International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 6 Issue 7 ǁ July 2017 ǁ PP. 18-23

Retinopathy of Prematurity – Incidence and Risk Factors in Bulgaria

Mladenov O.M.[1,2], Chernodrinska V.S.[1,2], Petkova I.T.[1,2], Dimitrova G.G.[1,2], Kemilev P.K.[1,2], Oscar A.H.[1,2], Veleva-Krusteva N.V.[1,2], Popova A.C.[2]
[1.] *Eye Clinic, University Hospital "Alexandrovska", Sofia, Bulgaria*
[2]. *Medical University, Sofia, Bulgaria*

Abstract
Purpose: *To determine the incidence of retinopathy of prematurity (ROP) in preterm infants, screened at Pediatric Eye Unit, Eye Clinic, University Hospital "Alexandrovska", Sofia, Bulgaria for a period of five years; to identify risk and prognostic factors for the manifestation and progression of the disease.*
Patients and Methods: *In the present study we examined 1490 infants, screened for ROP at Pediatric Eye Unit, Eye Clinic,University Hospital "Alexandrovska" Sofia; for the period from June 2010 to January 2016. We used diagnostic (binocular indirect ophthalmoscopy - BIO; digital fundus camera - RetCam III) and statistical methods.*
Results: *Signs of retinopathy of prematurity occurred in 339 of surveyed 1490 children(22.8%). The disease progressed to type 1 pre-threshold ROP, requiring treatment, in 110 children. The remaining 229 children showed signs of spontaneous remission. We identified significant and independent risk factors inthe child, for the development of ROP, as well as for the progression of already manifested disease to stages, requiring treatment. Such risk factors were not found in the mother.*
Conclusion: *Good early anatomical results of treatment of ROP can only be achieved witha good-functioning screening program,based on the major risk factors for onset and progression of ROP. There is a necessity of multidisciplinary approach at every stage of diagnosis and treatment of ROP.*
Keywords:*preterm infants, retinopathy of prematurity (ROP), risk and prognostic factors, screening program, treatment.*

I. INTRODUCTION

Retinopathy of prematurity (ROP) is a postnatal disorder of retinal vessels that develops in the incompletely vascularized retina of preterm infants [1]. Although this disorder regresses in most patients, it can lead to severe visual impairment. Developing countries, countries from Eastern Europe, South America, India and China are now victims of the third ROP epidemic. Thanks to the advances in neonatology and perinatal medicine in these countries, more and more premature infants born with very low and extremely low birth weight survive. This, in turn, leads to a significant increase in the number of children with vision – threatening ROP. ROP is the main cause of childhood blindness in Bulgaria, Eastern Europe, nevertheless our ROP screening and treatment guidelines [2].The main efforts are directed at the prevention of ROP, due to the fact that the prognosis of the visual function is pessimistic. This prevention is done by screening the risk groups of premature babies and early and adequate treatment.

Purpose

To determine the incidence of retinopathy of prematurity (ROP) in preterm infants, screened at Pediatric Eye Unit, Eye Clinic, University Hospital "Alexandrovska", Sofia, Bulgaria for a period of five years; to identify risk and prognostic factors for the manifestation and progression of the disease.

II. PATIENTS AND METHODS

We examined all preterm infants, screened for ROP at Pediatric Eye Unit, Eye Clinic, University Hospital "Alexandrovska", Sofia, Bulgaria,for the period June 2010 – January 2016 – 1490 children.Most children were born prematurely with birth weight less than 1500 grams and gestational age below 32 weeks; and some patients were born with birth weight less than 2500 grams with a complicated postnatal period– instrument ventilation, blood transfusion and exchange, phototherapy, underlying disease, cerebral hemorrhage.Ophthalmologists from our clinic performed screening for ROP in neonatal intensive units in the capital of Bulgaria - Sofia and children referred to our clinic by various centers in the country. Examination of the retina was performed after pupil dilation with mydriatic combination of Phenylephrine 2,5% and Cyclopentolate 0,5%, the application of local anesthesia (0,5% Proxymetacaine Hydrochloride) and eye

speculum. Retinal changes were documented with RetCam imaging system (Clarity Medical systems Inc., Pleasanton, CA, USA).Examinations were continued until the retina was fully vascularized. If it was necessary,the children were treated with transpupilary diode laser photocoagulation (IridexOculightSLx Tri-Mode 810nm Diode Laser®); cryotherapy (cryoablation) or intravitreal administration of anti-VEGF medications.The indication for treatment was pre-threshold type 1 ROP.

