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Przemysław Kiciński[1], Beata Małachowska[2], Krystyna Wyka[3], Ewa Gulczyńska[4]

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The role of fibroblast growth factor-2 in the development of bronchopulmonary dysplasia in very and extremely low birth weight infants

Rola czynnika wzrostu fibroblastów-2 w rozwoju dysplazji oskrzelowo-płucnej u noworodków z bardzo małą i ekstremalnie małą urodzeniową masą ciała

[1] Department of Angiology, Medical University of Lodz, Łódź, Poland
[2] Department of Biostatistics and Translational Medicine, Medical University of Lodz, Łódź, Poland
[3] Department of Paediatrics, Oncology and Haematology, Medical University of Lodz, Łódź, Poland
[4] Department of Neonatology, Polish Mother's Memorial Hospital – Research Institute, Łódź, Poland
Correspondence: Przemysław Kiciński, Department of Angiology, Medical University of Lodz, Żeligowskiego 7/9, 90-752 Łódź, Poland, e-mail: kicinskiprzemko@gmail.com

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ORCID iDs
1. Przemysław Kiciński https://orcid.org/0000-0001-5082-0216
2. Beata Małachowska https://orcid.org/0000-0003-4009-8797
3. Krystyna Wyka https://orcid.org/0000-0002-6599-8188
4. Ewa Gulczyńska https://orcid.org/0000-0003-2713-5258

Abstract

Introduction and objective: The aim of the study was to assess the association between serum levels of fibroblast growth factor-2 (FGF-2) in infants in the first week of life and the risk of developing bronchopulmonary dysplasia. **Materials and methods:** The study included 103 infants, born before 32 weeks of gestation with a birth weight ≤1,500 g. Serum FGF-2 levels were measured in all newborns on days 1 and 7 of life. **Results:** Analysing the dynamics of changes in serum FGF-2 level, a statistically significant positive correlation was observed for birth weight ($R = 0.20$, $p = 0.0423$) in the first week of life. However, no statistically significant correlation was found for gestational age ($R = 0.06$, $p = 0.5146$). Infants with bronchopulmonary dysplasia had significantly lower gestational age than those without bronchopulmonary dysplasia ($p < 0.0001$) and birth weight ($p < 0.0001$). No statistically significant correlation was found between the dynamics of changes in serum FGF-2 level in the first week of life and the risk of bronchopulmonary dysplasia development for the definition of bronchopulmonary dysplasia on day 28 of life ($p = 0.5330$), and for the definition as the need for supplemental oxygen and/or respiratory support at 36 weeks of postmenstrual age ($p = 0.7914$). **Conclusions:** The study found no association between the serum FGF-2 level in the first week of life and the risk of bronchopulmonary dysplasia development in infants born before 32 weeks of gestation with a birth weight ≤1,500 g. In the study group, a statistically significant positive correlation was found for birth weight. In our study, gestational age and birth weight were found to be among the major risk factors for the development of bronchopulmonary dysplasia.

Keywords: risk factors, bronchopulmonary dysplasia, lung development, fibroblast growth factor-2

Streszczenie

Wprowadzenie i cel: Czynnik wzrostu fibroblastów-2 (*fibroblast growth factor-2*, FGF-2) pełni ważną funkcję zarówno w procesach naprawy, jak i podczas tworzenia naczyń krwionośnych. Celem badania była ocena zależności pomiędzy stężeniem FGF-2 w surowicy w pierwszym tygodniu życia a ryzykiem rozwoju dysplazji oskrzelowo-płucnej. **Materiał i metody:** Badaniem objęto 103 noworodki urodzone przed 32. tygodniem ciąży z masą ciała ≤1500 g. Oznaczenie stężenia FGF-2 w surowicy wykonano u wszystkich noworodków w pierwszej i siódmej dobie życia. **Wyniki:** Analizując dynamikę zmiany stężenia FGF-2 w surowicy w pierwszym tygodniu życia, obserwowano istotną statystycznie dodatnią korelację dla urodzeniowej masy ciała ($R = 0{,}20$, $p = 0{,}0423$). Z kolei nie stwierdzono istotnego statystycznie związku w dynamice zmiany stężenia FGF-2 w surowicy w pierwszym tygodniu życia a wiekiem ciążowym ($R = 0{,}06$, $p = 0{,}5146$). Noworodki z dysplazją oskrzelowo-płucną miały istotnie statystycznie niższy wiek ciążowy ($p < 0{,}0001$) oraz urodzeniową masę ciała ($p < 0{,}0001$) niż dzieci bez dysplazji. Nie stwierdzono istotnego statystycznie związku pomiędzy dynamiką zmiany w poziomie FGF-2 w surowicy w pierwszym tygodniu życia a ryzykiem rozwoju dysplazji oskrzelowo-płucnej dla definicji dysplazji w 28. dobie życia ($p = 0{,}5330$) i dla definicji stosowania suplementacji tlenem i/lub wentylacji dodatnim ciśnieniem w 36. tygodniu wieku

