Original Article

http://journals.sbmu.ac.ir/jpn
https://doi.org/10.22037/jpn.v9i3.34482

Prognostic Role of Gestational Age and Birth Weight in Nephrotic Syndrome: A Retrospective Cross-Sectional Study

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Abstract

Background and Aim: Nephrotic syndrome (NS) is a common disease in children characterized by proteinuria, hypoalbunemia and hyperlipidemia. In some cases, NS is resistant to steroid therapy and may have frequent relapses. The aim of this study was to determine the prognostic role of gestational age and birth weight in the clinical outcomes of NS.

Methods: This retrospective cross-sectional study was conducted on 77 patients. The patients' data such as history of relapse and steroid resistance, birth weight, gestational age, and pathological variant were collected. Data was analysed using the SPSS software.

Results: Twenty-three patients were females and 54 were males. There was no significant association between the number of recurrences and premature birth (P value= 0.99). Mann-Whitney U test showed no significant difference between birth weight of patients who recurred less than two times during six months and those who recurred more than two times in six months (P= 0.336). Besides, Fisher's exact test showed no significant association between premature birth and the chance of developing steroid resistance (P value = 0.643). Moreover, there was no significant association between birth weight and steroid resistance (P-value = 0.768).

Conclusion: Low birth weight and premature birth did not have a role in the prognosis of nephrotic syndrome in our study population. Other factors including uterine-placental disorders, maternal underlying diseases, quality of weight gain in the first years of life, and ethnicity should also be examined in further investigations including larger samples of different ethnic groups.

Keywords: Nephrotic Syndrome; Streoid Resistance; Relaps; Gestational Age; Low Birth Weight.

Received: April, 2021
Revised: July, 2021
Accepted: July, 2021

Conflict of interest: The authors declare no conflict of interest.
Please cite this article as: Ghasemi KH, Montazeri S, Mokhtari A. Prognostic Role of Gestational Age and Birth Weight in Nephrotic Syndrome: A Retrospective Cross-Sectional Study. J Ped Nephrol 2021;9(3):1-5.
https://doi.org/10.22037/jpn.v9i3.34482

Introduction

A healthy human kidney uses different mechanisms to prevent excretion of protein into the urine; however, small amounts of protein are also present in the urine in normal conditions (1). However, protein exceeding 4 mg/m^2/hr is abnormal and is called proteinuria (2, 3). In most cases, proteinuria due to fever or after exercise does not require special treatment (4). However, if protein excretion is persistent, diagnostic and therapeutic measures should be taken. Nephrotic syndrome is one of the most common childhood diseases characterized by edema, proteinuria greater than 40 mg/m^2/hr, a serum albumin less than 2.5 g/dl, and increased levels of cholesterol and triglycerides (5).

Patients with NS are prone to infection (6), thrombosis (7), nutritional deficiencies (8, 9) and growth disorders (10) that require special attention. Infection is one of the most important causes of

disability and mortality in patients with nephrotic syndrome, which is due to the excretion of immunoglobulins (IgG) and complement (C2, C3), decreased antibody production, decreased splenic blood flow following hypovolemia, hypoalbuminemia, corticosteroids adverse effects, etc. (11, 12).

The milestone of treatment in the acute phase and recurrence of nephrotic syndrome is steroids and immunosuppressors (13). This disease can be resistant to steroids at the first manifestation or could be responder with further recurrences. More than 90% of the patients who respond to steroid therapy have Minimal Change Disease (MCD) (14). The prognosis of these patients is excellent; however, a small number might develop varying degrees of renal failure. Corticosteroids reduce the mortality rate of nephrotic syndrome by 3%, but it has its own side effects (10). Nonetheless, 60-80% of children with MCD experience recurrences. Meanwhile, about 40% of patients experience recurrence for more than 5 times (15, 16).

Recognizing the prognostic factors in the course of nephrotic syndrome can significantly reduce the complications, drug side effects, multiple hospitalizations, and treatment costs. According to some studies, low birth weight and low gestational age have been introduced as important factors in the prognosis and response to treatment in patients with nephrotic syndrome (17, 18). Therefore, in this study, the prognostic role of gestational age and intrauterine growth retardation (low birth weight) were investigated in patients with NS.

