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Original Article

Cerebral Palsy and Intellectual Disability in the Children of Women With Chronic Kidney Disease

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ABSTRACT

BACKGROUND: This study examined the risk of adverse maternal and neonatal outcomes, especially cerebral palsy and intellectual disability, in pregnant women with and without chronic kidney disease and their children. **METHOD:** In total, 156 pregnancies involving 139 women with chronic kidney disease who were treated at our center between 2001 and 2010 were identified. We also selected 3067 women without chronic kidney disease who delivered their infants without suffering any medical complications during the same period as control groups. Long-term neonatal prognosis was assessed based on the frequencies of cerebral palsy and/or intellectual disability. **RESULTS:** The pregnant women had the following types of chronic kidney disease: immunoglobulin A nephropathy (n = 54), glomerulonephritis (n = 17), chronic renal failure (n = 16), nephrotic syndrome (n = 12), nephritis (n = 11), diabetic nephropathy (n = 10), congenital malformations and deformations (n = 10), purpura nephritis (n = 7), and others (n = 19). Of the children who were born to mothers with chronic kidney disease, one developed cerebral palsy, and another developed cerebral palsy with intellectual disability. Seven of the children who were born to mothers without chronic kidney disease developed cerebral palsy. The posterior probability of these conditions was 0.01900 and 0.002610 in the children born to mothers with and without chronic kidney disease, respectively. A primiparous mother (odds ratio [OR]: 4.07, 95% confidence interval [CI]): 2.78 to 5.95), preeclampsia (OR: 6.44, 95% CI: 3.92 to 10.59), grade 1 to 4 intraventricular hemorrhaging (OR: 7.71, 95% CI: 2.05 to 28.92), and an Apgar score of less than 7 at five minutes (OR: 0.51, 95% CI: 0.27 to 0.96) were found to influence the risk of cerebral palsy and/or intellectual disability in children born to women with chronic kidney disease. **CONCLUSION:** We found that the incidence of cerebral palsy and/or intellectual disability is 7.2-fold higher in children born to women with chronic kidney disease than in those born to women without chronic kidney disease.

Keywords: cerebral palsy, chronic kidney disease, intellectual disability, preeclampsia, small for gestational age

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Introduction

Pregnant women with chronic kidney disease are at greater risk of maternal and fetal complications.[1-6] For example, Kendrick et al.[1] concluded that infants born to women with kidney disease are at a 71% greater risk of being admitted to the neonatal intensive care unit or death than infants born to women without kidney disease (odds ratio [OR]: 1.71; 95% confidence interval [CI]: 1.17 to 2.51) and that women with chronic kidney disease are at a two-fold higher risk of delivering low birth weight infants (OR: 2.38; 95% CI: 1.64 to 3.44). Moreover, Fink et al.[4] concluded that women with renal disease were also at increased risk of delivering infants that were small for their gestational age (SGA; OR: 5.3, 95% CI: 2.8 to 10.0) and/or had five-minute Apgar scores of less than 7 (OR: 3.9, 95% CI: 1.1 to 14.6). Although several reports have indicated that pregnant

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women with chronic kidney disease are at increased risk of adverse maternal and fetal outcomes, the long-term prognosis of neonates born to such women including their risk of cerebral palsy and intellectual disability is unclear.[1-6]

We performed a retrospective cohort study examining the risk of adverse maternal and neonatal outcomes, especially cerebral palsy and intellectual disability, in pregnant women with and without chronic kidney disease and their children.

Materials and Methods

This study was approved by the ethics committee of Tokyo Women's Medical University. The medical records of the mothers and infants were reviewed. In this study, 156 singleton pregnancies involving 139 women with chronic kidney disease whose infants were delivered between 22 and 41 weeks of gestation at the Maternal and Perinatal Center, Maternal-Fetal Division, Tokyo Women's Medical University Hospital, between January 1, 2001, and December 31, 2010, were examined. Chronic kidney disease was diagnosed based on the Kidney Disease Outcomes Quality Initiative definition of chronic kidney disease (the presence of kidney lesions or a glomerular filtration rate of less than 90 mL/min/1.73 m^2).[7] We also randomly selected 3067 women without chronic kidney disease who delivered their infants without suffering any medical complications during the same period as control groups. All pregnancies involving multiple pregnancies, fetal anomalies, intrauterine fetal death, or preconception dialysis were excluded from this study.

Gestational age was determined based on the last menstrual period and standard obstetric ultrasound examinations. All the patients had been permitted to continue their pregnancies by obstetricians and were managed in collaboration with nephrologists.

