Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Is preeclampsia an independent risk factor for feeding intolerance in extremely preterm infants?

Sarkhan Elbayiyev[a,*], Fuat Emre Canpolat[a], Gulsum Kadıoglu Simsek[a], Sehribanu Isik[a], Mehmet Buyuktiryaki[a], Hayriye Gozde Kanmaz Kutman[a]

[a] *University of Health Sciences, Ankara City Hospital, Department of Neonatology, Ankara, Türkiye*

ARTICLE INFO

Keywords:
Preeclampsia
Prematurity
Enteral nutrition
Feeding intolerance

Received: Jul 11, 2022
Accepted: Dec 13, 2022
Available Online: 23.12.2022

DOI:
10.5455/annalsmedres.2022.06.199

Abstract

Aim: The causative factors of neonatal feeding intolerance are poorly understood. Intrauterine environment and fetal conditions are important factors affecting gastrointestinal perfusion. Our aim was to evaluate whether maternal preeclampsia negatively affects preterm infants' enteral feeding tolerability.

Materials and Methods: Eight hundred and twenty preterm infants who were born between January 2015 and December 2016 and were under 1,500 grams and 30 weeks of gestational age were included in this entire cohort of which 701 were retrospectively analyzed because of missing records. Antenatal, perinatal, and neonatal outcome data were retrospectively analyzed.

Results: There were statistical differences between infants with maternal preeclampsia (n=128) and without preeclampsia (n=573), in terms of mean birth weight, mean gestational age, grade 3-4 IVH, platelet count, being under 3rd percentile of body weight during discharge from NICU and feeding intolerance. There was no significant difference on the first day of feeding, fully enteral feeding days, and time of catch-up birth weight. After correcting the data with birth weight, gestational age, and SGA as a cofactor; nominal regression revealed that PE strongly may be an independent risk factor for FI in this study group [OR: 5.469 (95%CI 1.099-2.929) p:0.019].

Conclusion: According to this study's results, we could say that preeclampsia is a significant risk factor for feeding intolerance in very low birth-weight preterm babies. For babies of mothers with preeclampsia, a nutrition plan should be made; interventions and treatments to minimize fetal effects should be investigated.

Introduction

Premature newborns who are exposed to preeclampsia (PE) have a multiplied short-term morbidity, mostly respiratory diseases such as respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) [1]. Gastrointestinal problems are also common, in spite of the fact that spontaneous intestinal perforation and necrotizing enterocolitis (NEC) have been reported as high risk this was not confirmed with a large number of studies [2, 3]. These problems may be related both to PE itself and to prematurity, small for gestational age (SGA), intrauterine growth restriction and/or exposure to magnesium sulfate (Magnesium sulfate 15%, Onfarma), which is frequently used in obstetrics [4-6]. However, other findings reveal the reasons to be caused by a direct effect of maternal sickness; these findings include an enlarged frequency of neutropenia and thrombocytopenia and a lower incidence of intraventricular hemorrhage and cerebral palsy disorders, primarily as a result of exposure to magnesium sulfate [7]. The assessment of long-term outcomes show larger evidence that PE has significant implications not only for the future health of the child but also for the mother's health. So, PE with a genetic component and complicated pathophysiology is not a simple gestational disorder but it is a clinical syndrome with an undefined etiology. This clinical condition includes important maternal and fetal vascular changes that may cause and lead to different sicknesses in later life. The deviation in results on outcomes for children exposed to PE could be the result of methodological differences in the retrospective case-control studies, but evidence-based results on prognosis are obtained from cohort studies [8]. In cohort studies, differences in patient characteristics such as the severity of maternal sickness, sample size, follow-up time, and main outcome measures certainly contribute to

*Corresponding author:
Email address: serxanelbayiyev@gmail.com (Sarkhan Elbayiyev)

the changes in the results in the literature. Therefore, our aim was to evaluate a possible relationship between PE and feeding intolerance (FI) which may contribute to and associate all long-term morbidities in preterm infants in a large retrospective cohort.

