstet Gynecol* 1990;162:311–6.
15 Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978;92:529–34.
16 International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol* 2005;123:991–9.
17 Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg* 1978;187:1–7.
18 Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723–9.

