## Research Article

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# Prenatal Risk Factors for Infantile Reflux Nephropathy

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**Introduction:** Vesicoureteral reflux (VUR) refers to the retrograde flow of the urine from the bladder to the ureter and kidney. In children with a febrile urinary tract infection (UTI), those with reflux are 3 times more likely to develop renal injury compared to those without reflux. Reflux nephropathy was once accounted for as much as 15-20% of end-stage renal disease in children and young adults. With greater attention to the management of UTIs and a better understanding of reflux, end-stage renal disease secondary to reflux nephropathy is uncommon. Reflux nephropathy remains one of the most common causes of hypertension in children. Reflux in the absence of infection or elevated bladder pressure does not cause renal injury. We sought to determine the association of infantile reflux nephropathy (IRN) with prenatal risk factors.
**Materials and Methods:** In this study, 96 infants with reflux-related renal injury and 96 infants with VUR without reflux nephropathy were evaluated. Maternal information was assessed. Data was analyzed using SPSS version 18.
**Results:** The results of this study showed that age more than 35 years, pre-gestational hypertension, preeclampsia and eclampsia, preterm delivery, very low birth weight (VLBW), pre gestational diabetes mellitus, and maternal BMI<18.5kg/m2 (underweight) were prenatal risk factors for infantile reflux nephropathy.
**Conclusions:** The data suggests that prenatal factors may affect the risk of IRN. Adequate prenatal care and good maternal support can be effective in the prevention of reflux-related renal injury.

**Keywords**: Vesico-Ureteral Reflux; Risk Factors; Prenatal; Infant.

**Running Title:** Prenatal Risk Factors for Infantile Reflux Nephropathy

## Introduction

Vesicoureteral reflux (VUR) is the retrograde flow of the urine from the bladder to the ureter or up to the kidney [1]. VUR mostly results from congenital incompetence of the ureterovesical (UV) junction that can be mature through early childhood. In a significant minority of children, structural UV abnormalities exist that never resolve [2].

VUR may be familial since 30% to 40% of the siblings of a child with VUR also have VUR. VUR may also be secondary to distal bladder obstruction or other urinary tract anomalies [3]. VUR exposes the kidney to increased hydrodynamic pressure during voiding and increases the likelihood of renal infection due to

incomplete emptying of the ureter and bladder [4]. Reflux nephropathy refers to the development and progression of renal scarring. This is a particular risk if VUR is associated with infection or obstruction. Even though a single urinary tract infection (UTI) may result in renal scarring, the incidence is higher in children with recurrent UTIs [5]. Renal scars noted in newborns screened because of familial VUR, along with genetic studies, suggest that renal dysplasia is associated with congenital VUR [6]. Because of the increasing use of maternal-fetal ultrasonography, a number of newborns are now identified with VUR before UTI has occurred, creating opportunities for early intervention and UTI prevention strategies [7]. We sought to determine the association of infantile reflux nephropathy (IRN) with prenatal risk factors, hypothesizing that these maternal conditions would increase the risk of infantile reflux-related renal injury. This is the first study to assess the relationship between maternal factors and IRN.

## Materials and Methods

We conducted a population-based, case-control study in 96 patients with infantile reflux nephropathy (control group) and 96 infants with VUR without reflux nephropathy. In infants with their 1st episode of clinical pyelonephritis—those with a febrile UTI or those with systemic illness—and a positive urine culture, irrespective of the temperature, a sonogram of the kidneys and bladder was performed to assess the kidney size, to detect hydronephrosis and ureteral dilation, to identify the duplicated urinary tract, and to evaluate bladder anatomy. Next, a DMSA scan was performed to identify whether the child had acute pyelonephritis. If the DMSA scan was positive and showed either acute pyelonephritis or renal scarring, a voiding cyst urethrogram (VCUG) was performed. All patients with first febrile urinary tract infection underwent renal sonography, VCUG and DMSA scan. We evaluated maternal characteristics of patients and used logistic regression analysis to assess the association of prenatal risk factors with infantile reflux nephropathy. Maternal characteristics of the infants with and without IRN were 1) age (years) <18,18-25,26-30,31-35 and >35, 2) education (below high school, high school diploma, bachelor's degree and master's degree), 3) residence in urban or rural areas, 4) smoking exposure, 5) previous pregnancy (0, 1, 2, 3, 4 and>4), 6) prenatal care (inadequate and adequate), 7) chronic and gestational hypertension, 8) maternal diabetes mellitus (gestational diabetes mellitus and chronic diabetes mellitus), 9) maternal BMI (kg/m2) (<18.5, 18.5-24.9 ,25-29.9 and >30), and 10) eclampsia. Infant characteristics were 1) age at diagnosis of study definition of IRN (<2, 3-6, and 7-12 months), 2) birth weights (VLBW<1500 g, LBW1500-2500 g, normal BW 2500-4000 g and HBW>4000 g), 3) gestational week (preterm <37, term 37-42, and post term>42), and 4) sex (male and female). Data was analyzed with SPSS 18.