postkoncepcyjnego (p = 0,7914). **Wnioski:** W przeprowadzonym badaniu nie znaleziono związku pomiędzy stężeniem FGF-2 w surowicy w pierwszym tygodniu życia a ryzykiem rozwoju dysplazji oskrzelowo-płucnej u noworodków urodzonych przed 32. tygodniem ciąży z masą ciała ≤1500 g. Jednakże w badanej grupie stwierdzono istotną statystycznie dodatnią korelację pomiędzy dynamiką zmiany stężenia FGF-2 w surowicy w pierwszym tygodniu życia a urodzeniową masą ciała. W naszym badaniu wiek ciążowy i urodzeniowa masa ciała są jednymi z głównych czynników rozwoju dysplazji oskrzelowo-płucnej.

Słowa kluczowe: czynniki ryzyka, dysplazja oskrzelowo-płucna, rozwój płuc, czynnik wzrostu fibroblastów-2

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a chronic lung disease associated with preterm birth[1,2]. It remains a major clinical problem, and its incidence has not decreased over the years[3–5]. The disruption in normal lung development and the requirement of oxygen therapy in premature infants are the key underlying causes of the disease. The current definition of BPD is based on the supplemental oxygen and/or respiratory support at 28 days of life and at 36 weeks postmenstrual age[1,2,6].

Improvements in perinatal and neonatal care enable even the most immature infants to survive. At the same time, over the years, a change in the clinical presentation of the disease has been observed. Recently, "new" bronchopulmonary dysplasia has been described. The new form of BPD occurs mainly in very and extremely low birth weight infants and is associated with the impairment in the physiological process of lung maturation[1,6].

Environmental and genetic factors play an important role in the process of lung maturation. Disadvantageous pre- and postnatal factors result in impairment and/or arrest in alveolar and blood vessel formation. Then, repair processes are initiated, leading to the formation of fewer and larger alveoli and a dysmorphic pulmonary vasculature[1,7,8].

Fibroblast growth factors are expressed in almost all tissues, where they play an important role in tissue maintenance, regeneration, repair, and metabolism. They are essential in the earliest stages of embryonic development as well as during organogenesis[9,10]. Fibroblast growth factor-2 (FGF-2), also known as basic fibroblast growth factor (bFGF), have a key role both in repair processes and in the formation of blood vessels[9,11]. FGF-2 was found to be expressed in a variety of human foetal tissues in early second trimester of pregnancy, suggesting its contribution to the process of development and maturation[12].

Our study aimed at identifying the mechanisms responsible for the process of lung maturation in premature neonates. Knowledge of the underlying molecular mechanisms may be important in better understanding the pathogenesis of BPD and may help in the formulation of new treatment options[1,4,13]. The role of fibroblast growth factors in the development of BPD in premature neonates is poorly understood. However, judging from research conducted mainly in animal models, it seems that they may be of great importance[5,6,9].

The aim of the study was to evaluate the association between serum FGF-2 level on days 1 and 7 of life and the risk of BPD in infants born before 32 weeks of gestation with very and extremely low birth weight.

MATERIALS AND METHODS

It was a prospective study conducted at the Department of Neonatology, Polish Mother's Memorial Hospital – Research Institute. The following inclusion criteria were applied:

- gestational age <32 weeks gestation (from $23^{0/7}$ to $31^{6/7}$);
- birth weight ≤1,500 g;
- lack of severe congenital anomalies or other congenital genetic syndromes;
- written consent of parents/legal guardians to the infant's participation in the study.

The study included a total of 103 infants. The median gestational age was 28.9 weeks, and the interquartile range (IQR) was 27.3–30.1 weeks. The median birth weight was 1,100.0 g, with the interquartile range (IQR) of 950.0–1,300.0 g. There were 58 (56.3%) male and 45 (43.7%) female infants.