Materials and Methods

Clinical Study Approval was obtained from the Zekai Tahir Burak Women's Health Education and Research Hospital's Clinical Researches Ethics Committee (2011-KAEK-19) and Education-Training Planning Coordination Committee before starting the study (Date: 29.05.2018, desicion number: 24/2018). Retrospectively, infants who were born before 30 weeks' pregnancy with less than 1,500 g birth weight and also underwent neurodevelopmental testing at a corrected age of 24 months during follow-up in our center were included.

The hospital records/files of all eligible infants during the study period (born between January 2015- December 2016, 24 months corrected age, and follow-up between 2017 and 2018) were retrospectively reviewed to summarize their antenatal, perinatal, and outcome data. Congenital anomalies, early deaths, infants lost follow-up and missing data were excluded from analysis, and infants with corrected ages of two years with complete follow-up were included in the study. Written informed consent was obtained from the patients/guardians.

Definitions

Preeclampsia is defined as the new onset of hypertension and proteinuria or the new onset of hypertension and important end-organ dysfunction with or without proteinuria after the 20th pregnancy week or postpartum in a previously normotensive woman. It should be noted that the diagnosis can still be made in the lack of proteinuria if the new-onset hypertension is accompanied by symptoms or significant signs of important end-organ dysfunction, as described in the American College of Obstetrics and Gynecology Bulletin [9].

Feeding intolerance

Feeding intolerance is defined as the lack of ability to digest enteral feeds, presenting gastric residual volume of more than 1/2 of the enteral feeding plan [10]. Abdominal tenderness, abdominal distension, vomiting, gastric residuals, and color change on the skin of the abdomen were the first findings of intolerance within a few hours after neonatal intensive care (NICU) admission. Gastric aspirate volume drawn before each feeding was accepted as pathological if outrunning 1/3 to 1/2 of the given nutrient and/or higher than 1 mL/kg per hour. If pathological on more than one occasion, we changed the feeding rate (from 6 to 8 times per day, or from 8 to 12 times per day), and decreased the amount correspondingly. If that did not work, we reduced the aggregate daily amount and at last changed to continuous intragastric drip-feeding as we used to accepting aggressive nutrition rules for preterm infant feeding [11].

Feeding problems were also defined as inefficient weight gain (<10 g/kg/day) over several days (at least three consecutive days), defecation problems (especially constipation or lag of stool passage because of increased gastric aspirate volume), and gastroesophageal reflux (excessive regurgitation of feeds, milk in mouth or oropharynx, rumination, coughing, bradycardia, resistant apnoea and failure to thrive), for which our three-step department treatment protocol was: (I) smaller and more frequent feeds; (II) 30° elevation in the prone position: and (III) dense feeds.

Small for gestational age (SGA) was defined as weight at birth below the 10th percentile for gestational age and gender [12]. Neonatal morbidities such as RDS, infants requiring surfactant [13], BPD, higher than 21% oxygen requirement, moderate and severe cases [14], NEC was defined as per Bell's classification of NEC (Bell stage ≥IIb) [15]. Patent ductus arteriosus (PDA) was diagnosed in infants with clinical evidence of left-to-right shunt, defined as a continuous murmur, bounding pulse, hyperdynamic precordium, widened pulse pressure, congestive heart failure, increased pulmonary vascularity, or chest x-ray showing cardiomegaly and/or increased need for oxygen. All clinically suspected PDAs were confirmed by echocardiography [16] (Vivid S5 Cardiovascular Ultrasound Machine, GE). Intraventricular hemorrhage (IVH) grade III and periventricular hemorrhagic infarction was defined as intraventricular hemorrhage with ventricular dilatation as Volpe's grading [17]. Retinopathy of prematurity (ROP) was defined according to the International Classification of Retinopathy of Prematurity (ICROP) [18]. Proven sepsis means an infant who clinically presents neonatal sepsis symptoms such as apnea, brady-tachycardia, hypo-hyperthermia, abdominal distension, poor perfusion, etc. with a positive blood culture. Osteopenia is diagnosed with high levels of alkaline phosphatase and typical radiologic signs of metabolic bone disease in preterm infants [19].