## Results

Most of the infants were 6-12 months of age at the time of reflux nephropathy diagnosis. There was a predominance of girls among cases and controls. A greater proportion of cases had a VLBW and a gestational age <37 weeks when compared with controls. The distribution of singleton versus multiple births was similar in case and control groups. Maternal characteristics race, education, urban/rural residence, prior pregnancy and multiple births, age at diagnosis of fetal hydronephrosis, sex, gestational hypertension, smoking exposure, overweight, obesity, and prenatal care were similar in cases or controls. The cases were more likely to have mothers with the following characteristics: aged>35 years (P-Value=0.003), chronic hypertension (P-Value=0.001), preeclampsia (p-value=0.03), preterm delivery (p-value=0.04), history of VLBW (p-value=0.004), chronic diabetes mellitus (p-value=0.02)و and BMI<18.5kg/m2 (underweight) (p-value=0.02). (Table 1)

**Table 1.** Maternal characteristics of study group

| Maternal characteristics | Case | Control | p-value | Odds Ratio (OR) |
|---|---|---|---|---|
| **Maternal BMI(kg/m2)<18.5** | 43 (87%) | 6 (13%) | 0.003 | 6.7 |
| **Chronic diabetic mellitus** | 39 (92%) | 3 (8%) | 0.001 | 1.15 |
| **Chronic hypertension** | 51 (72%) | 19 (28%) | 0.03 | 2.57 |
| **Mother age >35 years old** | 48 (82%) | 10 (18%) | 0.02 | 4.5 |
| **Gestational age <37 weeks** | 38 (84%) | 7 (16%) | 0.006 | 5.25 |
| **Mother preeclampsia** | 40 (81%) | 9 (19%) | 0.009 | 4.2 |
| **History of Very low birth weight (neonatal birth weight<1500g)** | 35 (81%) | 8 (19%) | 0.04 | 4.2 |

## Discussion

In this population-based, case-control study, we showed significant associations between reflux nephropathy and primary prenatal exposures of chronic HTN, preeclampsia, preterm delivery, VLBW, chronic DM, maternal age over 35 years old, and underweight. As mentioned earlier, previous data suggests that if we educate and provide early DM care to diabetic mothers, the rate of congenital malformations in births decreases to the normal population levels. Maternal underweight was also found to be associated with infantile reflux nephropathy. Moreover, very low birth weight was associated with development of reflux nephropathy in infants. This suggests that the risk of developing reflux nephropathy in infants may be largely determined in-utero and depends on maternal factors. Sokal R concluded that the prevalence of any Congenital Anomaly (CA) was 307/10,000 in males (95% CI, 302-313) and 243/10,000 in females (95% CI, 238-248). Overall, the risk of any CA was 26% greater in males (PR (male: female) 1.26, 95% CI, 1.23-1.30); however, there was considerable variation across specific diagnoses. Our PRs were highly consistent with those from previous studies. Sociodemographic and maternal factors do not appear to affect these risks [8] Räisänen S concluded that smoking cessation appeared to reduce pregnancy risks. Exposure to smoking in early pregnancy was, however, associated with an increased admission to neonatal intensive care (NICU) and an increased prevalence of major CAs [9]. Sheridan E reported that consanguinity was a major risk factor for CA. The risk remains even after adjustment for deprivation, and accounts for almost a third of anomalies in Pakistani babies. High level education is associated with a reduced risk in all groups. Our findings are valuable in health promotion, and to those commissioning pediatric, genetic, and antenatal services. Important advice and recommendations about the risks should be provided to at risk communities, and to couples in consanguineous unions, to assist them in making the best reproductive decision [10]. Retnacaran R. reported that male fetuses were associated with higher postprandial glycemia, a poorer β-cell function, and an increased risk of maternal GDM. Thus, fetal sex may influence maternal glucose metabolism during pregnancy [11]. The mean platelet count was higher in patients with reflux nephropathy than non-reflux nephropathy patients and the mean platelet volume was lower in the patients with reflux nephropathy than patients without reflux nephropathy. MPV can be used as an indicator in the diagnosis of reflux nephropathy in patients with VUR [1]. Sacral ratio abnormalities are more common in children with vesicoureteral reflux and reflux nephropathy than children with VUR without reflux nephropathy [2]. In subgroup analysis by the CKD subtype, low birth weight and maternal pregestational DM were significantly associated with an increased risk of renal dysplasia/aplasia. Low birth weight, maternal gestational DM, and maternal overweight/obesity were significantly associated with obstructive uropathy. The data suggests that prenatal factors may influence the risk of CKD [7]. Childhood-onset chronic kidney disease is the result of congenital anomalies of the kidneys and urinary tract in approximately two-thirds of all patients. An area of intense research in recent years, however, is the potential impact of maternal obesity on renal ontogenesis or postnatal renal function in the offspring [12].

## Conclusions

We hope that our results will serve as an impetus to larger prospective studies to evaluate the risk factors and clinical outcomes of infants with reflux-related renal injury with the goals of elucidating the pathophysiology and improving the outcomes for reflux nephropathy and to investigate whether modification of these factors can reduce the incidence of infantile reflux nephropathy. In subgroup analysis by CKD subtype, low birth weight and maternal pregestational DM were significantly associated with an increased risk of renal dysplasia/aplasia. Low birth weight, maternal gestational DM, and maternal overweight/obesity were significantly associated with obstructive uropathy. The data suggests that prenatal factors may influence the risk of CKD. Future studies should aim at determining whether modification of these factors could reduce the risk of childhood CKD.

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## Conflict of Interest

Authors have no conflict of interest to declare.

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