To perform the analysis, the infants were divided into the following groups: with diagnosed bronchopulmonary dysplasia – BPD (+) and those not meeting the criteria for the diagnosis of bronchopulmonary dysplasia – BPD (–). Oxygen requirement >21% of mixture of respiratory gases and/or respiratory support for at least 28 days were assumed as the criterion for BPD diagnosis. An additional analysis was performed using BPD definition as the need for supplemental oxygen and/or respiratory support at 36 weeks of postmenstrual age[2].

A review of the clinical picture, additional tests, and selected pre- and postnatal factors was performed in all infants. The respiratory system was assessed thoroughly, analysing the duration of respiratory support, mechanical ventilation, nasal continuous positive airway pressure (nCPAP) respiratory support, oxygen therapy, and oxygen concentration in gas mixture (FiO_2).

On days 1 and 7 of life, 1 ml of whole blood was drawn and then centrifuged at 4°C for 20 minutes at 1,000 × g. The obtained serum was stored at −80°C until determination.

Measurements of serum FGF-2 levels were performed using commercially available assays: Quantikine ELISA, Human FGF Basic Immunoassay (R&D Systems, Inc., Minneapolis, MN, USA) with MPR-96 Microplate Reader (Dynamica, Dietikon, Swiss). The measurements were performed at the Laboratory of Immunopathology and Genetics, Department of Paediatrics, Oncology and Haematology, Medical University in Lodz.

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The study was approved by the Bioethics Committee of Polish Mother's Memorial Hospital – Research Institute (No. 81/2017).

Statistical analysis

Nominal variables were given as numbers with appropriate percentages, whereas continuous variables were expressed as medians (*Me*) with interquartile ranges (IQR). For continuous variables, unpaired comparisons between BPD and no BPD groups were done with the Mann–Whitney test. Paired comparisons of FGF-2 levels were calculated using the Wilcoxon test. FGF-2 levels were log-transformed, and repeated ANOVA measures were performed to assess the association between the BPD status and change of FGF-2 at two time points. Post-hoc comparisons were not performed, as no ANOVA results passed the significance threshold. Correlation coefficients were calculated with Spearman's rank test. p values <0.05 were considered statistically significant. STATISTICA 13.0 (Statsoft, Tulsa, OK, USA) was used for statistical analysis.

RESULTS

In the studied group of 103 infants, the median of serum FGF-2 level on day 1 of life was 4.69 pg/mL (IQR 3.02–8.47 pg/mL), and on day 7 it was 4.96 pg/mL (IQR 2.75–8.73 pg/mL). The change was statistically insignificant (p = 0.8312). Analysing the dynamics of changes in serum FGF-2 levels, a statistically significant positive correlation was observed for birth weight (R = 0.20, p = 0.0423) in the first week of life (Fig. 1). However, there was no statistically significant correlation between the dynamics of changes in serum FGF-2 levels in the first week of life and gestational age (R = 0.06, p = 0.5146) (Fig. 2).

In accordance with the definition, on day 28 of life, a total of 51 (49.5%) patients were included in the BPD group and 52 (50.5%) patients in the group without BPD. Infants with BPD had significantly lower gestational age (p < 0.0001) and birth weight (p < 0.0001) than those without BPD. Demographics and clinical characteristics in the groups with and without BPD are shown in Tab. 1.

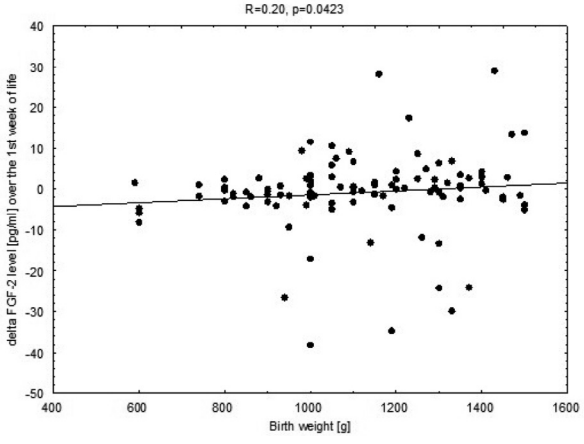

Fig. 1. Dynamics of changes in serum FGF-2 level in the first week of life and birth weight in the studied group of newborns