All infants underwent neurodevelopmental assessment using the Bayley-II at 24 months of corrected age and Mental Development Index (MDI) and Psychomotor Development Index (PDI) values were recorded as scores. Neurodevelopmental impairment (NDI) was diagnosed in infants with PDI or MDI scores below 70 and in infants who had vision or hearing impairment or borderline PDI and/or MDI scores and were assessed by the developmental pediatrician as having apparent neurodevelopmental delay.

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows version 22.0 (IBM Corp, Armonk, NY). The data obtained from the patients in both groups were recorded in an SPSS database. Mean and standard deviation (SD) values were calculated for continuous variables with normal distribution and median, minimum, and maximum values were determined for continuous variables with non-normal distribution. Statistical analyses were performed after determining whether the assumptions of normal distribution and homogeneity of variance for parametric tests were met.

The Kolmogorov-Smirnov test was used to determine whether numerical variables were normally distributed. For pairwise group comparisons, the independent samples t-test was used for normally distributed variables and the

Table 1. Clinical features of preterm infants with and without maternal preeclampsia.

	Maternal Preeclampsia n:128	Without Preeclampsia n:573	P value
Birthweight, gr ± SD	967 ± 229	1067 ± 226	0.010
Gestational age, weeks ± SD	27.8 ± 1.3	28.3± 1.2	0.012
Antenatal steroids, n(%)	96 (75)	412 (72)	0.548
Male gender, n(%)	66 (52)	292 (51)	0.992
Apgar Score at 5th minute median (min-max)	6(1-8)	6(1-8)	NS*
SGA, n(%)	32 (25)	57 (10)	0.001
Surfactant use, n(%)	85 (67)	429 (74)	0.630
Inotrope use in first week, n(%)	63 (49)	279 (48)	0.914
Patent ductus arteriosus, n(%)	57 (44)	229 (40)	0.050
Proven sepsis, n(%)	30(23)	114 (20)	0.369
NEC Stage 2-3, n(%)	4 (0.3)	10 (0.17)	0.313
BPD, moderate & severe, n(%)	28 (21)	120 (20)	0.810
IVH Grade 3 and PVHI, n(%)	11 (9)	96 (17)	0.020
ROP, requiring laser, n(%)	12 (0.9)	53 (0.9)	0.960
White blood cell /mm^3	14,700 ± 10,500	14,900 ± 11,301	0.860
Platelet count / mm^3	212,195±88,080	244,400 ± 98,469	0.010
Osteopenia of prematurity, n(%)	22 (17)	89 (15)	0.640
First day of feeding, ± SD	1,4±0,5	1,3±0,5	0.073
Fully enteral feeding day, ± SD	18,2±7,5	15,7±6,3	0.145
Day to catch birth weight, ± SD	12,5±4,1	13,4±6,1	0.084
Feeding intolerance, n(%)	71 (55)	211 (36)	0.001
<3rd percentile weight at discharge, n(%)	57 (44)	197 (34)	0.030
Neurodevelopmental impairment, n(%)	26 (20)	118 (20)	0.940
Day of discharge, ± SD	64,5±21.7	64,3±22,0	0.955
Mortality, n(%)	22 (17.1)	77 (13.4)	0.264

SD, standart deviation; NS, non-significant; SGA, small for gestational age, NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; PVHI, periventricular hemorrhagic infarction; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia p values obtained for, categorical variables with chi square; parametric data with t test, *non-parametric data with Mann Whitney U test.

Mann-Whitney U test for non-normally distributed variables. Receiver Operating Characteristic (ROC) analysis was performed to determine the sensitivity and specificity of predictive parameters.

Birth weight and gestational age were added as preliminary variables and corrected. SGA was included as another influencing factor. Multinomial logistic regression analysis was performed to determine independent risk factors for feeding intolerance. Gestational age and birth weight were added as covariates and SGA was added as the co-factor. The results were presented as an Odds ratio (OR) with a 95% confidence interval (CI). All differences were accepted as statistically significant if a p value was under 0.05. A posthoc power analysis also calculated by (sample A) in preeclamptic group proportion of FI was 0.55 and 0.36 (in sample B), a difference of proportions was 0.19, 95%CI (0.09-0.28), z: 3.931, p<0.0001, power: 0.9758.

