〈Case Report〉

Case reports of pregnancies complicated with kidney disease and their fetal prognosis

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ABSTRACT The number of patients with chronic kidney disease (CKD) has been increasing every year, with a current prevalence of one in eight adults. Although the frequency of complications due to kidney disease before pregnancy is not high (0.02–0.12%), frequency of pregnancy with CKD, including cases receiving continuous dialysis therapy is expected to increase in the future. The fertility and birth rates among dialysis patients are low, and perinatal management in these patients is currently difficult. However, even under such circumstances, the probability of having a live-born baby in pregnant women on dialysis has increased due to improvements in dialysis technology, perinatal management, and neonatal care. There are some case reports written about them, and I think that it is possible to approach term delivery with careful care through the cases experienced this time.

In this study, we examined the pregnant patients, on dialysis or requiring postpartum dialysis, at Kawasaki Medical School Hospital between January 2005 and March 2018. Six patients (86%) had a live-born baby, while one had a miscarriage. One patient underwent two pregnancies on dialysis; one case gave a full-term birth, while the rest had a premature delivery. The modes of delivery were vaginal delivery (n = 1), elective cesarean section (n = 3), and emergency cesarean section (n = 2). Five patients delivered successfully and had a good prognosis, while in one case, the neonate died.

Over the years, owing to continuous improvement at our hospital, we have achieved better pregnancy prognosis and longer gestation periods in the patients. In particular, one case, which

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had a natural second pregnancy, 9 years after the beginning of dialysis, was worthy of note; we were able to manage her second pregnancy using the process followed during her first pregnancy as reference.
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INTRODUCTION

The number of patients with chronic kidney disease (CKD) has been increasing every year, with a current prevalence of one in eight adults. In addition, a statistical survey conducted by the Japanese Society for Dialysis Therapy showed that the number of chronic dialysis patients exceeded 344,000 in 2019[1)]. Although the frequency of complications, due to kidney disease, before pregnancy has not been high (0.02 - 0.12%), frequency of pregnancy with CKD, including cases receiving continuous dialysis therapy is expected to increase in the future. Moreover, the fertility and birth rates among dialysis patients are low, and perinatal management in these patients is currently difficult. Even under such circumstances, the probability of having a live-born baby in pregnant women on dialysis has increased due to improvements in dialysis technology, perinatal management, and neonatal care.

Here, we retrospectively examined the pregnant patients, on dialysis or requiring postpartum dialysis, at our hospital; we report the cases with a review of the literature.

In this retrospective study, we examined seven pregnancies in six patients, who either were on dialysis or required postpartum dialysis; the enrolled patients were managed at Kawasaki Medical School Hospital between January 2005 and March 2018. The study was approved by the Ethics Committee of Kawasaki Medical School and its affiliated hospital (approval number: 3846).

CASE REPORTS

Case 1

The patient was a 25-year-old woman with a history of gravida 1, para 0. At the age of 16 years, she was diagnosed with type 2 diabetes and began treatment for it. Owing to poor control and compliance, she was diagnosed with diabetic nephropathy at the age of 21 years and had chronic nephritis by the age of 25 years. She was admitted to the nephrology department at our hospital because of deteriorating kidney function. Although the use of dialysis was considered based on the guidelines for dialysis initiation, peritoneal dialysis was chosen at the request of the patient. Her pregnancy was diagnosed when due to poor fluid removal, she was admitted to our hospital; her pregnancy was subsequently managed in our department. She underwent 4 hours of dialysis, three times per week, in the outpatient department. The treatment progressed free from any obvious signs of complications. Thereafter, she was admitted, when the frequency of dialysis was changed to six times per week, post 28 weeks of gestation. Her blood pressure was controlled with amlodin (amlodipine) and aldomet (methyldopa); the rapid-acting insulin was used for the treatment of type 2 diabetes. After admission, she underwent 3 hours of dialysis, six times per week. Her blood urea nitrogen (BUN) level was lowered to approximately 50 mg / dL, prior to dialysis. Despite the tendency of fetal growth restriction (FGR), the fetus had neither growth arrest nor marked hydramnios. At 33 weeks and 1 day of gestation, an emergency cesarean section was performed due to non-reassuring fetal status (reduced variability and appearance of variable deceleration in baseline fetal heart rate). The neonate was a boy, weighing 1,627 g, with an Apgar score of 7 / 8. The umbilical artery blood gas levels were as follows: pH, 7.38; partial