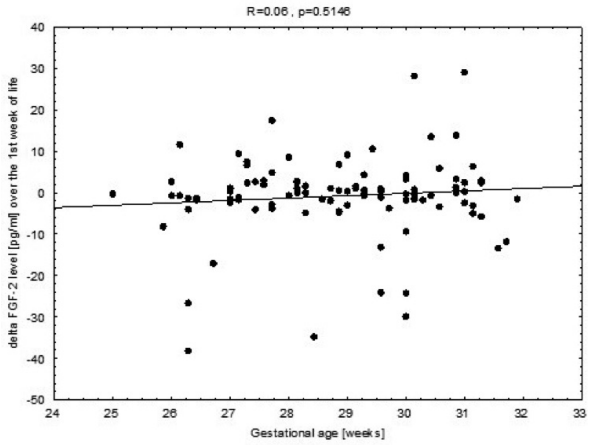

Fig. 2. Dynamics of changes in serum FGF-2 level in the first week of life and gestational age in the studied group of newborns

In the group of infants in whom BPD was diagnosed on day 28 of life, the median of serum FGF-2 level was 4.60 pg/mL (IQR 2.75–8.22 pg/mL) on day 1 of life, and in the group without BPD 4.91 pg/mL (IQR 3.29–8.63 pg/mL). On day 7 of life, the median of serum FGF-2 level in the study groups was 4.63 pg/mL (IQR 2.75–7.84 pg/mL) vs. 5.36 pg/mL (IQR 2.99–9.49 pg/mL), respectively. No statistically significant difference was observed in the dynamics of changes in serum FGF-2 levels between the studied groups (p = 0.5330) (Fig. 3).

At 36 weeks postmenstrual age, a total of 18 (17.5%) infants required supplemental oxygen and/or respiratory support, whereas 85 (82.5%) remained breathing on their own and required no supplemental oxygen. The median of serum FGF-2 level in the group of infants requiring supplemental oxygen and/or respiratory support was 4.34 pg/mL (IQR 2.96–6.67 pg/mL) on day 1 of life and 4.09 pg/mL (IQR 2.75–5.61 pg/mL) on day 7 of life. However, for newborns breathing air on their own it was 4.69 pg/mL (IQR 3.28–8.47 pg/mL) on day 1 of life and 5.12 pg/mL (IQR 2.68–9.24 pg/mL) on day 7 of life. No statistically significant difference in the dynamics of changes in serum FGF-2 (p = 0.7914) was observed between the analysed groups at 36 weeks postmenstrual age (Fig. 4).

DISCUSSION

In 1967, Northway et al. first described the classic form of BPD, which consisted mainly of pulmonary fibrosis and smooth muscle hypertrophy, respiratory epithelium metaplasia, and formation of bullae[14]. Prenatal steroids, surfactant supply, new, more protective ventilation strategies, monitoring blood oxygen levels, more effective nutrition as well as more successful treatment of patent ductus arteriosus (PDA) increased the survival rate of very and extremely

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	BPD (+) ***n* = 51**	**BPD (–)** ***n* = 52**	***p***
Gestational age [weeks] [*Me*, (IQR)]	27.3 (26.4–28.6)	30.0 (29.3–30.9)	**<0.0001**
Birth weight [g] [*Me*, (IQR)]	1,000.0 (850.0–1,150.0)	1,270.0 (1,100.0–1,385.0)	**<0.0001**
Gender: male/female [*n* (%)]	29 (56.9)/22 (43.1)	29 (55.8)/23 (44.2)	0.9109
Perinatal infection in mother [*n* (%)]	26 (51.0)	33 (63.5)	0.2004
Prenatal steroid therapy [*n* (%)]	36 (70.6)	46 (88.5)	**0.0448**
Way of delivery (C-section) [*n* (%)]	46 (90.2)	47 (90.4)	0.9742
PROM [*n* (%)]	14 (27.5)	13 (25.0)	0.9532
Apgar at 1' [score] [*Me*, (IQR)]	6.0 (6.0–7.0)	7.0 (6.0–7.0)	**0.0256**
Apgar at 5' [score] [*Me*, (IQR)]	6.0 (6.0–7.0)	7.0 (6.0–8.0)	**0.0091**
Umbilical pH [*Me*, (IQR)]	7.31 (7.22–7.35)	7.32 (7.24–7.36)	0.4207
RDS: **• without RDS [*n* (%)]** **• grade I [*n* (%)]** **• grade II [*n* (%)]** **• grade III [*n* (%)]** **• grade IV [*n* (%)]**	 0 (0.0) 7 (13.7) 34 (66.7) 10 (19.6) 0 (0.0)	 3 (5.8) 16 (30.8) 27 (51.9) 5 (9.6) 1 (1.9)	0.0533
PDA [*n* (%)]	22 (43.1)	10 (19.2)	**0.0160**
NEC [*n* (%)]	3 (5.9)	1 (1.9)	0.3827
ROP [*n* (%)]	20 (39.2)	4 (7.7)	**0.0002**
IVH: **• without IVH [*n* (%)]** **• IVH grade I/II [*n* (%)]** **• IVH grade III/IV [*n* (%)]**	 13 (25.5) 35 (68.6) 3 (5.9)	 29 (55.8) 21 (40.4) 2 (3.8)	**0.0045**
PVL [*n* (%)]	4 (7.8)	0 (0.0)	0.0565
Congenital infection [*n* (%)]	20 (39.2)	19 (36.5)	0.7794
Ureaplasma infection [*n* (%)]	2 (3.9)	3 (5.8)	1.0000