For the purpose of the study, our patients (1490 children) were divided into the following groups:

- Group I - patients who did not develop ROP (N = 1151)
- Group II - patients who developed ROP (N = 339)
- Group IIA - patients who developed ROP and who had spontaneous regression (untreated) - (N = 229)
- Group IIB - patients with progressive ROP, treated (N = 110).

The SPSS version 13.0 (USA, Chicago, SPSS Inc., Version 13.0) has been used to process statistically the survey data.Chi-square test was used to analyze qualitative variables. Fisher's test were used for quantitative variables. The coefficient of confidence of this study was 0.95. A difference with $P < 0.05$ was considered statistically significant.

III. RESULTS

Signs of ROP were observed in 339 children (22.8%) of all 1490 children. In 110 children, the disease progressed to type 1 pre-threshold ROP, requiring treatment (7.4% of the total screened group). The remaining 229 children (15.4% of the whole group) showed signs of spontaneous regression (type 2 pre-threshold ROP). Regarding the severity of ROP, from all 339 children, who developed the disease, 135 children (39.8%) hadROP Stage I; 86 children (25.4%) - Stage II; 103 children (30.4%) - Stage III; 4 children (1.1%) - Stage IVA and 11 children (3.2%) - Stage V.

Our main goal in this study was to identify pre-, peri- and postnatal risk factors on the part of the child and the mother, which may help early detection of children at risk of developing ROPandchildren with clinically manifested disease, that may progress to treatment-requiring stages (type 1 pre-threshold ROP).

In the assumed risk factors, selection of the statistically significant ones were made - for the development of ROP and for the regression or progression of an already developed disease - a comparison between the Group I and the Group II; and respectively between Group IIA and Group IIB. In the next step, a multiple logistic regression analysis of the significant risk factors was performed to establish whether there were independent significant risk factors for both development / non-development of ROP, as well as for the regression / progression of an existing disease.

We examined 23 (twenty three) potential risk factors inthe child in relation to treatment in a neonatal unit and developed diseases in pre-, peri- and neonatal period: birth weight (BW) and the degree of prematurity (Degree I - 2000 to 2499 g.; Degree II - 1500 to 1999 g.; Degree III - 1000 to 1499 g.; Degree IV- <999 g.), gestational age (GA), sex, singleton / multiple pregnancies, invasive mechanical ventilation (IMV), non-invasive mechanical ventilation (NIMV), oxygen supplementation, exogenous surfactant administration, phototherapy, number of blood transfusions (HT), respiratory distress syndrome (RDS) intrapartum asphyxia (IA), hyperbilirubinemia (HB), bronchopulmonary dysplasia (BPD), chronic lung disease (CLD), patent ductus arteriosus (PDA), intrauterine hypotrophy (IUH), anemia of prematurity, necrotizing enterocolitis (NEC), neonatal pneumonia, intraventricular hemorrhage (IVH) - by grade, subependymal hemorrhage (SEH)posthaemorrhagic hydrocephalus (Table I).

Table I. Potential risk factors in the child for development of ROP.

Groups	**Group I vs Group II**	**Group IIA vs Group IIB**
Risk Factors		
Degree I of prematurity	$p < 0.001$	$p > 0.05$
Degree IIof prematurity	$p < 0.001$	$p > 0.05$
Degree IIIof prematurity	$p < 0.001$	$p < 0.001$
Degree IVof prematurity	$p < 0.001$	$p < 0.001$
Gestational Age (GA)	$p < 0.001$	$p < 0.001$
Sex	$p = 0.575$	$p = 0.632$
Singleton / multiple pregnancies	$p = 0.763$	$p > 0.05$
Invasive mechanical ventilation (IMV)	$p < 0.001$	$p = 0.909$
Non-invasive mechanical ventilation (NIMV)	$p < 0.001$	$p = 0.154$
Exogenous surfactant administration	$p < 0.001$	$p = 0.532$
Number of blood transfusions (HT)	$p > 0.05$	$p > 0.05$
Phototherapy	$p = 0.042$	$p = 0.019$
Hyperbilirubinemia (HB)	$p = 0.057$	$p = 0.059$
Respiratory distress syndrome (RDS)	$p < 0.001$	$p = 0.903$
Intrapartum asphyxia (IA)	$p = 0.340$	$p = 0.281$
Bronchopulmonary dysplasia (BPD)	$p < 0.001$	$p = 0.169$
Chronic lung disease (CLD)	$p < 0.001$	$p = 0.391$