pressure of carbon dioxide ($PaCO_2$), 55.3 mm Hg; partial pressure of oxygen (PaO_2), 16.7 mm Hg; bicarbonate ion (HCO_3^-), 32.0 mmol/L, and; base excess (BE), 5.6 mmol/L. After delivery, because of premature birth, the boy was managed in the neonatal intensive care unit (NICU). In addition, post-delivery, the mother resumed 4 hours of maintenance dialysis, three times per week (Fig. 1).

Thereafter, the patient became naturally pregnant with her second child at the age of 34, which is 9 years after the start of dialysis. She continued on insulin for type 2 diabetes, and her blood pressure was well controlled with nifedipine. As in her first pregnancy, fluid was removed, aiming to reach a BUN level of 50 mg / dL or lower, prior to dialysis. During the period of outpatient management, although the fetus exhibited a tendency of FGR, the mother was free from any signs of obvious complications. Beginning at 31 weeks of gestation, the patient was admitted and underwent 3 hours of dialysis, six times per week. Although the tendency of FGR in the second pregnancy was more pronounced than that in the first pregnancy, no abnormalities were detected in the fetus on fetal ultrasonography. The amniotic fluid volume was slightly high until admission, but it decreased noticeably post-admission; it was thought to be due to fetal placental insufficiency or excess fluid removal for the strict setting of the dry weight. On reviewing the dry weight, the amniotic fluid volume could be brought within the normal range at 34 weeks of gestation. At 37 weeks and 6 days, via a selective cesarean section, the mother gave birth to a boy, weighing 1,943 g (-2.7 standard deviation [SD]), with an Apgar score of 8 / 9. The umbilical artery blood gas levels were as follows: pH, 7.38; $PaCO_2$, 55.3 mmHg; PaO_2, 16.7 mmHg; HCO_3^-, 32.0 mmol/L, and; BE, 5.6 mmol/L (Fig. 2). After delivery, because of low birth weight and characteristic facial appearance, the boy was admitted to NICU for close examination. Post-delivery, she resumed 4 hours of maintenance dialysis, three times per week. Since the patient was stable and had no complications, she was discharged 7 days after delivery.

The child was referred to the genetic outpatient

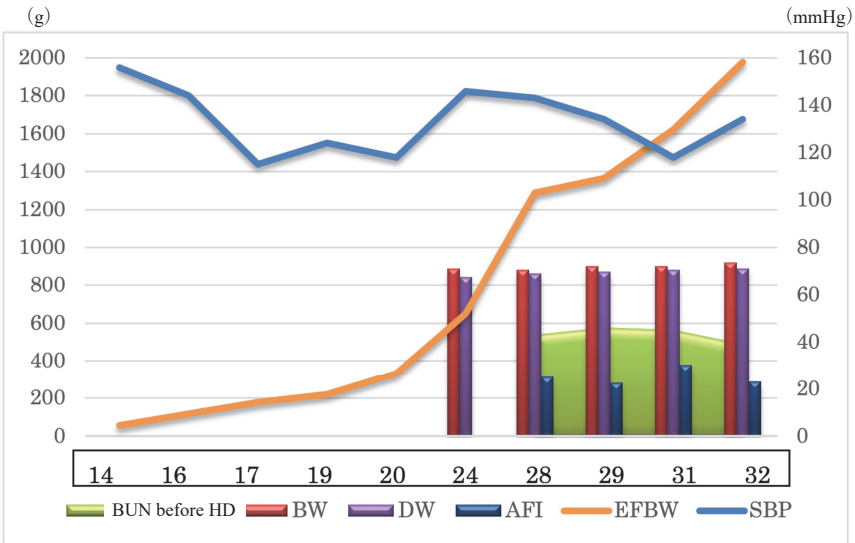

Fig. 1. The characteristics of the first pregnancy of Case 1.
AFI, Amniotic fluid index; BUN, blood urea nitrogen; BW, body weight; DW, dry weight; EFBW, fetal birth weight; HD, hemodialysis; SBP, systolic blood pressure