BPD – bronchopulmonary dysplasia; **IQR** – interquartile range; **IVH** – intraventricular haemorrhage; ***Me*** – median; **NEC** – necrotising enterocolitis; **PDA** – patent ductus arteriosus; **PROM** – preterm premature rupture of membranes; **PVL** – periventricular leukomalacia; **RDS** – respiratory distress syndrome; **ROP** – retinopathy of prematurity.

Tab. 1. Demographics and clinical characteristics in the group with and without BPD

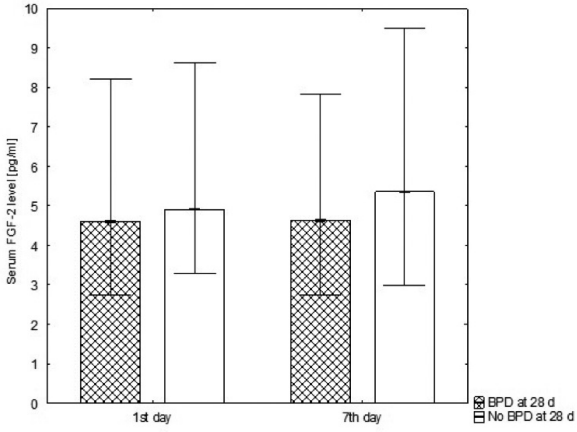

Fig. 3. Change of serum FGF-2 level on days 1 and 7 of life in the group of infants with and without BPD on day 28 of life (at 28 d). Median and interquartile range shown for each time point (p = *0.5330)*

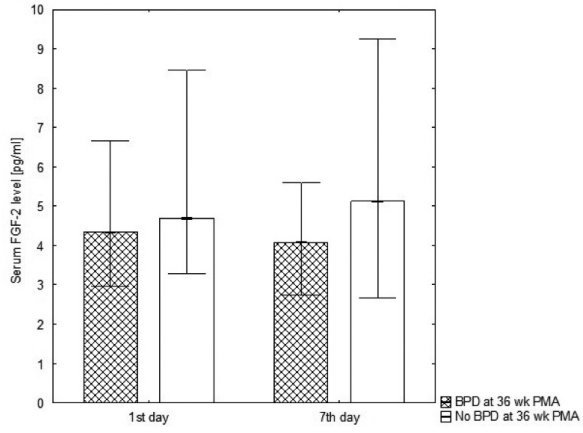

Fig. 4. Change of serum FGF-2 level on days 1 and 7 of life in the group of infants with and without BPD at 36 weeks post-menstrual age (at 36 wk PMA). Median and interquartile range shown for each time point (p = *0.7914)*

low birth weight infants[3,4,15,16]. Infants of very and extremely low birth weight are burdened with higher risk for developing BPD because the process of lung maturation is disturbed in the early period of their development[1,6].

FGF-2 plays an important role in repair and regeneration processes as well as in the process of blood vessel formation[9]. It is one of the better known factors which together with vascular endothelial growth factor (VEGF) stimulate angiogenesis[11,12]. VEGF has been shown to play an important role in the vascular and alveolar development of lungs. Thus, changes in VEGF level can subsequently lead to the development of BPD[1,4,17]. Studies on animal models have demonstrated that fibroblast growth factors are important for lung maturation[5,9].

In our analysis, similarly to other authors' studies, infants with BPD had significantly lower gestational age and

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birth weight than newborns without BPD. Lung immaturity is one of the major risk factors for the development of BPD[3,7,8,18–22]. Adverse effects of prenatal and postnatal factors may disturb the mechanisms of maturity in many areas. Among others, an imbalance of pro-inflammatory and anti-inflammatory mediators is observed and aberrant expression of growth factors. These cause the impairment and inhibition of alveolar and vascular growth[5–7]. As a result, repair mechanisms are activated, potentially leading to defective remodelling of lung tissue. Therefore, studies on molecular processes and mechanisms underlying lung maturation are of great importance[4,7,8].

