

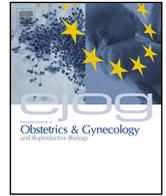
PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/171635>

Please be advised that this information was generated on 2021-09-23 and may be subject to change.



Terminating pregnancy for severe hypertension when the fetus is considered non-viable: a retrospective cohort study



Leonor Van Eerden^{a,*}, Miriam F. Van Oostwaard^b, Gerda G. Zeeman^c,
Godelieve C.M. Page-Christiaens^d, Eva Pajkr^e, Johannes J. Duvekot^f,
Frank P. Vandebussche^g, Swan G. Oei^h, Hubertina C.J. Scheepersⁱ, Jim Van Eyck^j,
Johanna M. Middeldorp^k, Steven V. Koenen^d, Christianne J.M. De Groot^a,
Antoinette C. Bolte^g

^a VU Medical Center Amsterdam, The Netherlands

^b Beatrix Hospital Gorinchem, The Netherlands

^c University Medical Center Groningen, The Netherlands

^d University Medical Center Utrecht, The Netherlands

^e Academic Medical Center Amsterdam, The Netherlands

^f Erasmus Medical Center Rotterdam, The Netherlands

^g Radboud University Medical Centre Nijmegen, The Netherlands

^h Maxima Medical Center Veldhoven, The Netherlands

ⁱ Maastricht Medical Center, The Netherlands

^j Isala Clinics Zwolle, The Netherlands

^k Leiden University Medical Center, The Netherlands

ARTICLE INFO

Article history:

Received 21 October 2015

Received in revised form 23 June 2016

Accepted 1 August 2016

Keywords:

Early-onset preeclampsia

Termination of pregnancy

Non-viable fetus

ABSTRACT

Objective: To investigate frequency and practise of termination of pregnancy for early-onset hypertensive disorders where the fetus is considered to be non-viable.

Study design: Retrospective cohort study in all Dutch tertiary perinatal care centres ($n = 10$), between January 2000 and January 2014. All women who underwent termination of pregnancy, without fetal surveillance or intention to intervene for fetal reasons, for early-onset hypertensive disorders in pregnancy, were analyzed. Women eligible for this study were identified in the local delivery databases. Medical records were used to collect relevant data.

Results: Between January 2000 and January 2014, 2,456,584 women delivered in The Netherlands, of which 238,448 (9.7%) in a tertiary care centre. A total of 161 pregnancy terminations (11–12 per year) for severe early-onset preeclampsia were identified, including 6 women with a twin pregnancy. Mean gestational age at termination was 172 days (GA 24^{4/7}) \pm 9.4 days. In 70% of cases termination was performed at or shortly after 24 weeks' gestation. 74.5% of women developed HELLP syndrome ($n = 96$), eclampsia ($n = 10$) or needed admission to an ICU ($n = 14$). Birth weight was below 500 g in 64% of cases. In 69% of the cases the estimated fetal weight was within a 10% margin of the actual birth weight.

Conclusion: Termination of pregnancy for early-onset hypertensive disorders without intervention for fetal indication occurs approximately 12 times per year in The Netherlands. More data are needed to investigate contemporary best practice regarding termination of pregnancy for early-onset hypertensive indications at the limits of fetal viability. Considering the frequency of maternal complications, termination of pregnancy and not expectant management should be considered for all women presenting with severe early onset hypertensive disorders at the limits of fetal viability.

© 2016 The Author(s). Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The incidence of severe early onset preeclampsia (PE) is increasing worldwide [1]. Preeclampsia is annually accountable for approximately 60,000 maternal deaths worldwide. Cerebral

* Corresponding author at: Maasstad Ziekenhuis Rotterdam, Department of Obstetrics and Gynecology, Maasstadweg 21, 3079 DZ Rotterdam, The Netherlands.
E-mail address: eerdenl@maasstadziekenhuis.nl (L. Van Eerden).

complications, such as eclampsia and intracranial haemorrhage account for at least 75% of these [2]. In situations where maternal health is severely compromised and where prognosis for intact fetal survival is virtually non-existent due to early gestational age complicated by severe growth restriction, termination of pregnancy may be considered [3–5,10]. In an authoritative review, Sibai et al. describe a maternal complication rate of 57%, and an overall fetal mortality rate of 83% when early-onset preeclampsia is managed expectantly. The authors therefore state that in case of severe preeclampsia before 24 weeks, termination of pregnancy should be seriously considered in order to prevent severe maternal morbidity or mortality [5].