Threatened preterm labor was defined as progressive dilatation of the cervix combined with regular uterine contractions that occurred between 22 and 36 weeks of gestation.[8] Premature rupture of membranes (PROM) was defined as the observation of amniotic fluid pooling in the vagina, ferning, or a reduction in the volume of amniotic fluid on ultrasound,[8] or a positive result during testing with Check PROM (an insulin-like growth factor binding protein-1 reagent). According to the criteria of the National High Blood Pressure Education Program, hypertensive disorders in pregnancy can be classified into chronic hypertension, pregnancy-induced hypertension, preeclampsia, and superimposed preeclampsia.[9] Women whose blood pressure reached 140/90 mm Hg or more after the 20th week of gestation, but who did not exhibit proteinuria, were diagnosed with pregnancy-induced hypertension.[10]

Preeclampsia was defined as systemic hypertension exceeding 140/90 mm Hg accompanied by proteinuria after the 20th week of gestation.[11] Proteinuria was defined as a 24-hour urinary protein level of $\geq$300 mg or a score of $\geq$1 during dipstick tests of random urine samples.[11] Chorioamnionitis was clinically diagnosed based on the patients' medical records. The clinical findings of chorioamnionitis were considered to include maternal fever (greater than 100.4°F) and at least one of uterine fundal tenderness, maternal tachycardia (greater than 100 beats/min), maternal leukocytosis, and foul-smelling amniotic fluid.[12,13]

Hospitalization was considered necessary for hypertension, pregnancy-induced hypertension, worsening renal dysfunction, new onset proteinuria, markedly worsening proteinuria, threatened preterm labor, PROM, and intrauterine growth restriction (IUGR).

Regarding the fetal assessments performed during the patients' hospitalization, the initial ultrasound scan was used to estimate fetal weight and amniotic fluid volume, and then further ultrasound evaluations were performed every seven days and used to evaluate fetal growth. Nonstress testing was performed daily, and biophysical profiles were obtained when necessary.

Delivery was allowed to occur after the onset of active labor in the presence of maternal indications, such as significant renal dysfunction, the onset of pregnancy-induced hypertension, or clinical chorioamnionitis, and fetal indications such as growth arrest, a nonreassuring fetal status, and a gestational age greater than 37 weeks. Caesarean sections were performed in patients who had previously undergone Caesarean sections and patients who did not respond to induction, a nonreassuring fetal status, fetal malpresentation, or maternal indications. Short-term neonatal prognosis was evaluated based on the following conditions: premature birth (less than 37 weeks of gestation), SGA (below the tenth birth weight percentile for the infant's gestational age), neonatal death (within 28 days of birth), and infantile death after discharge. Long-term neonatal prognosis was assessed based on the incidence of cerebral palsy and/or intellectual disability (an intelligence quotient or development quotient of less than 70).[14] Cerebral palsy was defined as a nonprogressive, nontransient central nervous system disorder that is characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture.[15] In addition to meeting the above criteria, the infants had to be aged at least 2 years at the most recent diagnosis to be definitively diagnosed with cerebral palsy. In patients with suspected cerebral palsy, the infants' physical findings were reviewed by a developmental pediatrician. In addition, a developmental quotient of less than 70 was interpreted as representing significantly delayed performance (intellectual disability).[15]

The infants were assessed for periventricular echodensity, intraventricular hemorrhaging (IVH), and periventricular leukomalacia (PVL). Periventricular echodensity was defined as confluent areas of increased echogenicity compared with the echogenicity of the choroid plexus. IVH was detected using cranial ultrasonography and was graded from 1 to 4 according to the classification developed by Papile et al.[16] PVL was diagnosed based on the presence of echodense or echolucent areas in the periventricular regions on coronal and sagittal views.[17]

Statistical analysis

The results are expressed as mean ± standard deviation values. Statistical analyses were performed using the chi-square test, Fisher exact probability test, the Mann–Whitney *U* test, the Student *t* test, or multiple regression analysis (SAS software, version 9.13, SAS Institute Inc). The significance of the differences between the with chronic kidney disease and without chronic kidney disease groups were assessed using the Student *t* test or Mann–Whitney *U* test for continuous variables and the chi-square test or Fisher exact probability test for categorical variables. *P* values of <0.05 were considered to be significant. OR and 95% CI were calculated to estimate how each factor influenced the relative risk of cerebral palsy and/or intellectual disability in the children of women with chronic kidney disease. The results were compared using both univariate and multivariate analyses, whereas logistic regression models were used to assess the influence of confounding factors. Posterior probabilities and highest probability densities were calculated to estimate the frequency of cerebral palsy and/or intellectual disability in the children of women with chronic kidney disease and the children of women without chronic kidney disease.

Results

The pregnant women exhibited the following types of chronic kidney disease: immunoglobulin A nephropathy (n = 54), glomerulonephritis (n = 17), chronic renal failure (n = 16), nephrotic syndrome (n = 12), nephritis (n = 11), diabetic nephropathy (n = 10), congenital malformations and deformations (n = 10), purpura nephritis (n = 7), and others (n = 19).

The maternal and neonatal outcomes involving pregnant women with and without chronic kidney disease are described in Table 1. The pregnant women with chronic kidney disease exhibited significantly higher frequencies of primipara (74.3%), preeclampsia (17.9%), preterm delivery (34.6%), and Caesarean sections (46.1%) than the pregnant women without chronic kidney disease ($P < 0.001$). There was no difference in the frequency of abruptio placentae, placenta previa, PROM, or chorioamnionitis between the two groups. The mean gestational age at delivery of the