Results

Eight hundred and twenty infants completed the corrected two years of age follow-up. Seven hundred and one infants had all clinical data (missing data n=119). There were statistical differences between infants with maternal preeclampsia (n=128) and without (n=573), in terms of mean birth weight, mean gestational age, grade 3-4 IVH, platelet count, being under 3rd percentile of body weight during discharge from NICU and feeding intolerance. There was no significant difference on the day of first feeding, fully enteral feeding day and time of catching birth weight. All clinical parameters are summarized in Table 1. Sensitivity, specificity, and AUC with 95%CI of parameters associated with feeding intolerance are mentioned in Table 2. ROC curves of statistically significant parameters associated with feeding intolerance are shown in Figure 1. After correcting the data with birth weight and gestational age and SGA as a cofactor, nominal regression revealed that PE strongly may be an independent risk factor for FI in this study group [OR: 5.469 (95%CI 1.099-2.929) p=0.019] (Table 3).

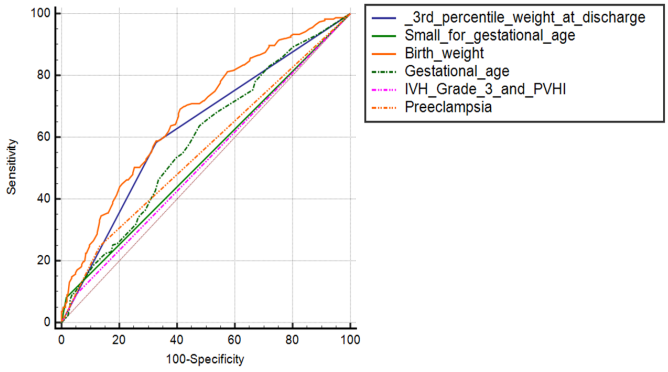

Figure 1. ROC curves of the parameters.

Table 2. Sensitivity, specificity and AUC of parameters associated with feeding intolerance.

Factor	AUC	CI (%95)	Sensitivity, %	Specificity, %	P value
Birth weight	0.695	0.658-0.730	72.3	58.4	<0.001
Gestational age	0.594	0.556-0.632	65.9	51.8	<0.001
SGA	0.533	0.492-0.573	8.1	98.4	<0.001
IVH Grade 3 and PVHI	0.537	0.498-0.576	12.7	94.7	0.012
Preeclampsia	0.560	0.521-0.598	25.1	86.7	<0.001
<3rd percentile weight at discharge	0.628	0.588-0.667	58.3	67.2	<0.001

AUC, area under curve; CI, confidence interval; SGA, small for gestational age; IVH, intraventricular hemorrhage; PVHI, periventricular hemorrhagic infarction.

Table 3. Logistic regression analyze of parameters associated with feeding intolerance.

Factor	OR	CI (%95)	P value
Birth weight	4.112	1.000-1.003	0.043
Gestational age	0.955	0.905-1.348	0.328
SGA	1.200	0.734-2.984	0.273
IVH Grade 3 and PVHI	0.969	0.712-2.791	0.325
Preeclampsia	5.469	1.099-2.929	0.019

OR, Odds ratio; CI, confidence interval; SGA, small for gestational age; IVH, intraventricular hemorrhage; PVHI, periventricular hemorrhagic infarction.

Discussion

After observing feeding intolerance in a significant portion of babies with maternal preeclampsia we have demonstrated with these data that PE may be an important risk factor in premature infants with gastrointestinal intolerance. Preeclampsia causes not only the retardation of the baby's intrauterine growth but also adverse effects on the gastrointestinal system leading to impaired absorption and motility of the intestine [20]. It is possible to say that intrauterine chronic hypoxia causes all of these and we can mention that some biochemical mechanisms also affect this result.

In our study, feeding intolerance occurs in the first 12-24 hours of life and since we did not try to feed with any food other than breast milk, another risk factor did not affect the development of intolerance. The fact that the baby shows signs of intolerance at their first feeding is also a supportive finding that this event starts antenatal.