Neonatal pneumonia	p < 0.001	p = 0.517
Patent ductus arteriosus (PDA)	p < 0.001	p = 0.278
Anemia	p < 0.001	p < 0.001
Necrotizing enterocolitis (NEC)	p = 0.525	p = 0.758
Intrauterine hypotrophy (IUH)	p = 0.008	p = 0.557
Intraventricular hemorrhage (IVH) – Grade I	p = 0.125	p = 0.247
Intraventricular hemorrhage (IVH) – Grade II	p = 0.684	p < 0.001
Intraventricular hemorrhage (IVH) – Grade III	p < 0.001	p = 0.643
Intraventricular hemorrhage (IVH) – Grade IV	p = 0.783	p = 0.661
Subependymal hemorrhage (SEH)	p < 0.001	p = 0.001
Posthaemorrhagic hydrocephalus	p = 0.475	p = 0.179

After a multiple logistic regression analysis, independent and significant risk factors for the onset of ROP werefound to be (Table II) -*Degree III and IV of prematurity; Gestational age (GA); IMV, NIMV; RDS, BPD, PDA, IUH, anemia of prematurity, IVH Grade III, SEH*. While *phototherapy* used to treat Hyperbilirubinemia (HB), has been a protective factor for the development of ROP after logistic analysis. We believe that phototherapy acts as a significant protective factor for the onset of ROP, because when it is applied adequately to avoid complications from advanced clinical HB, and there is no need for haemotransfusion, which is a risk factor for the development of ROP.

TableII. Independent and significant fetal risk factors for the development of ROP (a comparison between Group I and Group II)

Risk Factor	**OR**	**95% CI**		**p**
Degree IIIof prematurity	2,339	1,131	4,838	0,022
Degree IVof prematurity	3,650	1,570	8,487	0,003
Gestational Age (GA)	-0,693	0,639	0,752	<0,001
IMV	1,515	1,063	2,159	0,022
NIMV	2,853	1,914	4,253	<0,001
RDS	2,813	1,915	4,131	<0,001
BPD	2,755	1,953	3,885	<0,001
PDS	1,628	1,064	2,490	0,025
IUH	1,567	0,333	0,964	0,036
Anemia	1,601	1,168	2,195	0,003
IVH – Grade III	2,263	1,530	3,349	<0,001
SEH	2,769	1,973	3,887	<0,001

OR – Odds Ratio; CL – Confidence Interval

After a multiple logistic regression analysis, independent and significant risk factors were established (by the fetus) to progression of already developed ROP to treatment - requiring stages of ROP (Table III) - *Degree IV of prematurity; gestational age (GA); anemia, intraventricular hemorrhage (IVH) – Grade II, subependymal hemorrhage (SEH).*

TABLE III. Independent and significant fetal risk factors for the progression of an existing ROP to stages, requiring treatment (a comparison between Group IIA and Group IIB).

Risk Factor	**OR**	**95% CI**		**p**
Anemia	1,601	1,168	2,195	0,003
IVH – Grade II	1,246	0,107	0,567	0,001
SEH	2,051	1,220	3,448	0,007
Degree IVof prematurity	8,260	1,019	66,946	0,048
Gestational Age (GA)	-0,752	0,680	0,832	<0,001

OR – Odds Ratio; CL – Confidence Interval

We also tested 10 (ten) potential maternal risk factors for both development / non-development of ROP (a comparison between Group I and Group II), and spontaneous regression / progression of the disease to type 1 pre-threshold ROP, requiring treatment (a comparison between Group IIA and Group IIB) (Table IV): maternal-fetal infections (MFI) and intra-amniotic infection (IAI); mechanism of conception; mechanism of birth (PVN – per viasnaturalis; SC – Sectio Caesarea); premature rupture of membrane (PROM >24 h.); the presence of preeclampsia; placental detachment; interventions on the cervix of uterus; gestational diabetes and Hashimoto's thyroiditis.