The overall frequency and indications for termination of pregnancy for maternal indications were recently described by our group [6]. In the current manuscript we analyzed in more detail the group of women who presented with early-onset hypertensive disorders.

Aim of this study is to gain insight in Dutch practice patterns of all cases of termination of pregnancy for early-onset hypertensive disorders in pregnancies where the fetus is considered non-viable over the last 15 years. Secondly, we aimed to investigate the accuracy of fetal weight estimation on which fetal prognosis was based.

Methods

We performed a Dutch nationwide retrospective audit of all cases of termination of pregnancy for early-onset hypertensive disorders in pregnancies considered non-viable between January 2000 and January 2014. All women who underwent termination of pregnancy because of severe maternal hypertensive disorders between 22 and 27^{6/7} weeks of pregnancy in tertiary care centres were included. In all cases the fetus was considered to be non-viable, either because of the gestational age and/or because of severe growth restriction. According to Dutch guidelines, valid during the study period, a fetus at a gestational age of less than 24 weeks was considered non-viable [7]. Exclusion criteria were termination of pregnancy for other maternal indications, fetal congenital anomalies or intra-uterine fetal demise. Termination of pregnancy was defined as termination of a vital pregnancy and intention of primary non-intervention for fetal indications. All pregnancies were terminated using prostaglandins (i.e. intravenous sulprostone or misoprostol).

Recruitment was limited to the tertiary care centres ($n = 10$), because according to current practice and the Dutch Society of Obstetrics and Gynaecology guideline on hypertensive disorders in pregnancy, women who develop preeclampsia prior to 32 weeks' gestation should be referred to and treated in a tertiary care centre. These centres are equipped with a maternal obstetric high care unit as well as a Neonatal Intensive Care Unit (NICU) [8,9]. Cases were identified through a search in the local delivery databases. To control for potential underreporting, we cross-checked the prevalence data with the Netherlands perinatal registry (PRN-registry) [10]. Relevant demographic and clinical data were extracted from the medical records and transferred to a standardized data collection form. Demographic data included maternal age at termination, parity, and medical and obstetric history. Clinical data included information about the index pregnancy and delivery including gestational age at admission, gestational age at delivery, birth weight and gender. Furthermore, specific data used for clinical decision making were recorded; gestational age, the last estimated fetal weight (EFW) prior to termination and suspected growth restriction (EFW < 10th percentile).

Definitions of preeclampsia and HELLP syndrome were derived from the guidelines of the International Society for the Study of

Hypertension in Pregnancy (ISSHP) [11] and the NICE guideline Hypertension in Pregnancy [12]. Severe preeclampsia is 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 h) and one or more of the following: oliguria, cerebral or visual disturbances, pulmonary oedema, epigastric or upper-quadrant pain, impaired liver function, thrombocytopenia or fetal growth restriction, after 20 weeks of pregnancy. Severe maternal morbidity was defined as HELLP syndrome haemolysis (elevated lactate dehydrogenase (LDH) levels ≥ 600 U/L), elevated liver enzymes by levels of aspartate transaminase (ASAT) ≥ 70 U/L or alanine transferase (ALAT) ≥ 70 U/L and low platelets <100,000/mm), eclampsia or admission to an ICU.

Statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means with standard deviations (SD). We compared estimated fetal weight by ultrasound and actual birthweight. Differences between the groups were tested with a parametric (unpaired *t*-test) test as appropriate. *P* value less than 0.05 was considered to indicate statistical significance.

An acknowledged ethical advisory board approved the study (VUmc # 29-2010/200).

Results

Between January 2000 and January 2014, 2,456,584 women delivered in The Netherlands, of which 238,448 (9.7%) in a tertiary care centre. Pregnancy was terminated for early-onset preeclampsia in 161 women (6.5 per 100,000). Among these, 6 women had a twin pregnancy. A cross-check with the Netherlands Perinatal Registry demonstrated that 100% of the cases were identified [9].