Ambalavanan and Novak, in their pilot study, determined FGF-2 levels in tracheal aspirates collected within the first 24 hours of life. Infants who developed BPD at 28 days of life or died had statistically significantly elevated levels of FGF-2 compared to those in the group without BPD. However, no statistically significant difference was found in the FGF-2 levels in tracheal aspirates in infants requiring supplemental oxygen and/or mechanical ventilation versus those remaining on their own breath, breathing air at 36 weeks of postmenstrual age. Ambalavanan and Novak, in the analysis which comprised only surviving infants, did not find a statistically significant association of the level of FGF-2 in tracheal aspirates between the groups with and without BPD also for definitions at 28 days of life. The authors suggest the need for further research because it was a pilot study on a small group of infants[23].

In our study, serum FGF-2 level was assessed on days 1 and 7 of life in all newborns meeting the inclusion criteria. No statistically significant association was found between serum FGF-2 level on days 1 and 7 of life and the risk of developing BPD. The analysis was performed with BPD defined as the need for supplemental oxygen and/or respiratory support, both at 28 days of life and at 36 weeks of postmenstrual age. In our study, FGF-2 levels were determined in serum, which allowed us to obtain results for all newborns included in the study. Thus, the infants who did not require intubation and mechanical ventilation, who were subjected to less severe management strategies, were also considered. At the same time, it was possible to obtain serum samples from all enrolled patients at two time points. Ambalavanan and Novak found that FGF-2 was moderately inversely correlated with birth weight and gestational age in tracheal aspirates in the first 24 hours of life[23]. In our study, a statistically significant positive correlation was found between the dynamics of changes in serum FGF-2 level in the first week of life and birth weight. However, no association was observed between gestational age and the dynamics of changes in serum FGF-2 level in the first week of life. The available literature lacks data on changes in serum FGF-2 level depending on gestational age and birth weight.

Animal studies have indicated a minor role of FGF-2 in the processes of embryonic development. However, it is essential in the regulation of response to injury[9]. In animal models, a much greater role in lung development is attributed to FGF-10, FGF-9 and FGF-7[9,24,25]. Benjamin et al. showed a decreased expression of FGF-10 in the lung tissue sections of infants who died of BPD. At the same time, the authors pointed out that the patient autopsy samples were collected from infants at a more advanced stage of lung development[26].

Taking into account the role of FGF-2 in the process of recovery and repair, it seems that FGF-2 can play a more important role in the process of abnormal lung remodelling as a result of the effect of unfavourable factors in the subsequent weeks of life of infants born prematurely. The studies showed that FGF-2 played an important role at sites of inflammation and/or tissue injury[11]. Therefore, continuation of the pilot study evaluating serum FGF-2 levels in the later days of life in the context of the development of BPD is worth considering.

Our measurements of FGF-2 in the first week of life were associated with the assessment of its role in the early stages of lung maturation and with the search for the factor which, already in the first days of life, will allow to determine which preterm infants are particularly predisposed to BPD. Due to the increased risk of long-term hospitalisation and complications resulting from the impaired development of lungs, numerous studies were conducted in order to find early biomarkers of BPD[1,7,27–29]. Mechanisms responsible for lung maturation in premature infants are very complex and not fully understood[1,6,30–32]. Identification of new, early biomarkers would also help in establishing new management strategies at an early stage of disease development, which could contribute to further improvements of care for extremely immature newborns. Therefore, further studies are needed to fully understand the aetiopathogenesis of BPD[1,22,27,28].

CONCLUSIONS

The study revealed a statistically significant positive correlation between the dynamics of changes in serum FGF-2 level in the first week of life and birth weight. However, no association was observed between serum FGF-2 level in the first week of life and the risk of BPD development in infants born before 32 weeks of gestation with very and extremely low birth weight. In the study, lung immaturity was one of the major risk factors for the development of BPD. Infants with BPD had significantly lower gestational age and birth weight compared to those without BPD.

Conflict of interest

The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.

Author contributions

Original concept of study: PK, EG. Collection, recording and/or compilation of data: PK, BM, KW. Analysis and interpretation of data: PK, BM. Writing of manuscript: PK. Critical review of manuscript: PK, BM, KW, EG. Final approval of manuscript: PK, BM, KW, EG.

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