TABLE IV. Potential maternal risk factors for development of ROP.

Groups	**Group I vs Group II**	**Group IIA vs Group IIB**
Risk Factors		
Maternal-fetal infections (MFI)	p = 0.029	p = 0.020
Intra-amniotic infection (IAI)	p = 0.129	p = 0.924
Mechanism of conception	p < 0.001	p = 0.006
Mechanism of birth (PVN, SC)	p = 0.739	p = 0.394
Preeclampsia	p = 0.205	p = 0.909
Placental detachment	p = 0.141	p = 0.797
Premature rupture of membrane (PROM >24 h.)	p = 0.444	p = 0.314
Interventions on the cervix of uterus	p = 0.182	p = 0.781
Gestational diabetes	p = 0.473	p = 0.309
Hashimoto's thyroiditis	p = 0.475	p = 0.179

On the mother's side, a statistically significant difference between patients who did not have and who had signs of ROP (a comparison between Group I and Group II), and between spontaneously regressing and progressing to treatment requiring stages (a comparison between Group IIA and Group IIB) showed:*Maternal-fetal infections (MFI) and Mechanism of birth (PVN, SC).*After conducting a multiple logistic analysis, they did not prove as significant and independent risk factors for the onset and progression of ROP.

IV. DISCUSSION

Incidence of ROP in Bulgaria (22.8%) is comparable with other authors in developed and developing countries with similar demographic characteristics with our country –Brazil (25.5%) [3], 38.3% - 41.4% [4], 34% [5]; India (27%) [6], Norway (10%) [7], Oman (34%) [8], Finland (27.3%) [9], Australia (16%) [10] and Singapore (29.3%) [11].In Bulgaria, there is a tendency to increase the incidence of ROP - reported data are 5.4%, 11.2%, 18.5%, 25.7% to 30.3% [12]. The main reason for this is the progress in both obstetrics and neonatal care, which ensures the survival of more immature infants. This leads to increase not only in the incidence of ROP, but also in increase of the severe aggressive-posterior form of the disease - AP-ROP [12].

The results in our study, regarding birth weight (BW) and gestational age (GA), are comparable to those of other Bulgarian and foreign authors. The low BW and the high degrees of prematurity (Degree III and IV of prematurity) as well as the low GA [13,14,15,6,17]are significant risk factors for development and progression of the disease to treatment-requiring stages [13, 14, 15]. BW and GA are key indicators in the screening programs for ROP,both in the world and in Bulgaria.

ProlongedIMV and NIMV in a significant number of publications are found by the authors that are associated with an increased risk of development of ROP [13,17,18,19]. In our study the results are the same.

There are opposite views in literature concerning the fetal diseases, which are risk factors for the development and progression of ROP. Some authors, like us, find that RDS is a significant risk factor for the development of ROP [13,17];there are opposite opinions [15,20]. Some studies confirm our results that BPD is a significant risk factor for the development of ROP [21,22], while others reject them [23]. Our results confirm some publications, in which PDA is found to be significant risk factor for the onset of ROP [24, 25]. However, other publications deny the role of PDA [21, 26]. Some authors have reported, as in our study, that anemia of prematurity is a significant risk factor for the development of ROP [23,27]; while there are opposite views [28]. The IUH is considered to be a significant risk factor for the development of ROP in some studies [29, 30], while others deny this fact [31]. IVH – Grade IIIand SEH are identified significant risk factors for the development of ROP in some publications [17, 23], whereas according to other authors it is not the case[22, 26].

We believe that our established significant fetal risk factors for development of ROP and progression to stages, requiring treatment; should be considered by the screening ophthalmologist. Screening premature infants who developed signs of ROP that would progress to stages, needingtreatment is a key point in fighting with this socially significant disease.