Maternal characteristics and outcome are shown in Table 1. The mean maternal age was 31 years and 116/161 were nulliparous (72%). The medical history was unremarkable in 82/161 women (51%).

The mean gestational age at admission was 164 days (23^{3/7} weeks) ± 9.3 days and at termination this was 172 days (24^{4/7} weeks) ± 9.4 days. Ninety-two women (57%) were admitted at a gestational age of less than 24 weeks. In 23/92 women (25%), induction of labour was commenced immediately after initial stabilization. In the remaining 69/92 women (75%) pregnancy management was initially expectant. The mean interval between admission and start of termination was 9.3 days ± 5.4 days.

In 113/161 women (70%) termination was started at or beyond 24 weeks (mean GA 25^{2/7} ± 9.4 days). In these cases a multidisciplinary team, consisting of at least obstetricians, neonatologists, discussed the case and examined alternative options before providing a recommendation to the parents. The main reason to terminate a pregnancy after 24 weeks' gestation was rapid maternal deterioration, such as the development of progressive HELLP syndrome, eclampsia or refractory hypertension.

No maternal deaths were recorded. One patient with a uterine scar from a previous caesarean section underwent an emergency caesarean section after administration of prostaglandins because of uterine rupture and hypovolemic shock.

Table 2 shows the neonatal characteristics. Data of 167 neonates are available, originating from 155 singleton and 6 twin pregnancies. The mean birth weight for the entire cohort was 460 g ± 103 g. Birth weight was below 500 g in 62% of cases. In 145 neonates estimated fetal weight based on antenatal ultrasound parameters was recorded. The interval between measurement of EFW and day of birth was 5.4 days ± 2.1 days. In 69% of the cases the EFW was within a 10% margin of the actual birth weight. In 25 cases (22%)

Table 1
Maternal characteristics and outcome. Continuous data are presented as means (SD) or *N* (%).

	Mean (SD) or <i>N</i> (%)
Age (y)	30.6 (5.2) <i>N</i> = 161
Parity	
Nulliparous (no pregnancies > GA 16 weeks)	116 (72)
1 fetal loss <16 weeks	21 (18)
2 or more fetal losses <16 weeks	8 (6.9)
Multiparous	45 (28)
Total number of previous pregnancies	100
Live offspring	57 (57)
Previous perinatal death	15 (15)
Previous termination for maternal indication	2
Fetal loss <16 weeks	15 (33)
Previous PE or HELLP	14 (31)
Previous preterm delivery	13 (62)
Previous term delivery	24 (53)
Medical history ^a	
No preexisting disease	82 (51)
Nulliparous	61
Multiparous	21
Chronic hypertension	33 (21)
Nulliparous	23
Multiparous	10
Thrombophilia ^b	10 (6.2)
Nulliparous	5
Multiparous	5
Kidney disease	5 (3.1)
Nulliparous	3
Multiparous	2
Other ^c	16 (10)
Nulliparous	11
Multiparous	5
Gestational age at onset of termination (weeks)	24 ^{4/7} (22 ^{0/7} –27 ^{6/7}) ± 9.4 days
22–23 ^{6/7} weeks	48 (30)
24–25 ^{6/7} weeks	84 (52)
≥26 ^{0/7} weeks	29 (18)
Maternal outcome	
Maternal death	–
HELLP syndrome	95 (59)
Eclampsia	10 (6.2)
Admission to ICU ^d	14 (8.4)

^a Several women had more than one relevant condition in their history.

^b Thrombophilia: antiphospholipid syndrome, protein S deficiency, Factor V Leiden mutation.

^c Other: SLE, diabetes mellitus, Crohn's disease, haemoglobinopathy, malignancy.

^d Admission to ICU includes women with pulmonary oedema, refractory hypertension, eclampsia, heart failure and hypovolemic shock.

the EFW was more than 10% underestimated and in 10 cases (9%) the EFW was more than 10% overestimated.