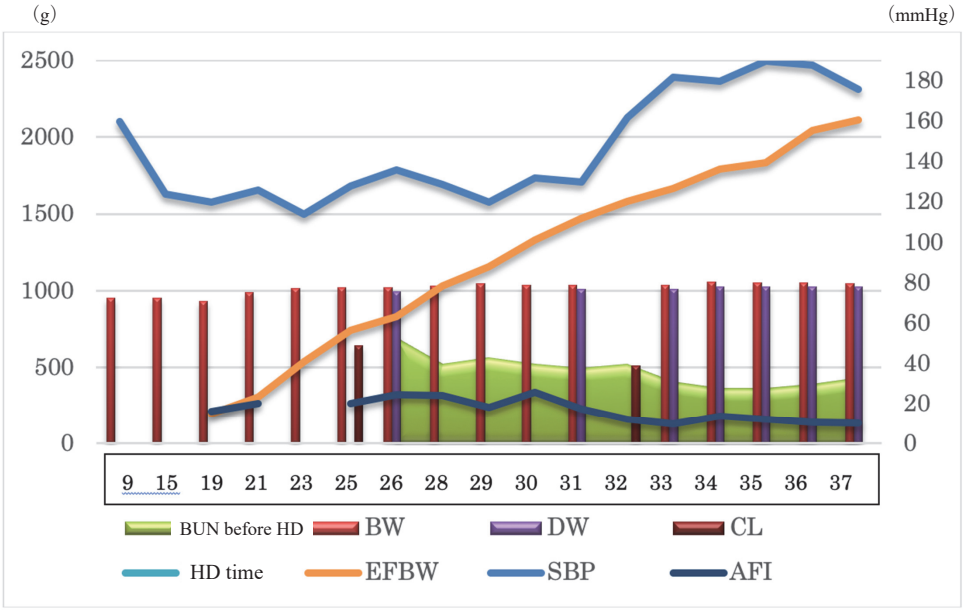

Fig. 2. The characteristics of the second pregnancy of Case 1.
AFI, Amniotic fluid index; BUN, blood urea nitrogen; BW, body weight; CL, cervical length; DW, dry weight; EFBW, fetal birth weight; HD, hemodialysis; SBP, systolic blood pressure

department for his distinctive facial features; distal 4p trisomy / distal 21q monosomy was revealed on array comparative genomic hybridization. The child is being followed-up in the pediatrics department for rehabilitation.

Case 2

The patient was a 33-year-old woman with a history of gravida 1, para 0. At the age of 10 years, proteinuria was detected on a school examination and she was diagnosed with nephrotic syndrome. She had developed kidney failure at the age of 12 years and began hemodialysis treatment at the age of 15 years. After the natural pregnancy was established and a scheduled date was determined by crown-rump length, the patient was referred to our department because of a high-risk pregnancy. At 16 weeks, due to the signs of uterine contraction, the patient started receiving ritodrine hydrochloride; on examination, the cervical length (42 mm) was found to be normal. Although the patient continued to have frequent contractions, there was no significant change in the cervical length at 17 weeks. However, at 19 weeks, the cervical length had shortened to 15 mm, and she was admitted for threatened abortion. Despite the use of tocolytic agents, such as ritodrine hydrochloride, progesterone, and Ca antagonist, the shortening of the cervical length progressed to 6 mm at 20 weeks. Thus, an emergency cervical cerclage was performed after the risks were fully explained to the patient. In addition, the number, of dialysis (for 3 hours) sessions, was increased to six times per week after admission. The patient tested positive for fetal fibronectin. Despite relatively mild uterine contractions and good intrauterine growth, high rupture of membranes occurred at 24 weeks and 6 days of gestation. The uterine contractions could not be controlled despite the administration of steroids and continuous infusion of tocolytic agents; the patient underwent labor induction at 25 weeks and 1 day. The neonate was a girl, weighing 733 g, with an Apgar Score of 1 / 4 / 8. The child was monitored in

NICU. After delivery, the mother resumed 4 hours of maintenance dialysis, three times per week.