Methods

The patients with idiopathic nephrotic syndrome referred to Shohadey-Khalij Fars Hospital affiliated to Bushehr University of Medical Sciences, Iran between 1999 and 2019 were included in this retrospective cross-sectional study. Inclusion criteria were proteinuria $\geq$ 40 mg/m^2, serum albumin $\leq$ 2.5 g/dl, and increased triglyceride and serum cholesterol levels of more than 200 mg/dl. Exclusion criteria were proteinuria due to other reasons rather than nephrotic syndrome, any underlying disease that could cause proteinuria, and reluctance to participate in the study. The patients' data including baseline characteristics, birth weight, and gestational age were recorded in researcher-made checklists. A number of the patients presented to our clinic since childhood and were still under surveillance at our center; therefore, some of the patients were older.

The collected data were analyzed using the SPSS software version 22 (SPSS Inc. Chicago, Il, The USA). Frequency, mean and standard deviation are used to report data. Fisher's exact test was applied to determine the association between gestational age and the number of recurrences or steroid resistance. Mann-Whitney test was administered to determine the association between birth weight and corticosteroid resistance and the number of recurrences. It was not possible to analyze the association between pathological findings and gestational age or birth weight due to missing data. P values less than 0.05 were considered significant.

The study protocol was explained to the legal guardians of the patients and informed consent was obtained before enrolment. All the steps of study were performed according to the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Bushehr University of Medical Sciences. The patients' data were anonymous and confidential.

Results

Seventy-seven patients entered the study, including 23 female and 54 male children. The age range of the children was 2 to 28 years and their weight ranged from 12 to 68 kg. Of 77 participants, 70 (90.9%) were term infants and 7 (9.1%) were born prematurely. Besides, 68 (88.3%) had a normal birth weight, 4 (5.2%) had low birth weight, and 5 (6.5%) had high birth weight. The birth weight of the children ranged from 1800 to 6000 grams. In addition, 63 (81.8%) experienced less than two and 13 (16.9%) had more than two recurrences in 6 months. The data of one patient was not available. Furthermore, 71 (92.2%) responded to steroid treatment and six (7.8%) were resistant. The age at disease onset was below 5 years in 81.8% of the patients and above 5 years in 18.2%. The baseline demographic characteristics of the study participants are presented in Table 1.

There was no significant association between the number of recurrences and premature birth (P value= 0.99). Moreover, the mean birth weight of the patients was 3.23 ± 0.63 kg in those experienced less than two recurrences in six months and 3.21 ± 0.32 kg in those who had at least two recurrences in six months. Mann-Whitney U test showed no significant difference in birth weight between

patients who recurred less than twice in six months and those who recurred more than two times in six months (P= 0.336).

Table 1. Demographic data of participants.

Variable	Value
Gender	
Male, (%)	54, (70.12%)
Female, (%)	23, (29.8%)
Gestational age	
Term, (%)	70, (90.9%)
Pre-term, (%)	7 (9.1%)
Birth weight	
Normal	68 (88.3%)
Low birth weight	4 (5.2%)
High birth weight	5 (6.5%)
Steroid therapy	
Respondent	71 (92.2%)
Resistant	6 (7.8%)

In addition, the Fisher's exact test showed no significant association between premature birth and the chance of developing steroid resistance (P value = 0.643). The mean birth weight of the patients with and without steroid resistance was 3.15 ± 0.2 and 3.23 ± 0.6 kg, respectively. Mann-Whitney U test showed no significant difference in birth weight between patients with and without steroid resistance (P-value = 0.768). Pathological data was available for 10 subjects (Figure 1), of whom 7 had FSGS (focal segmental glomerulosclerosis), one had MCNS (minimal change nephrotic syndrome), one had mesangial proliferation, and one had mild mesangial proliferation, all of whom had a normal birth weight and gestational age. Due to scarcity of pathological data, no analysis was performed.