In population-based studies, long-term gastrointestinal morbidity of preterm babies increases with being small for gestational age and low gestational age [21, 22]. According to these studies, babies with lower gestational age and birth weight who were small for gestational age had more gastrointestinal intolerance than others in our study.

The correlation between maternal hypertensive disorders during pregnancy and neonatal gastrointestinal disorders was controversial [23, 24]. According to the results of our study, we can easily say that preeclampsia may be an independent risk factor for feeding intolerance in preterm babies. In this literature, they showed that feeding problems and days of hospital stay are greater in preeclamptic patients' groups [11, 25]. Our results presented that feeding intolerance was common in the preeclamptic group, but hospital stay duration was not significant between groups. Feeding intolerance and delayed transition of preterm baby to full enteral feeding may lead to postnatal growth retardation, longer hospitalization and long-term neurological problems [26]. In another study, they showed lower gestational weeks, maternal hypertension, SGA, and PDA were predictors of time to fully enteral feeding [27]. According to our results, maternal PE was associated with feeding intolerance, but we found that the time to fully enteral feeding day was longer in the preeclamptic group, and we did not find significance between PE and time to fully enteral feeding. Therefore, this issue is very valuable for the healthy nutrition of the premature baby and for the good management of the process in the neonatal intensive care unit. More extensive studies are needed on this subject.

The limitations of the study were that it was retrospective and the number of patients was small. Another important point is that antenatal magnesium exposure of the patients was not recorded. For this reason, we could not make a statement about the preeclampsia and NEC relationship appointed by Cetinkaya et al [28]. But there was no significant difference in NEC stage 2-3 patient numbers in our study.

Conclusion

Based on the results of this study, we can say that PE affects many organs and systems in premature babies and emerges as an independent risk factor for feeding intolerance. When babies of PE mothers are born, this information should be reviewed and a nutrition plan should be made, interventions and treatments to minimize fetal effects should be investigated in PE antenatal management.

Ethics approval

Clinical Study Approval was obtained from the Zekai Tahir Burak Women's Health Education and Research Hospital's Clinical Researches Ethics Committee (2011-KAEK-19) and Education-Training Planning Coordination Committee before starting the study (Date: 29.05.2018, desicion number: 24/2018).

References

1. Bernardes TP, Zwertbroek EF, Broekhuijsen K, Koopmans C, Boers K, Owens M, 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 in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2019;53(4):443-53.