In the 113 pregnancies that were terminated at or beyond 24 weeks, the mean EFW was 495 g ± 113 g, while the mean actual birth weight was 508 g ± 117 g (mean difference between EFW and birth weight: 13.3 g; 95%CI: –24.30 to –2.30; *p* = 0.018). Fig. 1 shows the EFW and birth weight per neonate.

Table 3 shows the estimated fetal weight prior to decision of termination and actual birth weight per gestational week. At a gestational age of <23^{6/7} the estimated fetal weight or Doppler profile of the umbilical artery did not play an important role in the decision to perform termination of pregnancy. The decision to refrain from fetal monitoring and interventions for fetal indication was guided by poor fetal prognosis, based on: gestational age, EFW (51% <500 g), suspected growth restriction (73% EFW < 10th percentile) and lack of growth between 2 assessments.

The perinatal mortality was 99.6%. One baby girl was born alive and admitted to the NICU. After 4 years of follow up she has a normal development. The pregnancy was terminated for severe

Table 2
Neonatal outcome.

Neonatal outcome	Mean	<i>N</i> = 167 <i>n</i> (%)
Sex		167
Male		60 (36)
Female		99 (59)
Unknown		8 (4.9)
Perinatal mortality		166 (99.6)
Birth weight (g)	460 ± 103 g	
>10th percentile		36 (23)
<10th percentile		125 (78)
<5th percentile		106 (66)
Unknown		6 (3.5)

HELLP syndrome using intravenous sulprostone at a GA of 25^{5/7} weeks. Ultrasound prior to termination showed growth restriction and oligohydramnios and an EFW of 550 g. The birth weight was 600 g (16th percentile).

The number of terminations per centre per 10,000 deliveries varied from 2.1 per 10,000 deliveries in one centre to 17.2 per 10,000 deliveries in another centre.

Comment

Main findings

Between 2000 and 2014, 161 women underwent termination of pregnancy for early-onset hypertensive disorders when the fetus was considered non-viable (6.5/100,000). The main reason to terminate was rapid maternal deterioration (progressive HELLP syndrome, eclampsia or refractory hypertension). In 75% management was initially expectant. 75% of women developed HELLP syndrome, eclampsia or needed admission to an ICU. In the majority of women (70%) termination was performed at or beyond 24 weeks. For the decision to refrain from fetal monitoring and active neonatal support the following parameters were taken into consideration: gestational age, estimated fetal weight, growth restriction, and lack of interval growth. In 31% of the cases EFW was more than 10% underestimated or overestimated compared to the actual birth weight. All terminations were performed medically.

Strengths and weaknesses

This study describes a large nationwide cohort, considering the rareness of the condition. These data fill a knowledge gap concerning the frequency of termination of pregnancy for hypertensive disorders and concerning factors contributing to the decision to do so. Furthermore, detailed medical history and outcome information is available since data was gathered from the medical records. During the study period national guidelines for management of pre-eclampsia remained unchanged [8,9].

The most important limitation is that this is a retrospective study. We did however put a major effort to ensure completeness of cases.

Interpretation

Gestational age and fetal growth

In this cohort, 57% of women were admitted prior to a gestational age of 24 weeks'. Despite international literature and guidelines, stating that such women should be counselled towards termination, 75% of these pregnancies were initially managed expectantly and prolonged with 9.3 days on average. Expectant management resulted in significant maternal deterioration such that termination was considered inevitable.