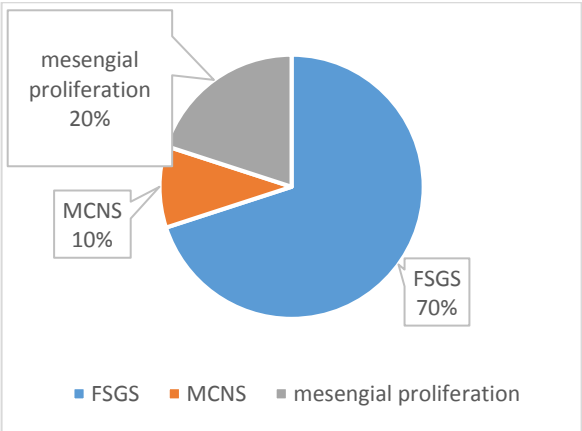

Figure 1. Pathologic findings of the patients (available for only 10 patients)

Discussion

Nephrotic syndrome is a common disease in children. There are still many ambiguities regarding its prognostic factors. Recent studies have paid special attention to birth weight and gestational age as two determining factors in the course of nephrotic syndrome (17-20). Since nephrons develop until the last weeks of pregnancy, according to the Brenner's theory, gestational age might have an impact on the development and course of nephrotic syndrome in children (21). However, the results of the present study showed no significant association between premature birth or low birth weight and the risk of recurrence.

In addition, there was no significant association between premature birth and the risk of steroid resistance. However, there are some controversial reports in the literature.

In a study by Ikuzemi in Japan (21), low birth weight and prematurity were identified as risk factors for nephrotic syndrome and decreased number of podocytes. They reported that low birth weight was more frequently found in patients with nephrotic syndrome (37.5% and 12.5% in FSGS and MCD, respectively) compared to the normal Japanese population (9.7%). These results are not consistent with our findings, which might be due to different study populations and ethnic differences.

Neyke Teeningia (19) also investigated the risk of steroid resistance and recurrence in patients with minimal change disease. They found an increased risk of steroid resistance in patients with low birth weight and a significant association between increasing risk of relapse and low birth weight. In this study, 201 patients with MCD were studied, of whom 25 were underweight at birth and 176 had a normal birth weight. In addition, they showed that the risk of steroid resistance and the need for cytotoxic drugs was significantly higher in those with lower weight. However, one-year recurrence was higher in the low birth weight group compared to the normal birth weight group, which is not consistent with our result. In addition, in a study conducted by Rezavand et al. (16) the risk of developing nephrotic syndrome was assessed in low birth weight patients. The rate of low birth weight in

patients with nephrotic syndrome was not significantly different from the control group, which is consistent with our study. This study was performed in Iran, the same country where our study was conducted, which might indicate the role of ethnicity and genetic diversity in the prognostic factors of nephrotic syndrome. In the study by Natalia Konstantelos et al. (18), 336 patients with nephrotic syndrome aged 1 to 18 years were enrolled. The risk of steroid resistance was about 3.16 times in children with low birth weight than those with normal birth weight. The results of this study are also in contrast to our findings. As mentioned earlier, more factors might be involved in the development and prognosis of nephrotic syndrome. Factors that should be considered along with low birth weight and premature birth include uterine-placental disorders, maternal underlying diseases, quality of weight gain in the first years of life, and ethnicity. Therefore, further investigations in larger samples of different ethnic groups are recommended.

Conclusion

We concluded that low birth weight and premature birth did not have a role in the prognosis of nephrotic syndrome. Other factors including uterine-placental disorders, maternal underlying diseases, quality of weight gain in the first years of life, and ethnicity should also be examined in further investigations including larger samples of different ethnic groups.

Acknowledgments

The authors would like to thank Dr. Mohammad Moradi (Farname Inc. Canada) for his assistance in the English edit of the manuscript.

Conflict of Interest

The author declares no conflicts of interest.

Financial Support

This study was supported by Bushehr University of Medical Sciences as part of a thesis to obtain final medical diploma.

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