In the available literature, there were publications that confirmed the negative results we found about the maternal risk factors, that are not significant and independent risk factors for the onset and progression of ROP: maternal-fetal infections (MFI) and intra-amniotic infection (IAI) [12], mechanism of birth (PVN, SC) [12, 31], mechanism of conception[12, 32], preeclampsia [33,34], placental detachment [12, 33], premature rupture of membrane (PROM >24 h.)[12,17,33]; interventions on the cervix of uterus [12,31] and gestational diabetes [121, 35, 36]. Although in our study maternal risk factors are not significant and independent risk factors for the developmentand progression of ROP, we believe that MFI, mechanism of birth and conception, preeclampsia, placental detachment, PROM > 24 hours; interventions on the cervix of uterus and gestational diabetes; should be considered by screening ophthalmologists, because they may cause premature birth and the negative consequences of it, ROP in particular.

V. CONCLUSION

Advances in neonatal and perinatal medicine create conditions for increased survivability of a growing number of children born prematurely. This determines the increasing number of children who are at risk of developing ROP and related early and late visual impairment and blindness. The good structural and functional results after therapy for ROP are achieved thanks to a functioning screening program (based on the main risk factors for the development and progression of ROP) for early detection of risk premature infants and timely and adequate treatment of the disease. It is necessary a multidisciplinary approach at each stage of the diagnosticsand treatment of ROP.

REFERENCES

[1] Phelps DL. Retinopathy of Prematurity. In: Martin RJ, Fanaroff AA, Walsh MC, eds. Fanaroff& Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. Vol 1 9th ed. Missouri: Elsevier Mosby, 2011: 1764-9.

[2] Chernodrinska V., Veleva N.,Kemilev P. Guidelines for screening and treatment of ROP in Bulgaria. Medical University – Sofia, Bulgaria, 2016.

[3] Fortes Filho JB, Echert GU, Valiatti FB. et al. Prevalence of retinopathy of prematurity: an institutional cross-sectional study of preterm infants in Brazil. Pan Am J Public Health 2009; 26(3):2016-220.

[4] Eliason KJ, Osborn JD, Amsel E, and Richards SC. Incidence, progression, and duration of retinopathy of prematurity in hispanic and white non-hispanic infants. J AAPOS 2007;11:447-451.

[5] Bullard SR., Donahue SP, Feman SS et al. The decreasing incidence and severity of retinopathy of prematurity. J AAPOS 1999;3:46-52.

[6] Maheshwari R, Kumar H, Paul VK, Singh M, Deorari AK, Tiwari HK. Incidence and risk factors of retinopathy of prematurity in a tertiary care newborn unit in New Delhi. Natl Med J India. 1996;9(5):211–4.

[7] Haugen OH, Markestad T. Incidence of retinopathy of prematurity (ROP) in the western part of Norway. A population-based retrospective study. ActaOphthalmol Scand. 1997;75(3):305–7.

[8] Bassiouny MR. Risk factors associated with retinopathy of prematurity: a study from Oman. J Trop Pediatr. 1996;42(6):355–8.

[9] Lappi M. Retinopathy of prematurity in southern Finland. ActaOphthalmol Suppl. 1993;(210):56–8.

[10] Smith J, Spurrier N, Goggin M. Retinopathy of prematurity in a South Australian neonatal intensive care unit. Australian and New Zealand Journal of Ophthalmology. 1995;23(1):49–54. doi: 10.1111/j.1442-9071.1995.tb01645.x.

[11] Shah VA, Yeo CL, Ling YL, Ho LY. Incidence, risk factors of retinopathy of prematurity among very low birth weight infants in Singapore. Ann Acad Med Singapore. 2005;34(2):169–78.

[12] Marinov V. Retinopathy of the Prematurity - Incidence, Predictive Factors, Stages and Behavior. Dissertation work. 2013, Bulgaria, Plovdiv

[13] Akkiyun I, Oto S, Yilmaz G. et al. Risk factors in development of mild and severe retinopathy of prematurity. J AAPOS 2006;10:49-453.

[14] Liu Q; Yin ZQ; Ke N. et al. Incidence of retinopathy of prematurity in southwestern China and analysis of risk factors. Medical Science Monitor 2014;20:1442-51.

[15] Ke XY, Ju RH, Zhang JQ. et al. Risk factors for severe retinopathy of prematurity in premature infants: a single-center study. J South Med Univ 2011;31(12):1963-1967.

[16] Fortes Filho JB, Eckert GU, Valiati FB. et al. The influence of gestational age on the dynamic behavioral of other risk factors associated with retinopathy of prematurity (ROP). Graefes Arch ClinExpOphthalmoldoi 10.1007/s00417-009-1248-6.