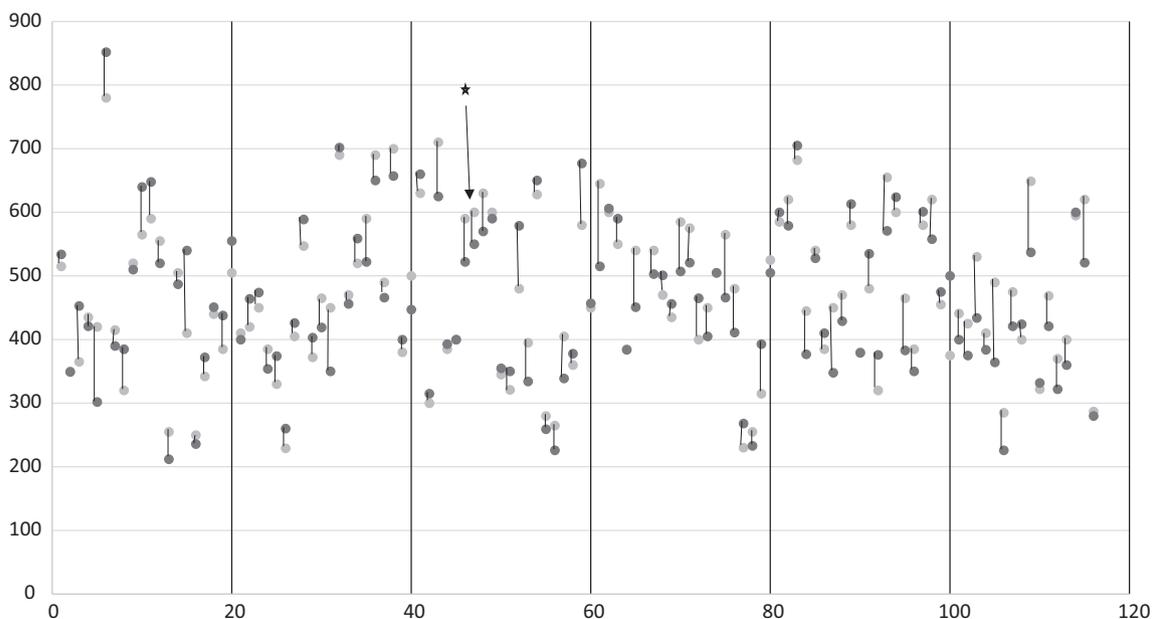


Fig. 1. Estimated fetal weight and actual birth weight per case.

In women who develop severe early-onset preeclampsia between 24^{0/7} and 32^{6/7} weeks' gestation, obstetric management will depend on prospects for intact survival of the infant [3–5]. This study presents a cohort that progressed beyond 24 weeks where disease severity and non-viable prognosis for the fetus led to the difficult decision to terminate the pregnancy precluding infant survival. In these cases prolongation of pregnancy with a risk of severe maternal complications but also a potential increase in number of surviving infants was weighed against termination of pregnancy with probable reduction of maternal complications but increased perinatal mortality. This decision was made after interdisciplinary consultation and parent counselling. Studies on

perinatal mortality and morbidity in these severely growth restricted premature infants do not support active neonatal management [13–16].

The accuracy of fetal weight estimation by ultrasound has been debated [17]. A recent study shows that determining the EFW in extreme preterm and SGA fetuses is less accurate than for AGA fetuses and that EFW is more likely to be overestimated [17]. Our study shows that in 22% of neonates the weight was more than 10% higher than estimated before birth. We recommend to take this inaccuracy into account when counselling parents with growth restricted fetuses at the limits of fetal viability.

Table 3

Estimated fetal weight (EFW) and actual birth weight, according to gestational age in weeks.

Gestational age at termination	Neonates (N)	Prenatal EFW N (%)	Birth weight N (%)
22 ⁰ –22 ⁶	22	<500 g: 20 (100) ≥500 g: – Unknown: 2	<500 g: 21 (100) ≥500 g: 0 Unknown: 1
23 ⁰ –23 ⁶	28	<500 g: 19 (90) ≥500 g: 2 (10) Unknown: 7	<500 g: 24 (100) ≥500 g: 0 Unknown: 4
24 ⁰ –24 ⁶	43	<500 g: 29 (71) ≥500 g: 12 (29) Unknown: 2	<500 g: 27 (64) ≥500 g: 15 (36) ^a Unknown: 1
25 ⁰ –25 ⁶	45	<500 g: 21 (51) ≥500 g: 20 (49) Unknown: 4	<500 g: 23 (51) ≥500 g: 22 (49) ^b
26 ⁰ –26 ⁶	23	<500 g: 5 (26) ≥500 g: 14 (74) Unknown: 4	<500 g: 7 (30) ≥500 g: 16 (70) ^c
27 ⁰ –27 ⁶	6	<500 g: 2 (33) ≥500 g: 4 (66) Unknown: –	<500 g: 1 (17) ≥500 g: 5 (83) ^d

Percentages are shown according to the number of available records.