Case 3

The patient was a 33-year-old woman with a history of gravida 2, para 0. At the age of 16 years, proteinuria was detected at a school examination. She was diagnosed with renal hypoplasia, on renal biopsy, at the age of 17 years; hemodialysis began at 27 years of age. Her previous pregnancy resulted in intrauterine fetal death at 13 weeks. Therefore, after a natural pregnancy was established, progesterone replacement was started at an early stage of pregnancy. In addition, the administration of nifedipine and methyldopa was initiated to control her blood pressure. Beginning at 21 weeks, the number of dialysis (of 3 hours) sessions was increased to six times per week. No obvious abnormalities were detected on fetal ultrasonography. However, FGR, which began at 28 weeks, gradually became severe; fetal growth arrest (-3.7SD) was observed at 33 weeks. Eventually, due to intrauterine growth retardation, an elective cesarean section was performed at 34 weeks and 1 day of gestation. The neonate was a boy, weighing 1,109 g, with an Apgar Score of 9 / 9. He was monitored in NICU. After delivery, the mother resumed 4 hours of maintenance dialysis, three times per week.

Table 1 and 2 summarizes seven pregnancies in

Table 1. The characteristics of seven pregnancies in six pregnant women on dialysis at our department between 2005 and 2018

	History of pregnancies	Medical history	Antihypertensive drugs	Tocolytic agents	Mode of delivery	Birth weight Apgar Score
Case 1	25 years old (Gravida 0)	16 years old: type 2 diabetes 21 years old: diabetic nephropathy 25 years old: start of dialysis	Methyldopa Ca antagonist	None	33 weeks and 1 day Emergency CS due to NRFS	Male 1627 g AS 7 / 8
	34 years old (Gravida 2, Para 1)		Methyldopa Ca antagonist β_2-blocker	None	37 weeks and 6 days elective CS	Male 1943 g AS 8 / 9
Case 2	33 years old (Gravida 0)	10 years old: nephrotic syndrome 12 years old: renal failure 15 years old: start of dialysis	None	Ritodrine hydrochloride Ca antagonist Indomethacin Progesterone replacement Cervical cerclage at 20 weeks	25 weeks and 1 day Vaginal delivery	Female 733g AS 1 / 4 / 8
Case 3	33 years old (Gravida 2, Para 0)	16 years old: detection of proteinuria 17 years old: renal hypoplasia 27 years old: start of dialysis	Methyldopa Ca antagonist	Progesterone replacement Ritodrine hydrochloride	34 weeks and 1 day Intrauterine growth retardation elective CS	Male 1109 g AS 9 / 9
Case 4	39 years old (Gravida 5, Para 0)	22 years old: IgA nephropathy 39 years old: start of dialysis	Methyldopa	None	36 weeks and 0 day Selective CS	Male 2553 g AS 8 / 9
Case 5	37 years old (Gravida 3, Para 0)	22 years old: SLE 30 years old: start of dialysis	Methyldopa Ca antagonist α-blocker	Progesterone replacement Ritodrine hydrochloride	20 weeks and 3 day Miscarriage due to difficulty in tocolysis	345 g
Case 6	35 years old (Gravida 0)	26 years old: high blood pressure	Methyldopa	None	25 weeks and 0 day Emergency CS due to NRFS	Female 343 g AS 2 / 5 / 7 Neonatal death

CS, Caesarean section; NRFS, Non-reassuring fetal status

Table 2. The characteristics of seven pregnancies in six pregnant women on dialysis at our department between 2005 and 2018

	From the start of dialysis to pregnancy	Pregnancy permission	Number of dialysis (before pregnancy → immediately before delivery → after delivery)	Deterioration of maternal renal function	Intrauterine growth	Amniotic fluid volume
Case 1 First pregnancy	Pregnancy was detected at the start of dialysis	Unknown	3 → 6 → 3 times per week	None	AGA	Hydramnion
Case 1 Second pregnancy	9 years	Unknown	3 → 6 → 3 times per week	None	FGR	Excess → decrease
Case 2	18 years	Unknown	3 → 6 → 3 times per week	None	AGA	Normal
Case 3	6 years	Unknown	3 → 6 → 3 times per week	None	FGR	Decreasing trend
Case 4	Pregnant after the start of dialysis	Unknown	3 → 5 → 3 times per week	None	AGA	Normal upper limit
Case 5	7 years	Explained that pregnancy is not impossible	3 → 4 → 3 times per week	None	AGA	Normal
Case 6	Dialysis was started after delivery	Unknown		Uncertain whether pregnancy affected	FGR	Normal