2. Marins LR, Anizelli LB, Romanowski MD, Sarquis AL. How does preeclampsia affect neonates? Highlights in the disease's immunity. J Matern Fetal Neonatal Med. 2019;32(7):1205-12.
3. Yılmaz Y, Kutman HG, Ulu H, Canpolat FE, Uraş N, Oğuz SS, et al. Preeclampsia is an independent risk factor for spontaneous intestinal perforation in very preterm infants. J Matern Fetal Neonatal Med. 2014;27(12):1248-51.
4. Belden MK, Gnadt S, Ebert A. Effects of Maternal Magnesium Sulfate Treatment on Neonatal Feeding Tolerance. The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG. 2017;22(2):112-7.
5. Girsen AI, Greenberg MB, El-Sayed YY, Lee H, Carvalho B, Lyell DJ. Magnesium sulfate exposure and neonatal intensive care unit admission at term. J Perinatol. 2015;35(3):181-5.
6. Havranek T, Ashmeade TL, Afanador M, Carver JD. Effects of maternal magnesium sulfate administration on intestinal blood flow velocity in preterm neonates. Neonatology. 2011;100(1):44-9.
7. Bozkurt O, Eras Z, Canpolat FE, Oguz SS, Uras N, Dilmen U. Antenatal magnesium sulfate and neurodevelopmental outcome of preterm infants born to preeclamptic mothers. J Matern Fetal Neonatal Med. 2016;29(7):1101-4.
8. Fanaro S. Feeding intolerance in the preterm infant. Early human development. 2013;89 Suppl 2:S13-20.
9. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin Summary, Number 222. Obstet Gynecol. 2020;135(6):1492-5.
10. Moore TA, Wilson ME. Feeding intolerance: a concept analysis. Advances in neonatal care : official journal of the National Association of Neonatal Nurses. 2011;11(3):149-54.
11. Ersch J, Baenziger O, Bernet V, Bucher HU. Feeding problems in preterm infants of preeclamptic mothers. Journal of paediatrics and child health. 2008;44(11):651-5.
12. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC pediatrics. 2013;13:59.
13. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Te Pas A, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2019 Update. Neonatology. 2019;115(4):432-50.
14. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach. American journal of respiratory and critical care medicine. 2019;200(6):751-9.
15. Terrin G, Stronati L, Cucchiara S, De Curtis M. Serum Markers of Necrotizing Enterocolitis: A Systematic Review. Journal of pediatric gastroenterology and nutrition. 2017;65(6):e120-e32.
16. Mitra S, Florez ID, Tamayo ME, Aune D, Mbuagbaw L, Veroniki AA, et al. Effectiveness and safety of treatments used for the management of patent ductus arteriosus (PDA) in preterm infants: a protocol for a systematic review and network meta-analysis. BMJ open. 2016;6(7):e011271.
17. Parodi A, Govaert P, Horsch S, Bravo MC, Ramenghi LA. Cranial ultrasound findings in preterm germinal matrix haemorrhage, sequelae and outcome. Pediatric research. 2020;87(Suppl 1):13-24.
18. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Paul Chan RV, Berrocal A, et al. International Classification of Retinopathy of Prematurity, Third Edition. Ophthalmology. 2021;128(10):e51-e68.
19. O'Reilly P, Saviani M, Tou A, Tarrant A, Capra L, McCallion N. Do preterm bones still break? Incidence of rib fracture and osteopenia of prematurity in very low birth weight infants. Journal of paediatrics and child health. 2020;56(6):959-63.
20. Kim SH, Kim YJ, Shin SH, Cho H, Shin SH, Kim EK, et al. Antenatal magnesium sulfate and intestinal morbidities in preterm infants with extremely low gestational age. Pediatrics and neonatology. 2021;62(2):202-7.
21. Ohana O, Wainstock T, Sheiner E, Leibson T, Pariente G. Long-term digestive hospitalizations of premature infants (besides necrotizing enterocolitis): is there a critical threshold? Archives of gynecology and obstetrics. 2021;304(2):455-63.
22. Steiner N, Wainstock T, Sheiner E, Segal I, Landau D, Walfisch A. Small for gestational age as an independent risk factor for long-term pediatric gastrointestinal morbidity of the offspring(). J Matern Fetal Neonatal Med. 2019;32(9):1407-11.
23. Pelícia SMC, Fekete SMW, Corrente JE, Rugolo L. Impact of early-onset preeclampsia on feeding tolerance and growth of very low birth weight infants during hospitalization. Revista paulista de pediatria : orgao oficial da Sociedade de Pediatria de Sao Paulo. 2022;41:e2021203.
24. Rocha de Moura MD, Margotto PR, Nascimento Costa K, Carvalho Garbi Novaes MR. Hypertension induced by pregnancy and neonatal outcome: Results from a retrospective cohort study in preterm under 34 weeks. PloS one. 2021;16(8):e0255783.
25. Leybovitz-Haleluya N, Wainstock T, Sheiner E. Maternal preeclampsia and the risk of pediatric gastrointestinal diseases of the offspring: A population-based cohort study. Pregnancy hypertension. 2019;17:144-7.
26. Moore TA, Wilson ME, Schmid KK, Anderson-Berry A, French JA, Berger AM. Relations between feeding intolerance and stress biomarkers in preterm infants. Journal of pediatric gastroenterology and nutrition. 2013;57(3):356-62.
27. Corvaglia L, Fantini MP, Aceti A, Gibertoni D, Rucci P, Baronciani D, et al. Predictors of full enteral feeding achievement in very low birth weight infants. PloS one. 2014;9(3):e92235.
28. Cetinkaya M, Ozkan H, Koksal N. Maternal preeclampsia is associated with increased risk of necrotizing enterocolitis in preterm infants. Early human development. 2012;88(11):893-8.