[17] Yang CY, Lien R, Yang PH. et al. Analysis of incidence and risk factors of retinopathy of prematurity among very-low-birth-weight infants in north Taiwan. Pediatrics and Neonatology 2011;52:321-326.

[18] Shin DH; Kong M; Kim SJ. et al. Risk factors and rate of progression for zone I versus zone II type 1 retinopathy of prematurity. J AAPOS 2014;18(2):124-8.

[19] van Sorge AJ; Termote JU; Kerkhoff FT. et al. Nationwide inventory of risk factors for retinopathy of prematurity in the Netherlands. Journal of Pediatrics 2014. 164(3):494-498.e1.

[20] Karna P, Muttineni J, Angell L, Karmaus W. Retinopathy of prematurity and risk factors: a prospective cohort study. BMC Pediatrics 2005;5:18 available at www.biomedcentral.com/1471-2431/5/18.

[21] Yau GS; Lee JW; Tam VT. et al. Incidence and risk factors for retinopathy of prematurity in extreme low birth weight Chinese infants. International Ophthalmology 2015;35(3):365-73.

[22] Weintraub Z; Carmi N; Elouti H; Rumelt S. The association between stage 3 or higher retinopathy of prematurity and other disorders of prematurity. Canadian Journal of Ophthalmology 2011;46(5):419-24.

[23] Yau GS; Lee JW; Tam VT. et al. Incidence and risk factors for retinopathy of prematurity in multiple gestations: a Chinese population study. Medicine 2015;94(18):e867.

[24] Sarikabadayi YU; Aydemir O; Ozen ZT. et al. Screening for retinopathy of prematurity in a large tertiary neonatal intensive care unit in Turkey: frequency and risk factors. Ophthalmic Epidemiology 2011;18(6):269-74.

[25] Kumar P; Sankar MJ; Deorari A. et al. Risk factors for severe retinopathy of prematurity in preterm low birth weight neonates. Indian Journal of Pediatrics 2011;78(7):812-6.

[26] Hakeem AH; Mohamed GB; Othman MF. Retinopathy of prematurity: a study of prevalence and risk factors. Middle East African journal of ophthalmology 2012;19(3):289-94.

[27] Zhu L; Shi WJ; Zhang SL et al. Evaluation of risk factors for retinopathy of prematurity. Chinese Medical Journal 2011;91(25):1749-52.

[28] Englert A, Saunders A, Purohit D. et al. The effect of anemia on retinopathy of prematurity in extremely low birth weight infants. Journal of Perinatology 2001;21:21-26.

[29] Dhaliwal CA, Fleck BW, Wright E, Graham C, McIntosh N. Retinopathy of prematurity in small-for-gestational age infants compared with those of appropriate size for gestational age. Arch Dis Child Fetal Neonatal Ed 2009; 94: F193–95.

[30] Lee JW, VanderVeen D, Allred EN, Leviton A, Dammann O. Prethreshold retinopathy in premature infants with intrauterine growth restriction. ActaPaediatr 2015;104(1):27-31. doi: 10.1111/apa.12799.

[31] Abrishami M, Maemori GA, Boskabadi H. et al. Incidence and Risk Factors of Retinopathy of Prematurity in Mashhad, Northeast Iran. Iran Red Crescent Med J 2013;15(3): 229–233.

[32] McKibbin M, Dabbs TR. Assisted conception and retinopathy of prematurity. Eye 1996;10:476-478.

[33] Higgins RD, Mendelsohn AL, De Feon MJ. et al. Antenatal dexamethasone and decreased severity of retinopathy of prematurity. Arch Ophthalmol 1998;116:601-605.
[34] Huang HC; Yang HI; Chou HC. et al. Preeclampsia and Retinopathy of Prematurity in Very-Low-Birth-Weight Infants: A Population-Based Study. PLoS ONE [Electronic Resource] 2015;10(11):e0143248.
[35] Kavurt S, Ozcan B, Aydemir O. et al. Risk of Retinopathy of Prematurity in Small for Gestational Age Premature Infants. Indian pediatrics 2014;51:804-806.
[36] Yu XD, Branch DW, Karumanchi SA, Zhang J. Preeclampsia and Retinopathy of Prematurity in Preterm Births. Pediatrics 2012;130(1):e101-e107.