AGA, gestational age; FGR, Fetal growth restriction

six pregnant women, who were on dialysis after 12 weeks of gestation; all patients were examined at our hospital. Six patients (86%) had a live-born baby, while one had a miscarriage. Case 1 underwent two pregnancies on dialysis. Only in one case, full-term birth could be achieved; rest all patients delivered prematurely. The modes of delivery in the six cases were: vaginal delivery (n = 1), elective cesarean section (n = 3), and emergency cesarean section (n = 2). Five patients delivered successfully and had a good prognosis, while in one, the neonate died.

Over the years, owing to continuous improvement at our hospital, we have achieved better pregnancy prognosis and longer gestation periods in the patients. In particular, Case 1, which had a natural second pregnancy, 9 years after the beginning of dialysis, was worthy of note; we were able to manage her second pregnancy using the process followed during her first pregnancy as reference.

DISCUSSION

According to a study published in 2012, conducted at our hospital, in pregnant patients with CKD, the CKD severity classification reflected perinatal prognosis[2]. Out of seven pregnancies in six patients, examined here, in six pregnancies, the patients were on dialysis during pregnancy, whereas in one pregnancy the patient underwent postpartum dialysis. Although pregnant women with chronic renal failure were not examined before the start of dialysis, we believe that the control of blood pressure and the use of tocolytics are important in the management of pregnancy after the start of dialysis. The guidelines for the management of pregnancy in CKD patients, published in 2017, states that "pregnant patients on dialysis have a lower probability of having a live-born baby than healthy pregnant women, and have a high frequency of premature birth and low birth weight infants"[3]. Infant immaturity due to premature birth is closely associated with perinatal mortality. A previous study showed that hydramnios is a common cause of premature birth with a complication rate of up to 83%[4]. Fetal osmotic diuresis, due to a high level of maternal BUN, has been indicated as the cause of hydramnios[3]. To prolong the gestation period, it is crucial to maintain a low BUN level in the maternal blood by performing frequent dialysis[5]. Therefore, to prevent hydramnios, we performed daily dialysis in the patients at the hospital, beginning

from mid- and late-pregnancy; in addition, we observed the BUN levels in the maternal blood. Moreover, the duration of dialysis sessions was set at approximately 4 hours to reduce the burden in patients, as much as possible, which resulted in only one case of hydramnios in seven pregnancies (14%). Advances in medical technology have made it possible to extend the gestation period as much as possible and bring the baby closer to full-term delivery by taking various measures and observing carefully even if the pregnancy is complicated by dialysis.

In Cases 2 and 5, in which the premature birth was unavoidable despite the normal amniotic fluid volume, we believe that tocolysis was difficult due to causes other than hydramnios. If these factors can be elucidated and uterine contractions can be controlled, premature birth during pregnancy on dialysis may be further reduced.

Pregnancy after kidney transplantation has a better prognosis than pregnancy on maintenance dialysis. According to the data obtained in 2019, however, the number of dialysis patients was 334, 640, which was overwhelmingly larger than 1,827 cases of living-donor kidney transplantations, 54 cases of kidney transplantations from cardiac death donors, and 176 cases of kidney transplantations from brain-dead donors[1, 6]. Undoubtedly, there are a certain number of patients, with CKD and on dialysis, who wish to become pregnant.

CONCLUSION

In this study, we examined seven pregnancies, in six pregnant women on dialysis, at our hospital. The results show that pregnant women on dialysis are able to deliver a live-born baby safely with medical treatment, in cooperation with nephrologists. In addition, the number of infants saved by neonatologists has increased, but we, as obstetricians and gynecologists, consider that premature births should be reduced even further; a decrease in premature births is important for the improvement of the perinatal prognosis.

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