^a Mean 560 g ± 117 g.

^b Mean 593 g ± 117 g.

^c Mean 612 g ± 122 g.

^d Mean 578 g ± 121 g.

Conclusion

Termination of pregnancy for early-onset hypertensive disorders in fetuses considered non-viable, is extremely rare in The Netherlands. We identified on average 1–2 cases per year per tertiary obstetric care centre. To reach the decision to terminate such pregnancies at the limits of fetal viability is very difficult for parents as well as health care providers. This is reflected in an average interval between admission and intervention of 9.3 days. However, considering the frequency of maternal complications termination of pregnancy and not expectant management should be considered for all women presenting with severe early onset hypertensive disorders at the limits of fetal viability. As neonatal intensive care continues to improve and enables survival at earlier gestational ages and lower birth weights it is prudent to continuously monitor the practice and outcomes to be able to define best-practices in the care of these complicated pregnancies.

Acknowledgements

There are no persons to acknowledge in this article.

This study was funded by the committee Late termination of pregnancy of the Dutch Society of Obstetrics and Gynecology.

References

- [1] Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early-versus late-onset disease. *Am J Obstet Gynecol* 2013;209:544.e1–544.e12.

- [2] Zeeman GG. Neurologic complications of pre-eclampsia. *Semin Perinatol* 2009;33(3):166–72.
- [3] 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* 2006;128: 216–21.
- [4] Bombrys AE, Barton JR, Nowacki EA, et al. Expectant management of severe preeclampsia at less than 27 weeks' gestation: maternal and perinatal outcome according to gestational age by weeks of onset of expectant management. *Am J Obstet Gynecol* 2008;199: 247.e1–e6.
- [5] 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–e9.
- [6] van Eerden L, Zeeman GG, Page-Christiaens GC, et al. Termination of pregnancy for maternal indications at the limits of fetal viability: a retrospective cohort study in the Dutch tertiary care centres. *BMJ Open* 2014;4(6): e005145.
- [7] NVOG guideline Perinataal beleid bij extreme vroeggeboorte; September 2010, Available at: www.nvog.nl/Sites/Files/0000001346_Richtlijn%20Perinataal%20beleid%20bij%20extreme%20vroeggeboorte.pdf.
- [8] NVOG Richtlijn Hypertensieve aandoeningen in de zwangerschap. Nederlandse Vereniging voor Obstetrie en Gynaecologie; 2011, Available at <http://nvog-documenten.nl/index.php>.
- [9] NVOG nota Verwijzing naar een perinatologisch centrum; September 2007. Available at: www.nvog-documenten.nl/index.php?pagina=richtlijn/pagina.php&fSelectTG_62=75&fSelectedSub=62&fSelectedParent=75.
- [10] The Netherlands Perinatal Registry. www.perined.nl.
- [11] Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertens* 2014;4(2):97–104.
- [12] NICE guideline hypertension in pregnancy; August 2010, Available at: www.nice.org.uk/guidance/CG107.
- [13] Jenkins SM, Head BB, Hautz JC. Severe preeclampsia at <25 weeks of gestation: maternal and neonatal outcomes. *Am J Obstet Gynecol* 2002;186:790–5.
- [14] Garite TJ, Clark R, Thorp JA. Intrauterine growth restriction increases morbidity and mortality among premature neonates. *Am J Obstet Gynecol* 2004;191: 481e7.
- [15] Tsai L-Y, Chen Y-L, Tsou K-I, Mu S-C. The impact of small for gestational age on neonatal outcome among very low birth weight infants. *Pediatr Neonatol* 2015;56(2):101–7.
- [16] Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. *Am J Obstet Gynecol* 2000;182:198–206.
- [17] Stefanelli S, Groom KM. The accuracy of ultrasound-estimated fetal weight in extremely preterm infants: a comparison of small for gestational age and appropriate for gestational age. *Aus N Z J Obstet Gynaecol* 2014;54(2):126–31.